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A Comparison of the Efficacy of Insulin Aspart and Regular Insulin for Managing Gestational Diabetes and their Effects on Delivery Outcomes

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ABSTRACT

Background & aim: Rapid-acting insulin analogs, such as insulin aspart, are used in type 1 and type 2 diabetes in pregnancy, and are approved for using in gestational diabetes mellitus (GDM). Nevertheless, there is a dearth of studies to compare their effectiveness with regular insulin. This study, therefore, compared the efficacy of aspart (NovoRapid) and regular insulin in managing GDM and their effects on delivery outcomes.

Methods: This retrospective record review was conducted on 150 pregnant women with GDM who were admitted to Shohada Tajrish Hospital, Tehran, Iran and managed with either insulin aspart or regular insulin (75 patients in each group). The primary outcomes were insulin dose, hypoglycemic episodes, length of hospitalization at the initiation of insulin therapy, length of insulin therapy, and rehospitalization frequency. The secondary outcomes were delivery type and neonatal outcomes. Data was extracted from patients' medical records and analysed using Chi-square, Fisher's exact test, t-test, and Mann-Whitney U test.

Results: Insulin dose and frequency of hypoglycemic episodes during the first hospitalization for the initiation of insulin therapy were significantly lower in the insulin aspart group. Also, the length of hospital stay and insulin therapy was significantly shorter in the insulin aspart group. In addition, the gestational age at delivery and frequency of normal vaginal delivery were significantly higher in the insulin aspart group.

Conclusion: Considering insulin dose, frequency of hypoglycemic episodes as well as length of initial hospital stay, insulin aspart was more efficient than regular insulin in controlling blood glucose in patients with GDM.

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Introduction

Gestational diabetes mellitus (GDM) is defined as the onset of hyperglycemia during pregnancy in a woman without a history of diabetes. The prevalence of this disease varies within the range of 1-20%, which is increasing consistent with increasing the prevalence of obesity and type 2 diabetes (1). The GDM is associated with adverse maternal outcomes (e.g., pregnancy-induced hypertension, preeclampsia, eclampsia, polyhydramnios, and preterm delivery) and neonatal outcomes (e.g., macrosomia, birth trauma, shoulder dystocia, and hypoglycemia) (2, 3); therefore, women with GDM are in a high-risk group (4). The results of some studies have

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shown that post-meal glucose control in pregnant women with GDM improves maternal and neonatal outcomes, which is associated with the risk of macrosomia and embryo development (5, 6). Therefore, it is of great importance to control blood glucose, especially post-meal glucose in patients with GDM.

Diet therapy and daily exercise could control blood glucose in some patients; however, if therapeutic goals are not achieved with these methods, there will be a need for drug therapy using insulin or anti-hyperglycemic agents. Generally, the type and timing of insulin administration depend on fasting and post-meal glucose levels. In the past, regular and Neutral Protamine Hagedorn insulins were commonly used for the treatment of GDM. However, rapid-acting insulin analogs are more favored than regular insulin in pregnancy, as they are associated with lower levels of hypoglycemia and may better control post-meal blood glucose (7, 8).

Although the use of both insulin lispro and aspart during pregnancy is approved (9) and they are currently administered for pregnant women with type 1 and type 2 diabetes (10-13), a limited number of studies have compared them to regular insulin in terms of the effects on blood glucose and maternal and fetal outcomes in women with GDM (7, 8, 14-22). Despite the similarities between rapid-acting insulin analogs and regular insulin in GDM, it is required to carry out further studies to evaluate the differences. Therefore, the current study aimed to compare the efficacy of aspart (NovoRapid®) and regular insulin in controlling gestational diabetes and their effects on delivery outcomes.

