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Drugs to Control Diabetes during Pregnancy

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Abstract

Diabetes is a common complication of pregnancy associated with both short- and long-term adverse maternal and offspring effects. All types of diabetes in pregnancy are increasing in prevalence. Treatment of diabetes in pregnancy, targeting glycemic control, improves both maternal and offspring outcomes, albeit imperfectly for many women. Pharmacologic treatment recommendations differ between pre-gestational and gestational diabetes; in each case, effectiveness appears limited by co-morbid obesity due to overlapping maternal and offspring risks associated with obesity and diabetes in pregnancy. Despite changes in patient characteristics and increasing evidence of heterogeneous pathophysiology contributing to diabetes in pregnancy, current practice still presupposes a single common treatment strategy, including pharmacologic agents and glycemic targets, with little distinction by diabetes type or pathophysiologic mechanism. Furthermore, while diabetes in pregnancy is associated with long-term offspring risks, few studies have assessed long-term outcomes following exposure to different diabetes treatments *in utero*. Improved treatment of diabetes in pregnancy will need to consider maternal disease heterogeneity and comorbidities as well as long-term offspring outcomes. In this review, we will summarize recent clinical studies to highlight established pharmacologic treatments for diabetes in pregnancy and provide suggestions for further research.

Introduction

Diabetes complicates 6–9% of pregnancies with the vast majority (90%) of cases due to gestational diabetes (GDM).^{1–4} The overall prevalence of all forms of diabetes in pregnancy

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is increasing, likely due to increases in obesity,^{3,5-7} along with changes in diagnostic criteria for GDM.⁸ The main goal of treating diabetes in pregnancy is to minimize maternal and fetal adverse events related to hyperglycemia. Outside of pregnancy, options for the management of diabetes include lifestyle interventions, including weight loss, oral glucose-lowering agents, and various forms of insulin. During pregnancy, weight loss and most oral glucose-lowering agents are not options.^{1,2,4} Also, while effective, insulin does not eliminate adverse maternal and fetal outcomes. In addition, patients and providers have demonstrated a clear preference for oral glucose-lowering agents⁹.

The compressed timeline of pregnancy and of opportunities for achieving glucose control are significant hurdles to effectively treating diabetes in pregnancy, especially GDM. The physiologic changes of pregnancy, including a progressive increase in insulin resistance, gestational weight gain, and changes in body composition can further complicate the treatment of diabetes in pregnancy. More recently, it has become clear that the patient population of diabetes in pregnancy is heterogeneous with respect to pathophysiology, possibly limiting the effectiveness of standardized therapies, thus demanding continued research. In this review, we will focus on recent studies that have evaluated treatment options for women with diabetes in pregnancy and recently updated professional guidelines.

Glucose metabolism during pregnancy

Optimal pharmacotherapy of diabetes during pregnancy depends on an understanding of the physiologic changes in glucose metabolism during normal pregnancy. During pregnancy, there are both increases and decreases in insulin sensitivity and beta cell function with advancing gestation in women with normal glucose tolerance. In early pregnancy (12–14 weeks), insulin sensitivity can either increase or decrease compared to preconception measures when assessed using the hyperinsulinemic euglycemic clamp method. However, by late gestation (34–36 weeks), insulin sensitivity decreases by 40–50% in virtually in all women,¹⁰ albeit with significant inter-individual variation (Figure 1). These changes in insulin sensitivity are more extreme in women developing GDM, due to their underlying subclinically altered glucose metabolism prior to pregnancy.¹¹

It is generally thought that the changes in insulin response mirror the changes in insulin sensitivity. For example, decreased insulin sensitivity leads to an increased insulin response in order to maintain normoglycemia. The situation in early pregnancy, however, is quite different in than in late pregnancy. In early pregnancy, insulin response is increased regardless of changes in insulin sensitivity (Figure 2). In women with type 1 diabetes in excellent control prior to conception, an increase in insulin sensitivity in early pregnancy may decrease insulin requirements in early gestation.¹² However, starting at approximately 18 to 20 weeks, insulin requirements increase progressively through the late third trimester. Insulin requirements may plateau, increase, or decrease in the late third trimester. Decreases may signal poor placental function and increasing risk of perinatal morbidity,¹³ while increased requirements may be due to late gestational increases in insulin clearance,¹⁴

