Maternal Glycemic Control and Hypoglycemia in Type 1 Diabetic Pregnancy

A randomized trial of insulin aspart versus human insulin in 322 pregnant women

ELISABETH R. MATHIESEN, MD, DMSC[1]
BRENDAN KINSLEY, MD, FRCPI[2]
STEPHANIE A. AMIEL, MD, FRCP[3]
SIMON HELLER, MD, FRCP[4]
DAVID MCCANCE, MD[5]
SANTIAGO DURAN, MD[6]
SHANNON BELLAIRE, MSC[7]
ANNE RABEN, PHD[7]
ON BEHALF OF THE INSULIN ASPART PREGNANCY STUDY GROUP

OBJECTIVE — To assess the safety and efficacy of insulin aspart (IAsp) versus regular human insulin (HI) in basal-bolus therapy with NPH insulin in pregnant women with type 1 diabetes.

RESEARCH DESIGN AND METHODS — Subjects (n = 322) who were pregnant or planning pregnancy were randomized to IAsp or HI as meal-time insulin in an open-label, parallel-group, multicenter study. Subjects had A1C ≤8% at confirmation of pregnancy. Insulin doses were titrated toward predefined glucose targets and A1C <6.5%. Outcomes assessed included risk of major maternal hypoglycemia, A1C, plasma glucose profiles, and maternal safety outcomes.

RESULTS — Major hypoglycemia occurred at a rate of 1.4 vs. 2.1 episodes/year exposure with IAsp and HI, respectively (relative risk 0.720 [95% CI 0.36–1.46]). Risk of major/major nocturnal hypoglycemia was 52% (RR 0.48 [0.20–1.143]; P = NS) lower with IAsp compared with HI. A1C was comparable with human insulin in second (IAsp-HI −0.04 [−0.18 to 0.11]) and third (−0.08 [−0.23 to 0.06]) trimesters. A total of 80% of subjects achieved an A1C ≤6.5%. At the end of first and third trimesters, average postprandial plasma glucose increments were significantly lower with IAsp than HI (P = 0.003 and P = 0.044, respectively), as were mean plasma glucose levels 90 min after breakfast (P = 0.044 and P = 0.001, respectively). Maternal safety profiles and pregnancy outcomes were similar between treatments.

CONCLUSIONS — IAsp is at least as safe and effective as HI when used in basal-bolus therapy with NPH insulin in pregnant women with type 1 diabetes and may potentially offer some benefits in terms of postprandial glucose control and preventing severe hypoglycemia.

Diabetes Care 30:771–776, 2007

From the [1]Department of Endocrinology, Rigshospitalet, Copenhagen, Denmark; the [2]Department of Endocrinology, Mater Misericordiae University Hospital Dublin, Dublin, Ireland; the [3]Diabetes Research Group, Kings College School of Medicine, London, U.K.; the [4]Northern General Hospital, Sheffield, U.K.; the [5]Regional Centre for Endocrinology and Diabetes, Royal Victoria Hospital, Belfast, U.K.; the [6]Unidad de Investigacion Diabetes, Hospital Virgen de Valme, Seville, Spain; and [7]Novo Nordisk, Copenhagen, Denmark.

Address correspondence and reprint requests to Elisabeth R. Mathiesen, Copenhagen Centre for Pregnant Women With Diabetes, Department of Endocrinology 2132, Rigshospitalet, Blegdamsvej 9, DK-2100 Copenhagen, Denmark. E-mail: em@rh.dk.

Received for publication 8 September 2006 and accepted in revised form 28 December 2006.

E.R.M. is a member of the scientific advisory panel for this study and has received monetary compensation for this consulting work. S.A.A. has served on advisory panels for Pfizer, Sanofi-Aventis, Novartis, MSD, Eli Lilly U.K., and Amylin. S.H. has served on advisory boards for, has received research funds from, and has given lectures sponsored by Novo Nordisk.

Additional information for this article can be found in an online appendix at http://dx.doi.org/10.2337/dc06-1887.

Abbreviations: HI, human insulin; IAsp, insulin aspart; ITT, intention-to-treat.

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

DOI: 10.2337/dc06-1887. Clinical trial reg. no. NCT00365170, clinicaltrials.gov.

Recent surveys show that the risk of perinatal complications remains increased in women with diabetes (1–5). Many maternal and fetal complications are associated with poor maternal glycemic control during pregnancy (6–9), and avoiding hyperglycemia improves pregnancy outcome (10–12). However, tightening glycemic control may increase the risk of major hypoglycemia (13–17), with potential adverse maternal outcomes including coma, seizures, and maternal death (16,18).

