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Use of insulin lispro during pregnancy in women with pregestational diabetes mellitus

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ABSTRACT

Background and objective: To assess the safety and efficacy of insulin analogues versus human insulin in pregnant women with pregestational diabetes.
Patients and methods: We collected data on pregnant women with type 1 or type 2 diabetes who were attended at the Diabetes and Pregnancy Unit between January 1998 and April 2008 (N = 351). Two hundred and forty one patients were treated with regular insulin and NPH and 110 were treated with different combinations of insulins including an insulin analogue (most of them with NPH and lispro).
Results: There was no significant difference in terms of congenital malformation rate between groups (3.3% and 3.6%). The group on insulin analogue had slightly higher mean HbA1c during the first trimester than the group on human insulin (6.6 [1.0]% vs 6.9 [1.1]%; P = 0,022) and needed smaller insulin doses during whole pregnancy. Severe hypoglycaemia was significantly less frequent among women treated with a rapid insulin analogue (2.3 vs 10.0%; P = 0,025). Neonatal hypoglycaemia was significantly more frequent in the group treated with a rapid insulin analogue (34.9 vs 23.6%; P = 0.043) due to the concomitant use of an insulin pump. Other obstetric and neonatal variables were not different between the two groups.
Conclusion: Our study shows that insulin analogues are safe during pregnancy in women with pregestational diabetes mellitus. Overall, glycaemic control, maternal and foetal outcome were similar to those with human insulin. The main advantage with respect to human insulin was to importantly reduce maternal severe hypoglycaemia.

Experiencia en el uso de insulina lispro durante el embarazo en mujeres con diabetes mellitus pregestacional

Palabras clave:
Diabetes mellitus tipo 1
Embarazo
Malformaciones congénitas
Análogos de insulina

RESUMEN

Fundamento y objetivo: Evaluar la seguridad y eficacia de los análogos de insulina en comparación con insulina humana en mujeres embarazadas con diabetes pregestacional.
Pacientes y métodos: Se recogieron datos de las embarazadas con diabetes tipo 1 o 2 que fueron atendidas en la Unidad de Diabetes y Embarazo entre enero de 1998 y abril de 2008 (n = 351). Doscientas cuarenta y una pacientes fueron tratadas con insulina regular y NPH, y 110 fueron tratadas con diferentes combinaciones de insulinas incluyendo un análogo de insulina (la mayoría con NPH y lispro).
Resultados: No hubo diferencias en cuanto a malformaciones congénitas entre ambos grupos (3,3 y 3,6%). El grupo con análogo de insulina tuvo una HbA_{1c} ligeramente más alta que el grupo con insulina humana durante el primer trimestre (6,9 [1,1]% vs 6,6 [1,0]%; p = 0,022) y necesitó menor dosis de insulina durante todo el embarazo. La hipoglucemia grave fue significativamente menos frecuente entre las mujeres tratadas con un análogo de insulina rápida (2,3 vs 10,0%; p = 0,025). La hipoglucemia neonatal fue significativamente más frecuente en dicho grupo (34,9 vs 23,6%; p = 0,043) en relación con el uso concomitante de bomba de insulina. Otras variables obstétricas y neonatales no fueron diferentes entre ambos grupos.

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Conclusión: Este estudio muestra que el uso de los análogos de insulina es seguro durante el embarazo en mujeres con diabetes mellitus pregestacional. En general, el control glucémico y los resultados maternos y fetales fueron similares a los obtenidos con insulina humana. La principal ventaja con respecto a la insulina humana fue la importante reducción en la hipoglucemia materna grave.

Introduction

Women with type 1 or type 2 pregestational diabetes and their infants are exposed to an increased risk of complications during pregnancy and labour, including spontaneous abortion, congenital malformations, macrosomia and perinatal mortality.[1,2] Tight glycaemic control during conception and pregnancy importantly contributes to a reduction of the risk of these complications. This is why the objective of prepregnancy and pregnancy care is to achieve and maintain glycaemia as near as possible to normal, without undue hypoglycaemia.[3,4]

