DIABETES-RELATED COMPLICATIONS OF PREGNANCY

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Diabetes mellitus is a major medical complication of pregnancy and is associated with an increased risk of maternal and perinatal morbidity and mortality. Although recent advances have improved outcomes dramatically, the increased incidence of congenital malformations remains a significant problem. In the past, it was believed that pregnancy worsened microvascular complications, and women with vasculopathy were counseled to avoid or terminate pregnancies. Recent evidence suggests that normalization of blood glucose levels and current management strategies can lead to improved outcomes even in women with vasculopathy. Today, with the exception of coronary artery disease, women with diabetes may be counseled toward a more favorable outcome. This article discusses preconception planning and contemporary treatment methods. (*J Natl Med Assoc.* 1993;85:537-545.)

Key words • diabetes mellitus • pregnancy complications

Diabetes mellitus is a heterogenous disorder of glucose intolerance. The degree of intolerance ranges from mild to severe. The more severe forms of glucose intolerance are associated with major vascular complications. Environmental as well as genetic factors are recognized as playing roles in the etiology of metabolic derangements. Diabetes is fairly common among pregnant women, occurring in approximately 1 out of every 200 pregnancies complicated by overt diabetes. An additional 5 in 200 pregnancies may develop gestational diabetes mellitus. Diabetes is a major medical complication of pregnancy and is associated with an increased risk for maternal and perinatal morbidity and mortality.

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CLASSIFICATION OF DIABETES IN PREGNANCY

The most well-known and widely used system to classify diabetes in pregnant women is the Priscilla White Classification.[1] This system is based on the assumption that there is a proportionality between age at onset, duration of disease, vascular complications, and the likelihood of complications during pregnancy. This classification system does not specifically include gestational diabetes. In 1979, the National Diabetes Data Control Group of the National Institutes of Health developed an internationally standardized classification system that included gestational diabetes, which was defined as the onset or recognition of carbohydrate intolerance during pregnancy and its disappearance after delivery.

HISTORICAL PERSPECTIVE

Advances in our abilities to achieve metabolic control and perform fetal surveillance have led to dramatic improvements in maternal-fetal outcomes. Today, pregestational diabetes is almost never a contraindication to pregnancy. However, prior to the discovery of insulin in 1922, the fetal death rate was approximately 60% to 70%, and maternal morbidity was approximately 30%. Maternal morbidity significantly decreased after the discovery of insulin but stillbirths and neonatal deaths continued to complicate more than a third of these pregnancies for many decades. Improvements in perinatal outcomes came about more slowly.

In 1954, Pederson demonstrated that the fetal mortality rate was significantly lower in patients who

were being followed over a long period of time than in those first seen later in pregnancy. Thus emerged a philosophy of close surveillance and the development of specialized diabetes care centers. Other new developments including blood glucose meters, neonatal intensive care units, and more sophisticated and advanced forms of antenatal testing led to further reductions in perinatal morbidity and mortality.[2]

In 1977, Karlson and Kjellmer demonstrated that there was a linear relationship between glycemic control and perinatal mortality.[3] These findings have subsequently been corroborated by others[4-5] and have led to a new era in diabetes-in-pregnancy management. Strict metabolic control has become the recognized goal of all diabetic pregnancies.[6] Today, most centers report an average perinatal rate of less than 5%.

Although significant strides have been made with regard to diabetes in pregnancy, the incidence of congenital anomalies has not changed significantly over time. Evidence from clinical and animal studies suggest these malformations are caused by derangements in metabolism during organogenesis.[7,8] Clinical efforts therefore have been targeted at metabolic control prior to conception. Preconception counseling and control is the focus of obstetrical care for the 1990s.

Women with diabetes are living longer and hence more women with vascular complications are becoming pregnant. The major cause of maternal death has shifted from diabetic ketoacidosis to cardiorenal complications. In the past, diabetic women with vasculopathy were counseled to avoid pregnancy or terminate pregnancy if it occurred. It was believed that pregnancy worsened microvascular complications. New data suggest that with the exception of coronary artery disease, pregnancy is not contraindicated in diabetic women. Perinatal outcomes also are not significantly different when strict metabolic control is maintained.

From a management perspective, diabetic patients can be classified into two groups—those with and those without diabetic vasculopathy. The first group includes White's classes A, A/B, B, C, and D (without hypertension). The second group consists of classes D with hypertension, F, FR, and H. The latter group has more advanced disease and is at greater risk for pregnancy-related complications; therefore, these patients require more intensive evaluation and surveillance both before and throughout their pregnancy.