Although there are multiple formulae to estimate insulin requirements in pregnancy, their use requires care, even in women with type 1 diabetes, because of variable insulin sensitivity

both before and during pregnancy.¹⁵ Further, women with either type 2 diabetes or GDM requiring insulin therapy manifest both greater insulin resistance compared to matched normoglycemic women during pregnancy and widely varying impairment of beta cell function.¹⁶ Together, these physiologic variables suggest that optimizing glucose control prior to conception would provide an easier transition to maintaining optimal glucose control during pregnancy.

Diabetes in pregnancy before and after the discovery of insulin

Before discussing the pharmacology of current drug management of diabetes in pregnancy, it is helpful to recount the history of diabetes in pregnancy. An excellent review by Dr. Steven Gabbe,¹⁷ which we commend to all readers, is summarized here. Prior to the discovery of insulin in 1921 by Banting, Best, Macleod and Collip, most women of reproductive age died shortly after the onset of what we now refer to as Type 1 diabetes. The primary treatment at that time was a ketogenic diet, resulting in the wasted phenotype previously associated with type 1 diabetes. The cause of death was diabetes related ketoacidosis, which was more likely to occur during pregnancy.¹⁸ In the small number of pregnancies reported prior to the use of insulin, maternal mortality was approximately 50%. Hence many obstetricians encouraged pregnancy termination.¹⁹ In 1922, Drs. Howard Root and Elliot Joslin administered the first dose of purified insulin to their patient, Miss Elizabeth Mudge, a 37-year-old nurse, who recovered and lived for another 25 years.

The use of insulin in pregnancy and the insight that fetal wellbeing depended critically on glycemic control was pioneered by Dr. Priscilla White of the Joslin Clinic in Boston.²⁰ In 1932, she described 3 successful pregnancies in women with type 1 diabetes.²¹ Insulin treatment decreased maternal mortality significantly, but perinatal mortality, stillbirths, and prematurity all remained common.²² In 1949, Dr. White classified diabetes in pregnancy by her schema which included the age of onset, duration and vascular complications, all impacting fetal survival.²³ Advances in the use of insulin, insulin analogues, and self-monitoring of blood glucose have further decreased perinatal mortality so that it now approaches that observed in women with normal glucose tolerance. Further refinements in the management of diabetes in pregnancy over the last 20 years have steadily decreased maternal and perinatal morbidity. We await further advances in the management of diabetes in pregnancy, such as closed loop systems, to further improve the perinatal outcomes of women with diabetes in pregnancy and their children.

Insulin

Insulin remains the preferred therapy for pregnant women with pre-gestational diabetes and a number of professional societies endorse its use as a first-line therapy in GDM.^{1,2,4} Treatment decisions regarding the type of insulin, timing of administration, and dose frequency are based on individual glycemic patterns. A comprehensive exploration of insulin formulations is beyond the scope of this review and we will limit the discussion to novel insulin analogues and technological devices.

