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PREGNANCY AND DIABETES MELLITUS AN OVERVIEW

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ABSTRACT

Pregnancy is not anymore rare in diabetic patients. Insulin therapy drastically reduced maternal mortality and morbidity. Perinatal mortality in diabetic pregnancies continued to be relatively high until the last decade. Marked reduction occurred since then and has been attributed to several factors: better understanding of the physiologic changes in carbohydrate metabolism in pregnancy, and the emphasis on the maintenance of glucose homeostasis in diabetic pregnancies as near to normal as possible, the introduction of methods to assess fetal well being and fetal lung maturity, and advances in neonatal intensive care. Active screening programs have been established to identify gestational diabetics. These patients' metabolic derangement can be controlled by dieting alone. Known diabetics require insulin, in addition. Insulin therapy should be continually adjusted to maintain euglycemic levels. Diabetic patients should be followed closely and monitored for any complications. Fetal well being should be evaluated using NST's, CST's, serial estriols, ultrasonography, and amniocentesis. Timing of delivery should depend on the adequacy of metabolic control, the presence of complications and on the results of fetal well being and fetal lung maturity studies. Modern management has resulted in marked reduction in perinatal mortality and morbidity. However, the increased incidence of congenital malformations in infants of diabetic mothers has not yet been reduced. Tight diabetic control in early pregnancy and probably also preconceptionally might be crucial in this regard.

KEY WORDS: *Diabetes Mellitus, Pregnancy, Diagnosis, Management, Results, Fetal Surveillance, Fetal Lung Maturity*

PREGNANCY AND DIABETES MELLITUS: AN OVERVIEW

There has been a marked improvement in the management of diabetes mellitus. Many "juvenile" diabetics not only reach their childbearing age, but also are fertile. In addition, adult onset diabetes mellitus can manifest itself in the childbearing period. Overt diabetes mellitus complicates 0.1[1] to 0.75%[2] of all pregnancies. Moreover pregnancy unmasks many "potential" diabetic women, the so-called gestational diabetics.

The incidence of gestational diabetes is directly proportional to the efforts made at screening for this abnormality, and varies between 2%[3] to 7%[4] of all pregnant women. A random fasting or 2 hours postprandial blood glucose measurement is all that is done in many instances. In other instances, a glucose tolerance test is ordered only when there are suggestive historic or clinical clues such as family history, previous gestational diabetes, previous macrosomic (> 4 kg) fetuses, unexplained stillbirth, obesity, fasting glycosuria, hypertensive disease, or polyhydramnios. Others, utilize a 50-g glucose loading test[5] to select patients for glucose tolerance testing. Blood glucose is measured 1 hour after this load; levels ≥ 130 mg per deciliter are considered abnormal and select the patients for glucose tolerance testing.

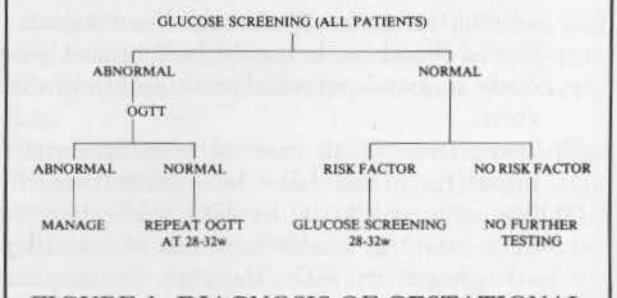

FIGURE 1: DIAGNOSIS OF GESTATIONAL DIABETES AT THE MEDICAL COLLEGE OF GEORGIA

Beginning in 1978, this glucose screening test has been performed on all patients in our institution at their initial prenatal visit, and if abnormal, have been followed by the oral glucose tolerance test (OGTT). If the screening test is normal, i.e., blood glucose is 130 mg per deciliter 1 hour after 50-g glucose load, while there are historic or clinical clues, the glucose screening test is repeated at 28 to 30 weeks of gestation. Also, if the glucose screening test is abnormal but the OGTT is normal, the latter is repeated at 28-32 weeks of gestation. This is because the diabetogenic effects of pregnancy are progressive and

will be more pronounced at this time (Fig. 1). This policy has resulted in an increase of the incidence of diagnosed gestational diabetes from 1.7% in the period of 1976 to 1978[6] to 5.7% in the year 1980.

