Progression of Retinopathy During Pregnancy in Type 1 Diabetic Women Treated With Insulin Lispro

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OBJECTIVE — To evaluate the progression of retinopathy during pregnancy and postpartum in (insulin-dependent) women with type 1 diabetes treated with insulin lispro or with regular human insulin.

RESEARCH DESIGN AND METHODS — A prospective open study of 69 pregnant women with diabetes was performed. A total of 36 of the women were treated with insulin lispro (lispro group) and 33 were treated with conventional short-acting human insulin (regular insulin group). The retinopathy level was estimated by color fundus photography every trimester and postpartum. Glycemic control during pregnancy, hypoglycemia (blood glucose level <3 mmol/l) in 24-h glucose profile, blood pressure, and proteinuria were registered.

RESULTS — HbA_{1c} values were similar at baseline in the first trimester but thereafter were lower in the lispro group than in the regular insulin group throughout pregnancy ($P = 0.022$, repeated-measures ANOVA). The number of hypoglycemic episodes did not differ between the treatment groups. In multivariable logistic regression analysis with retinopathy severity (Diabetes Control and Complications Trial level) in the third trimester as the dependent variable, only nulliparity qualified as a predictor in the model [Exp(B) = 4.0, 95% CI 1.1–13.7, $P = 0.030$]. Factors such as duration of diabetes, type of insulin used, mean HbA_{1c} level throughout pregnancy, blood pressure (systolic or diastolic), preeclampsia in the current pregnancy, smoking, or prepregnancy planning did not explain the retinopathy progression.

CONCLUSIONS — Insulin lispro improves glycemic control during diabetic pregnancy compared with regular insulin with no adverse impact on progression of diabetic retinopathy.

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Pregnancy is a risk factor for development and progression of retinopathy in women with diabetes (1,2). The prevalence of retinopathy in diabetic pregnancies is 10–27% (3). The duration of diabetes before onset of pregnancy is the prime risk factor for the presence, severity, and progression of retinopathy during pregnancy (4). Progression of retinopathy is also associated with early onset of diabetes, high retinopathy level and suboptimal glycemic control before pregnancy, and rapid normalization of hyperglycemic blood glucose levels during pregnancy, hypertension, proteinuria, and nulliparity (5–10).

Insulin lispro is a new rapidly absorbed insulin analog that has an inversion of the amino acids proline and lysine at positions 28 and 29 on the β-chain of the human insulin molecule (11). Insulin lispro has a faster occurring, higher, and shorter-lasting peak of serum levels than regular human insulin, and it mimics the physiologic secretion of insulin more closely than regular human insulin (12).

The safety of insulin lispro in nonpregnant subjects with diabetes has been demonstrated in a multicenter trial that did not show increased frequency of retinopathy in association with insulin lispro therapy (13). Only few studies have elucidated the safety of this insulin analog in human pregnancy. In one report, rapid acceleration of proliferative retinopathy was seen during pregnancy in 3 of 10 women with diabetes treated with insulin lispro (14). In other reports, insulin lispro was not associated with progression of diabetic retinopathy during pregnancy (15–17). Therefore, it remains unclear whether the type of insulin used affects the progression of retinopathy during pregnancy in women with chronic hyperglycemia. Therefore, we performed a prospective open study to evaluate the progression of retinopathy during pregnancy and postpartum in women with type 1 diabetes treated with insulin lispro or with regular human insulin.

RESEARCH DESIGN AND METHODS

— The local institutional review board accepted the study protocol according to the Declaration of Helsinki. Written informed consent was obtained from each participant.

Pregnant women with diabetes

From November 1998 to January 2002, 72 pregnant women with type 1 diabetes were followed at the Department of Obstetrics and Gynecology and at the Department of Ophthalmology, Helsinki University Central Hospital, in connection with a prospective study on retinal changes in diabetic pregnancy. A total of 37 women were treated with insulin lispro (Humalog) and 35 women were treated with regular human insulin (Actrapid), starting before pregnancy. Additionally, long-acting insulin (Protaphan)

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None of the authors has any proprietary interest in the medications used in the study.

