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ORIGINAL ARTICLE

Poor pregnancy outcome in women with type 1 diabetes is predicted by elevated HbA_{1c} and spikes of high glucose values in the third trimester

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Abstract

Objective: To analyse data from a randomised, controlled study of prandial insulin aspart versus human insulin, both with NPH insulin, in pregnant women with type 1 diabetes for potential factors predicting poor pregnancy outcomes.

Research design/method: *Post hoc* analysis including 91 subjects randomised prior to pregnancy with known outcome in early pregnancy and 259 subjects randomised prior to pregnancy/during pregnancy of <10 weeks' gestation with known late-pregnancy outcomes. Poor early-pregnancy outcomes included fetal loss <22 gestational weeks and/or congenital malformation ($n = 18$). Poor late-pregnancy outcomes included: composite endpoint including pre-eclampsia, preterm delivery and perinatal death ($n = 78$); preterm delivery ($n = 63$); and excessive fetal growth ($n = 88$).

Results: 18 patients experienced a malformed/lost fetus in early pregnancy – none preceded by severe hypoglycaemia. Albuminuria in early pregnancy was a significant predictor of poor late-pregnancy outcome (composite endpoint; $p = 0.012$). In the third trimester, elevated HbA_{1c}, ≥ 1 plasma glucose (PG) measurement >11 mmol/L (198 mg/dL) and %PG values outside 3.9–7.0 mmol/L (70–126 mg/dL) were significant predictors of poor late-pregnancy outcomes (all $p < 0.05$).

Conclusions: Elevated HbA_{1c}, high glucose spikes and out-of-range %PG in the third trimester, and albuminuria in early pregnancy, are associated with poor late-pregnancy outcomes.

Keywords

HbA_{1c}, glucose spikes, predictors, pregnancy outcome

History

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Introduction

It has long been recognised that pregnant women with type 1 diabetes experience higher rates of poor maternal, fetal and perinatal outcomes compared with normal pregnancies; indeed, large prospective studies have reported rates of congenital malformation and mortality around three-times higher than those observed in nondiabetic pregnancy [1,2]. Poor outcomes in type 1 diabetes pregnancy, such as preterm delivery or large for gestational age (LGA) babies, have been shown to be associated with hyperglycaemia and elevated HbA_{1c} [3–5]. In addition, the risk of developing pre-eclampsia is significantly higher in pregnant women with type 1 diabetes who had poor glycaemic control than in those with optimal HbA_{1c} control [6]. Even in pregnant women without diabetes, maternal glucose levels have been shown to be continuously associated with increased birth weight and other perinatal complications [7].

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Consequently, the aim of treatment in pregnant women with type 1 diabetes is to achieve strict glycaemic control, preferably from before conception, and to maintain low HbA_{1c} levels throughout pregnancy [8]. However, there are conflicting data concerning the trimester in which it is most important to intensify glycaemic control [5,9–12]. One study found that glycaemic control at conception and in the first trimester were the most important for reducing macrosomia [10], while a more recent study demonstrated that only increased second-trimester glucose levels were associated with LGA babies [5]. Two other studies reported that neonatal morbidity was most closely associated with glycaemic control in the second and third trimesters [9,11]. It has also been shown in animal models that severe hypoglycaemia can result in malformation [13], although human data in this area are sparse.

Prospective studies investigating insulin treatment in pregnant women with type 1 diabetes are limited. In this *post hoc* analysis, potential factors affecting poor outcomes in early and late pregnancy were examined. The data were generated from a randomised, controlled study in pregnant women with type 1 diabetes ($n = 322$) investigating the safety

and efficacy of a rapid-acting insulin analogue (prandial insulin aspart) versus prandial human insulin, both in combination with insulin NPH [14,15]. The trial included both women who were planning pregnancy and those who were pregnant.

