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Reviews

Pregnancy and Diabetes Management: Advances and Controversies

Kristin Castorino[1] and Lois Jovanovič[1*]

BACKGROUND: The treatment of diabetes in pregnancy has potentially far-reaching benefits for both pregnant women with diabetes and their children and may provide a cost-effective approach to the prevention of obesity, type 2 diabetes mellitus, and metabolic syndrome. Early and accurate diagnosis of diabetes in pregnancy is necessary for optimizing maternal and fetal outcomes.

CONTENT: Optimal control of diabetes in pregnancy requires achieving normoglycemia at all stages of a woman's pregnancy, including preconception and the postpartum period. In this review we focus on new universal guidelines for the screening and diagnosis of diabetes in pregnancy, including the 75-g oral glucose tolerance test, as well as the controversy surrounding the guidelines. We review the best diagnostic and treatment strategies for the pregestational and intrapartum periods, labor and delivery, and the postpartum period, and discuss management algorithms as well as the safety and efficacy of diabetic medications for use in pregnancy.

SUMMARY: Global guidelines for screening, diagnosis, and classification have been established, and offer the potential to stop the cycle of diabetes and obesity caused by hyperglycemia in pregnancy. Normoglycemia is the goal in all aspects of pregnancy and offers the benefits of decreased short-term and long-term complications of diabetes.

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Diabetes during pregnancy can greatly impact the health of both mother and child and should be managed with the utmost care. The ultimate goal in all types of diabetes in pregnancy is to create and maintain normoglycemia for both the mother and fetus. Normoglycemia throughout the day is the surest way to prevent complications of diabetes in pregnancy.

Diabetes during pregnancy can be divided into 2 subtypes: pregestational diabetes and gestational diabetes mellitus (GDM).[2] Pregestational diabetes includes both type 1 diabetes mellitus (T1DM) and type 2 diabetes mellitus (T2DM).

Pregestational Diabetes

Poorly controlled diabetes before conception can lead to major birth defects in 5%–10% of pregnancies, and spontaneous abortion in 15%–20% of pregnancies *(1)*. Optimizing maternal and fetal outcomes is best done with preconception planning for all types of diabetes in pregnancy. In pregestational diabetes, women who know they have T1DM or T2DM should achieve and sustain glycemic control before conception to minimize their risk of fetal malformation *(2–5)*. Organogenesis is essentially completed by 7 weeks gestation, often before the woman knows she is pregnant. Women with uncontrolled diabetes have a high prevalence of fetuses with congenital anomalies and spontaneous abortions *(6)*. A report from the California Diabetes and Pregnancy Project stated that major birth defects occur more frequently in offspring of mothers with T2DM compared to offspring in mothers with preexisting T1DM, likely because of a lack of preconception planning *(7)*. Pregestational counseling and preconception care can decrease the rate of fetal malformation and spontaneous abortion *(2)*.

A reliable indicator of glycemic control for healthcare professionals and patients alike is glycohemoglobin (Hb A_{1c}). Hb A_{1c} is formed from the nonenzymatic glycation of the N-terminal valine of the β-chain of hemoglobin in red blood cells, and is a reflection of the mean concentration of glucose in the blood. In pregnancy, during which there is increased turnover of red blood cells, Hb A_{1c} reflects the mean blood glucose in the prior 4–6 weeks *(8)*. Pregnant women show a decrease in Hb A_{1c} after 1 week of physician intervention,

[1] Sansum Diabetes Research Institute, Santa Barbara, CA.
* Address correspondence to this author at: Sansum Diabetes Research Institute, 2219 Bath St, Santa Barbara, CA 93110. Fax 805-682-3332; e-mail ljovanovic@sansum.org.
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[2] Nonstandard abbreviations: GDM, gestational diabetes mellitus; T1DM, type 1 diabetes mellitus; T2DM, type 2 diabetes mellitus; Hb A_{1c}, glycated hemoglobin; SMBG, self-monitored blood glucose; IADPSG, International Association of Diabetes and Pregnancy Study Groups; OGTT, oral glucose tolerance test; HAPO, Hyperglycemia and Adverse Pregnancy Outcomes; PCOS, polycystic ovarian syndrome; CGM, continuous glucose monitor; NPH, neutral protamine Hagedorn; RCT, randomized controlled trial.

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and with continued therapy Hb A_{1c} can decrease at a rate of 0.5% per week *(9)*. Point-of-care Hb A_{1c} determination is an integral tool in assessing a woman's glycemic control before and during pregnancy, especially during the critical period of fetal organogenesis *(10)*. Hb A_{1c} measurements and frequent self-monitored blood glucose (SMBG) should be used before conception to achieve control *(11)*. Women should practice reliable birth control measures until their Hb A_{1c} is <6% and their SMBG concentrations are at the goal. Observations have revealed that normalizing blood glucose concentrations in the pregestational period as well as the first trimester can reduce the risk of congenital anomalies and spontaneous abortions in women with diabetes to nearly that of women without diabetes *(12)*.