DIABETIC VASCULOPATHY

Diabetic Retinopathy

Class R diabetes mellitus includes pregnant patients with diabetic retinopathy. There are essentially two types of diabetic retinopathy: background diabetic retinopathy and proliferative diabetic retinopathy. Diabetic retinopathy is the leading cause of blindness in persons between the ages of 26 and 64. The first half of this period corresponds to the peak fertility and childbearing years. Retinal vascular disease can lead to impairment in vision either directly by causing macular edema or indirectly by causing vitreous hemorrhage or retinal detachment due to neovascularization. Proliferative diabetic retinopathy is the most frequent cause of blindness among patients with type I diabetes, and macular edema is the primary cause of blindness for those with type II diabetes.

Background and Proliferative Retinopathy

Background diabetic retinopathy is characterized by microaneurysms, small vessel obstruction, cotton wool spots or soft exudates, intraretinal microvascular venous abnormalities, retinal hemorrhages, hard exudates, disk edema, macular edema, and macular ischemia. Proliferative retinopathy is characterized by the growth of neovascular and fibrous tissue. The etiology of the neovascular growth is unknown but is believed to be a response to underlying retinal ischemia. The major determinants of the development or progression of retinopathy are the duration of diabetes and the severity of the retinopathy.[9]

Diabetic Retinopathy and Pregnancy

The popular belief is that retinopathy is worsened by pregnancy. While some studies have reported progression of retinopathy during pregnancy, others have reported no effect. Klein et al completed a prospective study on 171 pregnant and 298 nonpregnant insulin-dependent diabetic women.[10] Women were evaluated on referral and again during the postpartum period. The severity of diabetic retinopathy was based on grading photographs of the fundus in seven standard photographic fields. After adjusting for glycosylated hemoglobin levels, current pregnancy was significantly associated with progression of retinopathy. The risk of progression was 2.3 times higher in the pregnant diabetic group.

The Rigshospitalet study, on the other hand, suggested that patients with White's class B and C diabetes did not routinely develop retinopathy during pregnancy and that patients in class D with retinal deterioration often experienced regression within several months of delivery.[11]

Pregnancy is a physiologic condition that is tempo-

rary and accompanied by major changes in the distribution of blood flow. In addition, diabetic retinopathy is a condition that is known to progress over time. Progression of retinopathy can be seen in nonpregnant women and men over periods of time as short as 8 months. It is therefore not unexpected that diabetic retinopathy might progress during pregnancy. It also has been demonstrated that the rapid normalization of blood glucose levels in nonpregnant individuals accelerates retinopathy. Because tight metabolic control is the goal of diabetic pregnancies, this raises the possibility that this effect versus the pregnancy is responsible for the progression.

Treatment of Diabetic Retinopathy

Diabetic retinopathy during pregnancy should be treated in the same manner as in a nongravid diabetic patient. Argon laser photocoagulation for diabetic retinopathy during pregnancy appears to be as beneficial as similar therapy in nonpregnant patients. Panretinal photocoagulation is the standard treatment for proliferative retinopathy. Ideally, retinopathy should be detected and treated prior to conception but should laser therapy be needed during pregnancy, such is not contraindicated. The effect of fluorescein on the fetus is unknown, and therefore fluorescein angiography studies should be avoided during pregnancy.[12]

Total diabetic management during pregnancy should include a protocol for rigorous ophthalmologic follow-up for all insulin-requiring diabetics before, during, and following pregnancy. Pregnant diabetic women with background retinopathy or microvascular complications should undergo ophthalmoscopy at least once a month. Women in whom active proliferative retinopathy develops should receive panretinal scatter photocoagulation.[13]

Diabetic Nephropathy

Diabetic nephropathy is one of the most critical complications affecting the outcome of pregnancy and is the leading cause of death in diabetic patients under the age of 40. Diabetic nephropathy is a progressive disease characterized by proteinuria, hypertension, reduced glomerular filtration rate, and increasing renal failure. Because of the increase in glomerular filtration rate and the decreased tubular reabsorption of protein observed in pregnancy, the diagnosis of diabetic nephropathy in pregnancy is based on a value of >300 mg/day urinary protein during the first half of the pregnancy in the absence of a urinary tract infection.[14] Patients with diabetic nephropathy face unique risks when pregnancy occurs. The metabolic derangements of the diabetes itself, the renal dysfunction, and the frequently associated problem of hypertension can all adversely affect fetal growth and development and threaten the health of the mother.

Diabetic Nephropathy and Pregnancy

Whether pregnancy causes a worsening of diabetic nephropathy or hastens the progression to end-stage renal disease is controversial. Historically, patients with nephropathy, especially those with preexisting hypertension, were discouraged from pregnancy. However, more recent studies have demonstrated that maternal and perinatal outcomes have improved significantly in women with diabetic nephropathy.[15,16] Reece et al studied 31 pregnancies complicated by diabetic nephropathy.[17] Although there were significant increases in maternal blood pressure and proteinuria with nephrotic syndrome developing in 71% of pregnancies, all values returned to levels seen in the first trimester of pregnancy. The authors concluded there was no apparent adverse effect of pregnancy on the natural course of the underlying renal disease.

