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Original Research Article

Determination of required insulin dose to control blood sugar in patients with Gestational diabetes mellitus

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Abstract: Nowadays rate of gestational diabetes mellitus (GDM) is increasing and it has numerous complications for both mother and newborn, so appropriate and timely treatment of GDM is very important. Insulin is the most common treatment to control blood sugar in GDM. Knowing the amount of insulin required during pregnancy could help doctors to better control blood sugar in women with GDM. This study aimed to determine the amount of insulin required to control blood sugar in patients with gestational diabetes. This is a retrospective study, carried out using medical records of 225 pregnant women aged 18 to 45 years diagnosed with GDM for the first time referred to Imam Khomeini Teaching Hospital in Ahvaz during 2016. Total daily insulin dose (TID) during pregnancy was recorded as units per kilogram, and the amount of insulin required in women with GDM was evaluated based on the characteristics of mother. The collected data were analyzed using SPSS version 23.00 (SPSS Inc., Chicago, IL, USA). This study showed that the amount of insulin required to control blood sugar by increasing gestational age significantly increases. So that the required insulin in gestational age less than 12 weeks: 0.52±0.09 units / kg / day, in 13 to 26 weeks: 0.64±0.05 units / kg / day, in 27 to 35 weeks: 0.73±0.08 units / kg / day, and more than 36 weeks to birth: 0.85±0.03 units / kg / day ($P < 0.05$). The results also showed that factors such as maternal age, Body mass index (BMI), parity, history of macrosomia birth, history of infertility and diabetes among close relatives mother do not affect in determining the 24-hours insulin dose ($P > 0.05$). The results of this study showed that gestational age is only factor in determining the amount of insulin required to control blood sugar in GDM. Because the studies in this field are very low, also many factors such as nutrition and stress during pregnancy effect on insulin requirements, so definitive decision about prescribed amount of insulin required to control blood glucose in GDM, need to do more studies in a controlled manner in the future.
Keywords: Insulin requirements, pregnancy, gestational diabetes mellitus

INTRODUCTION

The prevalence of diabetes is rapidly increasing worldwide due to factors such as increased rate of obesity caused by urbanization lifestyle and aging societies. Unfortunately, this effect is more significant in developing countries including our country. Currently about 200 million of people in worldwide and more than 3 million people in Iran are affected by the diabetes. Diabetics are prone to the risk of complications such as vision disorders, cardiovascular attacks, amputation, and renal failure [1].

Gestational diabetes mellitus (GDM) is a form of diabetes that first appears in a pregnant woman and is usually resolved after termination of pregnancy [2]. GDM is the most common medical complication of pregnancy and 5% to 8% of pregnant women suffer from GDM, which usually happens around weeks 24 to 28 of pregnancy [3].

GDM is considered a high-risk status of pregnancy and patients with GDM need more care than others. Unfortunately, the prevalence of GDM has increased by 40 percent in recent years. This is because change in diet and increased the use of a variety of fast

foods, weight gain, increased the age of marriage and subsequently elevated pregnancy age [4].

High blood sugar during pregnancy is harmful to both of fetus and mother. Short-term and long-term complications of GDM for the mother and fetus are numerous. Adverse effects include an increased risk of GDM on the Infant macrosomia, neonatal hypoglycemia, hyperbilirubinemia, cardiac hypertrophy, hypocalcemia, polycythemia, obesity, and stillbirth. Other complications of diabetes include birth trauma, increased induction of labor or a cesarean section, and subsequent baby's obesity and diabetes [5].

The risk of fetal abnormalities and complications of pregnancy and delivery increases 4 to 10 times in pregnant women with uncontrolled GDM. The goal of GDM treatment is to normalize plasma glucose levels before and during pregnancy. According to research, fetal malformations will be avoided if the diabetes is controlled before 15th week of pregnancy [4, 6]. The prevalence of GDM depending on the population studied and the diagnostic tests from 1 to 14% have been reported. According to a study on the Metabolism Research Center, Tehran University of Medical Sciences, the prevalence of GDM in Tehran equivalent to 7/4% was reported [7]. With proper treatment, GDM complications, which include cardiac anomalies and fetal macrosomia, preterm delivery, and maternal and newborn deaths, can be prevented.

