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Predictors of Insulin Therapy Requirement in Gestational Diabetes: A Cohort Study

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ABSTRACT

Managing Gestational Diabetes Mellitus (GDM) typically involves a combination of dietary control and/or Antenatal Insulin Therapy (AIT). The aim of this study was to evaluate the efficiency of diverse maternal characteristics and biological indicators identified during GDM diagnosis in anticipating the requirement for AIT to achieve glucose targets.

It is a retrospective longitudinal study that included women diagnosed with GDM. A cohort of 380 women was examined, and a range of demographic and medical variables were evaluated.

The average age in our patient group was 34 ± 5 years, ranging from 20 to 46 years. Among them, 73% needed AIT, while 100 patients achieved glycemic goals solely through Medical Nutrition Therapy (MNT). Notably, those requiring insulin had prior history of obesity (24%), gestational diabetes (12%), and macrosomia (18%) (p=10-3). The average hemoglobin level was 12.4 g/dl, and none of our patients were anemic. Patients meeting glycemic targets via MNT had higher total carbohydrate intake upon GDM diagnosis (p=0.02). Those necessitating AIT were diagnosed at an average gestational age (GA) of 24±6 weeks, significantly earlier than the 25±6 weeks observed in patients following MNT (p < 10-3).

Recognizing the diverse spectrum of glucose intolerance severity among women with GDM necessitates a stratified classification for management strategies. Notably, a higher HbA1C at diagnosis signals the potential need for intensified monitoring by specialized healthcare providers.

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Introduction

Gestational Diabetes Mellitus (GDM), according to the criteria of the World Health Organization (WHO), is characterized by elevated glycemia levels resulting from impaired glucose tolerance first occurring or diagnosed during pregnancy, regardless of the required treatment or postpartum evolution [1].

GDM is one of the most common complications of pregnancy with an increased risk of fetal as well as maternal morbidity and mortality. Its prevalence ranges from 3.6% to 13.6% worldwide and can reach 20% with diagnostic criteria adopted by the International Association of Diabetes and Pregnancy Study Groups (IADPSG) [2]. This variability is linked to the heterogeneity of studied populations and the screening criteria used. Overall, the Middle East and North Africa displayed the highest prevalence of GDM, followed by Southeast Asia, South and Central America, Africa, and North America (median prevalence of 12.9%, 11.7%, 11.2%, and 8.9%, respectively), while Europe had the lowest prevalence (5.8%) [3]. The prevalence of GDM is steadily increasing worldwide in parallel with the surge in obesity and Type 2 Diabetes Mellitus (T2DM) epidemics. This rise observed in recent years may be attributed to changes in dietary habits, increased maternal age during pregnancies, and elevated Body Mass Index (BMI) [4].

To minimize the risks of perinatal mortality and morbidity, the primary aim in managing blood glucose levels during pregnancy in women with GDM is to maintain glycemic levels as close to the normative range as achievable [5].

Women diagnosed with GDM are recommended to conduct self-monitoring of blood glucose levels. If achieving the targeted glycemic control through dietary adjustments proves unsuccessful, the introduction of Antenatal Insulin Therapy (AIT) becomes necessary. Many studies have effectively pinpointed specific maternal characteristics or biochemical markers upon GDM diagnosis that correlate with the need for AIT [6]. They tried to validate predictive models for AIT. These models incorporate several independent variables identified at GDM diagnosis: age, pre-pregnancy BMI, Gestational Age (GA) at diagnosis, FBG, Glycated Hemoglobin (HbA1c) at diagnosis, family history of

T2DM, and previous history of GDM. Early screening using these predictors could be crucial in identifying high-risk women requiring prioritized attention at our diabetology department.

The aim of this study was to evaluate the efficiency of diverse maternal characteristics and biological indicators identified during GDM diagnosis in anticipating the inadequacy of Medical Nutrition Therapy (MNT) and the requirement for AIT to regulate glucose levels during the course of pregnancy.

Materials and Methods

This is a retrospective study conducted at a single center. We focused on women monitored for GDM. The diagnosis of GDM was confirmed through an Oral Glucose Tolerance Test (OGTT75mg) with a 75mg glucose load.