Many women with T1DM are well aware of these risks and are aggressive in their preconception planning and management of their diabetes. However, there is a steadily growing population with undiagnosed T2DM who are unaware of their risk. The obesity epidemic facing the world has had a large impact on the population of women of childbearing age. The rates of both T2DM and GDM are rising, partially because of obesity and metabolic syndrome *(13)*. Women who do not know they have T2DM cannot prevent hyperglycemia in the first weeks of pregnancy, which is the critical period of fetal organogenesis. Most pregnant women do not see their obstetrician until after 7 weeks gestation. For this reason, all women of childbearing age who have diabetes or are at risk for T2DM should use reliable birth control and be educated on the necessity of planning for a pregnancy. Risk factors for T2DM are nearly identical to GDM and include:

- Obesity
- Acanthosis nigricans
- Hypertension or metabolic syndrome
- Previous GDM or delivery of an infant weighing more than 4000 g
- Polycystic ovarian syndrome
- Parent or sibling with T2DM
- High-risk race/ethnicity (Hispanic, black, Native American)
- Mother's own birth weight >4000 g

A joint population study by the CDC, American Diabetes Association, and NIH led to the estimate that in 2007, 6 million people in the US had undiagnosed T2DM, and 1 in 10 women older than 20 years had T2DM. According to a CDC fact sheet, approximately 2 million adolescents have prediabetes *(13)*. Primary care providers will need to double their efforts to educate women of childbearing age regarding their risks, identify those with diabetes or risk factors for diabetes, and promote the appropriate birth control method.

Table 1. Threshold values of the 75-g OGTT for the diagnosis of GDM.[a]

Time of blood draw	Serum glucose concentration
Fasting glucose	≥92 mg/dL (5.1 mmol/L)
1 h	≥180 mg/dL (10.0 mmol/L)
2 h	≥153 mg/dL (8.5 mmol/L)

[a] One or more plasma glucose concentrations must be met or exceeded for a positive diagnosis of GDM.

Screening and Diagnosis during Pregnancy

Pregnant women with T1DM, T2DM, and GDM all have a goal during pregnancy: maintenance of normoglycemia. Women who develop a transient abnormality of glucose tolerance during pregnancy, or who develop GDM, must be identified efficiently and reliably. There has been great debate over the appropriate universal guidelines for the screening and diagnosis of GDM. In 2010, the International Association of Diabetes and Pregnancy Study Groups (IADPSG), an international consensus group with multiple obstetrical, pediatric, diabetic, and epidemiologic representatives, agreed on universal screening and diagnostic guidelines as well as new terminology *(14)*. It is likely that the American Diabetes Association will embrace these international guidelines in 2011.

The IADPSG guidelines for the diagnosis of GDM recommend a 1-step 75-g oral glucose tolerance test (OGTT) and are based on data derived from the Hyperglycemia and Adverse Pregnancy Outcomes (HAPO) study *(15)*. If the patient has 1 or more values that exceed threshold, she is identified as having GDM. Threshold values are listed in Table 1.

All pregnant women should be screened for GDM *(16)*. Screening for GDM is generally performed at around 28 weeks gestation. However, with the old 2-step diagnostic process, the diagnosis and treatment of GDM is often delayed until 30–34 weeks gestation, well after the effects of hyperglycemia have begun to cause macrosomia *(17)*. For this reason, the IADPSG recommends screening at-risk individuals during their first prenatal visit. Risk factors for GDM are similar to those for T2DM and also include overweight or obese state, family history of diabetes mellitus, history of abnormal glucose metabolism, history of poor obstetric outcome, history of delivery of an infant with a birth weight >4000 g, history of patient's own birth

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weight >4000 g, history of polycystic ovary syndrome (PCOS), and Latin American, Mexican American, non-Latin black, Asian American, Native American, or Pacific Islander ethnicity *(7, 16)*.

The IADPSG recommends screening all women at risk for GDM at their initial prenatal visit, and again at 24–28 weeks gestation if the first screening test was normal. Only women with no risk of GDM should wait to be screened at 24–28 weeks gestation *(14)*.