Insulin is the most common drug to control blood sugar in GDM. About 15 percent of women with GDM need to take insulin therapy. Insulin is a safe and effective drug that can reduce the risk of complications from GDM [8]. The required dose of insulin is determined based on blood glucose levels, the patient's weight, gestational age, and other conditions of the patient [9].

The best strategy to control GDM is to use insulin. considerable researchs has not been done on the treatment of GDM in Iran, so this study aimed to evaluate the medical records on pregnant women with GDM in order to determine the most suitable insulin dose according to gestational age in Iranian women for precise control of the disease such that it exerts maximum impact on glycemic control and minimum complications for both mother and fetus. The results of this research could help determine the standard dose of insulin for the treatment of gestational diabetes.

METHODS

This is a retrospective study carried out using medical records of pregnant women with diabetes referred to Imam Khomeini Teaching Hospital in Ahvaz during 2016. Sampling was conducted as random and the sample size was calculated based on a pilot study of 12 subjects and a confidence level of 95% with an accuracy of 0.03 for 225 individuals.

Inclusion criteria

- Being a diabetic for the first time during pregnancy
- Ages 18 to 45 years

Exclusion criteria

- Pregnant women with diabetes Type 1 and Type 2 diagnoses before pregnancy
- Women with incomplete follow-up
- Women with abortion before 20th weeks of pregnancy
- Multiple pregnancy

Demographic and clinical data including maternal age, height, weight, gestational age, parity, history of macrosomal birth, infertility history, and history of diabetes in close relatives, 24-h insulin dose, and complications of pregnancy status were collected from the patient's medical record at the clinic and recorded in an information checklist.

The need for daily insulin as total insulin dose (TID) includes basal insulin and insulin with meals, which was calculated based on the weight as insulin units per kg of body weight per day (units/kg /day).

Body Mass Index (BMI) was studied in kg/m^2 calculated for all subjects in four groups as follows:
18.5-24.9 = normal; 25-29.9= overweight; 30-34.9= moderate obesity; 35-40 = severe obesity.
Gestational ages of the patients were divided into four groups based on pregnancy weeks:

(Group 1): pregnant women with gestational ages of 1 to 12 weeks; (Group 2): pregnant women with gestational ages of 13 to 26 weeks; (Group 3): pregnant women with gestational ages of 27 to 35 weeks; (Group 4): pregnant women with gestational ages over 36 weeks.

In this study, clinical and demographic data of patients with GDM were collected by examining their medical records and compiled in an information checklist.

The software SPSS version 22 was used to perform statistical analyses. The graphs and charts were plotted by Excel software. Data obtained were analyzed by descriptive statistics including frequency, mean, standard deviation, percentage, and statistical charts and tables.

Normality of data and homogeneity of variance, respectively, were analyzed by Kolmogorov-Smirnov and Leven tests. Independent t-test and one-way ANOVA, respectively, were applied to assess the significance of differences and comparison of the quantitative variables. Chi-square test was used to compare qualitative variables. Mann-Whitney test was

employed in the case of a non-normal data distribution. A significance level of 0.05 was considered in all the tests.

RESULTS

Demographic and clinical characteristics

The results showed that average age of the samples was 31.88 ± 5.24 years with a mean BMI of 29.77 ± 3.25 kg/m^2 (Table 1). Also, most subjects (n=105) were overweight (BMI between 25 and 29.9) and normal weight (BMI between 18.5 to 24.9) was only observed in 13 patients (Fig. 1). Results showed a mean gestational age of 24.97 ± 9.57 weeks. Most patients (n=87) showed gestational ages between 27 and 35 weeks (Fig. 2). Parity or pregnancy times equaled 2 in most subjects (n = 86) with a mean parity of 2.43 ± 1.20 (Fig. 3). The results also showed that 64 patients had history of infertility (Fig. 4), 77 patients had history of macrosomia birth (Fig. 5), and 150 patients had diabetes in their first-degree relatives (Fig. 6).