We hypothesized that use of the rapid-acting insulin analog, insulin aspart (IAsp), for meal-related insulin replacement may be of benefit during pregnancy complicated by diabetes by providing better control of postprandial hyperglycemia with less hypoglycemia, compared with regular human insulin (HI). IAsp has onset of action within 10–20 min of injection, peak action within 40–50 min, and duration of action of 3–5 h (19). In clinical studies, compared with HI, IAsp provides superior postprandial glycemic control with less risk of major and nocturnal hypoglycemic episodes and small improvement in A1C (20–24). Safety and efficacy of the use of insulin analogs during pregnancy has yet to be confirmed in randomized controlled trials, although observational studies have not identified cause for concern (25–29).

The aim of this study was to evaluate the risk of major maternal hypoglycemia, metabolic control, and safety, including perinatal outcomes in pregnant women with type 1 diabetes on IAsp. This study presents data on maternal hypoglycemia, glycemic control, and safety. Data on perinatal outcomes are reported separately.

RESEARCH DESIGN AND METHODS

— A total of 417 women with type 1 diabetes participated in this open-label, randomized, parallel-group study conducted at 63 sites in 18 countries, mainly within Europe. The study

was performed in accordance with the Declaration of Helsinki and was approved by respective ethics committees and health authorities according to local regulations. Written informed consent was obtained from subjects before study start.

Eligible subjects were aged ≥18 years with insulin-treated type 1 diabetes for ≥12 months and were either pregnant with a singleton pregnancy (gestational age ≤10 weeks) or planning to become pregnant. A1C was ≤8% at confirmation of pregnancy. Subjects not pregnant at screening were withdrawn if not pregnant ≤12 months after randomization. Subjects with multiple pregnancy, fertility treatment, clinically significant gynecological conditions, diabetic nephropathy; or medical problems; a previous child born with major congenital malformations; multiple miscarriage; or stillbirths (more than two) were excluded.

Treatments

Subjects were randomized (1:1) to IAsp (100 units/ml; Novo Nordisk, Bagsvaerd, Denmark) or HI (100 IU/ml; Novo Nordisk) in combination with NPH insulin (Novo Nordisk) one to four times per day. Subjects were allocated to the lowest available treatment number at each center.

IAsp was injected immediately before meals and HI within 30 min before the meal. All insulins were injected subcutaneously using the NovoPen 3.0 (Novo Nordisk). Because study insulin injection timing varied, an open-label approach was used. The starting dose for both study insulins was 100% of dose at study entry. Insulin doses were titrated to optimal levels throughout the study based on self-monitored plasma glucose levels and the targets for blood glucose control: preprandial 4.1–6.1 mmol/l, 1 h postprandial <8.6 mmol/l, 2 h postprandial <7.5 mmol/l (according to American Diabetes Association guidelines), and A1C <6.5%.

Assessments

Subjects pregnant at screening attended a first-pregnancy assessment/randomization (P1) visit (<2 weeks after screening); clinic visits at the end of the first, second, and third trimester (P2–P4) (12, 24, and 36 weeks' gestation); delivery/termination (T); and follow-up visit 6 weeks postdelivery. Subjects not pregnant at randomization attended 3-monthly clinic visits until pregnant. On pregnancy confirmation, they attended visit P1. Thereafter, clinic visits were as described for subjects pregnant at screening. Study duration and number of visits varied between subjects depending on time of conception relative to screening. Maximum duration of participation was 22 months.

Primary study end point was major (requiring third-party assistance with plasma glucose <3.1 mmol/l or reversal of symptoms after food, glucagon, or intravenous glucose) hypoglycemia during pregnancy. Minor (plasma glucose <3.1 mmol/l with or without symptoms) and symptoms-only (no plasma glucose measurement or plasma glucose >3.0 mmol/l) hypoglycemia were also recorded by subjects in their diaries. Nocturnal hypoglycemia was taken as episodes between midnight and 0600 h.

Efficacy end points were A1C and self-measured 8-point plasma glucose profile. Subjects were asked to perform an 8-point plasma glucose profile during the week before randomization and clinic visits P1–P4 using a Medisense (Maidenhead, U.K.) blood glucose meter. Other safety assessments included maternal adverse events, obstetric complications, diabetes complications, pregnancy outcomes, and delivery details.

Treatment satisfaction was assessed using the Diabetes Treatment Satisfaction Questionnaire (30) at randomization and at follow-up visits for subjects pregnant at screening, visit P1, and at follow-up for subjects pregnant after screening. Subjects ranked eight items on a 7-point Likert scale to measure overall treatment satisfaction (satisfaction with treatment, flexibility, diabetes understanding, convenience, and willingness to continue treatment and recommend treatment) and perception of hyper- and hypoglycemia. Items were scored on a 0–6 scale then transformed to a 0–100 scale (higher scale = greater treatment satisfaction).

Laboratory analyses (A1C, hematology, biochemistry, and urinalysis) were performed by MDS Pharma Services Central Lab (Hamburg, Germany). A1C was analyzed using a National Glycohemoglobin Standardization Program–certified method (Diabetes Control and Complications Trial standard).