The term "overt diabetes" was coined to describe women who likely had preexisting diabetes, or early T1DM. A diagnosis of overt diabetes can be made in women who meet any of the following criteria at their initial prenatal visit:

- Fasting plasma glucose ≥126 mg/dL (7.0 mmol/L), or
- Hb A_{1c} ≥6.5% measured by using a standardized assay, or
- Random plasma glucose ≥200 mg/dL (11.1 mmol/L) that is confirmed by increased fasting plasma glucose or Hb A_{1c}

The rationale for developing the diagnostic term overt diabetes was to differentiate women who have diabetes that has not been diagnosed before conception. It is important to distinguish this subpopulation of women because they will likely require insulin during pregnancy and will need thoughtful postpartum care. Furthermore, approximately 10% of women formerly classified as GDM have circulating islet-cell antibodies. These women may have a "dormant" form of T1DM *(18)*. Specific HLA alleles (DR3 or DR4) appear to predispose women to the development of T1DM after delivery, as does the presence of islet-cell antibodies *(19)*. Some specialists argue that if 1 in 10 women may develop islet-cell antibodies, universal screening is warranted in this subpopulation. Critics contend that this strategy is not cost effective and will not alter the outcome because there is no cure for T1DM, even with early diagnosis. Alternatively, women who are identified through screening could possibly serve as future research participants for trials focused on primary prevention of T1DM.

Arguments against the new 75-g OGTT include the concern that the new universal guidelines will identify many more women as having GDM, and that these women will be subjected to increased intervention during their pregnancy, such as induction of labor or cesarean delivery. Evidence from the HAPO study suggests that the prevalence of diabetes is actually closer to 18% of the general population. There is a growing body of evidence demonstrating the deleterious long-term effects in infants of diabetic mothers, and the early and accurate identification of women at risk offers the opportunity for prevention of long-term sequelae in these children. In fact, according to some experts the new 75-g OGTT still lacks diagnostic sensitivity and will lead to underdiagnosis of diabetes in women *(20, 21)*. These experts have also reported that although changing to a 1-step diagnostic test is an improvement, the threshold values for a positive test are too high and that values should have been set at 1.5 times the estimated odds of outcomes in the HAPO trial, not 1.75. Results of multiple studies have shown that diagnosis and therapy based on normoglycemic targets is associated with decreased neonatal and obstetric morbidity and mortality compared to that of the nondiabetic population *(22–25)*.

Proponents of the new screening and diagnostic guidelines have argued that "glucose-mediated macrosomia" is a growing epidemic that may cause permanent metabolic derangement in the infant of the diabetic mother, and have cited the increasing numbers of reported studies in which the offspring of diabetic mothers were evaluated *(26–28)*. The central theory is that any increase of blood glucose concentrations above reference intervals can be detrimental to the fetus because the fetus is developing "blueprints" for its metabolic function, and high glucose concentrations errantly set a foundation for the development of obesity, T2DM, and metabolic syndrome *(29)*. Hyperglycemia in pregnancy, even in the prediabetic range, is associated with neonatal macrosomia and increased C-peptide concentrations *(30)*. Neonatal exposure to a hyperglycemic environment increases the risk of developing obesity and metabolic syndrome in childhood *(27, 28)*. Women with GDM have a 60% probability of developing T2DM later in their lifetime, with an annual risk of approximately 10% per year *(31)*. The screening and diagnostic test developed by O'Sullivan and Mahan *(31)* was designed to identify women who had at least a 10% risk per year of developing T2DM; however, data from these screening guidelines, which are followed by the American College of Obstetrics and Gynecology, have show that women who fail the glucose screen but pass the 3-h OGTT have a risk of developing T2DM nearly equal to that of women with GDM *(32)*. All these compelling reasons indicate that early and accurate identification of pregnant women with GDM will enable physicians to modify dietary recommendations to optimize nutrition in this population and prevent short- and long-term complications. In diabetic pregnant women who underwent evaluation by serial ultrasound examination, abdominal circumference was accelerated in those whose fetus was large for gestational age compared to controls *(33)*. With the growing crisis of obesity and T2DM in our adolescent and adult populations, the implications of "adding fuel to the fire" in the form of allowing for hyperglycemia in pregnancy has major public health ramifications.

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The concern about increased intervention in pregnant women with diabetes is a valid one. Obstetricians are charged with monitoring and intervening to prevent fetal and obstetrical complications. Examples include the increased rates of preterm and cesarean section delivery, shoulder dystocia, neonatal jaundice, and hypoglycemia. However, much of the perinatal and neonatal morbidity and mortality data were obtained from women with uncontrolled diabetes *(34, 35)*. Routine induction of labor and cesarean delivery in women with diabetes in pregnancy is considered an antiquated practice. Our recommendation is that spontaneous delivery at term may be attempted in women with diabetes who have maintained excellent glycemic control, defined by Hb A_{1c} ≤5.5%, and finger-stick blood glucose measurements at designated goals, and who have no other complications.