Table-1: Demographic profile of patients with GDM

Variable	Mean	SD	Min.	Max.
Age (year)	31.88	5.24	18	45
Stature (cm)	162.47	5.28	150	175
Weight (kg)	78.60	8.54	55	114
BMI (kg/m^2)	29.77	3.25	20.7	40.3
Gestational age (weeks)	24.97	9.57	5	40
Parity	2.43	1.20	1	7

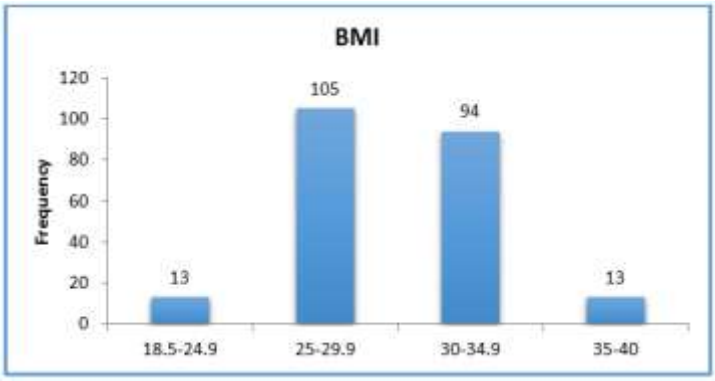

Fig-1: Distribution of GDM according to BMI

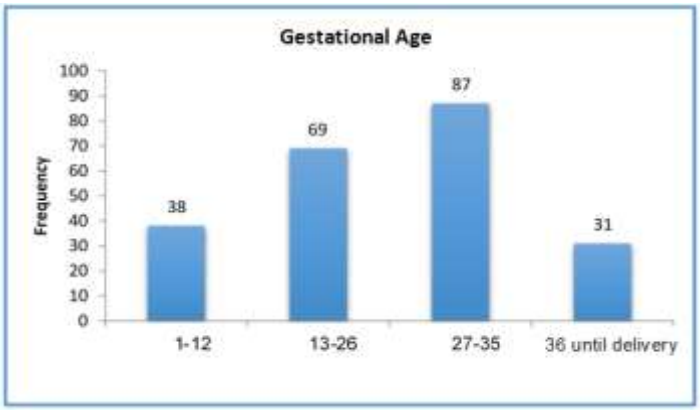

Fig-2: Distribution of GDM according to gestational age

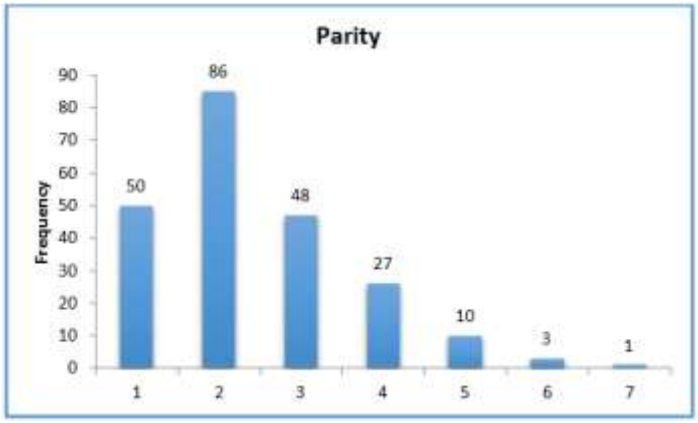

Fig-3: Distribution of GDM according to parity

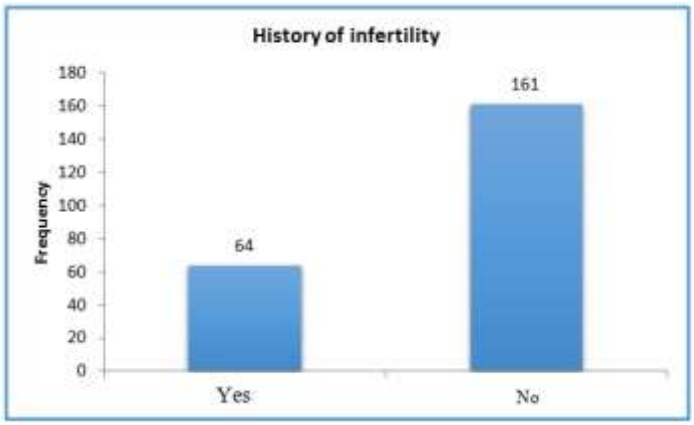

Fig-4: Distribution of GDM according to history of infertility

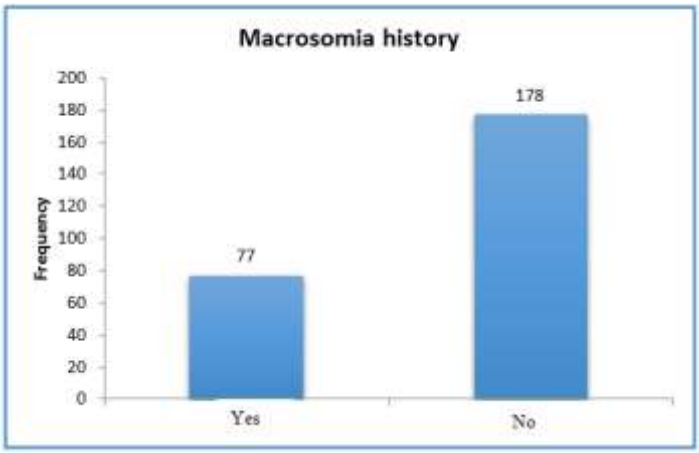

Fig-5: Distribution of GDM according to macrosomia birth history

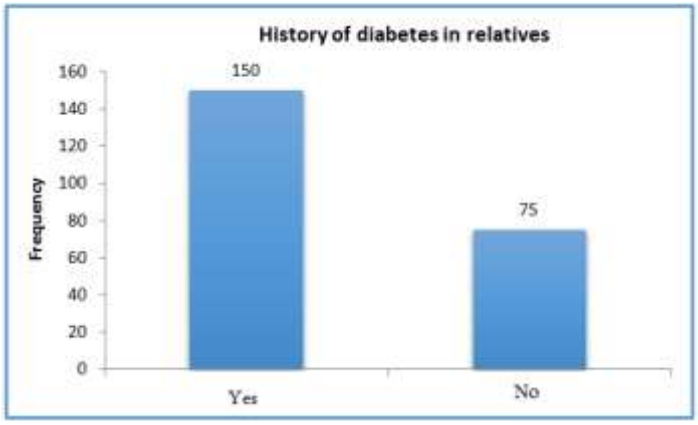

Fig-6: Distribution of GDM according to diabetes records in close relatives

The percentages of history of infertility, birth macrosomia, and a history of diabetes in first-degree relatives, respectively, were 28.4%, 34.2%, and 66.6%.

Results of insulin doses needed for blood sugar control

The doses of insulin needed to control blood glucose in women with GDM were evaluated according to different variables (Table 2).

Table-2: Doses of insulin needed based on different variables.

Variable	Group	Mean	SD	p-value
Maternal age (year)	< 30	0.65	0.092	0.449
	≥ 30	0.64	0.094	
Macrosomia birth record	Yes	0.66	0.090	0.314
	No	0.64	0.091	
History of infertility	Yes	0.64	0.092	0.838
	No	0.65	0.093	
History of family diabetes	Yes	0.64	0.092	0.960
