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Original Research

Oral Glucose Tolerance Test-Derived Glycemic Categories and Their Associations With Glycemic Control and Treatment Requirements in Pregnancy: A Dual-Center Cohort Study

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Abstract

Background: Gestational glycemia represents a continuous metabolic spectrum rather than a binary condition. Although the oral glucose tolerance test (OGTT) is routinely used to diagnose gestational diabetes mellitus (GDM), accumulating evidence suggests that distinct OGTT-derived glycemic patterns may confer distinct perinatal risks beyond the dichotomous GDM classification. **Methods:** This retrospective, dual-center cohort study included 1457 singleton pregnancies undergoing a 75-g OGTT between 24 and 28 weeks of gestation. Women were categorized into OGTT-derived glycemic groups based on fasting, 1-h, and 2-h plasma glucose values. The primary outcome was large-for-gestational-age (LGA) birth. Secondary outcomes included neonatal intensive care unit (NICU) admission and insulin therapy requirement. Multivariable logistic regression was used to assess the associations with LGA after adjustment for maternal age, pre-pregnancy body mass index (BMI), gestational weight gain (GWG), parity, smoking history, and study center. The predictive performance of fasting glucose and the combined multivariate model for LGA was evaluated using receiver operating characteristic (ROC) analyses. **Results:** Perinatal outcomes differed significantly across glycemic categories. The prevalence of LGA increased progressively from 6.3% among normoglycemic women to 26.6% in those with ≥2 abnormal OGTT values. In multivariable-adjusted analyses, LGA risk increased in a stepwise manner across glycemic categories, with the highest risk observed in women with fasting-dominant glycemic abnormalities. Fasting-driven glycemic categories were further associated with higher rates of NICU admission and insulin therapy requirement. Among individual OGTT time points, fasting glucose demonstrated the greatest discriminative ability for LGA prediction (area under the curve [AUC] = 0.64), while combined multivariate models yielded only modest incremental improvement (AUC = 0.67). **Conclusions:** Perinatal outcomes varied systematically across OGTT-derived glycemic categories. Fasting-dominant hyperglycemia and multiple abnormal OGTT values constituted the highest-risk metabolic phenotypes, whereas isolated post-load abnormalities were associated with comparatively milder perinatal consequences. Collectively, these findings suggest that risk stratification based on the temporal pattern of OGTT abnormalities may facilitate identification of clinically meaningful risk gradients, and prospective evaluation of this approach.

Keywords: gestational diabetes mellitus; oral glucose tolerance test; glycemic phenotype; fasting plasma glucose; large for gestational age; perinatal outcomes

1. Introduction

Gestational diabetes mellitus (GDM) is the most common metabolic disorder of pregnancy and a significant contributor to maternal and neonatal morbidity [1,2]. The Hyperglycemia and Adverse Pregnancy Outcome (HAPO) study reported that maternal glucose levels are continuously and progressively associated with adverse perinatal outcomes, providing the evidence base for the current International Association of the Diabetes and Pregnancy Study Groups (IADPSG) diagnostic criteria for the 75-g oral glucose tolerance test (OGTT) [3,4]. Nevertheless, women classified within the same GDM diagnostic framework may exhibit distinct metabolic characteristics and clinical outcomes, suggesting considerable underlying heterogeneity [1,5].

Recent studies indicate that the OGTT provides clinically meaningful information beyond a binary diagnosis, enabling the identification of distinct glycemic categories. Studies consistently suggest that fasting hyperglycemia may reflect more severe metabolic dysfunction than isolated post-load abnormalities and has been associated with greater insulin resistance, a higher likelihood of requiring insulin therapy, and increased perinatal risk [6,7,8]. Fasting-dominant glycemic categories have been associated with disproportionately higher rates of large-for-gestational-age (LGA) birth, preterm birth, and cesarean delivery, whereas isolated 1-h or 2-h post-load elevations typically reflect milder metabolic disturbances [6,7]. Several reports suggest that distinct OGTT-defined glycemic patterns may reflect underlying metabolic phenotypes with varying therapeutic requirements. Fasting-dominant hy-

perglycemia is more strongly associated with insulin resistance and a higher likelihood of pharmacologic intervention, whereas isolated post-load abnormalities may represent comparatively milder dysglycemic states that respond more favorably to lifestyle modification and postprandial management [6,7,9].

Even subtle elevations in fasting glucose within the normoglycemic range have been associated with increased offspring/childhood adiposity and adverse metabolic outcomes in offspring [10,11]. Taken together, these findings highlight the clinical relevance of glycemic patterning across the full OGTT spectrum; however, relatively few studies have comprehensively characterized the complete range of OGTT-defined glycemic categories in unselected, routine-care populations. Importantly, most prior studies have examined selected or high-risk populations, and evidence from routine-care, clinically heterogeneous cohorts remains limited. Existing evidence suggests significant clinical differences between fasting-dominant, post-load-dominant, mixed, and normoglycemic subgroups; however, the magnitude and relevance of these distinctions remain incompletely defined [6]. Furthermore, current diagnostic approaches remain predominantly dichotomous, potentially overlooking clinically important metabolic variation among women who meet or approach—diagnostic thresholds [1,5].

