

Diabetes in Pregnancy*

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CONTINUING MEDICAL EDUCATION

Goal

To provide guidelines based on the latest data for the management of pregnancy complicated by preexisting diabetes mellitus (DM) and gestational diabetes mellitus (GDM) in women.

Objectives

1. To describe optimal preconception care for women with DM in terms of glycemic control and risks including nephropathy, cardiopathy, retinopathy, and neuropathy in women.
2. To discuss prenatal care with regard to insulin management, maternal/fetal risks, and appropriate monitoring in women.
3. To address intrapartum and postpartum management with attention to the special concerns of DM/GDM, including cesarean delivery and insulin therapy during and after the birth in women.

Accreditation

This activity has been planned and implemented in accordance with the Essential Areas and Policies of the Accreditation Council for Continuing Medical Education (ACCME) through the joint sponsorship of Albert Einstein College of Medicine and Quadrant HealthCom Inc. Albert Einstein College of Medicine is accredited by the ACCME to provide continuing medical education for physicians.

This activity has been peer reviewed and approved by Brian Cohen, MD, professor of clinical OB/GYN, Albert Einstein College of Medicine. Review date: March 2005. It is designed for OB/GYNs.

Albert Einstein College of Medicine designates this educational activity for a maximum of 1 category 1 credit toward the AMA Physician's Recognition Award. Each physician should claim only that credit that he/she spent in the educational activity.

Participants who answer 70% or more of the questions correctly will obtain credit. To earn credit, see the instructions on page 71 and mail your answers according to the instructions on page 72.

Disclosure

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With the growing prevalence of type 2 and gestational diabetes, all physicians who treat pregnant women will be managing more patients in the diabetic setting. With appropriate measures starting before conception, these mothers can be helped to achieve the best possible maternal and fetal outcome.

Diabetes mellitus (DM) affects between 17 and 23 million people living in the United States. Many of these individuals are undiagnosed. The number of cases of type 1 DM is relatively constant, and the increase in prevalence of DM in the United States is attributed to a rise in type 2 DM cases. In reproductive-aged women, obesity, inappropriate diet, and sedentary lifestyle are risk factors for developing type 2 DM. Black, Hispanic, Asian, and Pacific Islander women are more prone to type 2 DM, and have rates of gestational diabetes mellitus (GDM) of up to 14%; GDM rates of up to 30% have been documented among American Pima Indians.¹ Diabetes mellitus complicates 2.5% to 7% of all pregnancies, with GDM representing most of the cases of DM in pregnancy.² A recent rise in the incidence of type 2 DM among obese children will increase the prevalence of DM in pregnancy even further. In the near future, it is possible that type 2 DM will become

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TABLE 1. Classification of Diabetes Mellitus

Type 1

- Autoimmune pancreatic β -islet cell destruction
- Human leukocyte antigen-associated (possible viral trigger)
- Often childhood-onset
- Insufficient insulin production (insulinopenia)
- At risk for diabetic ketoacidosis
- Complications include nephropathy, retinopathy, vasculopathy, and neuropathy

Type 2

- Insulin deficiency or tissue resistance
- Strong genetic component
- Associated with obesity and sedentary lifestyle
- Usually adult-onset
- Increasing incidence in children/adolescents
- Rarely associated with diabetic ketoacidosis

the predominant form of DM associated with pregnancy. Thus, obstetricians will be diagnosing DM and managing pregnancies complicated by DM with increasing frequency.

PATHOPHYSIOLOGY

Diabetes mellitus is the result of a derangement of insulin production or action that leads to hyperglycemia and its consequences. The underlying pathogenesis is a deficiency of insulin or resistance to insulin action. The etiologies are numerous and heterogeneous, including autoimmune pancreatic β -cell depletion; tissue resistance; defects in insulin receptors, insulin proteins, or enzymes; pancreatic injury; endocrinopathies; drug toxicity; viral infections; and various genetic syndromes. Diabetes mellitus is classified by the underlying pathogenesis or relationship to pregnancy as type 1, type 2, or gestational (Table 1).