The goal of exogenous insulin therapy in pregnancy is to mimic the physiologic profile of insulin in response to diet and metabolic demands in order to achieve and maintain euglycemia. The changes in glucose metabolism that characterize advancing pregnancy require corresponding changes in dose and timing of insulin administration.^{12,24,25} To improve treatment compliance and patient satisfaction, newer rapid-acting analogues were developed to limit the inconvenience of regular insulin administration half an hour before meals and “peakless” slow-acting analogues to limit the risk of hypoglycemia between meals and during sleep. The use of most insulin analogues in pregnancy is often extrapolated from experience in non-pregnant patients rather than studies in pregnant women. While the three rapidly-acting insulin analogues (i.e., lispro, aspart, glulisine) are comparable in immunogenicity to human regular insulin, only lispro and aspart have been investigated in pregnancy. They appear to have acceptable safety profiles, minimal transplacental transfer, and no evidence of teratogenicity.^{26–28} In one study, the use of short-acting insulin analogues reduced the risk of postprandial glycemic excursion and limited the risk of delayed postprandial hypoglycemia when compared with regular human insulin.²⁹ In an observational study, there were no differences in pregnancy outcome between pregnant women who used lispro and those who used regular insulin, but the former reported increased treatment satisfaction.²⁶ The long-acting insulin analogue, insulin detemir (FDA pregnancy category B by old nomenclature), was compared to NPH insulin in 310 pregnant women with type 1 diabetes mellitus, resulting in similar glycemic control (assessed as hemoglobin A1c [HbA1c] levels) and incidence of hypoglycemia.³⁰ Like detemir, insulin glargine can similarly provide a stable basal insulin during pregnancy. Likewise, the safety of glargine as a basal insulin during pregnancy was addressed in a systematic review of 8 observational studies involving a total 702 women with pre-gestational diabetes or GDM treated with either insulin glargine (n=331) or NPH (n=371) revealing similar maternal and neonatal outcomes between treatments.³¹ However, we lack adequate data for any insulin analog to ensure fetal safety equivalence with insulin and large studies are still needed to explore potential mechanisms of teratogenicity.

More recently, studies have focused on novel advances in insulin delivery and continuous glucose monitoring technologies. Continuous subcutaneous insulin infusion (CSII) devices can be programmed to deliver basal and subcutaneous insulin without any abrupt changes and limiting the need for additional subcutaneous injections. In non-pregnant individuals, CSII use results in lower HbA1c levels and fewer hypoglycemic episodes.³² By comparison, the benefit of CSII use during pregnancy is less clear.^{33–35} Some studies have noted lower HbA1c levels and lower insulin requirements at the time of delivery with CSII use in women with type 1 DM compared to multiple daily injections (MDI).³⁶ Yet, maternal and neonatal outcomes did not differ significantly when comparing CSII use to MDI regimens in studies of pregnant women with type 1 diabetes.^{34,36,37} In parallel with CSII devices, continuous glucose monitors (CGM) were developed to increase the frequency of glucose measurements while limiting the need for timed, self-collected capillary glucose values. The utility of CGMs was recently evaluated in the CONCEPTT study, which randomized 325 pregnant women with type 1 diabetes to real-time CGM technology or capillary glucose monitoring.³⁸ CGM users were within glucose target values more frequently (68 vs 61%, p=0.003) and exceeded glycemic goals less often (27 vs 32%, p=0.028) compared to women who

monitored their capillary glucose by intermittent self-sampling.³⁸ The study also noted a 50% reduction in rates of large for gestational age infants, NICU admission and neonatal hypoglycemia in women randomized to CGM use.³⁸ Interestingly, these results were independent of the mode of insulin delivery, CSII or MDI. Recently, sensor-augmented insulin pump devices have been developed to combine CSII and CGM technologies by automatically adjusting the CSII basal rate to create a closed-loop therapy system. In a proof of principle crossover trial performed in 16 pregnant women with type 1 diabetes, closed-loop therapy resulted in a higher percentage of time within glycemic goals (75 vs. 60%, $p=0.002$) than did sensor-augmented pump therapy (i.e., separate CGM and CSII).³⁹ However, there was no clear benefit for closed-loop therapy on adverse pregnancy outcomes as 13 of the 16 newborns in this small crossover study with open extension following the randomized comparison had a birth weight greater than the 90th percentile.³⁹ Also, two recent Cochrane database reviews found no evidence to support one type of insulin or insulin regimen over another and no evidence to suggest CGM over intermittent monitoring.^{40,41} Despite the significant advances in CSII and CGM technologies, overall rates of adverse pregnancy outcomes remain high, especially in women with type 1 diabetes, and further studies are needed to explore the use of these novel technologies to reduce maternal and fetal risks further.

