Original Article

Insulin aspart in patients with gestational diabetes mellitus and pregestational diabetes mellitus

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ABSTRACT

Aims: This study was undertaken to assess the effectiveness and safety of insulin aspart in patients with gestational and pregestational diabetes. **Settings and Design:** An open-label, prospective, nonrandomized, comparative, and observational study conducted at single center in India. **Subjects and Methods:** A total of 276 patients were in gestational diabetes mellitus (GDM) group, 79 were in the pre-GDM group. Patients were started on insulin therapy (insulin aspart ± neutral protamine hagedorn) once medical nutrition therapy for 2 weeks failed to achieve control, that is., fasting plasma glucose ≥90 mg/dL and/or 1.0 h postprandial plasma glucose ≥130 mg/dL. Insulin dose was titrated to keep the blood glucose values between 90 and 130 mg/dL. Patients were followed once every 4 weeks until the 28th week, then once every 2 weeks until 32nd week, then once every week until delivery, and the final visit was on 60 ± 7 days. The final outcome was assessed in terms of incidence of macrosomia (>3.5 kg body weight) between the two groups and episodes of confirmed (blood glucose <56 mg/dL) minor or major maternal hypoglycemia. **Results:** There was no statistically significant difference among the two groups in terms of incidence of macrosomia that is., it was 5.1%, 8.9% in GDM, pre-GDM group, respectively. **Conclusions:** Insulin aspart was found safe in pregnancy, however, more studies with double-blind, standard controlled studies are required to confirm the findings of this study.

Key words: Gestational diabetes mellitus, insulin aspart, pregestational diabetes mellitus

Introduction

Gestational diabetes mellitus (GDM) is defined as carbohydrate intolerance of varying degrees of severity with onset or first recognition during pregnancy.[1] Indian women have 11-fold increased risk of developing glucose intolerance during pregnancy compared to Caucasians.[2] The prevalence of GDM in India as per the WHO criteria of 2 h postprandial plasma glucose (PPG) ≥140 mg/dL is 16.55%.[3] GDM is responsible for 3–5% of complications of all births and is one of the most common complications of pregnancy.[4] Pregestational diabetes constitutes ~ 10% of cases of maternal diabetes with prevalence rates of 0.1–0.3% of all pregnancies. These pre-GDM and GDM pregnancies are at risk for both maternal and fetal complications in terms of spontaneous abortions, congenital malformations, macrosomia, maternal hypoglycemia, and increased perinatal mortality. The risk of macrosomia and/or disproportionate fetal growth is closely related to 1-h postprandial glucose concentration.[5]

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Access this article online	
Quick Response Code:	Website: www.ijem.in
	DOI: 10.4103/2230-8210.163202

Cite this article as: Deepaklal MC, Joseph K, Rekha K, Nandita T. Insulin aspart in patients with gestational diabetes mellitus and pregestational diabetes mellitus. Indian J Endocr Metab 2015;19:658-62.

Prevalence rates reported from medical centers for infants that are large-for-gestational-age (LGA, >90th percentile weight for age) in pregestational diabetic pregnancies have been in the range of 29–33% during the past decade.[6-8] The most common and significant neonatal complication associated with GDM is macrosomia[9] which occurs at rates as high as 40% of neonates in untreated GDM.[10]

As fetal macrosomia is the main complication of GDM and pre-GDM pregnancies, we did this observational study to see the effect of achieving targeted glycemic control (fasting plasma glucose [FPG] <90 mg/dL and/or 1.0 h PPG <130 mg/dL) by treating GDM and pre-GDM patients with insulin aspart with or without neutral protamine hagedorn (NPH) on incidence of fetal macrosomia. We also observed the treatment outcomes in terms of incidence of preterm deliveries, percentage of patients undergoing caesarean sections (CSs). This is an open-label, prospective, nonrandomized, comparative, observational study analyzed the effectiveness and safety of insulin aspart in Indian female patients with gestational and pregestational diabetes.

Subjects and Methods

Single center, open-label, prospective, nonrandomized, comparative, and observational study, conducted in GDM, and pre-GDM patients. Institutional ethics committee approval has been obtained for this study.

The mean age of females was 28.69 ± 4.34 in GDM group, 30.14 ± 5.20 in the pre-GDM group. For this study, uncontrolled glycaemia was defined by the following criteria: FPG ≥90 mg/dL and/or 1.0 h PPG ≥130 mg/dL. The above criteria were based on diabetes in pregnancy study group India guidelines.

