Comparison of an Insulin Analog, Insulin Aspart, and Regular Human Insulin With No Insulin in Gestational Diabetes Mellitus

DAVID J. PETTITT, MD[1]
PAULINA OSPINA, MHS[1]
JERZEY W. KOLACZYNSKI, MD, PHD[2]
LOIS JOVANOVIC, MD[1]

OBJECTIVE — To assess the short-term efficacy of insulin aspart in comparison with regular human insulin in women with gestational diabetes mellitus (GDM) during standardized meal tests.

RESEARCH DESIGN AND METHODS — The study included 15 women with GDM who had inadequate diabetes control with diet alone. On 3 consecutive days, breakfast meal tests were performed—the first with no exogenous insulin and the other two after the injection of either regular insulin or insulin aspart.

RESULTS — The peak insulin concentration was higher and the peak glucose and C-peptide concentrations were lower with both insulin preparations than with no exogenous insulin. Glucose areas under the curve above baseline were significantly lower with insulin aspart (180-min area, 7.1 mg · h · dl^{-1}; $P = 0.018$), but not with regular insulin (30.2 mg · h · dl^{-1}; $P = 0.997$), than with no insulin (29.4 mg · h · dl^{-1}).

CONCLUSIONS — This study demonstrates that effective postprandial glycemic control in women with GDM who required insulin was brought about by insulin aspart through higher insulin peak and lower demand on endogenous insulin secretion.

Diabetes Care 26:183–186, 2003

Gestational diabetes mellitus (GDM), defined as "carbohydrate intolerance of varying degrees of severity with onset or first recognition during pregnancy" (1,2), occurs in nearly 4% of all pregnancies in the U.S., but the actual prevalence differs with ethnicity and maternal age (3). Women with high blood glucose concentrations experience greater risk of adverse maternal and fetal outcomes, including preeclampsia, cesarean delivery, macrosomia, congenital anomalies, and increased risk for future development of type 2 diabetes (4). The most common and significant neonatal complication clearly associated with GDM is macrosomia (5), which occurs at rates as high as 40% of neonates in untreated GDM (6). In addition, neonatal macrosomia is associated with the metabolic syndrome of hyperinsulinemia and deposition of fat in the visceral cavity (7). The literature suggests that the risk of macrosomia rises as maternal glycemia increases (8–10). Specifically, the risk of macrosomia appears to increase with increasing postprandial glucose concentrations (11–13). Traditionally, in the guidelines for care of nonpregnant diabetic patients (14), a glucose concentration measured after eating has been recommended because of fear of hypoglycemia due to the peak action of human regular insulin. Because the peak postprandial glucose concentration is 1 h after eating (11), a rapid-acting insulin analog that reaches peak concentration at about 1 h after injection would be ideal. Data on nonpregnant diabetic patients document that the rapid-acting insulin analog, insulin aspart, peaks at 40 to 60 min after injection and thus can be used to blunt the peak postprandial glucose concentrations (15). Before insulin aspart can be prescribed in pregnancy, the safety and efficacy of this insulin analog will need to be studied. The aim of this article is to document the short-term efficacy of insulin aspart in pregnant women during a standardized meal.

RESEARCH DESIGN AND METHODS

— Women with GDM who had been unable to control their glucose concentrations with diet and exercise, and were therefore candidates for insulin therapy, were recruited to participate in a randomized trial of either insulin aspart or regular human insulin (Table 1). Before insulinization, three 4-h breakfast meal tests were administered, whenever possible, on 3 consecutive days. The

Table 1—*Characteristics of study participants* (n = 15)

	Mean ± SE	Range
Age at enrollment (years)	31.9 ± 1.9	20.4–46.5
Height (cm)	156.1 ± 1.6	149.0–173.5
Prepregnancy weight (kg)*	65.5 ± 3.9	51.8–102.3
BMI (kg/m^2)	26.8 ± 1.5	21.4–41.2
Fasting plasma glucose†	93.5 ± 3.4	76.0–120.0
Gravity	2.8 ± 0.4	1–7
Parity	1.7 ± 0.4	0–6

*Data missing for one participant. †At baseline meal test.

From the [1]Sansum Medical Research Institute, Santa Barbara, California; and [2]Novo Nordisk Pharmaceuticals, Inc., Princeton, New Jersey.

