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Insulin lispro and regular insulin in pregnancy

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Summary

We assessed the safety of insulin lispro in gestational, type 1 and type 2 diabetes mellitus, analysing 635 pregnancies over a period of 7 years. We also evaluated patient satisfaction, sending an internationally-accepted anonymous diabetes treatment satisfaction questionnaire to 22 patients (three type 1, 19 gestational diabetes) who received regular and lispro insulin in successive pregnancies. The success rate of pregnancies in women with gestational diabetes managed with diet alone ($n = 325$) was 99.3%. All 213 pregnancies in women with gestational diabetes requiring insulin were successful. There was no difference in maternal or fetal outcomes whether patients used regular insulin ($n = 138$) or insulin lispro ($n = 75$), but pre-delivery HbA1c was lower with insulin lispro ($p < 0.05$). Pregnancy loss in patients with pre-gestational diabetes (89 pregnancies in type 1 and eight in type 2 diabetes) was 18.6% for insulin and 3.7% for insulin lispro ($p = 0.10$). The incidences of congenital anomalies with regular insulin were 7.9% and 15.8% in gestational and pre-gestational diabetes, respectively; the figures for insulin lispro were 6.6% ($p = 0.79$) and 3.8% ($p = 0.16$), respectively. Nineteen of the 22 surveyed patients completed the questionnaire. Satisfaction was higher with insulin lispro (26.3 ± 2.3 vs. 18 ± 8.9, $p = 0.0005$). We found no increase in adverse outcome using lispro insulin in diabetic pregnancies, in either gestational or pre-gestational diabetes. Patient satisfaction favoured insulin lispro. Several patients with type 1 diabetes who used regular insulin during pregnancy, chose lispro after delivery, but all who used lispro in pregnancy preferred to continue.

Introduction

Insulin lispro (IL), an analogue of regular human insulin with a peak insulin action achieved within an hour of injection, significantly improves postprandial hyperglycaemia.[1–4] This is very important in diabetic pregnancy,[5] whether gestational or pre-gestational. Patient acceptability has also been higher with IL, which is very helpful in maximizing glycaemic control in pregnancy.[6,7]

Despite better acceptability, less hypoglycaemia and possibly better glycaemic control,[8–10] doubts were raised by two reported cases of congenital anomalies using IL.[11] Case reports are important influences on clinical practice, particularly when the event is rare, and can also be helpful in generating hypotheses or drawing attention to uncommon events, but should not be used to infer a cause-effect relationship, as any one-off association can easily be due to chance. It has taken decades for endocrinologists to reverse their views on the use of methimazole for treating hyperthyroidism in pregnancy, after rare reports of aplasia cutis.[12] Our objective was to assess maternal and fetal outcomes in pregnant women who used IL as their short-acting insulin along with isophane insulin in a twice-daily (free-mixed) or basal bolus regimen, compared to outcomes in women using regular insulin (IR) in similar regimens.

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Methods

The study cohort was drawn from a antenatal clinic run by one clinician who has managed pregnancies in diabetes for two decades. Pregnancies were identified from the hospital database. IL was used for the first time as a part of a phase 3 multicentric trial in 1995. Since then it has been widely used by our unit; the main benefit remains patient compliance, as no gap is required between injection and eating. The other benefits include less reporting of hypoglycaemia, better post-prandial control, and less weight gain. We have analysed the diabetic pregnancies for the last 7 years seen and followed at our clinic.

A total of 635 pregnancies with gestational and pre-gestational diabetes mellitus were managed by our unit. We also identified a subgroup of patients, both gestational diabetes mellitus (GDM) and type 1 diabetes mellitus (DM), who received human IR in one pregnancy and IL in the other. The Diabetes Treatment Satisfaction Questionnaire (DTSQ)[13] was sent to these patients with a short letter of explanation. A new question was added asking them whether they would prefer a particular type of insulin if they were considering another pregnancy, and if so which one. The local Research and Ethical committee approved this anonymous postal survey.