In our study, we included 380 pregnant women diagnosed with GDM based on diagnostic criteria adopted by the IADPSG, which align with the diagnostic criteria of the American Diabetes Association (ADA) [1,3].

According to these recommendations, it is advisable to conduct FBG testing in the first trimester of pregnancy in the presence of risk factors. Otherwise, testing of FBG and blood glucose levels one hour and two hours after the ingestion of 75 grams of glucose, between 24 and 28 weeks of gestation, is recommended. We did not include patients with Known diabetic patients before pregnancy and patients with FBG ≥ 1.26g/L during the 1st trimester.

A dietary survey conducted during a dietary interview and employing the 24-hour recall method coupled with dietary history. It was uniformly administered by the same dietitian for all patients. The outcomes were juxtaposed with the recommended nutritional intake guidelines delineated by the National Agency for Food Safety (ANSA) in 2019 [7].

Our patient management followed the guidelines of the ADA [8]. Dietary counseling was administered by the dietitian. Initiation of insulin therapy occurred if glycemic goals were unmet after 15 days despite MNT.

We computed absolute and relative frequencies (percentages) for qualitative variables. Means, medians, standard deviations, and extreme values were calculated for quantitative variables.

Comparisons between two means in independent datasets were conducted using the student's t-test. Quantitative variables underwent transformation into binary qualitative variables.

In determining the threshold, we used Receiver Operating Characteristic (ROC) curves. The Area Under the Curve serves as a comprehensive metric for evaluating the diagnostic accuracy of the tested classifier, with higher values indicative of superior discriminatory power. Percentage comparisons in independent datasets were assessed through Pearson's chi-square test or, when unsuitable, Fisher's exact two-tailed test for comparing two percentages. Risk factor exploration entailed calculating the Odds Ratio (OR) to gauge the event's likelihood when exposed to a factor versus non-exposure. A stepwise descending logistic regression multivariate analysis identified independently associated risk factors, estimating adjusted ORs to measure individual factor significance. The logistic regression model encompassed variables with univariate significance levels below 0.2 and clinically relevant variables (reported in the literature). All statistical tests maintained a significance threshold of 0.05.

Results

The mean age of our patients was 34 ± 5 years, ranging from 20 to 46 years. The average gravidity was 2±1, ranging from 1 to 10. The average parity was 1±1, ranging from 0 to 5.

The mean pre-gestational BMI was 27 ± 6 kg/m². Overweight and obesity were present in, respectively, 27% and 35%. Insulin was required by 73% of our patients, totaling 280 individuals. Most overweight patients (74%) required insulin to reach their glycemic targets (p=10-3) (Table1).

Table 1: Clinical Characteristics of Patients followed-up for GDM, Classified according to their Treatment

On AIT (n=280) Median [Q1–Q3] N(%)		On MNT (n=100) Median [Q1–Q3] N(%)	P
Age≥35 years (n=165)	129/280	36/100	0.081
Age <35 years (n=215)	151/280	64/100	
Hypertension	6/280	2/100	-
Obesity	92/280	34/100	10-3
GDM	47/280	15/100	10-3
Macrosomia	70/280	18/100	10-3
FBG* (mmol/l)	5.6 (4.9-5.9)	5.7 (5.1-6.5)	0.39
Glycemia at h1 (mmol/l)	10.8 (10.1-12.4)	10.8 (10-11.8)	0.93
Glycemia at h2 (mmol/l)	9.5 (6.8-9.5)	9.7 (8.3-10.8)	0.62
BMI<25kg/m²	180 (73%)	66 (26%)	10^{-3}
BMI≥25kg/m²	100 (74%)	34 (25%)	
Total carbohydrates (% of TEI)	53 (50-56)	55 (50-58)	0.02
Total fats (% of TEI)	35 (30-37)	33 (31-37)	0.054
Proteins (% of TEI)	10 (9-12)	11 (10-11)	0.065
Caloric intake (Kcal/day)	2656 (2200-3100)	2688 (2450-3177)	0.824
TSH (mU/l)	1.54 (1.08-2.2)	1.68 (1.18-2.3)	0.524
Cholesterol (mmol/l)	5.39 (4.9-6.1)	5.2 (4.6-6)	0.001