Another limitation to the new IADPSG guidelines is that more women will need individualized care and more frequent office visits. On the other hand, more frequent office visits may be advantageous to all women with diabetes during pregnancy because these visits provide an opportunity for education and intervention, and may lead to decreases in long-term complications of diabetes. Accurate diagnosis of diabetes in pregnant women offers the possibility to decrease the prevalence of obesity, T2DM, and metabolic syndrome in future generations.

Intrapartum Management, Diet, and Pharmaceutical Therapy

For optimal control of diabetes in pregnancy, experts advocate that obstetricians refer their patients early in pregnancy to a clinic specializing in diabetes during pregnancy and that pregnant women visit these clinics frequently. Excellent control of blood glucose is associated with a decrease in maternal and neonatal complications *(36, 37)*. An example of a clinical road map that is used in a diabetes-in -pregnancy clinic located in Santa Barbara, California, is shown in Fig. 1.

The cornerstones of excellent glycemic control are patient SMBG and weekly point-of-care Hb A_{1c} determination. The use of weekly Hb A_{1c} measurement in conjunction with frequent SMBG is a powerful tool to safely and aggressively adjust insulin concentrations and prevent hypoglycemia *(9)*.

Glycemic control can be achieved by frequent SMBG. Experts recommend that finger-stick blood glucose measurement be performed 6–8 times per day, specifically, first thing in the morning (fasting), premeal, 1 h after the start of each meal (postprandial glucose), and at bedtime. In pregnancy, postprandial serum glucose peaks at approximately 1 h after a meal *(38)*. Fasting and premeal blood glucose should be <90 mg/dL (5.0 mmol/L) and postprandial glucose should be <120 mg/dL (6.7 mmol/L). Educating patients on the definition of normoglycemia throughout daily routines and meals is imperative. Healthcare providers should encourage patients to modify the carbohydrate content in their meal to meet these goals. Patients soon learn that SMBG is a powerful and empowering tool for patient-initiated education and dietary modification as appropriate for each individual woman's needs. When women are given the definition of normoglycemia, they can often self-educate and modify their own diets accordingly. In GDM, frequent SMBG measurements are an adequate method to enable pregnant women to safely achieve normoglycemia *(39)*. Despite some assumptions, most pregnant women are dedicated to achieving normoglycemia and are more than willing to perform finger-stick blood glucose measurements 6–8 times per day. Pregnant women with T1DM will even check their blood glucose 10–15 times per day.

If pregnant women are unable to achieve normoglycemia or are experiencing severe hypoglycemia, SMBG may be combined with a continuous glucose monitor (CGM). CGM has been demonstrated to be safe in pregnancy *(39)*. In the case of T1DM, use of CGM is associated with improved glycemic control. Murphy has demonstrated that a short use of CGM in the third trimester is associated with lower infant birth weight and reduced risk of macrosomia *(40)*. Because there is little evidence on the appropriate monitoring regimen in T2DM, the choice of frequency and modality of monitoring should be based on attaining normoglycemia *(41)*.

The use of medications, most often insulin, is also important for achieving normoglycemia. Women with T1DM require an appropriate insulin regimen with frequent modifications throughout pregnancy. Insulin is also considered the gold standard in treatment of pregnant women with T2DM, overt diabetes, and GDM who have failed diet and lifestyle modification. The choices and regimens of injectable hypoglycemic medications are similar in all types of diabetes in pregnancy. Optimal glycemic control is achieved with a combination of long-acting and rapid-acting insulin, or basal-bolus dosing, with doses administered in a way that mirrors normal physiologic insulin concentrations. The types of insulin demonstrated to be safe and effective in pregnancy are listed in Table 2 *(41–46)*. Both regular insulin and glargine are inappropriate for use during pregnancy. Regular insulin cannot control the postprandial spike in blood glucose adequately unless it is administered 60–90 min before the onset of the meal *(41)*.