DIAGNOSIS

The criteria used for the diagnosis of DM outside of pregnancy have evolved, and lower thresholds of hyperglycemia

TABLE 2. American Diabetes Association Criteria for Diagnosis of Diabetes Mellitus³

Symptoms of DM (polyuria, polydipsia, weight loss) and a random plasma glucose \geq 200 mg/dL

OR

Fasting plasma glucose \geq 126 mg/dL confirmed on repeat test on a different day

OR

2-h glucose \geq 200 mg/dL with a 75-g OGTT confirmed on repeat test on a different day (not recommended for routine clinical care)

DM = diabetes mellitus; OGTT = oral glucose tolerance test.

were recently introduced. The American Diabetes Association (ADA) currently recommends three diagnostic strategies (Table 2).³ Two categories of prediabetes are now recognized as well: impaired glucose tolerance (IGT) and impaired fasting glucose (IFG) (Table 3). Individuals with IFG and IGT are at high risk for developing overt DM.³

When the diagnosis of DM is made during pregnancy, it is referred to as GDM. Using the ADA criteria, individuals with new-onset type 1 DM or previously undiagnosed type 2 DM are occasionally diagnosed with GDM, and postpartum testing is required to confirm the persistence of a metabolic disorder in these individuals. It is recommended that all pregnancies be screened for GDM by some method. The ADA advises that laboratory screening for GDM be omitted only in women whose history meets all of the low-risk criteria (Table 4). Screening involves a two-step approach, with a glucose challenge test (GCT) followed by a diagnostic OGTT when indicated (see "Testing Protocol").^{2,4} (Screen-

TABLE 3. American Diabetes Association Diagnostic Criteria for Prediabetes³

Intermediate Group	Test	Results (plasma glucose)
IFG	Fasting glucose	100-125 mg/dL
IGT	75-g 2-h OGTT	140-199 mg/dL

IFG = impaired fasting glucose; IGT = impaired glucose tolerance; OGTT = oral glucose tolerance test.

TABLE 4. Criteria for Low Risk of Gestational Diabetes Mellitus^{2,5}

- Age < 25 y
- Normal body weight
- No first-degree relative with DM
- Not a member of an ethnic group with a high prevalence of type 2 DM
- No history of abnormal glucose metabolism
- No history of poor obstetric outcome associated with DM

DM = diabetes mellitus.

ing thresholds are outlined in Tables 5 and 6).^{2,4} The ADA recommends the use of the Carpenter/Coustan modified criteria for the OGTT, whereas the American College of Obstetricians and Gynecologists (ACOG) states that either the Carpenter/Coustan or the National Diabetes Data Group (NDDG) criteria are appropriate for the diagnosis of GDM.^{2,5-7}

PRECONCEPTION CARE

To optimize maternal, obstetric, and neonatal outcomes, the management of pregnancies complicated by preexisting DM should begin prior to conception. Pregnancy should be planned only when glycemic control is excellent. Poor glycemic control during embryogenesis has been linked to congenital malformations and spontaneous abortion (SAB). Major congenital malformations of the cardiovascular, central nervous, skeletal, and genitourinary systems are the leading cause of neonatal morbidity and mortality, occurring in 7% to 18% of pregnancies in diabetic women.⁸⁻¹⁰ The degree of risk for congenital malformation and SAB is related to the degree of elevation in hemoglobin A1C above normal at the time of conception and during embryogenesis (Table 7).¹¹ Preconception glycemic control has been shown to reduce the risk of both SAB and congenital malformations. Genetic counseling and patient education regarding risk reduction with excellent glycemic control can be beneficial. Use of a reliable form of contraception should be encouraged in diabetic women who do not intend to conceive or who have suboptimal glucose control.

Risk Assessment

Testing Protocol for Gestational Diabetes Mellitus

Glucose Challenge Test

- Administer 50 g oral glucose solution at 24-28 wk*
- Nonfasting, randomly timed
- Patient to avoid oral intake during test
- Assess venous plasma glucose level at 1 h
- Venous plasma glucose levels > 200 mg/dL do not require OGTT, as gestational DM is probable

Oral Glucose Tolerance Test†

- Recommend 3 days of unrestricted diet, including at least 150 g of carbohydrates daily
- Advise usual physical activity
- Testing should be performed after an overnight fast (8–14 h)
- Administer 100 g oral glucose solution
- Patient should remain seated and abstain from smoking

*Earlier testing may be indicated in patients with history of GDM, obesity, prior obstetric complications, or a strong family history of DM.

†Two values meeting criteria are required for the diagnosis of gestational diabetes mellitus.

OGTT = oral glucose tolerance test; DM = diabetes mellitus; GDM = gestational diabetes mellitus.

In patients with preexisting DM, the preconception period is an opportune time to evaluate for evidence of complications, including retinopathy, nephropathy, neuropathy, and cardiovascular disease (CVD). The results of the baseline evaluation can be used to direct counseling.

