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Pregnancy complications and perinatal outcome in diabetic women treated with Humalog (insulin lispro) or regular human insulin during pregnancy

Authors' Contribution:

- A** Study Design
- B** Data Collection
- C** Statistical Analysis
- D** Data Interpretation
- E** Manuscript Preparation
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Summary

Background:

Pregnancy outcome in diabetic women is strictly related to glycemc control during pregnancy. The aim of our study was to compare pregnancy outcome between patients subjected to intensive insulin therapy using regular human insulin and those treated with insulin lispro (Humalog).

Material/Methods:

Group A (n=25) was treated with Humalog, and the control group B (n=46) with regular human insulin. Mean age, duration of diabetes, presence of chronic diabetic complications (according to the White classification) parity, and BMI did not differ between groups.

Results:

The mean HbA_{1c} concentrations in groups A and B were respectively: 7.8±1.4% vs. 7.5±1.5% in the first trimester, 6.4±0.8% vs. 6.5±1.6% in the second, and 6.7±0.7% vs. 6.3±1.2% in the third (no significant differences). The duration of pregnancy was 36.4±3.9 weeks in group A and 37.1±1.9 weeks in group B, while the mean neonatal birth weight was 3467±790 and 3367±666 g, respectively. Neither the frequency of preterm labor and cesarean section nor the frequency of fetal macrosomia and hypoglycemia differed between groups. There was only one malformed infant in the human insulin-treated group, and no statistical difference in the rate of spontaneous abortion between groups. Also, there were no differences in the frequencies of occurrence of hypertension (essential and pregnancy induced) and urinary tract infections.

Conclusions:

The course of pregnancy and perinatal outcome is comparable in intensively treated diabetic women regardless of the short-acting insulin used. 'Humalog' appears to be a safe alternative to human insulin in the treatment of diabetes during pregnancy.

key words:

insulin • pregnancy • glycemc control

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BACKGROUND

Before the early 20th century women with diabetes were often discouraged from pregnancy. Those who did in fact become pregnant faced a distressing prognosis: a maternal mortality rate of 6–45% [1] and a perinatal mortality rate of 60% [2]. The discovery of insulin was a major step forward in managing diabetic patients, but still, their pregnancies and perinatal survival were a major challenge for both obstetricians and diabetologists.

In the 1970s, Karlsson and Kjellmer published [3] a study that demonstrated the importance of glycemic control during pregnancy for decreased perinatal mortality. These findings led to the development of specialized pregnancy programs aimed at decreasing the dismal perinatal mortality. In 1989 the St. Vincent Declaration established a five-year target of reducing adverse pregnancy outcomes among insulin-dependent diabetic women to a level equal to that among non-diabetic women [4]. In 1997, Casson et al. published their findings from an unselected population in northwest England, in which the infants of women with pre-existent insulin dependent diabetes mellitus had a 10-fold greater risk of congenital malformation, and a 5-fold greater risk of being stillborn, than infants in the general population [5]. All these reports have led to the general conclusions that a more effective and safe treatment of diabetes for women in childbearing age is called for.

In 1996, insulin lispro was approved for clinical use in Europe and USA. Insulin lispro is an analogue of regular human insulin, with a peak insulin action achieved within an hour of injection. In spite of its popularity for young patients with type 1 diabetes, however, the drug has not been yet licensed by the FDA (Food and Drug Administration) for use in pregnancy. Nevertheless, insulin lispro is superior to soluble insulin in terms of reducing glycated hemoglobin (HbA_{1c}) and post-prandial glucose values, lowering the frequency of hypoglycemia, and improving the quality of life. Since a 1-hr post-prandial glucose value of 140 mg/dl is considered target during pregnancy, insulin lispro may be advantageous, as compared with soluble insulin, and its use during pregnancy could be a useful therapeutic tool [6].

In the present study we decided to compare the obstetrical and perinatal outcomes in diabetic women treated during pregnancy either with insulin lispro or with regular human insulin.

MATERIAL AND METHODS

The study was performed in a university teaching hospital. All women included in the study were patients of the Diabetic Outpatient Clinic associated with the Department of Endocrinology and Metabolic Diseases and the Department of Fetal-Maternal Medicine at the Polish Mother's Memorial Hospital – Research Institute in Lodz, Poland. Written consent was obtained from each of patient enrolled in the study.

The patients in both study groups had diabetes mellitus type 1. All subjects were seen by a care team that included a diabetologist, a dietician, a diabetes nurse educator, an obstetrician, and an ophthalmologist. All information on the index pregnancy was recorded on computerized database, including fetal data (miscarriage, fetal loss >24 weeks gestation, infant birth weight, neonatal death during first 28 days of life, perinatal mortality and morbidity, ie. congenital malformation) and maternal data (age, duration of diabetes, presence of chronic diabetic complications, body mass index – BMI, mode and time of delivery).

All patients were treated during pregnancy with the same type of insulin as before conception, only the doses of insulin were optimized. The study groups consisted of 25 women treated with insulin lispro (group A) and the control group (group B) of 46 women treated with regular human insulin. NPH or Ultralente was used in both groups as long-acting insulin.

