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*Original Research*

# Safety and Appropriateness in the Management of the Treatment Pathway of Pregnant Women with Gestational Diabetes

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**Abstract**

Gestational diabetes (GDM) is quite common during pregnancy, and its prevalence is rising because of the increased overweight and obesity rates. In patients with GDM, proper glycemic control, adherence to a suitable diet and antidiabetic treatments can reduce the likelihood of maternal-neonatal complications. For this reason, this study aims to assess the therapy adherence of pregnant women with GDM. Treatment adherence was assessed by both glucometer and diabetologist's analysis reported in the electronic medical record. Cohen's Kappa was used to assess the agreement between the two classifications. Moreover, a multivariate logistic regression analysis was performed to identify potential risk factors for non-adherence to treatment. Overall, 287 patients were enrolled, and 271 were available for follow-up. Low concordance between the glucometer and the diabetologist's analysis was found, mainly due to the complexity of patients with GDM. Indeed, 46% of patients were classified as not adherent due to glucometer results and 42% based on medical assessment. This study highlights the importance of monitoring patients with gestational diabetes to assess and increase adherence to therapy properly.

**Keywords:** gestational diabetes; adherence; glucometer analysis; diabetologist analysis

## 1. Introduction

Gestational diabetes (GDM), the most common medical disorder of pregnancy, is defined as "a glucose intolerance of variable magnitude that begins or is first diagnosed in pregnancy" and, in most cases, resolves after childbirth [1]. GDM usually arises in the second part of pregnancy; therefore, the optimal time for screening is the 24–28th week of gestation [2]. In some particularly high-risk conditions, such as obesity, previous GDM and altered fasting blood glucose (IFG) before or at the beginning of pregnancy can determine the early onset of GDM. In the highest-risk cases, an approach including lifestyle modifications and early screening at 16–18 weeks of gestation is recommended, to be repeated, if negative, at 24–28 weeks [1]. Although estimates of GDM are often thought to be low, prevalence estimates of this disease are around 11–13%, and they have a preeminent impact on resource management for diabetes and obstetric facilities [1]. The incidence of GDM is increasing due to progressing trends in obesity and advancement of maternal age. If not diagnosed and consequently not treated, GDM carries significant risks both for the mother (such as hypertension and more frequent recourse to cesarean delivery) and for the fetus and the newborn (increased incidence of macrosomia, hyperbilirubinemia, hypocalcemia, polycythemia, hypoglycemia) [3,4], even in its mild forms. GDM is also related to 7-fold increased risk of developing type 2 diabetes; therefore, a lack of screening after pregnancy could result in a missed opportunity to prevent the same in women who have had GDM [4,5].

Maintaining proper glycemic control and adherence to diet or antidiabetic treatment can reduce the likelihood of maternal-neonatal complications in patients with GDM [6,7]. However, various studies show that women are not fully adherent to treatment for GDM. For instance, Staynova R *et al.* [8] reported that 80% of patients with GDM are adherent to glycemic monitoring, while the remaining 20% are not.

For this reason, this study aims to assess the adherence to therapy of pregnant women with GDM.

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## 2. Materials and Methods

### *2.1 Study Subjects and Recruitment*

The study was approved by Friuli-Venezia Giulia Regional Ethical Committee (Project No. 0003915). It is a multicenter prospective observational study conducted at Diabetology Departments in Friuli Venezia Giulia between January 2019 and November 2021. The study evaluated adherence to proposed therapies (diet or drug therapies) through diabetologists and glucometer analysis. Eligible patients who fulfilled the inclusion criteria (age $\geq$18 years, pregnant woman with GDM, understanding the Italian language) were enrolled and signed the informed consent. Patients with cognitive difficulties and those with no gestational diabetes (diabetes type I and II) were excluded from the investigation.

### *2.2 Data Collection*

Data were collected in ad hoc electronic form using the REDCap platform. Patient data regarding personal data, allergies/intolerances, other pathologies, drug use, and adherence to diabetic therapies (diet or pharmacological treatment) were collected.

Patients with GDM were routinely followed up at the reference and diabetes centres. The diabetologist evaluation was included in the electronic file, and the patients were classified as adherent or non-adherent to the treatments. The pharmacist also noted the observance of the treatment by analyzing the glucometer. The patients were divided into two groups, adherent and non-adherent, according to the analysis made by the diabetologist and that performed by the glucometer. Patients were adherent if glucose analysis showed fasting blood glucose values $\leq$90 mg and 1 hour after a meal $\leq$130 mg. A further analysis was conducted to evaluate the concordance between the two analyses.