Statistical analysis

Data were compared using unpaired and paired two-tailed Students' t test and Fisher's exact test, as appropriate. $p < 0.05$ was considered significant.

Results

Local practice

The Preston Acute Hospital NHS Trust is situated in the northwest of the UK, serving a population of 350 000. As well as our weekly out-patient clinic, we have a facility for in-patient service when glycaemic control seems suboptimal. The main source of referral for GDM is the obstetrician. In case of type 1 and 2 diabetes, the aim is pre-conception care to maximize control and then to proceed to pregnancy. Patients are seen at least every two weeks until the 30th week, and then every week until they deliver. Our target of blood sugar control is fasting glucose <5 mmol/l, and 2-h post-prandial <7 but $\geqslant 4$ mmol/l. At every clinic visit, a capillary glucose is done to reconfirm the home glucose value, and more emphasis is given to glucose value than to HbA1c. The dietician sees every patient at the time of booking and thereafter when necessary. Diet is individualized, with particular attention to regular snacking to prevent the accelerated fasting seen in pregnancy, and carbohydrate content. The preferred insulin regimen is basal bolus, but the type of regimen or insulin is changed only when there is a pressing reason. Delivery time and mode are planned according to the patient's wish and obstetric indication. Patients on insulin are admitted at least 24 h before the induction of labour or elective section, to ensure maximal control. Patients' capillary glucose is monitored a minimum of hourly during delivery with insulin administration by intravenous infusion. In GDM, blood glucose is monitored similarly throughout delivery, but the insulin infusion is stopped immediately after delivery of the placenta. In cases of DM, the infusion rate is reduced by 50% with delivery of the placenta, and pre-pregnancy dose started as soon as possible. A 6 weeks post-partum glucose tolerance test is requested in all cases of GDM.

Gestational diabetes mellitus

A total of 538 pregnancies were available for analysis: 325 were managed with diet only, 138 with IR and 75 with IL as their short-acting insulin. There were no significant differences in booking week or the week insulin was started. There were two pregnancy losses in the diet-only group: one medical termination at 18 weeks for congenital malformation (imperforate anus, renal dysplasia with agenesis of ureters and bladder) and one intrauterine death at 25 weeks (normal chromosomes, no congenital malformation). There were no losses in the other two groups. The maternal and fetal details are shown in Tables 1–3. There were three twin pregnancies in the diet-only group, and one in the IL group. The major congenital anomalies were Down's syndrome; hydronephrosis and ventricular septal defect (four) in the diet group, tetralogy of Fallot, hydronephrosis and ambiguous genitalia in the IR group, and meningo-myelocoele in the IL group. Minor anomalies were hypospedias, polydactaly, webbed fingers, congenital dislocation of hip joints, undescended testes, tongue tie and cleft lip. The difference in the incidence of congenital anomalies between those using IR and those using IL was not statistically significant (OR 1.23, 95%CI 0.4–3.7).

Pre-delivery HbA1c was significantly lower in the IL group than in the IR and diet-only groups ($p < 0.05$, Table 1). The mean dose of short-acting insulin on the day before delivery was not different (26.7 and 24.5 in IR and IL, respectively).

Table 1 Maternal details

	Gestational diabetes mellitus			Diabetes mellitus	
	Diet	Regular	Lispro	Regular	Lispro
Patients (*n*)	226	89	68	42	21
Age (years) mean (range)	31 (20–40)	30 (17–40)	30 (19–41)	29 (19–40)	29 (22–37)
Pregnancies (*n*)	325	138	75	70	27
Pregnancy loss (%)	0.61	0	0	18.6	3.7
HbA1c pre-delivery (mean ± SD)	6.01 ± 0.80	6.08 ± 0.68	5.8 ± 0.40	6.86 ± 0.40	6.80 ± 0.61
Caesarean section delivery (%)	23	25	32	46	60

Diet, managed by diet alone; Regular, managed using regular insulin; Lispro, managed using insulin lispro.