Statistical analysis

Assuming an incidence of one major hypoglycemic episode during pregnancy with 7 months of insulin treatment (11), 305 subjects were required to be randomized and to complete the study to detect a treatment difference of 40% with a power of 80% (5% significance level). Planned recruitment was 380 pregnant women with 100 enrolled before pregnancy.

Results presented are based on the intention-to-treat (ITT) analysis set (all treated/exposed subjects confirmed pregnant during the study even if they did not complete all study visits, $ITT_{pregnant}$ n = 322, with 264 completers).

Risk of major maternal hypoglycemia was assessed from its incidence during pregnancy. Episodes were analyzed as recurrent events using a γ frailty model with treatment as covariate. This Cox regression model appropriately handles the recurrent aspects of episodes (30,31). Delayed entry was used for those pregnant at screening, to account for the different observation periods. The number of minor hypoglycemic episodes was analyzed using the same model.

As supportive analyses to the primary safety end point, a noninferiority criterion (<0.4% difference in A1C) was tested at visits P3 and P4 using a linear mixed model, with treatment and pregnancy status at screening as fixed effects and country as a random effect using a one-sided t test with a 2.5% significance level. Average plasma glucose increments (average postprandial values minus preprandial values), average 24-h plasma glucose, and each of the 8-point plasma glucose values at visits P2–P4 were analyzed based on the model described above.

Treatment differences in quality-of-life assessments at the follow-up visit were analyzed using the Wilcoxon rank-sum test. A significance level of 5% was used for statistical analyses, which were generated using SAS version 8.2 (SAS Institute, Cary, NC) on a UNIX platform or S-PLUS version 6.0 Professional for Windows (Microsoft, Seattle, WA).

RESULTS

— Subjects were recruited between September 2002 and August 2004; the last follow-up visit was in April 2005. In total, 412 subjects were randomized and treated. Of these, 322 (IAsp, 157; HI, 165) were pregnant during the study ($ITT_{pregnant}$ cohort). In total, 223 (IAsp, 113; HI, 110) were pregnant at screening, and 99 (IAsp, 44; HI, 55) became pregnant after screening. Withdrawal patterns in pregnant women were similar between treatments. Overall, 190 (IAsp, 102; HI, 88) of those pregnant and 74 (IAsp, 31; HI, 43) of those not pregnant at screening completed pregnancy and the trial intervention. Of 58 noncompleters (IAsp, 24; HI, 34), 31 were withdrawn due to adverse events (IAsp, 14;

Table 1—*Demographic and baseline characteristics of subjects*

Parameter	IAsp	HI
n	157	165
Age (years)	29.0 ± 4.7	29.0 ± 4.5
BMI (kg/m^2)	24.9 ± 4.0	24.6 ± 3.7
A1C (%)	7.0 ± 0.8	6.9 ± 1.0
Duration of diabetes (years)	12.2 ± 7.1	11.8 ± 7.4
Retinopathy	43 (27.4)	45 (27.3)
Neuropathy	7 (4.5)	4 (2.4)
Relative total daily insulin dose (units/kg)	0.77 ± 0.27	0.78 ± 0.24
Pretrial insulin (analog treatment)	73 (46.5)	80 (48.5)

Data are mean ± SD or *n* (%).

HI, 17) and 27 for other reasons (IAsp, 10; HI, 17). Age, A1C, BMI, duration of diabetes, and mean daily insulin requirements at baseline were similar between treatment groups (Table 1).

Hypoglycemic episodes

Observed rates of major maternal hypoglycemia were lower with IAsp than HI (Table 2). A 28% lower risk for major hypoglycemia (IAsp/HI; relative risk [RR] 0.720 [95% CI 0.36–1.46]) and a 52% lower risk for major nocturnal hypoglycemia (0.48 [0.20–1.14]) was estimated for the IAsp versus HI groups, respectively, although this did not reach statistical significance. Risks for major daytime (0.85 [0.40–1.78]), all (0.97 [0.66–1.44]), and minor (0.97 [0.66–1.43]) hypoglycemia were similar between treatments (Table 2). The estimated risk of any nocturnal hypoglycemia was 24% lower on IAsp (0.76 [0.57–1.03]). Risk of all daytime hypoglycemia was similar between treatments (1.08 [0.71–1.63]).

Efficacy

Glycemic control

Treatment with IAsp was noninferior to treatment with HI as assessed by A1C at the end of the second and third trimesters (mean difference [95% CI]) (IAsp minus HI: −0.04% [−0.18 to 0.11], P = NS; −0.08% [−0.23 to 0.06], P = NS). In both treatment groups, A1C decreased during the first two trimesters then increased toward delivery and follow-up (Fig. 1*A*). A1C was ≤6.5% for most subjects in both treatment groups during the second and third trimesters (P3: IAsp, 83%; HI, 79%; P4: IAsp, 78%; HI, 73%).

