

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 hypoglycemic coma 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]), a 10 years' longer diabetes duration (1.6 [1.0–2.4]), an HbA_{1c} level $\leq 6.5\%$ (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 HbA_{1c} level $\leq 6.5\%$, 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.

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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 HbA_{1c} 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

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Abbreviations: BG, blood glucose; CSII, continuous subcutaneous insulin infusion; DCCT, Diabetes Control and Complications Trial; MIT, multiple injection treatment; OR, odds ratio; SH, severe hypoglycemia; SMBG, self-monitoring of BG.

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

out sets of questionnaires at inclusion (at ~10 weeks gestation), at the end of the first trimester (at ~17 weeks), and during the third trimester (at ~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 injections (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 occur-

rence of hypoglycemic coma during the first trimester of pregnancy via a second questionnaire at ~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 ~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 ≥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 (≥300 mg/24 h or ≥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 ~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 monivariate 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 χ^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 25 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

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

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

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).

as compared with 35% at the end of the first trimester ($P < 0.001$). Hypoglycemia-related anxiety on average remained unchanged between the two assessments.

Monivariate analyses of risk indicators for uncomplicated SH and hypoglycemic coma during the first trimester

The characteristics of the study population are shown in the first column of Table 2.

Demographics. Age, BMI, and parity were not related to uncomplicated SH or hypoglycemic coma during the first trimester.

Diabetes and treatment. The duration of diabetes was on average longer in women with SH (all episodes) than in women without any SH (mean difference [95% CI]: 3 years [1–5], $P < 0.001$). Women with hypoglycemic coma more often had long-term diabetic complications (i.e., retinopathy and nephropathy) compared with women without any SH.

Virtually all women (98%) were treated with intensive insulin treatment already before pregnancy. Very few changes in treatment regimen were observed during early pregnancy (4%). This resulted in almost identical proportions of women on MIT and on CSII at the end of the first trimester (60 and 40%), as compared with the preconception period (64 and 36%). Women with hypoglycemic coma were treated significantly more often with MIT than women without any SH ($P = 0.02$). Insulin lispro was used by 7% of women with SH (all episodes) compared with 15% of women without any SH ($P = 0.06$). The total daily insulin

dose (units/kg) was significantly higher in the hypoglycemic coma group compared with the group without any SH ($P = 0.0001$). The frequency of SMBG was similar for all groups. In women with SH (all episodes), mean HbA_{1c} ($6.5 \pm 0.7\%$) was lower than in women without any SH during the first trimester ($6.8 \pm 0.7\%$, $P = 0.008$).

History of SH and hypoglycemia awareness

Women with reduced awareness of hypoglycemia (Clarke score) at inclusion were markedly more prone to uncomplicated SH or hypoglycemic coma during the first trimester: 22% of the uncomplicated SH group and 40% of the coma group had been assessed as being reduced-aware at inclusion, as compared with 7% of the women without any SH ($P \leq 0.001$ for both comparisons).

A history of SH (with or without episodes of Coma) during the last 4 months before conception was highly related to subsequent uncomplicated SH and hypoglycemic coma: 30% of the women without a history of pregestational SH experienced SH during their first trimester, whereas 69% of the women with pregestational uncomplicated SH and 83% of the women with pregestational coma subsequently experienced SH (either type) during the first trimester; 81% of the women with pregestational hypoglycemic coma again experienced at least one episode of coma during the first trimester (data not shown in Table 2).

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, HbA_{1c} $\leq 6.5\%$, 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 HbA_{1c} $\leq 6.5\%$ (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 HbA_{1c} of $7.8 \pm 1.2\%$ 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, which would be equivalent to an incidence of 890 episodes per 100 patient-years; before 20 weeks of gestation, they observed at least one hypoglycemic episode requiring active assistance in 66% of pregnancies. 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 HbA_{1c} ≤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 counterregulation 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 counterregulatory 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.