Table 2 Details of babies

	Gestational diabetes mellitus			Diabetes mellitus	
	Diet	Regular	Lispro	Regular	Lispro
Mean gestational age (weeks)	38.5	38.1	37.4	36.5	37.4
Birth weight (kg) (mean ± SD)	3.41 ± 0.57	3.31 ± 0.58	3.29 ± 0.57	3.26 ± 0.81	3.27 ± 1.04
Babies (*n*)	326	138	76	57	26
Hypoglycaemia (%)	13	30	17	19	20
Hyperbilirubinaemia (%)	17	17	28	23	40

Diet, managed by diet alone; Regular, managed using regular insulin; Lispro, managed using insulin lispro.

Table 3 Congenital anomalies

	Gestational diabetes mellitus			Diabetes mellitus	
	Diet	Regular	Lispro	Regular	Lispro
Pregnancies with live-birth (*n*)	323	138	75	57	26
Babies (*n*)	326	138	76	57	26
Total anomalies (%)	17 (5.2)	11 (7.9)	5 (6.6)	9 (15.8)	1 (3.8)
Major anomalies (%)	6 (1.8)	3 (2.2)	1 (1.3)	4 (7.0)	0 (0)
Minor anomalies (%)	11 (3.4)	8 (5.7)	4 (5.3)	5 (8.8)	1 (3.8)

Diet, managed by diet alone; Regular, managed using regular insulin; Lispro, managed using insulin lispro.

Diabetes mellitus

A total of 70 pregnancies with IR as short-acting insulin (69 type 1 and one type 2) and 27 pregnancies (20 type 1 and seven type 2) were identified in the study period. The baseline maternal characteristics, fetal outcomes and congenital anomalies are shown in Tables 1–3. The duration of diabetes was not different in the two groups (9.7 ± 5.38 and 9.4 ± 5.16 years in IR and IL, respectively). Sixty-five percent of pregnancies with IR and 54% with IL were seen in preconception care. The HbA1c of those seen in preconception care was not different between the groups (6.86 ± 0.46 vs. 6.83 ± 0.36), nor was the pre-delivery HbA1c. Only one patient was started on IL during pregnancy. She was seen for the first time at 14 weeks on pre-mixed insulin. The IL group required more short-acting insulin on the day before delivery (72 ± 43 vs. 54 ± 50 units, $p < 0.05$). There were 13 pregnancy losses with IR (11 early, two IUD at 25 weeks, all normal chromosomes, no anomaly) as against one early loss with IL (OR 5.9, 95%CI 0.8–26.2). There were two cases of perinatal loss (one in each group) due to septicaemia.

The four major congenital anomalies seen with IR were pulmonary stenosis, ventricular septal defect, truncus arteriosus and hydronephrosis. The minor anomalies were polydactaly, congenital dislocation of hip joints and hydrocoele (Table 3).

Table 4 Subgroup who received both regular and lispro insulin in successive pregnancies

	Regular insulin	Lispro insulin
Patients (*n*)	22	22
Age (years) mean (range)	27.5 (21–35)	30.3 (27–36)
Type 1 diabetes	3	3
Pregnancies (*n*)	23	23
Pregnancy loss weeks*	One, IUD 25 weeks, no congenital malformation*	One, miscarriage 11*
HbA1c before delivery (mean ± SD)	5.85 ± 0.78	5.84 ± 0.61
Birth weight (kg) (mean ± SD)	3.16 ± 0.78	3.24 ± 0.73
Delivery week (mean)	37.5	37.3
Congenital anomalies	One, minor	One, minor
DTSQ score (mean ± SD)	18 ± 8.9	26.3 ± 2.3**

DTSQ, Diabetes Treatment Satisfaction Questionnaire; IUD, intrauterine death. *Same mother with type 1 diabetes mellitus; **$p = 0.0005$.

