Hypoglycemia in Pregnant Women With Type 1 Diabetes

Predictors and role of metabolic control

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OBJECTIVE — In pregnancy with type 1 diabetes, we evaluated occurrence of mild and severe hypoglycemia and analyzed the influence of strict metabolic control, nausea, vomiting, and other potential predictors of occurrence of severe hypoglycemia.

RESEARCH DESIGN AND METHODS — A prospective observational study of 108 consecutive pregnant women with type 1 diabetes was conducted. At 8, 14, 21, 27, and 33 weeks of gestation, patients performed self-monitored plasma glucose (SMPG) (eight/day) for 3 days and completed a questionnaire on nausea, vomiting, hypoglycemia awareness, and history of mild (managed by the patient) and severe (requiring assistance from others) hypoglycemia.

RESULTS — Forty-nine (45%) women experienced 178 severe hypoglycemic events, corresponding to 5.3, 2.4, and 0.5 events/patient-year in the first, second, and third trimesters, respectively. The incidence of mild hypoglycemia was 5.5 events/patient-week in early pregnancy and decreased throughout pregnancy ($P < 0.0001$), regardless of presence of severe hypoglycemia. Prevalence of nausea and vomiting, mild hypoglycemia, and fraction of SMPG readings ≤3.9 mmol/l did not differ between women with and without severe hypoglycemia. A1C, median SMPG, and fluctuations in SMPG decreased during pregnancy, with no differences between women with and without severe hypoglycemia. Logistic regression analysis identified history of severe hypoglycemia the year preceding pregnancy (odds ratio 3.3 [95% CI 1.2–9.2]) and impaired awareness or unawareness (3.2 [1.2–8.2]) as independent predictors for severe hypoglycemia.

CONCLUSIONS — In pregnancy with type 1 diabetes, the incidence of mild and severe hypoglycemia was highest in early pregnancy, although metabolic control was tighter in the last part of pregnancy. Predictors for severe hypoglycemia were history of severe hypoglycemia and impaired awareness.

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Pregnancy outcome among women with type 1 diabetes is still significantly poorer than in the background population (1). Optimal glycemic control is crucial in order to reduce the risk of congenital malformations, stillbirth, macrosomia, preeclampsia, and preterm delivery (2–5). However, striving for near normoglycemia increases the risk of severe hypoglycemia (6), which is the major limiting factor for achieving optimal blood glucose control in pregnant women with type 1 diabetes (7).

Severe hypoglycemia is three times as frequent in early pregnancy compared with the period before pregnancy (8), and the incidence is highest in gestational week 8–16 and lower in the second part of pregnancy (7). Traffic accidents (9) and death (10) due to severe hypoglycemia in pregnancy are rare but significant problems. Pregnancy-induced nausea and vomiting have been proposed to be contributing factors for severe hypoglycemia in early pregnancy (7,8). Hypoglycemia unawareness is a major predictor for severe hypoglycemia in nonpregnant patients with type 1 diabetes (11), but its significance during pregnancy in type 1 diabetes is not known. It is not known whether the incidence of mild hypoglycemic events or the occurrence of hypoglycemia awareness change during pregnancy.

Clinical studies using prospective evaluation and documentation of mild and severe hypoglycemic events are lacking in pregnant women using modern insulin treatment with multiple daily insulin injections and self-monitored plasma glucose (SMPG) values. With the purpose to facilitate the development of clinical approaches that reduce the severity and frequency of severe hypoglycemia (12) in pregnant women with type 1 diabetes, we thoroughly evaluated the incidence of mild and severe hypoglycemia during different parts of pregnancy. Furthermore, we analyzed the influence of strict metabolic control, nausea, vomiting, and other potential predictors on the occurrence of severe hypoglycemia.

RESEARCH DESIGN AND METHODS

— In a 2-year prospective observational study, we consecutively included all Danish-speaking Caucasian women with pregestational type 1 diabetes ($n = 121$) referred to the Center for Pregnant Women with Diabetes, Rigshospitalet, before 14 completed gestational weeks with a single living fetus during the study period 1 September 2004 to 31 August 2006.

Women with psychiatric disorders,

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Abbreviations: SMPG, self-monitored plasma glucose; UAE, urine albumin excretion.