The number of women who used insulin or other antidiabetic treatments during the follow-up was detected. An average of three follow-ups was collected for each patient. Any error in therapy management, namely any medication not appropriate for pregnant women, was reported.

### *2.3 Data Analysis*

Categorical variables were reported as counts and percentages. Continuous variables were expressed as the median and interquartile range (IQR) since none of them fulfilled the normality assumption. Between-group differences (patients adherent to treatment vs non-adherent) were evaluated with the chi-square test (or the Fisher's exact test, when appropriate) for categorical variables and the Wilcoxon-Mann-Whitney test for continuous variables. Concordance between the two classifications (glucometer analysis vs diabetologist's assessment) was assessed by computing the Cohen's Kappa coefficient. Logistic regression analysis identified the risk factors for non-adherence to treatment. A significance level of 10% was applied as a criterion of inclusion for variables in multiple regression analyses based on previously estimated univariate models. Results were presented as Odds Ratios (ORs) with a 95% confidence interval (95% CI). Data were analyzed with StataCorp. 2019. Stata Statistical Software: Release 16. College Station, TX, USA: StataCorp LLC.

## 3. Results

The study revealed that the diagnosis of GDM was generally performed at a median gestational age of 27 weeks (IQR: 24–29 weeks). Overall, 287 patients were enrolled (Table 1). The median age was 34 years (IQR: 31–38 years). Familiarity with diabetes was reported in 54.2% of women. Comorbidities were observed for 77 women (26.8%), 75 of whom used drugs for the reported pathologies (26.1%).

**Table 1. Enrolled patients' characteristics.**

| Enrolled patients | N = 287 |
|---|---|
| Age (years) | 34 (31–38) |
| Gestational week | 27 (24–29) |
| Previous pregnancies | 1 (0–2) |
| Familiarity for diabetes | |
| No | 147 (51.2) |
| Yes | 140 (48.8) |
| Previous GDM | |
| No | 243 (84.7) |
| Yes | 44 (15.3) |
| Comorbidity | |
| No | 210 (73.2) |
| Yes | 77 (26.8) |
| BMI | 25.5 (22.5–29.8) |
| BMI classes | |
| Underweight | 1 (1.0) |
| Normal Weight | |
| Overweight | 79 (27.7) |
| Obesity I | 49 (17.2) |
| Obesity II | 15 (5.3) |
| Obesity III | 11 (3.9) |
| Diet therapy | |
| No | 29 (10.1) |
| Yes | 258 (89.9) |
| Insulin therapy | |
| No | 258 (89.9) |
| Yes | 29 (10.1) |
| textitTypes of insulin | |
| Long acting | 25 (86.2%) |
| Rapid acting | 1 (3.4) |
| Rapid and long acting | 3 (10.3%) |
| Other antidiabetic therapy | |
| No | 287 (100.0) |
| Yes | 0 |
| Drugs for other pathologies | |
| No | 212 (73.9) |
| Yes | 75 (26.1) |
| Contraindicated drugs | |
| No | 42 (56.0) |
| Yes | 33 (44.0) |

At the time of enrollment, 257 patients (89.6%) were on diet therapy alone, and all the 29 patients on medication (10.1%) took insulin. For one patient, the information about diet therapy was missing.

Most patients took long-acting insulin (n = 25, 86.2%). Off-label drugs were taken by 32 women (43.2%), and for 20 of them (60.5%), the drug was acetylsalicylic acid. The adherence evaluation was performed for 271 patients because 16 subjects did not participate in the visits scheduled by their diabetologists. Glucometer adherence data measured during follow-ups revealed that there were 126 patients reported as not adherent (46.5%) and 145 adherent patients (53.5%) (Table 2).

Correct fasting (95.9% vs 82.5%) and postprandial blood glucose (94.5% vs 81.0%) measurements were reported more frequently for patients adherent to treatment ($p < 0.001$). In addition, blood glucose values $\leq$90 mg fasting and $\leq$130 mg one hour after a meal were also more controlled in adherent than in non-adherent patients ($p = 0.005$, $p = 0.001$). The number of subjects on diet therapy alone was significantly higher in the adherent group (60.0% vs 33.3%; $p < 0.001$).

Diabetologists' analysis reported 116 non-adherent patients (42.8%) and 155 adherent patients (57.2%). The proportion of patients on diet therapy alone was significantly higher in the adherent group (53.6% vs 39.7%; $p = 0.023$). Consequently, insulin therapy was more frequently required for non-adherent patients ($p = 0.018$). During the follow-ups, acetylsalicylic acid in combination therapies or alone was prescribed as a new drug, despite being off-label during pregnancy.