In this dual-center cohort study, we investigated OGTT-derived glycemic categories among pregnancies undergoing a 75-g OGTT at 24–28 weeks of gestation. We examined whether different glycemic patterns were associated with LGA birth, NICU admission, and insulin therapy requirement. We also evaluated the discriminative ability of fasting, 1-h, and 2-h plasma glucose values for LGA prediction using receiver operating characteristic (ROC) analysis. Importantly, unlike studies conducted on untreated or experimentally selected populations, the present study reflects perinatal risk assessment within the context of routine clinical management.

2. Materials and Methods

This retrospective, dual-center cohort study was conducted at the Department of Obstetrics and Gynecology of Kütahya City Hospital and Simav State Hospital in Turkey, using delivery records from January 2021 through June 2025. During this period, approximately 10,000 deliveries occurred across both centers.

Gestational diabetes screening was performed according to routine clinical practice. The choice of screening strategy, including the use of a 50-g glucose challenge test or direct 75-g oral glucose tolerance test (OGTT), was determined by the attending clinician rather than a standardized study protocol. Accordingly, OGTT testing in this cohort reflects real-world clinician-directed practice rather than a universal screening approach.

For methodological consistency, only women who underwent a diagnostic 75-g OGTT between 24 and 28 gestational weeks were eligible for inclusion. A total of 1720 women underwent a 75-g OGTT during the study period. After applying predefined exclusion criteria, 1457 singleton pregnancies with complete exposure and outcome data constituted the final analytical cohort. To ensure independence of observations, only the first eligible pregnancy per woman during the study period was included. The final cohort comprised 424 pregnancies from Simav State Hospital and the remainder from Kütahya City Hospital. Exclusion criteria encompassed pregestational diabetes, chronic hypertension, multiple gestation, fetal structural or chromosomal anomalies, OGTT performed before 24 weeks, and incomplete exposure or outcome data. Restricting the cohort to singleton pregnancies minimized confounding attributable to the well-documented effects of multiple gestation on fetal growth and perinatal outcomes.

Because OGTT was not universally performed, the study cohort represents a clinically selected population, raising a possibility of selection bias. To address this, a comparison group of women who did not undergo OGTT was randomly selected from the same study period via computer-generated random sampling from the institutional electronic database, matched to the OGTT cohort in a 1:1 numerical ratio. Baseline maternal characteristics were compared between groups using standardized mean differences (SMD), with values <0.1 considered negligible. The non-OGTT group served exclusively as a reference for baseline comparability and was not included in any outcome analyses.

The OGTT was performed following an overnight fast of at least 8 hours. Venous plasma glucose concentrations were measured at fasting, 1 hour, and 2 hours following ingestion of a 75-g oral glucose load. Venous blood samples were collected and processed in accordance with routine institutional laboratory protocols. GDM was diagnosed according to the International Association of the Diabetes and Pregnancy Study Groups (IADPSG) criteria, defined as fasting ≥92 mg/dL, 1-h ≥180 mg/dL, or 2-h ≥153 mg/dL, consistent with current American Diabetes Association (ADA) recommendations [1,4].

To characterize metabolic heterogeneity beyond the binary GDM definition, women were further categorized into six glycemic groups: fasting <80 mg/dL, fasting 80–91 mg/dL, isolated fasting hyperglycemia, isolated 1-h hyperglycemia, isolated 2-h hyperglycemia, and ≥2 abnormal OGTT values. Although women meeting IADPSG criteria were classified as having GDM, isolated abnormalities were analyzed as distinct subcategories to enable finer characterization of glycemic risk [6,7]. The subdivision of the normoglycemia range into fasting glucose <80 mg/dL and 80–91 mg/dL subgroups was based on prior evidence suggesting that perinatal risk may increase progressively even within the normal fasting glucose range [11]. For outcome analyses, the two normoglycemic subgroups (fasting glucose <80 mg/dL and 80–91 mg/dL) were merged into

a single reference category. All OGTT-derived glycemic categories were defined *a priori* according to IADPSG-specified abnormal glucose time points and predefined normoglycemic fasting strata, prior to outcome analyses.

All women diagnosed with GDM received management in accordance with routine institutional protocols. Both centers followed comparable clinical management approaches, thereby minimizing potential inter-center variability. Initial management consisted of dietary counselling and lifestyle modification. Capillary self-monitoring of blood glucose (SMBG) was routinely performed four times daily, at fasting and 1-h postprandial. Glycemic targets were defined as fasting <95 mg/dL and 1-h postprandial <140 mg/dL. Insulin therapy was initiated when glycemic targets could not be achieved through lifestyle modification alone. In routine clinical practice, insulin therapy was generally initiated within one week of confirmed failure to meet glycemic targets despite dietary and lifestyle intervention. Women receiving insulin therapy were typically reviewed on a weekly basis, whereas those managed with diet alone were followed at bi-weekly intervals. All treatment decisions were made by attending clinicians, and no study-specific interventions were applied.

SMBG data were obtained from routine clinical follow-up records. For each patient, mean fasting and mean 1-h postprandial glucose values were calculated for all available measurements recorded prior to delivery, and rates of glycemic target attainment were derived accordingly. The frequency and duration of glucose monitoring were not standardized and reflected routine clinical practice. Where available, glycated hemoglobin (HbA1c) values were additionally analyzed as a supplementary marker of overall glycemic burden.