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

Addison's disease, and glucocorticoid-treated rheumatoid arthritis ($n = 5$) were excluded, as the medical treatment might influence the risk of severe hypoglycemia. If a woman had more than one pregnancy in the study period ($n = 2$), only the first pregnancy was included. A total of 108 (95%) eligible women accepted to participate in the study.

Reporting and classifying hypoglycemia

At inclusion at a median of 8 gestational weeks (range 5–13) and at the visits at gestational weeks 14 (12–16), 21 (20–23), 27 (25–29), and 33 (31–35), the women filled in a detailed questionnaire originally developed for a multicenter survey of hypoglycemia in nonpregnant subjects with type 1 diabetes (11,13). The questions encompassed the number of hypoglycemic events, state of hypoglycemia awareness, blood glucose level during hypoglycemia, causes of hypoglycemia, and sociodemographic data. The questionnaire was expanded to include questions about pregnancy-related vomiting and nausea during the preceding week.

Before the visits at weeks 8, 14, 21, 27, and 33, the women performed SMPG eight times daily for 3 days (including at 3:00 A.M.). Biochemical hypoglycemia was defined as an SMPG value ≤3.9 mmol/l (12). Based on the SMPG profiles, the proportions of hypoglycemic values, hyperglycemic values (≥10.0 mmol/l), and proportions outside the range of 4.0–9.9 mmol/l were calculated for each patient as a measure of glucose variability.

Mild hypoglycemia was defined as events with symptoms familiar to the patient as hypoglycemia and managed by the patient (14). The number of mild hypoglycemic events was assessed in each questionnaire, whereas the frequency of mild hypoglycemic events before gestation was assessed at the first pregnancy visit.

Severe hypoglycemia was defined as events with symptoms of hypoglycemia requiring help from another person to actively administer oral carbohydrate or injection of glucagon or glucose in order to restore the blood glucose level (12). Severe hypoglycemic events in the 1-year period preceding pregnancy (stated as "previous severe hypoglycemia" in the following) were reported retrospectively in the questionnaire at inclusion. To ascertain severe hypoglycemia during pregnancy, the women were asked to contact the investigators within 24 h after the event.

When reported, we performed a structured interview including questions about date and hour of the event, possible provoking factor(s), accompanying convulsions or unconsciousness, presence of nausea or vomiting the preceding 24 h, time to recovery, and type of treatment. Plasma glucose values during the hypoglycemic events were recorded, if measured. Events occurring during the early phase of pregnancy were recorded at the first visit. The interviews were mainly performed by telephone, but a few were performed during clinical visits or hospitalization following severe hypoglycemia.

Events of severe hypoglycemia were validated according to Whipple's triad: *1*) symptoms consistent with hypoglycemia, *2*) a blood glucose value ≤3.9 mmol/l, and *3*) adequate response to glucose/glucagon treatment. Events fulfilling all criteria were classified as definite, those fulfilling two criteria as probable, and the remaining as possible (15).

Self-estimated hypoglycemia awareness was derived from the patient's answer to the question, "Do you recognize symptoms, when you have a hypoglycemic event" (14). Subjects answering "always" were classified as having normal awareness, those answering "usually" as having impaired awareness, and those answering "occasionally" or "never" as having unawareness.

The glycemic threshold for mild hypoglycemic events before and during pregnancy was assessed by the question, "How low do you believe your blood glucose is, when you recognize a hypoglycemic event?" When the answer was given as a range, the mean value was used.

Management of diabetes in pregnancy

Routine SMPG was recommended at least seven times daily (before and 1.5 h after each main meal and at bedtime) every day during pregnancy and at 3:00 A.M. once a week. The patients registered their SMPG values in diabetes diaries, which were evaluated at each clinical visit. The values were not downloaded electronically from the glucose monitors. The diet and insulin dosage were adjusted accordingly. Continuous glucose monitoring systems were not generally available and were only used occasionally in a few of the patients.

The women were instructed to perform self-adjustments of insulin dosages between clinical visits based on the SMPG of the previous 3 days in order to maintain preprandial SMPG of 4.0–6.0 mmol/l, 1.5-h postprandial SMPG of 4.0–8.0 mmol/l, and prebedtime SMPG of 6.0–8.0 mmol/l. In case of symptoms of hypoglycemia and/or SMPG ≤3.0 mmol/l, oral carbohydrate intake was recommended. If a single premeal SMPG was ≥8.0 mmol/l, 1–2 extra units of fast-acting insulin was recommended. In case of SMPG ≥15.0 mmol/l, vomiting, and stomachache, urine ketones should be checked. They continued their usual insulin regimen, four to five injections daily or insulin pump treatment.