It is often difficult to achieve these challenging objectives during pregnancy in women with pregestational diabetes. Modern rapid insulin analogues (IA), lispro and aspart, provide better control of postprandial hyperglycaemia and decreased frequency of hypoglycaemia compared with regular insulin.[5] Studies in pregnant women confirm these facts, and show that these analogues are safe during pregnancy.[6–10] However, few controlled studies have compared the use of rapid IA with regular insulin during pregnancy in pregestational diabetes.[9,11–13]

Data about basal IA are scarce. According to published data, it seems that the incidence of congenital malformations with glargine is similar to that with human insulin.[14–17] A recent report on 10 pregnant type 1 diabetic women using detemir informed of no congenital malformations.[18]

The aim of our study is to retrospectively assess the efficacy and safety of various IA during pregnancy in women with pregestational diabetes. We compared congenital malformation rates and maternal and neonatal outcomes between women on IA and women on human insulin (HI).

Patients and methods

This study was performed at the Hospital Universitario La Paz, Madrid, Spain. Ethical approval for this research was provided by the Hospital Ethical Committee and all mothers gave their informed consent.

Data were retrospectively collected from type 1 or type 2 pregnant diabetic women who were attended at the Diabetes and Pregnancy Unit between January 1998 and April 2008. Spontaneous abortions and multiple pregnancies were excluded. Therapeutic abortions were included. The final size of the sample was 351 women.

Patients were seen on an outpatient basis, every 4 weeks during preconception care and every 1-2 weeks throughout pregnancy. They were requested to perform home blood glucose monitoring six times daily (three preprandial; three two hours postprandial). The glucose targets were: preprandial 3.9-5.6 mmol/l (70-100 mg/dl) and postprandial 5.6-7.8 mmol/l (100-140 mg/dl).

Thirteen women used continuous subcutaneous insulin infusion systems (CSII), and the remainder were on flexible basal bolus regimens. All women were trained to adjust their insulin dose to achieve the glucose targets.

Maternal glycosilated haemoglobin (HbA_{1c}) was measured every month using high performance liquid chromatography DCCT (Diabetes Control and Complications Trial)-aligned method (BioRad, Richmond, VA). The HbA_{1c} levels included in this study were the first HbA_{1c} measured during pregnancy and the mean HbA_{1c} of each trimester.

Gestational age was based on the last menstrual period and on foetal ultrasonography performed between 8^{th} and 12^{th} gestational week. Neonates under 10^{th} or above 90^{th} percentile using the Spanish neonatal growth standards were considered respectively small or large for gestational age (LGA).[19] Macrosomia was defined as a birth weight higher than 4,000 g.

Maternal severe hypoglycaemia was any episode of hypoglycaemia that required the assistance of another individual for recovery. If a capillary glucose under 3.3 mmol/L was documented, and the patient could manage symptoms herself, the episode was considered mild hypoglycaemia.

Chronic or preexisting hypertension was defined as systolic pressure $\geq$ 130 mmHg and/or diastolic pressure $\geq$ 85 mmHg that was present before pregnancy, started before the 20^{th} week of pregnancy, or persisted longer than 12 weeks postpartum. Gestational hypertension was defined as elevated blood pressure first detected after 20 weeks of gestation in the absence of proteinuria. Preeclampsia refers to the syndrome of new onset of hypertension and proteinuria after 20 weeks of gestation, or worsening hypertension with new onset proteinuria in a woman with preexisting hypertension (superimposed preeclampsia).

Only major malformations were considered in our study. We classified a malformation as major if it was fatal, potentially life threatening, likely to lead to serious handicap or major cosmetic defect, or requiring major surgery.

Study design

Of the 351 women, 241 were treated with neutral protamine Hagedorn (NPH) and regular insulin (control group) and 110 women were treated with IA. Before rapid IA were approved for their use in pregnancy, our practice was to discontinue them during prepregnancy care or, in women without prepregnancy care, in the first visit to the Diabetes and Pregnancy unit. For this reason, in 24 of the patients, rapid IA were only used during the first trimester of pregnancy, while in the remaining 86, rapid IA were used throughout pregnancy.

The group treated with an IA during the whole pregnancy included only lispro and aspart insulin. In all cases, use of insulin glargine or insulin detemir was stopped during the first trimester. Further details on groups of treatment and insulin therapy are shown on Figure 1.

