Management of Gestational Diabetes: Pharmacologic Treatment Options and Glycemic Control

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Diabetes mellitus is one of the most common medical complications of pregnancy; gestational diabetes mellitus (GDM) accounts for approximately 90% to 95% of all cases. GDM is defined as carbohydrate intolerance of variable severity with onset or first recognition during pregnancy. The definition is applicable regardless of whether insulin is used to treat the disease or if the condition persists after pregnancy. It does not exclude the possibility that unrecognized glucose intolerance may have antedated the pregnancy [1]. In the United States, approximately 135,000 to 200,000 women are diagnosed annually with GDM. Approximately 9% to 12% of undiagnosed type 2 diabetes is included in the GDM population. The overall increase in obesity including women of reproductive age parallels the increase in GDM and type 2 diabetes [2].

Pregnancy is characterized by hyperinsulinemia and insulin resistance in response to the diabetogenic effects of normal carbohydrate metabolism [3]. During the first trimester and early in the second trimester, increased insulin sensitivity occurs secondary to the relatively higher levels of estrogen. In contrast, in the late second and early third trimesters, there is increased insulin resistance and reduced sensitivity to insulin action. A variety of hormones—placental lactogen, leptin, progesterone, prolactin, cortisol and adiponectin—are instrumental in these changes.

GDM and type 2 diabetes share impaired insulin secretion and insulin resistance. Insulin resistance results in decreased glucose uptake in skeletal
muscles, white adipose tissue, and liver and suppression of hepatic glucose production. The risk factors associated with type 2 diabetes and GDM are comparable (eg, obesity, ethnicity, family history). β-Cell adaptation to insulin resistance is impaired in women with GDM and may be a universal response to insulin resistance because it is found in many ethnic groups. Women with a history of GDM are at an increased risk for subsequent development of type 2 diabetes (50%–80%). Type 2 diabetes and GDM arguably may be the same disease with different names [4–6].

Adverse perinatal outcome

Maternal hyperglycemia with resultant fetal hyperinsulinemia is central to the pathophysiology of diabetic complications in pregnancy. The infants of GDM women are at a 3 to 8 fold increased risk for stillbirth and aberrant fetal growth (macrosomia and growth restriction) and metabolic (eg, hypoglycemia and hypocalcemia), hematologic (eg, bilirubinemia and polycythemia), and respiratory complications that increase neonatal intensive care unit admission rates and birth trauma (eg, shoulder dystocia) [7,8].

Congenital anomalies and spontaneous abortions are more serious complications in pregestational diabetes than in GDM. Because of the relatively high rate of undiagnosed type 2 diabetic women in the GDM population (10%), a concerted effort should be made to rule out the presence of congenital malformations. Approximately 50% of all pregnancies are unplanned and do not have the advantages of preconception care. GDM in most cases is diagnosed between 20 and 30 weeks of gestation (after the organogenesis period), decreasing the rate of congenital malformations in this population is difficult to achieve [9–12]. In these cases, the main role of the obstetrician is early diagnosis in lieu of prevention. In addition, these patients and their fetuses are exposed to long-term complications, such as obesity in adolescence and later in life [13,14], higher rates of diabetes and potential intellectual impairment of the infant [15,16].

Achieving a normal glucose profile in pregnancy

Good glycemic control achieved with intensified therapy prevents microvascular and macrovascular complications [17] and improves pregnancy outcome and the overall quality of life [18]. The glucose profiles of normal pregnant women without diabetes are based on studies with small sample sizes, conducted for a single day during the third trimester in a hospital environment under strict dietary limitations [19,20]. One study [21] reported a gradual increase in mean blood glucose in the third trimester, whereas another study [22] measured continuous blood glucose in obese and nonobese nondiabetic women. The results of both studies imply that currently recommended normoglycemia criteria as targets for glycemic control in women
with diabetes do not target the actual normal levels in pregnancies of non-diabetic women (Table 1) [1,23,24].

Optimizing clinical outcome for various diabetic complications in pregnancy occurs at different levels of blood glucose. A decreased rate of congenital anomalies was observed when the postprandial threshold was less than 140 mg/dL or the preprandial threshold was less than 120 mg/dL [25–28]. In contrast, a mean blood glucose of less than 100 mg/dL to 110 mg/dL was associated with fewer large-for-gestational-age (LGA) or macrosomic newborns [10,18,29–31]. This association suggests that there are clinical thresholds for optimizing pregnancy rather than an absolute number for normoglycemia that in many cases is unobtainable. Because macrosomia and fetal hyperinsulinemia are the central complications in GDM, the targeted threshold needs to be mean blood glucose of 90 mg/dL to 100 mg/dL and postprandial blood glucose of 110 mg/dL to 120 mg/dL.

### Intensified therapy in pregnancy

It is well established that the level of metabolic control in nonpregnant patients with pregestational diabetes influences the incidence and development of retinopathy, nephropathy, and neuropathy. The levels of glycemia achieved in studies on nonpregnant subjects (DCCT, UKPDS) [17,32] were significantly higher, however, than the targeted levels of glycemia during pregnancy.