Materials and Methods

In order to compare the efficacy of aspart (NovoRapid®) and regular insulin in controlling GDM and their effects on delivery outcomes, this retrospective study was conducted on 150 women with GDM admitted to Shohada Tajrish Hospital in Tehran, Iran, in 2018 to initiate insulin therapy. With regard to the prevalence of macrosomia equal to 10% in the aspart insulin group and 15% in the regular insulin group (18) and values of α (0.05), β (0.2), P1 (0.15), and P2 (0.1), the sample size was determined to be 150 patients (75 subjects in each group) based on the following formula:

$$n = \frac{2 * \left(Z_{1-\frac{\alpha}{2}} + Z_{1-\beta}\right)^2 * P(1-P)}{(P1-P2)^2}$$

The GDM was diagnosed based on the American Diabetes Association criteria (23). The patients with a history of pre-existing type 1 or 2 diabetes mellitus or pregnancy-induced hypertension in the current pregnancy were excluded from the study. In a 6-month period, 150 patients admitted for gestational diabetes were selected according to the inclusion and exclusion criteria, among whom 75 were treated with insulin aspart and another 75 subjects were treated with regular insulin. According to the hospital's protocol of insulin administration for patients with GDM, insulin therapy was initiated with a low dose that increased until reaching a specified goal (fasting blood glucose [FBG] of < 5.3 mmol/L [95 mg/dL] and 1-hour post-meal glucose level of < 7.8 mmol/L [140 mg/dL]). After the stabilization of the insulin dose for at least 2 days, the patients were discharged with the same insulin dose and taught how to use insulin at home. The present study was approved by the Ethics Committee of Shahid Beheshti University of Medical Sciences, Tehran, Iran (IR.SBMU.MSP.REC.1398.020).

Using a form, the data were obtained for each patient medical record, including age, body mass index (BMI), history of hypertension, GDM or macrosomia in previous pregnancies, gravidity, parity, results of laboratory tests for the diagnosis of GDM (i.e., FBG, 1-hour post-meal blood glucose level, and 2-hour blood glucose tolerance with 75 g of oral glucose), duration of treatment with dietary regimen and exercise, data collected on admission for the initiation of insulin therapy (i.e., gestational age, FBG, 1-hour post-meal blood glucose level, final insulin dose, incidence of hypoglycemic episodes during hospitalization, and length of hospital stay), overall duration of insulin therapy, rehospitalization, delivery characteristics (i.e., gestational age at delivery, type of delivery, and delivery status in terms of elective or emergency delivery), and neonatal characteristics (i.e., 5-minute Apgar score, gender, weight, and weight percentile). The primary outcomes of the study were insulin dose, hypoglycemic episodes, length of hospitalization at the initiation of insulin

therapy, length of insulin therapy, and rehospitalization frequency. The secondary outcomes were delivery and neonatal outcomes.

The data were analyzed using SPSS software (version 25). The qualitative variables were described using frequency and percentage, and the quantitative variables were reported using mean and standard deviation or median and interquartile range (IQR). The Chi-square test, Fisher's exact test, independent samples t-test, and Mann-Whitney U test were used to compare the two groups of insulin aspart and regular insulin. A p-value of less than 0.05 was considered statistically significant.

Results

The mean age value of all the patients was 31±6 years (range: of 22-43 years), and the mean BMI value of the participants was 26.6±4.1 kg/m^2. In previous pregnancies, 18 (12%), 44 (29%), and 16 (11%) patients had hypertension, GDM, and macrosomia, respectively. In addition, 45 (30%), 50 (33%), and 55 (37%) women were nulliparous, primiparous, and multiparous, respectively. There was no significant difference between the two groups in terms of age, BMI, history of hypertension, GDM, macrosomia, and pregnancy status (Table 1).

The median (IQR) of gestational age at the time of diagnosis of GMD in all patients was reported as 22 weeks (range: 18-26 weeks). The median (IQR) of FBG at the time of diagnosis was 88 mg/dL (range: 84-94 mg/dL), and the median (IQR) of 1-hour post-meal blood glucose was 184.5 mg/dL (range: 180-190 mg/dL). Furthermore, the median (IQR) of 2-hour blood glucose tolerance was reported as 138 mg/dL (range: 129-144 mg/dL). There was no significant difference between the two groups in terms of gestational age at the time of diagnosis. The FBG and 2-hour blood glucose tolerance were significantly higher and the 1-hour post-meal blood glucose level was significantly lower in the insulin aspart group than those reported for the regular insulin group (Table 2).