Concordance analysis (Table 3) revealed a poor agreement between the classification made by the diabetologist and the one based on the glucometer results (Cohen's Kappa = 0.22). The multivariate analysis (Table 4) indicated that the risk of non-adherence increased significantly with gestational age (OR = 1.10, $p = 0.004$), insulin therapy (OR = 3.27, $p < 0.001$) and hyperglycemia (OR = 12.90, $p < 0.001$) in patients classified according to the glucometer results. On the other hand, when adherence was defined based on the diabetologist's assessment, frequent fasting glucose levels $\leq$90 mg were identified as a protective factor (OR = 0.91, $p < 0.001$).

## 4. Discussion

In our sample, the median gestational age at diagnosis of GDM was 27 weeks, following the Italian Guidelines, which recommend screening between 24–28 weeks [1].

The study highlighted the complexity of gestational diabetes patients' management. Multivariate analysis based on glucometer classification showed that insulin therapy and hyperglycemia are substantial risk factors for non-adherence [9]. On the other hand, the analysis based on the diabetologist classification indicated that patients who frequently have blood glucose $\leq$90 mg/dL tended to be more adherent to treatment. Concordance analysis between the two classification criteria provided poor results (Cohen's Kappa = 0.22), which indicated that the diabetologist should analyze treatment adherence because the glucometer results did not consider several factors which came into play.

In particular, weight gain leading to increased doses or the addition of insulin was not a parameter assessed by the glucometer, while it was considered in the adherence evaluation by the diabetologist. Indeed, at the beginning of the enrollment, 89.9% of patients were on diet-only therapy, whereas during follow-up, there was a decrease (52%) of patients on diet-only therapy.

In most cases, patients were on delayed insulin therapy. Delayed and rapid insulin were combined when the values were not in range. The number of patients with combined therapy increased during the follow-up (10.3% vs 15.6%). This result aligned with the guidelines [1] that reported introducing insulin if GDM was not under control after 2 weeks of therapy with diet alone. In addition, the guidelines recommended starting with delayed evening insulin and then switching to combination regimens if the patient did not respond to treatment. Following these policies, patients were prescribed aspart or lispro as rapid insulin and detemir insulin as delayed insulin in all cases. No adverse reactions were detected during therapy. This finding proved the safety of insulin use in pregnant patients with GDM. The addition of insulin allowed the patients to obtain average values. According to the glucometer analysis, these cases were classified as adherent but as non-adherent following the diabetic analysis. It was an essential parameter in deciding whether to introduce drug therapy with insulin or continue on a diet alone since the percentage of fasting blood value $\leq$90 mg was associated with a higher probability of adherence [7]. According to the diabetologist, the patient was compliant in several cases because she observed the indications. At the same time, following the glucometer analysis, she was not compliant because her blood glucose values were out of range despite the proper management of GDM.

Despite the low concordance between the two analyses, approximately 50% of enrolled patients were not adherent to treatment. The literature demonstrated that 80% of patients with GDM generally adhere to treatment [6,7,9,10]. We believed that such a low value of treatment adherence was also due to the SARS-CoV-2 emergency, which forced many patients to postpone their visits and caused the follow-ups to be less close [11]. Indeed, data from the Friuli Venezia-Giulia Region indicated that although patients newly diagnosed with GDM from 2019 to 2021 increased (1052 vs 1235), on the contrary, outpatient visits decreased due to the pandemic emergency.

Finally, another important point emerging from the study was that acetylsalicylic acid, which was contraindicated in the third trimester of pregnancy by the SmPC [12],

