Original Article

Determinants of Insulin Therapy among Women with Gestational Diabetes Mellitus: A Cross-Sectional Study

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ABSTRACT

Background: Gestational diabetes mellitus (GDM) is a common complication in pregnancy that occurs during the second half of pregnancy. In the majority of patients, medical nutritional therapy (MNT) alone is sufficient to achieve the glycemic goal. **Aim:** To evaluate the clinical and biochemical factors that predict the need for insulin therapy in women with GDM. **Materials and Methods:** Between March 2020 and November 2021, an analytic cross-sectional study was conducted on 127 women diagnosed with GDM at their final antenatal visit. Multivariate logistic regression was used to determine the variables associated with the likelihood of insulin requirement in patients with GDM. **Results:** To achieve glycemic control, 56.7% of the study population required insulin treatment. Fasting glucose, pre-conceptional body mass index (BMI), parity, and third-trimester glycated hemoglobin levels were all higher in the insulin-treated group ($P = 0.00$, 0.01, 0.01, and 0.02), respectively. Fasting glucose level is the main determinant of insulin use in patients with GDM (odds ratio [OR]: 1.110; 95% confidence interval [CI]: 1.001–1.191; $P = 0.004$). **Conclusions:** Fasting glucose level is the most important predictor of the need for insulin therapy.

KEYWORDS: *Gestational diabetes mellitus predictors, glucose tolerance test, insulin, medical nutritional therapy, obesity*

INTRODUCTION

Rising obesity and sedentary lifestyle have made diabetes increasingly common among women of reproductive age worldwide. Any degree of glucose intolerance that originates from or is initially recognized

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during pregnancy is termed gestational diabetes mellitus (GDM).[1,2] The global prevalence of GDM ranges from 2% to 14%.[3] Its prevalence in the Arab Gulf countries is among the highest in the world (varying from 5.1 to 37.7%) and is clearly increasing.[3,4] Based on the results of an oral glucose test, the incidence of GDM among Saudi women in Madinah was estimated to be significantly high (approximately 39.4%).[5] In the Jazan region, the frequency was observed to be 8.2%.[6] Another study using the International Association of Diabetes and Pregnancy Study Group criteria found that 41.5% of Saudi women in the Madinah region had GDM.

Clinicians have long struggled with the diagnosis of gestational diabetes. Several criteria have been established in various societies worldwide. In 1999, the World Health Organization (WHO) issued guidelines, which were updated in 2006 for consistency and are mainly followed. In 2013, the WHO revised and updated the diagnostic handbook for gestational diabetes. Untreated GDM is associated with an increased risk of fetal and maternal complications, which was also the basis for the new data set. Early detection and subsequent treatment of GDM have been shown to improve the outcomes of pregnancy.[7] Cesarean delivery, hypertension, premature birth, and birth trauma are examples of maternal outcomes, whereas neonatal outcomes include macrosomia, hypoglycemia, hyperbilirubinemia, and shoulder dystocia.[2,7] Although metabolic issues in newborns are most commonly associated with type 1 diabetic pregnancies, neonatal hypoglycemia has always been a concern in GDM.[8]

The optimal treatment for women with GDM has long been a source of contention. The key to managing GDM and reducing its associated comorbidities is early detection and an adequate treatment approach.[9,10] Diet, oral hypoglycemic medications, and insulin therapy are all viable treatment options. Reviews conducted to compare the efficacy of pharmacological drugs, such as oral hypoglycemic agents, to insulin explicitly stated that if exercise and diet alone fail to regulate blood glucose levels within 2 weeks, insulin should be administered along with dietary modifications and exercise.[10-13]

A few studies have attempted to identify the predictive characteristics that predispose women with GDM to the need for insulin for glycemic control, as opposed to women with GDM who can achieve glycemic control simply by dietary changes without the use of insulin. According to Zhang *et al*.,[14] higher fasting blood glucose level at the time of oral glucose tolerance test (OGTT), initial 75 g of OGTT 2-h plasma glucose value, and glycated hemoglobin (HbA1c) concentration upon diagnosis led to a higher likelihood of seeking insulin therapy. In a similar study, Aljohani *et al*.[15] highlighted seven highly significant risk factors: age, obesity, family history of diabetes, GDM <20 weeks, insulin therapy, recurrent GDM, and macrosomia. Women who received insulin therapy were five times more likely to develop type II diabetes mellitus than those who did not receive insulin therapy.