A total of 276 patients were selected based on the inclusion criteria in GDM group and 79 patients in the pre-GDM group. The average duration of diagnosis of pre-GDM was 4 years, which was prior to pregnancy. The study was duration based and diagnosis of GDM and pre-GDM carried out by oral glucose tolerance test as per Indian guidelines.[10] The prior mean value of HbA1c in pre-GDM subjects was 6.5%. None of the subjects had preexisting hypertension or PIH in this study. The inclusion criteria included GDM patients being treated with insulin aspart with or without NPH/or metformin; GDM patients on other rapid/short-acting insulins other than aspart and patients on Oral anti-diabetic drugs other than metformin were excluded from the study. The study was conducted with the primary objective to assess the frequency of macrosomia (>3.5 kg body weight) in GDM patients and pre-GDM patients. Other parameters that were assessed in the study were the mode of delivery, the percentage of patients undergoing CSs, mean insulin aspart dose at breakfast, lunch, dinner in GDM and pre-GDM group. Insulin aspart was given subcutaneously just before the meals in divided dose in accordance to postmeal surges with regular dose titration to maintain target FPG between 80 and 90 mg/dL, PPG between 100 and 130 mg/dL. Seshiah reported that for maintaining mean plasma glucose level ~105–110 mg/dL is desirable for a good fetal outcome. This is possible if FPG and 2-h postprandial peaks are ~90 mg/dL and ~120 mg/dL, respectively.[11] Use of other insulin, e.g. NPH insulin to control fetal blood sampling was based on clinical judgment and the requirement of each individual case. The diabetes educator used to teach the patients best practice of self-monitoring of glucose and self-injection technique. The minimum requirement was to do no <8–10 readings/week and report them. The patients received access online and/or through a tele-helpline for dosage adjustments of insulin.

Patients were monitored on regular basis with planned once every 4 weeks until the 28th week, then once every 2 weeks until 32nd week, then once every week until delivery and the final visit was on 60 ± 7 days after delivery. The number of visits depended on the date when insulin aspart was initiated and there were other unplanned visits if required. The hypoglycemic episodes observed by the investigator, reported by the patient or found from the blood glucose values or other laboratory values were to be documented by the investigator.

Statistical analysis

These results were expressed as number and percentages. Student's *t*-test, Chi-square test for proportions were used for comparing GDM, prepregnancy DM. $P < 0.05$ were considered to be significant.

Results

Demographic profile

The data from 276 patients with GDM, 79 patients with pre-GDM were analyzed in this study. Table 1 summarizes demographic profile of all group subjects.

The Table 1 reveals that age of the cases were ranging from 18.00 to 45.00 years with average being 28.69 ± 04.34 years among GDM, which was significantly less as compared to 30.14 ± 05.20 years among pre-GDM. The weight of the cases was ranging from 40.00 to 104.00 kg with average being 66.28 kg among GDM, which was comparable to 66.53 kg among pre-GDM and the difference was not statistically significant. Height of the cases was ranging

from 139.00 to 176.00 cm with average being 156.11 cm among GDM, which was comparable to 156.26 cm among pre-GDM and the difference was not significant.

The incidence of macrosomia was analyzed as less 5.1% (n = 14) of cases among GDM (n = 276) with birth weight >3.5 kg as compared to 8.9% (n = 7) of the cases among pre-GDM (n = 79). However, the difference was insignificant.

The data of the family history of diabetes was clearly evident that 82.3% of cases had a 1st degree family history in the pre-GDM group and 64.1% in GDM. The figures of bad obstetric history in different groups state that previous history of abortions was present in 30.08% of GDM and 29.1% of pre-GDM patients.

The normal mode of delivery was observed 46.7% of the cases among GDM, which was comparable to 50.6% of the cases among pre-GDM and the difference was not significant. No death was reported in both groups.

Table 2 shows that gestational age at the time of delivery in all groups. According to above Table 1, 47.1% of the cases among GDM had ≤36 weeks gestation that was comparable to 50.6% of the cases among pre-GDM and the difference was not significant.