	No	0.64	0.095	
BMI (kg/m^2)	18.5-24.9	0.60	0.086	0.272
	25-29.9	0.65	0.094	
	30-34.9	0.64	0.092	
	35-40	0.67	0.092	
Gestation age (weeks)	1 to 12	0.52	0.091	0.003
	13 to 26	0.64	0.058	
	27 to 35	0.73	0.085	
	> 36	0.85	0.039	

No significant differences were observed between the ages of pregnant women with GDM and insulin doses required to control blood sugar in the patients (P = 0.449) (Fig. 7). Evaluation of insulin needed for blood sugar control in GDM based on pregnancy age revealed that insulin requirements significantly rose with increasing age of pregnancy (P = 0.003) (Fig. 8).

The results showed no significant differences between the amounts of insulin needed to control blood sugar in patients with GDM and BMI (P = 0.272) (Figs. 9 and 10).

The results showed statistically significant associations between the doses of insulin needed to control blood sugar in patients with GDM and their parity (P = 0.275) (Fig. 11).

According to the results of statistical analyses, no significant differences were found between the amounts of insulin needed to control blood sugar in GDM and history of birth macrosomia (P = 0.314) (Fig. 12).

This study recorded no significant relationships between the amount of insulin needed to control blood sugar in patients with GDM and history of infertility (P = 0.838) (Fig. 13).

In addition, the amount of insulin needed to control blood glucose in GDM showed no significant relationships with history of diabetes in first-degree relatives of patients (P = 0.960) (Fig. 14).