Managing women with either pregestational diabetes or GDM using intensified therapy helps to establish adequate glycemic control. Such intensive therapy involves using memory-based self-monitoring blood glucose,

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**Table 1**

Recommended therapeutic thresholds for pregnant and nonpregnant subjects compared with the glycemic profile in nondiabetic pregnant women

<table>
<thead>
<tr>
<th>Criteriaa</th>
<th>Therapeutic objective studies [Ref.]</th>
<th>Glycemic profile in nondiabetics (first author [Ref.])</th>
</tr>
</thead>
<tbody>
<tr>
<td>Fasting (mg d/L)</td>
<td>70–120</td>
<td>60–90</td>
</tr>
<tr>
<td>Premeal (mg/dL)</td>
<td>70–120</td>
<td>60–105</td>
</tr>
<tr>
<td>Postmeal (mg/dL)</td>
<td>—</td>
<td>1 h &lt; 130–140</td>
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<tr>
<td></td>
<td>—</td>
<td>2 h &lt; 120</td>
</tr>
<tr>
<td></td>
<td>—</td>
<td>90–120 min &lt; 180</td>
</tr>
<tr>
<td></td>
<td>—</td>
<td>2 AM–6 AM &gt; 65</td>
</tr>
<tr>
<td>Mean (mg/dL)</td>
<td>NA</td>
<td>100</td>
</tr>
</tbody>
</table>

*Abbreviation:* NA, not available.

a To convert glucose values from mg/dL to mM/L, multiply by 0.056.

b Data for the nonpregnant state.
multiple injections of insulin or its equivalent, diet, and an interdisciplinary team effort. Regardless of the treatment strategy, the purpose of intensified therapy is to achieve the targeted level of glycemic control that diminishes the rate of hypoglycemia and ketosis and maximizes perinatal outcome. Although there is ample evidence associating glycemic control and the occurrence of maternal/fetal complications, association does not prove cause and effect. It does provide the rationale for glucose control, however.

In a prospective study involving 1145 intensified therapy and 1316 conventional therapy GDM patients, the author observed that intensified therapy resulted in a pregnancy outcome comparable to that in the general population [18]. Independent of the type of diabetes and the treatment modality employed, capillary self-monitoring blood glucose accurately quantifies blood glucose, providing sufficient data to make suitable adjustments in the timing and dose of insulin. Diabetic patients seem to accept the self-monitoring blood glucose technique readily, which provides a sense of empowerment and involves patients in the efforts to improve pregnancy outcome. These performance measures seem comparable for all ethnic groups [33–35]. When the pregnancy outcome of conventional therapy patients was compared with that of untreated GDM patients, there were similar rates of adverse outcome. This finding suggests the inability of conventional therapy to maintain targeted levels of glycemic control.

In a pilot randomized study in 1997, Garner and coworkers [36] studied the effect of strict glycemic control and tertiary care versus routine obstetric care in the management of women with normal fasting glucose levels (diet-controlled GDM). Among 300 GDM women studied, there were no differences in mean birth weight, macrosomia, or birth trauma. The mode of delivery also was similar between the two groups, whereas the treatment group did have lower preprandial and postprandial glucose levels during the third trimester.

This feasibility study reveals several areas of concern. The rate of macrosomia was 19% in the untreated group and 16% in the treated group. These macrosomia rates are 40% to 80% above the baseline rate reported in Canada for nondiabetic populations and raise the question of the quality of glycemic control in this study. The women in the control arm could have been self-treating by modifying their own diet on the basis of self-education. Ideally the control group should be unaware that they have GDM and should be blinded to their oral glucose tolerance test results. It is possible that the women in the control group received feedback from knowing the results of home glucose monitoring, with resultant behavioral changes. Ten percent of the untreated control group who tested their blood glucose levels 1 day each week were removed from the study and treated for hyperglycemia. Finally, the authors stated that there is “… no difference in maternal or fetal outcomes; the sample size was not large enough to allow any conclusions or recommendations on the effect of treatment versus no treatment in gestational diabetes mellitus” [36]. Nonetheless, regardless of the limitations of sample
size, they chose to conclude that “… The study suggests that intensive treatment of GDM may have little effect on birth weight, birth trauma, operative delivery, or neonatal metabolic disorders” [36].

Treatment modalities in gestational diabetes

The introduction of new pharmacologic alternatives for treatment (insulin analogues and oral antidiabetic agents) and their use in pregnancy make it worthwhile to consider proven and potential benefits during gestation. Although treatment modalities for achieving targeted levels of glycemic control in type 1 diabetes, type 2 diabetes, and GDM differ, diet, exercise, insulin, and oral antidiabetic drugs are the chief means of reducing blood glucose concentrations. In pregnant women with type 2 diabetes, oral antidiabetic drugs have not been tested adequately in terms of whether targeted glycemic levels can be achieved.

Diet and exercise: modalities that enhance glucose control

Diet is the mainstay of treatment in GDM whether or not pharmacologic therapy is introduced. Dietary control with a reduction in fat intake and the substitution of complex carbohydrates for refined carbohydrates seeks to achieve and maintain the maternal blood glucose profile essential during gestation. Two current approaches are recommended: decreasing the proportion of carbohydrates to 35% to 40% in a daily regimen of three meals and three to four snacks [1,23,24,37] or lowering the glycemic index so that carbohydrates account for approximately 60% of daily intake. The assignment of daily caloric intake is similar for women with either GDM or pregestational diabetes and is calculated based on prepregnancy body mass index (BMI) [1,23,24]. In general, for normal-weight women (BMI 20–25), 30 kcal/kg should be prescribed; for overweight and obese women (BMI > 25–34), calories should be restricted to 25 kcal/kg; and for morbidly obese women (BMI > 34), calories should be restricted to 20 kcal/kg or less. Caloric restrictions of 30% in obese patients are associated with the same rate of macrosomia as in the general population. When caloric restrictions are applied, free fatty acids and ketone bodies may increase (starvation ketosis), requiring daily assessment of the ketones in the morning urine; if positive, blood assessment needs to be done [38]. A moderate exercise program for pregnant diabetic women who are willing and able may improve postprandial blood glucose levels and insulin sensitivity [24,39]. Some women are less able to exercise owing to issues of socioeconomic limitations, obesity, and multiparity.