The oral glucose tolerance test (OGTT) is preferred over the intravenous test (IVGTT). After 3 days of a high carbohydrate diet (200 to 300 g per day), the patient is asked to fast after midnight. A fasting blood glucose is obtained, and a 100-g glucose load is given. Blood glucose levels are measured in samples drawn 1, 2, and 3 hours later. The OGTT is considered abnormal if any 2 of the 4 values equal or exceed 90, 165, 145, and 125 mg per deciliter, respectively [5, 6]. If glucose is measured in the plasma (or serum) instead of whole blood, the corresponding figures are 105, 190, 165, and 145 mg per deciliter, respectively[7] (table 1).

Table 1. Upper limits of glucose levels (mg/dl) in OGTT* during pregnancy

	Whole blood	Plasma or serum
Fasting	90	105
1 hour	165	190
2 hours	145	165
3 hours	125	145

*100-g glucose load.
Modified from O'Sullivan et al[5].

Glycosylated hemoglobins (HbA_1), which are adducts of glucose (and glycolytic intermediate products) with hemoglobin (Hb), are increased in diabetes mellitus. The adduction of glucose to Hb is a post-translational non-enzymatic irreversible process that occurs throughout the lifespan of the erythrocytes, and its rate is dependent upon the time-averaged blood glucose levels. We found that HbA_1 levels were significantly increased in gestational diabetes. However, there was an overlap of the results, and thus there was no specific level that can be used to diagnose gestational diabetes[8].

Classification

The most widely used classification of diabetes mellitus in pregnancy is White's classification[1, 9],.Patients who are not known to be diabetic prior to pregnancy and are discovered to have an abnormal OGTT during pregnancy constitute class A. They -by definition- can be managed by dieting alone. All others (i.e., known diabetics and those who require insulin) are considered overt diabetics. They are classified according to the age of onset of diabetes, duration of the disease, and the presence of vascular complications. A simplified version of the classification is given in table 2.

Table 2. White's classification of diabetes in pregnancy

Class	Age of onset (years)	Duration (years)	Vascular complications
A	Any	Any	---
B	20	10	---
C	10-19	10-19	---
D	10	20	Background retinopathy/ hypertension
F	Any	Any	Nephropathy
R	Any	Any	Proliferative retinopathy

Modified from White[1]

Fetal/Neonatal Complications

The metabolic derangement in the pregnant woman results in an abundant supply of substrates to the fetus; glucose, amino acids, ketones, fatty acids, and glycerol. The fetal pancreatic cells respond normally to the excess glucose levels by secreting excessive amounts of insulin, an anabolic hormone. The abundance of substrates in the presence of excess insulin results in an overgrowth of most of the fetal organs, marked deposition of fat in the subcutaneous tissues, and increased glycogen stores in the fetal liver. Macrosomia is therefore a frequent complication. However, in diabetics with vascular complications (classes D, F, R), placental insufficiency is a potential hazard, and fetal growth may be retarded rather than accelerated[1, 7, 10].

The most serious complication is sudden intrauterine fetal death. In some cases, this can be explained by maternal ketoacidosis, or severe pre-eclampsia, but in other cases, there is no obvious explanation. It is assumed that it results from a combination of metabolic derangement, electrolyte imbalance, and hypoxia[1, 7, 11]. It must be emphasized that this complication is very rare in well-controlled diabetics.

As a result of increased incidence of induction of labor, macrosomia, and fetal distress, there is an increased incidence of cesarean section deliveries of diabetics,[1, 3, 4, 6, 11] with consequent increased maternal morbidity. On the other hand, if macrosomic fetuses are allowed to deliver vaginally, shoulder dystocia and birth trauma are real dangers.

The neonate is particularly prone to develop hypoglycemia, hypocalcemia, and hyperbilirubinemia, and most seriously, respiratory distress syndrome (RDS)[7, 12]. The incidence of congenital malformations seems to be higher in infants of diabetic mothers, and this constitutes a major cause of the continued higher perinatal mortality in diabetic pregnancies[7, 11, 13].

Management

The goals of therapy are to maintain the health and well-being of the pregnant woman, to eliminate or minimize maternal complications, and to deliver a healthy term fetus. It has been shown that these goals can best be achieved by a combination of "strict" metabolic control, a program of fetal surveillance, an individualized policy of timing of delivery, proper intrapartum fetal monitoring, and neonatal intensive care.

