Risk Indicators Predictive for Severe Hypoglycemia During the First Trimester of Type 1 Diabetic Pregnancy

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OBJECTIVES — To investigate the frequency of severe hypoglycemia (SH) and hypoglycemia during the first trimester of type 1 diabetic pregnancy and in the 4 months before gestation and to identify risk indicators predicting first trimester SH in a nonselected nationwide cohort of pregnant women with type 1 diabetes.

RESEARCH DESIGN AND METHODS — We conducted a longitudinal cohort survey in 278 pregnant type 1 diabetic women using questionnaires at inclusion and at 17 weeks of gestation, addressing the frequencies of SH (i.e., external help required) and hypoglycemic coma, general characteristics, hypoglycemia awareness, blood glucose symptom threshold, and the Hypoglycemia Fear Survey.

RESULTS — The occurrence of SH (including hypoglycemic coma) rose from 0.9 ± 2.4 episodes per 4 months before gestation to 2.6 ± 6.3 episodes during the first trimester (P < 0.001), including an increase in episodes of coma from 0.3 ± 1.3 to 0.7 ± 3.7 (P = 0.03). The proportion of women affected by SH rose from 25 to 41% (P < 0.001). First-trimester SH was independently related to a history of SH before gestation (odds ratio [95%CI]: 9.2 [3.9–21.7]), an HbA1c level independently related to a history of SH before gestation (odds ratio [95%CI]: 9.2 [3.9–21.7]), a 10 years’ longer diabetes duration (1.6 [1.0–2.4]), an HbA1c level ≤6.5% (2.5 [1.3–5.0]), and a 0.1 unit/kg higher daily insulin dose (5.4 [1.5–18.9]), adjusted for a decreased symptom threshold.

CONCLUSIONS — In type 1 diabetic pregnancy, the risk of SH is increased already before pregnancy and rises further during the first trimester. A history of SH before gestation, longer duration of diabetes, an HbA1c level ≤6.5%, and a higher total daily insulin dose were risk indicators predictive for SH during the first trimester. Further research should aim to elucidate how the benefits of strict glycemic control balance with the markedly increased risk of SH early in pregnancy.

Diabetes Care 25:554–559, 2002

In pregnant women with type 1 diabetes, the importance of good glycemic control to avoid fetal malformations, obstetrical complications, and neonatal morbidity is now widely recognized (1). However, the price to pay when aiming for strict glycemic control comprises an increased risk of severe hypoglycemia (SH) requiring assistance from others (2). SH is obviously harmful to the mother and involves dangers that include loss of consciousness, seizures, and even death. Potentially harmful effects of maternal hypoglycemia to the fetus have received far less attention.

The results of clinical studies with respect to a potential relationship between adverse fetal outcome and exposure to maternal hypoglycemia in type 1 diabetic pregnancy may seem reassuring (3), but this can certainly not dispel all concerns (4). Recurrent hypoglycemia is associated with blood glucose (BG) fluctuations into the hyperglycemic range. It has been suggested that this may explain why the incidence of macrosomia continues to be increased, despite excellent HbA1c levels throughout pregnancy (5,6). From animal studies (in rodents), there is strong evidence that hypoglycemia occurring early in gestation might be teratogenic (7,8).

To prevent SH during pregnancy, it would be useful to know the characteristics of women who are most at risk for SH when becoming pregnant (9). The contribution of SH to the burden of type 1 diabetic pregnancy has not yet been quantified in terms of hypoglycemia-related anxiety and the perception of reduced hypoglycemia awareness.

We assessed the occurrence of SH, impairment of hypoglycemia awareness, and hypoglycemia-related anxiety during the 4 months before gestation and during the subsequent first trimester of pregnancy in a nonselected nationwide cohort of 278 type 1 diabetic women. In addition, we investigated risk indicators for SH during the first trimester of pregnancy.

RESEARCH DESIGN AND METHODS — In a cohort-based survey regarding the outcome of type 1 diabetic pregnancy in the Netherlands, all gynecologists, internists, and diabetes nurse educators in the Netherlands were asked to include all type 1 diabetic women presenting for antenatal care between 1 April 1999 and 1 April 2000. Eligible pregnant women were asked to fill...
out sets of questionnaires at inclusion (at \(\sim 10\) weeks gestation), at the end of the first trimester (at \(\sim 17\) weeks), and during the third trimester (at \(\sim 34\) weeks).