The primary outcome was LGA, defined as birth weight above the 90th percentile for gestational age and fetal sex according to the INTERGROWTH-21st standards. Secondary outcomes included small-for-gestational-age (SGA, <10th percentile), preterm birth (<37+0 weeks), cesarean delivery, neonatal intensive care unit (NICU) admission, and insulin therapy requirement during pregnancy. NICU admission was defined as any admission requiring continuous monitoring or medical support beyond routine neonatal care.

Prespecified covariates included maternal age, parity, smoking status, pre-pregnancy body mass index (BMI), and gestational weight gain (GWG). Pre-pregnancy BMI was calculated using self-reported weight at the first antenatal visit and measured maternal height.

All statistical analyses were performed using SPSS version 26.0 (IBM Corp., Armonk, NY, USA). and R version 4.2.2. Continuous variables were presented as mean ± standard deviation (SD) or median (interquartile range, IQR), depending on distribution assessed using the Shapiro–Wilk test, and categorical variables were presented as counts (n) and percentages (%). Group comparisons were performed using one-way analysis of variance (ANOVA) or Kruskal–Wallis tests for continuous variables and Chi-square or Fisher's exact tests for categorical variables.

Associations between glycemic categories and outcomes were evaluated using logistic regression models. Both crude and adjusted analyses were conducted, with adjustment for maternal age, parity, smoking status, pre-pregnancy BMI, GWG, and study center. Results were reported as odds ratios (ORs) with 95% confidence intervals (CIs). Linearity in the logit for continuous predictors was assessed using the Box–Tidwell test. Model stability was additionally evaluated using the events-per-variable (EPV) approach, with values >10 considered indicative of acceptable model robustness. Multicollinearity among fasting, 1-h, and 2-h glucose measurements was assessed using correlation coefficients, variance inflation factors (VIFs), and tolerance statistics.

Missing data were minimal (<3% for all variables), and complete-case analysis was applied. Differences in insulin therapy requirement across glycemic categories were assessed using Chi-square tests. Due to quasi-complete separation arising from the absence of insulin-treated patients in the normoglycemic reference category, Firth penalized likelihood logistic regression was applied to obtain bias-reduced and more stable parameter estimates. Linear trends across ordered glycemic categories were evaluated using the Cochran–Armitage trend test.

ROC curves were constructed to assess the predictive performance of fasting glucose and the combined multivariate model for LGA, and area under the curve (AUC) values were compared using the DeLong method [12]. Additional multivariable ROC models combining glucose parameters were evaluated to explore potential improvements in discrimination. Internal validation of ROC performance was performed using bootstrap resampling (1000 iterations) to estimate optimism-corrected discrimination measures.

3. Results

A total of 1457 singleton pregnancies were included in the analysis. The participant selection process is illustrated in Fig. 1.

To evaluate potential selection bias, baseline maternal characteristics were compared between women who underwent OGTT and those who did not (Table 1). Differences were minimal, with SMD <0.1 for most variables, suggesting limited imbalance between groups.

Maternal and biochemical characteristics across OGTT-derived glycemic categories are presented in Table 2. Maternal age was comparable between groups (p = 0.38), whereas pre-pregnancy BMI increased significantly with worsening glycemic status ($p < 0.001$; p for trend < 0.001). GWG showed modest variation without a consistent trend, and parity and smoking status were similar across categories.

Table 1. Comparison of baseline maternal characteristics between women who underwent OGTT and those who did not (selection bias analysis).

Variable	OGTT performed (n = 1457)	No OGTT (n = 1457)	*p*-value	SMD
Maternal age (years)	29.6 ± 5.0	28.9 ± 5.2	0.20	0.08
Pre-pregnancy BMI (kg/m^2)	26.7 ± 4.5	26.3 ± 4.6	0.21	0.09
GWG (kg)	11.6 ± 3.7	11.5 ± 3.8	0.74	0.03
Parity ≥1, n (%)	547 (37.5)	532 (36.5)	0.88	0.01
Smoking, n (%)	141 (9.6)	139 (9.5)	0.76	0.00

Footnote: Data are presented as mean ± SD or n (%). Continuous variables were compared using independent samples *t*-test or Mann–Whitney U test, as appropriate. Categorical variables were compared using Chi-square or Fisher's exact tests, as appropriate. SMD was calculated to assess the magnitude of differences between groups, with values <0.1 considered negligible. BMI, body mass index; GWG, gestational weight gain; SD, standard deviation; SMD, standardized mean difference.

Table 2. Maternal and OGTT-derived biochemical characteristics according to glycemic category.

Variable	Normoglycemic (combined)	1-h only	2-h only	Fasting only	≥2 abnormal	*p* overall	*p* trend
Maternal age (years)	29.6 ± 5.0	30.2 ± 5.1	29.8 ± 4.8	29.5 ± 4.6	29.3 ± 4.9	0.38	0.44
Pre-pregnancy BMI (kg/m^2)	25.5 ± 4.6	26.5 ± 4.7	27.5 ± 4.1	26.8 ± 4.7	27.5 ± 4.4	<0.001	<0.001
GWG (kg)	11.9 ± 4.0	11.6 ± 3.9	12.0 ± 3.9	10.8 ± 3.1	12.2 ± 3.6	<0.001	0.29
Parity ≥1, n (%)	212 (37.1)	90 (40.2)	60 (40.5)	77 (34.4)	108 (37.4)	0.72	0.88
Smoking status, n (%)	56 (9.8)	21 (9.4)	15 (10.1)	22 (9.8)	27 (9.3)	0.46	0.76
Fasting glucose (mg/dL)	80.2 ± 6.5	83.2 ± 3.6	82.7 ± 4.1	97.7 ± 3.4	93.7 ± 7.1	<0.001	<0.001
1-h glucose (mg/dL)	127.0 ± 18.4	195.9 ± 10.1	142.1 ± 17.7	145.4 ± 16.9	178.9 ± 28.0	<0.001	<0.001
2-h glucose (mg/dL)	109.3 ± 15.1	115.2 ± 16.6	164.4 ± 7.2	114.9 ± 12.9	149.5 ± 26.8	<0.001	<0.001