Metabolic control: Karlsson and Kjellmer[14] showed that the perinatal mortality was six times higher when the mean blood glucose level during the third trimester was greater than 150 mg per deciliter than if it was less than 100 mg per deciliter. Subsequent studies have confirmed the beneficial effect of "strict" metabolic control[15]. The aim of therapy is to maintain blood glucose levels as close as possible to those in normal pregnancy, i.e., less than 90 mg per deciliter in the fasting state, and less than 120 mg per deciliter in the postprandial state.

In class A diabetes, this degree of control can usually be achieved by dieting alone, while in overt diabetes, insulin is given in addition. At our institution, the daily caloric intake is calculated as 30 to 35 Kcal per kilogram ideal body weight. In teenagers, or in the more physically active women, 200 to 300 Kcal are added[6, 7].

Carbohydrates, proteins, and fats provide 45, 25, and 30% of the caloric intake respectively. In class A diabetics, the intake is divided between three meals and one bed-time snack; 2/7 for each meal and 1/7 for the snack. The dietary allowances are the same for the overt diabetics. However, it is usually divided into three meals and three snacks to minimize the excursions of the blood glucose levels throughout the day[6, 7].

In class A diabetics, if dieting is not enough, as indicated by two fasting blood glucose levels in excess of 100 mg per deciliter, insulin therapy in instituted, and the patient is classified as A/B[1, 6, 7]. Overt diabetics are treated with insulin. Oral hypoglycemic agents should not be used in pregnancy[3, 4, 6, 7, 11, 12, 15, 16].

In the first trimester, the daily dose may need to be reduced by one-third and then gradually increased in the second trimester. It is not unusual for the insulin requirements to be 200 to 300% of the pre-pregnant dose towards the end of pregnancy[1]. The most commonly used regimen utilizes a mixture of short (regular) and intermediate acting (NPH or lente) insulins. The daily dose is divided between a.m. and p.m. in a ratio of 2:1, and the ratio of intermediate to short-acting insulin is usually 2:1 in a.m. and 1:1 in p.m.[3, 4, 6, 7, 11, 12, 15].

The exact dosages will have to be adjusted, depending on the daily glucose profile. In the average case, a fasting and 2-hour postprandial (after each of the 3 meals) glucose levels are obtained. However, in some cases it will be necessary to measure the blood glucose more frequently (up to every 2 hours) to be able to better adjust the insulin dose[6].

In the more difficult cases, four doses of regular insulin at 6-hour intervals may be more practical to achieve the desired euglycemic control[16]. This is particularly true in the "brittle" diabetic when the response time to the intermediate insulin may be quite variable, and the peak action of the intermediate insulin given at one time may coincide with the peak action of the short insulin given at another time, causing severe hypoglycemia. Usually the control becomes much easier as pregnancy advances, and one can then switch back to the split-dose combination regimen described above.

In addition to blood glucose determinations, urine (double-voided specimens) should be checked frequently both at home and in hospitalized patients for the presence of glucose and/or ketone.

The initial adjustment of insulin dosage is usually done in the hospital. After this is accomplished, and the patient is discharged, adjustment is usually done on a bi-weekly or weekly basis as an outpatient. However, if strict metabolic control cannot be maintained the patient is re-hospitalized[6]. More recently, with the availability of home glucose monitoring, i.e., the use of dextrostix or chem-strips and Dextrometer or Glucometer (both from Ames Co., Elkhart, Indiana), or a stat tek (from Biodynamics/bmc, Indianapolis), the patient can check her own glucose profile as frequently as is required, and through consultation with her physician, insulin dose adjustment can be done daily as in hospitalized patients. Although the instrument and the strips are relatively expensive, it is quite cost-effective. In a motivated intelligent patient, one can reduce the length of the initial hospital stay, and subsequent hospitalizations for the sole purpose of achieving "strict" control, to a minimum. This approach is being more widely used and seems to be very promising[17].

An alternate approach for the evaluation of the adequacy of diabetic control is the serial measurement of HbA_1 levels. These were shown to correlate with the mean fasting blood glucose levels from the prior 8 weeks. Marked elevation of HbA_1 indicates poor control, but lesser values can be associated with wide range of fasting blood glucose levels to make them of little value. Actually mildly elevated or even normal levels of HbA_1 cannot assure the clinician that glucose control is satisfactory[18, 19].