We compared demographic variables, first trimester glycaemic control and congenital malformation rates between the group treated with an IA during the first trimester (IAFT) and the control group (n = 110 vs n = 241). Demographic variables, second and third trimester glycaemic contrbol, obstetric, foetal and neonatal outcomes were compared between the group treated with an IA during the whole pregnancy (IAWP) and the control group (n = 86 vs n = 241).

All the analyses of interest were adjusted for potential confounding factors.

Statistical analysis

Statistical analyses were conducted using SPSS version 15.0 statistical software (SPSS Inc., Chicago, IL, USA). Univariate

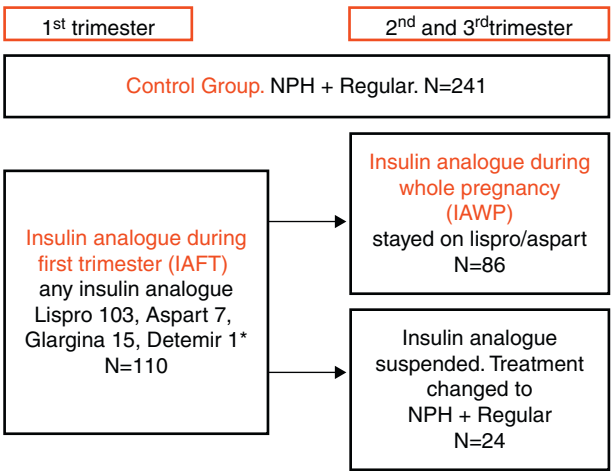

Figure 1. Insulin treatment groups. All the patients on long-acting insulin analogue (IA) were also on fast-acting IA.

comparisons between patients receiving and not receiving an IA were performed using Pearson's χ^2 test for categorical variables and Student's t-test for continuous variables. When comparing three groups (control group, IAFT and IAWP) we used Pearson's χ^2 test for categorical variables and one-way ANOVA for continuous variables. For multivariate analysis, logistic regression was performed.

Mean and standard deviation are reported for continuous variables, and number and percentage are reported for categorical variables. A p-value < 0.05 was considered significant.

Results

Demographic data

Pregnant women's clinical features are shown in Table 1. No significant differences were found between the groups in terms of age, body mass index (BMI), diabetes duration, type of diabetes, microvascular complications, number of patients who received prepregnancy care, and HbA_{1c} at the beginning of pregnancy.

First trimester exposition to teratogenous medications was more frequent among women on IA than among women on HI (IAFT: 13.6%; IAWP: 11.6%; HI: 5%; P = 0.013). These medications were metformin (13 patients), angiotensin converting enzyme inhibitors (4), angiotensin II receptor blockers (2), statins (1), sulphonilurea (2), fenofibrate (1), acarbose (1), and others (4).

The use of an insulin pump was more frequent in the groups on IA (11.8%, 15.1% and 2.5%, respectively; P = 0.000).

Congenital malformations

In the group on HI 8 (3.3%) neonates had one or more congenital malformation. This happened in 4 (3.6%) neonates in the group on IA (OR 1.10 [95% CI 0.32-3.73]). There were no significant differences in terms of the congenital malformation rate between groups (Table 2).

Congenital malformations comprised cardiovascular, urogenital and gastrointestinal anomalies, neural tube defects, and polymalformative syndromes (Table 3). There were 4 pregnancy terminations in our population sample, all of them because of congenital malformations.

Glycaemic control and insulin dose

The group on IA had higher mean HbA_{1c} in the first trimester than the group on HI [6.9 (1.1) vs 6.6 (1.0)%; P = 0.022; Table 2]. Second trimester mean HbA_{1c} was not different between groups. The group on IA had slightly higher mean HbA_{1c} in the third trimester [6.1 (0.5)% vs 6.0 (0.6)%; P = 0.051] but this difference was not statistically significant (Table 4).

The group on IA needed lower weight-adjusted insulin dose during each trimester of pregnancy (first trimester 0.5 [0.2] vs 0.6 [0.2] U/kg; P = 0.003; second trimester: 0.5 [0.2] vs 0.7 [0.2] U/kg, P = 0.000; third trimester 0.7 [0.2] vs 0.9 [0.3] U/kg, P = 0.000].