Triglycerides (mmol/l)	1.96 (1.53-2.83)	2.04 (1.52-2.59)	0.609
HDLc (mmol/l)	1.5 (1.1-1.6)	1.44 (1.13-1.65)	0.773
LDLc (g/l)	2.57 (2.2-3.6)	2.7 (2.2-3.5)	0.098

Note: MNT: Medical Nutrition Therapy, **AIT:** Antenatal Insulin Therapy, **GDM:** Gestational Diabetes Mellitus, **FBG:** Fasting Blood Glucose, **BMI:** Body Mass Index, **TEI:** Total Energy Intake, **TSH:** Thyroid-Stimulating Hormone, **HDLc:** High-Density, Lipoprotein Cholesterol, **LDLc:** Low-Density Lipoprotein Cholesterol.

Glycemic targets for GDM were achieved through MNT for 100 patients.

We observed that 46% of patients, on AIT, were over the age of 35 years (p=0.081).

The personal history of patients on AIT included obesity, GDM, and macrosomia at rates of 24%, 12%, and 18%, respectively ($p=10^{-3}$). The average GA at the diagnosis of GDM was 24±6 weeks among patients who required AIT, significantly lower than the average GA among patients who were on MNT 25±6, $p < 10^{-3}$.

There was a non-significant difference in FBG among our patients.

The findings indicated that the median HbA1c level of patients requiring AIT was 5.5% (5-5.9%), which is higher than the HbA1c levels observed in patients following MNT (5.3% (5-5.4%), $p=10^{-3}$). The average hemoglobin level was 12.4 g/dl, and none of our patients were anemic.

We observed that the total carbohydrate intake was higher at the time of diagnosing GDM among patients who achieved their glycemic targets through MNT (p=0.02).

We initially studied the different predictive factors for insulin use through both univariate and multivariate analyses, considering our previous results and data from the literature. These included personal history of hypertension, previous GDM, overweight, age over 35 years, carbohydrate intake, and HbA1C at the time of diagnosis.

However, elevated HbA1C emerged as an independent predictive factor for the need for insulin therapy (OR=4, CI (3-9), $p=10^{-3}$).

The conclusive model generated a Receiver Operating Characteristic (ROC) curve, displayed in (Figure 1), which revealed an Area Under the Curve (AUC) of 0.7, ascertained with a 95% confidence interval ranging from 0.67 to 0.74.

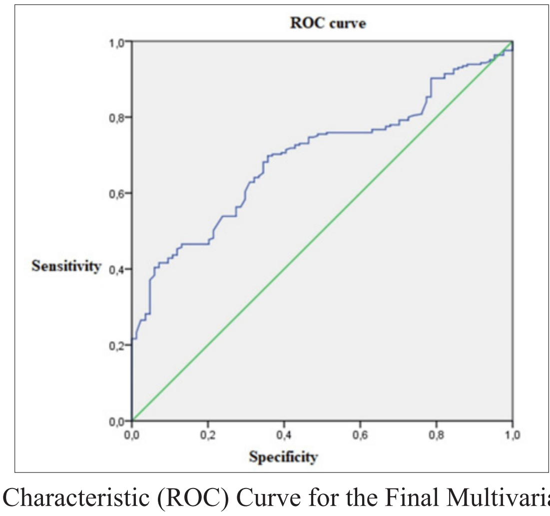

Figure 1: Receiver Operating Characteristic (ROC) Curve for the Final Multivariable Logistic Regression Model

Furthermore, through the assessment of predetermined cutoff points, we computed the model's sensitivity, specificity, positive predictive value (PPV), negative predictive value (NPV), and accuracy. These findings are presented in Table 2.

Table 2: Sensitivity, Specificity, Positive Predictive Value, Negative Predictive Value and Accuracy for Different Cut-Off Points of the Model

Cut-Off Point	Sensitivity	Specificity	PPV	NPV	Accuracy
50%	96.3	5	75.3	3	73.5
80%	44.4	88	91.5	35.2	55.6

Note: PPV: Positive Predictive Value, NPV: Negative Predictive Value

Discussion

Due to the rising prevalence of obesity among women in their reproductive years, the incidence of GDM is expected to keep rising. Studies have shown higher occurrences of obesity and glucose metabolism issues among peripubertal offspring whose mothers had mild, untreated GDM.