Available data are very limited regarding the safety and efficacy of glargine, with only 1 reported prospec-

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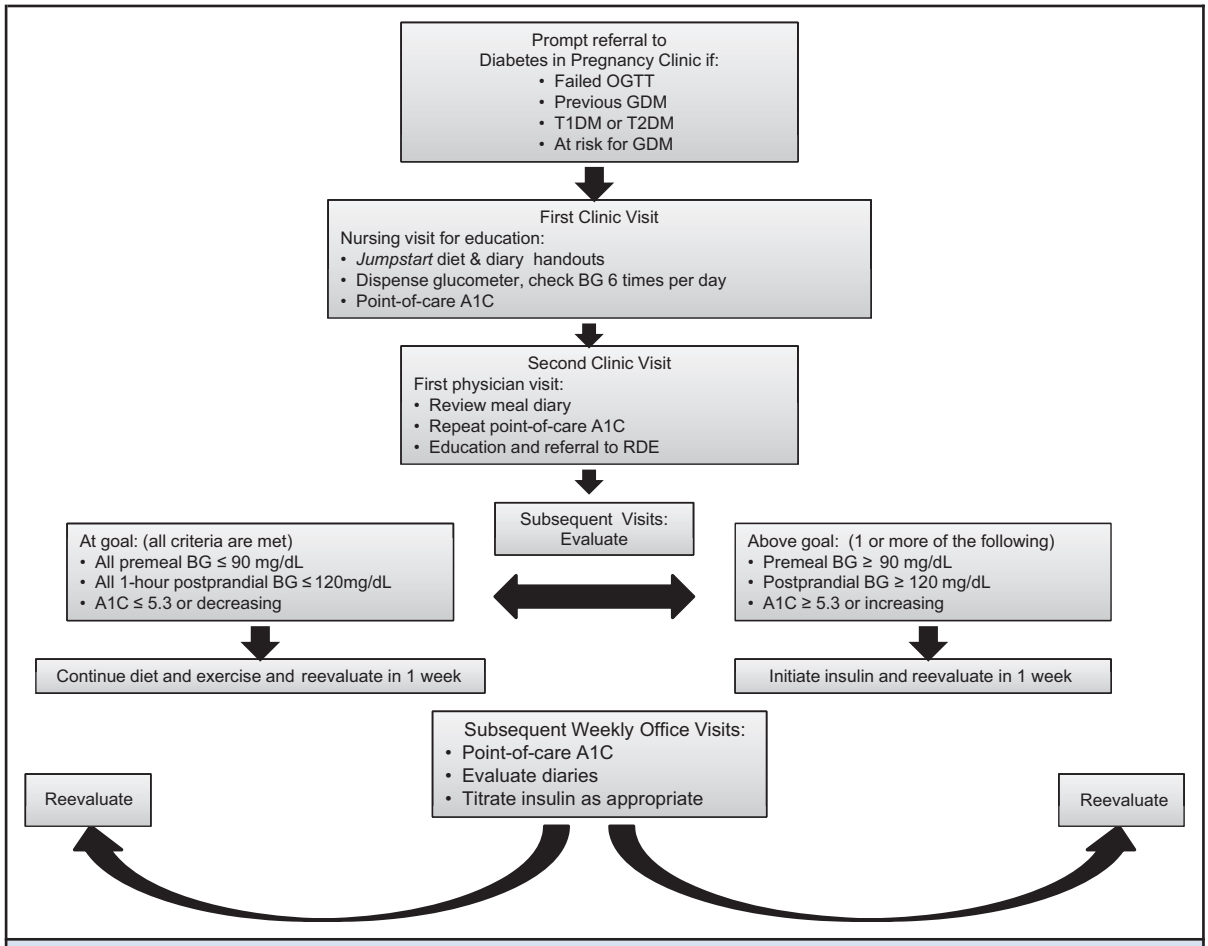

Fig. 1. Road map for high-quality and efficient care of pregnant women with diabetes in a pregnancy clinic. RDE, registered dietician; AIC, Hb A_{1c}.

tive randomized controlled trial (RCT) *(47, 48)*. A review of the available efficacy data suggests that glargine is nearly equivalent to neutral protamine Hagedorn (NPH) insulin. However, close examination of the primary and secondary outcome measures in these studies reveals that glargine does not adequately prevent the complications of diabetes in pregnancy *(49, 50)*.

In another study *(51)* investigators compared insulin and insulin-like growth factor 1 receptor–binding properties and metabolic/mitogenic potencies

Table 2. Insulins shown to be safe in pregnancy.

Insulin name	Type	Onset[a]	Peak effect[a]	Duration[a]	Recommended dosing intervals
Insulin aspart	Rapid acting (bolus)	15 min	60 min	2 h	At the start of each meal
Insulin lispro	Rapid acting (bolus)	15 min	60 min	2 h	At the start of each meal
Regular insulin	Intermediate acting	60 min	2–4 h	6 h	60–90 min before each meal
Insulin NPH	Intermediate acting (basal)	2 h	4–6 h	8 h	Every 8 h
Insulin detemir	Long acting (basal)	2 h	—	12 h	Every 12 h

[a] Clinical pharmacodynamics as observed by L.J. and as documented by Pettitt et al. *(42)*, Wyatt et al. *(43)*, Jovanovič et al. *(52)*, Wollitzer et al. *(53)*, and Peterson *(65)*.