Footnote: Data are presented as mean ± SD or n (%). Continuous variables were compared using one-way ANOVA or Kruskal–Wallis tests, as appropriate, and categorical variables using Chi-square or Fisher's exact tests. *p*-value overall indicates differences among all groups. *p*-value trend was assessed across increasing metabolic severity using linear contrast analysis for continuous variables and the Cochran–Armitage trend test for categorical variables.

OGTT glucose values demonstrated distinct category-specific patterns. Fasting glucose levels were highest in the fasting-dominant hyperglycemia group, whereas 1-h and 2-h glucose levels peaked in the respective isolated abnormality groups (all $p < 0.001$).

Perinatal outcomes differed significantly across glycemic categories (Table 3). LGA rates increased progressively from 6.3% in normoglycemic women to 26.6% in those with ≥2 abnormal OGTT values ($p < 0.001$; *p*-value for trend < 0.001) (Fig. 2). Similar gradient patterns were observed for NICU admission and cesarean delivery rates. Hypertensive disorders also demonstrated a modest but statistically significant increasing trend ($p = 0.002$), whereas preterm birth rates did not differ significantly across categories ($p = 0.19$).

The requirement for insulin therapy demonstrated the most pronounced gradient across glycemic categories (Table 3). No women in the normoglycemic group required insulin, whereas rates increased to 16–17% in those with isolated post-load abnormalities, 37.5% in the fasting-dominant group, and 52.9% in women with ≥2 abnormal OGTT values ($p < 0.001$; *p*-value for trend < 0.001). This distribution closely paralleled the gradient observed for LGA and other adverse perinatal outcomes, indicating a progressive increase in metabolic burden across categories.

SMBG-derived glycemic profiles differed significantly across OGTT-derived categories (Table 4). The fasting-dominant and multiple-abnormality groups exhibited higher mean fasting glucose levels and lower rates of glycemic target attainment, whereas isolated 1-h abnormality was characterized by higher postprandial glucose values. HbA1c levels were modestly but consistently higher in fasting-dominant and multiple-abnormality groups, supporting a more sustained dysglycemic burden in these subgroups. Collectively, these findings indicate that OGTT-derived categories correspond to distinct longitudinal glycemic patterns observed during routine clinical follow-up.

Statistical analyses confirmed these differences. Insulin requirement varied significantly across glycemic categories ($\chi^2 = 385.47$, $p < 10^{-80}$), with a highly significant linear trend across increasing metabolic severity (Cochran–Armitage $p = 8.0 \times 10^{-92}$). Crude ORs increased substantially across categories relative to the normoglycemic reference group, rising to approximately 146 in isolated 1-h hyperglycemia, 140 in isolated 2-h hyperglycemia, 426 in isolated fasting hyperglycemia, and 797 in women with ≥2 abnormal OGTT values. Penalized multivariable logistic regression, applied to address quasi-complete separation, demonstrated that fasting-driven categories and the

Table 3. Perinatal outcomes across OGTT-derived glycemic categories.

Outcome	Normoglycemic	1-h only	2-h only	Fasting only	≥2 abnormal	*p* overall	*p* trend
Insulin therapy	0 (0.0)	38 (17.0)	24 (16.2)	84 (37.5)	153 (52.9)	<0.001	<0.001
LGA	36 (6.3)	34 (15.2)	22 (14.9)	49 (21.9)	77 (26.6)	<0.001	<0.001
NICU admission	36 (6.3)	17 (7.6)	8 (5.4)	27 (12.1)	39 (13.5)	<0.001	<0.001
Preterm birth (<37 weeks)	36 (6.3)	14 (6.3)	10 (6.8)	17 (7.6)	20 (6.9)	0.19	0.13
Hypertensive disorders	23 (4.0)	13 (5.8)	11 (7.4)	17 (7.6)	18 (6.2)	0.023	0.002
Cesarean delivery	152 (26.6)	67 (29.9)	49 (33.1)	82 (36.6)	115 (39.8)	<0.001	<0.001
Birthweight (g), mean ± SD	3292 ± 431	3350 ± 450	3356 ± 516	3435 ± 430	3562 ± 454	0.048	0.022

Footnote: Data are presented as n (%) or mean ± SD. Categorical variables were compared using Chi-square or Fisher's exact tests, and continuous variables using one-way ANOVA or Kruskal–Wallis tests. *p* overall indicates differences among all groups. *p* trend was assessed across increasing metabolic severity using the Cochran–Armitage trend test for categorical variables and linear contrast analysis for continuous variables. LGA, large-for-gestational-age; NICU, neonatal intensive care unit.

Table 4. Longitudinal glycemic profiles derived from SMBG and HbA1c according to OGTT-derived glycemic category.