In all the patients, the median (IQR) of the duration of non-pharmacological treatment since the time of diagnosis was 4 weeks (range: 2-6 weeks). The median (IQR) of gestational age at the time of admission for the initiation of insulin therapy was 28 weeks (range: 22-33 weeks). At the aforementioned time, the median (IQR) of FBG in all the patients was 91 mg/dL (range: 90-92 mg/dL), and the median (IQR) of 1-hour post-meal blood glucose level was 113 mg/dL (range: 110-115 mg/dL). In addition, the median (IQR) of insulin dose for all the subjects was 22 units (range: 14-31 units), and the median (IQR) of the duration of hospitalization was 6 days (range: 4.5-7 days).

During the hospitalization, 35 patients (23%) had hypoglycemic episodes. The median (IQR) of the overall duration of insulin therapy was 10.5 weeks (range: 6-15 weeks), and 48 patients (32%) had a history of rehospitalization.

Table 1. Comparison of patients' characteristics between two groups

		Insulin Aspart group (n=75)	Regular insulin group (n=75)	P-value
Age (year) Mean±standard deviation		32±5	30±6	0.064*
BMI (kg/m^2) Mean±standard deviation		27±4.3	26.1±3.9	0.165*
History of hypertension n (%)		9 (12)	9 (12)	1.000**
History of GDM n (%)		18 (24)	26 (35)	0.151**
History of macrosomia n (%)		11 (15)	5 (7)	0.113**
Pregnancy status n (%)	Nulliparous	22 (29)	23 (31)	0.250**
	Primiparous	21 (28)	29 (38)	
	Multiparous	32 (43)	23 (31)	

* Independent samples t-test; ** Chi-square test
BMI: Body mass index; GDM: Gestational diabetes mellitus

Table 2. Comparison of patients' characteristics at time of diagnosis of gestational diabetes mellitus and hospital stay for initiation of insulin therapy between two groups

		Insulin aspart group (n=75)	Regular insulin group (n=75)	P-value
At time of GDM diagnosis	GA (week)	22 (18-28)	23 (18-23)	0.433*
	FBG (mg/dL)	92 (86-96)	85 (82-90)	<0.001*
	1-hour post-meal glucose level (mg/dL)	182 (178-187)	188 (182-191)	<0.001*
	2-hour blood glucose tolerance (mg/dL)	140 (130-149)	134 (129-140)	0.004*
At time of hospitalization for initiation of insulin therapy	Non-pharmacological treatment (week)	4 (2-7)	3 (2-5)	0.013*
	GA (week)	28 (24-33)	26 (20-30)	0.010*
	FBG (mg/dL)	92 (91-94)	90 (89-91)	<0.001*
	1-hour post-meal glucose level (mg/dL)	110 (109-112)	115 (114-117)	<0.001*
	Insulin dose (unit)	18 (13-31)	24 (19-36)	0.005*
	Hypoglycemic episodes	8 (11%)	27 (36%)	<0.001**
	Length of hospital stay (day)	5 (4-6)	7 (6-7)	<0.001*
Follow-up	Length of insulin therapy (week)	9 (5-14)	11 (7-18)	0.031*
	Rehospitalization	22 (29%)	26 (35%)	0.484**

* Mann-Whitney U test; ** Chi-square test
FBG: Fasting blood glucose; GA: Gestational age; GDM: Gestational diabetes mellitus
Statistics presented as median (interquartile range) or frequency (%)

In the aspart group, the duration of non-pharmacological treatment was significantly lower; however, the gestational age at the time of admission for insulin therapy was significantly higher. In addition, FBG on admission was significantly higher in this group; nevertheless, 1-hour post-meal blood glucose level was significantly lower. Insulin dose, duration of hospitalization, frequency of hypoglycemic episodes, and duration of insulin therapy after discharge were significantly lower in the aspart group. However, there was no significant difference between the two groups in terms of rehospitalization (Table 2).

