

Insulin Use in Pregnancy: An Update

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■ **IN BRIEF** Insulin remains the standard of care for the treatment of type 1 diabetes, type 2 diabetes, and uncontrolled gestational diabetes. Tight control maintained in the first trimester and throughout pregnancy plays a vital role in decreasing poor fetal outcomes, including structural anomalies, macrosomia, hypoglycemia of the newborn, adolescent and adult obesity, and diabetes. Understanding new insulin formulations and strengths is important in assessing risks, since no data on their use in human pregnancy exist.

As of June 2015 in the United States, 2.7% of women who are 18–44 years of age have a diagnosis of type 1 or type 2 diabetes (1). About 5% of all diagnosed diabetes is type 1 diabetes, and 90–95% is type 2 diabetes. It is projected that, by 2050, one in three people will have some type of diabetes. An estimated 5,000 new cases of type 2 diabetes will be diagnosed annually in American children <20 years of age (2). Gestational diabetes mellitus (GDM) could affect up to 8.7% of all pregnancies in the United States (3). The Centers for Disease Control and Prevention reports that these numbers are still on the rise (2). As the age of diabetes diagnosis decreases in U.S. youth, the prevalence of pregestational diabetes is likely to increase in the pregnant population.

Maternal diabetes causes complications in the embryo/fetus that start in the uterus, are present immediately after birth, and could potentially last a lifetime. Women with type 1 diabetes or type 2 diabetes diagnosed before or during the first trimester of pregnancy are at the greatest risk for fetal congenital anomalies and spontaneous abortions. This risk is associated with

both frequent and severe hyperglycemia before conception and during organogenesis (5–8 weeks after the last menstrual period) (4,5). The more severe the maternal hyperglycemia, the greater is the risk for fetal abnormalities. Structural anomalies are a common result, with ~37% of these affecting the cardiovascular system, 20% affecting the central nervous system, and 14% affecting the urogenital system (6). GDM develops and is diagnosed later in pregnancy, at 24–28 weeks' gestation, when impaired glucose tolerance is detectable. Therefore, women with GDM are most likely euglycemic during organogenesis and have a decreased risk for structural anomalies.

However, glucose control remains paramount in later stages of pregnancy for women diagnosed with GDM, type 1 diabetes, or type 2 diabetes. Hyperglycemia after organogenesis is a risk factor for large-for-gestational-age babies, macrosomic babies (>4,500 g), shoulder dystocia (birth injury), neonatal hypoglycemia, hyperbilirubinemia, and admission to the neonatal intensive care unit. Maternal outcomes include a higher risk for preeclamp-

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TABLE 1. Glycemic Targets in Pregnancy by National Guideline

	A1C (%)	Fasting Blood Glucose (mg/dL)	1-hour Post-Meal Glucose (mg/dL)	2-hour Post-Meal Glucose (mg/dL)
ADA: gestational diabetes (9)	<6	≤95	≤140	≤120
ADA: type 1 and type 2 diabetes (9)	<6	60–99 (includes bedtime and overnight)		100–129 (peak postprandial)
ACOG: gestational diabetes (10)	<6	≤95	≤140	≤120
ACOG: pre-gestational diabetes (11)	<6	60–99 (includes bedtime and overnight)	≤140	≤120
AACE/ACE (12)	<6.5	≤95	≤140	≤120
CDAPP Sweet Success Program (13)	<6	60–89		100–129 (peak postprandial)

sia, primary cesarean section, and preterm labor (7). Finally, long-term effects of maternal hyperglycemia on the child include a higher risk of childhood obesity and adult diabetes (8). Tight glycemic control before conception and throughout pregnancy can decrease the prevalence of these outcomes in women with any type of diabetes (6–8).

The American College of Obstetricians and Gynecologists (ACOG), the American Diabetes Association (ADA), and the American Association of Clinical Endocrinologists/American College of Endocrinology (AACE/ACE) are in agreement about glycemic targets during pregnancy. However, some practitioners choose stricter glycemic targets, as seen in the California Diabetes and Pregnancy Program (CDAPP) Sweet Success program (Table 1) (9–13). Tighter control, if achieved safely, has better outcomes (7).