Insulin therapy

Types of insulin to manage diabetes in pregnancy

Insulin production has progressed from animal species to human insulin preparations produced with recombinant DNA technology to the current
insulin analogues designed primarily to improve pharmacokinetic features for subcutaneous administration. This succession of advances represents almost a century of research [40,41]. When comparing insulin lispro (Humalog) and human insulins, placental transfer, efficacy, and the cost-to-benefit ratio must be considered. Insulin lispro, insulin aspart and human insulin have few differences in receptor binding and metabolic and mitogenic potency, although insulin lispro has slightly increased binding to the insulin-like growth factor-1 receptor [41–43]. Continuous subcutaneous infusion of insulin lispro in nonpregnant subjects with either type 1 diabetes or type 2 diabetes was associated with a decreased frequency of severe hypoglycemic episodes, limited postprandial glucose excursions, and a possible decrease in glycosylated hemoglobin. Insulin lispro provides greater convenience in the timing of administration (analogues administered 15 minutes after start of meal compared with soluble insulin taken 30 minutes before a meal) [41,43]. Currently, data are limited on the efficacy of the drug.

Human insulin is recommended during pregnancy because data using insulin analogues are lacking [24] (only 282 women, mostly type 1 diabetics, treated with insulin lispro and 15 women treated with aspart reported in the literature). Studies on insulin lispro showed an improvement in glycemic control, increased patient satisfaction, and a decrease in hypoglycemic episodes, but scant data on maternal and neonatal outcomes (Table 2). In the nonpregnant state, insulin glargine has been reported to have a theoretical toxicologic effect for the development of mammary, ovarian, and bone tumors and the development of retinopathy. There are currently seven case reports on the use of insulin glargine and no data on the use of detemir in pregnancy [41,43].

**Insulin analogues: placental transfer and safety concerns**

The association between proliferative retinopathy and type of insulin analogue used in gestation is controversial. In one report, 3 of 10 women, with type 1 or type 2 diabetes who had no evidence of retinopathy before pregnancy developed proliferative retinopathy that required laser therapy during the third trimester while receiving insulin lispro [44]. This observation has been hotly debated (see Table 2) [44–60]. The affected patients had abnormal glycemic levels; it is likely that poor glycemic control, not insulin lispro, led to proliferative retinopathy.

There are anecdotal case reports of congenital anomalies with the use of insulin analogues. The issue of whether insulin lispro and other analogues cross the placenta also is debated. Bauman and Yalow [61] showed that insulin by itself does not cross the placenta, but does so when complexed to insulin antibodies. Menon and coworkers [62] reported that animal and human insulin crossed the placenta in 51 mothers with type 1 diabetes in an amount directly related to the level of the mother’s anti-insulin antibodies. In another study, 4 of 19 women with gestational diabetes being treated with insulin lispro received intravenous infusion of the drug during
<table>
<thead>
<tr>
<th>Study (first author, year [Ref.])</th>
<th>Study design</th>
<th>Type of diabetes</th>
<th>No. of patients treated</th>
<th>DPR</th>
<th>Neonatal outcome</th>
</tr>
</thead>
<tbody>
<tr>
<td>Diamond, 1997 [46]</td>
<td>CR</td>
<td>1</td>
<td>2</td>
<td>—</td>
<td>2/2</td>
</tr>
<tr>
<td>Jovanovic, 1999 [45]</td>
<td>RCT</td>
<td>GDM</td>
<td>19</td>
<td>23</td>
<td>—</td>
</tr>
<tr>
<td>Kitzmiller, 1999 [44]</td>
<td>Retro</td>
<td>1 and 2</td>
<td>10</td>
<td>—</td>
<td>—</td>
</tr>
<tr>
<td>Bhattacharyya, 1999 [47]</td>
<td>Retro</td>
<td>1 and 2</td>
<td>16</td>
<td>21</td>
<td>NP</td>
</tr>
<tr>
<td>Buchbinder, 2000 [48]</td>
<td>Retro</td>
<td>1</td>
<td>12</td>
<td>42</td>
<td>NP</td>
</tr>
<tr>
<td>Persson, 2002 [50]</td>
<td>RCT</td>
<td>1</td>
<td>16</td>
<td>17</td>
<td>—</td>
</tr>
<tr>
<td>Loukovaara, 2003 [51]</td>
<td>Prosp</td>
<td>1</td>
<td>36</td>
<td>33</td>
<td>NP</td>
</tr>
<tr>
<td>Durand-Gonzales, 2003 [52]</td>
<td>CR</td>
<td>GDM</td>
<td>1</td>
<td>—</td>
<td>—</td>
</tr>
<tr>
<td>Carr, 2004 [55]</td>
<td>RCT</td>
<td>Diabetes</td>
<td>9</td>
<td>—</td>
<td>—</td>
</tr>
<tr>
<td>Idama, 2001 [56]</td>
<td>Retro</td>
<td>1</td>
<td>7</td>
<td>—</td>
<td>0/7</td>
</tr>
<tr>
<td>Cypryk, 2004 [57]</td>
<td>Retro</td>
<td>PGDM</td>
<td>25</td>
<td>46</td>
<td>—</td>
</tr>
<tr>
<td>Masson, 2003 [58]</td>
<td>Retro</td>
<td>1</td>
<td>50</td>
<td>26</td>
<td>P (6 cases)</td>
</tr>
<tr>
<td>Pettitt, 2003 [59]</td>
<td>RCT</td>
<td>GDM</td>
<td>—</td>
<td>15*</td>
<td>—</td>
</tr>
<tr>
<td>Devlin, 2002 [60]</td>
<td>CR</td>
<td>1</td>
<td>—</td>
<td>—</td>
<td>—</td>
</tr>
</tbody>
</table>

**Table 2**

Studies reporting the use of insulin analogs in pregnancy

<table>
<thead>
<tr>
<th>Study design</th>
<th>Type of diabetes</th>
<th>No. of patients treated</th>
<th>DPR</th>
<th>Neonatal outcome</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
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</tr>
</tbody>
</table>

**Abbreviations:** CR, case report; DPR, diabetes proliferative retinopathy; H, human; L, lispro; NP, no progression; P, progression; Prosp, prospective; RCT, randomized control trial; Retro, retrospective; —, no data.

