Treatment With Insulin and Its Analogs in Pregnancies Complicated by Diabetes

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Before the advent of insulin in 1922, <100 pregnancies in diabetic women were reported; most likely, these women had type 2 and not type 1 diabetes (1). Even with this assumption, these cases of diabetes and pregnancy were associated with a >90% infant mortality rate and a 30% maternal mortality rate. As late as 1980, physicians were still counseling diabetic women to avoid pregnancy. This philosophy was justified because of the poor obstetric history in 30–50% of diabetic women. Improved infant mortality rates finally occurred after 1980, when treatment strategies stressed better control of maternal plasma glucose levels, once self-monitoring of blood glucose and A1C became available. As the pathophysiology of pregnancy complicated by diabetes has been elucidated and as management programs have achieved and maintained near-normoglycemia throughout pregnancy complicated by diabetes, perinatal mortality rates have decreased to levels seen in the general population (2–5). This review reports the literature on the safety and efficacy of insulin analogs in pregnancy and thereby enables the clinician to choose the optimal insulin treatment protocol to achieve and maintain normoglycemia throughout pregnancies complicated by diabetes.

RATIONALE FOR THE USE OF NON-IMMUNOGENIC INSULINS DURING PREGNANCY

— Maternal glucose freely crosses the placenta. Maternal insulin does not cross the placenta unless it is bound to IgG antibody, which carries it through the placenta or insulin is forced through the placenta by high perfusion (6,7). Diabetic fetopathy is thought to be the result of fetal hyperinsulinemia (1–9). Thus, our treatment must be designed to normalize maternal blood glucose concentrations without the use of exogenous insulins that cross the placenta.

Placental transfer of insulin complexed with immunoglobulin has also been associated with fetal macrosomia in mothers with near-normal glycemic control during gestation. Menon et al. (8) reported that antibody-bound insulin transferred to the fetus was proportional to the concentration of antibody-bound insulin measured in the mother. Also, the amount of antibody-bound insulin transferred to the fetus correlated directly with macrosomia in the infant and was independent of maternal blood glucose levels. In contrast, Jovanovic et al. (9) discovered only improved glucose control, as evidenced by lower postprandial glucose excursions, but not lower insulin antibody levels, correlated with lower fetal weight. They showed that insulin antibodies to exogenous insulin do not influence infant birth weight.

Insulin lispro has been commercially available for 10 years. Insulin lispro, an analog of human insulin, has a peak insulin action achieved within 1 h after injection and thus significantly improves the postprandial glucose levels (10). Because normoglycemia is paramount in the treatment of pregnant diabetic women, the use of insulin analogs would appear beneficial in the care of these women if the safety profile can be documented.

Human and highly purified insulins are significantly less immunogenic than mixed beef-pork insulins (11,12). Human insulin treatment has been reported to achieve improved pregnancy and infant outcome compared with using highly purified animal insulins (9). In 1999, the first report of the safety and efficacy of the insulin analog, lispro (which has the amino acid sequence in the β-chain reversed at position B28 and B29), was reported and shown to be more efficacious than human regular insulin to normalize the blood glucose levels in gestational diabetic women (13). This insulin rapidly lowered the postprandial glucose levels, thereby decreasing the A1C levels, with fewer hypoglycemic episodes, and without increasing the anti-insulin antibody levels.

In a randomized open-label parallel-group clinical trial, Jovanovic et al. (13) studied the metabolic and immunologic effects of insulin lispro and regular human insulin combined with basal insulin in gestational diabetes mellitus (GDM) and found that during a meal test, the areas under the curve for glucose, insulin, and C-peptide were significantly lower in the lispro group. Mean fasting postprandial glucose and A1C levels were similar for the two groups. The lispro group had fewer hypoglycemic episodes. The two groups had similar neonatal outcomes. Insulin lispro was not detectable in cord blood when patients received continuous intravenous lispro and dextrose infusions intrapartum to assess placental transfer. However, in an in vitro perfusion study using human placentas, insulin lispro was found to cross the placenta at greater than normal therapeutic concentrations, with fetal perfusate concentration of lispro reaching up to 59% of maternal concentration (7). The mechanism of how the placenta handles therapeutic concentrations of lispro warrants further study.

The safety and efficacy of insulin lispro has been confirmed by others (14–18). In a large clinical trial among 213 patients who had GDM (14) and received insulin therapy (regular insulin, $n = 138$; lispro, $n = 75$), there were no significant differences in maternal or fetal outcomes and no increase in adverse events using lispro, but predelivery A1C values were lower and patient satisfaction was higher for insulin lispro ($P < 0.05$).

