INSULIN FOR GESTATIONAL and PREGESTATIONAL DIABETES

There have been several changes in the management of diabetes during pregnancy, including the use of insulin analogs. The Sweet Success Guidelines, revised in 2002 do not completely reflect this information since they were being revised just as the new therapies became available in pregnancy. This is intended to be a brief update to review insulin analog and their use during pregnancy for women with diabetes during pregnancy, including gestational diabetes.

Insulin Analogs in Pregnancy

Antibody-free human insulin is considered by most practitioners to be the gold standard for use in pregnancy because it does not cross the placenta and is highly effective. Yet even though insulin has an unlimited ability to control glucose, it is the ***most underused*** therapy for diabetes today (Riddle MC 2002). Ellie S. Strock, ANP, CDE, Chief Operating Officer of the International Diabetes Center, Minneapolis, Minn. describes the reasons for this underuse of insulin as "an adversity to injections (both the patient's and provider's), as well as the perceived complexity of initiating insulin therapy and a lack of understanding about how to use the insulins available." Those of us working with women with diabetes in pregnancy confirm these observations. Insulin analogs offer some advantages that may reduce "resistance" to the use of insulin during pregnancy. Currently available insulin analogs include rapid-acting mealtime insulins: **lispro** (Humalog) and **aspart** (Novolog), and long-acting basal insulin: **glargine** (Lantus).

Mealtime insulins (lispro, aspart) are used to control **postmeal** blood glucose levels. Here is how they work:

- In nondiabetic pregnant women endogenous insulin secretion generally peaks within one hour to coincide with the highest level of glucose after the meal (Paretti 2003). Once the meal-stimulated glycemia has subsided, insulin and glucose levels return to premeal levels within two hours.
- Women with gestational diabetes are unable to secrete sufficient insulin to overcome the resistance to its effect mediated by hormones and other factors during pregnancy. This is most often reflected as abnormally high one-hour glucose levels after the meal.
- Commonly prescribed regimens consisting of combined short-acting (Regular) and intermediate-acting insulins have been used to mimic endogenous insulin response. However, these regimens are at times incapable of adequately simulating the basal or meal-stimulated components of normal insulin secretion. (Mecacci 2003)
- The physiologic profile of insulin requires rapid changes in concentrations as a result of food ingestion or other factors, such as exercise. Regular human premeal insulin, which generally peaks in 1½ hours, must be injected at least 30 minutes before the meal to reach therapeutic concentrations in time to meet the highest post meal elevation of glucose.
- Inappropriate timing of insulin administration results in a mismatching of postmeal glucose absorption and post injection insulin peak. Regular human insulin is still present in the blood when peripheral glucose disposal occurs. This mismatch may predispose some patients to develop hypoglycemia.

- The new rapid-acting insulin analogs **lispro** and **aspart** are more effective at controlling postprandial hyperglycemia without an increased risk of hypoglycemia. This may reduce the need for snacks which may contribute to increased weight gain. (Jovanovic 1999, Pettit 2003).
- Insulin analogs achieve higher peak insulin concentrations in less time (40 - 60 minutes) and with a shorter duration of action (2- 4 hours) than **Regular** human insulin. Both, **aspart** and **lispro** have been widely used in pregnancy (Evers 2004) and do not seem to cross the placenta (Jovanovic 1999, Pettit 2003). The analogs seem to achieve lower 1-2 hour glucose concentrations than **Regular** (Jovanovic 1999, Pettit 2003,Mecacci 2003).
- There are no studies that specifically relate infant outcomes (ie. reduction in macrosomia) to the use of analogs versus **Regular** insulin.
- Lispro is not associated with an increased risk of progression of retinopathy (Buchbinder, 2000).
- The FDA lists l**ispro**, **Regular** and **NPH** insulins as pregnancy safety category B, a**spart** is listed as category C.*
- When switching from Regular premeal insulin to **lispro** or **aspart** equal doses can be used.

***Current Categories for Drug Use in Pregnancy**

Category	Description
A	Adequate, well-controlled studies in pregnant women have not shown an increased risk of fetal abnormalities.
B	Animal studies have revealed no evidence of harm to the fetus; however, there are no adequate and well-controlled studies in pregnant women. **or** Animal studies have shown an adverse effect, but adequate and well-controlled studies in pregnant women have failed to demonstrate a risk to the fetus.
C	Animal studies have shown an adverse effect and there are no adequate and well-controlled studies in pregnant women. **or** No animal studies have been conducted and there are no adequate and well-controlled studies in pregnant women.
D	Studies, adequate well-controlled or observational, in pregnant women have demonstrated a risk to the fetus. However, the benefits of therapy may outweigh the potential risk.
X	Studies, adequate well-controlled or observational, in animals or pregnant women have demonstrated positive evidence of fetal abnormalities. The use of the product is contraindicated in women who are or may become pregnant.