Retinopathy in individuals with DM is a result of poor glycemic control and genetic factors. Permanent visual impairment can be a complication of proliferative retinopathy. Pregnancy may or may not have long-term detrimental effects on retinopathy. The rapid glycemic control recommended for optimal pregnancy outcome plus normal gestational hormone alterations are often associated with a transient progression of retinopathy.¹² There are no well controlled trials evaluating the long-term effects of pregnancy on diabetic retinopathy. A preconception evaluation for retinopathy with retinal

TABLE 5. Glucose Challenge Test Threshold Values at One Hour^{2,4}

Venous plasma glucose (mg/dL)	Sensitivity (%)	Patients requiring OGTT (%)
> 130	90-100	25
> 135	98	20
> 140	80-90	15

OGTT = oral glucose tolerance test.

dilation should be performed by an ophthalmologist and repeated in early pregnancy. Subsequent retinal examinations can be scheduled during pregnancy and postpartum based on the presence or degree of retinopathy. Ideally, laser therapy should be completed prior to conception, but it can be performed safely during pregnancy if required.

Nephropathy affects 5% to 10% of pregnancies in women with DM.¹³ Poor glycemic control, hypertension, and genetic factors contribute to the development of DM-related renal disease. Maternal and perinatal complications are significantly increased when nephropathy is present. These complications include chronic hypertension, preeclampsia, preterm birth, and intrauterine growth restriction (IUGR). Preconception and early-pregnancy assessments of renal function should be performed in women with known microalbuminuria or long-standing DM. This is accomplished by testing blood urea nitrogen and serum creatinine, plus a 24-hour urine collection measuring excretion of protein and creatinine clearance. Microalbuminuria is early evidence of renal dysfunction and is defined by albumin excretion of 30 to 300 mg in 24 hours. Preexisting or early pregnancy urinary protein excretion exceeding 190 mg in 24 hours confers a 3-fold increased risk of hypertensive disease and a higher risk of IUGR.¹⁴ Overt nephropathy is defined as proteinuria of more than 300 to 500 mg in 24 hours. Preeclampsia complicates 50% of pregnancies with diabetic nephropathy; women with reduced creatinine clearance, proteinuria, and hypertension carry the highest risk of poor perinatal outcome, and should be counseled accordingly. Hypertension should be managed aggressively in this group of women, with target blood pressures of less than 130/80 mm Hg. Angiotensin converting

TABLE 6. Diagnostic Values on Oral Glucose Tolerance Test^{6,7*}

Time	Venous plasma glucose (mg/dL) ⁶	
Fasting	≥ 95	≥ 105
1 h	≥ 180	≥ 190
2 h	≥ 155	≥ 165
3 h	≥ 140	≥ 145

*A single abnormal value is nondiagnostic of GDM, but is associated with an increased risk of obstetric complications similar to GDM. One approach to management is to prescribe nutrition counseling and repeat the OGTT in 1 month.

GDM = gestational diabetes mellitus; OGTT = oral glucose tolerance test.

enzyme (ACE) inhibitors are frequently used for their beneficial effects on renal function, but pregnancy is a contraindication to ACE inhibitor use, so an alternative antihypertensive agent must be used once pregnancy is confirmed. Controversy surrounds the effects of pregnancy on progression of diabetic nephropathy. Proteinuria often increases during pregnancy, but long-term detrimental effects on renal function are rare.¹⁵ However, in women with hypertension, chronic renal failure, and serum creatinine levels of more than 1.5 to 3 mg/dL or creatinine clearance of less than 50 to 75 mL/min, progression of renal disease during pregnancy may lead to an irreversible decline in renal function or end-stage renal disease necessitating dialysis.^{11,12,16}

Coronary artery disease (CAD) is rare in pregnant women but can occur in the setting of long-standing DM, nephropathy, and hypertension. Preconception electrocardiography should be performed in all women with DM, but particularly in those who are older than age 35 years or who have hypertension, nephropathy, vascular disease, obesity, hyperlipi-

TABLE 7. Hemoglobin A1C and Risk of Congenital Malformations¹¹

Hemoglobin A1C (%)	Infants With Congenital Malformations (%)
< 7	None
7.2-9.1	14
9.2-11.1	23
> 11.2	25

demia, or DM of longer than 10 years' duration. Echocardiography can also be considered in women with long-standing DM or hypertension. Suspected CAD should prompt a thorough cardiac evaluation, with cardiac stress testing prior to conception. In women with CAD, pregnancy-related hemodynamic changes and hypoglycemic episodes can lead to acute coronary syndrome (ACS) during gestation. Older reports of DM-related ACS during pregnancy indicated that maternal mortality of up to 73% could be expected.¹⁷ Given the many advances in coronary care, the current risk of maternal mortality due to DM-related ACS is unknown, but appears to be lower than previous estimates. Successful pregnancies have been reported in women with CAD who have preserved myocardial function via percutaneous transluminal coronary angioplasty with or without stent placement or via coronary artery bypass grafting.¹⁴ Pregnancy should be undertaken cautiously in women with a history of treatment for CAD, and should be discouraged in those with untreated CAD or severe myocardial dysfunction.