Table 3. Comparison of delivery characteristics between two groups

		Insulin aspart group (n=75)	Regular insulin group (n=75)	P-value*
GA at delivery (week)	≥37	16 (21%)	34 (45%)	0.002
	≥38	59 (79%)	41 (55%)	
Delivery type	Normal	55 (73%)	35 (47%)	0.011
	Cesarean section	20 (27%)	40 (53%)	
Delivery status	Elective	44 (59%)	36 (48%)	0.190
	Emergency	31 (41%)	39 (52%)	

* Chi-square test
GA: Gestational age
Statistics presented as median (interquartile range) or frequency (%)

The gestational age at delivery was 37 weeks or less in 50 patients (33%) and 38 weeks or more in 100 participants (67%). Among all the women, 95 (63%) and 55 (37%) patients underwent normal vaginal delivery and cesarean section. Delivery status was emergency in 70 patients (47%) and elective in 80 subjects (53%). In the aspart group, the gestational age at delivery and frequency of normal vaginal delivery were significantly higher; however, there was no significant difference between the two groups in terms of delivery status (Table 3).

Among all the newborns, 1 (1%), 6 (4%), and 143 (95%) neonates were reported with 5-

minute Apgar scores of 7, 8, and 9, respectively. Moreover, 85 (57%) and 65 (43%) newborns were male and female, respectively. In addition, no anomalies were observed among the neonates. The median (IQR) of the weight of neonates at birth was 3,500 g (range: 3,326-3,700 g). Furthermore, 101 newborns (67%) had appropriate weight for gestational age, and 49 neonates (33%) were large for gestational age. There was no significant difference between the two groups in terms of the neonatal characteristics (Table 4).

Table 4. Comparison of neonatal characteristics between two groups

		Insulin aspart group (n=75)	Regular insulin group (n=75)	P-value
5-minute Apgar score	7	0 (0%)	1 (1%)	
	8	5 (7%)	1 (1%)	0.209*
	9	70 (93%)	73 (97%)	
Neonate gender	Male	46 (61%)	39 (52%)	0.249**
	Female	29 (39%)	36 (48%)	
Neonatal weight (g)		3500 (3350-3690)	3510 (3300-3710)	0.939***
Weight percentile	AGA	46 (61%)	39 (52%)	0.223**
	LGA	29 (39%)	36 (48%)	

* Fisher's exact test; ** Chi-square test; *** Mann-Whitney U test
AGA: Appropriate for gestational age; LGA: Large for gestational age
Statistics presented as median (interquartile range) or frequency (%)

Discussion

The results of this study showed that the insulin dose required to control blood glucose, frequency of hypoglycemic episodes during hospitalization, and length of hospital stay were lower in the insulin aspart group than those reported for the regular insulin group. Moreover, the duration of insulin therapy after discharge was lower in the insulin aspart group. In addition, the gestational age at delivery and frequency of normal vaginal delivery were higher in the insulin aspart group; however, there was no significant difference between the two groups in terms of delivery status. On the other hand, there was no significant difference between the two groups regarding neonatal weight and weight percentile.

When the blood glucose level in patients with GDM is not controlled by diet and exercise, it becomes necessary to start drug treatment, and insulin is the best choice under such conditions. Typically, regular insulin is used to control blood glucose. However, several studies have shown that rapid-acting insulin analogs can also be effective in controlling blood glucose and in some cases have better results than regular insulin.

Pettitt et al. in 2003 studied GDM patients with no response to diet, and for the first time they reported that the use of both insulin aspart and regular human insulin after a standard meal could increase insulin levels and reduce glucose and peptide C levels. In addition, they reported that insulin aspart was more effective than regular insulin in controlling post-meal glucose due to higher insulin peak and lower demand for endogenous insulin secretion (8). However, they only studied the short-term effects (up to 4 h) of a single dose of aspart and insulin in 2 consecutive days (8).

In another clinical trial study carried out on 27 women with GDM in 2007, it was observed that insulin aspart was more effective than human insulin in the reduction of postprandial glucose concentrations. It was also demonstrated that the injection of insulin aspart 5 min before meals was more convenient for patients than the injection of human insulin 30 min before meals. As a result, the safety and efficacy of insulin aspart were reported in comparison to those of regular insulin (14). Although the aforementioned study was a randomized clinical trial and lasted since the diagnosis of GDM up to 6 weeks postpartum, only 27 patients were studied (14 and 13 participants in the aspart and regular insulin groups, respectively).