Abbreviations: DCCT, Diabetes Control and Complications Trial; ETDRS, Early Treatment Diabetic Retinopathy Study; RP level, retinopathy level.

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

was used two to three times per day in both groups. The minimum duration of prepregnancy use of either short-acting insulin type was 6 months. One patient was excluded because of spontaneous abortion in early pregnancy (lispro group). Two patients were excluded from the regular insulin group. One patient elected to undergo an induced abortion, because of concerns about an increased risk for a congenital malformation associated with her high HbA_{1c} level (12–13%) in the first trimester, and the other had coexisting retinitis pigmentosa, which was a specific criterion for exclusion. Therefore, the final analyses were performed in 36 women treated with insulin lispro and 33 women treated with regular insulin. Furthermore, 8 (22.2%) women with type 1 diabetes belonged to White's class B (18), 1 (2.8%) belonged to class C, 22 (61.1%) belonged to class D, and 5 (13.9%) belonged to class R in the insulin lispro group. The corresponding numbers of women in the regular insulin group were 6 (18.2%), 11 (33.3%), 14 (42.4%), and 2 (6.1%), respectively.

Obstetric follow-up and management during pregnancy

The women with diabetes were enrolled in the study as soon as pregnancy was diagnosed, usually between 5 and 10 weeks' gestation. They were seen every 2–4 weeks for clinical evaluation and assay of HbA_{1c}. A 24-h glucose profile was usually performed between 8 and 12 and between 24 and 26 weeks' gestation and additionally when needed. Preprandial measurements were performed at midnight, 4:00 A.M., 8:00 A.M. (twice), and 4:00 P.M. and postprandial measurements at noon and 8:00 P.M. The aim was to achieve normoglycemia in all women. Fasting blood glucose level ≤5 mmol/l and 1-h postprandial level ≤7.5 mmol/l were recommended for all subjects. All hypoglycemic episodes (blood glucose level ≤3.0 mmol/l) were calculated from the measured 24-h glucose profiles, and out-of-hospital subjective hypoglycemic events were counted if home measurement showed blood glucose levels ≤3.0 mmol/l. Insulin was administered in three to five daily injections subcutaneously in both treatment groups. None of the women used a continuous-infusion subcutaneous insulin pump. No changes in the type of insulin used were made during pregnancy.

HbA_{1c} measurement

Levels of HbA_{1c} were assessed by ion-exchange high-performance liquid chromatography (Diamat; Bio-Rad Laboratories, Hercules, CA). The mean HbA_{1c} value by this method is 4.93% (SD 0.32) for healthy Finnish adults. Values <5.6% (+2 SD) were considered normal. Four values of HbA_{1c} were selected for this study: the mean values of all HbA_{1c} measurements taken during the first, second, and third trimesters and the mean value of all HbA_{1c} measurements taken throughout pregnancy.

Measurement of blood pressure and proteinuria

Blood pressure was measured after a 15-min rest with the subject in a sitting position. The measurements were performed as part of the routine obstetric follow-up by midwives and nurses with long clinical experience. Preeclampsia was defined as blood pressure ≥140/90 mmHg with proteinuria according to a dipstick test or ≥0.3 g/24 h after 20 weeks' gestation (19). Pregnancy-induced hypertension was defined as blood pressure ≥140/90 mmHg without proteinuria (19). Chronic hypertension was defined as hypertension diagnosed before pregnancy or before 20 weeks' gestation (19).

Ophthalmological examination

Ophthalmological examination was performed by one of the authors (S.L.) between 12 and 14, 24 and 26, and 34 and 36 weeks' gestation and at 3 and 6 months postpartum. The ophthalmological examination included testing of corrected visual acuity using a Snellen chart, slit-lamp biomicroscopy of the anterior segment, dilated indirect ophthalmoscopy with a 90-dioptre lens, and fundus photography. Intraocular pressure was normal in all women.

