

Abnormal fasting, post-load or combined glucose values on oral glucose tolerance test and pregnancy outcomes in women with gestational diabetes mellitus.

E. Papachatzopoulou^a, C. Chatzakis^b, I. Lambrinoudaki^a, K. Panoulis^a, K. Dinas^b, N. Vlahos^a, A. Sotiriadis^b, M. Eleftheriades^a

^a 2nd Department of Obstetrics and Gynecology Aretaieio Hospital, National and Kapodistrian University of Athens, Faculty of Medicine, Athens, Greece

^b 2nd Department of Obstetrics and Gynecology, Aristotle University of Thessaloniki School of Medicine, Thessaloniki, Greece

Introduction

Gestational diabetes mellitus (GDM) is the most common metabolic disorder during pregnancy. It develops in women whose pancreatic function is insufficient to overcome the insulin resistance associated with the pregnant state. The diagnosis of GDM is established according to the International Association of Diabetes and Pregnancy Study Groups (IADPSG) criteria. Pregnancies are GDM complicated when elevated plasma glucose is detected during a 75 g 2-hour oral glucose tolerance test (OGTT) between the 24th and 28th weeks of gestation. According to the Hyperglycemia and Adverse Pregnancy Outcome (HAPO) Study, approximately half of women diagnosed with GDM had abnormal fasting blood glucose, while the rest had abnormal post-prandial blood glucose values. Previous studies have concluded that abnormal fasting blood glucose is associated with increased need for insulin therapy in GDM complicated pregnancies.

Objectives

The aim of our study was to investigate, the differences between GDM complicated pregnancies with abnormal fasting, post-load or combined blood glucose values on OGTT, regarding outcomes of the pregnancy.

Materials & Methods

Participants

The participants were derived from the population of pregnant women who presented in our clinic from 2010 to 2018, in order to undergo the first-trimester combined screening test for aneuploidies and subsequently underwent screening for GDM by a 75 gr two-hour OGTT at 24–28 weeks of gestation. Women who were diagnosed with GDM according to the IADPSG criteria, blood glucose values equal or greater to 92 mg/dl at fasting, 180 mg/dl at 60 min and 153 mg/dl at 2 h after consumption of 75 gr of glucose were considered abnormal, were included. Pregnancies complicated with GDM were referred to a diabetes clinic for further management, initially treated with lifestyle modifications (physical exercise and diet) and to those who failed to reach the glycemic targets (fasting glucose < 95 mg/dl, 1 h postprandial glucose < 140 mg/dl and 2 h post-prandial glucose < 120 mg/dl) after two weeks of lifestyle modification insulin was administered.

According to their fasting blood glucose value on OGTT, women with GDM were categorized into three groups:

- GDM women with fasting plasma glucose levels > 92 mg/dl and normal post-load values (***T0 abnormal group***),
- patients with abnormal values at 600 and/or 1200 and normal fasting values (***T-post group***) and
- patients with combined fasting and post-load abnormal blood glucose values (***T-comb***).

Variables

The outcomes of interest included

- large for gestational age, defined as birth weight greater than the 90th centile
- birthweight centile, according to the birth weight curves recommended by the WHO
- need for insulin treatment for GDM.

