Hypoglycemia in type 1 diabetic pregnancy: the role of pre-conception insulin aspart treatment in a randomized study

Running title: Hypoglycemia and pregnancy in type 1 diabetes

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Objective: A recent randomized trial compared prandial insulin aspart (IAsp) with human insulin (HI) 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 HI administered 30 minutes before each meal in 99 subjects (IAsp:44, HI:55) randomized pre-conception and in 223 subjects (IAsp:113, HI:110) randomized in early pregnancy (<10 weeks). NPH insulin was the basal insulin. Severe hypoglycemia (requiring third-party assistance) was recorded prospectively pre-conception (where possible), during pregnancy, and postpartum. Relative risk (RR) of severe hypoglycemia was evaluated with a gamma frailty model.

Results: 23% of patients experienced severe hypoglycemia during pregnancy with peak incidence in early pregnancy. In the first half of pregnancy the RR of severe hypoglycemia in women randomized in early pregnancy/pre-conception 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 randomized pre-conception, severe hypoglycemia rates occurring before, during first and second half of pregnancy and postpartum for IAsp vs. HI were 0.9 vs. 2.4, 0.9 vs. 2.4, 0.3 vs. 1.2, and 0.2 vs. 2.2 episodes/patient/year, respectively (NS).

Conclusion: These data suggest that initiation of insulin analog treatment pre-conception rather than during early pregnancy may result in a lower risk of severe hypoglycemia in women with type 1 diabetes.
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% to 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, since 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.

Pre-conception 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 prior to pregnancy might also help to reduce the high rate of severe episodes of hypoglycemia post-conception, but this has yet to be demonstrated.

We recently completed a randomized, open-label, parallel-group, multinational, multi-center study investigating maternal and fetal outcomes in 322 women with type 1 diabetes treated with either prandial insulin aspart (IAsp) or human insulin (HI) (15-17). IAsp injected immediately before eating was as effective and well tolerated as HI administered 30 minutes before eating. Although the study was somewhat underpowered, there were strong trends towards improved postprandial glucose control and prevention of severe hypoglycemia in the IAsp group (15,16). This study supports the conclusions of trials in non-pregnant 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 pre-conception or early in the first trimester. Finally, we also compared the effect of the different insulins on rates of severe hypoglycemia according to the time of enrollment of (pregnant) women into the study.

Patients and Methods: A total of 322 women with type 1 diabetes participated in this open-label, randomized, parallel-group, multinational, multi-center 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 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 randomized (1:1) to mealtime IAsp (NovoRapid® 100 IU/mL Penfill®, Novo Nordisk, Inc.) injected immediately before each meal or HI (Human
Soluble Insulin; Actrapid® 100 IU/mL, 3 mL Penfill®, Novo Nordisk, Inc.) injected 30 minutes before each meal, in combination with NPH insulin (Human Isophane Insulin; 100 IU/mL, 3 mL Penfill®, Novo Nordisk, Inc.) 1 to 4 times per day.

In this exploratory analysis, the intent-to-treat pregnant population included all randomized 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 randomized prior to known pregnancy (IAsp: 44, HI: 55) and 223 subjects randomized in early pregnancy (IAsp: 113, HI: 110).

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 hours. Hypoglycemia was recorded prospectively pre-conception (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 pre-trial insulin regimen (use of analogs) were also recorded. Between study visits the women attended routine diabetic and obstetric care according to local practice.

**Statistical Analyses:** The primary endpoint 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 in order to detect a treatment difference of 40% with a power of 80% (5% significance level). Assuming a drop-out rate of approximately 20%, 380 subjects were to be randomized.

In this analysis, rates of severe hypoglycemia were compared between those women randomized pre-conception with those randomized in early pregnancy and between treatment groups. Relative risk 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/patient/year. The relationship between history of severe hypoglycemia and episodes during pregnancy is based on subjects who had at least 30 days’ pre-conception exposure to the trial drug, i.e. only those enrolled prior to pregnancy.

**RESULTS**

Baseline patient demographics The study includes the 99 of the 189 subjects making up the pre-conception group who became pregnant during the 12 months specified in the original protocol (15). Age, A1C, body mass index and duration of diabetes were similar in subjects randomized pre-conception or in early pregnancy and between treatment groups (Table 1).

Hypoglycemia in those randomized pre-conception vs. those randomized 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 ten or more episodes. Rates of severe hypoglycemia calculated for each week of pregnancy and post-partum are shown in Figures 1a and 1b, and combined into rates in early pregnancy, late pregnancy and postpartum in Figure 1c. 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 half of pregnancy are presented separately here. Rates of severe hypoglycemia in subjects randomized pre-conception or early in pregnancy, respectively, were 1.7 vs. 3.4 events/patient/year in the first half of pregnancy, 0.8 vs. 0.9 in the second half of pregnancy, and 1.5 vs. 2.1 in the postpartum period (Figure 1c).