All 118 Dutch hospitals participated in the study, and a total of 364 eligible women was reported to the study coordinator (I.M.E.) of the University Medical Center, Utrecht. Of these women, 86 (24%) were excluded from the analyses because of (spontaneous) abortion (7%), because they had type 2 diabetes or secondary diabetes (3%), or because of incomplete data (14%) due to other reasons. Analyses concerning the remaining 278 cases are reported here. The study had been approved by the ethical committee of the University Medical Center, Utrecht. Participants gave written informed consent after the nature of the study had been explained to them.

SH was defined as all episodes for which external help had been required (10,11). SH was divided into uncomplicated SH (i.e., SH episodes not complicated by coma, seizure, or treatment with glucagon or intravenous dextrose) and hypoglycemic coma (i.e., SH complicated by coma, seizure, or treatment with glucagon or intravenous dextrose).

Data included

**General characteristics.** The general characteristics included age, BMI, duration of diabetes, and parity.

**Insulin regimen at the end of the first trimester.** The insulin regimen at the end of the first trimester included treatment with continuous subcutaneous insulin infusion (CSII) or treatment with multiple (i.e., at least three per day) daily insulin infusion (CSII) or treatment with continuous subcutaneous insulin infusion (CSII) or treatment with multiple (i.e., at least three per day) daily insulin infusions (MIT). Frequency of self-monitoring of BG (SMBG) per day. Moreover, daily insulin dose and type of insulin were recorded.

**SH and hypoglycemic coma in the 4 months before pregnancy.** Subjects reported the occurrence of SH (all episodes) and the occurrence of hypoglycemic coma during the 4 months before pregnancy via questionnaire at inclusion. When completing this questionnaire, participants were informed about the fact that their experiences with hypoglycemia would be asked for again at two occasions during pregnancy, namely at the end of the first trimester and during the third trimester.

**SH and hypoglycemic coma in the first trimester.** Subjects reported the occurrence of SH (all episodes) and the occurrence of hypoglycemic coma during the first trimester of pregnancy via a second questionnaire at \(\sim 17\) weeks gestation.

**Hypoglycemia awareness.** Hypoglycemia awareness (according to Clarke et al. [12]) was reported at inclusion and at the end of the first trimester. Awareness was dichotomized into normal aware (including inconclusive) and reduced aware. Note that having experienced SH is part of this assessment.

**Perceived threshold BG.** The perceived threshold BG for the onset of hypoglycemic symptoms (at \(\sim 17\) weeks gestation) was assessed as a continuous measure (of BG in mmol/l). Later on, it was dichotomized into a threshold <3.0 mmol/l (i.e., a “decreased symptom” threshold) or \(\geq 3.0\) mmol/l (i.e., a “normal symptom” threshold). The presence of a decreased symptom threshold was investigated as an alternative (single) criterion for reduced hypoglycemia awareness.

**Hypoglycemia-related anxiety.** Hypoglycemia-related anxiety was assessed twice by means of the Hypoglycemia Fear Survey, Worry Scale (comprising a maximum score of 52 points on 13 items), translated and adapted from Cox et al. (13) and Snoek et al. (14).

**Presence of long-term diabetic complications.** Long-term diabetic complications were based on reports from the internists who treated the women. The complications were categorized and defined as follows: 1) retinopathy (as determined by an ophthalmologist): none, background, preproliferative, or proliferative; 2) nephropathy: none, microalbuminuria (30–300 mg/24 h or 20–200 mg/l at least once), or macroalbuminuria (\(\geq 300\) mg/24 h or \(\geq 200\) mg/l at least once), assessed before pregnancy; and 3) macrovascular complications: none, peripheral, and coronary. In the present analysis, diabetes was dichotomized into “uncomplicated diabetes” (absence of retinopathy, nephropathy, or macrovascular complications) and “complicated diabetes” (presence of any stage of retinopathy, nephropathy, or macrovascular complications).

**Overall glycemic control.** Glycemic control was assessed by means of HbA\(_1c\) levels at \(\sim 10\) weeks’ gestation. Samples for HbA\(_1c\) determination were assessed by high-performance liquid chromatography (HbA\(_1c\) Capillary Collection System on Diamat; Biorad, Veenendaal, the Netherlands), normal reference value 4.0–6.0%. Samples were self-obtained by the participants by means of a finger prick and mailed to a central laboratory (Department of Clinical Chemistry and Hematology, Queen Beatrix Hospital Winterswijk, the Netherlands). Only results of samples that were mailed between 8 and 14 weeks’ gestation were included in the present analysis (\(n = 217, 78\%\)).