**Table 2. Glucometer and diabetologist analysis of adherent and non-adherent patients.**

| | Glucometer analysis | | | | Diabetologist analysis | | |
|---|---|---|---|---|---|---|---|
| | Total | Not adherent | Adherent | *p*-value | Not adherent | Adherent | *p*-value |
| | N = 271 | N = 126 | N = 145 | | N = 116 | N = 155 | |
| Age at enrollment (years) | 34.0 (31.0–38.0) | 34.0 (31.0–38.0) | 34.0 (30.0–37.0) | 0.133 | 34.0 (30.0–37.5) | 34.0 (31.0–38.0) | 0.589 |
| Fasting blood glucose measured correctly | | | | <0.001 | | | <0.001 |
| No | 26 (9.6) | 21 (16.7) | 5 (3.4) | | 26 (22.4) | 0 | |
| Yes | 243 (89.7) | 104 (82.5) | 139 (95.9) | | 88 (76.9) | 155 (100.0) | |
| Not Known | 2 (0.7) | 1 (0.8) | 1 (0.7) | | 2 (1.7) | 0 | |
| Postprandial Glycemia measured correctly | | | | <0.001 | | | <0.001 |
| No | 30 (11.1) | 23 (18.3) | 7 (4.8) | | 30 (25.9) | 0 | |
| Yes | 239 (88.2) | 102 (81.0) | 137 (94.5) | | 84 (72.4) | 155 (100.0) | |
| Not Known | 2 (0.7) | 1 (0.8) | 1 (0.7) | | 2 (1.7) | 0 | |
| Fasting blood glucose ≤90 mg | 68.4 (40.0–86.7) | 60.3 (33.3-83.0) | 73.7 (46.0–90.3) | 0.005 | 33.3 (16.7–47.0) | 83.0 (70.1–94.1) | <0.001 |
| Blood glucose 1 hour post-lunch ≤130 mg | 88 (75.7–96.6) | 85.0 (72.0–94.0) | 91.2 (79.5–98.8) | 0.001 | 83 (67.6–91.0) | 92.1 (83.3–98.4) | <0.001 |
| Diet therapy alone | | | | <0.001 | | | 0.023 |
| No | 142 (52.4) | 84 (66.7) | 58 (40.0) | | 70 (60.3) | 72 (46.5) | |
| Yes | 129 (47.6) | 42 (33.3) | 87 (60.0) | | 46 (39.7) | 83 (53.6) | |
| Insulin Therapy | | | | <0.001 | | | 0.018 |
| No | 130 (48.0) | 43 (34.1) | 87 (60.0) | | 46 (39.7) | 84 (54.2) | |
| Yes | 141 (52.0) | 83 (65.9) | 58 (40.0) | | 70 (60.3) | 71 (45.8) | |
| Type of insulin | | | | 0.624 | | | 0.435 |
| Long acting | 107 (75.9) | 61 (73.5) | 46 (79.3) | | 56 (80.0) | 51 (71.8) | |
| Rapid acting | 12 (8.5) | 7 (8.4) | 5 (8.6) | | 4 (5.7) | 8 (11.3) | |
| Rapid and long acting | 22 (15.6) | 15 (18.1) | 7 (12.1) | | 10 (14.3) | 12 (16.9) | |
| Drugs for other pathologies | | | | 0.863 | | | 0.800 |
| No | 203 (74.9) | 95 (75.4) | 08 (74.5) | | 86 (74.1) | 117 (75.5) | |
| Yes | 68 (25.1) | 31 (24.6) | 37 (25.5) | | 30 (25.9) | 38 (24.5) | |
| Same drugs as enrollment | | | | 0.517 | | | 0.684 |
| No | 7 (10.3) | 4 (12.9) | 3 (8.1) | | 2 (1.7) | 5 (3.2) | |
| Yes | 61 (89.7) | 27 (87.19 | 34 (91.9) | | 28 (24.1) | 33 (21.3) | |
| Not Known | 203 (74.9) | 86 (74.1) | 117 (75.5) | | 86 (74.1) | 117 (75.5) | |
| New drugs prescription | | | | 1.000 | | | 0.286 |
| Acetylsalicylsalicylic acid | 3 (42.8) | 1 (25.0) | 2 (66.7) | | 0 | 3 (60.0) | |
| Montelukast 10 MG Oral Tablet | 1 (14.3) | 0 | 1 (33.3) | | 0 | 1 (20.0) | |
| Ferrosoferric phosphate | 1 (14.3) | 1 (25.0) | 0 | | 1 (50.0) | 0 | |
| Acetylsalicylsalicylic acid + Ferrosoferric phosphate | 1 (14.3) | 1 (25.0) | 0 | | 1 (50.0) | 0 | |
| Acetylsalicylsalicylic acid + Enoxaparin sodium | 1 (14.3) | 1 (25.0) | 0 | | 0 | 1 (20.0) | |
| Contraindicated drugs | | | | 0.486 | | | 1.000 |
| No | 3 (42.8) | 1 (25.0) | 2 (66.7) | | 1 (50.0) | 2 (40.0) | |
| Yes | 4 (57.2) | 3 (75.0) | 1 (33.3) | | 1 (50.0) | 3 (60.0) | |
| Contraindicated drugs | | | | | | | |
| Acetylsalicylsalicylic acid | 4 (100.0) | 3 (75.0) | 1 (33.3) | | 1 (50.0) | 3 (60.0) | 1.000 |

