Original Article

Efficacy of insulin lispro in improving glycemic control in gestational diabetes

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ABSTRACT

Aim: To assess the safety and efficacy of insulin lispro in improving glycemic control in patients with gestational diabetes. **Materials and Methods:** A retrospective observational study was conducted at a single center on 201 gestational women with diabetes. Subjects who received insulin lispro performed blood glucose self-monitoring and recorded the readings in the fasting state and 1 h after each meal. At each contact (in person or telephonic contact), the insulin dose was adjusted based on the readings measured. A total of 53 subjects also recorded glucose levels post-partum. Pregnancy and post-delivery glucose level and insulin requirements of these 53 patients were compared. **Results:** Analysis of glucose levels both fasting and post-prandial glucose levels revealed that after using insulin lispro, the number of episodes of post-prandial hyperglycemia (1 h plasma glucose >120 mg/dL) was minimal and so was the incidence of hypoglycemia. Hypoglycemia was defined as a blood sugar value of. There was neither any congenital abnormality except for a poorly formed pinna in the right ear of one baby nor any post-partum complications of note. **Conclusion:** Insulin lispro is an effective and safe treatment option in gestational diabetes.

Key words: Efficacy, gestational diabetes, hyperglycemia, hypoglycemia, insulin iispro, macrosomia

INTRODUCTION

Gestational diabetes mellitus (GDM) can be defined as an impaired carbohydrate metabolism observed for the first time in pregnant woman irrespective of insulin or diet modification required.[1] Globally, the prevalence of GDM has been increasing rapidly at a rate proportionate to type-2 diabetes. According to "Diabetes in Pregnancy Study Group India (DIPSI)," the prevalence rate of GDM in Indian population was found to be about 3.8-21% depending on the geographic location and methods applied during diagnosis.[2]

Autoimmune beta-cell dysfunction, genetic abnormalities, and chronic insulin resistance are the etiological factors contributing to gestational diabetes. Hyperglycemia during pregnancy is associated with both fetal and maternal complications. Some of the fetal complications include increased incidence of macrosomia, perinatal mortality, congenital anomalies, neonatal hypoglycemia, respiratory distress, and polycythemia. Glucose intolerance and obesity are the long-term complications observed in offspring of gestational diabetic women.[3]

Women with gestational diabetes are at an increased risk of type 2 diabetes with a conversion rate of approximately 3% per year. Other maternal complications include cesarean delivery, hypertension, and preeclampsia.[4,5] Neonatal hypoglycemia observed post-delivery is an outcome of fetal hyperinsulinemia resulted due to maternal hyperglycemia.[6]Thus, these complications during and after pregnancy demand the strict glycemic control as near as possible to normal, without frequent hypoglycemia during pregnancy. However, it is challenging for clinicians to achieve tight glycemic control and improve pregnancy outcomes.

Insulin lispro is a rapidly absorbed insulin analogue that reduces post-prandial hyperglycemia and nocturnal

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hypoglycemia when compared with regular human insulin and could be used to improve glycemic control in pregnant women with diabetes. Studies in pregnant women confirm these facts and show that these analogues are safe during pregnancy.[7-9]However, it may be appropriate to mention at this point of time that there is no Indian data on the usage of lispro in pregnancy.

In the present retrospective observational study, we analyzed the efficacy of insulin lispro for glycemic control and to find out the risk of hypoglycemia and macrosomia in women with gestational diabetes in South Indian population.

Materials and Methods

This study was performed on 201 South Indian gestational diabetic women. Subjects with any degree of glucose intolerance at any gestational age (from start to end of the gestation period) who failed to achieve adequate glucose control with diet and exercise were enrolled into the study. Subjects were given a 2-week trial for lifestyle modification before inclusion into the trial. Nutrition recommendations followed the Recommended Daily Allowance/American Diabetes Association (ADA) guidelines on dietary principles in the management of gestational diabetes. Exercise included regular household chores and daily stroll in the neighborhood/garden. The diagnosis is generally based on an abnormal oral glucose tolerance test (OGTT). An OGTT requires women to fast overnight before attending the hospital for the test the following morning. Usually, two blood samples are taken. Gestational diabetes is determined according to the following values.

Fasting plasma glucose values greater than 105 mg/dL; 1 h post-prandial glucose values greater than 190 mg/dL; 2 h post-prandial glucose values greater than 165 mg/dL; 3 h post-prandial glucose values greater than 145 mg/dL. Kindly note that the study was performed prior to the DIPSI guidelines being published. Therefore, we subjected the women to OGTT and used the ADA criteria for diagnosis of gestational diabetes. Patients who received prior treatment with insulin, who had pre-gestational diabetes with concurrent vascular damage were excluded from the study.