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Table 3. Initial insulin-dosing guidelines during pregnancy and the postpartum period.[a]

Weeks gestation	Constant to derive TDD in kilograms	Constant to derive TDD in pounds	Equation to derive insulin TDD[b]
First trimester	0.7	0.30	TDD = (0.7)(weight in kg), or (0.30)(weight in lbs)
Second trimester	0.8	0.35	TDD = (0.8)(weight in kg), or (0.35)(weight in lbs)
Third trimester	0.9	0.40	TDD = (0.9)(weight in kg), or (0.40)(weight in lbs)
Full term	1.0	0.45	TDD = (1.0)(weight in kg), or (0.45)(weight in lbs)
Postpartum (and lactation)[c]	0.55	0.25	TDD = (0.55)(weight in kg), or (0.25)(weight in lbs)

[a] This table is derived from data originally published by Jovanovič et al. *(52)*, with permission, which demonstrated the linear increase in insulin requirement with increasing gestational age.
[b] The total daily dose of insulin (TDD) should be split, so that 50% of TDI is used for basal insulin, and 50% is used for pre-meal boluses of rapid insulin.
[c] Night time basal insulin rate should be decreased by 50% in lactating women to prevent severe hypoglycemia.

of aspart, lispro, glargine, detemir, human insulin, and reference insulin analogs. Glargine had an increased insulin-like growth factor 1–receptor affinity and mitogenic potency compared to human insulin. In contrast, detemir had reduced receptor affinity and metabolic and mitogenic potency but did not change the balance between mitogenic and metabolic potencies.

For these reasons, glargine should not be used in pregnant women until it has clearly been demonstrated to be safe and effective in large RCTs. Insulin detemir is currently undergoing a large multinational RCT to investigate its use in pregnant women.

Both insulin requirements and insulin resistance increase with the gestational age of the neonate, and therefore the total daily insulin requirement increases in a linear fashion as the pregnancy progresses *(52)*. The calculation of initial insulin dose should be based on gestational age. A simplified version of initial insulin-dosing guidelines is illustrated in Table 3. These guidelines can be used for all women who require insulin during pregnancy, regardless of diabetes type. The initial insulin-dosing guidelines are also appropriate for patients on a low carbohydrate diet; women consuming meals containing more than 40% carbohydrates will require more insulin. Once the initial insulin dose has been prescribed, adjustments in the doses should be made on the basis of meal and blood glucose diaries in conjunction with the trend in the results of point-of-care Hb A_{1c} measurements.

Insulin pump use during pregnancy in women with T1DM is safe and effective, and is equivalent to NPH administered every 8 h *(53)*. Insulin aspart and lispro are considered the standard of care for use in insulin pumps. Regular insulin is still prescribed for use in pumps, though aspart and lispro are more commonly used owing to their more rapid action. Glulisine is approved for use in insulin pumps, but has not been studied in women during pregnancy.

The off-label use of oral hypoglycemic agents is likely to increase. All hypoglycemic agents used in pregnancy have not been cleared for such use by the FDA and may not be safe in pregnancy or enable pregnant women to adequately achieve normoglycemia. Most medications used to control blood glucose in diabetes are listed in Table 4.

The most common oral hypoglycemic agents used in pregnancy include metformin and glyburide. These agents have undergone limited studies in GDM but to date there have been no studies in pregnant women with T2DM *(54, 55)*.

The use of glyburide is becoming more prevalent with the increasing number of women with diabetes. Results of a randomized study of glyburide vs insulin that included 404 women with mild GDM showed no differences in the frequency of maternal and fetal adverse outcomes. This study, however, was criticized for not reaching normoglycemic targets and for lack of sufficient cord blood samples to accurately evaluate safety *(56, 57)*. Another study of 197 pregnant women, 73 of whom received glyburide, showed satisfactory control with glyburide alone. However, the macrosomia rate was 19%, which is comparable to an untreated control population *(58)*. If glyburide is used during pregnancy, prescribers should be aware that glyburide has been associated with prolonged hypoglycemia in neonates. If used during pregnancy, glyburide should be stopped 2 weeks before delivery and should not be used during lactation.