Variable	1-h only (n = 224)	2-h only (n = 148)	Fasting only (n = 224)	≥2 abnormal (n = 289)	*p* overall	*p* trend
Mean fasting SMBG (mg/dL)	87 ± 8	86 ± 7	95 ± 9	101 ± 10	<0.001	<0.001
Mean 1-h SMBG (mg/dL)	134 ± 15	129 ± 14	130 ± 15	136 ± 16	<0.001	<0.001
Fasting values within target (%)	87	80	74	69	<0.001	<0.001
1-h values within target (%)	72	85	86	69	<0.001	<0.001
HbA1c (%)	5.2 ± 0.3	5.2 ± 0.3	5.4 ± 0.4	5.5 ± 0.4	<0.001	<0.001

Footnote: Data are presented as mean ± SD or percentages. Continuous variables were compared using one-way ANOVA or Kruskal–Wallis tests, and categorical variables using Chi-square tests. *p* overall indicates differences among all groups. *p* trend was assessed across increasing metabolic severity using linear trend analysis for continuous variables and the Cochran–Armitage trend test for categorical variables. Glycemic targets were defined as fasting <95 mg/dL and 1-h postprandial <140 mg/dL. SMBG, self-monitoring of blood glucose; HbA1c, glycated hemoglobin.

multiple-abnormality values remained strongly associated with insulin requirement after adjustment for maternal age, pre-pregnancy BMI, GWG, parity, and smoking status.

In multivariable logistic regression analyses, OGTT-derived glycemic category remained independently associated with both insulin therapy requirement and LGA after covariate adjustment (Table 5). Compared with normoglycemic women, the odds of insulin therapy increased markedly across all abnormal categories, particularly among fasting-dominant and multiple-abnormality groups. Similarly, the risk of LGA rose progressively with glycemic severity, reaching an adjusted OR (aOR) of 10.52 (95% CI: 5.74–19.31) in women with ≥2 abnormal OGTT values.

The primary multivariable model for LGA included 218 outcome events and yielded an EPV ratio of 43.6, indicating satisfactory model stability. Formal model diagnostics demonstrated acceptable calibration and overall performance (Hosmer–Lemeshow $\chi^2 = 7.14$, df = 8, $p = 0.52$; Nagelkerke pseudo-$R^2 = 0.21$; overall classification accuracy = 74.2%). Correlation coefficients between fasting, 1-h, and 2-h glucose measurements ranged from 0.48 to 0.62. VIFs were 1.35, 2.58, and 2.12, respectively, with tolerance values remaining well above 0.10, indicating no evidence of clinically meaningful multicollinearity. The predictive performance of individual OGTT glucose values for key outcomes is presented in Table 6. For insulin therapy requirement, fasting glucose demonstrated good discriminative performance, with modest incremental improvement observed in combined models. For LGA prediction, overall discrimination was limited; fasting glucose showed the highest individual performance (AUC = 0.64), while combined models provided no clinically meaningful improvement (AUC = 0.67).

Bootstrap internal validation using 1000 resamples yielded an optimism-corrected AUC of 0.65 (95% CI: 0.60–0.70) for the combined LGA model, demonstrating stability of the original discrimination estimates.

Sensitivity analyses excluding all insulin-treated pregnancies (n = 299) were conducted to assess the potential influence of treatment-related confounding on outcome estimates. Although effect sizes were attenuated following exclusion, the association between worsening OGTT-derived phenotypes and LGA remained statistically significant. In particular, women with ≥2 abnormal OGTT values continued to demonstrate an increased risk of LGA (aOR approximately 6.5), supporting an underlying biological association independent of treatment intensity.

Table 5. Adjusted associations between OGTT categories and key clinical outcomes.

Group	Insulin therapy events / Total n (%)	Insulin therapy aOR (95% CI) [firth penalized]	*p*-value	LGA events / Total n (%)	LGA aOR (95% CI) [standard logit]	*p*-value
Normoglycemic	0/572 (0.0)	1.0 (Reference)	—	36/572 (6.3)	1.00 (Reference)	—
1-h only	38/224 (17.0)	18.4 (4.2–80.5)	<0.001	34/224 (15.2)	4.85 (2.52–9.32)	<0.001
2-h only	24/148 (16.2)	16.2 (3.8–69.1)	<0.001	22/148 (14.9)	4.97 (2.44–10.12)	<0.001
Fasting only	84/224 (37.5)	42.5 (9.8–184.2)	<0.001	49/224 (21.9)	8.13 (4.31–15.33)	<0.001
≥2 abnormal	153/289 (52.9)	75.1 (18.4–306.0)	<0.001	77/289 (26.6)	10.52 (5.74–19.31)	<0.001

Footnote: Data are presented as events/total n (%) or aORs with 95% CIs. Models were adjusted for maternal age, pre-pregnancy body mass index (BMI), GWG, parity, smoking status, and study center. The normoglycemic group served as the reference category. Firth's penalized likelihood logistic regression was applied to the insulin therapy model because of complete separation resulting from zero insulin-treated cases in the normoglycemic reference group. LGA estimates were derived from standard multivariable logistic regression models. aOR, adjusted odds ratio; CI, confidence interval.

Table 6. Discriminative performance of OGTT-derived glucose measures for predicting clinical outcomes (ROC analysis).