Mean 8-point plasma glucose profile at P2 is shown in Fig. 1*B*. Overall profiles were similar at P3 and P4 (data not shown), although estimated mean values of 24-h plasma glucose increased from visit P2 to P3, then decreased at visit P4 (IAsp: 6.82, 6.96, and 6.23; HI: 6.82, 7.10, and 6.48 mmol/l, respectively). Postprandial plasma glucose levels were consistently lower with IAsp after breakfast (B90), with statistically significant between-treatment differences at P2 (P = 0.044) and P4 (P = 0.0007) but not at P3 (P = 0.153). Preprandial (prebreakfast, prelunch, and predinner) plasma glucose levels were comparable between treatments at all visits.

Mean prandial plasma glucose increments (mean of difference in pre- and postprandial plasma glucose at breakfast, lunch, and dinner) during pregnancy were lower with IAsp than HI. Between-treatment differences were statistically significant at visits P2 and P4 (IAsp minus HI [in mmol/l] P2: −0.75 [95% CI −1.25 to −0.25], P = 0.003; P4: −0.40 [−0.80 to −0.01], P = 0.044).

Insulin dose

Mean total daily insulin doses were similar between treatments. Doses increased during pregnancy and were lower than prepregnancy doses after delivery. At visit P4, total insulin dose (mean ± SD) was 1.08 ± 0.38 and 1.15 ± 0.44 units/kg in the IAsp and HI groups, respectively. Mean daily requirement of bolus insulin during the study was lower in the IAsp group than in the HI group (IAsp: 0.60 ± 0.29; HI: 0.70 ± 0.38 units/kg at visit P4). At visit P4, mean mealtime doses were 0.19 ± 0.10 units/kg with IAsp and 0.23 ± 0.12 units/kg with HI. At visit P4, mean daily dose of NPH was 0.48 ± 0.21 units/kg in the IAsp group compared with 0.45 ± 0.25 units/kg in the HI group. In the third trimester, mean daily insulin doses in the IAsp group were similar between subjects achieving A1C <6.5% and those not meeting target (1.07 vs. 1.12 units/kg). In the HI group, doses tended to be higher in those achieving target (1.16 vs. 1.09 units/kg) due to a higher bolus dose (0.74 vs. 0.60 units/kg). During pregnancy, most (59–75%) pregnant subjects in both treatment groups used at least two basal insulin injections per day. At visit P4, 50% of subjects on IAsp were on two daily injections of NPH and 23.1% were on three or four daily NPH injections. In the NPH group, comparable proportions were 42.7 and 23.1%, respectively.

Table 2—*Hypoglycemic episodes during pregnancy by treatment group and by pregnancy status at randomization*

	IAsp (*n* = 157)					HI (*n* = 165)				
	n	*n* with episode	% with episode	*E*	Rate	*n*	*n* with episode	% with episode	*n* of episodes	Rate
Major	157	38	24.2	113	1.4	165	35	21.2	174	2.1
Minor	157	148	94.3	7,197	86.4	165	148	89.7	7,944	94.5
Symptoms only	157	85	54.1	1,055	12.7	165	85	51.5	742	8.8
Not classified	157	19	12.1	142	1.7	165	20	12.1	401	4.8
All	157	149	94.9	8,507	102.1	165	150	90.9	9,261	110.1
Pregnant at screening	113	108	95.6	6,556	111.1	110	99	90.0	6,246	120.9
Pregnant after screening	44	41	93.2	1,951	80.4	55	51	92.7	3,015	93.0

E, number of hypoglycemic episodes; Rate, number of hypoglycemic episodes divided by years of exposure in subjects in the population.