* Insulin aspart.

* Insulin glargine.
labor; insulin lispro was not detected in the umbilical cord blood of the infants [45].

Using an in vitro model in which human placentas were perfused, Chal-lier and coworkers [63] reported evidence of human insulin in the fetal perfusate after infusion into the maternal compartment of the placenta. Boskovic and coworkers [64] evaluated 11 term human placentas obtained from uncomplicated pregnancies immediately after delivery. No placental transfer was detected during perfusion with insulin lispro (100 μU/mL and 200 μU/mL). In contrast, there was a concentration-dependent transfer to the fetal perfusate at insulin lispro levels of 580 μU/mL and higher. Finally, the investigators compared actual maternal serum level and administered doses of insulin lispro. Mothers treated with 50 U of insulin lispro achieved serum concentrations greater than 200 μU/mL with an apparent linear correlation between dose and levels [64]. The investigators did not evaluate placentas of diabetic mothers, however. Placentas generally are affected by the disease, which may influence the perfusion characteristics. One can speculate that even in the presence of lower insulin doses, placental transfer may occur. Although it is unlikely that insulin lispro in therapeutic doses would cross the placenta, the high dose of insulin required in pregnancy, especially in GDM and type 2 diabetes, to achieve established levels of glycemic control needs to be weighed against the potential for placental transfer and adverse outcome for the fetus.

Before using insulin analogues to treat pregnant women, several issues need to be addressed: Can pregnant women achieve targeted levels of glycemic control with the use of insulin lispro? The response is yes; the quality of glycemic control parallels the accepted criteria recommended during pregnancy. Is the quality of glycemic control during pregnancy with the use of insulin lispro comparable to that with the use of regular insulin? Is the incidence of hypoglycemic incidents similar? Six published studies compared the use of insulin lispro and regular insulin in pregnancy. Most of the studies found no significant difference with respect to glycemic control and the incidence of hypoglycemia. Two of the studies were performed on women with GDM with a total of 60 women treated with insulin lispro. In the study by Persson and coworkers [50], there was a lower postprandial glucose concentration after breakfast and a slightly higher rate of hypoglycemia (< 55 mg/dL) in the insulin lispro group. If there is no advantage in using insulin lispro compared with regular insulin, is insulin lispro as safe in pregnancy as regular insulin? Insulin lispro may be more user-friendly with negligible differences in glycemic control and hypoglycemia. These assets cannot currently justify extensive use of the drug, however, before establishing its safety in well-controlled clinical trials.

Which patients should receive pharmacologic therapy?

When diet fails to achieve targeted levels of glycemic control, insulin and antidiabetic agents are validated treatment options. Available guidelines
differ regarding the threshold of fasting plasma glucose at which pharmacologic therapy (glyburide or insulin) should be initiated [23,24,65]. Some authors recommend a threshold of fasting plasma glucose 95 mg/dL or greater [1,65] whereas others recommend a threshold of 105 mg/dL or greater [23,24]. Using a fasting plasma glucose threshold of 95 mg/dL or greater decreases the rate of macrosomia and LGA infants [66,67].

Most authorities agree on initiation of drug therapy with elevated postprandial values (≥ 120 mg/dL for 2 hours or ≥ 140 mg/dL for 1 hour). Using these standards, approximately 30% to 50% of women with GDM require pharmacologic therapy when diet therapy alone fails to reduce glycemic levels. When patients who qualified for diet therapy were evaluated, only patients who achieved established levels of glycemic control improved insulin secretion and sensitivity. Patients who failed to achieve glycemic control, although exhibiting slightly improved insulin sensitivity, did not achieve the same level of insulin response and sensitivity as nondiabetic women [68]. Studies using continuous blood glucose monitoring have shed new light on the existing controversy whether to test blood glucose at 1 or 2 hours postprandial in pregnant women. The author found that the time from start of meal to the postprandial peak is approximately 80 to 90 minutes depending on the type of diabetes and regardless of level of glycemia. In nondiabetic pregnant women, the peak postprandial value was 110 mg/dL. The association between this physiologic characteristic and pregnancy outcome needs to be evaluated before changing current clinical thresholds [22,69].

Can the fetus provide a marker for pharmacologic initiation?

Three randomized controlled studies addressed the use of fetal abdominal circumference to guide insulin therapy. This approach combined maternal glucose and fetal growth parameters. The studies suggest that some women, despite glucose levels above established targets (≥ 105 mg/dL) may not derive a fetal benefit from intensified therapy [70–72]. In a randomized study with a large sample size, the author found similar results. In the author’s study, subjects who did not achieve targeted levels of glycemic control had higher rates of macrosomia and LGA infants, however, regardless of abdominal circumference [73]. The limitation of the use of abdominal circumference at 28 weeks’ gestation as a measure for insulin initiation is that it is snapshot information, whereas fetal growth is longitudinal. Most environmental effects (eg, glucose) occur during the third trimester, which is also the time of most fetal growth. A fetus at 28 weeks’ gestation in the 40th percentile of growth can double its weight and reach the 85th percentile under the influence of elevated blood glucose. Using the fetus as an additional marker for the decision-making process in initiating pharmacologic therapy is an attractive approach. It should not be used as a single predictor, but in conjunction with GDM severity parameters and level of glycemic control throughout pregnancy.
How long is diet therapy maintained before initiating pharmacologic treatment?

Consensus and hard data are lacking regarding how long diet therapy should be maintained before initiating pharmacologic treatment. In a study by the author, 70% of the subjects with initial fasting plasma glucose less than 95 mg/dL achieved targeted levels of glycemia within 2 weeks of dietary management, but no significant improvement occurred thereafter [74]. The failure to initiate insulin therapy in a timely manner may lead to fetal hyperinsulinemia and associated complications. Premature initiation of insulin therapy without knowing whether glycemic control can be achieved with diet alone may cause unnecessary drug treatment. When GDM is diagnosed after 30 to 33 weeks of gestation, and minimal time is available for achieving targeted glycemic control, pharmacologic therapy should be initiated. There is greater flexibility in treatment modalities when GDM is diagnosed early in the third trimester.