Based on the previous findings, several studies have investigated the predictive factors for GDM; however, only a few have examined the predictors of insulin therapy in general and in Saudi women. Therefore, this study explores the patient-related factors that make pregnant women more prone to insulin therapy for GDM management compared with patients being treated only using dietary modifications.

This study also aims to identify the clinical and biochemical factors associated with the need for insulin in women with GDM.

Subjects and Methods

Study participants

This was an analytical cross-sectional study. The data were collected between March 2020 and November 2021. A consecutive sample of 127 pregnant women was enrolled in the outpatient gestational diabetes clinic at the King Abdulaziz University Hospital, Jeddah, Saudi Arabia. GDM was confirmed using a two-step screening procedure (24–28 weeks of gestation). The patients were initially provided with 50 g of glucose, and a positive glucose challenge test (GCT) result was indicated if the plasma glucose level was >130 mg/dL. Patients with a positive GCT result underwent a 100-g 3-h OGTT. According to the Carpenter and Coustan criteria, GDM was diagnosed when two or more plasma glucose readings were abnormal (fasting plasma glucose value >95 mg/dL, 1-h plasma glucose value >180 mg/dL, 2-h plasma glucose value >155 mg/dL, or 3-h plasma glucose value >140 mg/dL).[16]

Baseline data collection

Written consent was obtained from all patients before enrollment in the study. The patients were recruited at the last antenatal visit before delivery. The data collection chart was filled through personal interviews, regardless of the type of therapy received. Women with pre-existing diabetes, those who refused to undergo an OGTT, and those who refused to participate in the study were excluded.

Study variables

Data on maternal age, parity, pre-pregnancy weight and height, previous history of GDM, current history of hypertension, and hypothyroidism were obtained through detailed interviews. Laboratory results, such as third-trimester HbA1c values, OGTT readings, and total maternal weight gain, were obtained from the files of the patients. According to the treatment plan, all the participants underwent dietary changes and received nutritional counseling. Insulin was administered if self-monitoring of blood glucose failed to achieve the glycemic goal of fasting glucose level <95 mg/dL and 2-h postprandial glucose level <120 mg/dL. The patients were divided into two groups based on the type of therapy received. The first group comprised patients with medical nutritional therapy (MNT), and the second group contained those who required insulin.

This study was conducted in accordance with the ethical standards and guidelines of the Declaration of Helsinki and was approved by the Research Bioethics Committee at the Faculty of Medicine, King Abdulaziz University Reference no. 119-20.

Statistical analysis

Statistical software for social science (SPSS version 20) was used for data processing and analysis. Quantitative data are expressed as the mean and standard deviation (SD), whereas qualitative data are expressed as frequencies and percentages. Statistical significance was defined as a P value < 0.05. A Student's t-test was used to investigate the relationship between quantitative variables and the Chi-square test to compare qualitative variables. A binary regression analysis was used to calculate the odds ratio (OR) and P values for the parameters related to insulin therapy.

Results

Characteristics of participants

This study included 127 pregnant women with a mean age of 34.58 ± 5.18 (mean ± SD) years. Table 1 shows the participant characteristics. The mean number of childbirths was 3.26 ± 1.71. The preconception body mass index (BMI) was 29.71 ± 5.59 kg/m^2, and the maternal weight gain was 8.13 ± 4.27 kg. The fasting, 1-h, 2-h, and 3-h OGTT results were 94.31 ± 12.67 mg/dL, 198.31 ± 33.40 mg/dL, 169.60 ± 36.69 mg/dL, and 137.64 ± 38.03 mg/dL, respectively.