Nonpregnant patients with diabetes have a multitude of choices for achieving tight glucose control. The past 2 years have seen an explosion in new insulins, novel delivery systems, and additional concentrations of existing insulins. The likelihood that a patient will become pregnant while taking these newer insulins will be ever increasing; understanding these insulins is therefore crucial. Additional pharmacokinetic and pharmacodynamic studies of these insulins in pregnancy are needed.

Differences in these insulins may affect a clinician's ability to make aggressive dosing adjustments. Additionally, there are differences in lengths of storage time, and this information should be given to patients.

Short-Acting Insulin and Rapid-Acting Insulin Analogs

Regular (U-100) insulin is identical to human insulin and is synthesized in *Escherichia coli* bacteria. It is used as a mealtime insulin to cover carbohydrate loads. Its time to onset of action is ~30 minutes but can range from 10–75 minutes. The maximum effect is in 3 hours (range 20 minutes to 7 hours), and the effect terminates at ~8 hours. U-100 vials can stay at room temperature for 31 days (14).

Regular (U-500) insulin is identical to human insulin but more concentrated than the U-100 formulation, and its kinetics differ from U-100. Onset is ~30 minutes, but duration of action can be up to 24 hours. Severe hypoglycemia can occur 24 hours after the initial dose, although case reports suggest that this is less of a concern in pregnancy (15). Some patients will require two to three injections daily as their solitary insulin regimen. A U-500 vial is good for 40 days at room temperature while in use (16). Dosing errors do occur because it is only available in a vial to be drawn up in U-100 insulin

syringes. Therefore, careful patient education is necessary.

Insulin aspart is an analog to human insulin produced in *Saccharomyces cerevisiae*, a type of yeast. This could potentially cause a site reaction in patients who are allergic to yeast. Aspart should be taken 5–10 minutes before meals. It can be used as injections or in an insulin pump. Its time to peak concentration is 40–50 minutes, and its duration of action is 3–5 hours. Pens, penfills, and vials are good for 28 days at room temperature while in use (17). Insulin aspart is associated with less hypoglycemia than regular insulin (18).

Insulin lispro (U-100 and U-200) is an analog produced in *E. coli*. Its onset of action is 10–15 minutes, its peak is in 30–90 minutes, and its duration of action is 3–4 hours. Injections in the abdomen are preferred to attain the highest absorption and shortest duration of action. It can be used in insulin pumps or as multiple daily injections. The U-100 and U-200 formulations are bioequivalent, having the same pharmacokinetics. Insulin lispro U-200 is only available in pens to avoid administration errors. Pens, penfills, and vials are good for 28 days at room temperature while in use (19).

Insulin glulisine is a recombinant insulin produced using *E. coli*. Its onset of action is in 10–15 minutes, its peak is in 55 minutes, and its

TABLE 2. Insulin Regimens for GDM and Pregnancy in Patients With Type 2 Diabetes

Regimen	Dose
Weight-based dosing (10)	0.7–1 units/kg daily in divided doses (no additional recommendations are provided)
Trimester + weight-based dosing	1st trimester TDD: 0.7 units/kg 2nd trimester TDD: 0.8 units/kg 3rd trimester TDD: 0.9–1 units/kg 2/3 of TDD given in the morning: <ul style="list-style-type: none"> • 1/3 insulin aspart or lispro with breakfast • 2/3 NPH 1/3 of TDD given in the evening: <ul style="list-style-type: none"> • 1/2 insulin aspart or lispro with dinner • 1/2 NPH before bed
One-dose-for-all regimen	NPH: 20 units in the morning and 20 units at bedtime Insulin aspart or lispro: 10 units at breakfast and 10 units at dinner

TDD, total daily dose.

duration is 3–5 hours. Although it can be used in some insulin pumps, it is not approved for all pump brands. The vial and the pen are good for 28 days at room temperature while being used (20).