**Statistical analysis**

Statistical analysis was performed using the statistical package SPSS version 10.0 (SPSS, Chicago, IL). For the monovariate analysis of risk indicators for uncomplicated SH and hypoglycemic coma, women were divided into three groups according to their first trimester experience with SH: 1) no SH; 2) uncomplicated SH only; and 3) at least one SH complicated by hypoglycemic coma, seizure, or treatment with glucagon or intravenous dextrose. Groups 2 and 3 were compared with group 1, which served as reference. In a multivariate model, groups 2 and 3 were considered together and are referred to as “SH (all episodes),” as opposed to “no SH” for group 1.

Within-subject differences between pregestational and first trimester data were analyzed using the paired Student’s \(t\) test to compare means (and nonparametric tests if appropriate) and the \(\chi^2\) test to compare proportions. Associations with \(P < 0.05\) were considered statistically significant. Adjusted odds ratios (ORs) and their 95% CIs were obtained by multiple logistical regression analysis of those characteristics that may serve as predictor variables for SH during the first trimester of pregnancy. Multiple logistical regression analysis included all variables with a \(P < 0.05\) in the univariate analysis.

**RESULTS**

**Occurrence of SH and hypoglycemic coma**

The occurrence rates of SH (all episodes) and of hypoglycemic coma were both increased during the first trimester of pregnancy as compared with the last 4 months before gestation (\(P < 0.001\) and \(P = 0.03\)) (Table 1). The proportion of the population affected by SH rose from 23 to 41% (\(P < 0.001\)), including a twofold increase in the percentage of women with at least one episode of hypoglycemic coma (from 9 to 19%, \(P < 0.001\)). Reduced awareness of hypoglycemia (Clarke score) was reported by 16% of the women at inclusion.
Hypoglycemia and pregnancy

Table 1—Occurrence of SH, reduced hypoglycemia awareness, and fear of hypoglycemia in 278 women with type 1 diabetes, contrasting the last 4 months before gestation and the first trimester of pregnancy

<table>
<thead>
<tr>
<th>Occurrence of SH (no episodes/4 months)</th>
<th>Pregestational</th>
<th>First trimester</th>
</tr>
</thead>
<tbody>
<tr>
<td>SH (all episodes)</td>
<td>0.9 ± 2.4</td>
<td>2.6 ± 6.3*</td>
</tr>
<tr>
<td>Hypoglycemic coma</td>
<td>0.3 ± 1.3</td>
<td>0.7 ± 3.7*</td>
</tr>
<tr>
<td>Proportion of patients with SH (all episodes)</td>
<td>25</td>
<td>41*</td>
</tr>
<tr>
<td>Uncomplicated SH only</td>
<td>16</td>
<td>22*</td>
</tr>
<tr>
<td>Hypoglycemic coma</td>
<td>9</td>
<td>19*</td>
</tr>
<tr>
<td>Reduced hypoglycemia awareness§</td>
<td>16</td>
<td>35*</td>
</tr>
<tr>
<td>Fear of hypoglycemia</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Hypoglycemia worry level</td>
<td>12 ± 9</td>
<td>12 ± 9</td>
</tr>
</tbody>
</table>

Data are means ± SD or %, *P<0.001, †P<0.05 as compared with pregestational, §Clarke et al. (12); Hypoglycemic Fear Survey, Worry Scale (points).

Sequelae of SH

Hypoglycemia-related anxiety (measured by means of the Hypoglycemic Fear Survey, Worry Scale) was a higher burden for women with uncomplicated SH and coma compared with women without any SH (both P < 0.001). At ~17 weeks gestation, more than half of the women in the uncomplicated SH group and in the coma group perceived a reduced threshold for symptoms (onset at BG <3.0 mmol/l); this was significantly more than in the group without any SH (37%) (P < 0.05 for both comparisons)

Multiple logistical regression analysis of risk factors predictive for SH (all episodes)
The occurrence of SH during the first trimester of type 1 diabetic pregnancy was prospectively determined. Univariate analysis showed that diabetes duration, HbA1c ≤6.5%, a history of SH before gestation, total daily insulin dose, and a decreased symptom threshold (BG <3.0 mmol/l) were related to the occurrence of SH (all episodes) during the first trimester (Table 2). Multiple logistical regression analysis showed that an increased risk of SH during the first trimester was independently related to the following risk indicators, after correction for a decreased symptom threshold: a history of SH before gestation (OR [95% CI]: 9.2 [3.9–21.7]), duration of diabetes 10 years longer (1.6 [1.0–2.4]), a daily insulin dose 0.1 unit/kg higher (5.4 [1.5–18.9]), and HbA1c ≤6.5% (2.5 [1.3–5.0]).