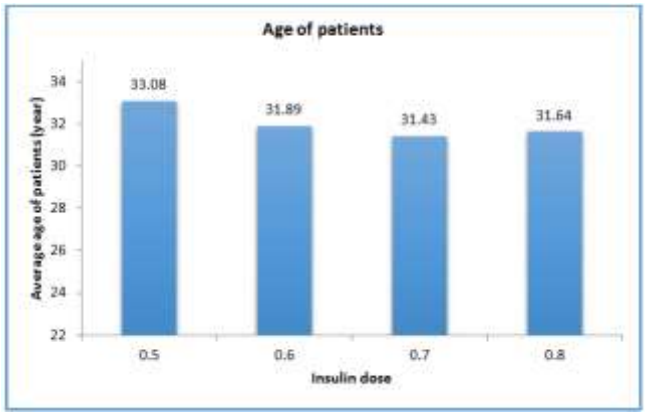

Fig-7: Average age of patients with GDM according to the insulin dose needed for blood sugar control

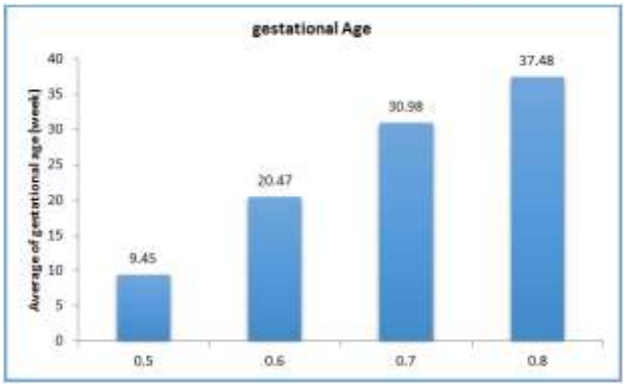

Fig-8: Average age of gestational age in patients with GDM according to the insulin dose needed for blood sugar control

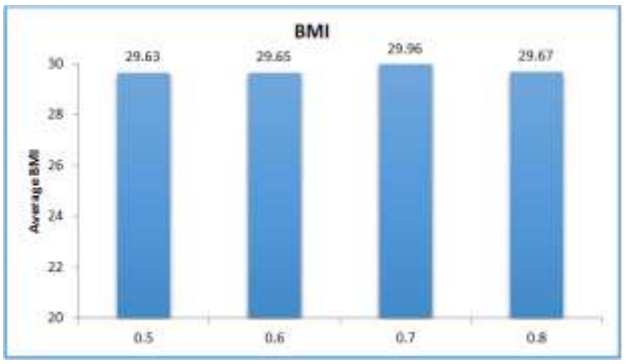

Fig-9: Average BMI values in patients with GDM according to the insulin dose needed for blood sugar control

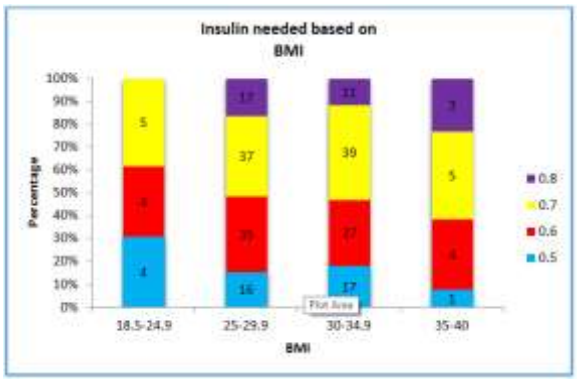

Fig-10: Doses of insulin needed to control blood sugar in GDM according to the patients' BMI values

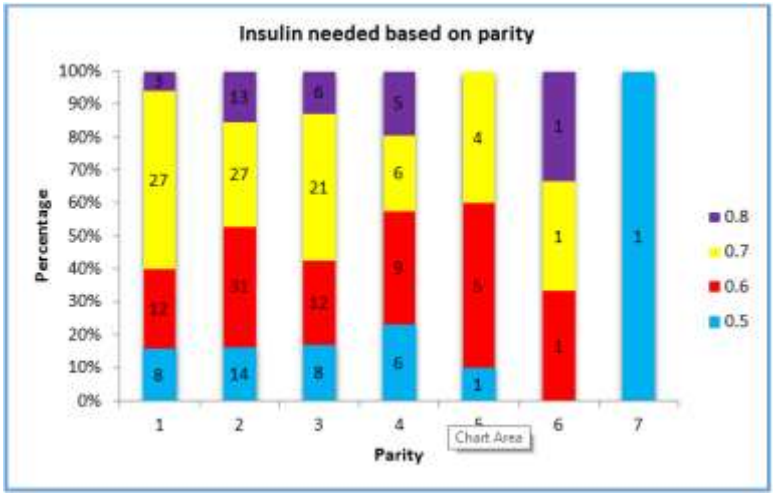

Fig-11: Doses of insulin needed to control blood sugar in GDM according to the patients' parity