Oral agents

Glyburide

Sulfonylureas stimulate insulin secretion primarily by interacting with ATP-sensitive K^+ channels to mimic effects of glucose metabolism coupling to insulin release in pancreatic β -cells. For approximately 50 years, until the recent introduction of alternative oral hypoglycemic drugs, sulfonylureas were the mainstay of type 2 diabetes treatment.⁴² Glyburide is the sulfonylurea most commonly used and studied in pregnancy, as early studies had suggested minimal transplacental transfer and thus presumption of fetal safety. This led to a landmark randomized clinical trial in which glyburide outcomes compared favorably to those with insulin in women with GDM.^{43–45} Glyburide use in pregnancy increased dramatically; by 2011, it had become the most frequently used treatment for women with GDM.⁴⁶ With its widespread use, data emerged on increased glyburide clearance due to its biotransformation during pregnancy and the potential need for higher or more frequent doses to mimic pharmacokinetics in non-pregnant patients. As well, more sensitive analytic methods revealed previously-unsuspected placental transfer of glyburide to the fetus, with cord blood concentrations of glyburide 50–70% of those in maternal plasma, albeit at very low levels and with very limited sampling.^{47,48} These findings were soon followed by various reports comparing pregnancy outcomes in women with GDM treated with glyburide or insulin. In a retrospective cohort study comparing outcomes in 4982 women treated with glyburide and 4191 women treated with insulin, glyburide treatment was associated with increased risks for NICU admission, respiratory distress, hypoglycemia, birth injury, and large for gestational age birth weight.⁴⁹ These data highlighted potential concerns with glyburide use, but the study was unable to conclude whether its findings were related to direct drug effects in the fetus. The study lacked any information about potential confounders, including pre-pregnancy BMI, and details about glycemic control were

missing. Several meta-analyses added to concerns about the appropriate use of glyburide in GDM.^{49–53} A meta-analysis by Balsells et al. described higher birth weight infants, more macrosomia, and more neonatal hypoglycemia following treatment with glyburide compared to insulin.⁵⁴ Together, these led to recent changes in professional guidelines; the American College of Obstetrics and Gynecology now recommends insulin as the first line agent for GDM treatment² and the Society for Maternal-Fetal Medicine endorses metformin as an alternative first-line agent to insulin.⁵⁵ Both the observational studies and meta-analyses of RCTs raise questions about the appropriate use of glyburide. However, the initial glyburide clinical trial, the largest to date, suggests that, as long as glycemic control is comparable, outcomes do not differ between groups.⁴⁵ The other trials included in these meta-analyses all had small sample sizes and differed in their approach to glyburide dosing. In addition, the observational studies demonstrating increased risk each have methodological inadequacies, including an inability to account for variation in glycemic control, often (6–20%) failing to achieve the excellent control observed in the original large randomized trial.⁵⁴ Several factors have been associated with higher rates of glyburide failure, including fasting plasma glucose >110 mg/dL (on the oral glucose tolerance test), older maternal age, multiparity, and GDM diagnosis prior to 25 weeks. Despite this, we still lack prediction tools to aid providers in selecting the women with GDM most likely to achieve optimal glycemic control with glyburide (or with other oral or parenteral hypoglycemic agents) or in tailoring dosing regimens so as to achieve glycemic control rapidly.^{56–59} Glyburide concentrations increase within 30–60 minutes of dosing, peak in 2–3 hours, and return to baseline by 8 hours.⁴⁷ This suggests, by contrast with usual practice, that optimal effect might be achieved with glyburide administration 30–60 minutes prior to meals to adequately target postprandial excursions and that more frequent, perhaps thrice daily dosing, may be needed to maintain glucose control throughout the day. It remains unclear if glyburide use increases the risk for fetal overgrowth independent of glycemic control. As well, the studies needed to critically examine new, pharmacokinetically-driven glyburide dosing strategies have not been reported.