A clinical trial was carried out by Cianni et al. in 2007 on 96 patients with GDM whose 1-hour

post-meal glucose level was not controlled by diet. Cianni et al. reported that the use of rapid-acting insulin analogs, such as aspart and lispro, was reported with better post-meal glucose levels, compared to the use of human insulin (15). As Cianni et al. themselves have pointed out, their study was conducted on a small population with a lack of adequate statistical power (15).

In 2010, Balaji et al. reported that the use of insulin aspart was safe in 76 women with GDM and more convenient for pregnant subjects. In the aforementioned study, the neonatal outcomes of insulin aspart were also comparable to those of human insulin (16). In another study carried out by Balaji et al. in 2012 on 323 women with GDM, it was reported that insulin aspart could be associated with better control of glucose levels (17). Both studies used premixed insulin aspart, containing 30% aspart and 70% intermediate-acting human insulin.

In a clinical trial study performed by Deepaklal et al. in 2015, no significant difference was observed between patients with GDM and pre-existing diabetes receiving insulin aspart in terms of macrosomia and hypoglycemic episodes. As a result, Deepaklal et al. concluded that the use of insulin aspart is safe in pregnancy; however, they suggested that it is required to carry out further studies in this regard (18) due to no comparison of insulin aspart to regular insulin.

You et al. in a retrospective study in 2016 compared pregnancy and neonatal outcomes in 197 pregnant women receiving regular or rapid-acting insulin analogs. They reported that rapid-acting insulin analogs were similar to regular insulin in terms of their efficacy in controlling blood glucose and effects on pregnancy and neonatal outcomes; however, considering patient comfort, insulin analogues may be regarded as better options during pregnancy (19). The results of the current study also confirmed that there were no significant differences in pregnancy and neonatal outcomes between the two groups; nevertheless, the findings of the present study showed that the required dose of insulin, length of initial hospital stay for treatment, and hypoglycemic episodes in the insulin aspart group were lower than those reported for the regular insulin group.

Recently, in a review study carried out by Toledano et al. in 2018, it is recommended to use rapid-acting aspart and lispro insulins for the treatment of hyperglycemia in pregnancy because they could decrease the risk of hypoglycemia. However, it has been suggested to perform further studies to examine the efficacy and safety of aspart and lispro insulins (24). The results of the current study confirmed the results of previous studies and showed that the dose of insulin aspart and length of hospital stay before reaching the desired blood glucose level were lower in patients receiving insulin aspart, compared to those reported for regular insulin. Moreover, the frequency of hypoglycemic episodes during hospitalization and duration of treatment with insulin aspart after initial discharge were also lower. Concerning pregnancy outcomes, the gestational age at delivery and frequency of normal vaginal delivery were higher in the insulin aspart group. There was no significant difference between the two groups in terms of neonatal outcomes.

With regard to the mechanism of action, due to changes in the structure of fast-acting insulin analogs preventing self-binding, they undergo different pharmacokinetic changes. Therefore, their concentration can be maximized twice faster than that of regular insulin (12, 13), resulting in a more rapid effect (15 min vs. 30 min), taking less time to reach their maximum effect (2-5 h vs. 7-8 h), and accelerating the control of post-meal glucose level, which is also more convenient for patients (10, 11, 13).

Finally, it can be concluded that in line with the results of previous studies, the current study also demonstrated that rapid-acting insulin aspart had favorable effects on glycemic control in patients with GDM, with no maternal and neonatal adverse outcomes. Therefore, the use of insulin aspart in GDM can be safe. However, with the consideration of the sample sizes of the present study and other studies in this field, it is required to perform multi-center clinical trials with a larger sample size to assess maternal, fetal, and neonatal outcomes in patients with GDM using rapid-acting insulin analogs. In addition, the present study was a retrospective study with some limitations, such as incomplete records (e.g., a lack of Hemoglobin A1c test) or impossibility to study confounding factors (e.g.,

diet).

Conclusion

The findings of the current study demonstrated that insulin aspart had better control over gestational diabetes than regular insulin without adversely affecting maternal and neonatal characteristics. Therefore, insulin aspart can be used in order to control gestational diabetes.

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Conflicts of interest

Authors declared no conflicts of interest.

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