Neuropathy is yet another potential complication of DM. Autonomic neuropathy may manifest as gastroparesis, presenting clinically as protracted, severe, and refractory nausea and emesis of pregnancy. Electrolyte disturbances, dehydration, malnutrition, aspiration syndromes, and complications of parenteral nutrition have been reported in women with gastroparesis during pregnancy.¹⁷ A history of digestive disorders prior to pregnancy may indicate gastroparesis. Orthostatic hypotension due to autonomic dysfunction may lead to falls, resulting in maternal or fetal injury. Peripheral neuropathy can predispose to maternal infectious complications. Preconception evaluation of orthostatic blood pressure, peripheral sensation, and integument integrity are recommended.

Glycemic Control

A history of diabetic ketoacidosis (DKA) and hypoglycemic episodes should be elicited. Attempts at strict glycemic control, coupled with the effects of fetal utilization of glucose, can predispose to maternal hypoglycemia. Hypoglycemic episodes occur in 73% of diabetic pregnancies, with nearly 50% of these episodes being severe.¹⁸ The patient and her family require education on recognition, testing, and treatment of hypoglycemia to avoid permanent neurologic sequela. Prescription of a glucagon pen is

advised, especially for women with type 1 DM or those who have had prior episodes of severe hypoglycemia. Diabetic ketoacidosis is a life-threatening derangement of glucose metabolism resulting from inadequate insulin action that leads to hepatic gluconeogenesis, lipolysis of adipose tissue, and ketone-body formation. Pregnant women with type 1 DM are prone to DKA, which occurs in up to 3% of their pregnancies and carries an 11% or greater fetal loss rate.¹⁹ By contrast, DKA is rare in women with type 2 DM or GDM. Early recognition of DKA, treatment of the associated hypovolemia, hypoglycemia, hypokalemia, hyponatremia, and hypophosphatemia, and return to normal acid-base status are of great importance to the health of mother and fetus. Maternal and fetal mortality are associated with delay in treatment, but immediate and aggressive therapy generally yields a good outcome.¹⁷

Preconception glycemic control is best accomplished by self-monitoring of blood glucose (SMBG), dietary modifications, exercise, frequent assessment by a care provider, and ongoing patient education. The preconception capillary plasma glucose levels recommended by the ADA are 70 to 110 mg/dL preprandial and 155 mg/dL 2 hours postprandial.² The goal A1C level should be 6.5% to 7% (ie, less than 1% above the upper limit of normal), which confers the lowest risk of fetal congenital malformations. Intensive preconception diabetic care reduces perinatal mortality and congenital anomaly rates in individuals with type 1 DM.²⁰ After conception, maternal glucose control is likewise important for the duration of the pregnancy. Individualization of the frequency and timing of SMBG is acceptable, but postprandial values should be included in the management of the pregnant diabetic patient. Postprandial glucose levels correlate best with maternal A1C levels and neonatal outcome.²¹ Self-monitoring at least 4 to 8 times daily—including measurements at fasting and 1- or 2-hour postprandial—is advised to guide adjustments in the insulin regimen and improve outcome. Recently, the ADA changed its recommendation for antepartum target capillary plasma glucose levels to less than 105 mg/dL fasting, less than 155 mg/dL 1 hour postprandial, and less than 130 mg/dL 2 hours postprandial. These levels are higher than the physiologic levels of glucose in normal pregnant women, which rarely exceed 110 mg/dL. Accordingly, lower glycemic goals with capillary plasma glucose levels of less than 95 mg/dL

fasting, 130 to 140 mg/dL 1 hour postprandial, and less than 120 mg/dL 2 hours postprandial are recommended by many authorities. The same thresholds are used to determine the need for insulin therapy in women with diet-treated GDM to reduce the risk of macrosomia and other perinatal complications. The major risks of strict glucose control are iatrogenic hypoglycemia and IUGR. Maternal mean blood glucose levels of less than 87 mg/dL are associated with IUGR.²²