Table 1: Descriptive data of patients with gestational diabetes mellitus

Variable	Number (127) mean±SD	Range
Age (years)	34.58±5.18	23
Parity	3.26±1.71	7
Maternal weight gain (kg)	8.13±4.27	33
Pre-conceptional BMI	29.71±5.59	24
Fasting glucose level	94.31±12.66	72
First-hour glucose level	198.31±33.40	190.80
Second-hour glucose level	169.60±36.69	203.4
Third-hour glucose level	137.64±38.03	198
Third trimester HbA1c	5.39±0.66	3.50

Descriptive data of patients with GDM

Approximately half of the enrolled patients (56.7%) required insulin therapy during pregnancy, whereas for the remaining 43.3%, MNT was sufficient to achieve glycemic control. Only 15.7% of the participants were observed to have a normal BMI, whereas the remaining 36.8% were overweight and 48% were obese. In a previous pregnancy, 38.6% of them were diagnosed with GDM. Hypothyroidism and hypertension were reported in 20.5% and 17.3% of the study population, respectively. The descriptive data for GDM are shown in Figure 1 and Supplementary Table S1.

Determinants of gestational diabetes therapy among patients with GDM

In the insulin and diet groups, the mean preconception BMI was 30.7 ± 5.68 kg/m^2 for insulin therapy patients and 28.3 ± 5.24 kg/m^2 for non-insulin therapy patients (P = 0.01). The mean age of participants using therapy was higher than that of those on a diet (35.32 ± 5.11 and 33.62 ± 5.16 years, respectively) (P = 0.06). The mean number of insulin-treated participants was higher (3.85 ± 1.72) than that of non-insulin-treated participants (2.84 ± 1.61) (P = 0.01). The insulin group had a higher mean HbA1c level (5.54 ± 0.71) than the diet group (5.170.52) (P = 0.01). All differences among the respective groups were statistically significant. The maternal characteristics of both study groups are shown in Table 2.

Results of binary regression

Table 3 shows the determinants of insulin use in patients with GDM. Except for HbA1c, which lacks substantial data, the potential influence of several variables was

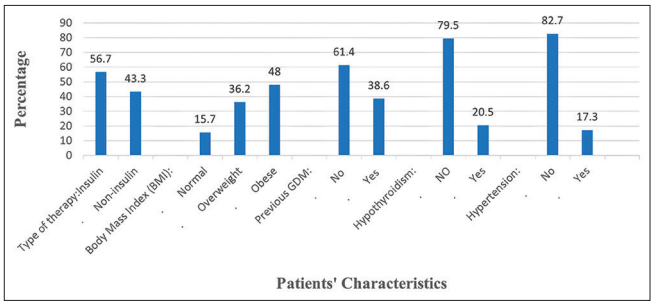

Figure 1: Descriptive data of patients with gestational diabetes mellitus (GDM)

Table 2: Maternal characteristics in the insulin and diet groups

Group variables	Insulin		Diet		*P*
	Number	%	Number	%	
History of previous gestational diabetes mellitus					
No	40	55.6	38	69.1	0.09
Yes	32	44.4	17	30.9	
Hypothyroidism					
No	55	76.4	46	83.6	0.22
Yes	17	23.6	9	16.4	
Hypertension					0.07
No	56	77.8	49	89.1	
Yes	16	22.2	6	10.9	
	Mean±SD		Mean±SD		*P*
Age (years)	35.32±5.11		33.62±5.16		0.07
Parity	3.85±1.72		2.84±1.61		0.01*
Pre-conceptional BMI	30.77±5.68		28.31±5.24		0.01*
Maternal weight gain	8.03±4.78		8.27±3.55		0.75
Fasting glucose level	98.01±14.82		89.79±7.28		0.00*
First-hour glucose level	203.40±37.47		192.36±27.05		0.08
Second-hour glucose level	173.33±38.62		165.23±34.15		0.24
Third-hour glucose level	141.23±41.59		133.86±34.05		0.42
Third trimester HbA1c	5.54±0.71		5.17±0.52		0.02*