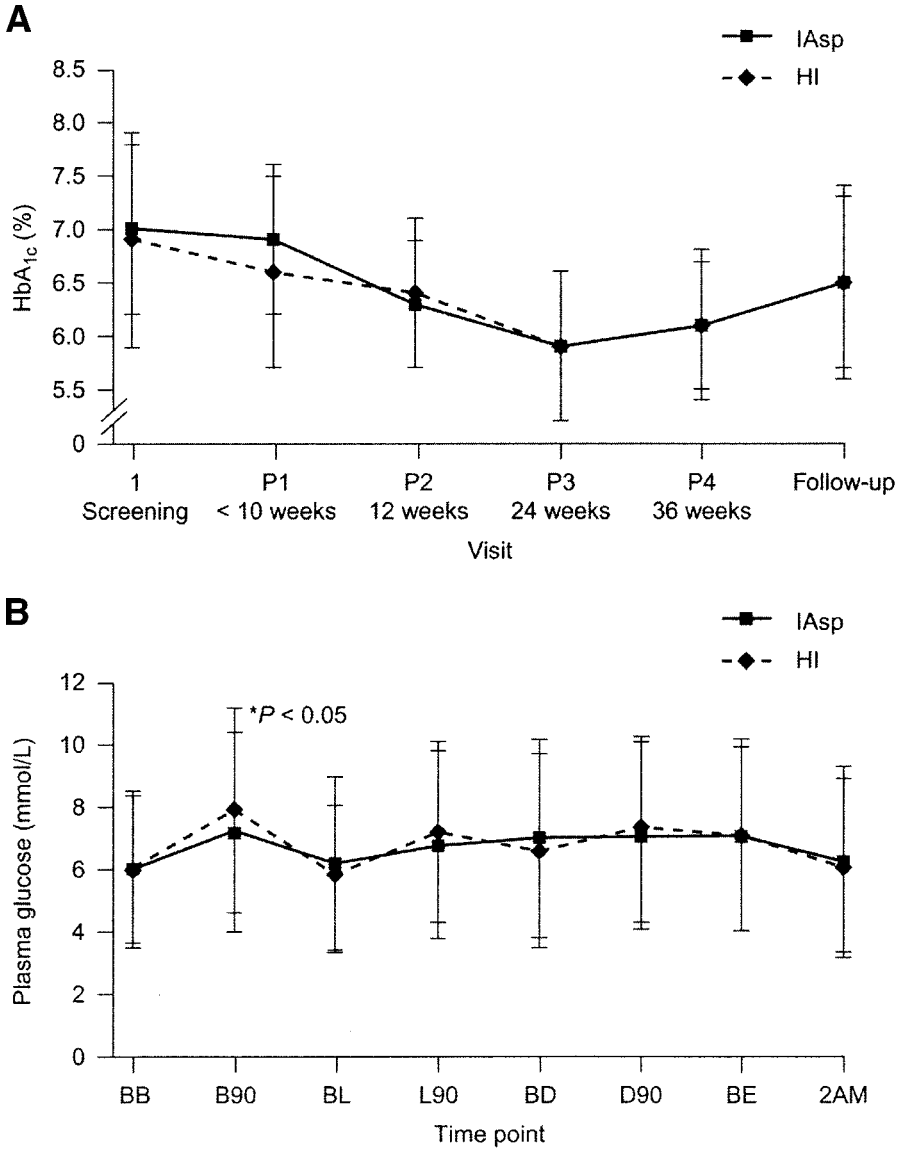

Figure 1—A: *Mean A1C (%) by treatment group during pregnancy and at the follow-up (6 weeks postpartum) visit. Data at visit P1 only includes data for subjects pregnant after screening. Data are means ± SD.* B: *Mean 8-point plasma glucose profile (mmol/l) (±SD) by treatment group at visit P2 (12 weeks of gestation). 2AM, 0200 h; B90, 90 min after breakfast; BB, before breakfast; BD, before dinner; BE, bedtime; BL, before lunch; D90, 90 min after dinner; L90, 90 min after lunch.*

Adverse events

No maternal deaths were reported. Both insulins were well tolerated, and the adverse event profiles were similar. Most events were mild or moderate and considered unlikely to be related to study products. Eighteen serious adverse events (IAsp, 6; HI, 12) were considered to have a possible relation to study medication (cesarean section [IAsp, 1; HI, 0], abortion [IAsp, 2; HI, 0], hypoglycemic coma [IAsp, 2; HI, 5], investigator-defined inadequate glycemic control [IAsp, 2; HI, 4], and hyperglycemia [IAsp, 0; HI, 3]). Two further events of hypoglycemic coma occurring before and after pregnancy were considered to be possibly related to treatment.

The frequency and profile of obstetric complications were similar between treatments. The most frequent complications were preeclampsia (IAsp, 13; HI, 11), threatened preterm labor (IAsp, 6; HI, 7), prolonged labor (IAsp, 5; HI, 7), and unplanned cesarean section (IAsp, 20; HI, 19).

Thirty-one subjects left the study because of adverse events (IAsp, 14; HI, 17). These were due to fetal loss (induced/spontaneous abortion or stillbirth) in 13 IAsp-treated and 14 HI-treated subjects. Most (IAsp, 79%; HI, 60%) fetal losses were spontaneous, occurring in the first 12 gestational weeks. Other withdrawals were due to hypoglycemia (IAsp, 1) and congenital malformation (HI, 3).

Diabetes complications and physical examination

No clinically significant difference in deterioration in fundoscopy was reported in either treatment group. Treatment groups were not different with respect to changes in vital signs, physical examination parameters, electrocardiograms, or clinical laboratory findings.

Pregnancy outcome

Comparison of pregnancy outcomes showed no significant between-treatment difference in live births (IAsp, 87.3%; HI, 79.4%), fetal losses (IAsp, 8.9%; HI, 12.1%), and congenital malformations (IAsp, 4.3%; HI, 6.6%). Pregnancy outcome was unknown for 20 subjects in the IAsp group and 6 subjects in the HI group. Additional data are reported in a separate study (M. Hod, P. Damm, R. Kaaja, F. Dunne, I. Demidova, A.-S.P. Mansen, H. Mersebach, unpublished data).