Nutrition counseling is a key component in the management of women with preexisting DM presenting for preconception care. Likewise, ongoing nutrition therapy is important in all pregnancies complicated by preexisting DM or GDM. Many women with GDM can be managed with medical nutrition therapy alone. Typically, an increase of 300 kcal per fetus per day above prepregnancy weight-based caloric intake is prescribed. The recommended weight gain for pregnant women with DM is the same as for nondiabetic women, and is based on prepregnancy weight (Table 8).²³

PRENATAL CARE

During pregnancy, insulin therapy is the mainstay of managing type 1 DM, type 2 DM, and GDM refractory to nutrition therapy. Insulin requirements are lowest early in pregnancy, and increase thereafter to peak at 28 to 32 weeks' gestation. Traditionally, combinations of short-acting and intermediate-acting insulin are administered intermittently by the subcutaneous route (Table 9; also see "Typical Three-Injection Intermittent Regimen"). Several types of insulin are available, but the most experience during pregnancy has been reported with short-acting human insulin injection

TABLE 8. Weight Gain Recommendations for Pregnancy Complicated by Diabetes Mellitus/Gestational Diabetes Mellitus^{22*}

Underweight (< 19.8)	28-40 lb
Average weight (19.8-25)	25-35 lb
Overweight (26-29)	15-25 lb
Obese (> 29)	15-25 lb

*Total weight gain by body habitus/body mass index.

TABLE 9. Insulin Therapy for Diabetes Mellitus in Pregnancy*

Trimester	Insulin (U/kg/d)
First	0.6-0.8
Second	0.7-1.0
Third	0.8-1.2

*Estimated insulin requirement by trimester.

and intermediate-acting isophane/protamine zinc insulin suspension (Table 10). Increasingly, though, the newer insulins and insulin analogs (eg, short-acting lispro, aspart) are being used during pregnancy and appear to be both effective and safe.^{24,25} There are minimal data on the use and safety of the newest long-acting insulin analogs detemir and glargine. Until more data are available regarding safety and efficacy in pregnancy, the use of these agents should be restricted to pregnant women who have demonstrated a history of inadequate glucose control on standard regimens. Use of long-acting insulins such as extended insulin zinc suspension

Typical Three-Injection Intermittent Regimen*

AM	2/3 total insulin dose	Breakfast/lunch	2/3 of AM dose as intermediate acting isophane/protamine zinc insulin suspension and 1/3 of am dose as regular or short acting insulin injection, combined
PM	1/3 total insulin dose	Dinner	1/2 of PM dose as regular or short acting insulin injection*
		Bedtime	1/2 PM of dose as intermediate acting isophane/protamine zinc insulin suspension

*A two-injection regimen administering mixed intermediate acting isophane/protamine zinc insulin suspension and regular or short acting insulin injection doses prior to dinner can be used in patients with type 2 diabetes mellitus or gestational diabetes mellitus, but higher fasting glucose levels and nocturnal hypoglycemia may occur.

TABLE 10. Human Insulin and Insulin Analog Action Profiles

Type	Onset (h)	Peak (h)	Duration (h)	Pregnancy testing/safety data
Insulin injection (Humulin R, Velosulin-H, Novolin R) (REGULAR)	0.5-1	1-5	5-12	Yes
Short-acting				
Insulin zinc suspension, prompt (SEMILENTE)	1-1.5	5-10	12-16	Yes
Insulin lispro (HUMALOG)	0.25	0.5-1.5	6-8	Yes
Insulin aspart (NOVOLOG)	0.25	1-3	3-5	Yes
Intermediate-acting				
Humulin insulin isophane/protamine zinc suspension (NPH)	1-1.5	6-12	24	Yes
Humulin insulin zinc suspension (LENTE)	1-2.5	6-12	24	Yes
Novolin L	~ 2.5	7-15	22	Yes
Novolin N	~ 1.5	4-12	24	Yes
Long-acting				
Glargine (LANTUS)	1	5	24	No
Protamine zinc insulin	4-8	14-24	36	Yes
Insulin zinc suspension, extended (ULTRALENTE)	4-8	10-30	36+	Yes
Insulin detemir (DETEMIR)	1-2	5	24	No

during pregnancy has been limited by the unpredictable pattern of action. An alternative method of insulin administration, the open-loop continuous subcutaneous insulin infusion (CSII) pump, has been shown to be safe and beneficial in the management of DM during pregnancy. While CSII is more convenient and provides glycemic and perinatal outcomes comparable to intermittent dosing, it is more expensive and reserved for women who are highly motivated and compliant.^{26,27}