These studies support the recommendations that those women with GDM who

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Abbreviations: GDM, gestational diabetes mellitus.
A table elsewhere in this issue shows conventional and Système International (SI) units and conversion factors for many substances.
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are not optimally managed with diet and exercise need insulin therapy. Insulin lispro causes fewer hypoglycemic events than human regular insulin, and it attenuates the postprandial response more than regular human insulin. Furthermore, the antibody levels in lispro insulin are not increased over those seen with regular human insulin. Insulin lispro, except with high-dose insulin lispro used during placental insulin studies (7), does not cross the placenta to the fetus and therefore may be considered a treatment option in patients with GDM.

Use of insulin lispro in pregestational diabetes is now better documented to be safe in type 1 diabetic women. Diamond and Kormas (18) first questioned the safety of using insulin lispro during pregnancy in a letter to *The New England Journal of Medicine* in 1997. They reported on two patients who used insulin lispro during pregnancies and deliveries. One of these pregnancies was terminated at 20 weeks' gestation, and the second pregnancy resulted in a seemingly healthy infant after elective cesarean delivery, but who subsequently died unexpectedly 3 weeks later. Both infants were discovered to have congenital abnormalities, which led the authors to question whether insulin lispro might have teritogenic effects on the fetus, in which case it should not be used during pregnancy. The report causes concerns about insulin lispro use during pregnancy, yet it does not provide conclusive evidence that insulin lispro is responsible for the malformations of the infants mentioned above. In fact, there is sufficient reason to doubt that insulin lispro is to blame in the cases described above, since these isolated case reports were not part of a study and there was no control group. Therefore, the findings should stimulate clinical trials testing the safety of insulin lispro during pregnancy, not as evidence that it is unsafe. During the initial clinical trials testing insulin lispro, pregnant women were excluded. However, some participants became pregnant unexpectedly during the trials and 19 infants were born by these mothers who were using insulin lispro. Of these births, one child had a right dysplastic kidney, but the other 18 were healthy (19).

Subsequently, Wyatt et al. (20) reported that insulin lispro is safe for the treatment of type 1 diabetic women. In this retrospective analysis of the 500 pregnancies in which the women were treated with insulin lispro before and during organogenesis, there were 27 malformed infants (5.4%). All 27 congenital anomalies occurred in those infants born to mothers who had an A1C level >2 SDs above the mean of a normal population.

Insulin aspart, an insulin analog that has been shown to produce a peak blood level at 40 min and lowers postprandial glucose levels significantly better than human insulin, has only 69% the IGF-I activity of human insulin. Insulin aspart was approved by the Food and Drug Administration for clinical use in 1999. Pharmacokinetic and pharmacodynamic studies of insulin aspart in nonpregnant healthy volunteers and patients with type 1 and type 2 diabetes have shown that insulin aspart has a quicker onset of action and lower postprandial glucose than regular human insulin (21–23). Reproduction and teratology studies performed with insulin aspart in rats and rabbits indicated that, like regular human insulin, insulin aspart at doses 3 to 200 times the typical human subcutaneous doses caused fetal abnormalities. The effects are probably secondary to maternal hypoglycemia at high doses (24).

Currently, there are very limited results regarding use of insulin aspart during pregnancy. Pettitt et al. (25) conducted the first clinical study to compare the short-term efficacy of insulin aspart, regular insulin, or no insulin in patients with GDM. Fifteen women with GDM received a standard meal test after administration of regular insulin or insulin aspart on 3 consecutive days (1 day was untreated baseline). The postprandial glycemic control (as measured by glucose area under the curve above baseline) was significantly improved by insulin aspart compared with no exogenous insulin administered, whereas regular insulin did not show a significant difference from no exogenous insulin administered. These same investigators then observed a sample size of 27 women randomized to receive either insulin aspart or regular insulin for prandial treatment of their carbohydrate intolerance. Both treatment groups maintained good overall glycemic control during the study. Insulin aspart was effective in reducing the postprandial glucose concentration from baseline. Insulin aspart treatment showed significantly lower C-peptide values than regular insulin, as demonstrated by the significantly greater reduction in the change-from-baseline C-peptide values. No major hypoglycemic events were reported in this study. Antibody binding specific to insulin aspart and regular insulin remained relatively low (<1.5% binding of the specific antibodies) for both treatment groups throughout the study. Cord blood serum samples, collected immediately after delivery, detected raised levels of insulin (either aspart or human regular insulin) only if relatively high infusion rates of insulin and glucose were administered during labor and delivery (26). The neonatal birth weights were similar in both groups, and no case of macrosomia was reported. This study demonstrates that the overall safety and effectiveness of insulin aspart was comparable to regular human insulin in pregnant women with GDM. Insulin aspart was more effective than regular human insulin in providing postprandial glycemic control in women with GDM.