Metformin

Metformin is recommended as first-line therapy for type 2 diabetes outside of pregnancy.^{60,61} Its glucose-lowering effect is thought to be related to its action on mitochondrial metabolism and cellular pathways reducing hepatic gluconeogenesis.⁶² Metformin likewise lowers glucose by improving insulin sensitivity, particularly in the liver, without excess weight gain or significant hypoglycemia. Results from the United Kingdom Prospective Diabetes Study, showed that it reduced both macrovascular events and mortality in obese individuals with type 2 diabetes.^{62,63} Metformin was recently endorsed as an alternative to insulin for the treatment of GDM.^{55,64} Given its popularity outside of pregnancy and the absence of excess congenital anomalies with first-trimester use, metformin use was explored for the treatment of GDM later in pregnancy.^{65,66} The Metformin in Gestational Diabetes (MiG) study remains the largest randomized controlled trial (RCT) to compare metformin to insulin therapy in women with GDM.⁶⁷ Glycemic control was similar between groups in MiG, yet 46% of women randomized to metformin required supplemental insulin.⁶⁷ Even though metformin improves insulin resistance, it primarily acts on hepatic insulin resistance while the increase in insulin resistance during pregnancy is mostly peripheral.^{11,16} Similar to

glyburide, metformin failure is more likely to occur in older women, those with higher fasting glucose, and those with GDM diagnosis earlier in pregnancy.⁶⁸ Furthermore, metformin clearance is increased during pregnancy.⁶⁹ The high rate of metformin failure in achieving glycemic control has raised questions about appropriate dosing. However, its concentration-effect relationship has not been determined, and may reach a plateau, making it unclear if higher doses would overcome increases in renal clearance to improved glycemic control in pregnancy.⁷⁰

Neonatal outcomes in MiG were similar between groups except for lower rates of neonatal hypoglycemia in women treated with metformin.⁶⁷ Maternal outcomes were mixed; metformin therapy was associated with lower gestational weight gain (0.4 ± 2.9 kg vs 2.0 ± 3.3 kg, $p < 0.001$) but higher rates of preterm birth (12.1 vs 7.6%, $p = 0.04$).⁶⁷ Recent meta-analyses and systematic reviews have suggested favorable pregnancy outcomes with metformin use in women with GDM. A recent network meta-analysis that included unpublished trials found lower risks of large-for-gestational age (LGA) births, macrosomia, NICU admission, neonatal hypoglycemia, and preeclampsia in women treated with metformin compared to insulin.⁵⁴ Furthermore, recent meta-analyses did not find any difference in preterm delivery between metformin and insulin treatment.^{71,72}

Several studies have also suggested a biologically plausible association between metformin use and decreased risk of hypertensive disorders of pregnancy. Metformin lowers soluble fms-like tyrosine kinase 1 (sFlt1) and soluble endoglin secretion from primary human tissues *in vitro*, perhaps mediated by its effect on mitochondrial electron transport and downstream inhibition of hypoxia inducible factor-1 α . These studies also demonstrated improvements in endothelial dysfunction, vasodilation, and angiogenesis, all impaired in the pathophysiology of preeclampsia.⁷³ Metformin was evaluated in a study of 400 obese women (BMI > 35 kg/m²) without diabetes who were randomized to metformin or placebo and its use was associated with less maternal weight gain and a lower incidence of preeclampsia (3.0 vs. 11.3%; OR, 0.24; 95% confidence interval, 0.10 to 0.61; $p = 0.001$).⁷⁴ This association was also described in a meta-analysis comparing metformin to placebo or insulin in pregnant women with insulin-resistance, whether related to GDM, type 2 diabetes mellitus, or PCOS.⁷⁵

Despite these recent findings and professional guidelines endorsing the use of metformin, several concerns remain regarding its use in women with GDM, including inadequate glycemic control requiring supplemental insulin in approximately half of women, its extensive transplacental transfer to the fetus, and unexplored concerns regarding long-term outcomes following *in utero* exposure to a drug that appears to inhibit the mTOR pathway.^{76,77} While metformin treatment failure in GDM may be influenced by its increased (renal) clearance in pregnancy,⁶⁹ it remains unclear whether higher doses would improve glycemic control. As well, metformin pharmacokinetics are complex, with slow accumulation in the liver and red blood cells, limiting our ability to determine the relevance of plasma drug concentrations to glycemic control.⁷⁸ Furthermore, this slow accumulation and thus lag between changes in dosing, plasma drug concentrations, and pharmacologic effect, limits the speed and confidence with which quick dose titration can translate into improved glycemic control.