Outcome	Predictor model	AUC	Sensitivity (%)	Specificity (%)
Insulin therapy	Fasting glucose	0.76	61	81
	Combined (fasting + 1-h + 2-h)	0.78	71	75
LGA	Fasting glucose	0.64	64	59
	Combined (fasting + 1-h + 2-h)	0.67	81	40

Footnote: Sensitivity and specificity were calculated at the optimal cut-off determined by the Youden index. Combined models were derived from multivariable logistic regression including fasting, 1-h, and 2-h glucose values. AUC, area under the curve; ROC, receiver operating characteristic.

4. Discussion

Gestational glycemia represents a continuous metabolic spectrum rather than a binary state, and the findings of this dual-center cohort further support this concept. Across 1457 pregnancies undergoing diagnostic 75-g OGTT, marked differences in perinatal outcomes were identified across OGTT-derived glycemic categories, demonstrating that the prognostic relevance of the OGTT extends well beyond the current dichotomous classification of GDM. The dominant prognostic role of fasting glucose was evident throughout the analysis: women with isolated fasting hyperglycemia and those with two or more abnormal OGTT values consistently exhibited the highest rates of LGA, NICU admission, and insulin therapy requirement. These observations align closely with contemporary evidence indicating that fasting dysglycemia reflects a more severe metabolic disturbance than isolated post-load abnormalities [6,7].

These findings support the notion that perinatal risk accumulates progressively along the glycemic continuum, extending below current diagnostic thresholds. This pattern mirrors insights from longitudinal studies demonstrating that sub-diagnostic glucose elevations are associated with offspring adiposity and adverse cardiometabolic profiles in later childhood [11]. The present findings therefore reinforce the concept that maternal glycemia, even within the conventionally defined normal range, contributes to fetal metabolic programming.

These results are consistent with prior reports examining gestational glucose physiology through a category-based framework. Zhang et al. [6] recently demonstrated that fasting-dominant glycemic categories carry disproportionately higher risks of LGA, hypertensive disorders, and preterm birth, underscoring the unique pathophysiological relevance of fasting glucose dysregulation. Accordingly, Athanasiadou et al. [7] reported that fasting-dominant GDM categories required pharmacologic therapy at markedly higher rates, reflecting a more severe underlying metabolic phenotype. The present data replicate and reinforce the central findings of these studies within a large real-world cohort, confirming the consistently elevated risk associated with fasting-driven glycemic categories. Although hypertensive disorders demonstrated a statistically significant increasing trend across categories, absolute differences were relatively modest and should therefore be interpreted with caution.

Studies evaluating isolated abnormal OGTT values provide further context for these findings. Anastasiou et al. showed over a decade ago that isolated fasting hyperglycemia confers a significantly higher risk of adverse outcomes than isolated post-load abnormalities [9]. The present study observed the same pattern: isolated fasting hyperglycemia was associated with substantially higher LGA risk than either isolated 1-h or 2-h hyperglycemia. This reinforces the principle that these subcategories are not clinically interchangeable, despite meeting the same binary diagnostic criteria.

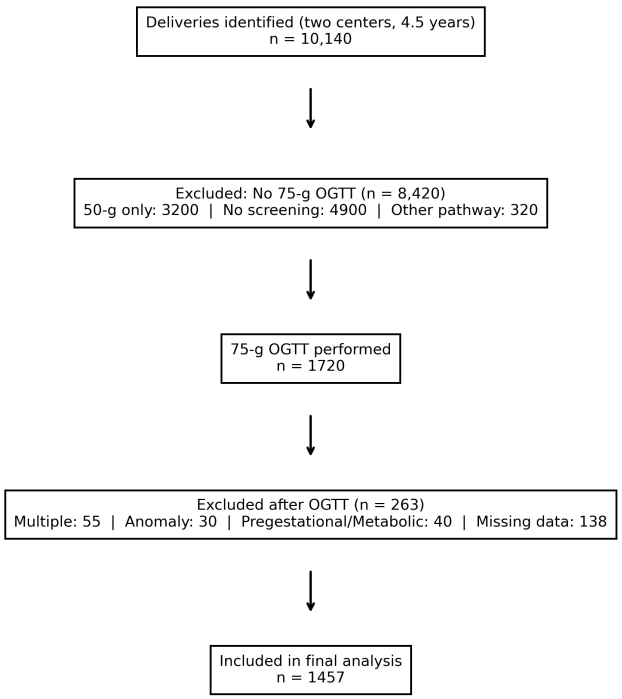

Fig. 1. Flow diagram of study population selection. Among 10,140 deliveries recorded across two tertiary centers over a 4.5-year period, women who did not undergo a diagnostic 75-g OGTT were ineligible for inclusion. After further exclusions for multiple gestation, fetal anomalies, pregestational or metabolic disorders, and missing data, 1457 singleton pregnancies were included in the final analysis. OGTT, oral glucose tolerance test.

The mechanisms underlying these outcome differences likely relate to maternal–fetal glucose kinetics. Catalano et al. [8] demonstrated that fasting hyperglycemia correlates strongly with increased placental glucose transfer and fetal hyperinsulinemia, which are central drivers of fetal overgrowth. The observed gradient in LGA and NICU admission rates across fasting-dominant categories is consistent with this metabolic model. In contrast, isolated post-load abnormalities may reflect a distinct, less severe metabolic pathway, characterized by delayed insulin secretion or impaired postprandial glucose disposal.

