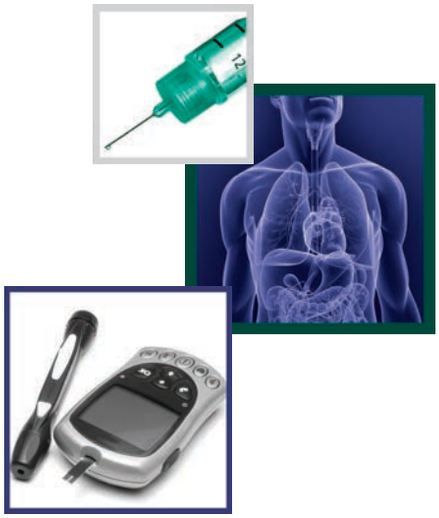
Managing gestational diabetes: timing, selection and use of pharmacotherapy



Stephen F Thung[1] & Mark B Landon*[1]

Practice Points

- Pregnancy is a state of increasing insulin resistance that predisposes women to hyperglycemia.
- Maternal hyperglycemia results in fetal hyperinsulinemia and may predispose to excessive fetal growth.
- Identifying and properly managing gestational diabetes is important as it reduces risks of adverse pregnancy outcomes such as cesarean section, pre-eclampsia and shoulder dystocia.
- Frequent glucose monitoring is critical to guiding therapy and occurs at least four times a day on a daily basis.
- Our own experience is to initiate therapy when at least 20% of recorded glucose values are above the target.
- A combination of rapid-acting and intermediate- or long-acting insulins is typically required to achieve euglycemia in women with frequent hyperglycemia.
- Glyburide stimulates the maternal pancreas to increase insulin production and is effective at achieving euglycemia.
- Metformin increases insulin sensitivity and typically does not cause significant hypoglycemia.
- Recent studies demonstrate that metformin is a viable alternative to insulin for gestational diabetes mellitus management; however, there is a high failure rate requiring insulin supplementation.

SUMMARY Recent data demonstrate that identifying and managing gestational diabetes is an important part of prenatal care to maximize perinatal outcomes. The variety of therapies available to maintain euglycemia continues to expand and it is important for obstetrical care providers to keep abreast of new therapeutic opportunities. Although injectable insulin has been available for decades, advances in insulin design have truly revolutionized how it is administered and, ultimately, improved glucose management. Beyond insulin, oral hypoglycemic agents such as glyburide and metformin continue to gain popularity due to patients' requests and ease of use. In this review, we present the available data to help providers understand what therapies are available, their unique strengths and weaknesses, and how to initiate and escalate doses to achieve maternal euglycemia.

[1]Department of Obstetrics & Gynecology, 395 West 12th Avenue, Suite 572, OH, USA
*Author for correspondence: mark.landon@osumc.edu

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More than ever before, providers must be familiar with the options for gestational diabetes mellitus (GDM) management. After decades of uncertainty, evidence confirming that treatment of GDM reduces adverse perinatal outcomes highlights the need to understand the strengths and weaknesses of the therapeutic options available for maintaining euglycemia [1,2]. The incidence of GDM continues to rise in the shadow of the obesity epidemic without any signs of easing [3,4]. Alternative screening and diagnostic proposals could double or triple the prevalence overnight, assuring that few medical providers would be exempt from managing large numbers of these women [3,5].

Physiology in brief

To understand how to manage GDM, it is useful to become familiar with the physiological changes in glucose metabolism that occur during pregnancy. Pregnancy is a state of accelerated starvation due to the increased metabolic needs of both the fetus and mother [6]. Most importantly, normal pregnancy is characterized by changes in the peripheral tissue response towards insulin [7]. Although pregnancy begins with a state of increased insulin sensitivity during the first trimester, the remainder of the pregnancy is stereotypically characterized by a prodiabetogenic state with reduced insulin sensitivity and compensatory hyperinsulinemia. These changes are most evident as the pregnancy advances beyond the first trimester [7,8]. In women with diabetes, there is a relative (GDM or diabetes mellitus [DM] Type 2) or absolute insulin deficiency (DM Type 1) and regardless of the etiology, the available insulin is insufficient to maintain euglycemia. The net result is new-onset hyperglycemia in the previously euglycemic mother (GDM) or more profound hyperglycemia requiring increased exogenous insulin (DM Type 1 and 2). Glucose, via facilitated diffusion, crosses the placenta to the fetus. The validated Pedersen hypothesis links maternal hyperglycemia with subsequent fetal hyperglycemia, which in turn stimulates fetal pancreatic B cells to secrete insulin and IGFs. It is this fetal hyperinsulinemia that predisposes the fetus to an anabolic state and leads to potential excessive fetal growth [9].