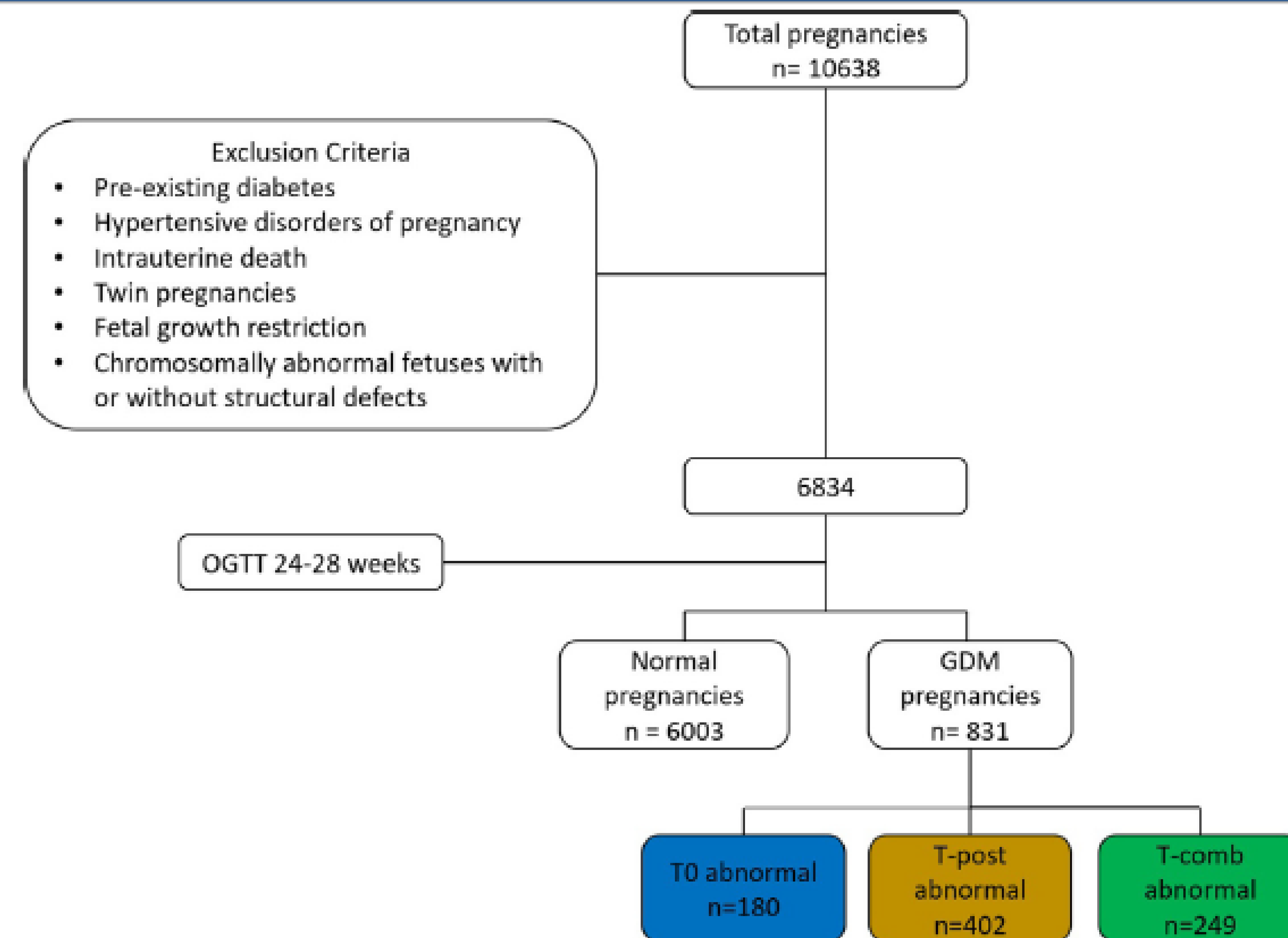


Figure 1. Selection process of the included population.

Statistical analysis

ANOVA or Kruskal-Wallis and Bonferroni test for post-hoc analysis were used for comparisons of continuous variables between the three groups. Chi-square or Fisher's exact test were used for pairwise comparisons of proportions, as appropriate, and odds ratios (ORs) along with their 95% Cis were calculated (p-value of < 0.05 was considered significant). Logistic regression (backward, by likelihood ratios) was performed for the outcome of macrosomia and insulin treatment and linear regression was performed for the outcome of birth weight centile, including maternal characteristics, laboratory results and clinical, sonographic findings as potential predictors and potential cofounders as well. (software R 2.15.1 was used)

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Results

From the initial cohort of 10.638 pregnancies, 6818 met the inclusion criteria, of which 831 (11.5%) were complicated by GDM.

- 180 (21.7%) had abnormal fasting only blood glucose at OGTT (**T0 abnormal group**),
- 402 (48.4%) had abnormal post-load only blood glucose (**T-post group**) ,
- 249 (30%) had combined fasting and post-load abnormal blood glucose values (**T-comb**).

The selection process of the included Cohort is presented in figure 1.

Table 1 displays the clinical, biochemical and sonographic findings of the tree categories.

The GDM patients who had combined abnormal blood glucose, had significantly greater BMI than T0 abnormal (p = 0.028) and post-load abnormal groups (p < 0.001). Women in the T0 abnormal group had higher BMI in comparison to women in the post-load group (p < 0.001). Maternal age (p = 0.028) and levels of maternal serum PAPPa (p = 0.042), were greater in the T0 abnormal group compared to post-load group. Percentage of smoking was greater in the T0 abnormal and combine groups compared to postload group (p = 0.19).