Normally, the amount of proteinuria increases as pregnancy progresses (due to the combination of the factors mentioned above) and regresses after delivery. On the other hand, a rise in the creatinine clearance is observed in only 32% of patients. Whether improved metabolic control allows for the normal expected rise in creatinine clearance is unknown.

Overall, the clinical course of diabetic nephropathy remains stable in most patients; however, 20% to 40% of women experience either a permanent or temporary decrease in kidney function. The mean rate of fall of creatinine clearance is 0.81 mL/minute/month. The presence of hypertension in association with renal insufficiency results in heavier proteinuria, decreased creatinine clearance, and mild azotemia. Most women experience a gradual increase in proteinuria during the first two trimesters with a more dramatic rise in the third trimester.

Diabetic nephropathy, more than any other vascular complication, has the greatest impact on perinatal outcome. The risks of preterm labor, stillbirth, neonatal death, and fetal distress are increased significantly among diabetic women with nephropathy. Intrauterine growth retardation is more common in women with diabetic nephropathy. Approximately 19% of infants are small for gestational age contrasted with 2.2% in diabetic women without renal disease. The frequency of fetal growth retardation doubles in the third trimester if

TABLE 1. PERINATAL OUTCOME OF PREGNANT WOMEN WITH DIABETES-ASSOCIATED RENAL DISEASE (WHITE'S CLASS F OR FR)*

	Study	
	Kitzmiller et al[15]	Reece et al[17]
No. of patients	26	31
Fetal death	2 (7.7%)	2 (6.4%)
Preterm (<34 weeks)	8 (30.8%)	10 (32%)
Small for gestational age	5 (20.8%)	5 (16%)
Large for gestational age	3 (12.5%)	4 (12.9%)
Appropriate for gestational age	18 (69.2%)	22 (72%)
Major congenital anomalies	3 (11.1%)	3 (9.6%)
Respiratory distress syndrome	6 (23%)	6 (19.3%)
Hypoglycemia	11 (44%)	2 (6.5%)
Hyperbilirubinemia phototherapy	11 (44%)	8 (25.8%)
Death	1 (4%)	0 (0%)
Perinatal survival rate	89.9%	93.6%

*Data adapted from references 15 and 17.

hypertension is also present. However, with contemporary means of evaluation and treatment, the perinatal survival in this group can exceed 90% if fetuses are delivered at >36 weeks gestation (Table 1).

Management Principles

Ideally, management should begin before conception with adequate counseling and glycemic control. Kidney function should be assessed by means of a 24-hour urine collection every trimester to determine creatinine clearance and the rate of protein excretion. Blood pressure should be monitored closely, and antihypertensive agents are continued if routinely taken prior to conception or introduced if hypertension is initially recognized during pregnancy. The drugs of choice include alpha-methyldopa or hydralazine. Experience with antihypertensive drugs in diabetic patients is limited, however. Angiotensin-converting enzyme inhibitors also have been used but their safety in pregnancy has not been established. Beta-blockers may intensify insulin-induced hypoglycemia and therefore are not recommended.

The presence of kidney failure, defined as creatinine clearance <30 mL/minute or creatinine >5 mg/dL, constitutes a particular management problem for patients with diabetic nephropathy. If such women are seen in a preconception clinic and are considering becoming pregnant, they should be advised to consider kidney transplantation or dialysis prior to pregnancy. There have been reports of successful cases of pregnancy following renal transplantation, even after combined pancreas-kidney transplantation, and in patients on either continuous ambulatory peritoneal dialysis or on hemodialysis.[18-20] However, if kidney failure develops during pregnancy, peritoneal dialysis or hemodialysis may be used. Patients with uncontrolled hypertension should be advised against conception.

Pregnancy does not appear to alter the natural course of diabetic nephropathy in patients with mild and moderate renal insufficiency. In the absence of severe hypertension or renal insufficiency, women with diabetic nephropathy can anticipate an outcome similar to other insulin-dependent diabetics.

DIABETIC NEUROPATHY

Neuropathic complications are commonly seen in individuals with both type I and type II diabetes. At the same time, pregnancy is also quite common in women with diabetes. Yet there is little in the scientific literature regarding pregnancy and diabetic neuropathy. Therefore, little is known about how diabetic neuropathy affects pregnancy outcome or how pregnancy affects neuropathy. Because of the many metabolic and circulatory changes that occur during pregnancy, one could speculate that pregnancy might in fact have some effect on neural function.

Diabetic neuropathy takes many forms and can affect virtually every organ system. Peripheral neuropathies are the most common type. The longest nerves are most often affected; this includes nerves to the feet, hands, and anterior thoracoabdominal region. The typical clinical presentation includes paresthesias. On physical examination, diminished reflexes and loss of vibratory and temperature sensation are seen, leaving the lower extremities susceptible to injury, ulceration, and infection.