The contrast between fasting-dominant and post-load glycemic categories also provides clinically relevant insight into treatment requirements. The gradient in insulin therapy rates across categories was pronounced: 0% in the normoglycemic group, approximately 17% in isolated 1- or 2-h abnormalities, 37.5% in isolated fasting hyperglycemia, and exceeding 50% in those with multiple OGTT abnormalities. This mirrors reports by Athanasiadou and others, who found that fasting-dominant categories exhibit the most profound insulin resistance and highest requirement for pharmacological treatment [7,13]. These findings suggest that category-based glycemic classification may provide additional information regarding metabolic heterogeneity and may help inform future risk-stratification approaches. However, prospective validation is required before any clinical implementation can be considered. Incorporating OGTT-derived glycemic categories into antenatal risk assessment may represent a promising avenue for future investigation, although the present findings should be considered as exploratory and hypothesis-generating.

The identification of clinically relevant differences within the normoglycemic fasting range raises important questions. These findings parallel those from the HAPO study and subsequent follow-up studies, which observed that glucose values well below diagnostic thresholds remain correlated with increased neonatal adiposity and later-life metabolic risk [10,11]. Taken together, this evidence suggests that traditional diagnostic thresholds may mask a subset of pregnancies at meaningful metabolic risk. Although clinical guidelines should not change based on these data alone, recognition of this glycemic gradient may encourage closer fetal growth surveillance in women at the upper end of the normoglycemic fasting range. Furthermore, these findings suggest that fasting glucose-based phenotyping may provide a more refined stratification of metabolic risk within the normoglycemic population, without altering existing diagnostic thresholds for GDM. However, the absolute differences within the normoglycemic range were relatively modest and should be interpreted with caution until validation in external cohorts.

From a clinical perspective, these results suggest that a category-based interpretation of OGTT findings may help refine antenatal risk stratification. Whether women with fasting-dominant glycemic categories would benefit from earlier nutritional intervention, more intensive monitoring, or tailored counselling regarding fetal growth expectations remains uncertain and warrants evaluation in future prospective interventional studies. Conversely, pregnancies with isolated post-load abnormalities, which demonstrated comparatively milder perinatal risk, may benefit from more targeted postprandial lifestyle modification strategies while avoiding unnecessary escalation of therapy. Such a selective management approach has the potential to optimize resource use, reduce patient burden, and improve perinatal outcomes. The higher cesarean delivery rates observed in fasting-dominant categories likely reflect, at least in part, the increased prevalence of fetal growth and LGA in these groups; however, individual physician decision-making and other obstetric indications were not separately evaluated in the present study.

Although statistically significant, the discriminative performance of OGTT-derived glucose values for LGA prediction remained modest (AUC <0.70), indicating limited standalone predictive utility. These findings suggest that OGTT values should be interpreted alongside other clinical factors rather than used in isolation.

These findings also have implications for future research. Future studies should therefore explore the

