Hypoglycemia in Type 1 Diabetic Pregnancy

Role of preconception insulin aspart treatment in a randomized study

Simon Heller, MD, FRCP[1]
Peter Damm, MD, DMSC[2]
Henriette Mersebach, MD, PHD[3]
Trine Vang Skjøth, MD[3]
Risto Kaaja, MD, PHD[4]
Moshe Hod, MD[5]
Santiago Durán-García, MD, PHD[6]
David McCance, MD[7]
Elisabeth R. Mathiesen, MD, DMSC[2]

OBJECTIVE — A recent randomized trial compared prandial insulin aspart (IAsp) with human insulin in type 1 diabetic pregnancy. The aim of this exploratory analysis was to investigate the incidence of severe hypoglycemia during pregnancy and compare women enrolled preconception with women enrolled during early pregnancy.

RESEARCH DESIGN AND METHODS — IAsp administered immediately before each meal was compared with human insulin administered 30 min before each meal in 99 subjects (44 to IAsp and 55 to human insulin) randomly assigned preconception and in 223 subjects (113 for IAsp and 110 for human insulin) randomly assigned in early pregnancy (<10 weeks). NPH insulin was the basal insulin. Severe hypoglycemia (requiring third-party assistance) was recorded prospectively preconception (where possible), during pregnancy, and postpartum. Relative risk (RR) of severe hypoglycemia was evaluated with a gamma frailty model.

RESULTS — Of the patients, 23% experienced severe hypoglycemia during pregnancy with the peak incidence in early pregnancy. In the first half of pregnancy, the RR of severe hypoglycemia in women randomly assigned in early pregnancy/preconception was 1.70 (95% CI 0.91–3.18, $P = 0.097$); the RR in the second half of pregnancy was 1.35 (0.38–4.77, $P = 0.640$). In women randomly assigned preconception, severe hypoglycemia rates occurring before and during the first and second halves of pregnancy and postpartum for IAsp versus human insulin were 0.9 versus 2.4, 0.9 versus 2.4, 0.3 versus 1.2, and 0.2 versus 2.2 episodes per patient per year, respectively (NS).

CONCLUSIONS — These data suggest that initiation of insulin analog treatment preconception rather than during early pregnancy may result in a lower risk of severe hypoglycemia in women with type 1 diabetes.

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Severe hypoglycemia is common in pregnant women with type 1 diabetes, with observed rates up to 15 times those reported by the Diabetes Control and Complications Trial (1), and severe hypoglycemia occurs in 19–44% of patients treated with intensive insulin therapy during pregnancy (2). The risk of experiencing a severe event is usually highest in early pregnancy, particularly during the first trimester (3–5).

The risk factors that predict severe hypoglycemic episodes during pregnancy include duration of diabetes, a history of previous severe episodes (recurrent events), hypoglycemic unawareness, a change in insulin treatment (such as regimen or dosing) or a high insulin dose, and A1C <6.5% (4,6,7). However, because normoglycemia is universally recommended in diabetic pregnancy (8,9), with A1C levels between 4.0 and 6.0% advocated to optimize pregnancy outcome (10,11), minimizing the risk of severe hypoglycemia is a major challenge to those caring for pregnant women with type 1 diabetes.

Preconception care programs are associated with both reduced malformations and fewer early fetal losses in pregnant women with type 1 diabetes (12–14), perhaps due to improved glycemic control in the first stages of pregnancy. It is possible that working with women to improve metabolic control and optimize their insulin regimen before pregnancy might also help to reduce the high rate of severe episodes of hypoglycemia postconception, but this has yet to be demonstrated.

We recently completed a randomized, open-label, parallel-group, multinational, multicenter study investigating maternal and fetal outcomes in 322 women with type 1 diabetes treated with either prandial insulin aspart (IAsp) or human insulin (15–17). IAsp injected immediately before eating was as effective and well tolerated as human insulin administered 30 min before eating. Although the study was somewhat underpowered, there were strong trends toward improved postprandial glucose control and prevention of severe hypoglycemia in the IAsp group (15,16). This study supports the conclusions of trials in nonpregnant individuals with type 1 diabetes, which suggest that the advantages of rapid-acting insulin analogs are most likely to be seen in those with tight control (18–20).

