Current Perspectives in the Diagnosis and Management of Diabetes in Pregnant Women

Dr V Mohan*, and Dr R Chandrika

Introduction

Diabetes in pregnancy poses numerous problems both for the mother and fetus. Before the insulin era, the mortality rate of a diabetic women with pregnancy was 45%[1]. However, several advances in diabetic and obstetric antenatal care have drastically reduced the occurrence of maternal morbidity and perinatal mortality in pregnant diabetics. Before we consider the diagnosis and management of diabetes associated with pregnancy, it would be worthwhile to look at the physiology of glucose metabolism in pregnancy.

Metabolism in normal pregnancy

Glucose is the main fuel for the growing fetus which continuously drains glucose from the mother. The fetal glucose in 10 to 20% lower than that of the mother. This differential enhances the transport of glucose from the mother to the fetus - a process which is called 'Facilitated Diffusion'[2]. During pregnancy, the fasting plasma glucose level is usually low while there is an increase in the postprandial plasma glucose level.

Advances in the diagnosis and management of diabetes mellitus during pregnancy has drastically improved maternal and perinatal outcome.

Decreased insulin sensitivity

Pregnancy decreases insulin sensitivity and is therefore diabetogenic. The mother's glucose tolerance depends on the ability of her beta cells to compensate for this decreased sensitivity. The first and second phase insulin responses in pregnancy increase approximately threefold by the third trimester in women who maintain normal glucose tolerance[3]. There is an increase in the synthesis and secretion of human placental lactogen and an enhanced degradation of insulin leading to insulin resistance in the second half of pregnancy.[4-6]

Address for correspondence :
** Director Madras Diabetes Research Foundation, 35, Conran Smith Road, Gopalapuram, Chennai - 600 086 India*

Enhanced lipolysis

Amino acids, particularly alanine, are actively transported across the placenta into the fetal circulation. Since the maternal liver is deprived of a gluconeogenic source, there is breakdown of maternal fat i.e. lipolysis[7]. The consequent increase in free fatty acids and triglyceride levels increase the tendency to ketogenesis. Ketone bodies pass through the placenta and serve as fuel to the fetus.

Metabolism in diabetic pregnancy

Carbohydrate tolerance deteriorates early in pregnancy in diabetic women, in parallel with the physiological decrease in insulin sensitivity. In pre-existing diabetes, glycaemic control worsens and insulin requirements increase during pregnancy. In non-diabetic women, gestational diabetes mellitus or glucose intolerance may be induced. Pregnancy induced lipolysis makes women with IDDM more susceptible to ketoacidosis even with relatively mild hyperglycemia.

Effects of diabetes on the fetus

This can be considered under the following headings

(a) Embryopathy

(b) Fetopathy

(c) Neonatal problems.

The problems to the fetus during pregnancy at different trimesters of pregnancy are tabulated in Table 1.

Malformation

Among the children of women with IDDM, the risk of being born with malformation is around 8% i.e., about 2-3 times higher than that of the general population[10]. Malfor-

mations of the heart and central nervous system are common. The more common of the latter defects is the caudal regression syndrome (Sacral agenesis) which is the agenesis of the lower vertebra and sacrum. Spina bifida is also more common in diabetic patients than in the general population and can be detected quite early in pregnancy using ultrasound scanning. The malformation rate is related to the severity of hyperglycaemia and may be mediated by oxygen derived free radicals or abnormalities of myoinositol and arachidonic acid metabolism[8,9]. Tight control of blood glucose can reduce the malformation rate. Spontaneous abortions are also very common.

Fetopathy

The adverse effect of maternal diabetes on the offspring during the fetal period of development, i.e. end of the ninth week after fertilization, is referred to as Diabetic Fetopathy, an example of which is macrosomia. In a fetus with macrosomia, there is enlargement of virtually all organs of the body.

Classification of diabetes in pregnancy

A. Pre-gestational diabetes

- Insulin Dependent Diabetes Mellitus (IDDM) complicating pregnancy
- Non Insulin Dependent Diabetes Mellitus (NIDDM) complicating pregnancy
- Fibrocalculous Pancreatic Diabetes (FCPD) complicating pregnancy

B. Gestational diabetes mellitus

Another classification of diabetes depending on the prognosis is the White's Classification which is rarely used now-a-days.

Gestational diabetes mellitus

Gestational Diabetes Mellitus is defined as carbohydrate intolerance of variable severity with onset or first recognised during pregnancy. Gestational Diabetes Mellitus develops in individuals who are unable to increase their insulin levels sufficiently to overcome the insulin resistance produced by pregnancy. It is usually diagnosed or develops in the second trimester of pregnancy during which time the fetal demand for glucose is very high.