Research design and methods

The trial included 322 women with type 1 diabetes who were planning pregnancy or were already pregnant, and has been described previously [14,15]. Metabolic control was measured at a randomisation/first-pregnancy assessment; at clinic visits at the end of the first, second and third trimesters (at approximately 12, 24 and 36 gestational weeks [GWs], respectively); and at delivery and follow-up 6 weeks postpartum [14,15]. Laboratory analyses (HbA_{1c}, haematology, biochemistry, and urinalysis) were performed by MDS Pharma Services Central Lab (Hamburg, Germany). HbA_{1c} was analysed using a National Glycohemoglobin Standardization program – certified method (Diabetes Control and Complications Trial standard) [14,15].

Poor outcomes in early and late pregnancy were categorised by their randomisation status. The analysis for congenital malformations (minor or major) and fetal loss in early pregnancy was confined to subjects who were randomised before pregnancy and with known outcome ($n = 91$). Those pregnant at randomisation were excluded from this analysis, as these subjects were not observed until GW 10, and thus fetal losses up to GW 10 may not have been recorded. The poor outcome in early pregnancy data set was, therefore, defined as all pregnant subjects randomised prior to pregnancy with either fetal loss before 22 completed GWs ($n = 17$) or known outcome after GW 22 ($n = 74$; Online Supplemental Figure 1). The composite endpoint for poor outcome in early pregnancy included fetal loss before GW 22 and/or congenital malformations.

The poor outcome in the late pregnancy analysis data set comprised subjects randomised both before pregnancy and in early pregnancy, and included 259 subjects with a successful pregnancy beyond GW 22 while excluding subjects with unknown outcome, fetal loss before GW 22 weeks and/or congenital malformations ($n = 63$; Online Supplemental Figure 1).

Three endpoints were examined for poor outcome in late pregnancy: 1) a composite endpoint including pre-eclampsia, preterm delivery (<37 weeks) and perinatal death ($n = 78$); 2) preterm delivery ($n = 63$); and 3) excessive fetal growth (LGA/macrosomia; $n = 88$). LGA was defined as birth weight >90th percentile according to local growth charts and macrosomia as birth weight >4000 g.

Factors investigated as predictors of poor outcome in early pregnancy included: $HbA_{1c} > 6\%$ (yes, no; measured at the first trimester visit); plasma glucose (PG) > 11 mmol/L (198 mg/dL; yes, no; measured from an 8-point PG profile performed within 1 week prior to the first-trimester visit); albuminuria at baseline (yes, no); retinopathy at baseline (yes, no); and major hypoglycaemia preceding the outcome. Major hypoglycaemia was defined as an episode where the subject was unable to treat herself and which had at least one of the following characteristics: PG < 3.1 mmol/L (56 mg/dL) and/or reversal of symptoms after either food intake or glucagon/intravenous (i.v.) glucose administration.

Possible predictors of poor outcome in late pregnancy included: HbA_{1c} at third-trimester visit (continuous variable); PG > 11 mmol/L (198 mg/dL; yes, no); and percentage of PG values outside the reference range (i.e. values below 3.9 mmol/L [72 mg/dL] or above 7.0 mmol/L [126 mg/dL]; all PG values were from an 8-point PG profile performed within 1 week prior to the third-trimester visit); insulin analogue as previous therapy (yes, no); including either analogues prescribed prior to trial or randomised insulin aspart; blood pressure; albuminuria (yes, no); and retinopathy (yes, no) at baseline for subjects pregnant at randomisation and at start of pregnancy visit for subjects not pregnant at randomisation. Albuminuria was defined as one or more measurements of albumin in a spot urine sample >30 mg/L. Retinopathy was defined as clinically significant abnormal funduscopy as determined by country-specific practice.

For predictors of poor outcome in early pregnancy, odds ratios and 95% confidence intervals were calculated using the continuity correction with corresponding Chi-square tests. Multivariate analysis was not performed due to the limited number of cases.

Predictors of poor outcome in late pregnancy were analysed using multiple logistic regression. The model included adjustment for BMI (kg/m^2), age (years), smoker (yes, no), duration of diabetes and parity (0 or ≥1 pregnancies) as basis [16,17]. In this model, possible individual predictors were entered one at a time. Hereafter, all predictor variables with $p < 0.10$ in each of the previous models, in addition to predictors in base model, were included in a multivariate logistic regression model. Of the plasma glucose variables, only PG > 11 mmol/L (>198 mg/dL) was included in the multivariate model, as both this variable and the percentage of PG readings outside the reference range (3.9–7.0 mmol/L [72–126 mg/dL]) were assumed to be highly correlated. Statistical significance for predictors in the full model was determined based on a 5% significance level.

