OBG MANAGEMENT

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Current management of diabetic pregnancy

Unlike conventional therapy, intensive drug therapy plus self-monitoring diminishes adverse obstetric outcomes in all types of diabetes

New agents such as insulin analogs (mainly insulin lispro) and oral antidiabetic drugs (mainly glyburide) have profoundly altered the management of diabetes, producing obstetric outcomes comparable to those among the general population. Furthermore, in all types of diabetes, self-monitoring of blood glucose plus intensified drug therapy may help women achieve glycemic control and enhance perinatal outcomes at a lower cost than conventional management—and patients readily accept this approach.

This article describes the rationale for intensive treatment with these agents and other interventions to prevent both hypoglycemia and hyperglycemia.

Intensive therapy requires:

- **memory-based self-monitoring** of blood glucose, which empowers patients to take charge of glycemic control and provides feedback on the timing and dose of insulin administration,
- **dietary regulation,**
- **strict criteria** for initiation of pharmacologic therapy,
- **multiple injections** of insulin or its equivalent when diet alone is insufficient, and
- **an interdisciplinary management team.**

Two breakthrough studies in nonpregnant patients first showed the effectiveness of intensive therapy: the Diabetes Control and Complications Trial[1] and the United Kingdom Prospective Diabetes Study.[2,3] In the first, intensive therapy reduced the risk of retinopathy and lowered rates of microalbuminuria, albuminuria, and clinical neuropathy. In the second, intensive therapy substantially reduced the risk of microvascular complications.

Neither race nor ethnicity predicts treatment duration or success.[5-7]

Blood glucose goals

Regardless of the treatment, the primary goal is always to achieve glycemic control, because it reduces the incidence of hypoglycemia, hyperglycemia, and ketosis. For type 1 and type 2 diabetes, glycemic control is important to prevent further deterioration of complications such as vasculopathy and nephropathy.

Goals of treatment are achieving the following blood glucose concentrations (in milligrams per deciliter):

- **mean:** 90 to 105
- **fasting:** 60 to 90
- **preprandial:** 80 to 95
- **postprandial:** less than 120

At each visit, the clinician evaluates these values and, when necessary, increases the dose of insulin or the oral agent to meet these goals.[4]

In the process, the clinician needs to anticipate how pregnancy will affect preex-

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isting disease, and how diabetes will affect pregnancy outcomes, in patients with any of the 3 types of diabetes.

2 diet protocols

For all types of diabetes, the foundation is diet—specifically, using nutritional therapy to achieve and maintain a maternal blood glucose profile comparable to that of a nondiabetic woman.

Two approaches are recommended:

- reducing carbohydrate intake to 40% to 50% of total calories or
- limiting carbohydrate consumption to foods with a low glycemic index for approximately 60% of calories.

Only women who achieve targeted levels of glycemic control improve insulin secretion and sensitivity. Those who fail to achieve it may exhibit slightly improved sensitivity, but do not attain the same level of insulin response and sensitivity as nondiabetic women.[4,5]

Calculating calories: Same for all

The daily caloric intake is based on the prepregnancy body mass index (BMI) and uses the same formula for all 3 types of diabetes[10,11]:

- For a BMI less than 20 (underweight), daily caloric intake should be 35 to 38 kcal/kg.
- For a BMI of 20 to 25 (normal weight), the patient should consume 30 kcal/kg.
- For a BMI of 26 and higher (overweight, obese, morbidly obese), caloric intake should be 20 to 25 kcal/kg.

Calories per day are then calculated according to the patient's weight during pregnancy and are adjusted throughout pregnancy as that weight increases.

In addition, the daily allotment of calories is divided into 3 main meals and 3 to 4 snacks, with adjustments for the patient's time constraints, work schedule, and other individual factors.

To encourage compliance, the diet also should reflect the patient's cultural preferences.

How do you know when diet fails?

Women with pregestational diabetes are usually already taking insulin or other pharmacologic agents by the time they conceive. There is no consensus or hard data on how long a woman who develops gestational diabetes mellitus should remain on a diet before starting drug treatment.

In a study evaluating the time required to achieve glycemic control with diet alone during a 4-week period, 70% of patients with fasting plasma below 95 mg/dL achieved established levels of glycemic control within 2 weeks with no substantial improvement thereafter.[8,9] In contrast, in patients with fasting plasma glucose of more than 95 mg/dL, most patients failed to achieve the desired level of glycemic control throughout the 4-week period.

Hypoglycemia after exercise can be a positive marker

I recommend 20 to 30 minutes of exercise 3 to 4 times weekly for gravidas with diabetes, provided they are willing and able to perform it, because it can improve postprandial blood glucose levels and insulin sensitivity.[12]

Blood glucose should be measured after exercise, especially in women with type 1 diabetes.