Table 1

Problems to fetus in diabetic pregnancy		
I Trimester	II Trimester	At Birth
Malformation	Hypertrophic Cardiomyopathy	Hypoglycemia
Growth retardation	Polyhydramnios	Hypocalcemia
Fetal wastage	Placental Insufficiency	Hyperbillirubinemia (Jaundice)
	Pre-Eclampsia	Macrosomia

Criteria for diagnosis of GDM

The oral glucose tolerance test is done with 100 gms of glucose. The O'Sullivan and Mahan Criteria (1964) is still the best criteria for diagnosis of GDM and is shown in Table 2.

The risk factors of development of GDM are listed in Table-3. Patients with these risk factors are to be screened early in pregnancy and the screening procedure is summarized in Table-4.

Management of diabetes during pregnancy

This can be discussed under the following heads:

a) Pre-pregnancy control
b) Control during pregnancy
c) Management of diabetic complications
d) Post pregnancy control.

(A) Pre-pregnancy control

A diabetic women needs to plan her future pregnancies and to understand the risks that a diabetic pregnancy involves. Frequent antenatal visits, close supervision, strict blood glucose control and appropriate diet advice are all very important to achieve a normal uncomplicated pregnancy.

Aims of pregnancy care

i). Assess fitness for pregnancy particularly paying attention to retinopathy, nephropathy and ischemic heart disease.

Table 2

Diagnostic criteria for gestational diabetes mellitus (O'Sullivan and Mahan) 1964		
FBS	-	>105 mg/dl
1 hour	-	>195 mg/dl
2 hour	-	>165 mg/dl
3 hour	-	>145 mg/dl
Two or more abnormal values are diagnostic of GDM.		

Table 3

Risk factors for the development of gestational diabetes mellitus (GDM)
i). Family history of diabetes
ii). Obstetric history
a. Large baby > 4 kgs
b. Unexplained intra uterine death
c. Poly hydramnios
d. Congenital malformation
iii. Obesity (>120% of the Ideal Body Weight)
iv. Glycosuria on 2 or more occasions during pregnancy
v. Age > 30 years
vi. Previous history of GDM.

ii). Ensure that pregnancies are planned and treat infertility as early as possible because of the increased risk to fetus due to long-standing diabetes.

iii). Obtain optimum glycaemic control before conception

iv). Identify the time of conception accurately

v). Encourage good general principles of health care and hygiene.

iv). Check immune status against rubella.

(B) Control during pregnancy

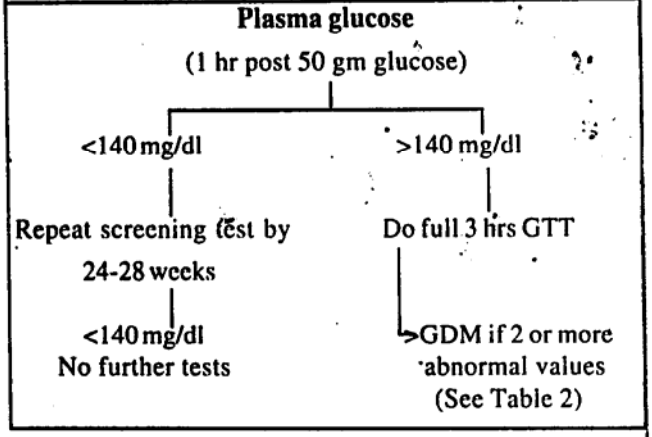
Assessment of diabetes control

All pregnant women should be seen early in the first trimester to optimise glycemic control during the critical period of organogenesis. Now-a-days, glycosylated hemoglobin (HbAlc) and fructosamine levels are done to assess the long term diabetic control status. *Glycosylated haemoglobin* (HbAlc) is useful in determining the past three months diabetic control. It also gives us a clue regarding pre-existing diabetes complicating pregnancy eg. if HbAlc is grossly elevated in the first trimester, most likely the lady had pre-existing diabetes preceding the pregnancy as GDM, which usually sets in by the second or third trimester. *Plasma Fructosamine assay* gives an idea about the past 2-3 weeks diabetes control. Both HbAlc and Fructosamine are important to predict the risk of congenital anomalies and the prognosis in general.

Gestational age of the fetus should be determined by an ultrasonogram even in patients who have a regular menstrual cycle, because the risk of pre-term delivery and fetal macrosomia in the second trimester can cause a discrepancy

Table 4

Screening for diabetes in pregnancy



in the fetal age. Specific congenital anomalies are to be excluded by an experienced sonologist.

General principles of diabetes management

Diet: Diet plays a very important role in the management of diabetes, particularly in those patients who have gestational glucose intolerance. Sufficient calories should be provided to meet the excess demand of the fetus during the period of development.