Address correspondence and reprint requests to David J. Pettitt, MD, Sansum Medical Research Institute, 2219 Bath St., Santa Barbara, CA 93105. E-mail: dpettitt@sansum.org.

Received for publication 17 May 2002 and accepted in revised form 26 September 2002.

Abbreviations: AUC, area under the curve; GDM, gestational diabetes mellitus.

A table elsewhere in this issue shows conventional and Système International (SI) units and conversion factors for many substances.

Table 2 —*Glucose, insulin, and C-peptide during three meal tests*

	No exogenous insulin			Regular insulin			Insulin aspart		
Time (min)	Glucose (mg/dl)	Insulin (μU/ml)	C-peptide (ng/ml)	Glucose (mg/dl)	Insulin (μU/ml)	C-peptide (ng/ml)	Glucose (mg/dl)	Insulin (μU/ml)	C-peptide (ng/ml)
−30	93.7 ± 3.1	14.4 ± 3.6	2.5 ± 0.4	93.0 ± 2.5	16.7 ± 3.1	2.3 ± 0.2	94.3 ± 2.7	15.2 ± 2.9	2.6 ± 0.4
0	93.5 ± 3.4	14.6 ± 3.3	2.5 ± 0.4	89.6 ± 2.5	18.2 ± 3.8*	2.5 ± 0.4	93.0 ± 2.6	14.6 ± 3.1†	2.6 ± 0.4
15	91.7 ± 2.7	16.0 ± 2.8	2.5 ± 0.3	87.3 ± 3.0‡	28.1 ± 6.9‡	2.5 ± 0.4	90.5 ± 2.6	20.0 ± 2.9‡	2.6 ± 0.3
30	101.7 ± 2.9	37.4 ± 3.9	4.0 ± 0.4	101.8 ± 2.9	51.5 ± 7.4‡	4.2 ± 0.4	102.2 ± 3.8	56.1 ± 6.5*	4.2 ± 0.4
60	122.8 ± 3.0	72.3 ± 9.7	6.8 ± 0.7	115.8 ± 2.9‡	84.7 ± 10.8‡	5.8 ± 0.4	111.6 ± 3.9*	95.9 ± 10.9*	5.5 ± 0.3‡
90	112.8 ± 2.8	53.9 ± 8.6	6.2 ± 0.6	108.4 ± 2.6‡	68.2 ± 10.4‡	5.8 ± 0.5	103.3 ± 4.3‡	77.4 ± 8.8*	5.4 ± 0.5
120	102.5 ± 2.5	35.6 ± 6.2	5.4 ± 0.7	100.6 ± 2.5	55.2 ± 9.4*	5.4 ± 0.6	93.1 ± 3.5*	51.7 ± 9.8*	4.8 ± 0.7
180	85.1 ± 2.1	20.0 ± 4.1	3.9 ± 0.5	79.9 ± 2.6‡	26.9 ± 4.5‡	3.1 ± 0.4	72.5 ± 3.4*†	24.6 ± 4.6	2.7 ± 0.4*†
240	74.7 ± 1.7	11.2 ± 3.0	2.6 ± 0.5	66.7 ± 2.0*	18.8 ± 3.3*	1.8 ± 0.4*	65.5 ± 2.0*	15.4 ± 1.9‡	1.5 ± 0.2*†

Data are means ± SE. *$P = 0.01$; †$P < 0.05$ vs. meal using regular human insulin; ‡$P < 0.05$ vs. meal with no exogenous insulin.

meal, which was plain yogurt (Alta Dena, City of Industry, CA), contained 11 g fat, 19 g carbohydrate, and 12 g protein per cup (227 g) and was topped with one-half sliced banana. This meal comprised ~40% carbohydrate, 20% protein, and 40% fat and was calculated to provide 20% of the woman's daily caloric requirement. The same volume of yogurt was given for each of the three meal tests. On day 1, a baseline meal was consumed without any exogenous insulin. On day 2, each woman was randomly assigned to take either regular human insulin or insulin aspart, and on day 3, she took the other insulin preparation. Regular insulin was administered 30 min before and insulin aspart 5 min before the meal. The same dose of insulin was given on both days and was two-ninths of the woman's calculated daily requirement (0.8 units · kg^{-1} · day^{-1} for gestational age <26 weeks; 0.9 units · kg^{-1} · day^{-1} for gestational age ≥26 weeks). An indwelling intravenous catheter was placed and blood was drawn for plasma glucose, serum insulin, and C-peptide concentrations at –30, 0, 15, 30, 60, 90, 120, 180, and 240 min. No other food was consumed during this time, but symptomatic hypoglycemia was treated with oral glucose tablets.