The presence and severity of diabetic retinopathy was assessed using two 50° color slides centered at the macula and the disk, respectively. Fundus photography was performed through dilated pupils (via use of tropicamide, 5 mg/ml) by a trained operator using a Topcon TRC 50IA retinal camera (Topcon, Tokyo, Japan) and Kodak Elitechrome 100 film (Eastman Kodak, Rochester, NY). The photographs were taken once in each trimester and compared with the patient's status before pregnancy if previous photographs were available. Ocular history, including laser photocoagulation treatment, was checked from the hospital records.

The photographs were evaluated by a retinal specialist (I.I.), who was masked to all clinical information. Retinopathy was graded using a modification of the Early Treatment Diabetic Retinopathy Study (ETDRS) grading system with ETDRS standard pictures (20). Differences in magnification and size of field were taken into account. For each eye, the maximum grade of diabetic retinopathy lesions was determined to produce an overall severity level for an eye (retinopathy level [RP level]). Retinal findings were classified into the following groups according to the ETDRS retinopathy scale: *1*) no retinopathy (RP level 10); *2*) very mild retinopathy (RP level 20); *3*) mild retinopathy (RP level 35); *4*) moderate retinopathy (RP level 43); *5*) moderate retinopathy, more extensive intraretinal microvascular abnormalities (RP level 47); *6*) severe nonproliferative retinopathy (RP level 53); and *7*) proliferative retinopathy (RP level >53). Finally, the retinopathy levels from both eyes were combined to give a final score of retinopathy severity for each patient (scale 1–11 according to the Diabetes Control and Complications Trial [DCCT]), where a score of 1 represents no retinopathy and a score of 11 represents proliferative retinopathy (21). In addition, the number of microaneurysms was counted from each fundus image.

Statistical methods

Normality tests were performed on the data. Statistical differences between the means of different variables were tested by the Mann-Whitney *U* test for continuous variables. For categorical variables, Fisher's exact test or the Mann-Whitney *U* test was used. Frequencies of retinopathy level were calculated with χ^2 test between the groups throughout pregnancy and postpartum. Repeated-measures ANOVA was performed to compare temporal changes in HbA_{1c} values between the treatment groups during pregnancy. Nonparametric Spearman's rank correlation coefficient was used for correlation analyses. Multivariable logistic regression analysis was performed, and the factors were put into the model simultaneously with the enter procedure. Differences were considered statistically significant when $P < 0.05$. Statistical analyses were performed with the SPSS software pack-

Table 1—*Characteristics of the women with type 1 diabetes treated with insulin lispro and regular insulin*

	Insulin lispro (n = 36)	Regular insulin (n = 33)	P
Age (years)	30.0 ± 4.4	30.6 ± 4.7	0.60
Duration of diabetes (years)	16.5 ± 7.9	14.7 ± 6.2	0.25
Prepregnancy BMI (kg/m^2)	24.9 ± 4.5	24.6 ± 3.5	0.97
Parity (%)			0.42
Nulliparous	22 (61.1)	15 (45.5)	
Uniparous	9 (25.0)	12 (36.4)	
Multiparous	5 (13.9)	6 (18.2)	
Smokers (%)	6 (16.7)	8 (24.2)	0.55
Preconception counseling (%)	20 (55.6)	17 (51.5)	1.0
Coexisting conditions (%)			
Chronic hypertension	5 (13.9)	4 (12.1)	1.0
Preeclampsia	7 (19.4)	4 (12.1)	0.41
Pregnancy-induced hypertension (%)	5 (13.9)	5 (15.2)	1.0
Blood pressure (mmHg)			
Maximum systolic (first trimester)	123 ± 13	121 ± 13	0.58
Maximum diastolic (first trimester)	77 ± 9	74 ± 11	0.39
Maximum systolic (second trimester)	128 ± 20	124 ± 14	0.86
Maximum diastolic (second trimester)	77 ± 12	74 ± 11	0.29
Maximum systolic (third trimester)	142 ± 24	142 ± 27	0.77
Maximum diastolic (third trimester)	87 ± 13	84 ± 14	0.26
Caesarean section	30 (83.3)	22 (66.7)	0.16
Insulin dosage (IU)			
At the beginning of pregnancy	53 ± 15	47 ± 13	0.08
At the end of pregnancy	70 ± 28	65 ± 21	0.51

Data are means ± SD or *n* (%).

age (version 9.0 for Windows; SPSS, Chicago, IL).