The aim of this exploratory analysis was to compare the incidence of severe hypoglycemia during pregnancy between women enrolled into the trial either preconception or early in the first trimester. Finally, we also compared the effects of the different insulins on rates of severe hypoglycemia according to the time of enrollment of (pregnant) women into the study.

From the [1]Northern General Hospital, Sheffield, U.K.; the [2]Rigshospitalet, University of Copenhagen, Copenhagen, Denmark; [3]Novo Nordisk, Soeborg, Denmark; the [4]Helsinki University Central Hospital, Helsinki, Finland; the [5]Rabin Medical Center, Tel-Aviv University, Petah-Tiqva, Israel; the [6]University of Seville, Seville, Spain; and the [7]Royal Victoria Hospital, Belfast, U.K.
Corresponding author: Simon Heller, s.heller@sheffield.ac.uk.
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RESEARCH DESIGN AND METHODS

— A total of 322 women with type 1 diabetes participated in this open-label, randomized, parallel-group, multinational, multicenter study conducted at 63 sites in 18 countries (15–17). The study was performed in accordance with the Declaration of Helsinki and was approved by the respective ethics committees and health authorities according to local regulations. Written informed consent was obtained from subjects before commencement of the study. Eligible subjects were aged ≥18 years, had insulin-treated type 1 diabetes for ≥12 months, and were either planning to become pregnant or were already pregnant with a singleton pregnancy (gestational age ≤10 weeks). A1C was ≤8% at confirmation of pregnancy. Subjects were randomly assigned (1:1) to mealtime IAsp (NovoRapid 100 IU/ml Penfill; Novo Nordisk) injected immediately before each meal or human insulin (human soluble insulin, Actrapid 100 IU/ml, 3 ml Penfill; Novo Nordisk) injected 30 min before each meal, in combination with NPH insulin (human isophane insulin, 100 IU/ml, 3 ml Penfill; Novo Nordisk) one to four times per day.

In this exploratory analysis, the intent-to-treat pregnant population included all randomly assigned subjects who were exposed to the trial drug and in whom pregnancy was confirmed at some point during the trial. This population consisted of 99 subjects randomly assigned before known pregnancy (44 to IAsp and 55 to human insulin) and 223 subjects randomly assigned in early pregnancy (113 to IAsp and 110 to human insulin).

Severe hypoglycemia was defined as an event requiring third-party assistance associated with plasma glucose <3.1 mmol/l and/or reversal of symptoms after food, glucagon, or intravenous glucose. Nocturnal hypoglycemia was defined as episodes occurring between midnight and 0600 h. Hypoglycemia was recorded prospectively preconception (where possible), during the first half of pregnancy (<20 weeks' gestation), during the second half of pregnancy (≥20 weeks' gestation), and postpartum. Subjects were followed throughout pregnancy with one visit per trimester and at 6 weeks postpartum. Hypoglycemic coma, glycemic control, duration of diabetes, and pretrial insulin regimen (use of analogs) were also recorded. Between study visits, the women received routine diabetes and obstetric care according to local practice.

Table 1—*Patient baseline demographics*

	IAsp + NPH		Human insulin + NPH	
	Randomly assigned preconception	Randomly assigned in early pregnancy	Randomly assigned preconception	Randomly assigned in early pregnancy
n	44	113	55	110
Age (years)	28.6 ± 3.7	29.2 ± 5.1	28.8 ± 4.3	29.2 ± 4.7
A1C (%)*	7.3 ± 1.0	6.8 ± 0.7	7.1 ± 1.2	6.8 ± 0.8
BMI (kg/m^2)	24.1 ± 3.6	25.2 ± 4.2	25.0 ± 4.0	24.4 ± 3.6
Duration of diabetes (years)	11.8 ± 6.4	12.4 ± 7.4	11.3 ± 6.7	12.0 ± 7.8
Pretrial insulin including insulin analogs	24 (54.5)	49 (43.3)	30 (54.5)	50 (45.5)
Dose (IU · kg^{-1} · 24 h^{-1})	0.79 ± 0.25	0.77 ± 0.27	0.75 ± 0.21	0.77 ± 0.27
Preconception exposure to trial drug (days)	153.8 ± 108.2	NA	110.3 ± 92.0	NA

Data are means ± SD or *n* (%). *A1C is from early pregnancy: at randomization in those randomly assigned in early pregnancy and at pregnancy confirmation in those randomly assigned preconception. NA, not applicable.