Rationale for therapy

It has long been known that GDM is associated with a variety of adverse outcomes such as fetal macrosomia, shoulder dystocia, birth trauma, need for cesarean section and pre-eclampsia [3]. Only in the last decade have we begun to accumulate high-quality evidence that identifying GDM and optimizing maternal glycemia with diet and pharmacotherapy improves maternal and fetal outcomes [1,2]. Although the US Prevention Service Task Force have determined that there are insufficient data to support screening and therapy, an update has been drafted recommending screening after 24 weeks [10,101]. Systematic reviews and meta-analyses have demonstrated that screening and treatment of GDM does reduce the risk of outcomes such as large for gestational age neonates, shoulder dystocia (and presumed birth injury) and pre-eclampsia [11–13].

Management

Current management of diabetes revolves around establishing optimal glycemic control. Glucose monitoring, lifestyle changes, attention and adherence to a judicious diet, and pharmacotherapy when diet fails to correct hyperglycemia are all important components of the care plan. Increasing insulin resistance with advancing gestational age often results in the need for pharmacotherapy in GDM women so as to reduce the frequency of hyperglycemia.

Glucose monitoring

Self-monitoring of blood glucose should be conducted before breakfast and 1 or 2 h after breakfast, lunch and dinner. The use of post- rather than pre-prandial levels to guide therapy has been associated with improved outcomes, including lower risk for macrosomia, neonatal hypoglycemia and lower cesarean delivery for labor dystocia [14]. Premeal glucose measurements may be added in more challenging cases. The optimal level of glycemic control has not been established. Continuous glucose monitoring has not been demonstrated to improve outcomes at this point in time and larger randomized trials are underway to determine the utility of glucose monitoring in GDM management [15,16]. The American College of Obstetricians and Gynecologists as well as the American Diabetes Association have made the following recommendations for target glucose levels. American College of Obstetricians and Gynecologists glucose recommendations [17]:

- Fasting <95 mg/dl;
- Premeal (if used) <100 mg/dl;

- 1 h postprandial <130–140 mg/dl;
- 2 h postprandial <120 mg/dl;
- Glycosylated HbA1c <6%.

American Diabetes Association recommendations [18]:

- Preprandial <95 mg/dl;
- 1 h postprandial <140 mg/dl;
- 2 h postprandial <120 mg/dl.

Diet & exercise

The objective of dietary therapy is, primarily, to control postprandial glucose levels and assure adequate maternal–fetal nutrition. An average weight woman will require 30–35 kcal/kg/day. Women who are underweight may require 30–40 kcal/kg/day, while those who are overweight (>120% ideal body weight) may require fewer calories. A diet high in carbohydrates (50–60%) has been thought to increase the risk for excessive weight gain and postprandial hyperglycemia, and this has supported the rationale that perhaps a lower proportion of carbohydrates would be more appropriate [19]. Data have demonstrated that a low glycemic index diet could be preferable to an unrestricted diet to minimize insulin use [20]. Given the potential concern for developing maternal ketones with differing diets, it is reassuring that a systematic review has not demonstrated any detrimental effects from a variety of differing diets, including low glycemic and lower carbohydrate (<45%) diets. Conversely, clear obstetrical benefits have not been demonstrated with any particular diet [21]. That being said, many centers commonly suggest three predictable meals per day with two interval snacks to minimize postprandial glucose excursions. We also recommend women to consume complex rather than simple carbohydrates for the same reason [3]. Daily physical exercise reduces insulin resistance. Although a randomized trial of 19 women demonstrated improved fasting and postprandial values in women who exercised 20 min a day, three times per week, most studies have shown mixed results concerning the benefit of exercise in GDM [22]. Currently, there are insufficient data to demonstrate significant advantages to glycemic control; although we believe that it is prudent to maintain regular exercise as part of a healthy lifestyle for women with and without GDM [3].