	All	No SH	Uncomplicated SH	Hypoglycemic coma	SH (all episodes)
<i>n</i>	278	165	61	52	113
Demographics					
Age (years)	30 ± 4	30 ± 4	30 ± 4	29 ± 4	30 ± 4
BMI (kg/m ²)	24.9 ± 3.8	24.8 ± 3.5	24.7 ± 3.7	25.5 ± 4.5	25.1 ± 4.1
Nullipara	53	52	50	60	55
Diabetes and Treatment					
Diabetes duration (years)	12 ± 8	11 ± 8	15 ± 7*	15 ± 6†	15 ± 7‡
Complicated diabetes	26	21	30	39*	34*
CSH	40	42	48	25*	37
Insulin lispro	12	15	7	8	7
Insulin dose/24 h (units/kg)	0.74 ± 0.29	0.69 ± 0.27	0.73 ± 0.31	0.88 ± 0.30‡	0.80 ± 0.31†
SMBG >4 times per day	73	70	78	79	78
HbA _{1c} first trimester (%)	6.7 ± 0.7	6.8 ± 0.7	6.5 ± 0.8*	6.6 ± 0.6*	6.5 ± 0.7†
HbA _{1c} distribution (%)					
≤6.5	46	39	59*	51	56*
>6.5	54	61	41	49	44
History of SH/Awareness					
History of SH (%)§	25	11	40‡	51‡	45‡
Reduced awareness (at inclusion) (12)	16	7	22†	40‡	30‡
Sequelae of SH (end of 1st trimester)					
Hypoglycemia Worry level	12 ± 9	9 ± 7	14 ± 8‡	19 ± 10‡	16 ± 9‡
Decreased threshold for symptoms (<3.0 mmol/l)	45	37	55*	59*	57†

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, very 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 borderline-significant, statistically, possibly due to the lack of power because only 32 of the women (12%) used insulin lispro. Our study indicates that good glycemic control (HbA_{1c} ≤6.5%) achieved at ~10 weeks gestation is predictive for an increased risk of SH during the first trimester. With respect to type 1 diabetes in general, a relationship between intensive insulin treatment (resulting in lower HbA_{1c} levels) and an increase in SH is well known, among others from the DCCT (18). Remarkably, previous studies of SH during type 1 diabetic pregnancy failed to detect differences in HbA_{1c} levels between patients with high rates and low rates (or absent) SH, despite mean HbA_{1c} levels comparable to those in the present study (16,26). Because the numbers of patients in those studies were much lower (~85 women), the power to detect a relationship between HbA_{1c} and the occurrence of SH may have been too small (26).

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. A history of SH before gestation, a longer duration of diabetes, a daily insulin dose 0.1 unit/kg higher, and an HbA_{1c} level ≤6.5% 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 risk of SH early in pregnancy. 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.

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References

1. Kitzmiller JL, Buchanan TA, Kjos S, Combs CA, Ratner RE: Pre-conception care of diabetes, congenital malformations, and spontaneous abortions (Review). *Diabetes Care* 19:514–541, 1996
2. Rosenn B, Siddiqi TA, Miodovnik M: Normalization of blood glucose in insulin-dependent diabetic pregnancies and the risks of hypoglycemia: a therapeutic dilemma. *Obstet Gynecol Surv* 50:56–61, 1995
3. Steel JM, Johnstone FD, Hepburn DA, Smith AF: Can prepregnancy care of diabetic women reduce the risk of abnormal

- babies? *BMJ* 301:1070–1074, 1990
4. Heller SR: Hypoglycaemia and pregnancy. In *Hypoglycaemia in Clinical Diabetes*. Frier BM, Fisher BM, Eds. Chichester, U.K., John Wiley & Sons, 1999, p. 147–166
5. Rosenn BM, Miodovnik M, Khoury JC, Siddiqi TA: Deficient counterregulation: a possible risk factor for excessive fetal growth in IDDM pregnancies. *Diabetes Care* 20:872–874, 1997
6. Kyne-Grzebalski D, Wood L, Marshall SM, Taylor R: Episodic hyperglycaemia in pregnant women with well-controlled type 1 diabetes mellitus: a major potential factor underlying macrosomia. *Diabet Med* 16:702–706, 1999
7. Buchanan TA, Schemmer JK, Freinkel N: Embryotoxic effects of brief maternal insulin-hypoglycemia during organogenesis in the rat. *J Clin Invest* 78:643–649, 1986
8. Smoak IW, Sadler TW: Embryopathic effects of short-term exposure to hypoglycemia in mouse embryos in vitro. *Am J Obstet Gynecol* 163:619–624, 1990
9. Rosenn BM, and Miodovnik M: Glycemic control in the diabetic pregnancy: is tighter always better? *J Matern Fetal Med* 9:29–34, 2000
10. Tattersall RB: Frequency, causes and treatment of hypoglycaemia. In *Hypoglycaemia in Clinical Diabetes*. Frier BM, Fisher BM, Eds. Chichester, U.K., John Wiley & Sons, 1999, p. 55–87
11. DCCT group: The effect of intensive treatment of diabetes on the development and progression of long-term complications in insulin-dependent diabetes mellitus: the Diabetes Control and Complications Trial Research Group. *N Engl J Med* 329:977–986, 1993
12. Clarke WL, Cox DJ, Gonder-Frederick LA, Julian D, Schlundt D, Polonsky W: Reduced awareness of hypoglycemia in adults with IDDM: a prospective study of hypoglycemic frequency and associated symptoms. *Diabetes Care* 18:517–522, 1995
13. Cox DJ, Irvine A, Gonder-Frederick L, Nowacek G, Butterfield J: Fear of hypoglycemia: quantification, validation, and utilization. *Diabetes Care* 10:617–621, 1987
14. Snoek FJ, Pouwer F, Mollema ED, Heine RJ: De Angst voor Hypoglycemie Vragenlijst (AHV): interne consistentie en validiteit. *Gedrag Gezondheid* 24:287–292, 1996
15. ter Braak EWMT, Appelman AMMF, van de Laak MF, Stolk RP, van Haeflen TW, Erkelens DW: Clinical characteristics of type 1 diabetic patients with and without severe hypoglycemia. *Diabetes Care* 23:1467–1471, 2000
16. Rosenn BM, Miodovnik M, Holberg G,