Hypoglycemic reactions during and after exercise may be positive markers of improved insulin sensitivity. Low blood glucose necessitates adjustment of the insulin dose and carbohydrate intake. Extra monitoring is warranted after evening exercise, as glucose uptake increases for several hours after exercise and can cause nocturnal hypoglycemia.

Intensive therapy: Why, when, how

The healthy body secretes insulin over 24 hours independent of nutrient intake. Basal insulin secretion maintains metabolic homeostasis by preventing excessive

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INTEGRATING EVIDENCE AND EXPERIENCE

Treatment or consequences

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When diabetic women receive adequate preconception care and counseling *and* achieve glycemic control, the rate of congenital anomalies declines to levels seen in the general population.[69-72]

On the other hand, maternal hyperglycemia and resultant fetal hyperinsulinemia are central to the pathophysiology of diabetic complications:

- **type 1 and type 2 diabetes**—congenital malformations
- **all pregnancies compromised by diabetes**—increased rates of deviant fetal growth (macrosomia and intrauterine growth restriction), neonatal metabolic, hematological and respiratory complications, birth trauma, stillbirth, cesarean delivery and intensive care admissions.

I tell patients, "Some improvement is better than none"

I explain to my patients how pregnancy itself imposes risk, and why it is crucial to follow protocols and achieve glycemic control. I explain the maternal and fetal complications associated with various glucose thresholds, and the added risks of maternal age, body composition, disease severity, and so on.

However, I also stress that even some improvement in glucose control is better than no improvement.

hepatic glucose production and the mobilization of free fatty acids from adipose tissue stores. This also helps maintain protein balance. Insulin secretion increases several times in response to the ingestion of food.

In the diabetic patient, the aim of intensive insulin therapy is to mimic normal physiology. Basal insulin is provided by administration of NPH, Lente, or Ultralente at bedtime and sometimes before breakfast as well. Insulin also is given before meals (0 to 15 minutes before for lispro, or 30 to 45 minutes before for regular insulin). This algorithm is the foundation of intensive therapy, which involves multiple injections daily versus 1 or 2 injections for conventional therapy.

Insulin dosage requires frequent adjustment

To determine the insulin dose needed to achieve glycemic control in pregnant gravidas, multiple blood glucose measurements are needed because insulin requirements steadily increase throughout pregnancy in women with pregestational diabetes.[13-16] Jovanovic and Peterson[13] quantified these increases as 0.7, 0.8, 0.9, and 1.0 U/kg per day in the first trimester and at weeks 18, 26, and 36, respectively.

Using memory-based reflectance meters to monitor blood glucose, my colleagues and I observed that insulin requirements during pregnancy in women with pregestational diabetes are triphasic (**TABLE**) and require frequent assessment with individualized adjustment of the insulin dose in each trimester.[16] Women with type 2 diabetes require significantly higher doses of insulin each trimester, compared with women with type 1 diabetes.

In women with gestational diabetes, we observed a biphasic increase in insulin requirements[17]:

- Insulin requirements increased up to the 30th week of gestation, necessitating frequent dose adjustments.
- After 30 weeks, insulin requirements stabilized, requiring minimal or no dose adjustments. Insulin requirements for obese subjects were 0.9 U/kg per day, compared with 0.8 U/kg per day for nonobese women.

The actual insulin dose varied more for obese than for nonobese women.

When to start drugs

Most women with pregestational diabetes are treated with insulin prior to pregnancy. Thus, the main task during pregnancy is maintaining or improving glycemic control. In gestational diabetes, pharmacologic therapy (insulin or glyburide) is initiated only when regulation of the diet fails to achieve the desired level of glycemic control or when the disease is severe enough to mandate therapy.

Authorities disagree on the threshold of severity that necessitates pharmacologic

intervention (glyburide or insulin). Some suggest a threshold of fasting plasma glucose of at least 95 mg/dL,[18-20] which will decrease the rate of macrosomic and large-for-gestational-age infants,[19,21] while others suggest at least 105 mg/dL.[19,22]

All authorities agree that drug therapy should be started when postprandial glucose levels are 120 mg/dL or higher at 2 hours or 140 mg/dL or higher at 1 hour.

Using these standards, 30% to 50% of women with gestational diabetes require pharmacologic therapy when diet alone fails to reduce glucose levels.

Determining insulin requirements

The insulin algorithm for women with gestational diabetes is based on prepregnancy BMI:

- For women with a BMI of 25 and less, the insulin dose is 0.8 U/kg.
- For women with a BMI of more than 25 (overweight and obese), it is 1.0 U/kg.