The women received oral and written information about expected changes in insulin dosage during pregnancy, including information about a suspected high risk of severe hypoglycemia at night between 10 and 16 weeks and the need for an increase in insulin dosage from week 20. A glucagon pen (GlucaGen) was prescribed.

All women visited our and/or their local diabetes clinic at 1- or 2-week intervals throughout pregnancy, where weight, A1C, and blood pressure were measured. A1C was measured on a DCA 2000 analyzer by a latex immunoagglutination inhibition method (DCA 2000; Bayer). Normal range outside pregnancy was 4.7–6.3%, in early pregnancy 4.5–5.7%, and in late pregnancy 4.4–5.6% (16). Blood pressure was measured with a digital blood pressure monitor after 5–10 min of rest. Normal blood pressure was defined as <140/90 mmHg. Two 24-h urine albumin excretions (UAEs) were performed at inclusion. Microalbuminuria was defined as median UAE ≥30 mg/24 h and nephropathy as UAE ≥300 mg/24 h.

Diabetic retinopathy was diagnosed with retinal photos at inclusion and at week 28. Obstetrical ultrasound scanning was performed on routine basis at inclusion; at weeks 14, 21, 27, and 33; and when indicated.

Information about insulin type and dosage and other medications were drawn from the patients' medical records. During the study period, 25 women received antihypertensive treatment, mainly methyldopa ($n = 22$). Antidepressive treatment (fluoxetin or paroxetin) was given in three women. Thyroid dysfunction was treated with levothyroxine in 16 and with thiamazole in 2 women, resulting in normal thyroid function in all 18 women during pregnancy.

All participants gave written informed consent. The research protocol was ap-

Table 1—*Baseline clinical data in 108 women with type 1 diabetes according to experience of severe hypoglycemia in pregnancy*

	Women without severe hypoglycemia in pregnancy	Women with severe hypoglycemia in pregnancy
n	59 (55)	49 (45)
Age (years)	31 (21–42)	30 (21–39)
Duration of diabetes (years)	13 (1–36)	19 (2.5–31)*
Gestational age at inclusion (days)	61 (37–94)	62 (42–93)
Last A1C before pregnancy (%)	7.5 (5.9–10.0)	7.0 (5.9–10.9)
BMI before pregnancy (kg/m^2)	24.1 (17.3–43.8)	24.4 (20.1–32.4)
Insulin type (human insulin/insulin analogs)	32 (54)/27 (46)	28 (57)/21 (43)
Number of daily insulin injections (4/5/CSII) (%)	56/42/2	67/25/8
Diabetic retinopathy	35 (59)	33 (67)
Microalbuminuria/nephropathy	6 (10)/3 (5)	4 (8)/3 (6)
Antihypertensive treatment at inclusion	5 (8)	10 (20)
Systolic blood pressure (mmHg)	119 (95–150)	119 (88–150)
Diastolic blood pressure (mmHg)	70 (55–86)	71 (59–85)
Severe hypoglycemia the year preceding pregnancy	10 (17)	23 (47)†
SMPG threshold for mild hypoglycemic events before pregnancy	3.0 (1.5–4.0)	2.7 (1.5–4.5)*

Data are median (range) or *n* (%) unless otherwise indicated. *$P < 0.01$; †$P < 0.001$. CSII, continuous subcutaneous insulin infusion.

proved by the regional committees for ethics and science and by the Danish Data Protection Agency.

Statistical analysis

Continuous variables were non-normally distributed and given as median (range). Discrete variables are given as numbers and proportions. Differences between groups were analyzed using χ^2 test for categorical variables and Kruskal-Wallis or Mann-Whitney tests when appropriate for continuous variables. Changes during pregnancy were tested assessing the within-subject differences between values at week 33 and week 8 using nonparametric tests. The incidence of severe hypoglycemia in the three trimesters was compared using Poisson regression analysis.

Univariate and multiple logistic regression analysis were conducted with "at least one severe hypoglycemic event in pregnancy" as the dependent variable. With 49 observations, the following five independent variables were chosen based on significance in the univariate analyses or a priori significance based on ref. 8: duration of diabetes >10 years, previous severe hypoglycemia, impaired awareness or unawareness (collapsed due to a low number of patients with unawareness), fluctuating SMPG (per 10% increment), and A1C ≤6.5% at inclusion. The results are expressed as odds ratios (ORs) and 95% CIs.