Statistical analyses

The primary end point in this study was severe hypoglycemia. Assuming an incidence of one severe hypoglycemic episode during pregnancy with 7 months of insulin treatment (21), 305 subjects were required to complete the trial to detect a treatment difference of 40% with a power of 80% (5% significance level). Assuming a dropout rate of ~20%, 380 subjects were to be randomly assigned.

In this analysis, rates of severe hypoglycemia were compared between those women randomly assigned preconception with those randomly assigned in early pregnancy and between treatment groups. Relative risk (RR) of severe hypoglycemia was estimated using a gamma frailty model with treatment as a factor. For women already pregnant at screening, delayed entry was used to account for the different observation periods. A Cox regression model accounted for recurrent aspects of episodes. Incidence of nocturnal severe hypoglycemia is presented here using descriptive statistics, as there were too few events for formal analysis. The observed rate is defined as number of episodes per patient per year. The relationship between history of severe hypoglycemia and episodes during pregnancy is based on subjects who had at least 30 days' preconception exposure to the trial drug, i.e., only those enrolled before pregnancy.

RESULTS

Baseline patient demographics

The study includes the 99 of the 189 subjects making up the preconception group who became pregnant during the 12 months specified in the original protocol (15). Age, A1C, BMI, and duration of diabetes were similar in subjects randomly assigned preconception or in early pregnancy and between treatment groups (Table 1).

Hypoglycemia in those randomly assigned preconception versus those randomly assigned in early pregnancy

Overall, 23% of subjects ($n = 73$) experienced at least one episode of severe hypoglycemia during the study, and many subjects experienced several episodes, including six subjects who experienced ≥10 episodes. Rates of severe hypoglycemia calculated for each week of pregnancy and postpartum are shown in Fig. 1*A* and *B* and are combined into rates in early pregnancy, late pregnancy, and postpartum in Fig. 1*C*. These rates appear to peak in early pregnancy, with low values in the second half of pregnancy except for a rise immediately before birth. Rates of severe hypoglycemia in the first and second halves of pregnancy are presented separately here. Rates of severe hypoglycemia in subjects randomly assigned preconception or early in pregnancy, respectively, were 1.7 versus 3.4 events per patient per year in the first half of pregnancy, 0.8 versus 0.9 events per pa-

