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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, 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: pre-eclampsia, preterm delivery, and infant mortality. Poor late-pregnancy outcomes included: pre-eclampsia, preterm delivery and perinatal death.

Results: In the third trimester, elevated HbA$_{1c}$ and glucose spikes were significant predictors 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.

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 non-diabetic 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]. 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 (HbA1c, haematology, biochemistry, and urinalysis) were performed by MDS Pharma Services Central Lab (Hamburg, Germany). HbA1c 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/macroamia; 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: HbA1c >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: HbA1c 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/m²), 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, HbA1c, 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
pregnancy had a higher mean HbA1c 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 HbA1c 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 HbA1c almost doubled the odds of preterm delivery (OR 1.75).
These results suggest that both elevated HbA1c 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 HbA1c 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, HbA1c 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 HbA1c 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 HbA1c 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 HbA1c levels than patients with poor outcomes, and this is evident throughout pregnancy.

When all significant predictors from the first models were analysed together, only HbA1c 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 HbA1c were also all significantly associated with LGA/macrosomia (Table 3), and both HbA1c 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 HbA1c 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 HbA1c when expressed categorically: HbA1c <5.5%, 19% of patients experiencing LGA/macrosomia; HbA1c 5.5–5.9%, 26%; HbA1c 6–6.4%, 35%; HbA1c >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 HbA1c 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 HbA1c 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.
variables are entered simultaneously. However, the full analysis establishes that HbA1c 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’ HbA1c 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 HbA1c indicates that high HbA1c levels are associated with a poor outcome, and the estimated odds ratios demonstrate that, for any increase in HbA1c or PG, the risk of experiencing preterm delivery or LGA/macrosomia increases. On the contrary, HbA1c < 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 HbA1c predicted higher birth weight. Macrosomia is associated with an increased rate of Caesarean section, shoulder dystocia, neonatal hypoglycaemia 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 HbA1c 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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