Plasma glucose concentration was determined by the glucose oxidase method. Serum insulin was determined with enzyme-linked immunosorbent assay (ELISA) (Roche Diagnostics, Indianapolis, IN) and serum C-peptide by radioimmunoassay (Diagnostic Products, Los Angeles, CA).

The serum insulin and plasma glucose areas under the curve (AUCs) above the baseline glucose (time 0) were calculated at 120, 180, and 240 min. Paired *t* tests were used to compare the insulin and glucose areas and the glucose, insulin, and C-peptide concentrations at each time point.

Fifteen women who met the criteria for inclusion in the study participated in all three meal tests. During one meal test, the intravenous catheter ceased to function after the 60-min sample was collected, and subsequent phlebotomy by venipuncture was unsuccessful. Consequently, blood was not obtained from one woman for glucose measurements after the 60-min time point during the meal at which she took regular insulin. With the exception of one skipped sample due to difficulty with a catheter, the other 14 women completed all three of the 4-h meal tests.

RESULTS — Table 2 shows the mean glucose, insulin, and C-peptide concentrations during each of the three meal tests. The peak insulin was at 60 min during each of the three meal tests and was significantly lower during the meal in which no exogenous insulin was administered (72.6 ± 9.7 μU/ml [mean ± SE]) than with either regular insulin (84.7 ± 10.8 μU/ml; $t = 2.35$, $P = 0.034$ compared with no insulin) or insulin aspart (95.9 ± 10.9 μU/ml; $t = 3.6$, $P = 0.009$). The insulin concentrations are plotted in Fig. 1. In contrast, serum C-peptide peak and overall response were lower after injection of insulin aspart (5.5 ng/ml) than after no insulin (6.8 ng/ml; $t = 2.40$, $P = 0.031$). The peak C-peptide after the injection of regular insulin (5.8 ng/ml) was only slightly lower than after no insulin, and the difference was not statistically significant ($t = 1.93$, $P = 0.074$). After the peak at 60 min, the C-peptide tended to be lower after the insulin aspart injection than after the human regular injection, and this reached stastical significance at 180 and 240 min (Table 2).

Similarly, the peak glucose was at the 60-min time point during all three meal

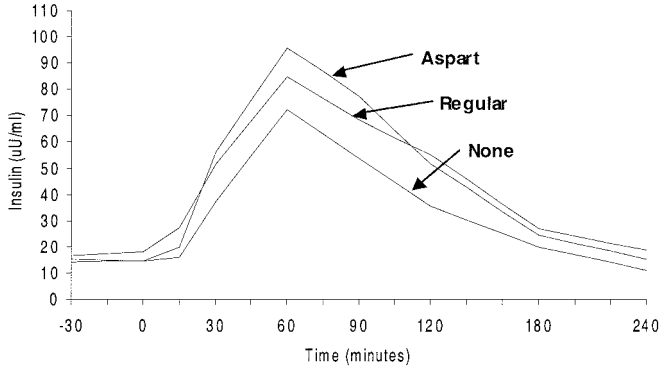

Figure 1—*Mean insulin concentrations during 4-h meal tests with no exogenous insulin, regular human insulin, or insulin aspart.*

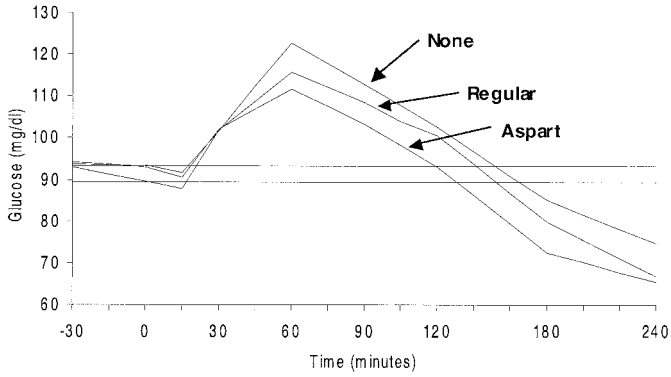

Figure 2—*Mean glucose concentrations during 4-h meal tests with no exogenous insulin, regular human insulin, or insulin aspart. The horizontal lines are the glucose concentrations at time 0 for the meal at which no exogenous insulin was administered (upper line) and for the meal at which regular insulin was administered (lower line).*