Outside of pregnancy, glucose control in women with type 2 DM is often achieved with oral glucose-lowering agents. In general, the sulfonylureas, secretagogues, meglitinides, biguanides, α -glucosidase inhibitors, and thiazolidinediones are not recommended in pregnancy because of the potential for teratogenicity, placental transfer, and neonatal hypoglycemia. A notable exception is the sulfonylurea glyburide, which (unlike its first-generation prede-

cessors) does not cross the placenta and is the only agent with data regarding treatment of pregnancy-related DM. A randomized clinical trial comparing glyburide to insulin therapy in third-trimester patients with GDM who have failed with diet control showed no difference in maternal glucose control or perinatal outcome.²⁸ A small cohort study looking at oral glucose-lowering agents used through the first trimester of pregnancy suggested a higher risk of congenital malformations.²⁹ The biguanide metformin has been used to treat infertility due to polycystic ovary syndrome, and case series have shown a reduced incidence of GDM and SAB in these patients compared with historic controls, with no increased risk of congenital malformations or maternal hypoglycemia.³⁰ On the other hand, metformin use in pregnancy has been associated with an increased risk of preeclampsia and a 10-fold increase in perinatal mortality.³¹ Cord-blood and

maternal measurements have demonstrated significant transplacental passage of metformin at term, and the mechanism of action through peripheral tissue uptake of glucose could theoretically increase the risk of macrosomia.³² Due to limited data in pregnancy, biguanides should not be prescribed routinely. In general, insulin therapy is recommended for the management of type 1, type 2, and GDM

TABLE 11. Protocol for Management of Preexisting Diabetes Mellitus in Pregnancy

Preconception

Contraception until pregnancy desired

Genetic counseling when planning pregnancy

DM education and medical nutrition therapy	Self-blood glucose monitoring 4-8 x/d including fasting, 1-2 h postprandial, and 3:00 AM if at risk for nocturnal hypoglycemia Target capillary plasma glucose levels are 70-110 mg/dL preprandial and < 155 mg/dL 2 h postprandial Educate patient and other reliable support persons regarding management of hypoglycemic episodes
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Optimize glucose control	Consider changing type 2 diabetic patients on oral agents to an insulin regimen Follow hemoglobin A1C every 1-3 mo and adjust regimen to reach target level < 1% above normal 3 mo prior to planned conception
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Baseline assessment for complications of DM	Blood pressure assessment Physical examination Electrocardiography 24-h urine collection for protein and creatinine clearance or spot protein/creatinine ratio Ophthalmology examination Thyroid function testing in type 1 diabetic patients
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Pregnancy

Early management	Early assessment for gestational dating and viability Genetic counseling if not performed in preconception period Nutrition counseling Diabetic education and reinforcement Optimize glucose control on insulin regimen Target capillary plasma glucose levels to 60-95 mg/dL fasting, < 140 mg/dL 1 h postprandial, and < 120 mg/dL 2 h postprandial Assess hemoglobin A1C Baseline assessment for DM complications if not completed in preconception period
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Ongoing management	Repeat ophthalmology examination as indicated by degree of retinopathy Repeat 24-h urine collection for protein and creatinine clearance each trimester if baseline evaluation abnormal Offer maternal serum α -fetoprotein screening at 15-22 wk Detailed fetal anatomic survey at 18-22 wk Fetal echocardiogram at 20-22 wk Serial ultrasonography to assess fetal growth at 28-32 wk and at term Fetal movement counts starting at 28 wk Nonstress testing 2 x/wk and amniotic fluid index weekly starting at 32 wk, biophysical profile as indicated by nonstress testing Deliver at 39-40 wk if testing reassuring and glucose well controlled
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DM = diabetes mellitus.

refractory to diet therapy during pregnancy.

In addition to glycemic control, medical nutrition therapy, and patient education, modifications in prenatal care must also be considered in diabetic pregnancies. Tables 11 and 12 outline the authors' approach to prenatal care in the context of preexisting DM and GDM. The diabetic pregnancy requires surveillance to detect congenital malformations and prevent late intrauterine fetal demise (IUFD). Fetal echocardiography is important to exclude major congenital cardiac malformations in women with high A1C levels in the preconception or early prenatal period.