Statistical analysis

For purposes of statistical analysis we used the Fisher test and the t-Student test, with the level of statistical significance established at $p < 0.05$.

RESULTS

The mean age, duration of diabetes and severity of diabetes according to the White classification, and BMI index in the study groups did not differ significantly. There were also no statistically significant differences in the level of metabolic control during pregnancy, measured as mean HbA_{1c} concentrations in the 1st, 2nd and 3rd trimester.

The duration of pregnancy, the frequency of LGA (large for gestational week) and SGA (small for gestational week), and the rate of occurrence of preterm labor and cesarean section did not differ between groups. There was only one malformed infant in the regular human insulin group (B), and there was no statistical difference in the rate of spontaneous abortion between the study groups. Also, no differences were found in the frequencies of hypertension (essential and pregnancy-induced) and urinary tract infections in the mothers.

The results are shown in Table 1.

DISCUSSION

Infants of women with GDM, as well as type 1 and 2 diabetes mellitus, have an increased risk of neonatal complications. The risk of congenital malformations is also higher in pregestational diabetic mothers (type 1) (5.2–16.8%) when compared to infants of non-diabetic mothers (1.2–3.7%) [5,7,8]. Pre-conception control and good glycemia during pregnancy, along with proper medical supervision, are the keys to success in achieving good perinatal outcomes.

Table 1. Specific distribution of gravidity status in study and control group.

		"Humalog" (A) N=25 (%)	Human insulin (B) N=46 (%)	p
Age (years)		25.9±5.5	26.1±3.7	n.s.
BMI (kg/m ²)		22.9±3.8	24.0±4.1	n.s.
BMI (kg/m ²)	up to25	22 (88.0)	33 (71.7)	n.s.
	26-30	2 (8.0)	8 (17.4)	
	>30	1 (4.0)	5 (10.9)	
Duration of DM (years)		9.2±6.3	9.2±6.3	n.s.
White	B	7 (25.0)	18 (39.1)	n.s.
	C	10 (40.0)	10 (21.7)	
	D	7 (28.0)	14 (30.4)	
	R	1 (4.0)	2 (4.4)	
	RF	0 (0.0)	2 (4.4)	
HbA _{1c} - 1 st trimester		7.8±1.4	7.5±1.5	n.s.
HbA _{1c} - 2 nd trimester		6.4±0.8	6.5±1.6	n.s.
HbA _{1c} - 3 rd trimester		6.7±0.7	6.3±1.2	n.s.
Hypertension/gestosis	1/3	(4/12)	1/6 (2.2/13.2)	n.s.
Urinary tract infections	1	(4.0)	6 (13.2)	n.s.
Pregnancy duration (weeks)		36.4±3.9	37.1±1.9	n.s.
Index Pregnancy	1	13 (52.0)	27 (58.6)	n.s.
	2	8 (32.0)	11 (23.8)	
	3	3 (12.0)	6 (13.2)	
	4	1 (4.0)	2 (4.4)	
Index Delivery	1	14 (56.0)	30 (65.2)	n.s.
	2	10 (40.0)	12 (26.1)	
	3	1 (4.0)	4 (8.7)	
Pregnancy duration	-up to 37 weeks	7 (30.4)	15 (34.8)	n.s.
	-over 37 weeks	16 (69.6)	28 (65.2)	
Vaginal birth		8 (32.0)	11 (23.9)	n.s.
Caesarian section		15 (60.0)	32 (69.6)	
Abortion		2 (8.0)	3 (6.5)	
Birth weight (g)		3467±790	3367±666	n.s.
Birth weight (percentile)	<10 (SGA)	2 (8.7)	1 (2.3)	n.s.
	10-90	11 (47.8)	29 (67.4)	
	>90 (LGA)	10 (43.5)	13 (30.3)	
Apgar score (1 min.)		8.0±1.1	8.3±0.9	n.s.
Apgar score (5 min)		8.6±0.8	8.6±0.6	n.s.
Neonatal hypoglycaemia (<40 mg/dl)		4 (17.4)	10 (23.3)	n.s.

Insulin lispro is a very convenient drug because it allows insulin application just before meals, and often reduces the need for small snacks in between main meals [9]. Since Lispro is becoming more and more popular among young women with diabetes type 1, unplanned pregnancies are bound to happen. This makes the question of the safety of use of insulin lispro in pregnancy very relevant. Data on insulin lispro use in pregnancy are limited, particularly evaluations of outcome compared with other types of insulin in populations of relevant size [10,11]. Jovanovic et al. showed in 1999 that there is no placental transfer of insulin lispro [12], and in 2003 this was confirmed by Boskovic et al. [13]. This makes the use of lispro even more attractive, since it has been suggested that HbA_{1c} levels are not a sufficient marker for well-controlled blood glucose in pregnancy, but postprandial glucose control is essential to avoid macrosomia in managing GDM [14]. Jovanovic et al. in their paper on the use of lispro in pregnancy point to improvement of glycemic control and patient satisfaction [12,15]. Bhattacharyya et al. reported on 634 pregnan-