Pharmacological therapy

In most cases, women with GDM may become euglycemic with diet modifications alone. However, 10–20% require pharmacological support [18]. Beginning and optimizing therapy is based on fasting and postprandial glycemic control once an appropriate diet is established. Risk factors for pharmacological assistance are similar to risk factors for overt Type 2 diabetes and include BMI >30, early gestational age at diagnosis and increasing glucose values on diagnostic testing [23]. Validated criteria for diet failure do not exist and most practitioners use persistent elevated fasting glucose levels of >95 mg/dl, 1 h postprandial >130–140 mg/dl or 2 h postprandial >120 mg/dl as indications for therapy. Others have initiated therapy with as little as two elevated glucose values over a 2-week period [1]. The proportion of values that must be above the target in order to initiate therapy is unknown. Our group commonly considers 20–50% of values at any given time point as a reasonable initiation point, and consider more aggressive management if fetal biometry on ultrasound suggests fetal hyperinsulinemia (estimated fetal weight approaching 90% or an abdominal circumference >75%) [24]. It appears that 2 weeks of diet management alone is a reasonable start in most cases, except when fasting values are over 95 mg/dl, as this group inevitably requires some pharmacological assistance [25].

Insulin

At present, insulin remains the standard of care for glycemic control. Insulin is used to control hyperglycemia and maintain levels below recommended goals. Insulin requirements increase throughout gestation. On average, insulin needs are 0.7–1.0 units/kg daily, given in divided doses [19]. For GDM, we typically divide insulin into prandial and basal insulin. Either rapid-acting (lispro or aspart) or short-acting (regular) prandial insulins are used to manage glucose excursions associated with meals. Intermediate-acting insulin (neutral protamine Hagedorn insulin [NPH]) or occasionally a long-acting insulin (glargine/detemir) are used as basal insulins to suppress maternal gluconeogenesis. Recently, lispro protamine (or neutral protamine lispro) has become available. Although not extensively studied during pregnancy, it should have similar properties to intermediate-acting NPH [26]. Data concerning commonly used insulins are shown in **Table 1**.

Rapid-acting insulin analogs (lispro and aspart) were developed through recombinant DNA technology and have largely replaced short-acting insulin as the prandial insulin of choice to manage glucose excursions associated with meals. Although either a rapid- or short-acting insulin may be used prior to meals, administration differs because of the onset of action. Regular insulin is given 30 min before a meal is planned and rapid-acting insulin is given at the commencement of a meal, a significant adherence advantage. Neither lispro nor aspart significantly cross the placenta, and both are associated with less frequent hypoglycemic episodes, reduced postprandial hyperglycemia, and have equivalent maternal and neonatal outcomes [27–29]. As such, rapid-acting insulin is the first choice for prandial insulin.

Long-acting (glargine and detemir) and intermediate-acting (NPH) insulins are intended to prevent hepatic gluconeogenesis between meals and during the fasting state. In the nonpregnant state, glargine and detemir are commonly given in conjunction with rapid-acting insulin. Although there have been concerns regarding increased mitogenic activity found in *in vitro* studies with glargine, retrospective studies demonstrate uncomplicated neonatal outcomes to date, mostly in the pregestational diabetes population [30]. In most cases of women with pregestational diabetes, we convert glargine to NPH; however, in women who are well controlled with glargine, we may continue this throughout pregnancy with little concern, as current data do not suggest significant transplacental transfer [31].

The most recent addition to our insulin options is insulin detemir, a long-acting analog that is being employed with increasing frequency in our pregestational diabetes population. Unlike glargine, there is a low IGF-1 receptor affinity and mitogenic potency, and it has a class B designation. When compared with NPH, the potential benefits of detemir include improved glucose control, lower variation and reduced nocturnal hypoglycemia. Mathiesen *et al.* demonstrated in a randomized controlled trial of pregestational diabetics that detemir, when compared with NPH, resulted in reduced fasting plasma glucose at both 24 and 36 weeks gestation; although no statistical differences in hypoglycemia or maternal weight gain were demonstrated [29]. Detailed studies on transplacental transfer have not yet been performed. At this point, we are in need of larger randomized controlled trials that include women with GDM in order to demonstrate potential advantages for perinatal outcomes with the longer-acting insulins compared with the gold standard NPH.

Insulin dosing

Many women with mild glucose excursions may be easily managed with a simple night time injection of NPH at a dose of 0.2 units/kg of body weight. For more complicated cases, the total insulin requirement may be estimated by weight for women who require both insulin injections to manage fasting and postprandial glucose. The greatest experience is with a combination of NPH and a rapid-/short-acting prandial insulin. Multiple regimens have been employed, with no evidence available that any are superior. A three-injection regimen is easy and commonly used as a starting point. Two-thirds of the total estimated dose is given before breakfast. This is divided into two-thirds intermediate-acting and a third short- or rapid-acting insulin. The evening dose is given prior to dinner and is a third of the total. NPH and short-/rapid-acting insulins are given in equal parts. Commonly, the NPH in the evening is delayed until bedtime to achieve euglycemia throughout the night and into the morning. Another simpler option for insulin is to divide the total calculated insulin dosing into 50% NPH given in the morning and prior to

Table 1. Commonly used insulin.