Variable	Fasting-abnormal (T0) n = 180 (21.7)	Post-load abnormal (T-post) n = 402 (48.4)	Combined abnormal (T-comp) n = 249 (30.0)	P value
Maternal BMI	26.13 (4.64)	23.96 (4.39)	27.34 (5.61)	<0.001 ^a , <0.001 ^b , 0.028 ^c , <0.001 ^d
Mean (SD)				
Maternal Age in years	33.06 (4.11)	33.68 (3.32)	34.31 (3.95)	0.028 ^a , 0.027 ^b
Mean (SD)				
Cigarette Smoking, n (%)	25 (13.9)	35 (8.7)	39 (15.7)	0.019 ^e
Conception by Art, n (%)	15 (8.3)	64 (15.9)	30 (12.0)	0.119 ^e
PAPPa MoMs	0.928 (0.511)	1.135 (0.632)	1.059 (0.637)	0.039 ^a , 0.042 ^b
Mean (SD)				
HCG MoMs	1.249 (1.066)	1.179 (0.862)	1.089 (0.760)	0.146 ^a
Mean (SD)				
UtA-z score in the 1st trimester	0.80 (0.90)	0.71 (1.11)	0.41 (0.43)	0.117 ^a
Mean (SD)				
UtA-z score in the 2nd trimester	−0.18 (1.08)	−0.33 (1.04)	−0.30 (1.26)	0.703 ^a
Mean (SD)				
LGA, n (%)	15 (36.6)	19 (13.0)	20 (19.4)	0.003 ^e
Birth weight centile Mean (SD)	65.27 (32.44)	52.69 (29.50)	58.45 (31.16)	0.016 ^a , 0.031 ^b
Need for insulin treatment, n (%)	27 (15)	44 (10.9)	74 (29.7)	<0.001 ^e
Gestational age at delivery in weeks	38.61 (1.5)	38.50 (1.7)	38.37 (1.3)	0.669 ^a
Mean (SD)				
SGA, n (%)	2 (4.9)	19 (13.0)	7 (6.8)	0.014 ^e
Quantitative variables are presented in mean and standard deviation. Comparisons between the groups were carried out using ANOVA and Bonferroni post-hoc test. ^a result of ANOVA test, ^b post-hoc (Bonferroni test): comparison between T0 abnormal and post-load abnormal, ^c comparison between T0 abnormal and combined abnormal, ^d comparison between post-load abnormal and combined. Qualitative data are presented in percentages. Chi-square test ^e . PAPPa-MoMs: Pregnancy-associated plasma protein a expressed in multiples of the median. HCG MoM: Human Chorionic Gonadotropin expressed in multiples of the median. UtA: Uterine artery. LGA: Large for Gestation Age. SGA: Small for Gestational Age.				

Table 1. Maternal factors and pregnancy outcomes in the three groups.

Pregnant women with abnormal fasting blood glucose had greater percentage of LGA babies compared to the T-post and T-comb groups (36.6 vs. 13 vs 19.4, respectively; p = 0.003) and the mean birth weight centile of the newborns was significantly higher in this group compared to post-load group (65.27 vs. 53.69, p = 0.004). GDM patients in the combined abnormal blood glucose group had greater need for insulin treatment, compared to the T0 and T-post groups (29.7% vs. 15% and 10.9%, respectively; p < 0.001) Fig. 2. No significant difference was found in the gestational age at delivery and Small for Gestation Age (SGA). (Table 1)

The independent contribution of three OGTT groups (T0, T-post and T-comb), along with maternal and fetal factors, on the outcomes of interest, was tested using regression analysis. Abnormal fasting blood glucose (group T0) was found to be the only independent predictive factor for macrosomia (p = 0.07) and birth weight centile (P = 0.044). Combined abnormal blood glucose values (group T-comb) was independent predictive factor for the need of insulin treatment (p < 0.001). (Table 2)

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Discussion

Since GDM is a result of inadequate maternal response to the physiological insulin resistance of pregnancy, it is expected expect that postprandial (i.e. post-loading) values would be elevated. However, approximately half of the GDM population has abnormal fasting blood glucose values which might indicate that GDM is not a single entity. Perhaps the different results on the OGTT are the manifestation of different pathophysiological mechanisms.

We found that women with abnormal fasting blood glucose have higher risk for macrosomic newborns (OR 2.91, 95% CI 1.33–6.36) and a higher mean birthweight centile (mean difference 10.25, ranging from 0.27 to 20.25 centiles) which comes in accordance with the HAPO study. This finding may be explained by the mechanism of fasting insulin resistance. In the fasting state, the fasting plasma glucose is primarily derived from the liver under the influence of insulin . The fasting plasma insulin is the main regulator of hepatic glucose production and fasting hyperglycemia can result when hepatocytes resistant to insulin action continue producing glucose. Thus, additional insulin is needed to overcome the hepatic insulin resistance. Increased explain the greater birth weight and the percentage of large for gestational age newborns, as insulin functions as anabolic factor in the regulation of fetal body size. Given the potential perinatal consequences of macrosomia, women and fetuses with abnormal fasting blood glucose at OGTT may need closer follow up.