Cranial neuropathies involving the third, sixth, and seventh cranial nerves also can be seen. They tend to have an abrupt, usually painless motor presentation. These neuropathies are generally self-limiting with complete patient recovery. The visceral neuropathies are caused by dysfunction of the bladder, bowel, or stomach. Of these, gastroparesis is the most troublesome and difficult to treat. Symptoms of the disorder include anorexia, early satiety, bloating, belching, weight loss, and vomiting of undigested food. Diabetic control is affected because gastroparesis makes the intake of adequate nutrition difficult and causes irregular absorption. Therefore, autonomic neuropathy has serious implications for both mother and fetus.

Autonomic Neuropathy

Although there have been no scientific studies in this area, six cases have been reported recently.[21-24] Two out of the six pregnancies resulted in fetal demise. However, even the four patients who had successful fetal outcomes experienced lengthy and difficult pre- and postnatal courses. All patients required multiple hospital admissions for nausea and vomiting, and one patient developed aspiration pneumonia and suffered an anoxic cardiac arrest.

It is evident from these reports that gastroparesis in pregnant diabetic women makes glycemic control more difficult to achieve and significantly affects the nutritional status of both mother and baby. Although successful fetal outcomes have been achieved in some cases, it has not been without significant maternal morbidity. Therefore, prenatal counseling is strongly recommended for all insulin-dependent diabetic women with autonomic neuropathy. If pregnancy does occur, early parenteral feeding should be included in the management of these women if more conservative therapies are not successful in controlling vomiting.

CORONARY ARTERY DISEASE

White's class H diabetes is defined as the presence of coronary artery disease in pregnant diabetic patients. Diabetes mellitus is associated with an increased risk for the development of coronary artery disease. Coronary artery disease differs in diabetics than in nondiabetics; in diabetics, it occurs more frequently, at a younger age, and with greater severity. Although the overall incidence of myocardial infarction and coronary artery disease in pregnancy is low, the diagnosis has grave prognostic implications. Myocardial infarction during pregnancy was first described in 1921. Since then, less than 100 cases have been reported.[25]

Risk Factors

Diabetes is recognized as a major risk factor for coronary artery disease along with high cholesterol, hypertension, obesity, stress, cigarette smoking, a positive family history of premature coronary artery disease, and oral contraception (especially in women over the age of 35 who smoke). The precise mechanism by which glucose intolerance leads to an increased risk of cardiovascular disease is not well understood.[25] Several mechanisms have been postulated:

- a carbohydrate-induced elevation in VLDL and glucosamine-glycan,
- hyperinsulinemia-induced stimulation of smooth muscle cell proliferation,
- sorbitol-induced cellular damage, and
- diabetes-induced abnormalities in cells, platelets, or lipoprotein metabolism.[25]

Diagnosis

Pregnant patients diagnosed with ischemic myocardial disease are at high risk for maternal mortality (Table 2). Thus, if pregnancy occurs, tight metabolic control and intensive fetal and maternal monitoring are necessary. However, hypoglycemia also can cause myocardial ischemia and must be avoided. Blood glucose levels of >70 mg/dL fasting and close to 120 mg/dL postprandially sould be sought.[26]

If coronary artery disease is diagnosed before pregnancy, patients should be advised against pregnancy. Patients may elect to undergo bypass surgery to improve their overall medical condition. There have been reports of two successful pregnancy outcomes following bypass surgery.[27,28] The absence of congestive heart failure and single vessel involvement are felt to be associated with improved outcome.

Others[26,29] also have reported successful outcomes for class H pregnancies. It is likely that class H represents varying degrees of ischemic cardiac disease. Because of limited experience, it is difficult to predict outcomes for both mother and baby. However, it appears that there is a subset of patients with class H diabetes in whom pregnancy can be successful.[30] Meticulous attention to both glycemic and cardiac statuses by a specialized perinatal team is necessary in these patients.

Diagnosis of coronary artery disease ideally should be made before pregnancy occurs. Radionuclide and radiographic studies are associated with radiation exposure to the fetus and therefore are contraindicated. Similarly, submaximal exercise tests often cannot be performed during pregnancy. Therefore, diagnosis must be made based on signs and symptoms such as angina or myocardial infarction. Patients with angina can be treated with selective beta-blockers.

Most problems occur from the third trimester through the postpartum period. Significant hemodynamic alterations occur during these periods. During normal pregnancy, blood volume and cardiac output increase by as much as 50% (this percentage is even higher with multiple births). This places a significant load on the maternal cardiovascular system. The later in pregnancy a myocardial infarction occurs, the worse the prognosis for both mother and fetus. When myocardial infarction occurs during the third trimester, approximately two thirds of patients die. Fetal death rates are also high due to maternal death.