Maternal and foetal outcome (Table 4)

Severe hypoglycaemia was significantly less frequent among women treated with an IA. In this group, only 2 (2.3%) women had one or more episode; whereas in the HI group, 24 (10.0%) women were affected (P = 0.025; OR 0.22 [95% CI 0.05-0.93]). The analysis was repeated using as covariates: BMI, teratogenous medications, preconception care, use of an insulin pump, presence of microvascular complications, mean HbA_{1c} of the first, second and third trimesters, and weight-adjusted insulin dose. The use of an IA was still independently associated with less severe maternal hypoglycaemia (adjusted OR 0.08 [95% CI 0.01-0.67]). A higher dose of insulin during the first trimester was also significantly related to maternal severe hypoglycaemia (adjusted OR 11.23 [95% CI 1.13-111.45]).

No difference was detected in the frequency of hydramnios, preeclampsia, gestational hypertension, week of delivery, and rate of caesarean section.

Table 1
Demographic data.

	HI, N = 241	IA first trimester, N = 110	IA whole pregnancy, N = 86	P-value
Age (years)	32.0 (3.9)	32.4 (4.0)	32.5 (3.8)	0.467
Body mass index (kg/m^2)[a]	24.7 (4.2)	23.8 (3.8)	24.0 (3.9)	0.127
Diabetes duration (years)	12.2 (7.9)	12.1 (8.2)	11.9 (8.2)	0.935
Age at diagnosis (years)	19.7 (8.4)	20.3 (8.9)	20.5 (8.9)	0.687
Number of pregnancies	2.1 (1.3)	1.9 (1.2)	2.0 (1.3)	0.586
HbA_{1c} at conception (%)	6.8 (1.1)	7.0 (1.2)	6.8 (1.1)	0.291
Type 1 diabetes	208 (86.3%)	96 (87.3%)	72 (83.7%)	0.764
Retinopathy	50 (20.7%)	16 (14.5%)	10 (11.6%)	0.106
Nephropathy	12 (5%)	4 (3.6%)	2 (2.3%)	0.544
Chronic hypertension	24 (10%)	9 (8.2%)	6 (7.0%)	0.673
Prepregnancy care	129 (53.5%)	49 (44.5%)	49 (57.0%)	0.171
Use of teratogenous medications	12 (5%)	15 (13.6%)	10 (11.6%)	0.013
Continuous subcutaneous insulin infusion	6 (2.5%)	13 (11.8%)	13 (15.1%)	0.000

Values are mean (standard deviation [SD]) or number and percentage.
HI: human insulin; IA: insulin analogue.
[a] Body mass index just before pregnancy.

Table 2
First trimester variables.

	HI, N = 241	IA first trimester, N = 110	P-value
Total infants with major malformations	8 (3.3%)	4 (3.6%)	0.880
HbA_{1c} first trimester (%)	6.6 (1.0)	6.9 (1.1)	0.022
Insulin dose first trimester (U/kg)	0.6 (0.2)	0.5 (0.2)	0.003

Values are mean (standard deviation [SD]) or number and percentage.
HI: human insulin; IA: insulin analogue.

Table 3
Congenital malformations.

Case	First HbA_{1c}	Use of IA	Teratogenous medications	Congenital malformations	Outcome
1	7.3%	No	No	Hypoplastic left heart syndrome. Skeletal agenesis. Renal malformation	Termination of pregnancy
2	8.9%	No	No	Ventricular septal defect	Vaginal delivery. 36 w. AGA
3	6.3%	No	No	Bilateral ureteropelvic junction obstruction	Caesarean delivery. 38 w. LGA
4	7.2%	No	No	Epispadias	Caesarean delivery. 39 w. AGA
5	8.1%	No	No	Ventricular septal defect, transposition of the great arteries	Termination of pregnancy
6	6.9%	No	No	Ureteropelvic junction obstruction	Vaginal delivery. 37 w. LGA
7	9.7%	No	No	Bilateral inguinal hernia. Right undescended testis	Caesarean section. 33 w
8	5.8%	No	No	Exencephaly	Termination of pregnancy
9	6.9%	Lispro	Fibrate	Exencephaly	Termination of pregnancy
10	9.0%	Lispro	No	Anterior displaced anus, atrial septal defect	Caesarean section. 40 w. LGA
11	5.5%	Lispro	No	Hypertrophic pyloric stenosis	Forceps. 39 w. LGA
12	6.4%	Lispro	No	Alpert syndrome	Vaginal delivery. 34 w. LGA

AGA: appropriate for gestational age; IA: insulin analogue; LGA: large for gestational age; SGA: small for gestational age; W: week.