RESULTS — The baseline characteristics of the women with type 1 diabetes treated with insulin lispro and those treated with regular insulin were similar (Table 1). There was no difference in insulin quantity (units) in the insulin lispro group compared with the regular insulin group during the first trimester or at the end of pregnancy (Table 1).

Six (16.7%) women in the insulin lispro group and four (12.1%) women in the regular insulin group had previously undergone laser treatment (P = 0.74), but none of the women had active proliferative or preproliferative retinopathy. Before current pregnancy, four women in the insulin lispro group and one woman in the regular insulin group had received bilateral retinal panphotocoagulation.

Follow-up during pregnancy

The mean HbA_{1c} level was similar in both groups in the first trimester, but thereafter, the mean HbA_{1c} level was lower in women treated with insulin lispro than in those treated with regular insulin throughout pregnancy (Fig. 1; repeated-measures ANOVA, P = 0.022). The number of hypoglycemic episodes reported by the women was similar in the two groups; 8 (22.2%) women in the insulin lispro group reported hypoglycemic episodes during pregnancy compared with 11 (33.3%) women in the regular insulin group (P = 0.42). In the 24-h glucose profiles, 20 (55.6%) women treated with insulin lispro and 12 (37.5%) treated with regular insulin had no hypoglycemic episodes during the first trimester (P = 0.13). During the second trimester, the corresponding percentages were 71.4 and 59.4%, respectively (P = 0.58). During the third trimester, the percentages were 87.5 and 75.0% (P = 0.73).

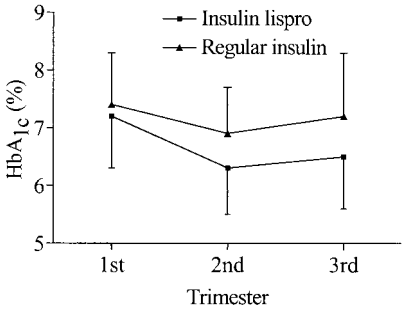

Figure 1—*Glycemic control (HbA_{1c}) in women with type 1 diabetes treated with insulin lispro (black squares) and regular insulin (black triangles) during pregnancy* (P = *0.022 between the groups, repeated-measures ANOVA).*

Level of retinopathy and its progression

Table 2 summarizes the frequencies of retinopathy level during pregnancy in the two treatment groups. There was a trend toward less increase in nonproliferative retinopathy in the insulin lispro group than in the regular insulin group (P = 0.052). During pregnancy, retinopathy severity level remained stable or improved in 21 (58.3%) women and 21 (63.6%) women, worsened one level in 8 (22.2%) and 1 (3.0%), and worsened more than one level in 5 (13.9%) and 8 (24.2%) in the insulin lispro and regular insulin groups, respectively. Two (5.6%) women in insulin lispro group had preterm delivery before 33 weeks' gestation, and therefore, data on retinopathy level in the third trimester are missing for these patients. In the regular insulin group, three (9.1%) deliveries occurred before 33 weeks' gestation.

Proliferative retinopathy developed in four (11.5%) patients with moderate diabetic retinopathy in the insulin lispro group and two (6.0%) patients in the regular insulin group (P = 0.46). The baseline retinopathy severity levels (DCCT scale) in these four women with diabetes were in the insulin lispro group as follows: one level 4, one level 6, and two level 7. In the regular insulin group, women who progressed to neovascularization had level 6 and level 7 at baseline. In the insulin lispro group, two patients had started laser treatment during pregnancy and two started laser treatment after delivery. In the regular insulin group, both patients underwent laser treatment 6 months postpartum.