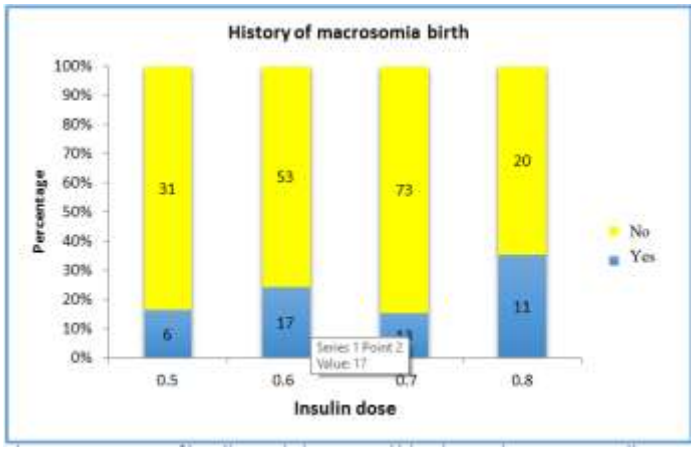

Fig-12: Doses of insulin needed to control blood sugar in GDM according to the history of macrosomia birth in patients

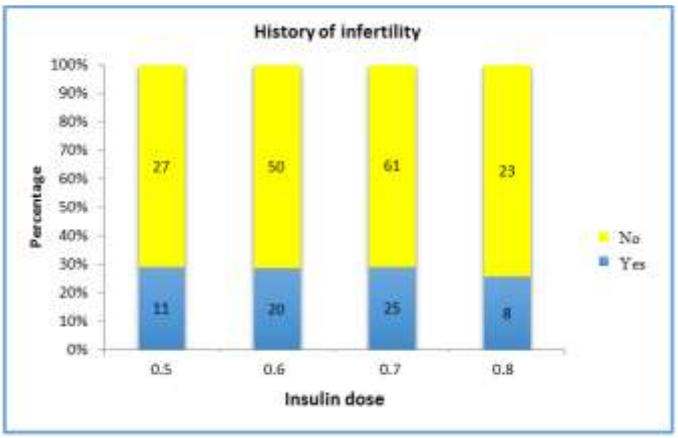

Fig-13: Doses of insulin needed to control blood sugar in GDM according to the history of infertility in patients

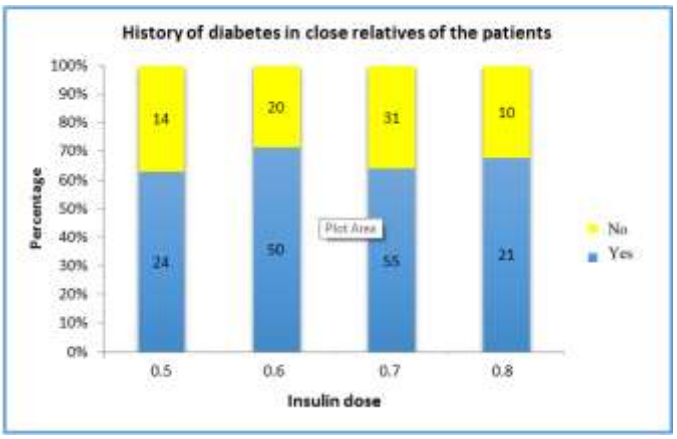

Fig-14: Doses of insulin needed to control blood sugar in GDM according to the history of diabetes in close relatives of the patients.

DISCUSSION

Due to the increasing incidence of GDM and the resultant multiple complications for both mother and infant, appropriate and timely treatment of this disease is of utmost importance. Insulin is the most common treatment for diabetes to control blood sugar in GDM [8].