Metformin is frequently used in prediabetes, T2DM, metabolic syndrome, and PCOS. It is often used in women of childbearing age, and many women become pregnant while being treated with metformin. Women with PCOS who start metformin treatment should be encouraged to use birth control, because metformin will often lead to ovulation. Metformin use in T2DM and pregestational diabetes has been associated with good outcomes *(59, 60)*. It is widely known

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Table 4. Safety and evidence for use of diabetes medications during pregnancy and lactation.[a]

Class and mechanism of action	Medication (brand name)	Pregnancy class	Lactation	Fetal exposure	LOE and grade of recommendation[b]
Insulin	Insulin aspart (Novalog®)	B	Safe	Unlikely	LOE 1, grade A
	Insulin lispro (Humalog®)	B	Safe	Unlikely	LOE 1, grade A
	Insulin glulisine (Apidra®)	C	Probably safe	Unlikely	LOE 4, grade D
	Insulin NPH (Humulin N®, Novolin N®)	B	Safe	Unlikely	LOE 2, grade A
	Insulin detemir (Levemir®)	B	Safe	Unlikely	LOE 1, grade A
	Insulin glargine (Lantus®)	C	Probably safe	Unlikely	LOE 2, grade B
Secretagogues: increase insulin secretion	Glipizide (Glucotrol®)	C	Unsafe	Crosses placenta	LOE 4, grade D
	Glyburide (DiaBeta®, Micronase®)	B	Unsafe	Crosses placenta	LOE 2, grade B
	Glimepiride (Amaryl®)	C	Unsafe	Crosses placenta	LOE 4, grade D
	Repaglinide (Prandin®)	C	Unsafe	Unknown	LOE 4, grade D
	Nateglinide (Starlix)	C	Probably safe	Unknown	LOE 4, grade D
Biguanides: reduce hepatic glucose production	Metformin (Glucophage®)	B	Unsafe	Crosses placenta	LOE 1, grade A
Thiazolidinediones: enhance insulin sensitivity	Rosiglitazone (Avandia®)	C	Safety unknown	Crosses placenta	LOE 3, grade C
	Pioglitazone (Actos®)	C	Safety unknown	Unknown	LOE 3, grade C
					Studies relating to PCOS
α-Glucosidase inhibitors: decrease carbohydrate absorption in gut	Acarbose (Precose®)	B	Safety unknown	Unlikely	LOE 3, grade C
	Miglitol (Glyset®)	B	Safety unknown	Unlikely	LOE 4, grade D
Incretin mimetic: activates GLP-1,[c] (stimulate insulin release, inhibit postprandial glucagon release, slow absorption, increase satiety)	Exenatide (Byetta®)	C	Safety unknown	Unlikely	LOE 4, grade D
	Liraglutide (Victoza®)	C	Unsafe	Unknown	LOE 4, grade D
Amylin mimetic: regulate glucose influx by suppressing glucagon and slowing gastric emptying	Pramlintide (Symlin®)	C	Safety unknown	Unlikely	LOE 4, grade D
DPP4 I: slows inactivation of incretins and GLP1	Sitagliptin (Januvia®)	B	Safety unknown	Unknown	LOE 4, grade D

[a] Data from the table are a composite of FDA drug-prescribing guidelines from the online *Physician's Desk Reference (76)* as well as an unpublished PubMed *(77)* literature review of clinical trials that was conducted by the authors in August 2010.
[b] Levels of evidence (LOE) represent the level of scientific substantiation in evidence-based medicine and contribute to the grade of recommendation.
[c] GLP1, glucagon-like-peptide 1; DDP4 I, dipeptidyl peptidase 4 inhibitor.

that metformin crosses the placenta and is unsafe during lactation. There are no long-term safety data on the effects of neonatal metformin exposure. We should expect to see more data as children exposed to metformin in utero and as neonates mature.

Metformin and glyburide do not adequately control the peak postprandial glucose. Clinicians may need to consider alternative or additional medical therapy to maintain normoglycemia at all times of the day in women who are being treated with these drugs.

Pioglitazone has been used during pregnancy for the treatment of PCOS in a retrospective cohort of 9 women, 7 of whom conceived. Four of these women had successful pregnancies, and 3 suffered miscarriages

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in the first trimester *(61)*. The use of pioglitazone has not been studied in diabetes in pregnancy.

Other agents such as incretin and amylin mimetics are not used during pregnancy. Rosiglitazone has been shown to cross the human placenta at 10–12 weeks gestation *(62)*.

Choice of the appropriate medical therapy, in conjunction with an appropriate diet, should be individualized for each patient *(63)*. The goals of medical therapy include achieving normoglycemia, preventing postprandial glucose excursions, and optimizing compliance *(64)*. Point-of-care Hb A_{1c} measurement is extremely useful, in conjunction with patient diaries, to assist patients to achieve excellent glycemic control and prevent the complications of diabetes in pregnancy. Patients should be seen weekly to assess safety and compliance.

Throughout pregnancy, women should be counseled on healthy low-carbohydrate dietary choices, appropriate weight gain, and exercise *(65)*. Pregnant women with diabetes should be referred to a registered dietician specializing in pregnancy.