*$P \leq 0.05$, considered significant

Table 3: Binary regression analysis for the factors associated with insulin therapy among patients with GDM

Variable	B. coefficient	OR	95% CI for (OR)		*P*
			Lower bound	Upper bound	
Age	0.001	1.001	0.888	1.129	0.986
Parity	0.347	1.415	0.959	2.087	0.08
Pre-conceptional BMI	-0.007	0.993	0.885	1.115	0.907
Maternal weight gain	-0.086	0.917	0.752	1.119	0.394
Fasting glucose level	0.104	1.110	1.034	1.191	0.004*
First-hour glucose level	0.008	1.008	0.972	1.046	0.657
Second-hour glucose level	0.011	1.011	0.981	1.042	0.483
Third-hour glucose level	-0.008	0.992	0.869	1.014	0.464
Previous GDM	0.599	1.821	0.562	5.902	0.318
Hypertension	0.251	1.286	0.265	6.238	0.755
Hypothyroidism	0.073	1.076	0.276	4.195	0.916

GDM, gestational diabetes mellitus

investigated. The results were estimated to be as follows: OR = 1.821, 1.415, 1.286, 1.110, 1.011, 1.008, 1.001, and 1.076 for previous GDM history, number of childbirths, hypertension, fasting glucose level, second-hour glucose level, first-hour glucose level, age, and hypothyroidism, respectively. This was statistically significant ($P = 0.004$) for fasting glucose levels.

Discussion

The prevalence of GDM is observed to be on the rise. Here, the potential risk factors underlying the use of insulin for treating GDM in women visiting King Abdulaziz University Hospital in Jeddah were assessed. The fasting glucose level, HbA1c level, BMI, and parity were significantly higher in patients who required insulin. Notably, the only significant predictor of insulin use was the fasting glucose level.

All clinical and biochemical variables were included in the binary regression analysis, except the HbA1c level, which was excluded owing to missing data. All OGTT readings were higher in the insulin group; however, only the fasting glucose reading showed statistical significance and was the significant predictor of insulin use. Other studies have shown that the fasting and second-hour OGTT results are predictors of insulin use in women with GDM.[17] In a healthy pregnancy, insulin resistance increases in the late second trimester to levels comparable to those observed in

type 2 diabetes mellitus. Due to adequate beta-cell compensation for higher insulin secretion, most women remain normoglycemic. However, GDM develops when the beta-cell compensation is insufficient for the level of insulin resistance and hepatic glucose production.[18] These findings could be attributed to pregnant women having lower fasting glucose levels than non-pregnant women. In normal pregnancy, a decrease in the fasting glucose level (2 mg/dL) occurs between gestational weeks 6 and 10.[19] If starting the second trimester of pregnancy with a higher fasting glucose level could indicate a disturbance in the normal physiological adjustments in fasting glucose levels, it could, in turn, explain the concordant results of this study and previous studies.

In this study, the mean age of the pregnant women was 34.58 ± 5.18 years. In an earlier study on Saudi women visiting the Maternity and Children Hospital in the Medina region (2011–2014), the mean age of the Saudi women involved was 30.5 ± 6.1 years.[5] In another Saudi study on women visiting the primary healthcare unit in the Riyadh region, the mean age ranged between 26 and 30 years.[20] Therefore, it is apparent that the mean age in our study was higher than that reported in previous studies. This higher mean age could be related to several factors, including the raised age of marriage in Jeddah city because the percentage of women who complete higher education has increased.[21] Another reason is that the patients visiting our hospital as a tertiary care center could be those with high-risk features, including older age and multi-parity women, in comparison to earlier studies. It has been documented that age is one of the predictors of insulin therapy in women with GDM first treated with metformin.[22] The explanation for the previous data could be related to diminished insulin sensitivity, impairment of lipid metabolism, and impaired glucose tolerance with advancing age. Additionally, middle-aged women are more likely to become obese,[23] which is in accordance with this study, as older women and those with a higher BMI showed a need for insulin therapy.