For example, a woman at 28 weeks' gestation who currently weighs 85 kg and who is classified as overweight or obese on the basis of her prepregnancy BMI, would be given an insulin dose of 85 U (85 kg x 1 U).

Once the total insulin dose is calculated, it is divided so that two thirds is administered in the morning and one third in the afternoon or evening. The morning dose is further divided in a ratio of 2 to 1 (intermediate and rapid-acting) and the evening dose into a ratio of 1-to-1 (rapid-acting and intermediate). The rapid-acting dose is administered with the evening meal, while the intermediate dose is given just before bedtime.

If the patient with gestational diabetes has not achieved the desired level of glycemic control after 3 to 7 days, increase the total dose by 10% to 20% and thereafter adjust it when needed.

Fine points of insulin therapy

The actual total insulin dose in women with gestational diabetes is 40% higher than the calculated dose[16]; this provides a margin of safety and avoids severe hypoglycemic episodes. As a rule of thumb, self-monitoring of blood glucose is necessary before every administration of insulin.

The failure to introduce insulin therapy in a timely fashion may lead to fetal hyperinsulinemia and associated complications. Conversely, premature initiation of insulin in women who could have achieved glycemic control with diet alone leads to unnecessary drug treatment.

When gestational diabetes is diagnosed after 30 to 33 weeks' gestation and there is little time left to gain the desired level of control, pharmacologic intervention is recommended. There is greater flexibility when gestational diabetes is diagnosed early in the third trimester.

Which form of insulin is best?

Human insulin is recommended when insulin is prescribed during pregnancy, and the same type of insulin is used for pregestational and gestational diabetes. The main differences:

TABLE

Insulin requirements during pregnancy for women with pregestational diabetes

TRIMESTER	INSULIN REQUIREMENT (UNITS/KG/DAY)	
	TYPE 1 DIABETES	TYPE 2 DIABETES
1	0.86	0.86
2	0.95	1.18
3	1.19	1.62

Insulin requirements vary with gestational diabetes

- use of the insulin pump in type 1 diabetes and
- the insulin dose, which is based on insulin requirements for each type of diabetes.

The most common form of insulin today is biosynthetic human insulin. Short- or rapid-acting insulin is administered before meals to reduce glucose elevations associated with eating. Longer-acting forms are used to contain hepatic glucose production between meals and during fasting.

Regular insulin and insulin lispro are the 2 most common rapid-acting forms of insulin in use.

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In my opinion, insulin lispro can and should be used in pregnancy because it produces more physiologic insulin patterns

Pros and cons of insulin lispro

Mounting evidence of the benefits of insulin lispro for type 1 and type 2 diabetes in nonpregnant individuals includes:

- fewer episodes of severe hypoglycemia,
- limited postprandial glucose excursions, and
- a possible decrease in glycosylated hemoglobin when the drug is administered by continuous subcutaneous infusion.[23]

Insulin lispro also offers greater convenience in the timing of administration: Analogs can be administered up to 15 minutes after the start of a meal, in contrast to soluble insulin, which must be taken 30 minutes before the meal.

Neither the American Diabetes Association[22] nor the American College of Obstetricians and Gynecologists[19] endorses the use of insulin analogs. The reason: these drugs have not been adequately tested in pregnancy, although insulin lispro is categorized as a class B drug.

Data on insulin lispro are limited and abstracted from studies with relatively small sample sizes (only 244 gravidas reported thus far in the literature). Most case reports describe improved glycemic control, increased patient satisfaction, and fewer hypoglycemic episodes, but lack sufficient data on maternal and neonatal outcomes. Even so, many obstetricians have administered the drug with no adverse outcome.

In my opinion, insulin lispro can and should be used in pregnancy because of its ability to produce more physiologic insulin patterns and because the data against it are anecdotal. In contrast, insulin aspart and glargine should be avoided in pregnancy because data on their effects are limited.[24-40]

Individualizing the insulin regimen

A relatively high dose of insulin (about 50–90 U) is needed to achieve glycemic control in gestational diabetes. In contrast, in type 1 diabetes, a lower dose is necessary (50–60 U). Because of the different glycemic profile of women with type 1 diabetes, individualizing the insulin regimen is accepted practice.

The carbohydrate algorithm. For every 15 g of carbohydrates ingested at mealtime, 1 U of rapid-acting insulin analog (insulin lispro or insulin aspart) is required.

If postprandial glucose is continuously elevated (>120 mg/dL) at 2 hours, an increase in rapid-acting insulin is required. Thus, the carbohydrate algorithm may change to 1 U of insulin for every 12 g of carbohydrates until the appropriate ratio is achieved.