Type	Onset of action	Peak action	Duration of action (h)	Type
Regular	30–60 min	2–3 h	8–10	Short
Lispro	5–15 min	30–90 min	4–6	Rapid
Aspart	5–15 min	30–90 min	4–6	Rapid
NPH	2–4 h	4–10 h	12–18	Intermediate
Glargine	2–4 h	None	24	Long
Detemir	3–4 h	None	20	Long

NPH: Neutral protamine Hagedorn.
Data taken from [47].

bedtime and 50% prandial management with a rapid-acting insulin [3]. We use the weight-based insulin requirements as a guideline rather than a rule. We follow glucose measurements for at least 1 week prior to initiation of insulin, identifying which portion of the day is associated with consistent hyperglycemic episodes. Insulins are initiated at half the calculated weight-based dose and targeted to cover periods of hyperglycemia. Insulins are increased rapidly to obtain euglycemia. In rare cases of extreme maternal insulin resistance, we have used U-500 insulin to good effect; although more studies are required to offer more systematic advice [32,33].

Continuous subcutaneous insulin infusion (insulin pump) is an effective therapy typically employed by endocrinologists in the management of highly motivated and knowledgeable patients with Type 1 diabetes. It may be used as an alternative to insulin injections and is dosed to mimic physiological insulin. A basal insulin infusion is accompanied by boluses before meals. Experience with the pump suggests that excellent glucose control may be obtained with the insulin pump. However, there have been no studies that have demonstrated an advantage during pregnancy over multiple insulin injections [34].

Oral hypoglycemic agents: glyburide

Although insulin has been the standard of care for GDM with persistent hyperglycemia, glyburide treatment for GDM has become widely accepted among obstetricians. A decade ago, Gabbe and Graves noted that glyburide had become the first choice of their patients with GDM who require therapy beyond diet due to the ease of administration, patient satisfaction and adherence, and the favorable cost-effective profile [35]. Glyburide, a second-generation sulfonylurea may overcome the disadvantages of insulin treatment, which include patient discomfort, inconvenience and expense [36]. Glyburide enhances insulin secretion by binding to pancreatic B-cell receptors to increase endogenous insulin secretion. The seminal randomized trial by Langer *et al.* compared insulin with glyburide and found them to be equivalent with no statistical differences in mean maternal blood glucose, frequency of large-for-gestational-age infants, neonatal respiratory complications, neonatal hypoglycemia and length of neonatal intensive care unit stays [37]. The study was not powered for less common but relevant fetal or neonatal complications [37]. Although glyburide has imbedded itself into routine GDM management, it is important to understand the potential drawbacks. Although initial studies demonstrated that glyburide did not find its way into the fetal compartment, Hebert *et al.* subsequently identified mean umbilical to maternal glyburide concentration ratios of 0.7 ± 0.4 [38]. More recently, Lain *et al.* demonstrated that glyburide does not significantly increase neonatal fat mass compared with insulin, although there is some concern regarding the additional findings of increased birth weights and a significantly increased incidence of macrosomia in the glyburide-treated group in this study. Whether this was a result of glyburide action or suboptimal glucose management and insufficient utilization of insulin adjuncts remains unclear, but warrants further study [39]. Currently, systematic reviews have found no significant differences between glyburide and insulin for short-term outcomes, although long-term outcomes clearly require further study [40].

Risk factors for failing glyburide include pregestational diabetes, advancing maternal age, multiparity, obesity, high fasting glucose measurements and early gestational age at diagnosis [41,42]. In women with early diagnosis and fasting glucose values above 115 mg/dl, we generally avoid glyburide altogether and begin with insulin [3]. Current contraindications include: DM Type 1, significant hepatic or renal impairment, and coumadin use. Women with a known adverse reaction to sulfonamides, sulfonylurea, carbonic anhydrase inhibitors, thiazides or loop diuretics should not be prescribed glyburide. For women who are not tolerating oral feeding, glyburide should be discontinued due to the risk for hypoglycemia.