Table 3 indicates the mean insulin aspart dose used in GDM and pre-GDM patients at breakfast, lunch and dinner. At breakfast, above analysis reveals that mean insulin dose used at Enrolment period was 6.82 ± 04.51 among GDM which was significantly less as compared to 11.48 ± 07.20 among pre-GDM. At Term, mean insulin dose showed a significant rise of 2.18 times among GDM and 2.24 times among pre-GDM from Enrolment. If compared, the rise was significantly more among pre-GDM than GDM. At lunch, mean insulin dose employed at Enrolment was 6.36 ± 04.03 among GDM, which was significantly less as compared to 11.12 ± 07.16 among pre-GDM. At Term, mean insulin dose indicated a significant rise of 1.63 times among GDM and 1.04 times among pre-GDM from Enrolment. If compared, the rise was comparable to both the groups and the difference was not significant.

At dinner, mean insulin dose used at enrolment was 6.41 ± 04.05 among GDM which was significantly less as compared to 10.84 ± 06.72 among pre-GDM. At term, mean insulin dose showed a significant rise of 1.09 times among GDM and 1.34 times among pre-GDM from Enrolment. If compared, the rise was significantly more among pre-GDM than GDM. Two patients in GDM group had reported minor episodes of hypoglycemia (BG <70 mg/dL) while no episode of hypoglycemia was reported in the pre-GDM group.

Table 1: Demographic profile

Parameters	GDM	Pre-GDM	*P*
Number of cases	*n*=276	*n*=079	
Age (years)	*n*=275	*n*=077	
Mean±SD	28.69±04.34	30.14±05.20	0.025*
Range	18.00-45.00	20.00-43.00	
Weight (kg)	*n*=252	*n*=074	
Mean±SD	66.28±11.88	66.53±11.72	0.872 NS
Range	040.00-104.00	040.00-101.00	
Height (cm)	*n*=274	*n*=077	0.833 NS
Mean±SD	156.11±005.77	156.26±005.45	
Range	139.00-176.00	147.00-167.00	

*GDM compared with pre-GDM. By student's *t*-test. NS: Not significant, GDM: Gestational diabetes mellitus, SD: Standard deviation

Table 2: Gestational age at the time of delivery in all groups

Parameters	GDM (*n*=276) *n* (%)	Pre-GDM (*n*=79) *n* (%)	*P*
Preterm (≤36 weeks gestation)	130 (47.1)	40 (50.6)	0.579 NS
Term (≥37-40 weeks gestation)	146 (52.9)	39 (49.4)	

By Chi-square test. NS: Not significant, GDM: Gestational diabetes mellitus

Table 3: Mean insulin aspart dose used in GDM and pre-GDM patients at breakfast, lunch, and dinner

Period	Enrolment	Term	Mean change (*P*)
At breakfast			
Mean dose (x̄±SD)			
GDM (*n*=233)	06.82±04.51	21.73±17.89	14.91±17.43 (0.001)*
Pre-GDM (*n*=69)	11.48±07.20	37.30±24.24	25.82±23.01 (0.001)*
P	0.001*		0.001*
At lunch			
Mean dose (x̄±SD)			
GDM (*n*=230)	06.36±04.03	16.77±13.83	10.41±13.20 (0.001)*
Pre-GDM (*n*=68)	11.12±07.16	22.79±15.32	11.67±14.59 (0.001)*
P	0.001*		0.523 (NS)
At dinner			
Mean dose (x̄±SD)			
GDM (*n*=231)	06.41±04.05	13.41±10.97	7.00±10.13 (0.001)*
Pre-GDM (*n*=69)	10.84±06.72	25.39±19.59	14.55±16.95 (0.001)*
P	0.001*		0.001*

*Significant. Student's *t*-test. NS: Not significant, GDM: Gestational diabetes mellitus, SD: Standard deviation

Discussion

In this study, insulin aspart with or without NPH maintained targeted glycemic control with FPG <90 mg/dL and/or 1.0 h PPG <130 mg/dL). This in turn resulted in a lesser incidence of macrosomia in both GDM and pre-GDM groups. In this study, birth weight of babies >3.5 kg was found in 5.1% of GDM group, 8.9% pre-GDM. There was no statistically significant difference between two groups. Balaji *et al*. mentioned birth weight >3.45 kg was considered as macrosomia in Indian population. The