MNT stand as a fundamental aspect of treatment for all women diagnosed with GDM. Around 80% to 90% of these women can achieve therapeutic targets through nutritional therapy. Numerous advantages have been linked to lifestyle interventions, encompassing reduced risks of macrosomia and neonatal adiposity, as well as an enhanced probability of reaching postpartum weight objectives [9]. When MNT doesn't achieve the desired glycemic targets, pharmacological intervention becomes necessary. Insulin stands as the initial choice for pharmacotherapy in GDM due to its limited placental crossing [10]. Basal insulin (long-acting or intermediate-acting) addresses fasting hyperglycemia, while prandial insulin (rapid-acting) targets postprandial hyperglycemia.

According to our results, we observed a significant AIT rate of 73%, aligning with several studies (30%-50%) [11,6]. This difference could be attributed to our systematic and proactive management approach, underpinned by rigorous multidisciplinary oversight.

Many studies have investigated maternal factors such as age, pre-pregnancy BMI, ethnicity, or prior history of GDM, along with biological markers like FPG, elevated HbA1c (>5.4%), and increased values in OGTT75 aiming to establish their correlation with AIT.

According to our results, 46% of patients, on AIT, were over the age of 35 years (p=0.081).

Our result is consistent with that of Barnes et al., where the age (>30 years) emerged as a predictor for requiring insulin therapy, which differs from the outcomes reported in a sizable study conducted by González-Quintero et al. involving 2365 participants [12,13].

Advanced age is often associated with other risk factors such as higher weight and abdominal fat [14]. Indeed, the incidence of GDM increases with maternal age, reaching a plateau around the age of 40.

According to Fulop et al., advanced maternal age is linked to reduced insulin sensitivity along with dysfunction in pancreatic β cells, which may explain the exacerbation of insulin resistance in older patients and the AIT requirement in this population [15].

We found that a personal history of GDM, and macrosomia was more frequent among patients on AIT, at rates of 12%, and 18%, respectively (p<10-3).

In a broad retrospective study conducted in Australia, covering a range of ethnic backgrounds, a predictive model was established for AIT [12]. This model effectively forecasts the need for AIT by analyzing seven significant independent variables identified during GDM diagnosis. Among these variables, previous GDM emerged as an independent factor alongside others such as age, pre-pregnancy BMI, GA at diagnosis, FBG, HbA1c, and family history of T2DM [12].

In our study, among patients necessitating AIT, the average GA at GDM diagnosis stood at 24±6 weeks, notably lower compared to patients employing MNT, whose average GA was 25±6 weeks (p < 10-3). However, in research conducted by Bakiner et al. about 300 patients, they found that patients needing just MNT were diagnosed with GDM at an average GA of 26.1 ± 5.1 weeks, a notably earlier stage compared to those managing GDM with AIT, whose average GA was 27.6 ± 4.4 weeks (p=0.008) [16].

Amanda et al. highlighted that maternal BMI was the sole variable showing a statistically significant correlation with the necessity for AIT. These results align with the research conducted by Meshel et al., further confirming that, among various factors, higher maternal BMI notably correlates with the need for AIT [17]. According to our study, most overweight patients (74%) required insulin to reach their glycemic targets (p=10-3).

In a thorough retrospective study, outcomes were assessed across different pre-pregnancy BMI categories and among groups who were either on MNT or AIT [18]. Among obese women diagnosed with GDM, achieving targeted glycemic levels was linked to improved outcomes, notably observed within the subset of women undergoing AIT.

A literature review, based on observational studies and published in 2016, established a link between diet and the incidence of GDM but didn't explore the relationship between nutritional profile and AIT requirement in GDM [19]. In our study we observed that the total carbohydrate intake was higher at the time of diagnosing of GDM among patients who achieved their glycemic targets through MNT. One study involved two groups, each comprising six women diagnosed with GDM at 31 weeks of gestation. The first group followed an isocaloric diet (40% carbohydrates, 45% fats, 15% proteins), while the second group followed a different diet with macronutrients distributed as follows: 60% carbohydrates, 25% fats, 15% proteins. This study demonstrated that the second diet regimen reduced maternal insulin resistance, whereas the first regimen did not show the same effect [20].