Quality-of-life assessments

At follow-up, the IAsp group reported a significantly greater ($P = 0.031$) overall treatment satisfaction (87.6 ± 12.0) than the HI group (83.4 ± 15.3). Between-treatment differences were largely due to more IAsp-treated subjects reporting satisfaction with flexible treatment (Diabetes Treatment Satisfaction Questionnaire scores) (IAsp, 85.9 ± 15.0; HI, 75.8 ± 23.8) and willingness to continue on present treatment (IAsp, 90.1 ± 16.2; HI, 81.9 ± 25.2). No statistical testing was performed on subitems.

CONCLUSIONS — This is the largest, randomized, controlled study to date of a rapid-acting insulin analog in pregnant women with type 1 diabetes. Although glycemic control, assessed by A1C, was similar with IAsp and HI, postprandial hyperglycemic excursions were lower with IAsp than with HI, especially after breakfast, with no difference in preprandial glucose control and no increase in major hypoglycemia. Indeed, the observed rate of major episodes was lower for IAsp-treated than HI-treated subjects.

Hypoglycemia, especially nocturnal

episodes, is more frequent during pregnancy (16–18), especially during intensified insulin treatment (16,32). In the present study, rates of major hypoglycemia (all and nocturnal episodes) tended to be lower with IAsp than with HI treatment. Similarly, Garg et al. (28) reported relatively few major hypoglycemic episodes in 62 insulin lispro-treated pregnant women with type 1 diabetes. The lack of statistical significance in the risk estimates may be because rates of major hypoglycemia in the present study were lower than expected, reducing its statistical power. Furthermore, the mean duration of exposure during pregnancy was slightly less than the planned 7 months (IAsp, 6.5 months; HI, 6.2 months), and fewer pregnant subjects than planned (264 vs. 305) completed the study.

Postprandial glucose excursions were generally lower with IAsp than with HI treatment, particularly during the first and third trimesters, with significantly lower glycemic excursions after breakfast. Preprandial plasma glucose values were similar between treatment groups. The improvement in postprandial glycemic control with IAsp in this study was similar to that reported in nonpregnant subjects (22,33–36). Lower postprandial glucose levels during pregnancy have been linked to decreased neonatal risks and perinatal complications (37).

Mean A1C levels during pregnancy were not different between treatments, and similar proportions of subjects achieved A1C <6.5% with a trend toward a lower incidence of major hypoglycemia in IAsp-treated subjects. Although recent data suggest that this target should be reevaluated as A1C levels are as low as 4.4–5.6% in the healthy pregnancy (36,38), this has to be balanced against the risk of hypoglycemia.

In the current study a minor deterioration in glycemic control with trend toward increasing A1C in the last trimester occurred in both treatment groups. Total daily insulin doses during this trimester were similar between IAsp-treated subjects achieving and not achieving target A1C <6.5% levels, but HI-treated subjects not meeting target had lower bolus insulin doses, suggesting that they could have benefited from further dose increments.

Throughout pregnancy, total daily insulin doses were similar between treatment groups, although bolus insulin doses were consistently lower for patients receiving IAsp than HI. Despite increases in bolus insulin doses toward the end of pregnancy, dose titration may have been insufficient to maintain or optimize postprandial glycemic control during pregnancy due to changes in insulin sensitivity, body weight, food consumption, and reduced exercise. By the end of the third trimester, doses of IAsp and HI were at their highest, and it was at this point that IAsp was again superior to HI with regard to control of postprandial hyperglycemia. The apparently lower incidence of major hypoglycemia with IAsp may allow more aggressive dose titration late in pregnancy to optimize glycemic control.

The greater treatment satisfaction score seen with IAsp compared with HI has been described previously in trials of rapid-acting analogs and may reflect the differences in the timing of injection relative to eating (34,39). Safety profiles of IAsp and HI were comparable. No maternal deaths were reported and pregnancy outcome was comparable between treatments.

In conclusion, treatment with IAsp resulted in superior postprandial glycemic control to HI with a nonsignificantly lower incidence of major hypoglycemia at comparable levels of A1C, which were mostly ≤6.5%. Maternal safety profiles were similar between treatments, and patients showed greater treatment satisfaction with IAsp. These data suggest that IAsp is at least as safe and effective as HI when used as mealtime insulin in a basal-bolus regimen with NPH insulin in pregnant women with type 1 diabetes and has the potential to offer some clinical benefits in terms of postprandial glucose control.

Acknowledgments— This trial was sponsored by Novo Nordisk.

We thank the Insulin Aspart Pregnancy Study Group: M.H., Peter Damm, Risto Kaaja, Gerard H.A. Visser, Fidelma Dunne, Irina Demidova, Anne-Sofie Pade-Hansen, Henriette Mersebach, E.R.M., B.K., S.A.A., S.H., D.M., S.D., S.B., A.R., Linda Elise Jensen, Julie Marie Fiona Clyde, Mark White, Anne Romstad, Karin Kanc Hanzel, Julius Anthony Vaz, and Benedikte Jade Lertoft. We also thank all investigators who participated in this trial (online appendix 1 [available at http://dx.doi.org/10.2337/dc06-1887]).