possibility of macrosomia is closely related to 1 h post-PPG concentration.[12] Several studies have showed that peak glucose concentration occurs 1 h after eating.[3,5,10] Ju *et al*. reported incidence of macrosomia 6.5%[13] in GDM group, while in a study by Di Cianni *et al*. macrosomia was seen in 15.6% of human insulin group, 12.1% in insulin lispro group and 9.6% in insulin aspart group and data did not reach statistical significance.[14] The incidence of macrosomia was 12.7% in a study conducted in South India with GDM patient treated with insulin lispro.[15] The reported incidence of macrosomia in pre-GDM women was 5.2–8.9% in Asian Americans by National Centre for health statistics.[16] The present study reports that much lesser incidence of macrosomia compared to historical data. In this study, only the macrosomia was studied as a fetal outcome measure with both the pre-GDM and GDM subjects and the incidence of the same was 8.9% and 5.1% respectively. In this study, 76.1% patients in GDM group, 84.8% patients in the pre-GDM group had a family history of diabetes. Out of which 64.1% in GDM, 82.3% in pre-GDM had a positive history in first-degree relatives. One study conducted by Bhat *et al*. in South India reports that 37.3% patients with GDM and 12% patients in control group had family history of diabetes in first-degree relatives which is much less than reported in our study. This number in our study is definitely alarming and gives a signal that in India screening for GDM should be made mandatory for all pregnant females first antenatal visit and also between 24 and 28 weeks of gestation.[17]

The history of abortions was present in 30.08% of GDM and 29.1% of pre-GDM patients. The intra-partum maternal complications included CSs, 53.3% patients in GDM group, 49.4% in pre-GDM group underwent CSs. Wherein CS rates were comparable in GDM, pre-GDM group, and there was no significant difference was found between groups. One study by El Mallah *et al*. reported the CS rates of 17% in both GDM and pre-GDM group.[18] Although this is double the CS rate in the rest of our obstetric population, it is still lower than most of the published CS rates, which usually fall between 20 and 60%.[19,20]

In this study, 47.1% patients in GDM group and 50.6% patients in pre-GDM group had preterm deliveries out of which 46% and 49.4% were in 33–36 weeks of gestation in GDM and pre-GDM groups respectively. In GDM group 52.9% patients and 49.4% patients in pre-GDM had term deliveries in 37–40 weeks of gestation.

Mimouni *et al*.[21] reported an incidence of 31.1% for spontaneous premature labor in insulin-dependent, diabetic pregnancies. Though the number of patients undergoing preterm deliveries was much higher in this study compared to historical data but majority of them were in range of 33–36 weeks, did not result in any fetal complication and had no correlation with incidence of macrosomia.

The dose of insulin aspart at the enrolment was significantly less in GDM group as compared to the pre-GDM and at the end of the term mean insulin aspart dose showed a significant increase in both the groups. Furthermore, breakfast and dinner insulin requirements at term were significantly higher in pre-GDM group than GDM group to maintain the targeted blood glucose levels. The mean rise in the requirement of insulin dose in both the pre-GDM and GDM groups was 25.82 ± 23.01 and 14.91 ± 17.43 for breakfast, 11.67 ± 14.59 and 10.41 ± 13.20 for lunch, 14.55 ± 16.95 and 7.00 ± 10.13 for dinner respectively.

Insulin aspart was found to be safe as there was no episode of minor or major hypoglycemia reported in this study and this finding is in line with other studies done with insulin aspart like Pettitt *et al*.[22] and Di Cianni *et al*.[14]

The study has several limitations like sample size was not statistically calculated; lab investigations were done as per routine clinical practice, and patient's sonography findings were not taken into the analysis. This study did not have a comparator arm, although a comparator arm would have benefitted to the analysis element. Calculation of sample size was not assumed, as this was duration based study. The present study provides additional data to support the scientific basis of clinical effects of insulin aspart in GDM and pre-GDM subjects especially in South Indian population.

Conclusion

The results of this study indicates that Insulin aspart was safe in pregnancy, however, more studies with double-blind, standard controlled studies are required to confirm the findings of this study. The results show that by achieving targeted glycemic control of FPG <90 mg/dL and/or 1.0 h PPG <130 mg/dL by insulin aspart ± NPH in GDM and pre-GDM cases improves the perinatal outcomes in terms of reducing the incidence of macrosomia, preterm and postterm deliveries and complicated mode of deliveries. As the history of diabetes in first-degree relatives is commonly seen in most of GDM, pre-GDM cases the importance of screening for all pregnant women becomes utmost important and it should be made mandatory in first trimester itself. This study also shows the incidence of maternal and fetal complications in GDM is similar to pre-GDM patients. Both GDM and pre-GDM pregnancies, therefore, should be monitored and managed identically.

Although the study had its own limitations, however, this real life data shows the role of insulin aspart in achieving targeted glycemic control for improving clinical outcomes in GDM and pre-GDM patients.

Financial support and sponsorship
Nil.

Conflicts of interest
There are no conflicts of interest.

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