Insulin requirements in gestational diabetes

To evaluate the insulin dose required to achieve targeted levels of glycemic control, multiple blood glucose determinations should be performed [18,75]. Insulin requirements may change during GDM. The author observed a biphasic increase in insulin requirements among 57 women with GDM who then had normal oral glucose tolerance tests postpartum [76]. The first phase was characterized by a significant weekly increase until the 30th week of gestation, after which the insulin dose remained unchanged. Insulin requirements for obese subjects in the study were 0.9 U/kg compared with 0.8 U/kg for nonobese patients. There was a significant difference in variability as measured by the coefficient of variation (45% versus 25%; $P < .01$). The total insulin dose required to reach the established level of glycemic control for most patients is 40 U to 90 U (body-weight–dependent). Women with GDM seem to benefit from frequent visits during the 20th to 30th weeks of gestation for insulin adjustment.

In a pregnant diabetic patient, the rationale for insulin therapy is based on mimicking the physiology of insulin secretion. The basal insulin is supplied by the administration of NPH/lente/ultralente insulin at bedtime or before breakfast and at bedtime. The meal-related (glucose excursion) insulin includes the use of insulin lispro before meals (0–15 min) or Regular insulin before meals (30–45 min). This algorithm provides the foundation for the use of intensified therapy (multiple injections daily) versus conventional therapy (one to two injections daily) [77].

The calculation for the insulin dose in GDM women is based on prepregnancy BMI. For nonobese patients, 0.8 U/kg is used and for overweight and obese women, 0.9 to 1 U/kg is used, then current maternal pregnancy weight is multiplied by the amount of insulin. A woman at 28 weeks’ gestation currently weighing 85 kg but based on prepregnancy BMI, classified as overweight/obese would require a total calculated insulin dose of
85 × 1 (unit) = 85. The total insulin dose is divided so that two thirds is administered in the morning, which is further split in a ratio of 2:1 (intermediate and rapid-acting), and one third is administered with supper and bedtime in a ratio of 1:1 (rapid-acting and intermediate). The rapid-acting dose is administered with supper, and the intermediate dose is taken before bedtime. If after 3 to 7 days the GDM patient has not achieved the desired level of glycemic control, the total insulin dose should increase by 10% to 20% and thereafter adjusted when needed. The actual total insulin dose in GDM women is 40% higher than the calculated (starting) dose [76]. The decreased insulin sensitivity characterizes pregnancy and in particular GDM patients. As a rule of thumb, before every insulin administration, self-monitoring blood glucose assessment needs to occur.

**Oral antidiabetic agents as alternatives to insulin therapy**

A variety of oral agents may be alternatives to insulin therapy for women with GDM. Sulfonylureas are insulin secretagogues (eg, glyburide and glipizide). The primary action of glyburide is to increase insulin secretion, decreasing hepatic glucose production with resultant reversal of hyperglycemia and indirect improvement of insulin sensitivity [78] Antidiabetic drug groups include meglitinides (insulin secretagogues, such as the rapid-acting repaglinide, which limit postprandial hyperglycemia), biguanides (eg, metformin, which decreases insulin resistance), α-glucosidase inhibitors (eg, acarbose, which reduces intestinal absorption of starch and glucose), and thiazolidinediones (eg, rosiglitazone and pioglitazone). All have been used successfully in the treatment of nonpregnant patients with type 2 diabetes. Each may be used alone or in combination with other oral agents or insulin.

Most of these drugs have not been studied in pregnancy or only minimally so. The most data regarding safety in pregnancy for oral antidiabetic drugs are with the use of glyburide. To date, 1261 women treated with glyburide have been reported in the literature. For insulin analogues and oral antidiabetic drugs, none of the studies were blinded (Table 3). Many experts and authoritative bodies have recommended using glyburide as an alternative to insulin [65,79–83]. Others have not firmly advocated the use of oral agents in pregnancy and recommend further evaluation [24,84,85]. The use of oral agents is a pragmatic alternative to insulin therapy in pregnancy because of ease of administration and patient satisfaction with a noninvasive treatment. However valid these reasons, the introduction of a new drug is unjustified if improvements in pregnancy outcome and cost-effectiveness are not evaluated definitively.