Metformin's extensive transplacental passage is unsurprising since it is a small hydrophilic molecule with low protein binding. Metformin umbilical cord serum concentrations may approximate or even exceed maternal concentrations.^{69,79} However, there is no significant increase in neonatal complications when metformin is used in women with GDM.^{54,67,71,72} While there is no evidence of perinatal risk, long-term observations of children exposed to metformin *in utero* are concerning. Several studies have examined offspring of women with PCOS treated with metformin during pregnancy and found that the offspring of mothers randomized to metformin weighed more at 1 year of age compared to those who received placebo.^{80,81} Another follow-up study of women with PCOS treated with metformin during pregnancy noted higher offspring weight and BMI z-scores at 4 years of age, with twice as many overweight and obese children in the metformin-exposed group compared to placebo.⁸² In women with GDM, offspring data following metformin exposure are limited to the MiG study cohort. At 2 years of age, offspring exposed to metformin *in utero* had higher subcutaneous fat mass without a decrease in visceral fat.⁸³ A subset of offspring was also followed-up at 7 and 9 years of age.⁸⁴ In this subset from New Zealand, offspring exposed to metformin *in utero* were heavier, had higher arm and waist circumferences and waist:height ratios ($p<0.05$), and trended toward higher BMI and abdominal fat volume by MRI (all $p=0.05$).⁸⁴ There were no differences in glucose, lipids, insulin resistance, or liver function test measures in the metformin- compared with insulin-exposed offspring.⁸⁴ By contrast, follow-up of the subset from Australia found no differences comparing the offspring exposed to metformin or insulin.⁸⁴ While these observations are limited to only the subset of original MiG study cohort who had long-term follow-up and are unable to support a direct link between drug exposure and adverse long-term outcomes, they raise the concern of potential long-term harm following exposure to metformin *in utero*. These data were included in a meta-analysis of 10 follow-up studies from RCTs that compared metformin to placebo or insulin used in pregnant women with GDM or insulin,⁸⁵ suggesting that metformin increased offspring weight (mean difference 0.26kg, 95% CI, 0.11–0.41), albeit without changes in height or BMI.⁸⁵

In addition to RCT data, our improved understanding of metformin effects, including its suppression of mitochondrial respiration, cellular growth inhibition, and gluconeogenic impact, suggest a possible impact on childhood development and support the need for further investigations regarding its use in pregnancy.^{86,87} Collectively, these findings support the need for long-term offspring follow-up in studies evaluating GDM treatment and suggest a need for discretion in the use of metformin during pregnancy.

Other agents

Myo-Inositol—Myo-inositol is a nutritional supplement also present in foods such as melons, citrus fruits, various vegetables, and legumes. Myo-inositol is hypothesized to function as an insulin sensitizer by acting through complex pathways that ultimately shift glucose intracellularly and then into fatty acid synthesis.^{88,89} An ongoing study (NCT02149992) is assessing myo-inositol as a treatment for GDM, despite negative previous results.⁹⁰ By contrast, a mixed but encouraging literature has evaluated myo-inositol supplementation for GDM prevention in women at elevated risk.^{91–93} myo-inositol (1,100 mg, in combination with *D*-chiro-inositol) failed to show benefit in an RCT including

240 pregnant women with a family history of diabetes,⁹⁴ while a pooled analysis of 3 RCTs, using 2,000 mg myo-inositol and including 595 women, demonstrated >60% reduced risk of GDM in gravidas at increased risk due to overweight, obesity, or parental history of type 2 diabetes mellitus.⁹⁵ Larger studies with varying doses of myo-inositol are needed to evaluate its potential role in pregnancy.