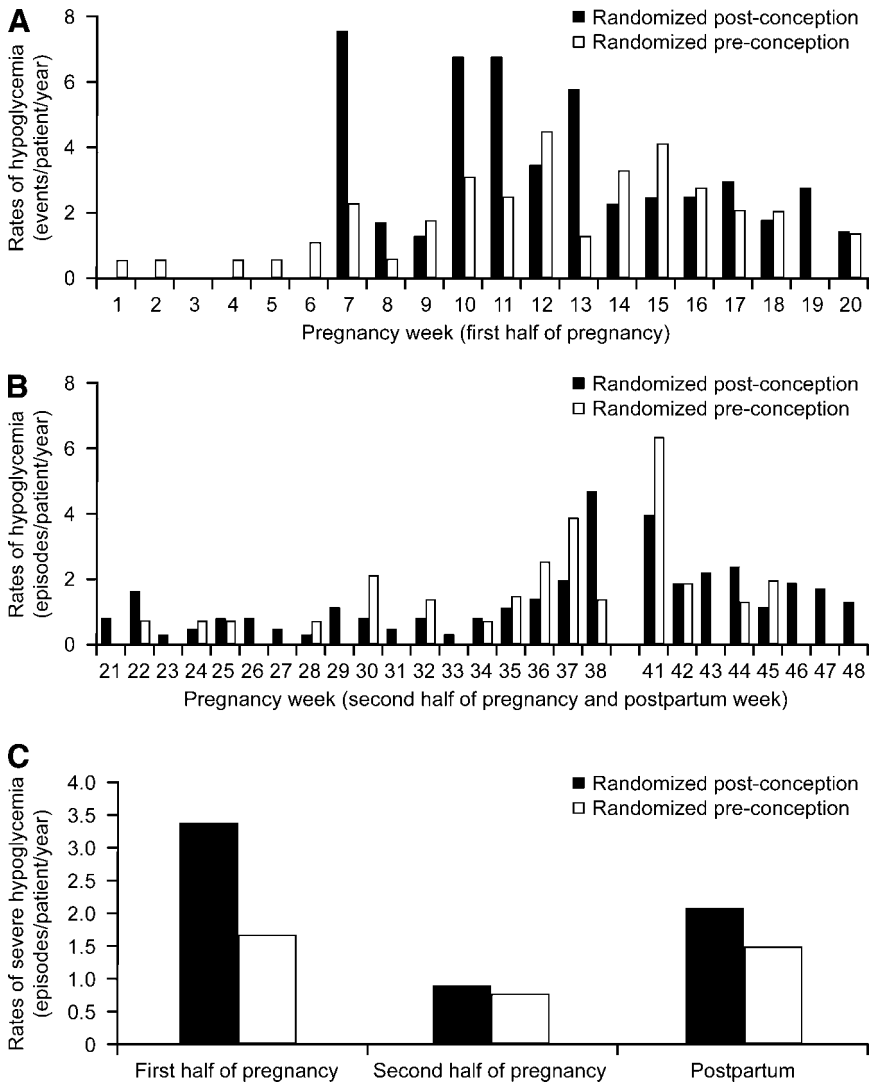

Figure 1—*Rate of severe hypoglycemia in pregnancy, grouped according to timing of randomization in the first half of pregnancy* (A)*, in the second half of pregnancy and postpartum* (B)*, and in the first and second half of pregnancy and postpartum* (C).

tient per year in the second half of pregnancy, and 1.5 versus 2.1 events per patient per year in the postpartum period (Fig. 1*C*).

In the first half of pregnancy, the estimated risk of severe hypoglycemia was 70% higher in subjects randomly assigned in early pregnancy versus those randomly assigned preconception (RR 1.70 [95% CI 0.91–3.18], $P = 0.097$); in the second half of pregnancy the RR was 1.35 (0.38–4.77) ($P = 0.640$). Observed rates for severe nocturnal hypoglycemia in subjects randomly assigned preconception versus postconception were 0.7 versus 0.9 events per patient per year, respectively, in the first half of pregnancy; 0.4 versus 0.2 events per patient per year in the second half of pregnancy; and 0.5 events per patient per year versus 0.6 postpartum.

Hypoglycemia in subjects treated with IAsp and those treated with human insulin

Subjects randomly assigned preconception had consistently lower observed rates of severe hypoglycemia with IAsp versus human insulin, respectively, preconception (0.9 vs. 2.4 events per patient per year), in the first half of pregnancy (0.9 vs. 2.4 events per patient per year), in the second half of pregnancy (0.3 vs. 1.2 events per patient per year), and postpartum (0.2 vs. 2.2 events per patient per year, NS for all) (Fig. 2). In subjects randomly assigned preconception, the estimated risk for severe hypoglycemia during the first and second halves of pregnancy tended to be lower with IAsp than with human insulin (RR 0.37 [95% CI 0.10–1.32], $P = 0.13$ vs. 0.20 [0.02–1.85], $P = 0.16$, respectively). Estimated risk with IAsp was 66% lower for the preconception period (0.34 [0.07–1.71], $P = 0.19$ [NS]) and 92% lower postpartum (0.08 [0.01–0.84], $P = 0.04$) (Fig. 2).