Intermediate Insulin and Long-Acting Insulin Analogs

Insulin isophane (NPH) is a U-100, intermediate-acting insulin. It is produced in *E. coli*. It is identical to human insulin and is in a suspension. Its onset of action is 1–2 hours, with an average peak of 4 hours (range: 4–8 hours). Duration of action is 10–20 hours. Vials are good for 31 days at room temperature, and pens are good for 14 days (21).

Insulin detemir (U-100) is a long-acting analog produced in *S. cerevisiae*. This can potentially cause a reaction for patients who are allergic to yeast. Detemir lacks a defined peak and lasts for up to 20 hours. Its time to onset of action can be 1–2 hours. The pen and vial last up to 42 days at room temperature while in use (22). Detemir has less incidence of hypoglycemia compared to NPH in pregnant women (23).

Insulin glargine (U-100) is a long-acting analog produced in *E. coli* and has a unique distribution mechanism. The acidic solution is

neutralized in subcutaneous tissue and microprecipitates are formed. These microprecipitates slowly release glargine over 24 hours, resulting in no peak. Its onset of action is 1–2 hours, and its duration of action is 24 hours. Vials and pens are good for 28 days at room temperature while in use (24).

Insulin glargine (U-300) is a long-acting insulin that is not bioequivalent to glargine U-100. Approved in February 2015, glargine U-300 is produced in *E. coli* and has the same structure as glargine U-100. Its onset of action develops over 6 hours and continues for a full 24 hours. Serum concentrations decline after 16–36 hours. It is dosed once daily. Glargine U-300 is only available in a pen to decrease dosing errors. It is good for 42 days at room temperature while being used (25).

Insulin degludec U-100 and U-200 are long-acting analogs approved by the U.S. Food and Drug Administration (FDA) in September 2015. The U-100 and the U-200 are considered bioequivalent. Insulin degludec undergoes recombinant DNA modification in *S. cerevisiae*, and patients can potentially have a reaction to the yeast, if allergic. Insulin degludec’s mode of slow absorption and prolonged action is

the formation of soluble multi-hexamers. Insulin degludec has no peak, and its onset of action is ~1 hour. It takes 8 days to reach steady state, and, once achieved, its duration of action is up to 42 hours. It is dosed once daily; however, because of its long duration of action, it can be dosed at any time of day. Patients who are inconsistent with dosing because of forgetfulness or lifestyle constraints may inject their dose at intervals of 8–40 hours without significant decreases in A1C compared to taking it at the same time every day. U-100 and U-200 degludec are only dispensed in pens to decrease administration errors. Pens are good for up to 56 days at room temperature while in use (26).

Novel Insulin Delivery

Human insulin inhalation powder was approved by the FDA in 2014. Inhaled human insulin is produced in *E. coli* and is adsorbed onto fumaryl diketopiperazine and polysorbate 80 carrier particles. Inhalation powder is equivalent unit-for-unit to insulin lispro. Its onset is 12–15 minutes, and its time to peak is ~57 minutes. Duration is ~2 hours. Inhaled human insulin carries a boxed warning for bronchospasms in patients with chronic lung disease. Sealed blister

TABLE 3. Summary Table of Available Insulin and Associated Pregnancy Category (14–27)

Insulin	Time to Onset	Peak Time	Duration	Pregnancy Category
Regular U-100	30 min	3 hours	8 hours	B
Regular U-500	30 min	3 hours	Up to 24 hours	B
Aspart	10–15 min	40–50 min	3–5 hours	B
Lispro U-100 and U-200	10–15 min	30–90 min	3–5 hours	B
Glulisine	10–15 min	55 min	3–5 hours	C
NPH	1–2 hours	4–8 hours	10–20 hours	B
Detemir	1–2 hours	None	24 hours	B
Glargine U-100	1–2 hours	None	24 hours	No human pregnancy data (previously C)
Glargine U-300	>6 hours	None	24 hours	No human pregnancy data
Degludec U-100 and U-200	1 hour	None	42 hours (at steady state)	C
Inhaled human insulin	12–15 min	57 min	2 hours	C

cards at room temperature must be discarded after 10 days. If kept in the refrigerator, they are good up to 1 month (27).