tests and was significantly lower with insulin aspart (111.6 ± 3.9 mg/dl; $t = 4.2$, $P < 0.001$) and with regular insulin (115.8 ± 2.9 mg/dl; $t = 2.4$, $P = 0.034$) than without exogenous insulin (122.8 ± 3.0 mg/dl). Fifteen minutes into the meal, the women had a lower glucose concentration after taking regular insulin (87.3 mg/dl [95% CI 81.4–93.1]) than they did during the baseline meal test (91.7[95% CI 86.4–97.1]; $t = 2.5$, $P = 0.025$), and the glucose was lower at 60, 90, 120, and 240 min. With insulin aspart, the glucose was lower at all time points from 60 min onward.

The rise in glucose concentration from the nadir at 15 min to the peak at 60 min was similar during the meals in which regular insulin (28.1 ± 2.9 mg/dl) and no insulin (31.1 ± 2.9 mg/dl) were used ($t = 0.8$, $P = 0.432$). The rise during the meal in which aspart was used was lower (21.1 ± 3.7 mg/dl; $t = 3.3$, $P = 0.006$ compared with no insulin).

The glucose concentrations are plotted in Fig. 2, and the glucose areas are shown in Table 3. The 120-, 180-, and 240-min glucose AUCs were lower for insulin aspart ($P = 0.05$, 0.02, and 0.005, respectively). The AUC for regular insulin was similar to that for no insulin throughout the meal test.

Seven women had glucose concentrations <60 mg/dl during one or both of the meal tests at which insulin was administered, but no hypoglycemic episode occurred before 3 h after the meal. There were no glucose concentrations <50 mg/dl, the hypoglycemia cut point for this study.

CONCLUSIONS — The major finding of this study is that insulin aspart was very effective in reducing the peak postprandial glucose concentration, resulting in a significantly lower glucose area than without insulin. Regular human insulin failed to make a significant impact in lowering the postprandial glucose concentration. Because the insulin assay used in this study measured total insulin (i.e., both exogenous and endogenous insulin), the contribution of the endogenous insulin to the postprandial glycemic profile can be ascertained by comparison of the C-peptide response. From the 60-min time point onward, the C-peptide tended to be lower after the insulin aspart injection than after the human regular insulin. This difference, which was statistically significant after 180 min, indicated that after the insulin aspart injection there was a lower demand for endogenous insulin than after human regular insulin.

In a review summarizing a Medline database search performed to examine the pharmacology, therapeutics, pharmacokinetics, dosing guidelines, adverse effects, and drug interactions of insulin aspart in nonpregnant healthy volunteers and nonpregnant type 1 and type 2 diabetic patients (16), it was reported that when insulin aspart is administered immediately before a meal, it is at least as effective as regular human insulin in control of postprandial blood glucose concentrations. In all published reports of nonpregnant persons, insulin aspart achieved higher peak insulin concentrations in less time and with a shorter duration of action than regular human insulin. The authors of the review concluded that, based on these data, insulin aspart is a convenient premeal insulin for use by patients requiring mealtime insulin, and furthermore, due to favorable pharmacokinetics, insulin aspart blunts the postprandial blood glucose concentrations at least as well as regular human insulin and contributes to improved quality of life. Our present report of the use of insulin aspart in women with gestational diabetes is the first clinical trial to study the use of insulin aspart in comparison with regular human insulin in pregnant women. Although there are reports of the use of another short-acting insulin analog, insulin lispro, in women with gestational diabetes, those reports do not compare the rapid analog with no insulin (17).

In this study, insulin aspart was effective in decreasing the postprandial glucose concentration when administered 5 min before a meal to women with GDM. Because elevated postprandial glucose concentrations have been associated with an increased risk of macrosomia (11–13), decreased postprandial glucose concentrations with insulin aspart in women with insulin-requiring GDM should result in an improvement in birth weight. Follow-up of a sufficient number of women requiring insulin during pregnancy will be needed to verify this finding and to ensure the safety of this insulin analog in pregnant women with diabetes.