Observed rates of severe nocturnal hypoglycemia in subjects treated with IAsp preconception were likewise consistently lower than those for human insulin–treated subjects preconception (0.3 vs. 1.5 events per patient per year), during the first half of pregnancy (0.1 vs. 1.2 events per patient per year), during the second half of pregnancy (0.1 vs. 0.7 events per patient per year), and postpartum (0.2 vs. 0.7 events per patient per year), respectively. The numbers in this group were too small for a meaningful analysis of statistical significance. In subjects randomly assigned in early pregnancy, rates of severe nocturnal hypoglycemia were similar for the IAsp and human insulin treatment groups during the first half of pregnancy (0.7 vs. 1.0 events per patient per year), the second half of pregnancy (0.2 vs. 0.2 events per patient per year), and postpartum (0.6 vs. 0.6 events per patient per year), respectively.

Rates of hypoglycemia were higher in subjects randomly assigned in early pregnancy to an insulin regimen differing from their previous treatment. In subjects who changed insulin regimens and were randomly assigned to IAsp, the hypoglycemia rate was 3.0 versus 2.1 events per patient per year for subjects who did not change regimens. The same values for those randomly assigned to human insulin in early pregnancy were 4.5 events per patient per year for subjects who changed regimens versus 3.3 events per patient per year for those already treated with human insulin.

History of severe hypoglycemia

Of subjects reporting episodes of severe hypoglycemia preconception (during the trial), 67% (10 of 15) had severe hypoglycemia during pregnancy versus only 9% (6 of 67) of subjects with no preconception episodes.

Hypoglycemic coma

Eight episodes of hypoglycemic coma were observed during pregnancy in this study (three episodes with IAsp and five episodes with human insulin), all in

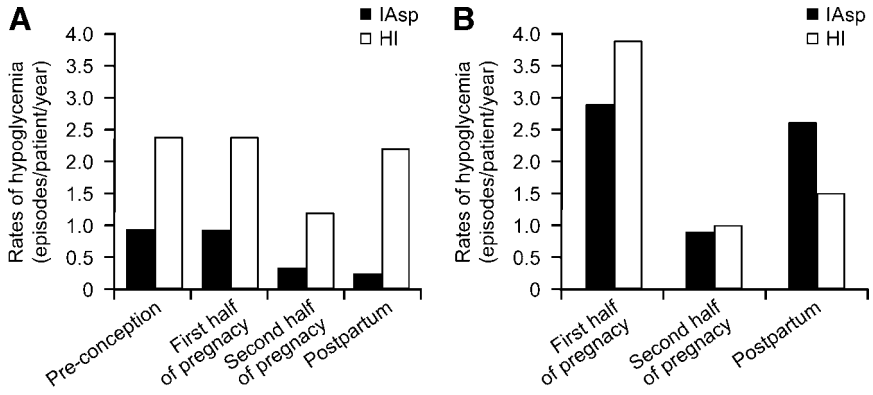

Figure 2—*Observed rates of severe hypoglycemia in subjects randomly assigned preconception* (A) *or early in pregnancy* (B) *treated with either IAsp or human insulin (HI).*

subjects randomly assigned in early pregnancy.

Glycemic control

During pregnancy, mean A1C and average plasma glucose levels were comparable between treatment groups throughout the study (Table 2). Plasma glucose was derived as the average of the 8-point profile for each subject. Profiles were taken on a normal weekday within the week before the visit and included values premeal, 90-min postmeal, at bedtime, and at 0200 h.

CONCLUSIONS — This exploratory analysis was based on data obtained from the largest randomized controlled trial to date involving an insulin analog in the treatment of pregnant women with type 1 diabetes. Despite the limitations imposed by the observational design, we believe that exploring the influence of the timing of entry into the trial on risk of hypoglycemia is clinically relevant. The data suggest that women enrolled in a clinical trial preconception experience fewer hypoglycemic episodes than those enrolled postconception. Although the RRs in women randomly assigned preconception are not statistically significant because of a lack of power, the marked trend to lower rates in this group is of interest.