TABLE 2. REPORTED CASES OF DIABETES-ASSOCIATED CORONARY ARTERY DISEASE*

Study	Case No.	Gravidity/ Parity	Age (yr)	Classification	Coronary Disease	Occurrence	Maternal Outcome	Fetal Outcome
Brock et al[35]	1	4/4	34	B	MI	1st trimester	Survived	Survived
Siegler et al[36]	2	1/1	38	B	MI	1st trimester	Survived	Survived
Delaney & Ptacek[37]	3	—	32	B	MI	3rd trimester	Died	—
White[38]	4	—	35+	B	MI	1st trimester	Died	Aborted
	5	—	35+	B	MI	1st trimester	Died	Aborted
	6	—	35+	B	MI	1st trimester	Died	Aborted
Hubbard[39]	7	1/1	36	R	MI	1st trimester	Died	Aborted
Hare & White[40]	8	—	—	—	MI	Prior to pregnancy	Survived†	Survived
	9	—	—	—	MI	3rd trimester	Died	Survived
	10	—	—	—	MI	4 weeks postpartum	Died	Survived
	11	—	—	—	MI	4 weeks postpartum	Died	Died
Silfen et al[29]	12	1/1	23	D	MI	Prior to pregnancy	Survived	Survived
Reece et al [27]	13	1/1	32	HFR	Severe angina; occlusion of LAD artery	Prior to pregnancy	Survived†	Survived

Abbreviations: LAD = left anterior descending and MI = myocardial infarction.
*Reprinted with permission from Reece EA, Egan JFX, Coustan D, Tamborlane W, Bates SE, O'Neill TM. Coronary artery disease in diabetic pregnancies. *Am J Obstet Gynecol.* 1986;154:150-151. Copyright ©1986, Mosby-Year Book.
†Coronary artery bypass procedure prior to pregnancy.

Intrapartum Management

The optimum delivery route is controversial. There are risks associated with both caesarean and vaginal deliveries. On the one hand, the co-existence of pregnancy and myocardial infarction is stressful, while on the other hand, patients are at an increased risk of dying if they undergo surgery 3 to 6 months after myocardial infarction. This risk applies to caesarean sections for obstetrical indications as well. No absolute recommendation can be made at this point.

In summary, the management principles for class H pregnancies include:

- continued assessments of cardiac function throughout the pregnancy,
- meticulous metabolic control,
- appropriate maternal and fetal surveillance, and
- a timely delivery.

GENERAL DIABETES MANAGEMENT DURING PREGNANCY

Preconception Planning

The incidence of congenital anomalies among children of diabetic women is four to 10 times higher than among their nondiabetic counterparts. Current evidence suggests that normalization of blood glucose in the preconceptual period and the maintenance of normal glycemic control throughout the critical phase of organogenesis results in a reduced incidence of anomalies.[31-34] The advantages of prepregnancy glycemic control include improved cooperation among those involved in the care of these patients, an increased proportion of planned pregnancies, earlier antenatal care, and identification of infertility.

Management Goals and Approach

Achievement and maintenance of euglycemia during pregnancy requires a combined treatment approach that includes diet, exercise, intensive insulin regimens, and multiple daily blood glucose determinations. The management approach at Temple University is outlined in Table 3. Except for class A patients, blood glucose levels are monitored at least five times per day (fasting, 2 hours after lunch, before and after dinner, and at bedtime) throughout the course of pregnancy. A first trimester ultrasound examination is performed to date the pregnancy and to establish growth parameters against which future examinations can be compared. At 18 to 20 weeks, all insulin-dependent diabetic patients receive a fetal echocardiogram to rule out cardiac malformations. This examination is often repeated at 34

TABLE 3. TEMPLE DIABETES-IN-PREGNANCY PROGRAM PROTOCOL FOR MANAGING THE DIABETIC PREGNANT PATIENT*

Class A & A/B
1. Glucose determination weekly
2. Biweekly visits until 34 weeks, then weekly
3. Ultrasound examination every month
4. Nonstress test at 34 weeks, then weekly
5. HbA_1c not necessary
6. No 24 h urine, ophthalmologic evaluation, or fetal ECG necessary
7. Daily fetal movement counts

Class B & C
1. Daily home glucose monitoring
2. Biweekly visits until 34 weeks, then weekly
3. Ultrasound: dating at 20 weeks (profile and echocardiogram), then monthly
4. HbA_1c monthly
5. Nonstress test at 33 weeks, then weekly
6. Ophthalmologic evaluation, follow-up according to findings
7. 24 h urine initially and in each trimester
8. Daily fetal movement counts

Class D

Above plus the following: EKG initially, uric acid, liver function tests, fibrinogen, and fibrin split products in each trimester

Delivery time:

Class A & B: <42 weeks gestation

Class C & D: at term gestation or pulmonic maturity (weekly amniocentesis starting at 38.5 weeks)

Labor:
1. Blood glucose to be maintained at <100 mg/dL
2. Intravenous: D^5 ½ normal saline solution and 10 units of regular insulin cc/h ◊ 1 unit insulin/h
3. D^5 ½ normal saline solution piggy-backed to the insulin-carrying solution to adjust glycemia
4. Hourly finger-stick blood glucose determinations

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weeks gestation to exclude myocardial septal hypertrophy.