In the first half of pregnancy, estimated risk of severe hypoglycemia was 70% higher in subjects randomized in early pregnancy vs. those randomized pre-conception (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 randomized pre- vs. post-conception were 0.7 vs. 0.9 events/patient/year, respectively, in the first half of pregnancy, 0.4 vs. 0.2 in the second half of pregnancy, and 0.5 vs. 0.6 postpartum. Hypoglycemia between subjects treated with IAsp and those treated with HI

Subjects randomized pre-conception had consistently lower observed rates of severe hypoglycemia with IAsp vs. HI, respectively, pre-conception (0.9 vs. 2.4 events/patient/year), in the first half of pregnancy (0.9 vs. 2.4), in the second half of pregnancy (0.3 vs. 1.2), and postpartum (0.2 vs. 2.2) (\( P = \text{NS} \) for all; Figure 2).

In subjects randomized pre-conception, the estimated risk for severe hypoglycemia during the first and second half of pregnancy tended to be lower with IAsp than with HI (RR: 0.37, 95% CI: 0.10–1.32, \( P = 0.13 \) vs. RR: 0.20, 95% CI: 0.02–1.85, \( P = 0.16 \), respectively). Estimated risk with IAsp was 66% lower for the pre-conception period (RR: 0.34, 95% CI: 0.07–1.71, \( P = 0.19 \) [NS]) and 92% lower postpartum (RR: 0.08, 95% CI: 0.01–0.84, \( P = 0.04 \)) (Figure 2).

Observed rates of severe nocturnal hypoglycemia in subjects treated with IAsp pre-conception were likewise consistently lower than those for HI-treated subjects pre-conception (0.3 vs. 1.5 events/patient/year), during the first half of pregnancy (0.1 vs. 1.2 events/patient/year), during the second half of pregnancy (0.1 vs. 0.7 events/patient/year), and postpartum (0.2 vs. 0.7 events/patient/year), respectively. The numbers in this group were too small for a meaningful analysis of statistical significance.

In subjects randomized in early pregnancy, rates of severe nocturnal hypoglycemia were similar for the IAsp and HI treatment groups during the first half of pregnancy (0.7 vs. 1.0 events/patient/year), the second half of pregnancy (0.2 vs. 0.2 events/patient/year) and postpartum (0.6 vs. 0.6 events/patient/year), respectively.

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

History of severe hypoglycaemia. Sixty-seven percent (10/15) of subjects reporting episodes of severe hypoglycemia pre-conception (during the trial) had severe hypoglycemia during pregnancy vs. only nine percent (6/67) of subjects with no pre-conception episodes.

**Hypoglycemic Coma:** Eight episodes of hypoglycemic coma were observed during pregnancy in this study (IAsp: 3, HI: 5), all in subjects randomized in early pregnancy.

**Glycemic Control:** During pregnancy, mean A1C and average plasma glucose levels were
comparable between each treatment group 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 prior to the visit, and included values pre-meal, 90-minutes post-meal, at bedtime, and at 0200.

CONCLUSION

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 into a clinical trial pre-conception experience fewer hypoglycemic episodes than those enrolled post-conception. While the relative risks in women randomized pre-conception are not statistically significant due to 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 suggests that the incidence of severe hypoglycemia does not peak in early pregnancy in women who were enrolled pre-conception. This group had a low rate of severe hypoglycemic episodes comparable to the 1.3 events/patient/year seen in the non-pregnant background population (22).

It is possible that patients who entered the trial pre-conception were more motivated and experienced in diabetes self-management than those enrolling post-conception, as represented by tighter control and less hypoglycemia. However, glycemic control (A1C and plasma glucose) was similar between those randomized in early pregnancy and those randomized pre-conception. An alternative explanation is that the extra professional input in the pre-conception period led to optimized insulin therapy and a lower risk of hypoglycemia. Although pre-conception counselling 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 pre-conception 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 remaining on the same insulin in the trial were too small to undertake formal comparisons. Nevertheless, switching to IAsp after HI 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 prior to birth. This might relate to a fall in insulin requirements in the immediate pre-delivery 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 HI (20) tended to be most pronounced in women who were randomized pre-conception. This may be related to their experience with use of insulin IAsp prior to the influence of the metabolic changes of pregnancy.

The rate of severe hypoglycemia immediately postpartum was considerably higher than in the last half of pregnancy, and was also higher than that seen in observational data in non-pregnant diabetic populations (22), suggesting that women should focus on reducing their postpartum insulin dose and returning to pre-conception glycemic control goals.