Insulin lispro was given to subjects enrolled in to the study with glucose intolerance not responding to medical nutrition therapy and physical activity, at any gestational age. The dose of insulin was determined by the principal investigator according the fasting and post-prandial values. The subjects were informed to perform self-monitoring of blood glucose and record the readings in the fasting state and after each meal from the time of entry into the study to post-partum. The subjects were advised to visit the study center once a week with the recorded readings (fasting, 1 h post-breakfast, post-lunch, post-dinner, and post-meal). Insulin dose was adjusted in patients who failed to obtain 1 h post-prandial standard blood glucose concentration of 120 mg/dL. Patients were instructed to administer insulin lispro before each meal. Neutral protamine hagedorn (NPH) insulin was given only if the fasting plasma glucose was above 95 mg/dL.

Hypoglycemia was defined as a blood glucose measurement ≤60 mg/dL. The subjects were expected to report any episode of hypoglycemia immediately for further insulin dosage alterations. Frequency of hypoglycemic episodes was assessed at each weekly visit as recorded by a patient in her diary. Well-being of the fetus was monitored throughout the study with ultrasonography and fetal non-stress tests; these were performed at the discretion of the obstetric team. SAS software version 9.1.3 was used for statistical analysis. Mean and standard deviation were calculated for continuous variables, and number and percentage were reported for categorical variables. A $P < 0.05$ was considered significant.

Fasting and post-prandial (post-breakfast, post-lunch, post-dinner, and post-meal) glucose values, frequency of hypoglycemic episodes, and percentage of hypoglycemic patients were measured. Adverse fetal outcomes like percentage of congenital anomalies, neonatal hypoglycemia, and birth weight of the neonates were analyzed. Neonatal glucose was measured by the obstetric team by cord blood estimation at birth and thereafter at regular intervals until normoglycemia was restored under the supervision of the neonatologist. The neonates were treated with intravenous dextrose (if indicated), and initiated to early breastfeeding. Post-partum blood glucose was included wherever available.

Results

Demographic data
The mean age of the subjects ($n = 201$) was 29.22 years, minimum age was 18 years and the maximum age 41 years. The mean pre-pregnancy weight was 62 kg ($n = 161$), with a minimum of 37 kg and maximum of 95 kg. The mean height was 155 cm ($n = 200$), with a minimum of 140 cm and maximum of 179 cm. A total of 77.1% subjects were found to have a positive family history of diabetes and 26.6% subjects had a previous history of gestational diabetes. Table 1 summarizes the demographic details at the time of entry in to the study.

Mean glucose and insulin values

The mean value of fasting blood glucose at the time of entry into the study was 99.01 mg/dL. The entry level post-breakfast values were 126.9 ± 44.2 mg/dL and at delivery, 106.5 ± 18.8 mg/dL; post-lunch entry level glucose was 125.5 ± 38.3 mg/dL and at delivery was 111 ± 18.4 mg/dL, whereas post-dinner values at entry were 127.2 ± 38.6 mg/dL and at delivery was 111.8 ± 19.5 mg/dL.

GDM mothers were instructed to monitor the capillary blood glucose at home and inform us on a daily basis with at least four point estimations, that is, fasting plasma glucose and three post-meal values taken 1 h after consuming the meal. Once a satisfactory level of approximately 120 mg/dL was achieved; thereafter, the mother monitored their glucose at least 2 times each week (four point blood sugar estimations) and reported the same to us via e-mail, fax, or through telephonic contact. The dosage adjustment was done by the physician and the same was conveyed to the subjects. Additional estimations were done when the patient felt symptoms of hypoglycemia or at physician's discretion. There were at least two visits in a month: One to the obstetric team and one to the diabetes clinic.

The initial insulin lispro requirements were 9.3 ± 5.7, 7.8 ± 6.7, and 8.3 ± 4.7 units given just before breakfast, lunch, and dinner. For women with pre-gestational diabetes, the initial dose of NPH insulin was 8.5 ± 7.3 units. Around delivery, the insulin doses (lispro) had increased to 32 ± 19.4 units, 27.2 ± 18.4, and 28.3 ± 17.3 before breakfast, lunch, and dinner in that order. The NPH dose around delivery was 19 ± 15.1 units. The mean values of insulin dose (u/mL) at pre-breakfast, post-breakfast, pre-lunch, post-lunch, pre-dinner, and post-dinner at entry time and at delivery time are provided in Table 2. The mean glucose values at fasting and post-meal were 85.7 and 116.5 mg/dL. These levels were significant ($P < 0.0001$).The mean glucose value of post-breakfast was 116.2 ± 17.9 and post-lunch was 115.9 dinner level was 117.5 units.HbA1c was not measured in any of these patients.