The associations were considered to be statistically significant at a two-sided *P* value <0.05. All statistical analyses were performed using SAS (version 9.1; SAS Institute, Cary, NC).

RESULTS

Severe hypoglycemia

Forty-nine (45%) women experienced 178 severe hypoglycemic events throughout pregnancy (Table 1). Eighty percent of the events occurred before 20 weeks with a peak at 9 weeks (supplemental Fig. 1 [available in an online appendix at http://dx.doi.org/10.2337/dc07-1066]). The incidence rates were 5.3, 2.4, and 0.5 events/patient-year in the first, second, and third trimesters, respectively ($P < 0.0001$). Thirty-four women had more than one event, including 11 women with five or more events (5–31) accounting for 106 (60%) of all events. The first event occurred before 20 weeks in 95% of the women. Thirty-three (31%) women experienced at least one (1–30) severe hypoglycemic event the year preceding pregnancy (1.1 event/patient-year).

There was no difference in weight gain during pregnancy in women with or without severe hypoglycemia (15.2 kg [range 5.6–26.8] vs. 15.0 kg [7.6–34.4]). There was no difference in the prevalence of diabetic retinopathy in early pregnancy (Table 1) or in the number of women with retinopathy progression during pregnancy (11 [22%] vs. 12 [20%]).

Structured interviews about severe hypoglycemic events were obtained after 167 (94%) of the recorded events. According to Whipple's triad, 92 events (55%) were definite, 74 (44%) were probable, and 1 was possible. Median SMPG was 1.8 mmol/l (range 1.0–3.9) ($n = 92$). Unconsciousness (30 min [2–360]) occurred at 30 (18%) and convulsions at 13 (8%) events. No traffic accidents or major injuries were reported.

Eighteen (11%) events were treated with intramuscular glucagon and seven (4%) with intravenous glucose. Seven events required hospitalization ≥2 h. Recovery time after the event was 30 min (range 5–360).

At 94 (56%) events, no possible cause was identified. At 23 (14%) events, the reason was reported to be excessive insulin dosages, at 38 (23%) events insufficient caloric intake and/or a postponed meal (30–240 min), at 4 (2%) events vomiting, and at 3 (2%) events planned physical activity. Five (3%) events were preceded by recurrent mild hypoglycemic events.

Mild hypoglycemia

The incidence of mild hypoglycemia was 3.4 events/patient-week before pregnancy and 5.5, 5.1, 4.2, 3.8, and 3.8 events/patient-week at weeks 8, 14, 21, 27, and 33, respectively, with a significant decrease from 8 to 33 weeks ($P < 0.0001$) and no difference between women with and without severe hypoglycemia (Table 2).

Biochemical hypo- and hyperglycemia

The fraction of biochemical hypoglycemia was stable during pregnancy, whereas the fraction of SMPG values ≥10.0 mmol/l decreased significantly from 8 weeks to 33 weeks with a concomitant tendency toward a reduction in median SMPG (Table 2).

Table 2—*Metabolic parameters in 49 women with (+SH) and 59 women without (−SH) severe hypoglycemia in pregnancy with type 1 diabetes*