Table 4
Second-third trimester variables. Obstetric and neonatal outcomes.

	HI, N = 241	IA whole pregnancy, N = 86 (83 with lispro, 3 with aspart)	P-value
Insulin dose 2nd trimester (U/kg)	0.7 (0.2)	0.5 (0.2)	0.000
Insulin dose 3rd trimester (U/kg)	0.9 (0.3)	0.7 (0.2)	0.000
HbA_{1c} second trimester (%)	6.1 (0.7)	6.2 (0.6)	0.138
HbA_{1c} third trimester (%)	6.0 (0.6)	6.1 (0.5)	0.051
Diabetic ketoacidosis	3 (0.9%)	1 (0.3%)	0.953
Maternal severe hypoglycemia	24 (10%)	2 (2.3%)	0.025
Hydramnios	9 (3.7%)	3 (3.5%)	0.917
Preeclampsia	18 (7.5%)	12 (14.0%)	0.074
Gestational hypertension	66 (27.4%)	17 (19.8%)	0.163
Week of delivery	37.3 (1.6)	37.6 (1.5)	0.273
Caesarean section	154 (64.7%)	47 (54.7%)	0.100
Fetal ponderal index	1.14 (0.18)	1.16 (0.18)	0.374
Infant weight (g)	3,365 (614.3)	3,493 (617.2)	0.097
Macrosomic infant	34 (14.3%)	15 (17.4%)	0.493
Infant large for gestational age	91 (38.4%)	43 (50.0%)	0.061
Infant small for gestational age	2 (0.8%)	0	0.393
Neonatal hypocalcaemia	11 (4.6%)	6 (7.1%)	0.393
Distress respiratory syndrome	24 (10.1%)	10 (11.6%)	0.698
Neonatal hypoglycaemia	56 (23.6%)	30 (34.9%)	0.043
Neonatal polycythemia	26 (11.0%)	8 (9.3%)	0.666
Neonatal hyperbilirubinaemia	70 (29.5%)	16 (18.6%)	0.049
Neonatal sepsis	5 (2.1%)	4 (4.7%)	0.220
Birth injury	9 (3.8%)	8 (9.3%)	0.050
Stillbirth	4 (1.7%)	1 (1.2%)	0.747

Values are mean (standard deviation [SD]) or number and percentage.

There was a trend to larger birth weight among offspring of mothers on IA. Proportion of LGA babies was higher in the IA group (50.0 vs 38.4%, P = 0.061; OR 1.60 [95% CI 0.98-2.64]). According to this, there were more birth injuries among the group on IA (9.3 vs 3.8%; P = 0.050; OR 2.60 [95% CI 0.97-6.97]). These differences almost achieved statistical significance.

In the logistic regression analysis for LGA, the use of IA lost significance (adjusted OR 1.56; 95% CI [0.81-3.02]); and LGA infant was explained by higher third trimester HbA_{1c} (OR 3.81; 95% CI [1.69-8.58]). The covariates were BMI, teratogenous medications, preconception care, use of an insulin pump, presence of microvascular complications, and mean HbA_{1c} of the first, second and third trimesters.

Neonatal hypoglycaemia was significantly more frequent in the group treated with IA (34.9 vs 23.6%, P = 0.043; OR 1.73 [95% CI 1.01-2.96]). In the multivariate analysis, the use of IA again lost significance (OR 1.06; 95% CI [0.53-2.12]); excess of neonatal hypoglycaemia was explained by the use of an insulin pump (OR 3.47; 95% CI [1.17-10.31]).

No difference was found in the rates of neonatal hypocalcaemia, distress respiratory syndrome, sepsis, and stillbirth.