Fetal surveillance: A baseline ultrasonographic examination is usually performed at 20 weeks for accurate determination of gestational age, using biparietal diameter (BPD), femoral length (FL), head circumference (HC), and abdominal circumference (AC) measurements. Subsequent examinations are scheduled at 6-week intervals for evaluation of fetal growth. Careful examination is mandatory to detect potentially diagnosable fetal malformations[7].

Antepartum fetal heart testing should be started at 30-34 weeks on all overt diabetics (earlier in the more advance cases). Nonstress tests (NST's) are used primarily. They are repeated weekly or twice a week. If the fetus is non-reactive, i.e., no fetal movements or 2 accelerations of the fetal heart with fetal movements in a 20-minute period, contraction stress testing (CST) is mandatory. A positive CST, i.e., persistent late decelerations with three uterine contractions occurring in a 10-minute period indicates fetal jeopardy[6, 7, 11].

Estriol (E_3) assays are also useful in monitoring the fetal well being. E_3 can be measured in serum, or in 24-hour urine samples. This is usually initiated at 30 to 32 weeks and performed weekly if the patient is ambulatory, and more frequently later. During the predelivery hospitalization, E_3 assays should be done daily. A significant drop is defined as a 35% reduction from the mean of the three highest consecutive levels. Such a drop is very suggestive of fetal jeopardy[6, 7, 11].

Fetal lung maturity is usually determined by measuring the lecithin/sphingomyelin (L/S) ratio in the amniotic fluid. A ratio of 2 indicates pulmonary maturity in nondiabetics. Some authors claim that the same is true for diabetic pregnancies, while most investigators believe that a higher ratio (2.5 - 3.5) is more appropriate.

In our institution (MCG), the concentration of lecithin phosphorus in the amniotic fluid is used, a level of 0.1 mg per deciliter is consistent with pulmonary maturity in both diabetic and nondiabetic pregnancies[21]. The presence of phosphatidylglycerol (PG) is now believed to be the most accurate criterion of fetal lung maturity[20].

Predelivery admission: Overt diabetics are usually admitted prior to delivery, at 30 to 34 weeks in the most advanced cases (classes D, F, and R), at 34 to 36 weeks in class C, and 36 to 38 weeks in class B. Complicated class A diabetics, i.e., patients with hypertensive disease, or those with a previous stillbirth, are admitted as class B patients. Uncomplicated class A patients are admitted at 40 weeks if labor does not ensue[6, 7].

Timing of delivery: In the past, diabetic pregnancies were terminated at specific times depending on the class, e.g., class A at 38 weeks, class B at 36 to 38 weeks, class C at 35 to 37 weeks, etc. This resulted in a decrease in stillbirth rate, but a marked increase in neonatal death rate from RDS. Thanks to the availability of the above described fetal monitoring and maturity tests, this policy has been abolished. Timing of delivery is individualized, and depends on the degree of diabetic control and the results of these tests[3, 4, 6, 7, 11, 12, 15].

Uncomplicated class A diabetics are allowed to go into spontaneous labor. If labor does not ensue by 40 weeks, they are admitted. Labor is induced if the cervix is favorable. If not, they should be closely monitored (daily E_3 and twice a week NST). Labor is induced whenever the cervix becomes favorable, or there is evidence of fetal jeopardy[6, 7, 11].

In a well-controlled diabetic, amniocentesis for fetal lung maturity studies is delayed until 37 to 38 weeks, but in poorly controlled or complicated cases, it is usually done earlier. Pregnancy is terminated when there is a mature "tap" i.e., L/S ratio of 2, and PG is present (or if lecithin phosphorus concentration is 0.1 mg per deciliter - at MCG), and the cervix is favorable. If the cervix is unfavorable, induction can be delayed as long as the NST's are reactive and E_3 continues to rise[6, 7].

If the tap is immature, close observation is continued, and the amniocentesis is repeated in a week's time. If there is suspicion of fetal jeopardy, i.e., positive CST in the presence of normal E_3 excretion or a drop in E_3 excretion with a negative CST, pregnancy is allowed to continue until there is evidence of fetal lung maturity.

On the other hand, if there is evidence of fetal compromise, i.e., positive CST and drop in E_3, the risk of fetal death in utero is so high that the delivery of the fetus - even if the fetal lungs are immature- is justified[6, 7].

Method of delivery: Vaginal delivery should be the aim, except if there is an obstetric indication, e.g., previous cesarean section, malpresentation, fetal distress, etc. However, if the fetus is predicted to weigh 4 kilograms, or if there is evidence of rapid deterioration of the fetal condition, i.e., marked drop in E_3 excretion while the cervix is unfavorable, cesarean section should be resorted to[6, 7, 11]. In other cases, labor is induced.