References

1. Casson IF, Clarke CA, Howard CV, McKendrick O, Pennycook S, Pharoah PO, Platt MJ, Stanisstreet M, van Velszen D, Walkinshaw S: Outcomes of pregnancy in insulin dependent diabetic women: results of a five year population cohort study. *BMJ* 315:275–278, 1997
2. Hawthorne G, Robson S, Ryall EA, Sen D, Roberts SH, Ward Platt MP: Prospective population-based survey of outcome of pregnancy in diabetic women: results of the Northern Diabetic Pregnancy Audit 1994. *BMJ* 315:279–281, 1997
3. Hadden DR: When and how to start insulin treatment in gestational diabetes: a UK perspective. *Diabet Med* 18:960–964, 2001
4. Evers IM, de Valk HW, Visser GH: Risk of complications of pregnancy in women with type 1 diabetes: nationwide prospective study in the Netherlands. *BMJ* 328: 915, 2004
5. Macintosh MC, Fleming KM, Bailey JA, Doyle P, Modder J, Acolet D, Golightly S, Miller A: Perinatal mortality and congenital anomalies in babies of women with type 1 or type 2 diabetes in England, Wales, and Northern Ireland: population based study. *BMJ* 333:177, 2006
6. Temple R, Aldridge V, Greenwood R, Heyburn P, Sampson M, Stanley K: Association between outcome of pregnancy and glycaemic control in early pregnancy in type 1 diabetes: population-based study. *BMJ* 325:1275–1276, 2002
7. Lepercq J, Coste J, Theau A, Dubois-Laforgue D, Timsit J: Factors associated with preterm delivery in women with type 1 diabetes: a cohort study. *Diabetes Care* 27:2824–2828, 2004
8. Nielsen GL, Sorensen HT, Nielsen PH, Sabroe S, Olsen J: Glycosylated hemaoglobin as preictor of adverse fetal outcome in type 1 diabetic pregnancies. *Acta Diabetol* 34:217–222, 1997
9. Suhonen L, Hiilesmaa V, Teramo K: Glycemic control during early pregnancy and fetal malformations in women with type 1 diabetes mellitus. *Diabetologia* 43:79–82, 2000
10. McElvy SS, Miodovnik M, Rosenn B, Khoury JC, Siddiqi T, Dignan PS, Tsang RC: A focused preconceptional and early pregnancy program in women with type 1 diabetes reduces perinatal mortality and malformation rates to general poultaion levels. *J Matern Fetal Med* 9:14–20, 2000
11. DCCT Research Group: Pregnancy outcomes in the Diabetes Control and Complications Trial. *Am J Obstet Gynecol* 174: 1343–1353, 1996
12. Manderson JG, Patterson CC, Hadden DR, Traub AI, Ennis C, McCance DR: Preprandial versus postprandial blood glucose monitoring in type 1 diabetic pregnancy: a randomized controlled clinical trial. *Am J Obstet Gynecol* 189:507–512, 2003
13. Rosenn B, Miodovnik M: Medical complications of diabetes mellitus in pregnancy. *Clin Obstet Gynecol* 43:17–31, 2000
14. Kimmerle R, Heinemann L, Delecki A, Berger M: Sever hypoglycemia, incidence and predisposing factors in 85 pregnancies of type 1 diabetic women. *Diabetes*