Acarbose—Acarbose, an alpha-glucosidase inhibitor, inhibits the conversion of polysaccharides into monosaccharides, thus reducing postprandial glucose excursions. Data regarding acarbose use in women with GDM are limited. Two initial reports, totaling 11 women, did not reveal any safety concerns.^{96,97} Another small study from Brazil randomized 70 women with GDM to insulin (n=27), glyburide (n=24), or acarbose (n=29), with similar fasting and postprandial glucose levels and average newborn weights across treatment groups.⁹⁸ However, glycemic goals were achieved more often with glyburide than acarbose (79% and 58%, respectively) and incidence of LGA infants were 3.7%, 25.0%, and 10.5% of the infants born to mothers treated with insulin, glyburide, and acarbose, respectively. None of these apparent differences were statistically significant due to heterogeneity and small sample size.⁹⁸

Future directions

Diabetes in pregnancy is a public health problem associated with both adverse pregnancy outcomes and long-term maternal and offspring risks. Diabetes prevalence is increasing in the setting of the obesity epidemic, increasing maternal age and, for GDM, a change in diagnostic criteria. While treatment of diabetes in pregnancy mitigates some of the perinatal risks, many questions about the management of diabetes in pregnancy remain unanswered. In women with pre-gestational diabetes, recent efforts have focused on improved glucose monitoring and insulin delivery. However, while these efforts have improved the rates of hypoglycemia and control of HbA1c levels, these benefits have not translated into improved pregnancy outcomes. In women with GDM, the optimal timing and method for diagnosis as well as our ability to individually predict responses to each of the available drug treatments, individually or in combination, are still undetermined. There is also evidence of significant metabolic and pathophysiologic heterogeneity in women with GDM, which may translate into variation in pregnancy outcomes.⁹⁹ Given the higher failure rate with metformin in women with GDM and the data on long-term childhood outcomes, further research is needed to address a potential role for glyburide to treat women with GDM. Overall, there is a need to: (1) determine the long-term offspring outcomes associated with different drug treatments, (2) explore novel treatment strategies, including therapies that do not focus on glycemic control, but rather on decreasing pre-pregnancy weight in overweight and obese women, and (3) design and evaluate individualized therapies that would match the mechanisms of diabetes drugs or drug combinations with the heterogeneous and distinct pathophysiologic mechanisms contributing to hyperglycemia and to adverse pregnancy outcomes. Individualized and gestation-specific strategies based on underlying maternal pathophysiology are needed to address the increasing frequency and complexity of diabetes in pregnancy.

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Figure 1: Longitudinal changes in insulin sensitivity.

Changes in insulin sensitivity in the pregravid, early pregnancy (12–14 weeks) and late pregnancy (34–36 weeks) period is shown in women with normal glucose tolerance based on hyperinsulinemic-euglycemic clamps. (mean $\pm$ SD; p-values are shown based on ANOVA).

Figure 2: Longitudinal changes in insulin response.

Changes in insulin response in the pregravid, early pregnancy (12–14 weeks) and late pregnancy (34–36 weeks) period is shown in women with normal glucose tolerance based on first phase insulin response to an intravenous glucose tolerance test (0–10 min). (mean $\pm$ SD; p-values are shown based on ANOVA).

Table 1.

Professional guidelines for diabetes pharmacologic management during pregnancy

	ACOG ^{1,2}	ADA ⁴	SMFM ⁵⁵	NICE UK ⁶⁴
Glucose targets for gestational and pregestational diabetes	Fasting <95mg/dL 1-hour postprandial <140 mg/dL <120 mg/dL	Fasting <95mg/dL 1-hour postprandial <140 mg/dL <120 mg/dL	Not specified	Fasting <95mg/dL 1-hour postprandial 2-hour postprandial <115 mg/dL
HbA1c targets for pregestational diabetes	<6%	6–6.5%; <6% if without significant hypoglycemia and <7% if necessary to prevent hypoglycemia	Not specified	If no hypoglycemia <6.5%
Drug therapy	Insulin preferred agent for diabetes in pregnancy	Insulin preferred agent for diabetes in pregnancy	Metformin reasonable and safe first-line alternative to insulin	Pregestational: - NPH first choice for long-acting insulin therapy GDM: - metformin first line - add insulin if blood glucose targets are not met