It is well known that severe hypoglycemia is common during pregnancy and is most likely to occur during the first trimester (3,4). One observation from our data is that the incidence of severe hypoglycemia does not peak in early pregnancy in women who were enrolled preconception. This group had a low rate of severe hypoglycemic episodes comparable to the 1.3 events per patient per year seen in the nonpregnant background population (22).

It is possible that patients who entered the trial preconception were more motivated and experienced in diabetes self-management than those enrolling postconception, as represented by tighter control and less hypoglycemia. However, glycemic control (A1C and plasma glucose) was similar between those randomly assigned in early pregnancy and those randomly assigned preconception. An alternative explanation is that the extra professional input in the preconception period led to optimized insulin therapy and a lower risk of hypoglycemia. Although preconception counseling is associated with a reduced malformation rate in the offspring of women with type 1 diabetes (12–14), we are unaware of previous studies exploring the impact of preconception input on severe hypoglycemia during the ensuing pregnancy.

It is conceivable that subjects who changed their insulin regimen may have had higher rates of hypoglycemia than those who did not change their insulin regimen; however, the numbers of those taking the same insulin in the trial were too small to undertake formal comparisons. Nevertheless, switching to IAsp after human insulin treatment during pregnancy did not seem to worsen the risk of hypoglycemia, confirming the results of a smaller earlier study (23).

Our data show an apparent rise in hypoglycemia in the weeks immediately before birth. This finding might relate to a fall in insulin requirements in the immediate predelivery period. A further intriguing finding was that the benefit of a rapid-acting insulin analog (IAsp) associated with a lower risk of severe hypoglycemia than that with human insulin (20) tended to be most pronounced in women who were randomly assigned preconception. This result may be related to their experience with the use of insulin IAsp before the influence of the metabolic changes of pregnancy. The rate of severe hypoglycemia immediately postpartum was considerably higher than that in the last half of pregnancy and was also higher than that seen in observational data in nonpregnant diabetic populations (22), suggesting that women should focus on reducing their postpar-

Table 2—*A1C and plasma glucose values*

	IAsp + NPH		Human insulin + NPH	
	Randomly assigned preconception	Randomly assigned in early pregnancy	Randomly assigned preconception	Randomly assigned in early pregnancy
n	44	113	55	110
A1C (%)				
First visit	7.3 ± 1.0	6.8 ± 0.7	7.1 ± 1.2	6.8 ± 0.8
First trimester visit	6.3 ± 0.7	6.3 ± 0.6	6.2 ± 0.7	6.4 ± 0.7
Second trimester visit	6.0 ± 0.7	5.9 ± 0.7	6.0 ± 0.6	5.9 ± 0.7
Third trimester visit	6.2 ± 0.5	6.0 ± 0.7	6.2 ± 0.5	6.1 ± 0.7
Follow-up (6 weeks postpartum)	6.6 ± 0.7	6.5 ± 0.9	6.6 ± 0.8	6.4 ± 0.8
Average plasma glucose (mmol/l)				
First visit	7.9 ± 1.8	6.8 ± 1.7	7.9 ± 1.9	7.1 ± 1.4
First trimester visit	7.1 ± 1.6	6.6 ± 1.4	6.7 ± 1.7	6.6 ± 1.3
Second trimester visit	7.1 ± 1.2	6.7 ± 1.4	7.1 ± 1.5	6.8 ± 1.4
Third trimester visit	6.2 ± 1.0	6.2 ± 1.2	6.4 ± 1.3	6.4 ± 1.3

Data are means ± SD.

tum insulin dose and returning to preconception glycemic control goals.

This analysis suggests that the initiation of insulin analog treatment preconception as opposed to during early pregnancy results in a lower risk of severe hypoglycemia in women with type 1 diabetes. The reasons for this finding remain unclear but might include the influence of preconception planning. Although the limitations of exploratory analyses prevent any firm conclusions, these data suggest another potential advantage of prenatal care that is worthy of further investigation. The observation should also be taken into account in future clinical trials during pregnancy in women with type 1 diabetes.

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