This analysis suggests that the initiation of insulin analog treatment pre-
conception as opposed to during early pregnancy results in a lower risk of severe hypoglycemia in women with type 1 diabetes. The reasons for this remain unclear, but might include the influence of pre-conception planning. While 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.
REFERENCES


### Table 1. Patient baseline demographics. All values mean (SD) unless otherwise stated. IAsp, insulin aspart; NPH, neutral protamine Hagedorn; HI, human insulin.  
*A1C is from early pregnancy: at randomization in those randomized in early pregnancy, and at pregnancy confirmation in those randomized pre-conception.*

<table>
<thead>
<tr>
<th></th>
<th>IAsp + NPH</th>
<th>HI + NPH</th>
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<tbody>
<tr>
<td></td>
<td>Randomized pre-conception</td>
<td>Randomized in early pregnancy</td>
</tr>
<tr>
<td><strong>N</strong></td>
<td>44</td>
<td>113</td>
</tr>
<tr>
<td><strong>Age, years</strong></td>
<td>28.6 (3.7)</td>
<td>29.2 (5.1)</td>
</tr>
<tr>
<td><strong>A1C, %</strong></td>
<td>7.3 (1.0)</td>
<td>6.8 (0.7)</td>
</tr>
<tr>
<td><strong>BMI, kg/m²</strong></td>
<td>24.1 (3.6)</td>
<td>25.2 (4.2)</td>
</tr>
<tr>
<td><strong>Duration of diabetes, years</strong></td>
<td>11.8 (6.4)</td>
<td>12.4 (7.4)</td>
</tr>
<tr>
<td><strong>Pre-trial insulin including insulin analogues, n %</strong></td>
<td>24 (54.5)</td>
<td>49 (43.3)</td>
</tr>
<tr>
<td><strong>Dose, IU/kg/24h</strong></td>
<td>0.79 (0.25)</td>
<td>0.77 (0.27)</td>
</tr>
<tr>
<td><strong>Pre-conception exposure to trial drug, days</strong></td>
<td>153.8 (108.2)</td>
<td>N/A</td>
</tr>
</tbody>
</table>

### Table 2. Mean (SD) A1C and plasma glucose values. IAsp, insulin aspart; NPH, neutral protamine Hagedorn; HI, human insulin.

<table>
<thead>
<tr>
<th></th>
<th>IAsp + NPH</th>
<th>HI + NPH</th>
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<tbody>
<tr>
<td></td>
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</tr>
<tr>
<td><strong>N</strong></td>
<td>44</td>
<td>113</td>
</tr>
<tr>
<td><strong>A1C, %</strong></td>
<td>7.3 (1.0)</td>
<td>6.8 (0.7)</td>
</tr>
<tr>
<td><strong>First visit</strong></td>
<td>6.3 (0.7)</td>
<td>6.3 (0.6)</td>
</tr>
<tr>
<td><strong>Second trimester visit</strong></td>
<td>6.0 (0.7)</td>
<td>5.9 (0.7)</td>
</tr>
<tr>
<td><strong>Third trimester visit</strong></td>
<td>6.2 (0.5)</td>
<td>6.0 (0.7)</td>
</tr>
<tr>
<td><strong>Follow-up (6 weeks postpartum)</strong></td>
<td>6.6 (0.7)</td>
<td>6.5 (0.9)</td>
</tr>
<tr>
<td><strong>Average plasma glucose, mmol/L</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>First visit</strong></td>
<td>7.9 (1.8)</td>
<td>6.8 (1.7)</td>
</tr>
<tr>
<td><strong>First trimester visit</strong></td>
<td>7.1 (1.6)</td>
<td>6.6 (1.4)</td>
</tr>
<tr>
<td><strong>Second trimester visit</strong></td>
<td>7.1 (1.2)</td>
<td>6.7 (1.4)</td>
</tr>
<tr>
<td><strong>Third trimester visit</strong></td>
<td>6.2 (1.0)</td>
<td>6.2 (1.2)</td>
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**Figure Legends**

**Figure 1:** Rate of severe hypoglycemia in pregnancy, grouped according to timing of randomization (a) in the first half of pregnancy; (b) in the second half of pregnancy and postpartum; (c) in the first and second half of pregnancy and postpartum.

**Figure 2:** Observed rates of severe hypoglycemia in subjects randomized pre-conception or early in pregnancy treated with either insulin aspart (IAsp) or human insulin (HI).
Figure 2

- Randomized pre-conception
  - Rates of hypoglycemia (episodes/patient/year)
  - IAsp
  - HI

- Randomized in early pregnancy
  - Rates of hypoglycemia (episodes/patient/year)
  - IAsp
  - HI