	Week 8	Week 14	Week 21	Week 27	Week 33
Median SMPG (mmol/l)					
−SH	6.4 (4.0–11)	6.8 (4.3–11)	6.7 (4.0–10)	6.8 (3.9–11)	5.9 (4.2–10)*
+SH	6.8 (4.0–13)	6.7 (3.9–14)	6.7 (4.6–12)	6.8 (4.9–9)	6.4 (4.1–10)
Biochemical hypoglycemia SMPG ≤3.9 mmol/l (%)					
−SH	16 (4–44)	13 (0–46)	13 (0–48)	12 (0–50)	15 (0–39)
+SH	17 (0–50)	17 (0–54)	14 (0–35)	13 (0–36)	17 (0–46)
SMPG outside the range of 4.0–9.9 mmol/l (%)					
−SH	34 (8–70)	36 (8–82)	36 (4–59)	29 (0–65)	29 (4–58)†
+SH	48 (16–84)‡	39 (8–81)	36 (0–69)	27 (0–61)	36 (0–58)†
Biochemical hyperglycemia SMPG ≥10.0 mmol/l (%)					
−SH	16.7 (0–57)	16.7 (0–57)	18.2 (0–48)	14.3 (0–50)	8.3 (0–40)†
+SH	21.5 (0–72)	21.7 (0–67)	19.5 (0–65)	12.5 (0–42)	9.1 (0–52)*
Median SMPG at 3:00 A.M.§					
−SH	5.9 (1.8–14)	6.5 (2.2–18)	6.2 (1.9–14)	5.7 (1.9–13)	5.1 (2.1–16)*
+SH	7.9 (2.1–16)	7.0 (2.6–16)	6.3 (3–13)	7.0 (2.9–11)	5.8 (2.7–13)
A1C (%)					
−SH	6.7 (4.9–8.8)	6.4 (5.2–7.9)	6.0 (4.9–7.1)	5.9 (4.9–6.9)	5.9 (5.0–7.3)†
+SH	6.5 (5.2–10.5)	6.3 (5.1–7.8)	6.0 (5.0–7.7)	5.9 (5.0–7.2)	5.9 (4.8–7.2)†
Insulin dosage (IU/kg)					
−SH	0.76 (0.4–1.2)	0.68 (0.4–1.2)	0.78 (0.4–1.4)	0.90 (0.5–1.7)	1.12 (0.5–1.9)†
+SH	0.76 (0.3–1.7)	0.68 (0.3–1.5)	0.73 (0.3–1.2)	0.90 (0.4–1.6)	1.04 (0.5–1.6)†
Self-estimated impaired awareness					
−SH	25 (43)	25 (49)	28 (54)	25 (46)	26 (47)
+SH	36 (75)‖	33 (73)¶	35 (85)‡	34 (81)‡	31 (72)¶
Number of mild hypoglycemic events previous week					
−SH	5 (0–21)	4.5 (0–12)	4 (0–12)§	3 (0–13)	4 (0–14)*
+SH	4 (0–21)	4 (0–14)	3 (0–8)	3 (0–25)	3 (0–15)*
SMPG threshold for mild hypoglycemic events					
−SH	2.8 (1.5–4.0)	3.0 (1.8–4.5)	3.0 (1.9–4.0)	3.0 (1.9–4.0)	2.8 (1.8–3.8)
+SH	2.7 (1.5–4.0)	2.8 (1.6–4.0)	2.7 (1.8–3.8)	2.7 (1.8–4.0)	2.8 (1.9–4.0)
Nausea or vomiting previous week					
−SH	37 (63)	25 (50)	17 (32)	12 (22)	19 (34)#
+SH	27 (56)	14 (30)	11 (26)	9 (21)	11 (25)*

Data are median (range) or *n* (%). *$P < 0.05$, †$P < 0.0001$, and #$P < 0.001$ between week 33 and week 8. ‡$P < 0.01$, ‖$P < 0.001$, and ¶$P < 0.05$ between the two groups. Data were obtained from 85 to 100% of the patients except §where 75% of samples were obtained.

Nocturnal hypoglycemia

Ninety-two (52%) severe hypoglycemic events occurred during sleep, of which 65 (37%) events occurred at night (12:00–8:00 A.M.). The year preceding pregnancy, 54% of the reported severe hypoglycemic events occurred during sleep.

The incidence of mild nocturnal hypoglycemia was 1.6, 1.3, 0.8, 0.7, and 0.8 events/patient-week at weeks 8, 14, 21, 27, and 33, respectively, with a significant decrease from 8 to 33 weeks ($P < 0.001$) and no difference between women with and without severe hypoglycemia.

Assessment of awareness of hypoglycemia

A total of 45 (42%) women reported normal hypoglycemia awareness at inclusion, 56 (52%) reported impaired awareness, and 7 (6%) reported unawareness. During pregnancy, the women did not report any significant changes in hypoglycemia awareness (Table 2). Likewise, the glycemic threshold for perception of warning symptoms did not change (Table 2).

Predictors of severe hypoglycemia at inclusion

Univariate analysis showed that women with severe hypoglycemia in pregnancy more often had previous severe hypoglycemia (OR 4.3 [95% CI 1.8–10.5]), diabetes duration >10 years (3.3 [1.3–8.2]), impaired hypoglycemia awareness or unawareness (3.9 [1.7–9.0]), and SMPG readings outside the range of 4.0–9.9 mmol/l at week 8 (1.6 [1.2–2.1] per 10% increment).