If hypoglycemia or relative hypoglycemia occurs, the amount of carbohydrates should increase for each unit of insulin. For example, the adjusted dose would be 1 U of insulin for every 18 g of carbohydrates.

The range of these algorithms is influenced by prepregnancy BMI, disease severity, type of diabetes, and type of carbohydrate (ie, complex versus simple).[41]

CONTINUED

2 destructive complications

RETINOPATHY

Poor glucose control may contribute to or worsen diabetic retinopathy—the leading cause of blindness in diabetic patients 24 to 64 years of age—by increasing intracellular accumulation of glucose and its metabolic products. This damages the tiny blood vessels inside the retina, beginning with the formation of microaneurysms and progressing to blockage and, potentially, proliferation of fragile, abnormal, new blood vessels. If vessels leak blood, vision can be severely impaired or obliterated.

Patients at risk should achieve glycemic control gradually. Rapid initiation of stringent glycemic control can cause short-term progression of retinopathy, especially in hypertensive patients, although there are no apparent long-term effects.

DIABETIC NEPHROPATHY

This complication increases the risk of preeclampsia, chronic hypertension, and fetal growth restriction, and is the most common cause of end-stage renal disease. Proteinuria often increases during pregnancy in diabetic women, but renal function generally remains stable. Nevertheless, advanced diabetic nephropathy (serum creatinine >1.5 mg/dL or creatinine clearance of ≤90 mL/min) can cause further deterioration.

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Hypoglycemic episodes occurred in 63% of insulin-treated women with gestational diabetes, but in only 28% of women taking glyburide

Recognizing patterns of severity. The second algorithm involves identifying the glucose severity pattern (ie, hyperglycemia, hypoglycemia). For example, the total dose of insulin required (0.8–1.0 U/kg) is divided into a ratio of 60% for intermediate or long-acting insulin (basal dose) and 40% for the premeal dose. If the glucose level falls above the targeted level, a single unit of insulin lispro or insulin aspart is added for every 30 mg/dL, but not exceeding 3 U at one time. If glucose levels remain high, redistribute the calculated insulin dose to obtain an improved actual dose (ie, reconfigure the new calculated dose throughout the day based on patient need).

Also pay attention to the lag effect (time from administration of the drug to the start of action), and to stacking, especially in patients with type 1 disease.[42] Insulin stacking occurs when the residual insulin dose (after NPH or regular insulin peak of action) from a prior injection during a meal or between meals is combined with a later dose. This later dose—when added to the residual insulin—may cause hypoglycemia.

The stacking effect explains why most women with gestational diabetes need no regular or rapid-acting insulin at lunchtime yet are still able to maintain the desired level of glucose control.

Special needs in type 1 disease

Because glucose levels in women with type 1 diabetes typically vary widely on a daily or even hourly basis, the insulin dose should be flexible. For example, the patient may need 1 U of rapid-acting insulin for every 25 mg/dL of blood glucose above 125 mg/dL, or 1 U for every 20 mg/dL above 120 mg/dL, and so on. I encourage patients to titrate based on half-unit increments, which can be measured in an insulin syringe.

Insulin pumps. Insulin lispro and insulin aspart are approved for administration as a continuous subcutaneous infusion. However, use of the pump in pregnancy has been limited—as has its research.

Improved metabolic control is a potential advantage of the pump. When the patient is motivated and alert, use of the pump can reduce nocturnal hypoglycemia and morning hyperglycemia caused by the "dawn phenomenon" (an abrupt rise in glucose level in the early morning).

Disadvantages of the pump include cost, diabetic ketoacidosis, and hypoglycemia (caused by malfunction or infection at the infusion site). Maternal and fetal outcomes are comparable whether the insulin pump or intensive therapy is used. However, improvements in lifestyle and metabolic control may justify use of the pump in women who have trouble achieving glycemic control.[43]

The many advantages of glyburide

Oral agents can be a pragmatic alternative to insulin in pregnancy because they are easy to administer and noninvasive. Many experts and authoritative bodies in the US recommend glyburide (sulfonylurea) as an

alternative pharmacologic therapy during pregnancy.[20,44-48] Others recommend further evaluation.[19,22,49,50]

Although some oral agents cross the placenta, they do not necessarily cause a toxic or teratogenic effect on the fetus. Glyburide, a class B drug, does not cross the placenta.[51-53] It increases insulin secretion and diminishes insulin resistance by lowering glucose toxicity. Its onset of action is about 4 hours, and the duration of action is about 10 hours. Thus, after achieving the targeted therapeutic level, glyburide covers the basal requirement as well as postprandial glucose excursions.