FDA Website http://www.fda.gov/fdac/features/2001/301_preg.html#categories

Basal insulins (**NPH, glargine, lente, and ultralente**) are used to control **between-meal** and **overnight** blood glucose levels.

- **NPH** continues to be the basal insulin of choice because it has more predictability than **lente** or **ultra lente** (Lindstrom 2000).

- The insulin analog, **glargine** has a steady rate of absorption and effect and can be given once a day. Insulin **glargine** has an acidic pH, resulting in slow absorption from the subcutaneous tissue. Because of the acidic pH, insulin glargine cannot be mixed in the same syringe with other insulins. Although it is a long acting or basal insulin, it is a **clear** solution. Results from clinical trials show less overnight hypoglycemia with **glargine** and in many cases lower fasting glucose levels (Fulcher 2002). A promising new therapy is once-daily insulin glargine administered in combination with mealtime rapid-acting insulin (**lispro or aspart**). However, **use of glargine in pregnancy is not yet recommended** since it associated with a 6 and 8 fold increase in binding to IFG receptor and mitogenic potency respectively as compared with Regular human insulin. Glargine is a category C drug since only case reports of its use in pregnancy and no data exists at this time (2005) concerning use of glargine in pregnancy. If a woman with type 1 or 2 diabetes is planning pregnancy she should consider switching from **glargine** to **NPH** or the continuous subcutaneous insulin pump **before** becoming pregnant. A period of poor control may follow the switch while the appropriate dose of NPH is determined. The dose of **glargine** may need to be divided in to 3 smaller doses of NPH given about 8 hours apart to mimic the steady state achieved by glargine.

Table 1. Action of Above Insulins

Type of Insulin	Examples	Onset of Action	Peak of Action	Duration of Action
Rapid-acting	Humalog (lispro) Eli Lillly	15 minutes	30-90 minutes	3-5 hours
	NovoLog (aspart) Novo Nordisk	15 minutes	40-50 minutes	3-5 hours
Short-acting (regular)	Humulin R Eli Lilly Novolin R Novo Nordisk	30-60 minutes	50-120 minutes	5-8 hours
Intermediate-acting (NPH)	Humulin N Eli Lilly Novolin N Novo Nordisk	1-3 hours	8 hours	20 hours
Lente		3-4 hours	6-12 hours	16-20 hours
Ultra lente		2 -4 hours	8- 16 hours	24-26 hours
Long-acting	Lantus (glargine) Aventis	1 hour	None	24 hours

Adapted from the FDA website: http://www.fda.gov/fdac/features/2002/chrt_insulin.html

Mealtime and basal insulins are used in various combinations to achieve close to normal glycemia during pregnancy. (See Table 2 for blood glucose targets) Self Monitoring of Blood Glucose values assist in determining an effective dose and regimen and therefore should be obtained immediately pre and one hour post meal during insulin therapy (as needed).

Table 2. Self-monitored Blood Glucose (SMBG) Plasma Goals

Fasting Target	65-100 mg/dL (<95 mg/dL used by most affiliate sites)
Premeal target	<100 mg/dL
One hour post meal plasma target	110-135 mg/dL. 1-hr. after the start of each meal (breakfast, lunch and dinner)
Usual regimen	Fasting plus pre and post meal until control is acceptable, then fasting and post meals. Women with type 1 or type 2 diabetes who exhibit variable fasting blood glucose levels, should check HS and 3 am BG's for 2 or 3 days, to differentiate rebound vs. dawn phenomena.

*Adapted from Sweet Success Guidelines 2002, p 14.

The type of regimen and number of injections per day are determined with the patient based on the individual's needs and lifestyle. Insulin regimens usually consist of 2, 3, or 4 injections per day. Since the advent of rapid acting insulins, many providers and patients prefer the insulin analogs to Regular. Several authors suggest that regular insulin is less effective in lowering the 1 hour glucose elevation and less convenient to administer than the analogs. (Ilic1999, Jovanovic1999, Bhattacharyya 2001, Pettitt 2003). In one study, all women who were switched to lispro during pregnancy preferred to continue once they delivered. (Bhattacharyya 2001)

Calculating Insulin Dosages

Dosage monitoring and administration regimens are adjusted based on individual response to nutrition interventions, exercise and insulin administration techniques. For a woman who first presents during pregnancy for care, whether she has type 1, type 2 or gestational diabetes, an insulin dose based on gestational age and current weight provides a starting point (total daily dose) for further adjustments based on activity, meal plan and other factors. Stress, sepsis, steroids, obesity and advancing pregnancy increase insulin needs. Multiple daily injections provide the most optimal control during pregnancy. (Jovanovic 2000)

Table 3. Suggested Starting Total Daily Insulin During Pregnancy

Weeks Gestation	Total Daily Insulin
Week 1 - 18	0.7 U/kg actual body weight
Weeks 18 - 26	0.8 U/kg actual body weight
Weeks 26 - 36	0.9 U/kg actual body weight
Weeks 36 - 40	1.0 U/kg actual body weight