CONCLUSIONS — This study demonstrates a two- to threefold increase over time in SH during the first trimester of type 1 diabetic pregnancy, as compared with the last 4 months before pregnancy. The incidence of SH (all episodes) before gestation was equivalent to 270 episodes per 100 patient-years, including 90 episodes of hypoglycemic coma. These incidences of SH and coma during the 4 months before pregnancy are almost 50% higher than occurrence rates we have previously reported for a population of 195 unselected nonpregnant type 1 diabetic patients, who had a mean HbA1c of 7.8 ± 1.2% and a duration of diabetes of 20 ± 12 years, with 82% on MIT or CSII (15). In the present study, the subset of women affected by SH during the 4 months before pregnancy was 25%, including 9% affected by coma. In comparison, in our
previous study, 40.5% of these type 1 diabetic patients retrospectively reported SH (all episodes) over a period of 1 year, including a subset of 19% with hypoglycemic coma.

During the first trimester of pregnancy, the incidence of SH was equivalent to 780 episodes of SH (all episodes) per 100 patient-years, including 210 episodes of coma. The proportion of the women affected during the first trimester (4 months) increased to 41% for SH (all episodes) and to 19% for hypoglycemic coma. The first trimester occurrence of SH is slightly lower than that previously found by Rosenn et al. (16). They reported an average overall occurrence of 6.7 SH episodes per patient per pregnancy in 278 women with type 1 diabetes. Although it would have been interesting to know whether there might have been a shift in the proportion of nocturnal hypoglycemic episodes, data regarding this were not available.

Patients generally tend to underestimate the frequency with which they experience hypoglycemia (17). We cannot exclude that recall bias affected the retrospective report of SH before pregnancy to a larger extent than the report of SH during the first trimester. After all, the latter was assessed after we had informed the participants in advance that we would ask them to report on this. The reliability of the reported frequencies for pregestational and first-trimester SH may therefore not be equivalent. In particular, the frequency of SH before gestation might even be higher than what we have reported here, which would result in a somewhat smaller increase in SH between the two assessments.

Multiple logistical regression analysis showed four main risk indicators that independently predicted an increased risk of SH (all episodes) during the first trimester. These risk indicators were: a history of SH in the 4 months before gestation, a 10 years’ longer duration of diabetes, a daily insulin dose 0.1 unit/kg higher, and an HbA1c ≤6.5%.

Antecedent hypoglycemia is well recognized as an important risk factor for subsequent SH in type 1 diabetes (18). The underlying mechanism is a threshold shift for the activation of glucose counter-regulation toward lower BG levels due to (recurrent) exposure to decreased BG levels (19). Impaired glucose counterregulation has also been shown to be related to tight glycemic control (20,21). Pregestational SH comprised a markedly higher risk (OR [95% CI]: 9.2 [3.9–21.7]) of subsequent first-trimester SH. This suggests that the proposed mechanism of “hypoglycemia begetting hypoglycemia” is at least partially responsible for the rise in risk of SH during early pregnancy. Although impairment of glucose counter-regulatory hormonal responses was not

### Table 2 — Risk indicators and sequelae of no SH, SH (all episodes), uncomplicated SH, and hypoglycemic coma during the first trimester of pregnancy in 278 women with type 1 diabetes.