Patients are seen for clinical evaluation every 2 weeks until 32 weeks gestation, after which point they are seen weekly. Nonstress tests and biophysical profiles are done weekly after the 32nd week (Table 4). Fetal lung maturity studies are undertaken if elective delivery is planned, due to maternal or fetal indications such as preeclampsia, placenta previa, or poor glycemic control. Otherwise, patients are allowed to go into labor spontaneously.

TABLE 4. TARGET PLASMA GLUCOSE LEVELS IN PREGNANCY

	Glucose Level
Fasting	60 to 90 mg/dL
1 h postprandial	<140 mg/dL
2 h postprandial	<120 mg/dL
Nocturnal	60 to 120 mg/dL

Diet. Pregnancy demands an additional intake of 300 to 400 Kcal/day above basal requirements. No additional calories are required for diabetic pregnant patients. The diet is 50% to 60% carbohydrates, 12% to 20% protein, and <10% saturated fats with the remainder of fat coming from monounsaturated and polyunsaturated sources. Sodium restriction is not recommended. Similarly, no weight-loss diets should be prescribed. Three meals a day with one or two snacks are usually sufficient for type I diabetic patients. Snacks may be omitted for type II diabetic patients, except at bedtime. We recommend a bedtime snack that includes complex carbohydrate and protein to prevent hypoglycemia and starvation ketosis during the night. A weight gain of 22 to 30 pounds is considered acceptable, with 2 to 4 pounds occurring in the first trimester and 0.5 to 1 pound/week thereafter.

Exercise. A combination of insulin therapy and exercise has been shown to produce a greater reduction in blood glucose levels than the administration of insulin alone in nonpregnant individuals. However, the data are too limited to assess the risk/benefit ratio of either occasional or regular exercise in the pregnant women with type I, type II, or gestational diabetes. We follow the general exercise guidelines recommended by the American College of Obstetricians and Gynecologists. Exercise should not be prescribed for patients with antecedent hypertension, pregnancy-induced hypertension, macro- or microvascular disease, autonomic dysfunction, or hypoglycemia unawareness. Finally, physician supervision is necessary in the prescription of exercise to diabetic pregnant women.

Insulin Therapy. The goal of insulin therapy is to simulate normal plasma glucose levels as closely as possible, as outlined in Table 4. The type of insulin preparation and the mode of insulin administration constitute the two major technical aspects of insulin treatment. Insulin preparations can be animal or human in source. Human insulin is the insulin of choice in pregnant women because immunoglobulin (IgG) antibodies cross the placenta taking exogenous insulin with them. Also, human insulin offers the possible advantage

TABLE 5. INSULIN ACTION TIME

	Onset	Peak	Duration
Rapid acting	½ to 1 h	2 to 4 h	5 to 8 h
Intermediate acting	2 to 4 h	6 to 10 h	12 to 24 h
Long acting	3 to 4 h	14 to 20 h	24 to 36 h

of improved metabolic control because there is less antibody binding to circulating insulin to cause variations in the levels of free insulin. Human insulin can be of two forms: semisynthetic or recombinant insulin.

Routes of Insulin Administration

Although various routes of insulin administration have been explored including intranasal, intraportal, and pancreatic and islet cell transplantation, the subcutaneous route is used most often in clinical practice. A variety of insulin preparations and dosing patterns can be used to mimic normal insulin profiles (Table 5). The split mixed dose is the most common regimen. It includes a morning and evening dose of both a short- and intermediate-acting insulin. Two thirds of the daily dose are given in the morning, with a 2:1 ratio of intermediate- and short-acting insulin. The remaining third is given before dinner in a 1:1 ratio. An alternative approach is to use three daily injections: the usual morning dose, a second administration of regular insulin at dinner, and a third injection of intermediate insulin at bedtime.

The latter regimen allows for smoother control of fasting blood sugar levels and minimizes the risk of middle-of-the-night hypoglycemia. Occasionally, patients need to be treated with short-acting insulin before each meal and with intermediate- or long-acting insulin at bedtime. We have been able to achieve euglycemia in 85% of patients using only two injections; three daily injections were required by 10% of the patients, and 5% of the patients required four daily injections.[32]

Continuous subcutaneous insulin infusion is also available. Regular insulin can be administered through the use of portable, battery-operated pumps that deliver the insulin in a continuous manner. Newer infusion pumps can be programmed to deliver insulin at up to four different basal rates during a 24-hour period. In addition, preprandial boluses also can be given to control postmeal blood glucose levels. Although insulin pumps most closely mimic the physiologic insulin secretion of the pancreas, clinical studies have failed to show any significant advantages over multiple daily injections in terms of fetal outcome, mean blood glucose, glycosylated hemoglobin, or mean amplitude of glycemic excursions.