Results

Eighteen women had a malformed fetus ($n = 1$), fetal loss ($n = 15$) or both ($n = 2$). No significant predictors were found for this poor outcome in early pregnancy (Online Supplemental Table 1). For the pregnancies resulting in congenital malformation or early fetal loss, there was no documentation of major hypoglycaemia in the first trimester.

The composite endpoint of poor outcome in late pregnancy included preterm delivery ($n = 53$), pre-eclampsia ($n = 12$), both preterm delivery and pre-eclampsia ($n = 10$), stillbirth ($n = 2$) and death within 1 week postnatally ($n = 1$).

In the initial analysis of the composite endpoint, HbA_{1c}, at least one PG measurement >11 mmol/L (>198 mg/dL), %PG values outside of the reference range in the third trimester, and presence of albuminuria at baseline were significant predictors of poor outcome in late pregnancy (Table 1). When all significant predictors from the first analysis were entered simultaneously into the full model, only albuminuria at baseline remained statistically significant. Patients who had a poor outcome as defined by the composite endpoint in late

Table 1. Predictors of poor outcome in late pregnancy given a successful outcome in early pregnancy.

Predictor	Successful outcome ($n = 181$)	Poor outcome ($n = 78$)	Odds ratio (CI), model 1	p Value, model 1	p Value, model 2
Base model					
BMI (mean, SD), kg/m^2	24.7 (3.9)	24.7 (3.5)	0.99 (0.92,1.07)	0.765	0.707
Age (mean, SD), years	28.9 (4.7)	29.1 (4.8)	1.01 (0.95,1.08)	0.791	0.842
Smoker, yes	13 (7%)	8 (10%)	1.66 (0.64,4.30)	0.297	0.724
Duration of diabetes (mean, SD), years	11.8 (6.9)	12.5 (8.5)	1.01 (0.97,1.06)	0.525	0.830
Parity					
0	84 (46%)	42 (54%)	0.72 (0.41,1.24)	0.236	0.252
1 or more	97 (54%)	36 (46%)			
Predictors					
Systolic BP (mean, SD), mmHg	114.0 (10.0)	114.0 (12.0)	1.00 (0.98,1.03)	0.720	NA
Diastolic BP (mean, SD), mmHg	70.2 (8.7)	69.8 (8.4)	1.00 (0.97,1.03)	0.884	NA
Insulin analogue treatment, yes	97 (54%)	35 (45%)	0.69 (0.40,1.19)	0.184	NA
Presence of albuminuria, yes	6 (3%)	9 (12%)	4.11 (1.36,12.43)	0.012	0.007
Presence of retinopathy, yes	18 (10%)	8 (10%)	0.99 (0.40,2.47)	0.990	NA
PG > 11 mmol/L [>198 mg/dL], yes	34 (19%)	26 (34%)	2.12 (1.14,3.92)	0.017	0.092
PG outside range (mean, SD), %	44.5 (23)	51.6 (23)	1.01 (1.00,1.02)	0.045	NA
HbA_{1c} (mean, SD), %	6.0 (0.6)	6.2 (0.7)	1.68 (1.08,2.61)	0.022	0.058

Statistics are mean (standard deviation [SD]) for continuous predictors and frequency (percentage) for categorical predictors. All values apart from plasma glucose (PG) > 11 mmol/L (>198 mg/dL), %PG in range and HbA_{1c} (%) are taken from baseline or screening for subjects pregnant at randomisation and from start of pregnancy visit for subjects not pregnant at randomisation.

%PG outside of range indicates those PG values falling below 3.9 mmol/L (70 mg/dL) or above 7.0 mmol/L (126 mg/dL). PG and HbA_{1c} values were taken from the third-trimester study visit. If the third-trimester study visit value was missing, the second-trimester study visit value was used.

p Value model 1: logistic regression adjusting for BMI, age, smoking, duration of diabetes and parity.

p Value model 2: model 1 + predictors with a p value from model 1 < 10%.