**Is there increased risk for fetal anomalies with the use of oral antidiabetic drugs?**

For a drug to be potentially effective and safe in pregnancy, it should not cross the placenta or should not be detrimental to the fetus at concentrations
<table>
<thead>
<tr>
<th>Study (first author, year [Ref.])</th>
<th>Study design</th>
<th>Type of diabetes</th>
<th>No. of patients</th>
<th>Achievement of good control</th>
<th>Neonatal outcome</th>
</tr>
</thead>
<tbody>
<tr>
<td>Langer, 2000 [78]</td>
<td>RCT</td>
<td>GDM</td>
<td>201 203</td>
<td>82% and 88%</td>
<td>No difference in metabolic complications, congenital anomalies, and PNM</td>
</tr>
<tr>
<td>Lim, 1997 [93]</td>
<td>Prosp, observ</td>
<td>GDM</td>
<td>33 21</td>
<td>No significant difference</td>
<td>No significant difference in metabolic complications and PNM</td>
</tr>
<tr>
<td>Conway, 2004 [94]</td>
<td>Prosp, observ</td>
<td>GDM</td>
<td>75</td>
<td>84%</td>
<td>NA</td>
</tr>
<tr>
<td>Kremer, 2004 [95]</td>
<td>Prosp, observ</td>
<td>GDM</td>
<td>73</td>
<td>81%</td>
<td>Macrosomia: 19%</td>
</tr>
<tr>
<td>Chmait, 2004 [96]</td>
<td>Prosp, observ</td>
<td>GDM</td>
<td>69</td>
<td>82%</td>
<td>Caesarean section: 36%</td>
</tr>
<tr>
<td>Study</td>
<td>Design</td>
<td>Population</td>
<td>GDM</td>
<td>Comparators</td>
<td>Rate (insulin)</td>
</tr>
<tr>
<td>---------------------</td>
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</tr>
<tr>
<td>Gilson, 2002 [97]</td>
<td>Prosp, observ</td>
<td>GDM</td>
<td>22</td>
<td>22</td>
<td>82%</td>
</tr>
<tr>
<td>Fines, 2003 [98]</td>
<td>Retro case-control</td>
<td>GDM</td>
<td>40</td>
<td>44</td>
<td>NA</td>
</tr>
<tr>
<td>Velazques, 2003 [99]</td>
<td>Case series</td>
<td>GDM</td>
<td>31</td>
<td>7</td>
<td>Improved level of glycemic control in the glyburide group: 82%</td>
</tr>
<tr>
<td>Pendsey, 2002 [100]</td>
<td>RCT</td>
<td>GDM</td>
<td>2</td>
<td>23</td>
<td>Repaglinide: 23</td>
</tr>
<tr>
<td>Glueck, 2004 [90]</td>
<td>Prosp, observ</td>
<td>PCOS</td>
<td>42</td>
<td></td>
<td>GDM developed in 7.1% of patients</td>
</tr>
<tr>
<td>Glueck, 2002 [91]</td>
<td>Prosp and retro, observ</td>
<td>PCOS</td>
<td>33</td>
<td>w/o metformin: 39</td>
<td>GDM developed in 3% of patients treated with metformin vs 27% w/o treatment</td>
</tr>
</tbody>
</table>

*(continued on next page)*
<table>
<thead>
<tr>
<th>Study (first author, year [Ref.])</th>
<th>Study design</th>
<th>Type of diabetes</th>
<th>No. of patients</th>
<th>Achievement of good control</th>
<th>Neonatal outcome</th>
</tr>
</thead>
<tbody>
<tr>
<td>Coetzee, 1984 [101]</td>
<td>Retro</td>
<td>Glyburide</td>
<td>2</td>
<td>78</td>
<td>Drug deemed safe in first trimester</td>
</tr>
<tr>
<td>Coetzee, 1986 [102]</td>
<td>Retro</td>
<td>GDM and 2</td>
<td>126</td>
<td></td>
<td>Reduced PNM</td>
</tr>
<tr>
<td>Coetzee, 1979 [103]</td>
<td>Prosp, observ</td>
<td>GDM and 2</td>
<td>60</td>
<td>GDM: 81.4%</td>
<td></td>
</tr>
<tr>
<td>Hellmuth, 2000 [104]</td>
<td>Prosp, observ</td>
<td>GDM</td>
<td>42</td>
<td>50 Sulfonylurea: 68</td>
<td>No significant difference in neonatal morbidity. Higher rate of preeclampsia (32% vs 10%) and PNM (11.6% vs 1.3%) in metformin group</td>
</tr>
<tr>
<td>Author/Year</td>
<td>Study Type</td>
<td>Population</td>
<td>n1</td>
<td>n2</td>
<td>Treatment</td>
</tr>
<tr>
<td>-------------</td>
<td>------------</td>
<td>------------</td>
<td>----</td>
<td>----</td>
<td>-----------</td>
</tr>
<tr>
<td>Notelovitz, 1971 [105]</td>
<td>RCT GDM and 2</td>
<td>52</td>
<td>Tolbutamide chlorpropamin: (2 \times 52)</td>
<td>Using oral hypoglycemic: 80%</td>
<td>No significant difference in PNM, metabolic complications, and congenital anomalies</td>
</tr>
<tr>
<td>Yogev, 2004 [106]</td>
<td>Prosp GDM</td>
<td>25 30</td>
<td>Diet treated: 27</td>
<td>Mean blood glucose similar in all groups</td>
<td>Significantly lower rate of maternal hypoglycemia in glyburide group</td>
</tr>
<tr>
<td>Moore, 2005 [107]</td>
<td>RCT GDM</td>
<td>31 32</td>
<td>Blood glucose similar</td>
<td>Perinatal outcome similar</td>
<td></td>
</tr>
<tr>
<td>Ramos, 2005 [108]</td>
<td>Retro GDM</td>
<td>236 316</td>
<td>Blood glucose similar</td>
<td>Perinatal outcome similar</td>
<td></td>
</tr>
</tbody>
</table>

*Abbreviations:* NA, not available; Observ, observational; PNM, perinatal mortality; Prosp, prospective; RCT, randomized control trial; Retro, retrospective; w/o, without.
that are clinically indicated for the mother. Case reports and small retrospective studies in women receiving first-generation sulfonylureas raised concern about congenital anomalies [86,87]. Potential effects on the fetus, mainly hypoglycemia and growth stimulation [87], were reported. A report of increased rates of congenital malformations involved 20 type 2 diabetes patients who had hyperglycemia before conception (hemoglobin A1c > 8). It is impossible to determine if the reported rate of anomalies was due to the use of the drug or the preexisting hyperglycemia [86]. In contrast, several studies showed that anomalies in the infants of women who received oral antidiabetic agents were associated with altered maternal glucose metabolism and not the drug [88]. A meta-analysis failed to show an increased risk for fetal anomalies with sulfonylureas [89]. Metformin seems to be unassociated with congenital malformations in patients with polycystic ovary syndrome and reduces the occurrence of GDM and spontaneous abortion (see Table 3) [90–92].