- Khoury JC, Siddiqi TA: Hypoglycemia: the price of intensive insulin therapy for pregnant women with insulin-dependent diabetes mellitus. *Obstet Gynecol* 85:417–422, 1995
17. Heller S, Chapman J, McCloud J, Ward J: Unreliability of reports of hypoglycaemia by diabetic patients [see comments]. *BMJ* 310:440, 1995
 18. DCCT group: Epidemiology of severe hypoglycemia in the diabetes control and complications trial: the DCCT Research Group [see comments]. *Am J Med* 90:450–459, 1991
 19. Cryer P: Hypoglycemia is the limiting factor in the management of diabetes. *Diabet Metab Res Rev* 15:42–46, 1999
 20. Amiel SA, Sherwin RS, Simonson DC, Tamborlane WV: Effect of intensive insulin therapy on glycemic thresholds for counterregulatory hormone release. *Diabetes* 37:901–907, 1988
 21. Clarke WL, Gonder-Frederick LA, Richards FE, Cryer PE: Multifactorial origin of hypoglycemic symptom unawareness in IDDM: association with defective glucose counterregulation and better glycemic control. *Diabetes* 37:680–685, 1991
 22. Sacks DA, Chen W, Greenspoon JS, Wolde-Tsadik G: Should the same glucose values be targeted for type 1 as for type 2 diabetics in pregnancy? *Am J Obstet Gynecol* 177:1113–1119, 1997
 23. Nachum Z, Ben Shlomo I, Weiner E, Shalev E: Twice daily versus four times daily insulin dose regimens for diabetes in pregnancy: randomised controlled trial. *BMJ* 319:1223–1227, 1999
 24. DCCT group: Pregnancy outcomes in the Diabetes Control and Complications Trial: the DCCT Research Group. *Am J Obstet Gynecol* 174:1343–1353, 1996
 25. Holleman F, Schmitt H, Rottiers R, Rees A, Symanowski S, Anderson JH: Reduced frequency of severe hypoglycemia and coma in well-controlled IDDM patients treated with insulin lispro: the Benelux-UK Insulin Lispro Study Group. *Diabetes Care* 20:1827–1832, 1997
 26. Kimmerle R, Heinemann L, Delecki A, Berger M: Severe hypoglycemia incidence and predisposing factors in 85 pregnancies of type I diabetic women. *Diabetes Care* 15:1034–1037, 1992
 27. Rosenn BM, Miodovnik M, Khoury JC, Siddiqi TA: Counterregulatory hormonal responses to hypoglycemia during pregnancy. *Obstet Gynecol* 87:568–574, 1996
 28. Bjorklund A, Adamson U, Andreasson K, Carlstrom K, Hennen G, Igout A, Lins PE, Westgren M: Hormonal counterregulation and subjective symptoms during induced hypoglycemia in insulin-dependent diabetes mellitus patients during and after pregnancy. *Acta Obstet Gynecol Scand* 77:625–634, 1998
 29. Cox DJ, Gonder-Frederick LA, Kovatchev BP, Young-Hyman DL, Donner TW, Julian DM, Clarke WL: Biopsychobehavioral model of severe hypoglycemia. II. Understanding the risk of severe hypoglycemia. *Diabetes Care* 22:2018–2025, 1999