cies evaluated over a seven-year period. All 213 gestational diabetics requiring insulin had successful deliveries; no differences in maternal or fetal outcomes were seen between the regular insulin and 'Humalog' groups. Insulin dose, glycemic control and birth weight were comparable between groups, while a non-significant trend in increased congenital anomalies was noted in the regular insulin group for both gestational and pre-gestational diabetic patients. Patient satisfaction scores were higher in the insulin lispro group. The authors concluded that no adverse fetal-maternal outcomes were noted in the evaluated patients [16]. In a report published by Cohen et al., 5 women conceived while receiving lispro therapy and decided to continue with lispro, and 6 were switched from regular insulin to lispro after conception (7 to 17 weeks of gestation). Mean HbA_{1c} values decreased from 7.25 to 6% in women switched to lispro. No congenital malformations were observed in any infant [17]. Garg et al. also reported the decrease in HbA_{1c} values in the lispro group compared to regular insulin group. They observed as well that the need for

caesarian section was significantly lower in the lispro group versus the regular insulin group [18].

In the present study we compared the pregnancy outcomes in two groups of diabetic women treated with regular insulin or insulin lispro. We did not observe statistically significant differences in either the mothers' or the newborns' parameters. We noticed only one malformed infant in the human insulin treated group. This malformation was observed in a woman with an HbA_{1c} of 7.7% in the first trimester.

CONCLUSIONS

The use of insulin lispro seems to be a safe alternative to regular insulin during pregnancy. More observations are needed to confirm this thesis.

REFERENCES:

- Gabbe SG: Medical complications of pregnancy in the management of diabetes: six decades of experience. In: Pitkin RM, Zlatnik FJ, editors. Yearbook of obstetrics and gynecology. Chicago Year Book: Medical Publishers; 1980: 37-39
- Recce EA: The history of diabetes mellitus. In: Recce EA, Coustan DR (eds): Diabetes mellitus in pregnancy. New York: Churchill Livingstone; 1995: 1-10
- Karlsson K, Kiellmeri: The outcome of diabetic pregnancies in relation to the mothers' blood sugar level. Am J Obstet Gynecol, 1972; 112: 213-220
- Workshop report. Diabetes care and research in Europe: The St. Vincent Declaration. Diabet Med 1990; 7: 360
- Casson IF, Clarke CA, Howard CV et al: Outcomes of pregnancy in insulin-dependent diabetic women: results of a five-year population cohort study. BMJ, 1997; 315: 275-278
- Calle-Pascual AL, Bagazgoitia J, Calle JR et al: Use of insulin lispro in pregnancy Diab Nutr Metab, 2000; 13: 173-177
- Becerra JE, Khonry MJ, Cordero JF, Erickson JD: Diabetes mellitus during pregnancy and the risk for specific defects: a population-based control-study. Pediatric, 1990; 85: 1-9
- Hawthorne G, Snodgrass A, Tunbridge M: Outcome of diabetic pregnancy and glucose intolerance in pregnancy: an audit of foetal loss in Newcastle General Hospital 1977-90. Diabetes Res Clin Pract, 1990; 25: 183-90
- Kotsanos JG, Vignati L, Huster W et al: Health-related quality of life results from multinational clinical trials of insulin Lispro. Diabetes Care, 1997; 20(6): 948-958
- Ilic S, Javanovic L, Pettitt D et al: Insulin lispro: safe and effective treatment option for GDM. Diabetologia, 1998; 41: A48
- Garg S, Pennington M, Anderson J: Maternal and fetal outcomes between human regular and Humalog insulin treated pregnancies in type 1 diabetes. Diabetologia, 1999; 42: A437
- Jovanovic L, Ilic S, Pettitt DJ et al: Metabolic and immunologic effects of insulin lispro in GDM. Diabetes Care, 1999; 22: 1422-1427
- Boskovic R, Feig DS, Derewlany L et al: Transfer of insulin lispro across the human placenta: *in vitro* perfusion studies. Diabetes Care, 2003; 26: 1390-4
- Jovanovic-Peterson L, Peterson CM, Reed GF et al: Maternal postprandial glucose levels and infant birth weight: the diabetes in early pregnancy study. Am J Obstet Gynecol, 1991; 164: 103-111
- Javanovic L, Ilic SS, Gutierrez M, Bastyrrii EJ: Insulin lispro improves postprandial glucose without increased immunogenicity or hypoglycaemia in GDM women. Diabetes, 1998; 47: 190
- Bhattacharyya A, Brown S, Hughes S, Vice PA: Insulin lispro and regular insulin in pregnancy. QJMed, 2001; 94: 255-260
- Cohen M: Use of lispro insulin in pregnancy: a 2-year experience. Diabetes, 1999; 48: A468
- Garg SK, Anil S, Gottlieb P et al: Better glycaemic control and reduced need for caesarian section with insulin lispro treated pregnancies in type 1 diabetes. Diabetes, 2001; 50: A383