Internal fetal heart rate monitoring should be started as soon as feasible. However, if active labor is not established after 6 to 8 hours or if fetal distress supervenes, cesarean section should be performed.

Peripartal insulin administration: It has been customary to administer, in the morning of planned delivery, one-half of the prepregnant insulin dose in the form of regular insulin, if labor is to be induced, and only one-third of that dose if cesarean section is planned[6, 7]. More recently, low-dose continuous intravenous administration of regular insulin has been successfully used,[22] and is currently used routinely in our patients.

An intravenous injection of 5% dextrose in 0.45% sodium chloride is started at a rate of 125 ml per hour, i.e., 6.25 g glucose (or 25 Kcal) per hour. The total caloric intake is divided by the total insulin dose in the previous day to get the calorie-unit ratio for the patient. The hourly intake of 25 Kcal is then divided by this calorie-unit ratio to give the hourly insulin requirement. Blood glucose levels are measured either hourly or every 2 hours, and the rate of insulin infusion adjusted accordingly (table 3).

Once the patient is delivered, insulin infusion is discontinued. Blood glucose levels are checked every 2 hours, and then at less frequent intervals. Insulin is only administered when indicated by high blood glucose levels. This might not occur until the second or third postpartum day[7].

Results

The modern approach to the management of diabetic pregnancies resulted in a dramatic decrease in the maternal mortality and morbidity as well as the perinatal mortality rates (PNMR). The incidence of hypoglycemic coma or diabetic ketoacidosis has dropped significantly. Their treatment is not different from the treatment in nonpregnant individuals, and have been detailed elsewhere[7].

The cesarean section rate has been reduced from a high of 75% in the older literature[1] to 24% in our series[6]. This is due to the tendency to carry pregnancy closer to term, resulting in a greater proportion of successful inductions of labor, and to the decreased incidence of macrosomic fetuses, reducing the probability of cephalopelvic disporportion[6]. The PNMR has decreased from 10% in the late 60's to 3% in the late 70's,[24] and continues to decrease. In a recently reported series from the author's institution, including 84 gestational and 23 overt diabetics, the PNMR was 0.9%[6].

Antepartum fetal death has been largely prevented by the careful utilization of available techniques for monitoring of the fetal well being described above. Moreover, there is evidence that improved diabetic control does reduce the likelihood of deterioration of fetal placental function, and thus the risk of fetal death[15].

More than half of the reported deaths in the neonatal period were due to RDS. The incidence of RDS has been dramatically reduced as a result of the policy of postponement of delivery until there is evidence of fetal pulmonary maturity. In our series, only one patient, a class C diabetic, was delivered in spite of immature tap because of evidence of fetal jeopardy, i.e., positive CST and a significant drop of E_3. Her infant was the only one to develop RDS[6]. Moreover, fetal hyperinsulinism and other metabolic derangements are believed to be the cause of suppression of surfactant production and the observed increased incidence of RDS in infants of diabetic mothers. The recent emphasis on strict metabolic control of the mother may have resulted in normalization or amelioration of the fetal metabolic milieu, with consequent reduction in the incidence of RDS[6]. In addition to the decreased incidence of RDS, deaths from RDS have decreased dramatically because of improved neonatal management. Modern management has also resulted in reduced neonatal morbidity, particularly hypoglycemia. The incidence of LGA and macrosomic neonates has also been reduced[12].

There is some evidence that the increase in the incidence of congenital malformations in infants of diabetic mothers may be partly due to less than optimal diabetic control at or around the time of conception. Emphasis on strict metabolic control before a planned conception may result in a reduced incidence of congenital malformation,[25] the remaining major cause of perinatal deaths in infants of diabetic mothers.

Table 3. Continuous intravenous infusion of regular insulin for intrapartum management

1. Intravenous infusion of 5% dextrose in 0.45% sodium chloride at a rate of 125 ml per hour = 6.25 g glucose or 25 Kcal per hour.
2. Total caloric intake/total insulin dose in the previous day (Calorie-unit ratio).
3. Rate of regular insulin infusion per hour = 25/calorie-unit ratio.
4. Check blood glucose hourly until stable then every 2 hours. Adjust the rate of insulin infusion accordingly.

Modified from Linzey[22]

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