Discussion

In this retrospective study performed in women with pregestational diabetes, the outcome of women treated with an IA and their

offspring was not substantially different from those treated with HI. A recent systematic review about rapid IA versus regular HI remarked that most published studies were of poor methodological quality.[5] It is difficult to find articles using a control group when evaluating IA in pregnancy, a fact that gives strength to the results of our study. We found some differences among the demographic characteristics of our study groups. Of note, in the group on IA there were more women exposed to teratogenous medications, and more women used an insulin pump. These differences were controlled in the analysis phase.

The rate of congenital anomalies was similar between groups (3.3% in the HI group and 3.6% in the IA group), a rate comparable to others in the medical literature.[1,2,8] The present study adds more evidence to published data stating that the use of IA in pregnancy does not increase the risk of congenital malformations. It is known that better glycaemic control and prepregnancy counseling reduce the risk of congenital malformations.[4] However, HbA_{1c} under 7% is not enough; and adverse outcomes remain increased.[1] In our series there were six women with HbA_{1c} below 7% (two with HbA_{1c} lower than 6%) who still had major congenital malformations. This apparent contradiction is most probably due to the small size of the sample (only 12 affected mother-infant pairs). Of these six women with good glycaemic control one had been on a fibrate during conception (case 9) and two pregnancies were finished. The remaining four infants were LGA. Our data are in concordance with the fact that HbA_{1c} is not a perfect means of expressing glycaemic control, especially in pregnant women.[20,21]

Overall the glycaemic control was good in both groups. We found that first trimester HbA_{1c} was significantly higher in patients treated with an IA, although HbA_{1c} at the beginning of pregnancy was not different between groups. Most of the patients were treated with insulin lispro (103/110 = 93.6%). Other studies in patients with pregestational diabetes comparing either lispro or aspart with regular insulin did not find any differences in HbA_{1c}.[7,11,22] There was also a trend to higher mean HbA_{1c} during the third trimester in the IA group, but this difference did not reach statistical significance.

Importantly, women on IA had fewer episodes of severe hypoglycaemia. This was related to the use of an IA itself and also to a lower insulin dose. This is consistent with previous studies.[6] Women with pregestational diabetes have a high frequency of hypoglycaemia during pregnancy, and this is an important factor to consider during this period of their lives.[23]

Some recent studies have found that CSII reduces the frequency of severe hypoglycaemia, but none of them has included pregnant women.[24] Other meta-analyses about the same subject –one of them including pregnant women- did not find any differences in the frequency of severe hypoglycaemia[25,26]; the authors explained that this could be related to the rareness of such events, different definitions and insufficient reporting. In our study, the group on insulin analogue had significantly less episodes of severe hypoglycaemia. There were more patients on CSII in this group, and we were aware that the reduction in hypoglycaemia could be due to CSII rather than to the IA itself. For this reason we adjusted the analysis for potential confounding factors; the significant relationship between IA and lower frequency of maternal severe hypoglycaemia persisted.

There was a non-significant higher frequency of offspring LGA in the group treated with an IA. This was explained by the higher mean HbA_{1c} during third trimester. In other reports, increased weight of the neonate was the only difference between mothers treated with insulin lispro and those treated with regular.[12,27]

Neonatal hypoglycaemia was significantly more frequent among newborns from mothers treated with an IA. The frequency of neonatal hypoglycaemia is not specified in other comparative studies.[11] In a descriptive study on type 1 diabetic women treated with lispro, 40.8% of the babies had neonatal hypoglycaemia.[28] This complication, owing to intrauterus beta-cell islet hyperplasia, has been related to poor glycaemic control during pregnancy, and is more frequent among macrosomic newborns.[29] In our study, after adjustment for glycaemic control and other covariates, neonatal hypoglycaemia was associated with the use of an insulin pump, a fact that has previously been reported.[30] A smaller subcutaneous insulin depot in pump users may contribute to maternal hyperglycaemia during delivery.

In summary, treatment with an IA during pregnancy resulted in similar maternal and neonatal outcomes to those with HI. There was no increase in congenital malformation rate. Women treated with an IA had lower incidence of severe hypoglycaemia. Regarding neonatal outcomes, the rate of neonatal hypoglycaemia was higher in the IA group. This potential disadvantage of the use of IA in pregnancy needs to be confirmed in other studies.

Declaration of competing interests

The authors declare no conflicts of interest.

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