Hypoglycemia

Both chemical and clinical hypoglycemic episodes occur during the course of pregnancy and are believed to result, in part, from intensive insulin treatment for achieving and maintaining euglycemia. Recently, we conducted insulin clamp studies in pregnant diabetic patients to induce progressive symptomatic hypoglycemia. These studies demonstrated a blunted counterregulatory hormone response in diabetic patients who experienced multiple hypoglycemic episodes.[33]

It remains unclear whether such results can be attributed to long-standing diabetes, pregnancy, or simply to tight glycemic control. There is little in the literature regarding the adverse effects of hypoglycemia on the fetus. Buchanan et al suggest that hypoglycemic episodes can have teratogenic effects on rat offspring.[34] There are no clinical data to confirm a potential teratogenic effect of hypoglycemia in humans. In the insulin clamp study previously described, fetal surveillance was performed throughout the study and demonstrated no evidence of fetal compromise. Fetal heart rate, fetal behavior, and Doppler studies performed in the umbilical artery and fetal aorta were within normal limits.

Ketosis

The presence of ketone bodies signifies a state of cellular starvation due to hypoglycemia or to a relative lack of insulin with concomitant hyperglycemia. Ketoacidosis has been associated with a 50% to 90% fetal mortality rate. In addition, maternal ketonuria may have an adverse effect on neurological development in the fetus. Therefore, ketosis should be vigorously treated and prevented.

Literature Cited

1. White P. Diabetes mellitus in pregnancy. *Clin Perinatal.* 1974;1:331-347.

2. Reece EA. The history of diabetes mellitus. In: Reece EA, Coustan DR, eds. *Diabetes Mellitus in Pregnancy.* New York, NY: Churchill Livingstone Inc; 1988:3-15.

3. Karlson K, Kjellmer I. The outcome of diabetic pregnancies in relation to the mother's blood sugar level. *Am J Obstet Gynecol.* 1972;112:213-220.

4. Roversi GD, Gargiulo M, Nicolini U, et al. A new approach to the treatment of diabetic women. *Am J Obstet Gynecol.* 1979;135:567-576.

5. Jovanovic L, Druzin M, Peterson CM. Effect of euglycemia on the outcome of pregnancy in insulin-dependent diabetic

women as compared with normal control subjects. *Am J Med.* 1981;71:921-927.

6. Coustan DR, Berkowitz RL, Hobbins JC. Tight metabolic control of overt diabetes in pregnancy. *Am J Med.* 1981;71:921-927.

7. Reece EA, Hobbins JC. Diabetic embryopathy: pathogenesis, prenatal diagnosis and prevention. *Obstet Gynecol Surv.* 1986;41:325-335.

8. Fuhrman K, Reiher H, Semmler K, Fischer F, Fischer M, et al. Prevention of congenital malformations in infants of insulin dependent diabetic mothers. *Diabetes Care.* 1982;6:219-223.

9. Puklin JE. Diabetic retinopathy. In: Reece EA, Coustan DR, eds. *Diabetes Mellitus in Pregnancy: Principles and Practice.* New York, NY: Churchill Livingstone Inc; 1988:469-488.

10. Klein BEK, Moss SE, Klein R. Effect of pregnancy on progression of diabetic retinopathy. *Diabetes Care.* 1990;13:34-40.

11. Serup L. Influence of pregnancy on diabetic retinopathy. *Acta Endocrinol (Copenh).* 1986;277:122-124.

12. Elman KD, Welch RA, Frank RN, Goyert GL, Sokol RJ. Diabetic retinopathy in pregnancy: a review. *Obstet Gynecol.* 1990;75:119-127.

13. Sinclair SH, Nesler CL, Schwartz SS. Retinopathy in the pregnant diabetic. *Clin Obstet Gynecol.* 1985;28:536-552.

14. Reece EA, Quintero R. Management of pregnant diabetic patients. In: Lebovitz H, ed. *Therapy for Diabetes Mellitus and Related Disorders.* Alexandria, Va: American Diabetes Association; 1991:16-23.

15. Kitzmiller JL, Brown ER, Phillippe M, Stark AR, Acker D, Kaldany A, et al. Diabetic nephropathy and perinatal outcome. *Am J Obstet Gynecol.* 1981;141:741-751.

16. Jovanovic R, Jovanovic L. Obstetric management when normoglycemia is maintained in diabetic pregnant women with vascular compromise. *Am J Obstet Gynecol.* 1984;149:617-623.