Blood sugar, OGTT, and insulin values

The number of hypoglycemic episodes was nine in exactly four patients. All the episodes were minor and the subjects did not require any assistance for recovery from hypoglycemia. All episodes of hypoglycemia were in conformation of the Whipple's triad. Each subject on an average performed about 200 self-monitoring blood glucose and reported the same to the center either via telephonic contact, e-mail, sms, or fax.

Maternal complications (antenatal)

Urinary tract infection was noticed in 2.2% of the gestations. Candidiasis was not reported, however. No account of eclampsia or candidiasis was found in these subjects.No cases of eclampsia were noted since the obstetric team managed pregnancy induced hypertension (PIH) using α methyldopa. Blood pressure was maintained <130/80 mm Hg.

Mode of delivery

A total of49.4% of the deliveries were normal deliveries. Caesarean section delivery was done in 50.6% [Table 3]. The mode of delivery was left to the discretion of the obstetric team. In most cases the mothers had opted for C-section, while fetal distress was not a major cause for C-section; since most of the pregnancies were precious pregnancies all registered for antenatal checkup at fertility centers and those who conceived after a treatment for infertility opted voluntarily for C-section. The pregnancies were all delivered at a mean gestational age of 37 weeks.No cases of eclampsia were reported.

Neonatal outcomes

The mean gestational age of the subjects at the time of delivery was 36.7 ± 4.9 weeks and the mean birth weight

Table 1: Demographic details at the time of entry in to the study

Variable	Values
Age (years), median (range) (*n*=201)	29 (18-41)
Family history positive for diabetes (%) (*n*=201)	77.1
Pre-pregnancy weight (kg), median (range) (*n*=161)	62 (37-95)
Height (cm), median (range) (*n*=200)	155 (140-179)
Previous positive GDM (%) (*n*=195)	26.6
Parity median (range) (*n*=198)	2 (0-6)
Week of gestation at diagnosis (weeks), median (range) (*n*=190)	21.75 (4-38)

GDM: Gestational diabetes mellitus

Table 2: Insulin values

Insulin dose (U/mL)	At entry	At delivery
Pre-breakfast	9.36±5.77	32.03±19.43
Post-breakfast	126.90±44.26	106.51±18.8
Pre-lunch	7.81±6.71	27.24±18.44
Post-lunch	125.56±38.35	110.09±18.42
Pre-dinner	8.36±4.71	28.36±17.37
Post-dinner	127.29±38.68	111.87±19.55
Night NPH dose	8.51±7.30	19.06±15.16

NPH: Neutral protamine hagedorn

Table 3: Labor details

Outcome	Values
Complications at delivery (%) (*n*=174)	
Eclampsia	0
Cesarean section delivery	50.6
UTI	2.2
Candidiasis	0
Post-partum OGTT (mg/dL) (mean±SD) (*n*=45)	
Fasting	105.35±40.21
1 h	171.25±66.29
2 h	150.72±80.25

UTI: Urinary tract infection, OGTT: Oral glucose tolerance test, SD: Standard deviation

of the children was 2.98 ± 0.41 kg [Table 4]. The birth weight data were available for only 172 new born infants, of which 22 were with a birth weight >3.5 kg, that is, macrocosmic (or LGA or large for gestational age) and 19 were <2.5 or LBW (low birth weight) or SGA (small for gestational age). Percentage of hypoglycemia was 1.1 and congenital anomalies were 0.5%. None of the babies were >4 kg. The only congenital anomaly noted was a poorly formed pinna in the right ear.

Post-partum OGTT

OGTT was performed only in 45 subjects whose fasting plasma glucose was 105.35 ± 40.21, while 1 and 2 h post-glucose recorded as 171.25 ± 66.29 and 150.72 ± 80.25 [Table 3]. Only those who had pre-gestational diabetes continued to take therapy for the same with their local general practitioner's, while all the GDM mothers were lost in follow-up. This was in spite of repeated reminders made by diabetic team that diabetes prevention is possible.

DISCUSSION

Infants of diabetic mothers are at an increased risk of macrosomia, hypoglycemia, hyperglycemia, and hyperbilirubinemia compared to non-diabetic mothers. Recent advances substantiate that poor maternal glycemic control during pregnancy is associated with risk of maternal and fetal complications.