Daily nutritional requirement for diabetic patients during pregnancy:

The total calories allowed per day is about 35-45 kcal/kg. for ideal body weight or about or 300 calories per day above non pregnant needs.

60-65% of the calories should be in the form of carbohydrates (i.e. around 250-300 gms/day).

15-20% should be in the form of protein i.e. about 30 gm above non pregnant needs.

The rest i.e. 15-20% of the calories should be in the form of fat 40-60 gm/day.

Sufficient iron, calcium and folic acid should also be available in the diet.

A bed time snack is also essential to prevent nocturial hypoglycemia, particularly in IDDM patients. An ideal snack should provide about 25 gm of carbohydrate and some protein.

Insulin treatment

All pregnant diabetic women should be treated only with insulin. Women with diabetes complicating pregnancy who are on oral hypoglycemic agents should be switched over to insulin and this should ideally be done even before

pregnancy or early in the first trimester. Oral hypoglycaemic agents (OHA) are contraindicated during pregnancy because of risk of teratogenicity. Moreover, OHA cross the placental barrier and thus cause hyperplasia of the fetal cells leading to macrosomia and neonatal hypoglycaemia.

Glucose monitoring during pregnancy

The glycaemic targets are the same in all the groups of pregnant diabetics (NIDDM/GDM or IDDM). The ideal levels of glycaemic control are listed in Table 5. It is to be noted that tight control of diabetes should be achieved during pregnancy.

When insulin is indicated

If FBS is >105 mg/dl or PPBS >140 mg/dl on 2 or more occasions, insulin is usually indicated. In very high risk cases, even a minor abnormality of glucose tolerance may necessitate insulin.

Insulin regimes

In mild NIDDM complicating pregnancy or in patients with GDM a once daily dose of an intermediate acting insulin may usually suffice. However if the fasting blood sugar is high, a twice daily insulin regime is indicated. Usually, a pre-mixed insulin (30:70 mixture of short and intermediate acting insulin) is preferred because it is convenient to use.

Combined efforts of the diabetologist, obstetrician and neonatologist are the key factors for successful outcome of these pregnancies.

In the case of IDDM complicating pregnancy, atleast 3 doses of insulin/day would be needed and sometimes even 4 or 5 doses a day to achieve good glycaemic control. Divided doses of short acting insulin are usually given before breakfast and lunch and a combination of a short and intermediate acting insulin before dinner.

Monitoring glycaemic control

Insulin doses need to be modified according to the blood glucose, glycosylated hemoglobin and fructosamine levels. Periodic frequent checkups are ideal to maintain tight control. Fasting blood sugar should be in the range of 70-100 mg%, postprandial blood sugar 100-130 mg%, glycosylated hemoglobin (HbAlc) below 6% and fructosamine below 180 umol/l (Table/4).

In an obese diabetic, avoid excess weight gain but do not attempt weight reduction during pregnancy.

Table 5

Ideal levels of glycemic control during pregnancy		
	Ideal level	
Fasting plasma glucose	-	<100 mg
Post-prandial plasma glucose	-	<130 mg
Glycosylated hemoglobin (HbAlc)	-	<6%
Plasma Fructosamine	-	<180 umol/L.

Monitoring fetal growth

Frequent ultrasound scans are to be performed to assess the fetal growth and liquor volume and also to look for any congenital malformations.

(C) Management of diabetic complications during pregnancy

Nephropathy: Blood pressure should be tightly controlled during pregnancy. Usually, methyldopa is used as ACE-inhibitors are contraindicated. During the third trimester, worsening nephropathy may be difficult to distinguish from pre-eclampsia.

Retinopathy: Ideally, fundoscopy should be performed in all diabetic women before conception as there is a chance of progression of retinopathy during pregnancy. Hypertension during pregnancy is also associated with progression of retinopathy and optimal BP control is very important. Patients with retinopathy require laser photocoagulation which can be done during pregnancy. This represents an important tool in the management of diabetic retinopathy.

Special monitoring during third trimester

The insulin requirements start to climb during the third trimester and plateaus off around 34-36 weeks of gestation. This is a physiological phenomenon attributable to the increased transfer of glucose to the fetus in late pregnancy.

Assessment of fetal maturity is particularly important at this stage because respiratory distress syndrome has been a major cause of neonatal morbidity and mortality in diabetic pregnancies. A six fold higher incidence of respiratory distress syndrome (RDS) has been reported for any given gestational age in diabetic compared with non diabetic pregnancies[11]. The incidence of RDS has fallen dramatically in the last four decades from 27% in the 1960's[12] to 2.4% in the 1980s[13] coincident with the fall in elective premature delivery and improvements in diabetic management.

It is difficult to predict the risk of RDS in a diabetic pregnancy. Amniocentesis is widely used to assess prematurity by measuring the lecithin: sphingomyelin (L:S) ratio in the aminotic fluid.