*Does glyburide cross the placenta?*

The placenta of the diabetic mother is characterized by capillary dilation, relatively immature villous structure, and chronic disturbances in intervillous circulation. The author examined the placentas of nondiabetic and diabetic mothers in vitro and showed that glyburide (glibenclamide) does not cross the human placenta from the maternal to fetal circulation in significant amounts. There was virtually no drug transport even when concentrations three to four times higher than peak therapeutic levels were employed [109–111]. The author also showed that first-generation sulfonylureas diffused across the placenta most freely [109–111]. There is evidence that the qualitative aspects of transfer are comparable between placentas obtained during the first and third trimesters [64,112]. In mothers treated with therapeutic plasma concentrations of glyburide, the drug was undetectable in the cord blood of their neonates [78]. No data exist on the long-term effects on the infant when oral antidiabetic drugs and insulin analogues are used in the mother. Glyburide exhibits less transfer across the placenta compared with other agents, underscoring its potential therapeutic usefulness.

Because glyburide does not cross the placenta, it cannot affect neonatal hypoglycemia or fetal anomalies. In addition, most GDM patients are identified between 24 and 28 weeks’ gestation. The fetus is not exposed to the drug during organogenesis. In rare cases of early diagnosis in the first trimester (perhaps type 2) and recognized type 2 diabetes, current data suggest that the use of glyburide or metformin would not increase the rate of anomalies influenced by the level of glycemic control. Although a randomized study would be the ideal model to address this issue, it is highly unlikely that it would be performed for ethical considerations (see Table 3).

**Glyburide pharmacology and administration**

The pharmacologic mechanism of action of glyburide is to increase insulin secretion, and its secondary effect is to decrease insulin resistance by
reducing glucose toxicity. Its onset of action is approximately 4 hours, and duration of action is about 10 hours. After achieving the targeted therapeutic level, the drug covers the basal requirement and the postprandial excursions of glucose. The starting dose is 2.5 mg orally in the morning. If the targeted level of glycemia has not been reached, 2.5 mg is added to the morning dose. If indicated (after 3–7 days), 5 mg is added in the evening. Thereafter, the dose is increased by 5 mg to a total of 20 mg/day. If patients fail to achieve established levels of glycemic control, long-acting insulin can be added to the regimen [78].

The abnormal level of glycemia in GDM can be controlled by monotherapy with glyburide and probably metformin. Can monotherapy with glyburide achieve targeted levels of glycemia required in pregnancy in type 2 patients? Although this issue has not been studied extensively, one can speculate that monotherapy may not be sufficient. Combination therapy with other oral antidiabetic drugs, with proven efficacy and safety, would help subjects achieve established levels of glycemic control. Another alternative is the combination of insulin and glyburide, which would result in a lower dose of insulin compared with the use of monotherapy with insulin.

**Glyburide compared with insulin**

Several studies evaluated the efficacy of oral antidiabetic agents during pregnancy (see Table 3). Most studies showed that these agents were comparable to insulin in achieving established levels of glycemic control and pregnancy outcome. The author compared glyburide with standard insulin therapy in a randomized controlled trial in 404 GDM women [78]. The primary outcome was the ability to achieve established levels of glycemic control; insulin and glyburide had comparable results. The success in achieving glycemic control with glyburide was reconfirmed by several studies (Tables 3 and 4). Adequate glycemic control was obtained with significantly fewer hypoglycemic episodes in the glyburide group compared with the insulin group [78]. Using a continuous glucose monitoring system that recorded data every 5 minutes for 72 continuous hours with 288 measurements per day, asymptomatic hypoglycemic events (> 30 consecutive minutes of glucose values < 50 mg/dL) occurred in 63% of subjects receiving insulin compared with 28% of subjects receiving glyburide [106].

The insulin-treated patients and glyburide-treated patients achieved comparable results in many variables: cord-serum insulin concentrations, incidence of macrosomia, increased Ponderal index, LGA infants, neonatal metabolic complications (hypoglycemia, polycythemia, and hyperbilirubinemia), respiratory complications, and cesarean delivery [78]. The perinatal outcome in the glyburide and the intensified therapy subjects was comparable (see Table 4).

The author analyzed the association among glyburide dose, GDM severity, and selected maternal and neonatal factors [113]. Glyburide and insulin were equally efficacious for treatment of women with GDM of varying
severity when fasting plasma glucose results were between 95 mg/dL and 139 mg/dL. Of patients, 71% required a 10-mg daily dose of glyburide to achieve glycemic control. In all disease severity levels, glyburide and insulin-treated subjects had similar success rates in achieving targeted glucose levels and pregnancy outcomes [113]. Achieving the established level of glycemic control, not the mode of therapy, seems to be the key to improving pregnancy outcome in GDM.

Is glyburide therapy less costly than insulin therapy?

The costs of alternative therapies should be addressed when different medications exhibit similar effectiveness and safety. Goetzel and Wilkins [114] compared the costs of insulin and glyburide and observed that glyburide is considerably less costly (average savings per patient of $166–$200 based on rates in 2000). Glyburide is a cost-effective, patient-friendly, potentially adherence-enhancing therapy that produces perinatal outcome comparable to insulin therapy.
Table 5
Oral antidiabetic drug classification