Hod (27) recently presented the study design for a large multinational multicenter randomized clinical trial observing the safety and efficacy of insulin aspart for the treatment of type 1 diabetes. This trial in 17 countries at 90 centers randomized 330 type 1 diabetic women to receive either human regular insulin or insulin aspart. Thus far, there have been no insulin-associated maternal or fetal complications and no evidence that insulin aspart is teratogenic.

LONG-ACTING INSULIN ANALOGS

— Insulin glargine is a long-acting insulin analog approved by the Food and Drug Administration in 2000 for use as a "basal" insulin. Insulin glargine has a glycine substitution in the α-chain at position 21 and two arginines attached to the β-chain terminal at position 30. It is soluble insulin and has been shown to provide peakless sustained predictable 24-h action. Of note, insulin glargine has a sixfold increase in IGF-I activity over human insulin. No results of randomized clinical trials of insulin glargine use during pregnancy are currently available. There are to date only a total of four letters to the editor (28–31) reporting 14 cases of type 1 diabetic women treated with insulin glargine during pregnancy. The glucose control varied from 5.1 to 8.9%. There were no malformations in this small number of pregnancies, but the birth weight varied from 2,000 to 4,800 g.

Insulin detemir is another long-acting insulin analog, pending Food and Drug Administration approval. The mechanisms of protracted action of insulin detemir include increased hexamer stability, binding to albumin at the subcutaneous

Table 1—*Receptor binding and metabolic and mitogenic potency of insulin analogs*

	Insulin receptor affinity	Metabolic potency	IGF-I receptor affinity	Insulin receptor off-rate (%)	Mitogenic potency (Saos/B10 cells)
Human insulin	100	100	100	100	100
B10 Asp	205 ± 20	207 ± 14	587 ± 50	14 ± 1	975 ± 173
Insulin lispro	84 ± 6	82 ± 3	156 ± 16	100 ± 11	66 ± 10
Insulin aspart	92 ± 6	101 ± 2	81 ± 9	81 ± 8	58 ± 22
Insulin glargine	86	60 ± 3	641 ± 51	152 ± 13	783 ± 13
Insulin detemir	~18–46	~27	16 ± 1	204 ± 9	~11

Data are means ± SD. Adapted from Kurtzhals et al. (43).

injection site and in the circulation (32–34). The benefits of insulin detemir, such as improved glycemic control, lower within-subject variation, reduced nocturnal hypoglycemic events and no weight gain, have been shown in patients with type 1 diabetes (35,36). There are no clinical studies performed using insulin detemir in pregnant women with diabetes. Animal reproduction studies in rabbits and rats have not revealed any differences between insulin detemir and human insulin regarding embryotoxicity and teratogenicity (37).

POTENTIAL RISKS ASSOCIATED WITH INSULIN ANALOGS

Insulin and IGF-I receptor binding affinity

There are medical reasons to consider increased IGF-I activity undesirable in pregnancy. During gestation, the female reproductive system undergoes dramatic changes to accommodate the development of the fetus. IGF-I facilitates the implantation of the human embryo in the endometrium. Disturbance of IGF-I functions could result in spontaneous miscarriage, preeclampsia, and defects of the embryo (38). It is well known that the incidence of spontaneous miscarriage because of malformations of the fetuses during early pregnancies is much higher in women with poorly controlled diabetes than in nondiabetic pregnancies. The mechanisms for the abortion and malformation are not completely understood. There are some factors that presumably play important roles in this process: inherited genetic abnormalities of the fetus, lack of endogenous insulin in maternal serum in the case of type 1 diabetes, and embryotoxic effects of the diabetic serum (39). Some researchers suspect that altered insulin and IGF-I serum levels are candidates to account for dysregulation of trophoblast proliferation and invasion (40). In late pregnancy, the placenta produces a large amount of human placental growth hormone to regulate the flow of nutrients to the placenta to support fetal growth. Like growth hormone, the effects of human placental growth hormone are mediated through IGF-I and IGF-binding proteins. An insulin analog that has high affinity for the IGF-I receptor might influence the natural processes mediated by IGF-I. Furthermore, increased human placental growth hormone and progesterone levels also account for increased insulin resistance and reduced insulin sensitivity during the last trimester.