Insulin Dosing in Pregnancy

Insulin has long been considered the standard of care to attain optimal glucose control in pregnancy, although multiple methods are available to initiate insulin. Weight-based dosing, weight plus gestational age-based dosing, and even a “one-dose-for-all” type of dosing have been used (Table 2). Without clear evidence for one approach over another, the choice of protocol usually is based on clinician comfort and preference.

Although there are several methods for initiating insulin, the national guidelines lack an algorithm for adjusting doses in pregnancy. Adjustments outside of pregnancy are made in small increments over a long period of time. Pregnancy does not have the luxury of time because the risk of fetal harm develops rapidly, and quick control is imperative. The CDAPP Sweet Success program offers some guidance on adjustments, sug-

gesting changes by 2–4 units (~10%) in short- and intermediate-acting insulins every 2–3 days. Women with GDM or type 2 diabetes rarely have hypoglycemia unawareness; they quickly recognize and treat hypoglycemic events. Therefore, the most aggressive adjustments can safely be made in this population. In practice, adjustments can be made every couple of days until control is attained, if personnel and time allow.

New long-acting insulin analogs may provide a barrier to aggressive dosing because of the difficulty in adjusting doses as rapidly as with NPH. Insulin detemir can be safely titrated every 3 days by 3 units in nonpregnant patients (28). However, insulin glargine U-100 has two suggested options for dosing adjustments in nonpregnant patients: either by 1 unit every day or by 2 units every 3 days (29). Insulin glargine U-300 and insulin degludec should only be adjusted every 3–4 days, and there is no recommendation regarding the number of units for each adjustment (25,26). These recommendations are designed to decrease hypoglycemic

events associated with rapid dose titration but can pose a strict timetable for achieving optimal control in the pregnant population.

Accurate and timely adjustments depend on accurate blood glucose testing, type of insulin used, and consistent carbohydrate levels for meals. Fasting, preprandial, 1-hour postprandial, and bedtime blood glucose levels are all important to monitor all types of diabetes during pregnancy. Patients with type 2 diabetes or GDM may test up to 10 times daily to achieve euglycemia while on insulin. Patients with type 1 diabetes may test up to 16 times daily when pre- and postprandial blood glucose data are needed. Additionally, patients with type 1 diabetes can experience insulin sensitivity in the first trimester, with increasing resistance in the second and third trimesters, requiring additional testing for the treatment of low blood glucose levels.

Extra testing can be an extreme burden on patients but may be necessary for a short time for aggressive insulin treatment to achieve glycemic goals in a timely manner. Regardless

TABLE 4. FDA Pregnancy Categories (not used after 30 June 2015) (30)

A	Controlled studies in pregnant women have failed to demonstrate a risk to the fetus in the first trimester of pregnancy (and there is no evidence of a risk in later trimesters). Possibility of fetal harm appears remote.
B	Animal reproduction studies have not demonstrated a fetal risk, but there are no controlled studies in women, AND the benefits from the use of the drug in pregnant women may be acceptable despite its potential risks. OR Animal studies have shown an adverse effect that was not confirmed in controlled studies in women.
C	Animal reproduction studies have shown an adverse effect on the fetus, there are no controlled studies in women, AND the benefits from the use of the drug in pregnant women may be acceptable despite its potential risks. OR Animal studies have not been conducted, and there are no controlled studies in women.
D	There is positive evidence of human fetal risk based on adverse reaction data from investigational or marketing experience or studies in women, BUT the potential benefits from the use of the drug in pregnant women may be acceptable despite its potential risks.
X	Studies in animals or women have demonstrated fetal abnormalities. OR There is positive evidence of fetal risk based on adverse reaction reports from investigational or marketing experience or both, AND the risk of the use of the drug in a pregnant woman clearly outweighs any possible benefit.

of the method of initiating or adjusting insulin, aggressive management is necessary to attain quick glucose control. Maintaining tight control throughout pregnancy will require close and frequent monitoring to prescribe appropriate doses.