Fetal well-being assessment is recommended due to an increased risk of IUFD in pregnancies complicated by preexisting DM and poorly controlled GDM.³³ The timing of initiation of biophysical testing may be individualized, but assessment is generally commenced at 32 to 34 weeks in pregnancies complicated by preexisting DM and GDM requiring insulin. Biophysical testing may be started at 36 to 40 weeks in pregnancies complicated by diet-controlled GDM.³⁴ Earlier biophysical testing may be indicated if glycemic control is poor, there are other maternal medical complications, or there is evidence of a fetal growth disorder. No biophysical testing regimen has been proved superior, but once-weekly nonstress test-

ing is insufficient to monitor the diabetic pregnancy.³⁵

Due to the higher incidence of fetal growth disorders in diabetic pregnancies (IUGR and macrosomia) ultrasonography is often performed for fetal growth assessment. Ultrasonographic assessment has been used successfully to determine the need for initiating insulin therapy in pregnancies complicated by diet-treated GDM.³⁶ However, it is difficult to predict macrosomia accurately by either clinical estimates or ultrasonography.³⁷ Furthermore, the ability to predict which fetuses will sustain birth trauma such as shoulder dystocia is limited. Late third-trimester ultrasonography can be associated with low sensitivity and a high false-positive rate in the prediction of fetal weight greater than 4,000 g,^{38,39} leading to a near doubling of the risk of cesarean delivery for macrosomia.⁴⁰ Despite this inaccuracy, many authorities (including ACOG) recommend considering cesarean delivery in diabetic pregnancies with fetuses whose estimated weight exceeds 4,500 g to avoid birth trauma. Others recommend consideration of cesarean delivery if the estimated fetal weight exceeds 4,000 or 4,250 g. A cost-analysis study reveals that 443 to 489 cesarean deliveries costing \$880,000 to \$930,000 are required to prevent one case of permanent brachial plexus injury when the estimated fetal

TABLE 12. Protocol for Management of Gestational Diabetes Mellitus

General	Medical nutrition therapy Diabetic education Self-blood glucose monitoring 4-8 x/d, fasting, and 1- or 2-h postprandial until adequate glucose control achieved; then testing frequency can be reduced if insulin therapy not required Target plasma blood glucose levels are 60-95 mg/dL fasting; < 140 mg/dL 1 h postprandial; and < 120 mg/dL 2 h postprandial insulin therapy should be considered if capillary plasma glucose levels remain > 95-105 mg/dL fasting, > 130-155 mg/dL 1 h postprandial, or >120 mg/dL 2 h postprandial after dietary manipulation
Diet-controlled	Fetal movement counts starting at 28 wk Consider ultrasonography at term Nonstress testing 2 x/wk starting at 40 wk Biophysical profile as indicated by nonstress test results Deliver for usual obstetric indications if glucose well controlled
Insulin-controlled	Fetal movement counts starting at 28 wk Ultrasonography at 32 wk and at term Nonstress testing 2 x/wk and weekly amniotic fluid assessment starting at 32 wk Biophysical profile as indicated by nonstress test results Deliver for usual obstetric indications if glucose well controlled

Intrapartum Insulin Protocol

- Glucose assessment on arrival for labor and delivery, then reassessment every 1-2 h with bedside glucose monitor
- Record amount and type of last insulin dose
- IV infusion initiated with lactated Ringer solution or 0.9% normal saline solution containing 5% dextrose at 100-125 mL/h unless hyperglycemic at presentation
- IV short-acting insulin-injection infusion is started if glucose levels exceed 110-120 mg/dL
- Mix 15 regular insulin injection in 150 mL normal saline solution and start infusion at 1 U/h

IV = intravenous.

weight is 4,000 to 4,500 g in the presence of DM.⁴¹ Each pregnancy must be assessed individually based on obstetric history, best estimate of fetal weight, and maternal pelvimetry.

INTRAPARTUM CARE

Delivery should be timed to optimize neonatal outcome. If maternal glucose control is excellent and fetal biophysical testing is reassuring, expectant management can permit the onset of spontaneous labor. Delivery is advised by 40 to 41 weeks in the pregnancy complicated by preexisting DM and GDM requiring insulin. In pregnancies with diet-controlled GDM and an absence of fetal macrosomia, delivery can be accomplished using the same guidelines as for nondiabetic pregnancies. Induction of labor at 38 to 39 weeks has been reported to decrease neonatal macrosomia and shoulder dystocia without increasing the rate of cesarean delivery in pregnancies with GDM.^{42,43} When delivery is to be performed prior to 39 weeks for reasons other than maternal, fetal, or obstetric indications or the gestational dating is unreliable, amniocentesis should be considered to assess fetal lung maturity. Fetal lung maturation may be delayed in diabetic pregnancies with poor glycemic control, and respiratory distress syndrome may complicate the neonatal course. However, caution should be exercised when interpreting these tests; a phosphatidylglycerol level exceeding 3% is the

best predictor of lung maturity.