The group receiving IL had no major anomaly and one minor anomaly (hydrocoele). In total, 15.8% of the IR group had congenital anomalies (7% major) as against 3.8% (none major) in the IL group. The difference in incidences did not reach statistical significance (OR 4.7, 95%CI 0.6–21.4). Thirteen of the 42 patients with type 1 DM in the IR group opted for IL after delivery, but all 21 in the IL group preferred to continue with IL.

Satisfaction survey

Twenty-two patients had 46 pregnancies (23 with IR and 23 with IL; one patient with type 1 DM had four pregnancies, two with IR and two with IL). There were no significant differences in maternal and fetal outcome or glycaemic control. The mean time difference between the last delivery and the questionnaire survey was 10 months. Nineteen patients replied (one incomplete). Patients who received IL were more satisfied (Table 4). All but three said they would prefer IL as their short-acting insulin in future pregnancies.

Discussion

Infants of women with GDM and type 1 and 2 diabetes mellitus have an increased risk of macrosomia, hypoglycaemia and hyperbilirubinaemia.[15–18] The major issue, however, is increased risk of congenital anomalies. In pregnancies in patients with diabetes mellitus, congenital anomalies have been reported to be 5.2–16.8%, compared to 1.2–3.7% in infants of non-diabetic mothers.[15,16,19] The incidence of congenital anomalies is also increased in GDM, although to a lesser extent.[16] Pre-conception control and good glycaemia during pregnancy along with proper supervision are the keys to success; however, the risk remains high in well-controlled patients.[16,20] With the improvement of pre-, ante- and postnatal care, an improvement in outcome is expected. The St. Vincent declaration of 1989 set as a 5-year target the reduction of adverse pregnancy outcomes among insulin-dependent DM patients to the same level as in non-diabetic women.[21] Unfortunately, we have yet to achieve this result, mainly because of the incidence of congenital anomalies.[15]

The controversy as to whether IL increases the risk of congenital anomalies began, we believe, when two cases of major congenital anomalies were reported in infants of diabetic mothers from Australia.[11] In controlled clinical trials involving more than 2000 patients treated with IL, pregnant women were excluded. Nineteen live births occurred as a result of unplanned pregnancies and one infant had an abnormality (a right dysplastic kidney).[7,22]

Data on IL use during pregnancy are limited,[23–26] particularly evaluations of outcome compared with other types of insulin. The available literature does not suggest an increase in congenital anomalies, but does suggest improvement of glycaemic control and patient satisfaction.[24,27] In our survey, with a reasonable number of pregnancies managed with IL and IR, pregnancy loss and congenital anomalies were seen more with IR, although this did not reach statistical significance. Glycaemic control did not vary with type of insulin used in type 1 and 2 DM, but did improve in GDM managed with IL. However, most patients who used both IL and regular insulin were more satisfied with IL, and 83% said they would prefer IL in subsequent pregnancies.

Recently, Kitzmiller *et al.*[28] reported on three patients with no diabetic retinopathy at the first

ophthalmoscopic examination during pregnancy who were started on IL in the first trimester of gestation. Bilateral proliferative retinopathy was treated in the third trimester for marked visual impairment, and in two cases there was vitreous haemorrhage. Our observation of using IL in pregnancy and regular insulin in type 1 DM did not support their hypothesis that type of insulin is related to the worsening of retinopathy.[29] Reassuringly, a recent study has shown that IL is not detectable in the cord blood.[30]

In summary, no human or animal insulin has been indicated specifically by the Food and Drug Administration for pregnant women with diabetes mellitus, neither is there any mention in the British National Formulary. We observed no increase in adverse fetal or maternal outcomes with the use of IL. IL is viewed as more satisfactory by the patients. The possibility that outcome may be improved with IL needs further evaluation.

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