The actions of insulin are mediated through binding of the insulin molecules to the insulin receptors located on the membrane of the target cells. The IGF-I receptor shares structural similarity to the insulin receptor. IGF-I can bind to the insulin receptor and insulin is capable of binding to the IGF-I receptor. However, natural insulin binds to IGF-I receptor with 1,000-fold lower affinity than insulin binding to the insulin receptor, and insulin has a 1,000-fold lower affinity than IGF-I for the IGF-I receptor (40). The new insulin analogs all have modifications in their amino acid sequences or posttranslational modifications, such as acylation of the insulin molecules in the case of insulin detemir. Such structural modifications sometimes lead to enhanced or reduced affinity for the insulin receptor and IGF-I receptor. The potential mitogenic risks and the properties of the insulin analogs are summarized in Table 1 (33,38–43).

However, in other studies using differentiated cultured human skeletal cells from nondiabetic and diabetic subjects, it has been reported that human insulin and insulin glargine had similar mitogenic effects as determined by thymidine uptake into DNA, and the sensitivities and potencies were greatly reduced compared with IGF-I (<1% of IGF-I). These researchers concluded that in a cell system representative of the relative insulin and IGF-I receptor expression in human skeletal muscle cells, insulin glargine and native human insulin are comparable in receptor binding and metabolic responses and that glargine does not display augmented mitogenic effects (44).

Although the long-acting insulins, insulin detemir and insulin glargine, present intriguing alternatives for the administration of the basal insulin requirement (that insulin delivered to keep the blood glucose normal between the meals and in the fasting state), there have been no clinical trials to date that would provide enough data to show the safety and efficacy of these new long-acting insulin analogs. In fact, it may be that these long-acting analogs are too flat and that their insulin pharmacodynamics are not suited to the diurnal variation of the basal insulin requirement during pregnancy. Thus, the safety and efficacy of these new insulin analogs will need to be further assessed in pregnant women with diabetes.

SUMMARY AND NEEDED RESEARCH

— Clinical decision making can be driven by patient preference, and the undoubted advantages of the new insulin analogs in reducing hypoglycemic risk and facilitating a more normal lifestyle in women with longstanding type 1 diabetes have often overridden medical caution in a pregnant woman's personal choice. Thus, the decision to begin insulin may be a choice for a gestational diabetic woman and her physician when the medical nutritional therapy is too difficult to maintain.

Depending on the type, severity, and stage of diabetes, patients may have only elevated postprandial glucose levels and normal fasting blood glucose levels, or the fasting glucose levels may be elevated as well. If postprandial glucose is the target

of treatment, the rapid-acting insulin lispro and insulin aspart appear to be as safe and effective as regular human insulin in women with GDM and achieve better postprandial glucose concentrations with less late prandial hypoglycemia. If the patient has elevated fasting and postprandial blood glucose levels and requires multiple daily injections to achieve good glycemic control, a basal-bolus regimen should be considered.

The long-acting insulin analogs do not have as pronounced a peak effect as NPH insulin and therefore cause less nocturnal hypoglycemia. However, the safety of these insulin analogs needs to be further established in pregnant women. Issues that will need to be further clarified include the question of whether these insulin analogs have teratogenic effects on the developing fetus, alter the balance between the binding affinity to IGF-I receptor and insulin receptor, are associated with increased risk of retinopathy, or show increased antibody levels. Because of the lack of information in animal studies and relatively high risk of clinical trials, it is unrealistic to expect results from large-scale controlled clinical trials for evaluation of the safety profiles of these insulin analogs. For now, clinicians will have to rely on their knowledge of the pharmacology of the treatments, sporadic case reports, and their own judgment when making decisions regarding whether or not an insulin analog should be used in pregnant women with diabetes. Future research must also include the development of insulins that perfectly match physiological insulin profiles during pregnancy. Although both portal insulin delivery and inhaled insulin delivery have been associated with a closer match to endogenous insulin secretory profiles than subcutaneously injected insulin, the safety and efficacy of these routes of insulin delivery for pregnant women also need to be studied.

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