Insulin Safety in Pregnancy

Most insulins carry an FDA Pregnancy Category (29). However, in 2015, the FDA ruled that the lettering system will no longer be used. A summary of available insulins and current associated pregnancy categories illustrates these changes (Table 3). All medications approved after 30 June 2015 will only report known animal and human data for the medication in the new format. The lettering system (Table 4) will be phased out slowly for medications approved on or after 30 June 2001. Therefore, a risk assessment must be done on an individual patient basis.

Regular insulin (U-100 and U-500), insulin aspart, insulin lispro (U-100 and U-200), NPH, and insulin detemir all carry a pregnancy category B. For these insulins, the FDA has received sufficient human data allowing these to be considered

low risk in pregnancy. Insulin glulisine, insulin degludec, and inhaled human insulin are all category C agents because there is no human data during pregnancy (20,25,26). Insulin glargine no longer has a pregnancy category, and its package inserts simply state that there are “no well-controlled clinical studies in pregnant women” (24,25).

In rat studies, insulin glulisine had no effects on embryo or fetal development at doses 10 times the human dose. In rabbits, early pregnancy loss and skeletal defects were seen at doses 0.5, 0.2, 0.25, and 0.1 times the average human dose based on mg/m². Both effects are associated with toxic maternal effects and maternal hypoglycemia. These effects did not differ from animal studies done on regular insulin (20). In insulin degludec studies, rats were given doses that provided five times the human exposure, and rabbits were given 10 times the human exposure. Effects such as early loss and visceral/skeletal defects were similar to effects seen in studies with NPH and associated with maternal hypoglycemia rather than effects of the insulin analog itself (26). Inhaled human insulin

has sufficient data on the insulin, so only the carrier particles, absent insulin, were tested for teratogenicity. No negative effects were seen in rats at exposures 14–21 times the human systemic exposure. Decreased epididymis and testes weight and impaired learning was observed in pups (27). Insulin glargine (U-100 and U-300) has recently removed its former pregnancy category. Female rats received up to seven times the human dose, and rabbits received two times the human dose based on mg/m². Outcomes were similar to those of regular insulin (24,25).

Without traditional pregnancy categories, some clinicians may find it difficult to accurately assess the safety of new products in pregnant patients. Although animal studies are not always directly correlated with human outcomes, most of these newer insulins have similar animal data outcomes to their comparators in the B category: either NPH or regular insulin. Manufacturers and the FDA will not change a pregnancy category based on animal data alone. Therefore, insulins will not all be rated on a class effect, and the newer insulins now in category C will not

be moved to category B without further human data.

In the absence of human data, clinicians must do a risk assessment. The risks of hyperglycemia to fetuses are well known, and the benefits of well-controlled blood glucose outweigh the potential risks of insulin. It is a reasonable assessment to keep patients with well-controlled blood glucose on their current insulin. In contrast, in patients with poorly controlled blood glucose, pregnancy provides a prime opportunity to change to an insulin regimen with known safety outcomes in pregnancy. Insulin use in pregnancy must meet the needs of the patient, and the existing level of control may be more important than the pregnancy category. In the absence of human data, the risk assessment and recommendation should then be shared with the patient so she is informed and involved in the care plan.

Conclusion

Insulin therapy remains the standard of care for type 1 diabetes, type 2 diabetes, and uncontrolled GDM during pregnancy. Regular insulin, insulin aspart, insulin lispro, and NPH have the most human pregnancy data. Insulin detemir is quickly gaining data and provides an additional option for basal coverage. As we move into a new era of insulin technology, patients may be on insulin that has no human data for pregnant patients prior to becoming pregnant. Accurately assessing the risks and benefits of changing insulin therapy will become a crucial role for clinicians. Furthermore, sharing the analysis with the patient to include her in determining the best insulin regimen is essential. Regardless of the regimen chosen, tight glycemic control throughout pregnancy is essential for the best fetal outcomes.

Duality of Interest

No potential conflicts of interest relevant to this article were reported.

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