The required insulin doses in GDM are determined based on the patient's condition. For a pregnant woman affected by diabetes for the first time, initial dose of insulin is determined as daily dose needed based on gestational age and weight of the patient, which will be regulated later according to the activity, nutritional regime, and other factors. Stress, infection, steroids, obesity, and gestational age all increase insulin requirements [9].

Most previous studies have focused on the treatment of women with Type II diabetes, but the increasing prevalence of diabetes in pregnancy necessitates more studies on the treatment of such patients. This study, therefore, aimed to assess the doses of insulin required to reduce blood sugar in GDM taking into account several factors including maternal age, pregnancy age, BMI, parity, history of infertility, macrosomia birth, and history of diabetes in close relatives.

Two forms of diabetes in pregnancy have been studied: diabetes before pregnancy and diabetes first appears during pregnancy. In this study, however, pregnant women with a diagnosis of any diabetes before pregnancy were excluded from the study.

The results showed an average age of 31.88 ± 5.24 years and a mean BMI of 29.77 ± 3.25 kg/m^2 (in the range of 20.7-40.3) for women with GDM. Also, most patients (46.7%) were overweight and normal weight was only observed in 5.7% of the subjects.

The results showed no significant differences among age, BMI, parity, history of macrosomia, birth, infertility history, and history of diabetes in first-degree relatives of patients and insulin doses needed to control blood sugar in patients with GDM.

The results presented by Padmanabhan *et al.* [11] showed no relationships between insulin requirements in GDM, age, parity, and maternal complications such as retinopathy, proteinuria, hypertension, and smoking.

McManus *et al*. [14] showed no relationships between GDM, insulin needs, and the patient's age, BMI, and weight gain during pregnancy, or problems related to mother and fetus. These results are consistent with the findings of present study.

Padmanabhan *et al.* [11] reported an average BMI value of 31.1 kg/m^2 (ranging from 27 to 36.7) in patients with GDM with no normal weights in the subjects. They further showed that BMI and weight gain during pregnancy could have a role in determining the doses of insulin needed. Their results do not correspond with the findings of this study.

Padmanabhan *et al*. [11] detected a significant relationship between weight gain during pregnancy and the final dose of insulin. This is because increased amounts of lipids are associated with greater production of cytokines and proinflammatory adipokines such as α-TNF and leptin, which are directly related to changes in insulin sensitivity (10, 14, and 15). Accordingly, weight gain in pregnancy can have major metabolic effects leading to varying degrees of insulin resistance in pregnancy.

The discrepancies in results may be due to differences in subject population (genetic, lifestyle, diet, calories, etc.) and also to treatment protocol. Furthermore, weight gain in pregnancy was not evaluated in this study.

Iversen *et al*. [16] studied women with GDM with matched age, weight, and BMI and found that

increased maternal parity had no roles in insulin sensitivity or beta cell function, which corresponds with the findings of this study. As a result, parity or pregnancy times cannot determine the doses of insulin to reduce blood glucose in GDM.

The results of insulin doses needed to control blood sugar in GDM based on gestational age in this study reveals that insulin requirements significantly increases with rising pregnancy age. Similarly, Padmanabhan *et al*. [11] noted that doses of insulin required lowering blood glucose in GDM increased with elevating gestational age. They also showed that doses of insulin needed in the third trimester of pregnancy were almost double the amounts required in the second trimester. Contrarily, a 10% increase in the insulin requirement was observed between four intervals (1-12, 13-26, 27-35, and 36 weeks to term) in our study. The differences in results can be attributed to the effects of BMI and weight gain during pregnancy. This is because our study did not intend to consider weight gain during pregnancy and the relationship between weight gain and doses of insulin were not evaluated. In the research of Padmanabhan *et al*., [11] on the other hand, weight gain contributed to the insulin doses needed in addition to gestational age and BMI values.

In the study of Padmanabhan *et al*. [11], average insulin dose required in the first, second, and third trimester, respectively, were 0.36 (0.1-0.7), 0.61 (0.69-0.95), and 0.95 (0.53-1.32) units/kg/day.

A reduced amount of insulin needed in the first trimester of pregnancy is because of the temporary decrease in progesterone levels, thereby, a shift in the production of luteinizing hormone to the placenta as well as diminished need for food caused by severe pregnancy nausea and vomiting [12].