Furthermore, all four women who had received bilateral retinal panphotocoagulation before current pregnancy remained stable in the insulin lispro group. In the regular insulin group, the woman with diabetes who had received bilateral

Table 2—*Frequencies of retinopathy level in women with type 1 diabetes treated with insulin lispro and regular insulin throughout pregnancy and postpartum*

Retinopathy severity level (%)	Insulin lispro	Regular insulin	*P*
At initial examination	*n* = 36	*n* = 33	
No or mild (DCCT ≤3)	15 (41.7)	21 (63.6)	0.18
Moderate (DCCT 4–8)	21 (58.3)	12 (36.4)	
Proliferative (DCCT 11)	0 (0)	0 (0)	
During the 24–26 weeks' gestation	*n* = 35	*n* = 33	
No or mild (DCCT ≤3)	13 (37.1)	19 (57.6)	0.21
Moderate (DCCT 4–8)	21 (60)	14 (42.4)	
Proliferative (DCCT 11)	1 (2.9)	0 (0)	
During the 34–36 weeks' gestation	*n* = 34	*n* = 30	
No or mild (DCCT ≤3)	11 (32.4)	12 (40)	0.60
Moderate (DCCT 4–8)	21 (61.8)	18 (60)	
Proliferative (DCCT 11)	2 (5.8)	0 (0)	
3 months postpartum	*n* = 35	*n* = 33	
No or mild (DCCT ≤3)	13 (37.1)	14 (42.4)	0.36
Moderate (DCCT 4–8)	19 (54.3)	19 (57.6)	
Proliferative (DCCT 11)	3 (8.6)	0 (0)	
6 months postpartum	*n* = 35	*n* = 33	
No or mild (DCCT ≤3)	12 (34.3)	18 (54.5)	0.56
Moderate (DCCT 4–8)	19 (54.2)	13 (39.5)	
Proliferative (DCCT 11)	4 (11.5)	2 (6.0)	

Data are *n* (%). *P* values were calculated with χ^2 test.

panphotocoagulation developed local neovascularization in the other eye 6 months postpartum.

Prepregnancy retinopathy level correlated significantly with the retinopathy severity scale in the third trimester ($r = 0.682$, $P < 0.0001$), and so did duration of diabetes ($r = 0.391$, $P = 0.001$). Furthermore, a positive correlation was found between mean systolic blood pressure and mean HbA_{1c} in the third trimester ($r = 0.255$, $P = 0.037$).

Multivariable logistic regression analysis

A multivariable logistic regression model was performed to assess factors associated with retinopathy progression. With the retinopathy severity (DCCT level) in the third trimester as the dependent variable, parity qualified best as a predictor in the model. Retinopathy progressed significantly in nulliparous women with diabetes when compared with parous women [Exp(B) = 4.0, 95% CI 1.1–13.7, $P = 0.030$]. Factors such as duration of diabetes, type of insulin used, the mean value of all HbA_{1c} measurements taken throughout pregnancy, blood pressure (systolic or diastolic), preeclampsia in the current pregnancy, smoking, or prepregnancy planning did not explain the retinopathy progression.

CONCLUSIONS — Our main finding was that insulin lispro seems to improve glycemic control throughout pregnancy in women with type 1 diabetes better than regular insulin with no adverse impact on progression of diabetic retinopathy. We had fewer (although not significantly) hypoglycemic episodes in the insulin lispro group than in the regular insulin group, giving support to previous reports suggesting that there are fewer hypoglycemic episodes in women with diabetes treated with insulin lispro than in those treated with regular insulin (22,23).