<table>
<thead>
<tr>
<th>Drug (trade name)</th>
<th>Mechanism of action</th>
<th>Pregnancy category</th>
<th>Decrease in FPG (mg/dL)</th>
<th>Decrease in hemoglobin A1C (%)</th>
<th>Cross placenta</th>
<th>Excreted in breast milk</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Sulfonylureas</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Glimepiride (Amaryl)</td>
<td>Increase insulin secretion</td>
<td>C</td>
<td>60–70</td>
<td>1.5–2</td>
<td>Unknown</td>
<td>Unknown</td>
</tr>
<tr>
<td>Glipizide (Glucotrol)</td>
<td></td>
<td>C</td>
<td></td>
<td></td>
<td>Minimal</td>
<td>Unknown</td>
</tr>
<tr>
<td>Glipizide-GITS (Glucotrol XL)</td>
<td></td>
<td>—</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Glyburide (DiaBeta, Glynase, Micronase)</td>
<td></td>
<td>B</td>
<td></td>
<td></td>
<td>No</td>
<td>No</td>
</tr>
<tr>
<td><strong>Meglitinides</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Nateglinide (Starlix)</td>
<td>Increase insulin secretion</td>
<td>C</td>
<td>9–21</td>
<td>0.5–0.8</td>
<td>Unknown</td>
<td>Unknown</td>
</tr>
<tr>
<td>Repaglinide (Prandin)</td>
<td></td>
<td>C</td>
<td></td>
<td></td>
<td>Unknown</td>
<td>Unknown</td>
</tr>
<tr>
<td><strong>Biguanide</strong></td>
<td>Decreases hepatic gluconeogenesis; increases insulin sensitivity</td>
<td>B</td>
<td>59–78</td>
<td>0.9–2</td>
<td>Yes</td>
<td>No</td>
</tr>
<tr>
<td>Metformin (Glucophage)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Glitazones</strong></td>
<td>Increase insulin sensitivity; decrease hepatic glucose production</td>
<td></td>
<td>59–80</td>
<td>1.4–2.6</td>
<td>Unknown</td>
<td>Animals</td>
</tr>
<tr>
<td>Pioglitazone (Actos)</td>
<td></td>
<td>C</td>
<td></td>
<td></td>
<td>Unknown</td>
<td>Animals</td>
</tr>
<tr>
<td>Rosiglitazone (Avandia)</td>
<td></td>
<td>C</td>
<td></td>
<td></td>
<td>Unknown</td>
<td>Animals</td>
</tr>
</tbody>
</table>

(continued on next page)
<table>
<thead>
<tr>
<th>Drug (trade name)</th>
<th>Mechanism of action</th>
<th>Pregnancy category</th>
<th>Decrease in FPG (mg/dL)</th>
<th>Decrease in hemoglobin A₁C (%)</th>
<th>Cross placenta</th>
<th>Excreted in breast milk</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Alpha-glucosidase inhibitors</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Acarbose (Precose)</td>
<td>Slow absorption of carbohydrates in the intestine</td>
<td>B</td>
<td>20–30</td>
<td>0.5–1</td>
<td>Unknown</td>
<td>Animals</td>
</tr>
<tr>
<td>Miglitol (Glyset)</td>
<td></td>
<td>B</td>
<td></td>
<td></td>
<td>Unknown</td>
<td>Animals</td>
</tr>
<tr>
<td><strong>Insulin</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Aspart (Novolog)</td>
<td></td>
<td>B</td>
<td></td>
<td></td>
<td>Unknown</td>
<td>No</td>
</tr>
<tr>
<td>Lispro (Humalog)</td>
<td></td>
<td>B</td>
<td></td>
<td></td>
<td>Minimal</td>
<td>No</td>
</tr>
<tr>
<td>Regular</td>
<td></td>
<td>B</td>
<td></td>
<td></td>
<td>No</td>
<td>No</td>
</tr>
<tr>
<td>NPH</td>
<td></td>
<td>B</td>
<td></td>
<td></td>
<td>No</td>
<td>No</td>
</tr>
<tr>
<td>Lente</td>
<td></td>
<td>B</td>
<td></td>
<td></td>
<td>No</td>
<td>No</td>
</tr>
<tr>
<td>Glargine (Lantus)</td>
<td></td>
<td>C</td>
<td></td>
<td></td>
<td>Unknown</td>
<td>No</td>
</tr>
<tr>
<td>Ultralente</td>
<td></td>
<td>B</td>
<td></td>
<td></td>
<td>No</td>
<td>No</td>
</tr>
</tbody>
</table>
Glyburide and lactation

Data are scant on the effect of oral antidiabetic drugs on lactation. Data from two centers, in Canada and in California, suggested that glyburide is not present in the milk of lactating mothers when measured in vivo and in vitro [115].

Summary

Although not universally accepted, the introduction of insulin analogues (mainly insulin lispro, class B), oral antidiabetic agents (mainly glyburide [class B]) (Table 5), and the use of intensified therapy have altered profoundly the management approach in the treatment of diabetes in pregnancy with outcomes comparable to the general population (see Table 4). Insulin lispro is not likely to cross the placenta with the clinically used dose in most type 1 and type 2 diabetic patients. The benefits of this drug are the reduction of nocturnal hypoglycemic episodes and postprandial levels and the ease of patient use. With the establishment of the efficacy for the use of glyburide (and possibly metformin), there is an equally effective alternative to insulin therapy. Glyburide is a cost-effective, patient-friendly, and potentially compliance-enhancing therapy that produces perinatal outcome in GDM pregnancies comparable to traditional insulin therapy. For GDM patients who require pharmacologic therapy, glyburide is the drug of choice, and only patients who fail to achieve glycemic control should begin insulin therapy.

The major obstacles to the creation of evidence-based criteria to guide benefit/risk in pharmacologic therapy in obstetrics is the fear of the potential adverse drug effects on the fetus and the resultant paucity of research. The history of the Food and Drug Administration regulations for prescription drug labeling in pregnancy adds an additional layer of difficulty. The ethical, legal, and medical rhetoric surrounding this dilemma may have exaggerated the potential for fetal harm. There may be greater risk to the fetus in withholding certain medications than in prescribing them. The current evidence-based data for insulin lispro and glyburide support their use in pregnancy. A large-scale multicentric study to evaluate glyburide and insulin analogues would be a practical and enlightening endeavor.

References


[83] Ryan EA. Glyburide was as safe and effective as insulin in gestational diabetes. Evidence Based Medicine 2001;6:79.