Table 3—*Glucose AUC (mg · h · dl^{-1}) at 120, 180, and 240 min during three meal tests*

	No exogenous insulin	Regular insulin	Insulin aspart
120 min	29.1 (4.9)	29.8 (4.2)	17.3 (5.4)
		$P = 0.960$	$P = 0.052$
180 min	29.4 (7.5)	30.2 (6.1)	7.1 (7.9)
		$P = 0.997$	$P = 0.018$
240 min	15.8 (10.1)	11.0 (8.2)	−16.9 (10.4)
		$P = 0.888$	$P = 0.005$

P values are relative to no exogenous insulin.

Acknowledgments— This study was supported in part through a contract with Novo Nordisk Pharmaceuticals, Inc.

References

1. Metzger BE, Coustan DR, The Organizing Committee: Summary and Recommendations of the Fourth International Workshop-Conference on Gestational Diabetes Mellitus. *Diabetes Care* 21 (Suppl. 2): B161–B167, 1998
2. Jovanovic L (Ed.): *Medical Management of Pregnancy Complicated by Diabetes*. Alexandria, VA, American Diabetes Association, 2000
3. Engelgau M, German R, Herman W, Aubert R, Smith J: The epidemiology of diabetes and pregnancy in the U.S., 1988. *Diabetes Care* 18:1029–1033, 1995
4. McCance DR, Pettitt DJ, Hanson RL, Jacobsson LTH, Knowler WC, Bennett PH: Birth weight and non-insulin-dependent diabetes: thrifty genotype, thrifty phenotype, or surviving small baby genotype? *BMJ* 398:942–945, 1994
5. Langer O, Mazze R: The relationship between large-for-gestational-age infants and glycemic control in women with gestational diabetes. *Am J Obstet Gynecol* 159: 1478–1483, 1988
6. Persson B, Hanson U: Neonatal morbidities in gestational diabetes mellitus. *Diabetes Care* 21 (Suppl. 2):B79–B84, 1998
7. Jovanovic L, Crues J, Durak E, Peterson CM: Magnetic resonance imaging in pregnancies complicated by diabetes predicts infant birthweight ratio and neonatal morbidity. *Am J Perinatol* 10:432–437, 1993
8. Hod M, Rabinerson D, Peled Y: Gestational diabetes mellitus: is it a clinical entity? *Diabetes Rev* 3:603–613, 1995
9. Ogata ES: Perinatal morbidity in offspring of diabetic mothers. *Diabetes Rev* 3:652–657, 1995
10. Langer O: Is normoglycemia the correct threshold to prevent complications in the pregnant diabetic patient? *Diabetes Rev* 4:2–10, 1995
11. Jovanovic L, Reed GF, Metzger BE, Mills JL, Knopp RH, Aarons JH: Maternal postprandial glucose levels and infant birth weight: the Diabetes in Early Pregnancy Study. The National Institute of Child Health and Human Development–Diabetes in Early Pregnancy Study. *Am J Obstet Gynecol* 164:103–111, 1991
12. Combs CA, Gunderson E, Kitzmiller JL, Gavin LA, Main EK: Relationship of fetal macrosomia to maternal postprandial glucose control during pregnancy. *Diabetes Care* 15:1251–1257, 1992
13. deVeciana M, Major CA, Morgan MA: Postprandial versus preprandial blood glucose monitoring in women with gestational diabetes mellitus requiring insulin therapy. *N Engl J Med* 333:1237–1241, 1995
14. Schade DS, Santiago JV, Skyler JS, Rizza RA: Self-monitoring of blood glucose. In *Intensive Insulin Therapy*. Amsterdam, Excerpta Medica, 1983, p. 176–193
15. Moses RG, Lucas EM, Knights S: Gestational diabetes mellitus: at what time should the postprandial glucose level be monitored? *Aust NZ J Obstet Gynecol* 39: 457–460, 1999
16. Setter SM, Corbett CF, Campbell RK, White JR: Insulin aspart: a new rapid-acting insulin analog. *Ann Pharmacother* 34: 1423–1431, 2000
17. Jovanovic L, Ilic S, Pettitt DJ, Hugo K, Gutierrez M, Bowsher RR, Bastyr EJ: Metabolic and immunologic effects of insulin lispro in gestational diabetes. *Diabetes Care* 22:1422–1427, 1999