Insulin lispro could be associated with retinal neovascularization during pregnancy because it has been reported to have 50–70% more binding to IGF-1 receptors than human insulin (24). However, our results do not show worsening of diabetic retinopathy during pregnancy. In a previous study of 12 women treated with insulin lispro compared with a historical cohort of 42 women treated with regular insulin, insulin lispro treatment was not associated with progression of retinopathy during pregnancy (16). In another study, six patients with diabetic retinopathy treated with insulin lispro went through nine pregnancies and the condition worsened in none (15). In a study by Kitzmiller et al. (14), insulin lispro was implicated in development of bilateral proliferative retinopathy; marked vision impairment occurred during pregnancy in 3 of 10 women (1 with type 1 and 2 with type 2 diabetes) whose initial retinal status was normal. Our study included only women with type 1 diabetes, and the four women in the insulin lispro group in whom proliferative retinopathy developed (one during midpregnancy, one during the third trimester, one 3 months postpartum, and one 6 months postpartum) had moderate nonproliferative diabetic retinopathy during early pregnancy. Thus, our findings confirmed the results of the Diabetes in Early Pregnancy (DIEP) Study (1995), which showed that women with moderate or more severe retinopathy at conception are at greater risk for progression of retinopathy during pregnancy (25). In contrast to the study by Kitzmiller et al. (14), none of the women whose initial retinal status was normal progressed to the proliferative stage. In addition, the visual outcome was mostly very good in our patients with progression.

Furthermore, two patients in the regular insulin group progressed to the proliferative stage 6 months postpartum in the other eye. Both of these women had moderate nonproliferative diabetic retinopathy at baseline. One patient had been panphotocoagulated in the right eye, where the local neovascularization developed. The other patient had received local bilateral laser treatment. In addition, the latter patient had proteinuria, was a smoker, was nulliparous, and had a previous psychiatric diagnosis.

Some concern arose because 2 of the 34 women treated with insulin lispro developed bilateral proliferative retinopathy by the end of pregnancy, compared with none of the 30 women treated with regular insulin. However, in the four women progressing to proliferative retinopathy in the insulin lispro group, there were factors other than insulin itself that may explain the progression. Two women had hypertensive pregnancies, mild preeclampsia developed in one, and the two other women experienced rapid improvement of glycemic control in early pregnancy. Both preeclampsia (1,7,26) and rapid improvement of glycemic control in nonpregnant (27,28) and pregnant patients with diabetes (29) have been shown to be associated with progression

of retinopathy. In addition, three of four patients developing retinal neovascularization were nulliparous, which was significantly associated with retinopathy progression in our study. Therefore, our study confirmed the previous EURODIAB IDDM Complications Study (30), in which it was shown that the women most vulnerable to progress rapidly to proliferative diabetic retinopathy included nulliparous women. In that study, the prevalence of proliferative retinopathy was 16% in nulliparous women, 7% in uniparous women, and 8% in multiparous women. Furthermore, in our study, all patients in the insulin lispro group with progression to proliferative retinopathy belonged to White's class D, which has also been associated with retinopathy progression in 41% of patients during pregnancy in a recent prospective study (31). The relatively small number of patients may also have affected our results. Previously, Buchbinder et al. (16) calculated that 319 pregnant women with diabetes would be required in each group (a total of 638) to demonstrate a 100% increase in rates of progression of retinopathy from 6 to 12%.

In our study, the insulin type was chosen before the current pregnancies and was not controlled by the investigators. This is a potential source of bias. It is possible, for example, that women with more labile control of diabetes had their medication changed to insulin lispro before pregnancy. However, as HbA_{1c} levels, which were rather optimal for pregnancy during the first trimester, were similar in both groups, this potential source of bias was not a major concern.

In conclusion, our results suggest that better control of HbA_{1c} levels can be obtained with insulin lispro than with regular human insulin during pregnancy in women with type 1 diabetes, with a potentially better outcome of pregnancy. Our results do not suggest an increased risk of retinopathy with the use of the insulin lispro. Other factors, i.e., high HbA_{1c} levels and existing retinopathy, remain important factors for the progression of diabetic retinopathy, and these women should be followed closely throughout pregnancy. Our results should be considered as results of an uncontrolled study. Therefore, further randomized controlled studies are needed.

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