Care 15:1034–1037, 1992
15. Rayburn W, Piehl E, Jacober S, Schork A, Ploughman L: Severe hypoglycaemia during pregnancy: its frequency and predisposing factors in diabetic women. *Int J Gynaecol Obstet* 24:263–268, 1986
16. Rosenn BM, Miodovonik M, Holcberg G, Khoury JC, Siddiqi TA: Hypoglycemia: the price of intensive insulin therapy for pregnant women with insulin-dependent diabetes mellitus. *Obstet Gynecol* 85:417–422, 1995
17. Evers IM, Ter Braak EWMT, de Valk HW, van Der Schoot B, Janssen N, Visser GH: Risk indicators predictive for severe hypoglycemia during the first trimester of type 1 diabetic pregnancy. *Diabetes Care* 25:554–559, 2002
18. Ter Braak EW, Evers IM, Willem Erkelens D, Visser GH: Maternal hypoglycemia during pregnancy in type 1 diabetes: maternal and fetal consequences. *Diabetes Metab Res Rev* 18:96–105, 2002
19. Lindholm A, McEwen J, Riis AP: Improved postprandial glycemic control with insulin aspart: a randomized, double-blind cross over trial in type 1 diabetes. *Diabetes Care* 22:801–805, 1999
20. Howey DC, Bowsher RR, Brunelle RL, Woodworth JR: [Lys(B28), Pro(B29)]-human insulin: a rapidly absorbed analogue of human insulin. *Diabetes* 43:396–402, 1994
21. Heinemann L, Kapitza C, Starke AA, Heise T: Time-action profile of the insulin analogue B28Asp. *Diabet Med* 13:683–684, 1996
22. Owens DR, Zinman B, Bolli GB: Insulins today and beyond. *Lancet* 358:739–746, 2001
23. Heller SR, Colagiuri S, Vaaler S, Wolffenbuttel BH, Koelendorf K, Friberg HH, Windfeld K, Lindholm A: Hypoglycaemia with insulin aspart: a double-blind, randomised, crossover trial in subjects with type 1 diabetes. *Diabet Med* 21:769–775, 2004
24. Perriello G, Pampanelli S, Porcellati F, Avogaro A, Bosi E, Petrella G, Squatrito S, Furneri S, Marra G, Vitali L, Previti M, Cucinotta D: Insulin aspart improves meal time glycaemic control in patients with type 2 diabetes: a randomized, stratified, double-blind and cross-over trial. *Diabet Med* 22:606–611, 2005
25. Persson B, Swahn ML, Hjertberg R, Hanson U, Nord E, Nordlander E, Hansson LO: Insulin lispro therapy in pregnancies complicated by type 1 diabetes mellitus. *Diabetes Res Clin Pract* 58:115–121, 2002
26. Masson EA, Patmore JE, Brash PD, Baxter M, Caldwell G, Gallen IW, Price PA, Vice PA, Walker JD, Lindow SW: Pregnancy outcome in type 1 diabetes mellitus treated with insulin lispro (Humalog). *Diabet Med* 20:46–50, 2003
27. Loukovaara S, Immonen I, Teramo KA, Kaaja R: Progression of retinopathy during pregnancy in type 1 diabetic women treated with insulin lispro. *Diabetes Care* 26:1193–1198, 2003
28. Garg SK, Frias JP, Anil S, Gottlieb PA, MacKenzie T, Jackson WE: Insulin lispro therapy in pregnancies complicated by type 1 diabetes: glycemic control and maternal and fetal outcomes. *Endocr Pract* 9:187–193, 2003
29. Cypryk K, Sobczak M, Pertynska-Marczewska M, Zawodniak-Szalapska M, Szymczak W, Wilczynski J, Lewinski A: Pregnancy complications and perinatal outcome in diabetic women treated with Humalog (insulin lispro) or regular human insulin during pregnancy. *Med Sci Monit* 10:PI29–PI32, 2004
30. Bradley C: Diabetes Treatment Satisfaction Questionnaire (DTSQ). In *Handbook of Psychology and Diabetes: A Guide to Psychological Measurement in Diabetes Research and Practice*. Bradley C, Ed. Chur, Switzerland, Harwood Academic Publishers, 1994, p. 111–132
31. Hougaard P: Shared frailty models for recurrent events. In *Analysis of Multivariate Survival Data*. Hougaard P, Ed. New York, Springer-Verlag, 2002
32. Hellmuth E, Damm P, Molsted-Pederesen, Bendtson P: Prevalence of nocturnal hypoglycemia in first trimester of pregnancy in patients with insulin-treated diabetes mellitus. *Acta Obstet Gynecol Scand* 79:958–962, 2000
33. Tamas G, Marre M, Astorga R, Dedov I, Jacobsen J, Lindholm A, the Insulin Aspart Study Goup: Glycaemic control in type 1 diabetic patients using optimised insulin aspart or human insulin in a randomised multinational study. *Diabetes Res Clin Pract* 54:105–114, 2001
34. Home PD, Lindholm A, Riis A, the European Insulin Aspart Study Group: Insulin aspart vs. human insulin in the management of long-term blood glucose control in type 1 diabetes mellitus: a randomized controlled trial. *Diabet Med* 17:762–770, 2000
35. Raskin P, Guthrie RA, Leiter L, Riis A, Jovanovic L: Use of insulin aspart, a fast-acting insulin analog, as the mealtime insulin in the management of patients with type 1 diabetes. *Diabetes Care* 23: 583–588, 2000
36. Nielsen LR, Ekbom P, Damm P, Glumer C, Frandsen MM, Jensen DM, Mathiesen ER: HbA_{1c} levels are significantly lower in early and late pregnancy. *Diabetes Care* 27:1200–1201, 2004
37. de Veciana M, Major CA, Morgan MA, Asrat T, Toohey JS, Lien JM, Evans AT: Postprandial versus preprandial blood glucose monitoring in women with gestational diabetes mellitus requiring insulin therapy. *N Engl J Med* 333:1237–1241, 1995
38. Radder JK, van Roosmalen J: A1C in healthy, pregnant women. *Neth J Med* 63: 256–259, 2005
39. Bott U, Ebrahim S, Hirschberger S, Skovlund SE: Effect of the rapid-acting insulin analogue insulin aspart on quality of life and treatment satisfaction in patients with type 1 diabetes. *Diabet Med* 20:626–634, 2003