Macrosomia is defined as a birth weight higher than 4.0 kg. If capillary glucose was under 3.3mmol/L (<60 mg/dL), and the patient could manage symptoms herself, the episode was considered mild hypoglycemia. Results have clearly proved that glucose control levels, hypoglycemia, birth weight of infants, and macrosomia of subjects on insulin lispro are very much similar to the subjects on human insulin.[10]The results of this study are consistent with findings seen in previous studies by, Seshiah *et al*.[7] Jovanovic *et al*.[8] and Meccaci *et al*.[11] The present study also shows that the plasma glucose levels of subjects on insulin lispro were similar within normal limits but with a lower risk of hypoglycemia.

The risk of macrosomia is closely related to 1 h post-prandial glucose concentration.[12] Several studies have showed

Table 4: Neonatal outcomes	
Variable	Values
Gestational age at delivery (weeks), (Mean±SD)	37.11±3.25
Birth weight (kg) (Mean±SD) (*n*=172)	2.98±0.50
No. of babies with a birth weight>3.5 kg (*n*=172)	22
No. of babies with a birth weight<2.5 kg (*n*=172)*	19
Hypoglycemia (%) (*n*=172)	1.1
Congenital anomalies (%) (*n*=172)	0.5

SD: Standard deviation

that peak glucose concentration occurs 1 h after eating. Regular human insulin does not control the post-prandial at 1 h as effectively as rapid acting analogs. Moreover, the risk of post-meal hypoglycemia is noticed in patients on regular human insulin; this is not seen in patients using rapid acting insulin analogs. This is due to the varying kinetics between the two types of insulin. Prompt acting analogues achieve higher peak insulin levels in lesser time and with a shorter duration of action than HI when they are given 5 min before a meal.[13,14] Insulin therapy is required whenever strict normal glycemia cannot be achieved by medical and nutritional therapy alone. Insulin lispro with its short-acting pharmacokinetic property could be more efficient in pregnancy than regular human insulin.[7,15] As rapid acting lispro was found to be safe and effective in achieving the targeted post-prandial glucose value during pregnancy, US Food and Drug Administration approved lispro analogue for the treatment of gestational diabetes in pregnant women.[2]

The first randomized study that evaluated the effect of insulin lispro treatment in pregnancy was conducted by Jovanovic *et al*.[8] in which they evaluated 19 GDM patients on insulin lispro and 23 on regular insulin. The number of pre-breakfast maternal hypoglycemic episodes was lesser in patients on lispro than in patients on regular insulin. The percentage of post-prandial hyperglycemia episodes was significantly lesser with less amount of hypoglycemia[7] in patients on insulin lispro than those in patients on regular insulin. Moreover, when compared the treatment of insulin lispro with that of regular insulin, lispro caused an appreciable reduction in HbA1c levels at the third trimester. Evaluated insulin lispro insulin in pregnancy and concluded that risk differences for malformations or unusual pregnancy courses were not higher in the insulin lispro group compared to the controls. Rapid absorption of insulin lispro from subcutaneous site allows for a faster peak insulin concentration than is found with regular human insulin.[16,17]

According to Ilic *et al*. patients on insulin lispro reported greater compliance and satisfaction with this therapy than those on regular insulin.[18] Mecacci *et al*. compared maternal glucose levels and neonatal outcome in 49 GDM women randomly assigned to treatment with regular insulin (*n* = 24) or insulin lispro (*n* = 25).[11] Blood glucose values 1 h post-prandial were significantly lower in patients on insulin lispro than in those on regular insulin. Pregnant woman with plasma glucose 120-139 mg/dL required follow-up after 1 h as 2 h plasma glucose >140 mg/dL resulted in short- and long-term morbidity of the off springs.[12,19,20]

Furthermore, it was noted that 19 women has a birth weight of <2.5 kg. This was not due to overcorrection of

glycemia rather it reflected the problems that are noted with initiation of insulin therapy. The pregnant mother continues to reduce her intake of food due to rising dose of insulin and the traditional thinking that "diabetic diet is equal to starvation" needs to be corrected.

It is quite painful to note that the number of subjects who returned for an OGTT either at the diabetes clinic or the obstetric center was abysmally low. This was in spite of reminders to them all throughout their gestation, that future type 2 diabetes is preventable. All it requires is lifestyle modification. A combined effort by all clinicians and more awareness is required to spread the message of diabetes prevention since a long latent period exists before women with GDM turn into overt type 2 diabetes.

Post-partum details of number of subjects differed with number of subjects enrolled in to the study. The other limitations of the study are that it was a single center trial and there was no control arm. In conclusion, the results of this retrospective study proved the efficacy, safety, and tolerability of insulin lispro in gestational diabetic pregnant women, which showed that there is no risk of abnormality or strange course of pregnancy with the treatment of fast-acting insulin analogue, insulin lispro.

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