The starting dose is 2.5 mg orally in the morning. If the targeted level of glycemia is not attained, add 2.5 mg to the morning dose. If indicated (after 3 to 7 days), add 5 mg in the evening. Thereafter, increase the dose in 5-mg increments, up to a total of 20 mg per day. If the patient does not achieve acceptable glycemic control, add long-acting insulin.

Evidence on oral agents. Several retrospective and randomized studies evaluated oral agents in pregnancy. Most demonstrated that these agents are comparable to insulin in glycemic control and pregnancy outcome.[54-61]

In a randomized study, my colleagues and I found comparable pregnancy outcomes for glyburide and insulin.[56] Recently we reconfirmed our original observation[62] that hypoglycemic episodes are more common in insulin-treated patients than in those taking glyburide. In this study, we used continuous glucose monitoring and found hypoglycemic episodes in 63% of the insulin-treated women with gestational diabetes, but only in 28% of those taking glyburide.

We further analyzed the association between glyburide dose, gestational diabetes severity, and selected maternal and neonatal factors.[63] Not surprisingly, we found that the glyburide dose increased with the severity of gestational diabetes. The success rate (ie, achievement of glycemic control) decreased as disease severity increased. However, there was no difference between glyburide- and insulin-treated patients at each level of severity. Thus, achieving glycemic control—not any particular mode of pharmacologic therapy—is the key to improving pregnancy outcome in gestational diabetes.

When costs of insulin therapy and glyburide treatment are compared, the latter is considerably less expensive.[64]

Ensuring fetal health and a safe delivery

Three principles form the basis of obstetric care for women with diabetes:

- fetal testing to prevent stillbirth and compromised fetal states at delivery,
- lung-maturity testing to prevent hyaline membrane disease, and
- determining the best time and method of delivery to prevent fetal compromise, macrosomia, and shoulder dystocia.

Fetal testing

At our institution, we begin fetal testing at 32 weeks' gestation in all women regardless of diabetes type—even earlier in women with vascular/hypertensive disorders. This includes assessing fetal movements 3 times daily and nonstress testing weekly. This approach has led to a stillbirth rate of 2.5 per 1,000, compared with 4 per 1,000 in the general population.[4]

Is amniocentesis warranted to determine lung maturity?

A major goal of fetal surveillance in gestational diabetes is preventing lung disease. Inadequately controlled gestational diabetes can increase the risk of respiratory distress syndrome or delay lung maturity. Thus, assessing fetal pulmonary status by confirming gestational age or fetal size can be misleading.[65,66]

The delay in lung maturity among infants of diabetic mothers is 1 to 2 weeks.[67] This delay was associated with poorly controlled diabetes in several studies.

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Compromised lung maturity in a live infant is preferable to healthy lungs in a deceased infant

Thus, this subgroup of patients stands to benefit most from amniocentesis.

At our institution, the common practice is to test for lung maturity before any elective delivery at less than 38 weeks' gestation. However, when the clinician determines that delivery would be beneficial, as in cases of poorly controlled diabetes, noncompliance, or other obstetric indications, we deliver the infant regardless of lung maturity. These fetuses experience minimal lung morbidity after 37 weeks' gestation.

The bottom line: Compromised lung maturity in a live infant is preferable to a deceased infant with healthy lungs.

Timing of delivery

Most experts agree that women with diabetes should be delivered at term—though the definition of "term" ranges from 38 to 42 weeks' gestation.

At our institution, in addition to the established routine obstetric indications for delivery, 4 additional indications mandate elective delivery for women with diabetes:

- Fetal macrosomia (weight >4,000 g). For large-for-gestational-age fetuses (>90th percentile), induction of labor may be appropriate when fetal weight ranges from 3,800 to 4,000 g and the gestational age is at least 38 weeks.

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Delivering these fetuses reduces the risk for shoulder dystocia, an ominous complication of diabetes in pregnancy.

- History of previous stillbirth—often the result of poorly controlled diabetes—also warrants induction of labor.
- Poor compliance or glycemic control. This includes the failure to test blood glucose enough to determine glycemic control; inability or unwillingness to adhere to the diabetic protocol, such as fetal testing; and missed appointments.
- Presence of vasculopathy-related hypertension.

Using this approach, we had a labor induction rate of approximately 20% and an overall cesarean section rate of about 15% to 20%—not significantly higher than rates among the nondiabetic population.[4]

The road ahead

More pharmacologic alternatives are on the horizon and may include metformin and other oral antidiabetic drugs, insulin glargine and oral insulin, and a technologically improved insulin pump that can interact directly with blood glucose levels. ■

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