17. Reece EA, Coustan DR, Hayslett JP, Holford T, Coulehan J, O'Connor TZ, et al. Diabetic nephropathy: pregnancy performance and fetomaternal outcome. *Am J Obstet Gynecol.* 1988;159:56-66.

18. Tyden G, Brattstrom C, Bjorkman U, Landgraf R, Baltzer J, Hillebrand G, et al. Pregnancy after combined pancreas-kidney transplantation. *Diabetes.* 1989;38(suppl 1):43-45.

19. Rudolph JE, Schwetzer RT, Bartus SA. Pregnancy in renal transplant patients: a review. *Transplantation.* 1979;27:26-29.

20. Ackrill P, Goodwin FJ, Marsh RP, Stratton D, Wagman H. Successful pregnancy in patients on regular dialysis. *Br Med J.* 1975;2:172-174.

21. Macleod A, Smith SA, Sonksen PH, Lowy C. The problem of autonomic neuropathy in diabetic pregnancy. *Diabet Med.* 1990;7:80-82.

22. Hare JW. Diabetic neuropathy and coronary heart disease. In: Reece EA, Coustan DR, eds. *Diabetes Mellitus in Pregnancy: Principles and Practice.* New York, NY: Churchill Livingstone Inc; 1988:517-518.

23. Steel JM. Autonomic neuropathy in pregnancy. *Diabetes Care.* 1989;12:170-171.

24. Scott AR, Tattersall RB, McPherson M. Improvement of postural hypotension and severe diabetic autonomic neuropathy during pregnancy. *Diabetes Care.* 1988;11:369-370.

25. Reece EA, Assimakopoulos E. Coronary artery disease in pregnancy. In: Gleicher N, ed. *Principles of Medical Therapy in Pregnancy.* Norwalk, Conn: Appleton & Lange; 1991:817-822.

26. Gast MJ, Rigg LA. Class H diabetes and pregnancy. *Obstet Gynecol.* 1985;66:55-75.

27. Reece EA, Egan JFX, Coustan D, Tamborlane W, Bates SE, O'Neill TM. Coronary artery disease in diabetic pregnancies. *Am J Obstet Gynecol.* 1986;154:150-151.

28. Chestnut DH, Zlatnik FJ, Pitkin RM, Varner MW. Pregnancy in a patient with a history of myocardial infarction and coronary artery bypass grafting. *Am J Obstet Gynecol.* 1986;155:372-373.

29. Silfen SL, Wapner RJ, Gabbe SG. Maternal outcome in class H diabetes mellitus. *Obstet Gynecol.* 1980;55:749-751.

30. Goldman JA, Dicker D, Feldberg D, et al. Pregnancy outcome in patients with insulin dependent diabetes mellitus with pre-conceptional diabetic control: a comparative study. *Am J Obstet Gynecol.* 1986;155:293-297.

31. Mills JL, Knopp RH, Simpson JL, Jovanovic-Peterson L, Metzer BE, Holmes LB, et al. Lack of relation of increased malformation rates in infants of diabetic mothers to glycemic control during organogenesis. *N Engl J Med.* 1988;318:671-676.

32. Coustan DR, Reece EA, Sherwin RS, Rudolf MCJ, Bates SE, Sockin SM. A randomized clinical trial of the insulin pump vs intensive conventional therapy in diabetic pregnancies. *JAMA.* 1986;255:631-636.

33. Diamond MP, Reece EA, Caprio S, Jones T, Amiel S, et al. Impairment of counter-regulatory hormone secretion in response to hypoglycemia in pregnant women with insulin dependent diabetes mellitus. *Am J Obstet Gynecol.* 1993;166:70-84.

34. Buchanan TA, Freinkel N, Schemmer JK. Maternal insulin-hypoglycemia impairs embryo development in the rat: implications for diabetic control in early pregnancy. *Diabetes.* 1986;35(suppl 1):47A.

35. Brock HJ, Russel NG, Randall CL. Myocardial infarction in pregnancy: report of a case with normal spontaneous vaginal delivery seven months later. *JAMA.* 1953;152:1030-1031.

36. Siegler AM, Hoffman J, Bloom O. Myocardial infarction complicating pregnancy. *Obstet Gynecol.* 1956;7:306-311.

37. Delaney JJ, Ptacek J. Three decades of experience with diabetic pregnancies. *Am J Obstet Gynecol.* 1970;106:550-556.

38. White P. Life cycle of diabetes in youth. 50th anniversary of the discovery of insulin (1921-1971). *J Am Med Wom Assoc.* 1972;27:293-303.

39. Hibbard LT. Maternal mortality due to cardiac disease. *Clin Obstet Gynecol.* 1975;18:27-36.

40. Hare JW, White P. Pregnancy in diabetes complicated by vascular disease. *Diabetes.* 1977;26:953-955.