Throughout pregnancy, there were no significant differences between women with and without severe hypoglycemia regarding the fraction of biochemical hypoglycemia, self-reported SMPG threshold for perception of warning symptoms, median SMPG, A1C, or other metabolic parameters (Table 2). The drop in A1C from before gestation to week 8 among women with and without severe hypoglycemia was comparable (−0.5% [−1.8 to 0.4] vs. −0.6% [−1.4 to 0.9], respectively).

Women experiencing severe hypoglycemia tended to report nausea or vomiting less frequently than women

who did not experience severe hypoglycemia (Table 2).

Multiple logistic regression analysis identified previous severe hypoglycemia (OR 3.3 [95% CI 1.2–9.2]) and impaired hypoglycemia awareness or unawareness (3.2 [1.2–8.2]) as independent predictors of severe hypoglycemia.

There was a significant interaction between impaired hypoglycemia awareness and previous severe hypoglycemia ($P < 0.01$). Severe hypoglycemia during pregnancy was seen in 21 of 22 (95%) women with both impaired hypoglycemia awareness and previous severe hypoglycemia (corresponding to 7.4 events/patient-year), in 16 of 41 (39%) women with impaired hypoglycemia awareness without previous severe hypoglycemia, in 2 of 11 (18%) women with normal hypoglycemia awareness and previous severe hypoglycemia, and in 10 of 34 (29%) women with normal hypoglycemia awareness without previous severe hypoglycemia (corresponding to 1.7 events/patient-year).

Pregnancy outcome

Nine (8%) women developed preeclampsia. Ketoacidosis was not seen. Twenty-three women (21%) delivered preterm (<37 weeks), mainly between week 34 and 36 due to preeclampsia, large for gestational age infants, or preterm premature rupture of the membranes. Birth weight was 3,440 g (range 2,040–4,760) in infants of women with severe hypoglycemia and 3,532 g (2,475–5,620) in infants of women without severe hypoglycemia (P = NS). One neonatal death and no severe congenital malformations were registered.

CONCLUSIONS

— This prospective study of 108 women with type 1 diabetes is based on the distribution of thoroughly validated prospectively recorded events of severe hypoglycemia according to a well-established definition (12), and 95% of all eligible women participated. Our findings are in accordance with previous observations (8,9), which either included only the first trimester of pregnancy (8) or twin pregnancies and the same women in two pregnancies (9). We studied the whole pregnancy and included only singleton pregnancies to avoid the potential bias of complications of twin pregnancies, and all women were included only once to secure independent observations.

Structured interviews were obtained after 94% of all reported events of severe hypoglycemia, but it cannot be ruled out that a small degree of underdocumentation occurred. To ensure a complete registration of severe hypoglycemia in early pregnancy, events before the first visit were included. Subjects with type 1 diabetes recall severe hypoglycemic events well during a 1-year period (14), and thus the obtained incidence rates are considered to be reliable.

Women who, at the first pregnancy visit, are characterized by previous severe hypoglycemia and impaired hypoglycemia awareness or unawareness have a three times higher risk of severe hypoglycemia in pregnancy compared with women without these characteristics. Fluctuating plasma glucose values and a longer duration of diabetes might also contribute to a higher risk of severe hypoglycemia, whereas the number of mild hypoglycemic events per week, a lower A1C, or the fraction of biochemical hypoglycemia did not predict the risk of severe hypoglycemia in these women.

We aimed to investigate whether many low values recorded by the women in the routinely used SMPG could identify women at high risk of severe hypoglycemia. However, that was not the case, possibly due to insufficient sensitivity of the method. We cannot exclude that use of continuous glucose monitoring system—a tool that is more sensitive to record periods of hypoglycemia and fluctuations in glucose values—might have given other results.

The prevalence of retinopathy in early pregnancy and the number of women with retinopathy progression during pregnancy was comparable in women with and without severe hypoglycemia. Thus, an association between severe hypoglycemia and progression of retinopathy during pregnancy was not seen. Likewise, the numbers of women with microalbuminuria and nephropathy were comparable among women with and without severe hypoglycemia, but the numbers were too small to make any conclusions.