Women with diabetes should be advised to modify their diet to prevent large increases in blood glucose. Sugars and simple carbohydrates should be eliminated from women's diets because they have limited nutritional value and a high glycemic index. The ideal carbohydrate sources for pregnant women with diabetes include fresh vegetables and some fruits. Dairy products may be used sparingly. Many women find that replacing bread, rice, pasta, tortillas or potatoes with vegetables such as spinach, green beans, cucumber, asparagus, and jícama will prevent postprandial hyperglycemia. The classic food pyramid model, which recommends that carbohydrates such as bread, cereal, rice, and pasta comprise the majority of the meal, is now antiquated. It has been replaced with a new meal-planning target that emphasizes more vegetables and whole grains *(66)*. The most powerful means for determining which foods do not cause hyperglycemia and which need to be eliminated is the patient's self-monitoring of postprandial blood glucose.

Appropriate weight gain during pregnancy should be adjusted according to each diabetic pregnant woman's prepregnancy body mass index. More evidence is being published that supports a minimal weight gain for pregnant women who are obese, which is a large portion of the GDM and T2DM population. Women should be encouraged to attempt to meet their specific weight goal while eating a balanced diet and participating in regular exercise *(67)*. The topic of weight gain in pregnant women who are obese is controversial, and some experts believe that in this special population it may be safe to gain little or no weight during pregnancy *(68)*. Further studies are needed to make conclusive recommendations.

Physical activity is an integral component of a healthy pregnancy. Pregnant women should be encouraged to participate in daily activity if they have no contraindications *(63)*. Cardiovascular exercise such as walking, if done after meals, is a means to control the postprandial increase in glucose, though it has not been studied in the setting of diabetes in pregnancy *(69)*.

Women should receive counseling for diabetes management during labor, delivery, and the immediate postpartum period. The goal during labor and delivery is also to maintain normoglycemia in the safest way possible. Increased blood glucose 4–6 h before delivery is associated with transient neonatal hypoglycemia *(70)*. Women with T1DM and insulin-dependent diabetes should be managed by an endocrinologist or diabetes specialist during labor and delivery and should create a plan for glycemic control during the third trimester. Most hospitals use protocols to achieve normoglycemia and avoid dangerous fluctuations in blood glucose. Women with GDM controlled with insulin should be instructed to stop insulin use once labor starts, and then reevaluate their glycemic control with frequent SMBG testing in the postpartum period.

Postpartum Care

Glyburide and metformin are secreted into breast milk and should not be used during lactation in women with T2DM. Instead, insulin should be continued. Breastfeeding causes a decrease in insulin requirement due to the lactose in breast milk *(71, 72)*. This can be beneficial, especially in women with T2DM. Breastfeeding can cause life-threatening hypoglycemia for lactating women on insulin, especially those with T1DM. Women who are both breastfeeding and on a form of basal insulin must either decrease their basal rate during lactation or eat a carbohydrate-containing snack before breastfeeding. Women should be well educated on this risk of hypoglycemia during lactation so they can create a breastfeeding environment that is safe for both mother and infant.

Women with a personal or family history of T1DM who may be carriers of HLA-DR3 and -DR4 should be counseled on the medical evidence suggesting that infant formula derived from cow's milk may be associated with T1DM by stimulating antibody formation to the β-cells *(73, 74)*. Some experts recommend that bovine-based infant formula be completely avoided during the first year of life in these cases. If formula is required, soy-based products should be used.

Summary

Diabetes during pregnancy is the most common complication of pregnancy. Pregestational planning is im-

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perative for all women with preexisting diabetes. Pregnant women who have no known diabetes but who have any risk factors for GDM should be screened with the 75-g OGTT at the initial prenatal visit, and all women should be screened by 28 weeks gestation. Clinicians should be prepared for an increase in the number of women identified with diabetes during pregnancy and develop a thorough and efficient model for outpatient management. Patient education is the foundation for successful management of diabetes during pregnancy. The goal of therapy will continue to be normoglycemia before, during, and after all pregnancies complicated by diabetes.

The world of diabetes is rapidly evolving, with many new tools on the horizon for diagnosis, monitoring, and treatment. These tools will make the management of diabetes in pregnancy easier and possibly safer. Some promising developments for diabetes in pregnancy include weekly point-of-care Hb A_{1c} testing, the routine use of CGMs in T1DM, and the implementation of universal screening guidelines. With these potentially cost-effective advances in diabetes during pregnancy comes the hope of preventing macrosomia and decreasing the prevalence of childhood obesity and T2DM in the offspring of diabetic mothers *(75)*.

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