**Table 3. Concordance between glucometer and diabetologist analysis.**

| | Diabetologist analysis | | | | | |
|---|---|---|---|---|---|---|
| | Not adherent | Adherent | *p*-value | Agreement | Kappa di Cohen | *p*-value |
| Glucometer analysis | | | <0.001 | 61.62% | 0.22 | <0.001 |
| Not adherent | 69 (59.5) | 57 (36.8) | | | | |
| Adherent | 47 (40.5) | 98 (63.2) | | | | |

**Table 4. Analysis of multivariate and bivariate logistic regression analysis of factors associated with not-adherence.**

| Glucometer analysis | Bivariate analysis | | | Multivariate analysis | | |
|---|---|---|---|---|---|---|
| | OR | 95% CI | *p*-value | OR | 95% CI | *p*-value |
| Age at enrollment | 1.04 | [0.99; 1.10] | 0.086 | 1.06 | [1.00; 1.12] | 0.068 |
| Pregnancy week | 1.06 | [1.00; 1.12] | 0.040 | 1.10 | [1.03; 1.17] | 0.004 |
| % of postprandial glycemia $\leq$130 mg/dL (%) | 0.99 | [0.97; 1.00] | 0.056 | 0.99 | [0.98; 1.00] | 0.558 |
| % fasting glycemia $\leq$90 mg/dL (%) | 0.98 | [0.98; 0.99] | 0.009 | 0.99 | [0.98; 1.00] | 0.056 |
| Insulin therapy | 2.89 | [1.76; 4.75] | $<$0.001 | 3.27 | [1.79; 5.99] | $<$0.001 |
| Hyperglycemia | 11.02 | [4.52; 6.83] | $<$0.001 | 12.90 | [4.79; 34.75] | $<$0.001 |
| Hypoglycemia | 2.65 | [1.59; 4.44] | $<$0.001 | 2.52 | [1.32; 4.83] | 0.005 |
| Diabetologist analysis | Bivariate analysis | | | Multivariate analysis | | |
| | OR | 95% CI | *p*-value | OR | 95% CI | *p*-value |
| % of postprandial glycemia $\leq$130 mg/dL (%) | 0.96 | [0.94; 0.97] | $<$0.001 | 0.98 | [0.96; 1.01] | 0.274 |
| % fasting glycemia $\leq$90 mg/dL (%) | 0.91 | [0.89, 0.93] | $<$0.001 | 0.91 | [0.89; 0.93] | $<$0.001 |
| Insulin therapy | 1.80 | [1.11; 2.93] | 0.018 | 1.08 | [0.48; 2.41] | 0.854 |
| Hypoglycemia | 0.51 | [0.31; 0.87] | 0.012 | 1.00 | [0.44; 2.27] | 0.992 |

was nevertheless prescribed as a new drug.

Pregnancy was accompanied by a haemo-coagulative imbalance towards the pro-coagulant pathway, with an increased risk of thrombotic events (deep vein thrombosis and/or pulmonary embolism). Venous thromboembolism was 4 times higher than the thromboembolic risk in non-pregnant women. International guidelines [13] recommended using of low-molecular-weight heparins for prophylaxis and therapy of thromboembolism in pregnancy and puerperium in women at risk. Due to its molecular size, enoxaparin was considered relatively safe because it did not cross the placenta or reach the fetus. However, the American College of Obstetricians and Gynecologists guidelines [14] recommended a low dose prescription of acetylsalicylic acid to prevent the high risk of preeclampsia. The guidelines reported no risk in pregnant women with a high chance of preeclampsia and suggested the prescription of this drug before the 16th pregnancy week and its continuation until childbirth. According to this line, enrolled patients with GDM introduced to this drug during the follow-ups were at high risk of preeclampsia in the data analysis.

## 5. Conclusions

This study highlighted the importance of monitoring patients with gestational diabetes to properly assess and increase adherence to therapy. Besides, the complexity of assessing the adherence of patients with diabetes emerged, showing that the adherence could not be evaluated only from glucometer analysis but also by diabetes specialists. Furthermore, this study emphasised the importance of diabetes centres in treating patients with GDM. The only effective strategy to improve adherence to treatment of patients with GDM was to monitor them frequently and with scheduled visits.

## Author Contributions

RC, MPT, PR and AA designed the research study. GF and ES performed the research. BB and SA provided help and advice on the data collected. GZ analyzed the data. GF and AA wrote the manuscript. All authors contributed to editorial changes in the manuscript. All authors read and approved the final manuscript.

## Ethics Approval and Consent to Participate

The study was approved by Friuli-Venezia Giulia Regional Ethical Committee (Project No. 0003915).


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## Conflict of Interest

The authors declare no conflict of interest.

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