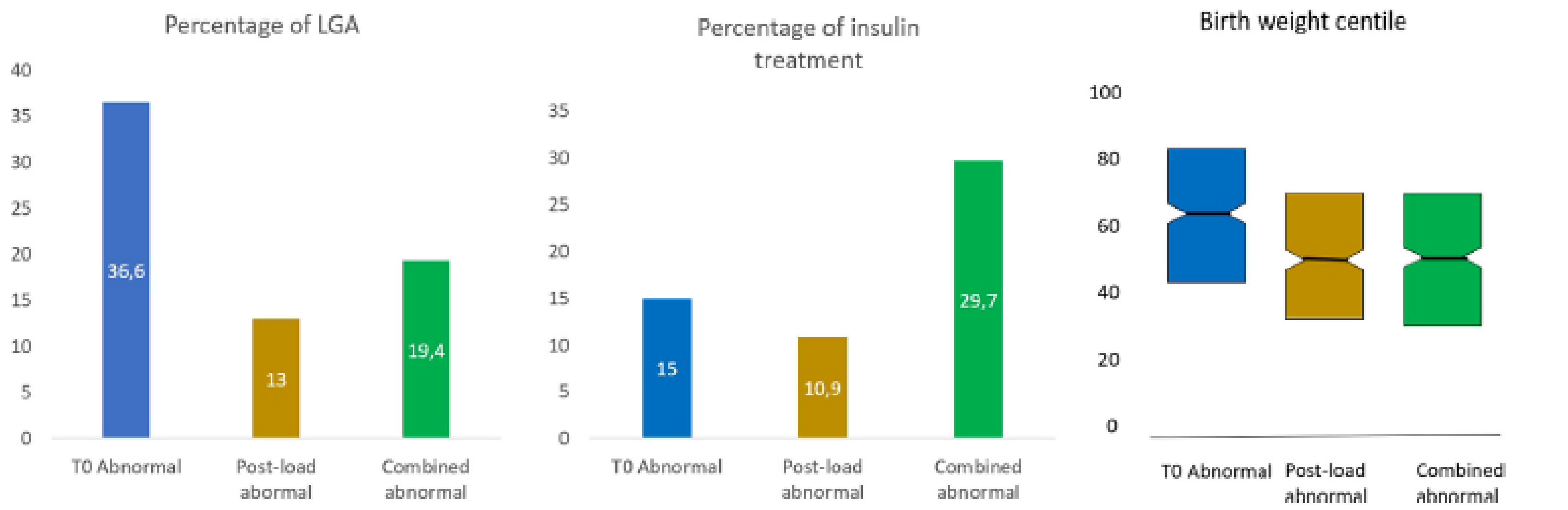


Figure 2. Boxplots of the outcomes of A) Large for Gestational Age (LGA), B) Insulin treatment, C) Birth weight centile, in the groups of fasting abnormal (abnormal T0), post-load abnormal (T-Post) and in the Combined abnormal (T-comb).

	Large for Gestational Age	Birth weight percentile	Insulin treatment
Predictors			
Abnormal fasting blood glucose	2.91 (1.33 – 6.36), p = 0.007	10.25 (0.27 – 20.25), p = 0.044	
Maternal BMI			1.06 (1.02 – 1.10), p = 0.002
Combined abnormal blood glucose			2.94 (1.93 – 4.47), p < 0.001

Table 2. Regression coefficients of the independent predictive factors for maternal and perinatal outcomes, along with their 95% Confidence Intervals.

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We also found that women with combined abnormal blood glucose have higher need for insulin treatment (OR 2.94, 95% CL 1.93–4.47). Studies in the general population showed that patients presenting with T-comb at OGTT manifest a decrease in pancreatic early-phase insulin response to oral glucose. Early-phase insulin secretion primes the liver and inhibits the endogenous glucose production.A defect in early-phase insulin secretion would impair the suppression of hepatic glucose production resulting in abnormal fasting blood glucose and rise in plasma glucose during the first 60 min of OGTT. Therefore, pregnant women with combined abnormal blood glucose may have impaired pancreatic insulin secretion and exogenous insulin administration may be needed.

Conclusions

Women with GDM and abnormal fasting blood glucose are at increased risk for large for gestational age neonates, while women with GDM and combined fasting and postload abnormal blood glucose are at increased risk for insulin therapy.