Management of labor and delivery

Earlier, most diabetic women used to undergo caesarean

sections at 37-38 weeks. Now-a-days, due to good obstetric care during pregnancy, normal vaginal delivery is increasingly being achieved. If there are no obstetric or fetal problems, one can continue till 38 weeks of pregnancy and then make a decision based on the clinical status of the patient and the degree of risk involved.

Diabetic control during labour

Insulin requirements are low in labour. Hence, blood sugars are to be checked frequently. Short acting insulins are best given as an infusion with dextrose. The following schedule is highly recommended. 5 units of insulin is added to 5% dextrose and a drip rate of 100 ml/hour is maintained. This will deliver 5 gms of glucose and 1 unit of insulin per hour. If higher insulin rates are required, more insulin can be added to the drip. Once the baby is delivered, insulin requirements tend to fall rapidly. The insulin infusion can be stopped or halved. In patients with gestational diabetes, the mother will not require insulin after delivery and blood glucose levels should be monitored after a few weeks to assess the diabetic status.

The neonate should be examined by a neonatologist and should be kept under observation in a neonatal ward. Hypoglycemia occurs in 50% of the neonates, especially in macrosomic infants,[14] but they usually respond to oral feeds. Capillary blood glucose should definitely be checked at birth if the baby is unduly sleepy or is feeding poorly. The other complications listed in Table 1 are to be excluded.

Pre term labor

Overall, 26% of diabetic women deliver before 37 weeks gestation compared with 10% in the general population[15].

Post partum monitoring of diabetes mellitus

In an IDDM patient the insulin requirements begin to fall. Usually, we can switch back to twice daily insulins or their pre-pregnancy insulin schedule. In an NIDDM patient, oral hypolycemic drugs can be re-started. The follow-up of a GDM patient is very important as 50% of GDM patients are known to develop overt diabetes mellitus within 5-10 years. The GTT (with 75 gm glucose) is to be repeated 6-8 weeks after delivery and annually thereafter, if indicated, (in those with a family history of diabetes).

In summary, the combined efforts of the diabetologist, obstetrician and neonatologist have considerably improved the prognosis of diabetes complicating pregnancy.

References

1. Reece EA. The history of diabetes mellitus. In: Reece EA Coustan DR eds, Diabetes Mellitus in pregnancy: New York Churchill Livingstone, 1988:3-15.
2. Freinkel N. Banting lecture 1980: of pregnancy and progency Diabetes. 1980;29:1023-1035.
3. Buchanan TA, Metzger BE, Frienkel N, Bergman RN. Insulin sensitivity and beta cell responsiveness to glucose during late pregnancy in lean and moderately obese women with normal glucose tolerance or mild gestational diabetes. Am J Obstet Gynecol 1990;162:1008-1014.
4. Ryan EA, Enna L. Role of gestational hormones in the induction of insulin resistance. J Clin Endocrinol Metab 1988;67:341-347.
5. Cousins L. Insulin sensitivity in pregnancy. Diabetes 1991;40(Suppl 2):39-43.
6. Handwerger S. Clinical counterpoint: the physiology of placental lactogen in human pregnancy. Endocr Rev. 1991;12:329-336.
7. Martin JW, Friesen HG. Effect of human placental lactogen on the isolated islets of langerhans. Endocrinology 1969;84:619-622.
8. Eriksson UJ, Borg LA. Diabetes and embryonic malformations. Role of substrate-induced free oxygen radical production for dysmorphogenesis in culture rate embryos. Diabetes 1993;42:411-419.
9. Baker L, Piddington R, Goldman A, Moehring J. Myoinositol and prostaglandins reverse the glucose inhibition of neural tube fusion in cultured mouse embryos. Diabetologia 1990;33:593-596.
10. Baker L, Piddingtong R. Diabetic embryopathy: a selective review of recent trends. Journal of Diabetes Complications 1993;7:204-212.
11. Robert MF, Nelf RK, Hubbell JP, Tacush HW, Avery ME Association between maternal diabetes and respiratory distress syndrome in the newborn. New Engl Jour Med 1976;294:357-360.
12. Hubbell JP, Muirhead DM, Drorbough JE. The newborn infant of the diabetic mother. Med Clin North Am. 1075;49:1035-1052.
13. Drury MI, Stronge JM, Foley ME, MacDonald DW. Pregnancy in the diabetic timing and mode of delivery. Obstet Gynaecol. 1983;62:279-282.
14. Mountain KR. The infant of the diabetic mother. Bailliere's Clinical Obstet Gynaecol. 1991;5:413-442.
15. Greene MF, Hare JW, Krache M et al. Prematurity among insulin requiring diabetic gravid women. Am J Obstet Glynaecol. 1989;161:106-111.