How to use glyburide

After failing diet modification to achieve euglycemia, glyburide is initiated at a starting dose of 2.5 mg orally every morning (30–60 min before breakfast) or evening depending upon the time of day that glucose values are elevated. An additional 2.5 mg may be added if adequate control is not achieved within 3–7 days. Twice-daily dosing may be utilized depending on the daily glycemic profile. If euglycemia is not achieved at 5 mg/day, increases of 5 mg may be made to a maximum dose of 20 mg/day, although our own experience would suggest little additional benefits beyond 5 mg twice a day. The onset of action

is between 15 and 60 min, with peak action at 4 h. Insulin is substituted for glyburide if control is not obtained with maximal glyburide dosing. Conway demonstrated that 84% of women who require treatment for hyperglycemia will achieve satisfactory control with glyburide [42].

Oral hypoglycemic agents: metformin

Metformin is a biguanide that is used as a first-line oral agent outside of pregnancy for diabetes due to the ease of use and lack of significant side effects, apart from the rare complication of lactic acidosis [18]. It has been demonstrated to cross the placental interface; although, until now, has not been associated with neonatal hypoglycemia. Unlike insulin or glyburide, it reduces peripheral insulin resistance and does not have the common concerning side effects of insulin and glyburide, including weight gain and severe hypoglycemia. To date, metformin has not gained the same popularity of use as glyburide in the USA as an alternative oral hypoglycemic agent; although most obstetricians have some experience with metformin during pregnancy due to the popularity of use in women with polycystic ovarian syndrome. Recently, short- and some long-term outcomes concerning metformin exposure for GDM have become available, which is important information as metformin is known to cross the placenta to the fetal compartment in significant concentrations [43]. Rowan *et al.* demonstrated equivalence in a randomized trial between metformin and insulin for GDM; however, over 40% of women randomized to metformin required some insulin supplementation [44]. Glycemic control was similar, as were maternal and neonatal outcomes, but there was a high rate of metformin failure (46%) requiring supplemental insulin to achieve euglycemia. There was an unexplained increase in prematurity, but this did not appear clinically significant. Advantages to metformin were noted, including decreased maternal weight gain as well as increased patient satisfaction. The former is particularly important for future health given the propensity for women with GDM to have weight concerns prior to pregnancy [44]. Unlike the experience with glyburide, the offspring of the original randomized controlled trial are being followed-up after 2 and 5 years, with high-quality neonatal data to assure no unexpected long-term consequences to the offspring. The first evaluation of the offspring at age 2 years demonstrated minimal concerns. Although overall fat was similar in both insulin and metformin groups, some specific biometric measurements (upper arm circumference and subscapular skin folds) were slightly increased in the metformin group and the clinical significance remains uncertain [45]. Ro *et al.* followed offspring 8 years after a randomized trial involving metformin and polycystic ovary syndrome and found no biometric differences, but also found potential increases in blood pressure and fasting glucose levels in metformin-exposed children [46].

To date, there are no prescribed methods for offering metformin; although the protocol used in the Rowan trial should serve well, starting with an initial dose of 500 mg once or twice daily and increased over a period of 1–2 weeks to the maximal daily dose of 2500 mg. At present, our group often replace metformin with insulin for women with pregestational diabetes. Given the rigorous evaluations of metformin, we believe that metformin may find a more prominent role in GDM management in the near future, perhaps more so than glyburide. Currently, the efficacy and safety of oral agents and injectable insulins are similar. Based on our own experience and review of the literature, the immediate risks of oral hypoglycemic agents appear no different to insulin and there are significant advantages for their prescription, including ease of use, patient satisfaction, adherence and cost. However, there are situations where oral hypoglycemic agents are likely to be inappropriate, especially as the maternal phenotype comes to resemble individuals with pregestational diabetes more and more. Questions remain concerning the long-term safety of oral hypoglycemic agents and these limitations should be reviewed with women when deciding between insulin and an oral agent.

Conclusion & future perspective

As the obesity epidemic continues to rage in the USA it is clear that we will care for more women with diabetes during pregnancy. Over the last decade, new options have quickly become available and there is every reason to believe that this trend will continue. At times, some of these options have not been rigorously tested for safety before they gained popularity and the women we care for will have increasingly more options to choose from. It will become incumbent upon providers, with even greater rigor, to insist upon strong short- and long-term data to support their

use and safety during pregnancy, and to provide this information to women so that the best individualized decisions can be made.

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