The protocol for insulin therapy on presentation for labor and delivery is described in the "Intrapartum Insulin Protocol" box. Strict intrapartum glucose control is important to avoid fetal hypoxemia, neonatal depression and hypoglycemia, and maternal complications such as DKA (Table 13). Selected patients using CSII can self-manage intrapartum glucose control with the assistance of the medical team. Patients with diet-controlled GDM can be managed with less intensive monitoring, provided that excessive calories are not supplied orally or parenterally.

POSTPARTUM CARE

Insulin requirements decrease postpartum. Care of the patient with type 1 or type 2 DM requires reduction of the insulin dosage. Effective regimens are approximately 33% to 50% of the late-pregnancy dosage, or 50% of the prepregnancy dosage. Glycemic control can be relaxed to avoid hypoglycemic episodes, but glucose levels should be maintained below 200 mg/dL. Goals for continued postpartum diabetic care should be consistent with the guidelines for management of DM in nonpregnant patients. Ideally, plasma glucose levels should be maintained at 90 to 130 mg/dL preprandial and less than 180 mg/dL postprandial. Women with type 2 DM may resume oral glucose-lowering agents unless contraindicated in breast-feeding.

Insulin therapy may be discontinued after delivery in women with GDM. In these women, fasting and postprandial glucose levels on the morning of postpartum day 1 or 2 can help to exclude an ongoing metabolic disorder; the criteria for diagnosing overt DM can be applied in this setting. Women who have had GDM should undergo testing for DM, IGT, and IFG with a 75-g 2-hour OGTT 6 weeks' postpartum. Because many of these patients will develop type 2 DM, they should be advised to undergo periodic screening.⁴⁴ Breast-feeding should be encouraged in women with DM, but therapy should take into account that insulin requirements are lower during lactation.¹⁸ Women with DM are at increased risk of cesarean wound complications and require close monitoring.⁴⁵ A reliable method of contraception should be offered to all women with DM. Uncomplicated DM does not pose a contraindication to any specific form of birth control, and the method should be selected based on patient preference, reliability,

TABLE 13. Intrapartum Insulin Management

Capillary Plasma Glucose (mg/dL)	IV Insulin (U/h)
< 60	Briefly discontinue IV insulin and increase IV infusion rate of fluids containing 5% dextrose*
60-80	Decrease current rate by 0.5 U/h and increase IV infusion rate of fluids containing 5% dextrose†
81-120	No change
121-140	Increase current rate by 0.5 U/h
141-160	Increase current rate by 1.0 U/h
161-180	Increase current rate by 1.5 U/h
181-200	Increase current rate by 2.0 U/h
> 200	Bolus 2-5 U, then increase current rate by 2.5 U/h; physician should reassess

*IV insulin infusion may be discontinued in type 2 DM and GDM, but dextrose infusion should be increased in type 1 DM to avoid ketoacidosis.

†When converting from IV to subcutaneous, IV insulin infusion should not be discontinued until intermittent subcutaneous doses of short-acting insulin are effectively resumed in type 1 DM.

Dextrose-containing solutions can be omitted in patients with type 2 DM and GDM unless hypoglycemic at presentation.

IV = intravenous; DM = diabetes mellitus; GDM = gestational diabetes mellitus.

and safety profile with comorbidities such as hypertension and CVD.

Infants of diabetic mothers are at increased risk of morbidity in the newborn period. Preterm birth occurs in 36% of diabetic pregnancies, with 14% occurring prior to 34 weeks. In one case series, these infants had a macrosomia risk of approximately 14%, yielding a 7% risk of birth trauma and a 30% risk of respiratory distress syndrome.⁹ Other possible complications include hypoglycemia, polycythemia, hypocalcemia, and hyperbilirubinemia. These complications are related to in-utero exposure to high glucose levels and resultant fetal hyperinsulinemia, and the risk of neonatal hypoglycemia correlates with the degree of maternal glucose control in the period preceding delivery. Infants of mothers with poor glycemic control should be delivered in a facility equipped to manage the potential complications. Long-term, these children are at increased risk of overweight and obesity, hypertension, IGT, and early development of type 2 DM—again probably attributable to in-utero fetal programming.

CONCLUSION

With intensive preconception and prenatal care, women with uncomplicated preexisting DM and GDM can anticipate a good obstetric outcome. Nonetheless, the offspring of diabetic pregnancies

are at increased risk of complications that extend well beyond the perinatal period. To improve maternal and neonatal outcomes, physicians must make appropriate modifications in every phase of prenatal care provided for women with DM.

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