<table>
<thead>
<tr>
<th></th>
<th>All</th>
<th>No SH</th>
<th>SH (all episodes)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Demographics</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Age (years)</td>
<td>30 ± 4</td>
<td>30 ± 4</td>
<td>29 ± 4</td>
</tr>
<tr>
<td>BMI (kg/m²)</td>
<td>24.9 ± 3.8</td>
<td>24.8 ± 3.5</td>
<td>25.5 ± 4.5</td>
</tr>
<tr>
<td>Nullipara</td>
<td>53</td>
<td>52</td>
<td>60</td>
</tr>
<tr>
<td>Diabetes and Treatment</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Diabetes duration (years)</td>
<td>12 ± 8</td>
<td>11 ± 8</td>
<td>15 ± 7</td>
</tr>
<tr>
<td>Complicated diabetes</td>
<td>26</td>
<td>21</td>
<td>30</td>
</tr>
<tr>
<td>CSH</td>
<td>40</td>
<td>42</td>
<td>48</td>
</tr>
<tr>
<td>Insulin lispro</td>
<td>12</td>
<td>15</td>
<td>8</td>
</tr>
<tr>
<td>Insulin dose/24 h (units/kg)</td>
<td>0.74 ± 0.29</td>
<td>0.69 ± 0.27</td>
<td>0.88 ± 0.30</td>
</tr>
<tr>
<td>SMBG &gt;4 times per day</td>
<td>73</td>
<td>70</td>
<td>79</td>
</tr>
<tr>
<td>HbA1c first trimester (%)</td>
<td>6.7 ± 0.7</td>
<td>6.8 ± 0.7</td>
<td>6.6 ± 0.6</td>
</tr>
<tr>
<td>HbA1c distribution (%)</td>
<td>≤6.5</td>
<td>46</td>
<td>51</td>
</tr>
<tr>
<td>History of SH/Awareness</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>History of SH (%)</td>
<td>25</td>
<td>11</td>
<td>40</td>
</tr>
<tr>
<td>Reduced awareness (at inclusion)</td>
<td>16</td>
<td>7</td>
<td>40</td>
</tr>
<tr>
<td>Sequelae of SH (end of 1st trimester)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Hypoglycemia Worry level</td>
<td>12 ± 9</td>
<td>9 ± 7</td>
<td>19 ± 10</td>
</tr>
<tr>
<td>Decreased threshold for symptoms (&lt;3.0 mmol/l)</td>
<td>45</td>
<td>37</td>
<td>59</td>
</tr>
</tbody>
</table>

Data are means ± SD or %. P values as compared with no SH. *P<0.05, †P<0.005, ‡P<0.001; §≥1 SH episode (with or without coma) prior to gestation; [Hypoglycemic Fear Survey, Worry Scale (points).]
documented in this study, we believe that our data may illustrate the above. A lower limit of (preprandial) BG treatment goals as low as 3.3 mmol/l has been reported by various authors (22,23). To preclude a vicious circle of hypoglycemia and impaired glucose counterregulation, prevention of BG levels in the hypoglycemic range (i.e., <3.9 mmol/l) should be included when tightening glycemic control before and during pregnancy.

The observations that a substantially longer duration of diabetes (i.e., by 10 years) and a daily insulin dose 0.1 unit/kg higher were associated with an increased risk of SH are in agreement with the Diabetes Control and Complications Trial (DCCT) (18). In our population, a few changes in treatment regimen were observed. The majority (98%) of the women was already on intensive insulin treatment (either MIT or CSII) before pregnancy. Only 4% changed from MIT to CSII treatment early in pregnancy; therefore, it was not possible to detect a potential relationship between changing treatment regimen and SH, as was shown to be of importance in the DCCT (24).

The use of insulin lispro (outside pregnancy) has previously been shown to be associated with a significant lowering of hypoglycemic episodes (25). In our study, the relationship between the use of insulin lispro and absence of SH was only studied in the first trimester. Only 4% changed from MIT to CSII treatment early in pregnancy; therefore, it was not possible to detect a potential relationship between changing treatment regimen and SH, as was shown to be of importance in the DCCT (24).

Intrinsic factors related to pregnancy itself may also be partially responsible for the further increase of SH during early gestation. Nausea and vomiting are quite common during the first trimester and may contribute to hypoglycemia due to fluctuations in carbohydrate ingestion. The results of previous studies also raise the possibility that glucose counterregulatory responses are diminished by pregnancy per se (27,28).

Hypoglycemia-related anxiety was a higher burden for women with SH (with or without coma) than for women without any SH during the first trimester. Worry levels were similar to the worry levels we reported previously in nonpregnant unselected type 1 diabetic patients (15).

In conclusion, this study shows that in pregnant women with type 1 diabetes, the risk of SH already increases pregestationally, with a further rise during the first trimester. To preclude a vicious circle of impaired glucose counterregulation by antecedent hypoglycemia, prevention of low BG levels (<3.9 mmol/l) should be included in BG treatment goals for these women too. Education should include paying attention to the risks of high daily amounts of insulin. Pregestational educational intervention, e.g., with BG awareness training (BGAT) programs (29), may be helpful to reduce the high risk of SH associated with type 1 diabetic pregnancy.

Acknowledgments—This study was supported by Novo Nordisk.

References
15. Rosenn BM, Miodovnik M, Holberg G,