The observed correlation could be clarified, also, by the significant impact of lifestyle adjustments, specifically dietary interventions, on glycemic outcomes, particularly postprandial glycemia, in individuals with a history of higher carbohydrate intake. Variations in macronutrient distribution likely play a critical role in regulating postprandial glucose levels, subsequently influencing maternal insulin resistance among those diagnosed with GDM.

Various studies have identified elevated values in Oral Glucose Tolerance Tests (OGTT) - beyond FBG levels - as independent indicators necessitating insulin therapy. Earlier studies indicated that elevated 1-hour blood glucose levels during OGTT were independent predictors. Additionally, Wong et al. identified an elevated 2-hour OGTT value as an independent predictor for the need for insulin therapy [10]. In our study, there was a non-significant difference in FBG among patients.

Akinci and colleagues highlighted a significant link between FBG over 105 mg/dL and the requirement for additional insulin therapy in cases of GDM [21].

Similarly, Langer's study revealed a compelling correlation between FBG surpassing 105mg/dl and adverse maternal-perinatal outcomes, including fetal macrosomia, neonatal hypoglycemia, hypertensive syndromes, and a higher likelihood of cesarean delivery [11]. Their findings strongly suggest that FBG beyond this threshold signal the necessity for initiating insulin therapy. Additionally, they observed that only 70% of pregnant women maintaining fasting glucose levels below 95 mg/dL were able to achieve adequate glycemic control through dietary interventions alone.

Indeed, women diagnosed with GDM demonstrate deficiencies in both insulin sensitivity and insulin secretion [22]. The literature supports the idea that FBG can predict insulin needs, emphasizing the significant impact of deficiencies in basal insulin secretion

Our results revealed that the median HbA1c level among patients needing AIT stood at 5.5% (5-5.9%), surpassing the HbA1c levels seen in patients adhering to MNT, which averaged at 5.3% (5-5.4%) (p=10-3). Elevated HbA1C emerged as an independent predictive factor for the need for insulin therapy (OR=4, CI (3-9), p=10-3). The absence of anemia within our study population substantiates the robustness of the HBA1C cutoff derived from our analytical investigation.

Similar to FBG assessed during an OGTT, HbA1C has arisen as a reliable predictor for insulin requirement in pregnant patients with GDM [23]. Our study findings align with Gonzalez-Quintero and Sapienza's research [13,24], affirming HbA1C as a robust marker indicative of glycemic control in GDM cases. Furthermore, recent investigations by Clayton et al. underline a correlation between elevated HbA1C levels like other clinical parameters with the necessity for AIT in GDM. Considering these clinical markers for early assessment of glycemic control in pregnant patients may facilitate the early identification of high-risk GDM to prevent potential complications [25].

These results align with the research conducted by Ducamme et al. and two other studies, one by Wong et al. and another by Alunni et al., shed light on the significance of HbA1c levels in pregnant women diagnosed with GDM [10,26].

Wong et al.'s retrospective study suggested that close monitoring during pregnancy is crucial for women with elevated HbA1c levels (>5.4%) at diagnosis, although they didn't specifically consider HbA1c as a predictor for requiring pharmacological treatment. However, Alunni et al.'s more recent research focused on this aspect, revealing a strong correlation between higher HbA1c levels at GDM diagnosis and the need for AIT for glycemic control [27].

Conclusions

Our research emphasizes on the significance of HbA1c levels during GDM diagnosis as an independent predictor for requiring AIT to manage glycemic targets during pregnancy. These findings provide valuable insights guiding GDM management. It's crucial to educate all physicians managing pregnant women with GDM about the clinical and biological factors present at GDM diagnosis that predict the need for AIT. This precise identification of high-risk population holds practical implications for healthcare providers, aiming to prevent maternal and fetal complications associated with GDM. Developing and validating a predictive score for AIT necessity in GDM management aims to enable early intervention for these patients.

Ethics Approval: Our study followed ethical standards outlined by the responsible committee on human experimentation and the Helsinki Declaration. Approved by the Institutional Review Board of the Faculty of Medicine of Sousse, Tunisia (2020-08-049).

Consent for Publication: Not applicable.

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