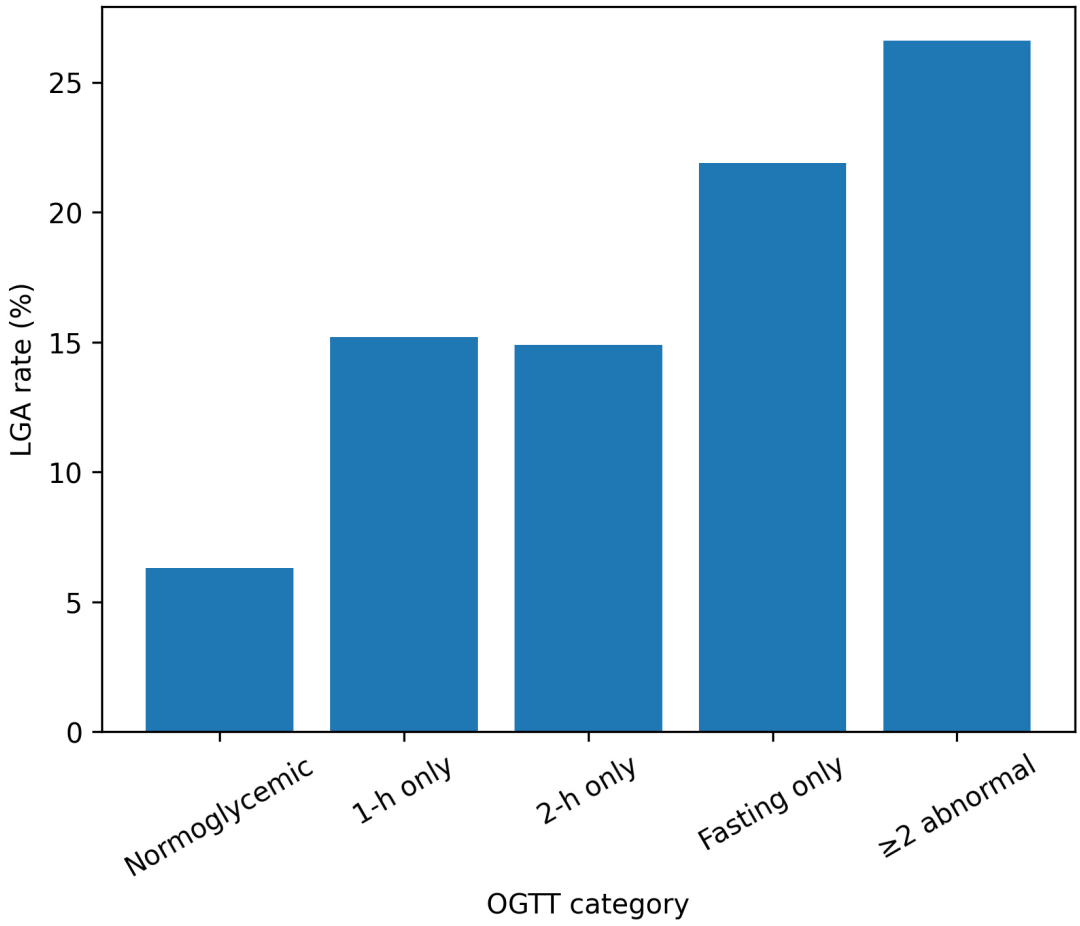

Fig. 2. Rates of LGA births across OGTT-derived glycemic categories. LGA prevalence increased progressively with worsening glycemic status, rising from 6.3% in the normoglycemic group to 26.6% in women with ≥2 abnormal OGTT values, demonstrating a graded in risk pattern across glycemic categories.

metabolic physiology that differentiates fasting-dominant from post-load glycemic categories. Detailed metabolic profiling, including insulin response curves, C-peptide measurements, lipid indices, and continuous glucose monitoring, may help characterize category-specific pathways. Furthermore, longitudinal follow-up is warranted to evaluate whether these glycemic patterns predict differences in postpartum glucose tolerance, risk of type 2 diabetes, and offspring metabolic outcomes.

Interventional trials will also be required to determine whether category-tailored therapeutic strategies outperform standard GDM treatment. For example, fasting-dominant categories may benefit from early pharmacological therapy, while post-load glycemic categories may respond preferentially to meal-timing and postprandial exercise intervention approaches. Incorporating category variables into predictive machine-learning models may further enhance individualized risk assessment, especially when combined with maternal BMI, GWG, and additional biochemical markers.

The strengths of this study include its large sample size, dual-center design, comprehensive category classification, and rigorous statistical methodology, including the application of penalized logistic regression to address separation and validated AUC comparison techniques. Glycemic categories were defined using real-world OGTT data, enhancing the generalizability and clinical relevance of the findings to routine antenatal care populations.

Limitations

Several limitations should be acknowledged. First, the retrospective design of the present study introduces the possibility of residual confounding despite multivariable adjustment. Second, insulin and C-peptide measurements were not available, limiting more detailed metabolic characterization of glycemic categories. Third, although both centers followed broadly similar clinical management protocols, thresholds for insulin initiation may have varied slightly between clinicians and centers, potentially influencing treatment-related outcomes. Additionally, although the use of INTERGROWTH-21st standards provided a standardized framework for birth weight assessment, the applicability of ethnicity-specific fetal growth ref-

erences was not evaluated. GWG may also have been influenced by dietary counselling and treatment interventions initiated following GDM diagnosis, the effects of which could not be fully accounted for in this retrospective design. Finally, these findings reflect a routine antenatal care cohort from a specific population and may require external validation in more diverse populations. Additionally, insulin resistance indices, inflammatory biomarkers, lipid parameters, and advanced metabolic markers were not routinely available in this retrospective cohort. Some effect estimates were associated with wide CIs, likely reflecting sparse event counts within specific glycemic subcategories. Furthermore, sensitivity and specificity estimates derived from internally optimized Youden index thresholds may overestimate predictive performance within the study cohort. Although internal validation was performed using bootstrap resampling, external validation was not available in this study. Therefore, the generalizability of these findings to other populations should be interpreted with caution pending confirmation in independent prospective cohorts.

5. Conclusions

This study demonstrates that OGTT-derived glycemic categories are differentially associated with perinatal outcomes. Fasting-dominant abnormalities represent the highest-risk metabolic phenotype, whereas isolated postload hyperglycemia constitutes a clinically distinct and milder category. Collectively, these findings further underscore the metabolic heterogeneity of gestational glycemia and suggest that category-based stratification may enhance the precision of perinatal risk assessment. Given the retrospective observational design, these findings should be interpreted as associations rather than causal relationships. Prospective studies incorporating external validation are required before these observations can be translated into routine clinical decision-making.

Availability of Data and Materials

The datasets used and analyzed during the current study are available from the corresponding author on reasonable request.

Author Contributions

MK designed the study. MK and OBC collected the data. MK performed the statistical analysis and drafted the manuscript. OBC critically revised the manuscript. Both authors read and approved the final manuscript. Both authors have read, participated sufficiently in the work, and agreed to be accountable for all aspects of the final manuscript.

Ethics Approval and Consent to Participate

This study was retrospectively authorized by the Kütahya University of Health Sciences Non-Interventional Clinical Research Ethics Committee (approval number: 2025/10-27; approval date: 11 August 2025). Due to the retrospective design and the use of anonymized routinely collected data, the requirement for informed consent was waived by the ethics committee. The study was conducted in accordance with the principles of the Declaration of Helsinki.

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Conflicts of Interest

The authors declare no conflicts of interest.

Declaration of AI and AI-Assisted Technologies in the Writing Process

During the preparation of this manuscript, AI-assisted language tools, including Gemini 1.5 and ChatGPT-4o, were used only for grammar and language refinement. All scientific interpretation, data analysis, and final manuscript revisions were performed and approved by the authors.

Supplementary Material

Supplementary material associated with this article can be found, in the online version, at https://doi.org/10.31083/CEOG53317.

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