BP, blood pressure; CI, confidence interval; NA, not included in model.

Table 2. Predictors of preterm delivery in late pregnancy.

Predictor	Delivery at term ($n = 194$)	Preterm delivery ($n = 63$)	Odds ratio (CI) model 1	p Value model 1	p Value model 2
Base model					
BMI (mean, SD), kg/m^2	24.7 (3.8)	24.7 (3.7)	0.99 (0.91,1.07)	0.748	0.774
Age (mean, SD), years	28.8 (4.6)	29.3 (4.9)	1.02 (0.95,1.09)	0.620	0.670
Smoker, yes	13 (7%)	8 (13%)	2.35 (0.89,6.18)	0.083	0.328
Duration of diabetes (mean, SD), years	11.7 (6.9)	12.8 (8.8)	1.02 (0.98,1.07)	0.377	0.646
Parity					
0	90 (46%)	34 (54%)	0.69 (0.38,1.24)	0.215	0.284
1 or more	104 (54%)	29 (46%)			
Predictors					
Systolic BP (mean, SD), mmHg	114.0 (10.0)	113.0 (12.0)	0.99 (0.96,1.02)	0.574	NA
Diastolic BP (mean, SD), mmHg	70.3 (8.6)	69.2 (8.5)	0.99 (0.95,1.02)	0.529	NA
Insulin analogue, yes	103 (53%)	28 (44%)	0.70 (0.39,1.25)	0.224	NA
Presence of albuminuria, yes	8 (4%)	7 (11%)	2.98 (0.99,8.94)	0.051	0.036
Presence of retinopathy, yes	19 (10%)	7 (11%)	1.08 (0.42,2.82)	0.868	NA
PG > 11 mmol/L [>198 mg/dL], yes	38 (20%)	21 (34%)	2.00 (1.04,3.84)	0.038	0.204
%PG outside range (mean, SD)	44.4 (23)	53.4 (23)	1.02 (1.00,1.03)	0.024	NA
HbA_{1c} (mean, SD), %	6.0 (0.6)	6.3 (0.7)	1.75 (1.08,2.82)	0.023	0.045

Statistics are mean (standard deviation [SD]) for continuous predictors and frequency (percentage) for categorical predictors. All values apart from plasma glucose (PG) > 11 mmol/L (>198 mg/dL), %PG in range and HbA_{1c} (%) are taken from baseline or screening for subjects pregnant at randomisation and from start of pregnancy visit for subjects not pregnant at randomisation.

%PG outside of range indicates those PG values falling below 3.9 mmol/L (70 mg/dL) or above 7.0 mmol/L (126 mg/dL). HbA_{1c} values were taken from the third trimester study visit. If the third-trimester study visit value was missing, the second-trimester study visit value was used.

p Value model 1: logistic regression adjusting for BMI, age, smoking, duration of diabetes and parity.

p Value model 2: model 1 + predictors with a p value from model 1 < 10%.

CI, confidence interval; NA, not included in model.

pregnancy had a higher mean HbA_{1c} during pregnancy (based on a total of three measurements taken at the end of each trimester) compared with those who did not have a poor outcome (not analysed statistically; Online Supplemental Figure 2A).

%PG values outside of the reference range, at least one measurement of PG > 11 mmol/L (>198 mg/dL) and HbA_{1c} in the third trimester, and albuminuria at baseline were also significant predictors of preterm delivery in the initial analyses (Table 2).

The odds ratio of 2.00 for at least one measurement of PG > 11 mmol/L (>198 mg/dL) indicates that these patients are twice as likely to experience preterm delivery compared to patients with all PG measurements <11 mmol/L (<198 mg/dL). Likewise, a 1%-point increase in HbA_{1c} almost doubled the odds of preterm delivery (OR 1.75).

Table 3. Predictors of LGA/macrosomia in late pregnancy.