Jovanovic, Clin Obstet Gynecol. 2000

Table 4. Initiating Insulin Therapies with Mild Hyperglycemia

Glycemic Derangement	Suggested Insulin Type and Dose
Persistent **FPG >95 mg/dL <120 mg/dL**	Start **8 - 20 units NPH at bedtime** (0.165 or 0.2 units per kg. actual body weight)
One hour post breakfast plasma value **>135 mg/dL <180 mg/dL**	Start **2 - 4 units lispro or aspart** pre-breakfast
One hour post lunch plasma value **>135 mg/dL <180 mg/dL**	Add **6-10 units NPH** to pre-breakfast injection (And eat lunch 4-5 hrs after breakfast) **OR** Give 2- 4 units lispro or aspart pre-lunch
One hour post dinner plasma value **>135mg/dL <180mg/dL**	Give 2- 4 units lispro or aspart pre-lunch

Region 1 California Diabetes and Pregnancy Program Insulin Guidelines adapted from ADA 3rd edition Medical management of pregnancy complicated by diabetes 2000.

Table 5. Determining Effective Insulin Regimens

Glycemic Derangement	Suggested Insulin Type and Dose
If pre-dinner plasma values are **>100 mg/dL**	Increase AM dose of NPH if dinner is within 8 hrs. of the AM injection. If the patient eats a late dinner, NPH with lunch is often more effective -add 4 units NPH at lunch and titrate as needed
If increasing the AM NPH dose is ineffective in controlling post lunch glucose	*Add 2 - 4 units lispro or aspart pre lunch
Titrate these doses up or down by 1 - 4 units based on BG values that are out of range for 2 to 3 days at a time.	

* Region 1 California Diabetes and Pregnancy Program Insulin Guidelines adapted from ADA 3rd edition Medical management of pregnancy complicated by diabetes 2000.

To initiate insulin therapy with **marked hyperglycemia** throughout the day, start insulin using split doses of rapid-acting and intermediate acting insulin.

1. Calculate **total daily dose** using Table 1 (above).
2. Approximately **2/3** of the total dose is given in the **morning** (33% rapid-acting, 66% intermediate-acting) and **1/3** in the **evening** with half as **rapid-acting insulin before dinner** and half as **intermediate insulin before bed**.

Example: A 74 kg woman at 30 weeks gestation.

1. Calculate 24-hour total dose: 0.9 x 72 = ~66 units total insulin per day.
2. Give 2/3 total dose (~45) in the AM and 1/3 (~21) in the PM as follows:

Insulin Type	Before Breakfast	Before Dinner	Before Bed
lispro or aspart	15 units	10 units	
NPH	30 units		11* units
**The dawn (early morning hyperglycemia) is increased in pregnancy and often requires larger doses of NPH than ½ of the evening dose*			

It is important to note that these doses will need to be adjusted (i.e. increased for insulin resistant, obese, type2, or GDM; and decreased for thin, insulin-sensitive, type 1 DM)

Table 6. Examples of Various Insulin Regimens

Pre breakfast	Pre Lunch	Pre Dinner	Bedtime
			Intermediate
Rapid acting Intermediate			
*Rapid acting	Rapid acting	Rapid acting	Intermediate
Rapid acting	Rapid acting	Rapid acting Intermediate	Intermediate
Rapid Acting Intermediate		Rapid acting	

* Allows greater precision and more flexibility

Another **relatively new insulin preparation is premixed insulin using 75% NPL (neutral protamine lispro), which is not NPH but similar, with 25% lispro** in place of Regular insulin. Premixed insulins such as this one and 70/30 do not allow the ability to regulate the dose of one type of insulin without the other being altered. Certain clinical situations such as compliance issues may warrant the use of premixed insulin.

Key Points for Using Insulin Therapy

Self-monitoring of blood glucose by using a meter with memory (including date and time of test) is essential for optimal diabetes management with insulin. Monitor blood glucose immediately premeal and 1 hour after the start of the meal and adjust rapid-acting insulin by 1-2 units every 2-3 days until within target range. Review the results with the patient at each visit. Once control is established and premeal values are consistently within target range, monitoring can be reduced to fasting and one hour after the start of meals (breakfast, lunch, dinner).

Educate patients to understand the progressive nature of **insulin resistance** in pregnancy and the fact that doses will change over time. Initiating insulin must include instruction on insulin **injection technique, carbohydrate counting** to control postmeal peak glucose, and **prevention and treatment of hypoglycemia**. Teach patients how to self-adjust insulin based on glucose patterns. **Pattern control** is an easily understood and effective method for insulin self-adjustment.

Tailor the insulin regimen to the needs and lifestyle of the patient.
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Use enough insulin! Individuals with gestational, type 2 diabetes and /or obesity and pregnant are insulin-resistant and often require a total daily insulin dose as much as 1 unit/kg or more to achieve optimal control (over 100 units per day in a 100-kg patient!).

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