The number of women who begin pregnancy with an increased BMI is rising. According to previous data, most women fail to adhere to the recommendations of the Institute of Medicine criteria, which are based on the pre-conception BMI.[24] It has been reported that the maternal BMI during pregnancy is an important predictor of pregnancy outcomes[17] because below-average weight gain is associated with preterm labor and infants with low weight at birth. An above-average gain is associated with an increased risk of gestational hypertension, type 2 diabetes mellitus, cesarean sections, and infants with higher than recommended weight at birth. It has been recommended that pre-pregnant obese women should gain lesser weight (~5–9 kg) than non-obese women (~11.5–16 kg).[25-27]

The mean BMI of the women involved in this study was 30.7 ± 5.68 and 28.3 ± 52.4 kg/m^2 in the insulin and non-insulin groups, respectively, which indicates a high BMI in most of the study sample. It is apparent from the data that the maternal weight gain was less than the average physiological limit (~8 kg, with no significant differences between the study groups). According to previous reports, the average increase in body weight differs based on several factors, including the number of fetuses per pregnancy and pre-pregnancy BMI.[28,29] Additionally, this below-average weight gain is a good sign for diet control during pregnancy to prevent the side effects of weight gain in patients with gestational diabetes. Researchers have found that obese women gain less weight than lean women during pregnancy. Furthermore, obese women may not show a change in the carbohydrate/insulin requirement ratio compared to lean women.

The investigators suggest that this could be related to the mitigation of the apparent increase in insulin resistance by weight loss that occurs in early pregnancy in obese women.[30] During pregnancy, placental hormones, such as estrogen, progesterone, and human placental lactogen, lead to changes in the maternal metabolic state causing insulin resistance. Consequently, insulin secretion is significantly enhanced to overcome this resistance. Therefore, the impaired ability of pancreatic beta cells to cope with these physiological changes is the basis of GDM.[31] Obese women are expected to develop insulin resistance late in pregnancy.[32] Several factors may contribute to the efficacy of non-insulin therapy in obese women. The level of activity during pregnancy may contribute to higher insulin sensitivity and hence prevent the need for insulin.[33]

Earlier studies have found a higher rate of GDM recurrence in multiparous women than in primiparous women.[34] However, other studies have reported contradictory data. According to the WHO and American Diabetes Association criteria, a previous study on Saudi multiparous women in Riyadh showed that GDM was 8.29 times more likely to occur in multiparous women than in nulliparous women. After controlling for maternal age and abortion history, nulliparous women were 2.95 times more likely to develop GDM than parous women. When the age of parous women increased from 20 to 40 years, their chance of developing GDM increased from 2% to 21%. A high prevalence of GDM among grand multiparas could be explained by

the confounding effect of maternal age.[35] This study showed that insulin requirement is higher in multiparas; however, parity is not a predictor of insulin use.

It can be concluded from our findings that the major predictor for the need for insulin therapy in women with GDM is the fasting blood glucose level. However, our findings cannot be generalized owing to the relatively small sample size and lack of HbA1c data. Moreover, several intervening factors, such as the level of activity, family history of diabetes mellitus, and ethnicity of the pregnant women, should be taken into consideration.

Conclusion

The most important predictor of the need for insulin therapy is the fasting glucose level. A risk assessment model including clinical, and biochemical factors, as well as physical activity is required to predict whether women will require insulin therapy along with MNT during their pregnancy to achieve glycemic control.

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Conflicts of interest

There are no conflicts of interest.

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Supplementary Table S1: Descriptive data of GDM patients

Variable	Number (%)
Type of therapy	
Diet	55 (43.3%)
Insulin	72 (56.7%)
BMI categories	
Normal	20 (15.7%)
Overweight	46 (36.2%
Obese	61 (48%)
Previous GDM	
Yes	49 (38.6%)
No	78 (61.4%)
Hypothyroidism	
Yes	26 (20.5%)
No	101 (79.5%)
Hypertension	
Yes	22 (17.3%)
No	105 (82.7%)

GDM, gestational diabetes mellitus