Predictor	No ($n = 169$)	Yes ($n = 88$)	Odds ratio (CI) model 1	p Value model 1	p Value model 2
Base model					
BMI (mean, SD), kg/m^2	24.8 (3.7)	24.5 (3.8)	0.98 (0.91,1.05)	0.587	0.615
Age (mean, SD), years	28.9 (4.7)	28.9 (4.6)	0.99 (0.93,1.05)	0.687	0.496
Smoker, yes	16 (9%)	5 (6%)	0.55 (0.19,1.60)	0.274	0.392
Duration of diabetes (mean, SD), years	12.1 (7.1)	11.8 (8.1)	1.00 (0.96,1.04)	0.993	0.756
Parity					
0	87 (51%)	37 (42%)	1.55 (0.90,2.65)	0.113	0.099
1 or more	82 (49%)	51 (58%)			
Predictors					
Systolic BP (mean, SD), mmHg	114.0 (10.0)	113.0 (12.0)	0.99 (0.97,1.02)	0.530	NA
Diastolic BP (mean, SD), mmHg	70.4 (8.7)	69.3 (8.2)	0.98 (0.95,1.01)	0.282	NA
Insulin analogue, yes	91 (54%)	40 (45%)	0.72 (0.42,1.21)	0.216	NA
Presence of albuminuria, yes	12 (7%)	3 (3%)	0.48 (0.13,1.80)	0.278	NA
Presence of retinopathy, yes	19 (11%)	7 (8%)	0.63 (0.25,1.62)	0.341	NA
PG > 11 mmol/L [>198 mg/dL], yes	29 (17%)	30 (35%)	2.72 (1.47,5.06)	0.002	0.027
%PG outside range (mean, SD)	43.9 (23)	51.9 (23)	1.02 (1.01,1.03)	0.004	NA
HbA_{1c} (mean, SD), %	6.0 (0.6)	6.3 (0.6)	2.73 (1.72,4.33)	0.000	0.001

Statistics are mean (standard deviation [SD]) for continuous predictors and frequency (percentage) for categorical predictors. All values apart from plasma glucose (PG) > 11 mmol/L (>198 mg/dL), %PG in range and HbA_{1c} (%) are taken from baseline or screening for subjects pregnant at randomisation and from start of pregnancy visit for subjects not pregnant at randomisation.

%PG outside of range indicates those plasma glucose values falling below 3.9 mmol/L (70 mg/dL) or above 7.0 mmol/L (126 mg/dL). PG and HbA_{1c} values were taken from the third-trimester study visit. If the third-trimester study visit value was missing, the second-trimester study visit value was used.

p Value model 1: logistic regression adjusting for BMI, age, smoking, duration of diabetes and parity.

p Value model 2: model 1 + predictors with a p value from model 1 < 10%.

CI, confidence interval; NA, not included in model.

When all significant predictors from the first models were analysed together, only HbA_{1c} in the third trimester and albuminuria at baseline remained statistically significant.

At least one measurement of PG > 11 mmol/L (>198 mg/dL), %PG values outside of range and HbA_{1c} were also all significantly associated with LGA/macrosomia (Table 3), and both HbA_{1c} and at least one measurement of PG > 11 mmol/L (>198 mg/dL) remained significant predictors when analysed in the full model. Again, patients experiencing preterm delivery or LGA/macrosomia appeared to have a higher mean HbA_{1c} over time compared with patients who delivered at term or had normal-weight babies (not analysed statistically; Online Supplemental Figure 2B and C). The percentage of patients experiencing LGA/macrosomia increased with increasing third-trimester HbA_{1c} when expressed categorically: HbA_{1c} < 5.5%, 19% of patients experiencing LGA/macrosomia; HbA_{1c} 5.5–5.9%, 26%; HbA_{1c} 6–6.4%, 35%; HbA_{1c} >6.4%, 52%. Other potential predictors (previous use of insulin analogues, blood pressure, retinopathy in early pregnancy) did not predict any of the three outcomes ($p > 0.10$).

Discussion

These results suggest that both elevated HbA_{1c} and spikes of high glucose levels have a negative impact on pregnancy outcomes in women with type 1 diabetes, especially on excess growth of the fetus. This emphasises the importance of keeping HbA_{1c} within the normal range throughout pregnancy, and not only during a particular trimester. Our findings therefore support the recommendation to also strive for optimal glycaemic control in late pregnancy in women with type 1 diabetes.