Pregnancy-related nausea and vomiting might be contributing factors for severe hypoglycemia in pregnancy (7,8). Using questionnaires five times during pregnancy and in interviews after each event of severe hypoglycemia, we could rule out that nausea and vomiting are major contributing factors for severe hypoglycemia in pregnancy.

Self-estimated impaired hypoglycemia awareness or unawareness was associated with severe hypoglycemia as previously described in nonpregnant patients with type 1 diabetes (11); in particular, the combination of impaired hypoglycemia awareness and previous severe hypoglycemia was associated with a high risk of severe hypoglycemia. However, preserved hypoglycemia awareness did not completely protect against severe hypoglycemia in pregnancy. Noteworthy, there was no change in hypoglycemia awareness during pregnancy to explain the varying risk of severe hypoglycemia. Hypoglycemia awareness was determined by the women's self-estimated understanding of awareness, and they had to distinguish whether they were "always," "usually," "occasionally," or "never" able to feel a hypoglycemic event. The same question was addressed prospectively, five times in pregnancy, and we noted a very high agreement in each woman and in the whole study population indicating that the women had a good sensation of their awareness in pregnancy.

A decline in the SMPG threshold for mild hypoglycemia was seen at onset of pregnancy in women without severe hypoglycemia in pregnancy, but the SMPG threshold for mild hypoglycemic events did not change significantly in any of the groups during pregnancy. This indicates that other factors than change in hypoglycemia awareness account for the lower incidence of severe hypoglycemia in the second part of pregnancy.

Despite a higher incidence of severe hypoglycemia in pregnancy, the proportion of events during sleep was comparable before and during pregnancy. More than one-half of the severe hypoglycemic events occurred during sleep, of which 37% occurred at night. This is comparable with what was reported in nonpregnant patients with type 1 diabetes (17).

The vast majority of the women experienced their first event of severe hypoglycemia before week 20. This implies that women who have not experienced severe hypoglycemia before week 20 have a low risk of such events in the remaining part of pregnancy, enabling these women to strive for an even stricter metabolic control in the last part of pregnancy.

A declining insulin requirement in the late first trimester of pregnancy with type 1 diabetes was previously reported (18), and overinsulinization has been suggested as a contributing reason for severe hypoglycemia in early pregnancy (18). In our study, the insulin requirement decreased from week 8 to week 14 and increased from week 14 onwards. Throughout pregnancy, median SMPG

and A1C decreased, and there was no difference in insulin dosage or A1C before or during pregnancy between women with and without severe hypoglycemia.

Severe hypoglycemia was associated with more fluctuating plasma glucose in our study and in the study by Rosenn et al. (7). This might reflect less compliance with the diabetes diet and probably overcompensatory caloric intake during hypoglycemia. We did not record supplementary insulin injections, but overinsulinization due to frequent supplementary insulin injections might play a role for the high incidence of severe hypoglycemia. This is underscored by the fact that at 14% of the severe hypoglycemic events, the women reported excessive insulin dosages, and in 23% of the events insufficient calorie intake and/or a postponed meal were identified as possible causes of severe hypoglycemia. This suggests that clinicians should pay more attention to the diet and the use of supplementary fast-acting insulin during pregnancy.

Prolonged periods with low plasma glucose values increase the risk of severe hypoglycemia in nonpregnant patients with type 1 diabetes (19). In our study, only 3% of the severe hypoglycemic events were preceded by recurrent mild hypoglycemic events. Neither biochemical nor mild hypoglycemia were more frequent among women with severe hypoglycemia. This indicates that other yet unknown factors influence the predisposition to severe hypoglycemia in pregnancy.

Early identification of women at increased risk of severe hypoglycemia in pregnancy is important, since special education and individual modification of glucose monitoring, diet, and insulin treatment might be relevant to prevent severe hypoglycemic events. Those identified as high-risk subjects may benefit from intensified glycemic analysis in terms of continuous glucose monitoring with an alarm to warn the women about hypoglycemic values (20) and subsequent transition to alternative treatment modalities such as insulin pump (21) or treatment with a rapid-acting insulin analog (22).

In summary, 45% of women with type 1 diabetes experienced at least one severe hypoglycemic event during pregnancy. The incidence was highest in early pregnancy, although the metabolic control was tighter in last part of pregnancy. Predictors were previous severe hypoglycemia and impaired hypoglycemia awareness or unawareness.

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