In a study, Jovanovic stated that the amount of insulin required increased with rising gestational age, so that the required weekly dose of insulin at weeks 1-18, 18-26, 26-36, and 36-40, respectively, were equal to 7.0, 8.0, 9.0, and 1.0 units/kg/day [9]. Likewise, a 10% increase in the amount of insulin needed at various intervals was observed with increasing pregnancy age.

Roversi *et al*. [13] in a study on 280 women with GDM demonstrated that the need to insulin elevated from 15 weeks of pregnancy until delivery, and that average maximum tolerated dose of insulin (MTD) increased as 38 units per day from week 15 of pregnancy until delivery time. Similar to present study, other studies also showed increased amounts of insulin demand with rising gestational age, but they have not presented detailed information (14 and 17).

Several studies have shown that the production of hormones including human lactogen, progesterone, cortisol and chorionic growth hormone responsible for increased insulin resistance are raised by the placenta through postreceptor effect in the second half of pregnancy (10 and 18) indicating an elevated need for insulin with increasing gestational age.

Langer *et al*. studied 40 patients with GDM and their insulin need for every 5 weeks (weeks 8, 11, 16, and 19) and showed elevated insulin doses with increasing gestational age [19]. This result is also consistent with the findings of current study.

In another study, Langer *et al*. [20] investigated 57 pregnant women with GDM and found that insulin doses needed to control levels of glucose in the diabetics significantly increased up to 30 weeks of pregnancy in spite of constant glucose levels. Afterwards, no significant increases were observed in the amounts of insulin required in patients. This result does not correspond with the findings of present study. The dissimilarity can be related to differences in the population's studied as well as to the influences of factors such as insulin therapy protocol, nutrition, physical activity, and genetic factors.

In this study, the amount of insulin needed by patients (Group 1) in the first trimester averaged 0.52 units/kg/day, which increased in the next groups by about 10 percent.

The results offered by Jovanovic *et al*. [12] on insulin needs in the first trimester of pregnancy showed a significant increase of 18% in average weekly dose of insulin between 3-7 weeks (from 0.67 to 0.80 units/kg/day) followed by a significant reduction of 9% in insulin needs (from 0.80 to 0.72 units/kg/day) between 7-15 weeks of pregnancy (12). The results of their study do not agree with those detected in here. The reason for the higher amounts of insulin needed in their study compared to those found in present study could be because most patients had a history of diabetes before pregnancy in the study of Jovanovic *et al*. [12] while in our study, diabetes was first diagnosed in pregnancy.

The reduced insulin requirements in the second half of the first trimester can partly be because of poor control of blood sugar at the onset of pregnancy and also of the need for high doses of insulin to promptly control this situation. Additionally, insulin dose reduction is necessary to prevent hypoglycemia after glucose control. This possible overshoot may make it difficult to determine required amounts of insulin in GDM.

Studies in the field of GDM treatment in women with previous diabetes and those with first-time diabetes diagnosed in pregnancy have shown that diabetic women prior to the second trimester of pregnancy require more insulin than those needed by

first-time diabetics. In the third trimester, however, insulin levels were similar in both groups [11].
The results of this study, as a number of other similar studies, revealed that the doses of insulin required to lower blood sugar in pregnancy diabetes increase with gestational age, but there are differences on some details.

CONCLUSION

The results of this study indicate that factors such as maternal age, BMI, parity, history of macrosomia birth, maternal history of infertility, and diabetes among close relatives have no impacts in determining 24-h insulin in GDM. Moreover, gestational age is the only factor in determining the amount of insulin needed to control blood sugar in GDM, so that the required amounts of insulin for blood sugar control elevate by increasing gestational age.

The doses of insulin required at different gestational ages are as follows:

- Less than 12 weeks: 0.52 ± 0.09 units/kg/day
- 13 to 26 weeks: 0.64 ± 0.05 units/kg/day
- 27 to 35 weeks: 0.73 ± 0.08 units/kg/day
- 36 weeks to term: 0.85 ± 0.03 units/kg/day

Nonetheless, as studies in this area are very limited, detailed comparisons of our results with those of others are not possible. In addition, many factors including nutrition, stress, and activity levels affect insulin requirements during pregnancy. Therefore, definitive conclusions and decisions about prescribing doses of insulin required to control blood glucose in GDM need to be further investigated in a controlled manner.

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