The literature on early fetal loss in type 1 diabetic pregnancy is very limited despite considerable interest, especially from patients. None of the cases of malformation or fetal death in early pregnancy were preceded by an episode of severe hypoglycaemia. The 12 patients who experienced a major hypoglycaemic episode in the first trimester all had a successful outcome in early pregnancy; therefore, a link between major hypoglycaemia and poor pregnancy outcome is not supported by this study.

Poor outcomes in late pregnancy were most strongly predicted by albuminuria and by measures of glucose control. It is well recognised that the prevalence of adverse pregnancy outcome is higher among women with albuminuria, mainly due to pre-eclampsia [18]. In terms of glucose measures, HbA_{1c} and PG, in particular any PG measurement >11 mmol/L (>198 mg/dL), were significant predictors of poor outcome in late pregnancy. This suggests that, not only should HbA_{1c} be maintained at a low level throughout pregnancy, but also day-to-day glucose profiles should be kept stable, and high peaks of glucose should be avoided. Elevated HbA_{1c} and PG are associated with a poor outcome in late pregnancy. In this respect, these data support the already well-recognised association of hyperglycaemia with increased maternal, fetal and perinatal morbidity. Our data indicate, however, that patients with successful outcomes for the composite endpoint, preterm delivery and LGA/macrosomia have lower HbA_{1c} levels than patients with poor outcomes, and this is evident throughout pregnancy.

There is potential for multicollinearity when considering a large number of predictors. HbA_{1c} is closely associated with mean and high PG and, therefore, it is not remarkable when considering poor late-pregnancy outcome or preterm delivery that PG is no longer significant in the full model, where both

variables are entered simultaneously. However, the full analysis establishes that HbA_{1c} on its own explains part of the variance in the prediction of preterm delivery and LGA/macrosomia.

To our knowledge, this is one of the first studies seeking to establish the effects of spikes of high glucose values on pregnancy outcome [19]. Pregnant women and their diabetes caregivers may fear such glucose excursions; however, the occurrence of glucose spikes is not easily detected as these may not always be reflected in patients' HbA_{1c} values. Additionally, data from two randomised trials have suggested that effectively managing postprandial glucose levels is more likely to be associated with a successful pregnancy outcome than controlling fasting glucose levels [20,21], highlighting the importance of recognising and treating high glucose spikes. In the present study, spikes of high glucose values (PG > 11 mmol/L [>198 mg/dL]) were a stronger predictor for LGA/macrosomia than for preterm delivery. This is supported by the fact that LGA/macrosomia is directly influenced by glucose levels, whereas preterm delivery is also influenced by many other factors.

Examination of LGA/macrosomia by category of HbA_{1c} indicates that high HbA_{1c} levels are associated with a poor outcome, and the estimated odds ratios demonstrate that, for any increase in HbA_{1c} or PG, the risk of experiencing preterm delivery or LGA/macrosomia increases. On the contrary, $HbA_{1c} < 5.5\%$ is associated with a relatively low incidence of LGA/macrosomia. These findings are in line with a recent study [22], which demonstrated that increased third-trimester HbA_{1c} predicted higher birth weight. Macrosomia is associated with an increased rate of Caesarean section, shoulder dystocia, neonatal hypoglycemia and longer hospitalisation [23]. In addition to this, children born to mothers with type 1 diabetes may have an increased risk of being overweight and of developing metabolic syndrome and/or type 2 diabetes in early adulthood [24,25].

Therefore, the results from this *post hoc* analysis confirm that glucose levels and HbA_{1c} should be carefully controlled throughout the entire pregnancy to ensure a successful outcome in patients with type 1 diabetes.

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Declaration of interest

E. R. M. is a member of an international scientific advisory board and has received fees for giving talks for Novo Nordisk. J. R. and H. M. are employees of Novo Nordisk and own stock in the company. D. R. M. is a member of an international scientific advisory board, contributed to advisory committees, and has received honoraria from Novo Nordisk in the past for giving lectures. P. D. is a member of an international scientific advisory board for Novo Nordisk. M. H. and R. K. have no conflicts of interest to declare.

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