

The impact of environmental temperature on the diagnosis of gestational diabetes mellitus

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Abstract

Objective: To investigate a probable impact of seasons on the diagnosis of GDM, as well as the specific effect of the environmental temperature on the diagnosis of this clinical entity.

Patients and methods: Two observational studies, one retrospective and one prospective, were conducted in a referral center. Study A included retrospectively 7618 pregnant women who underwent a 3-h 100 g OGTT during the 3rd trimester of gestation. Study B prospectively included 768 pregnant women tested in the 3rd trimester of gestation with a 75 g OGTT. Temperature was recorded every day at 09:00 h.

Results: Retrospective Study A: GDM prevalence differed significantly by season: winter = 28.1%, summer = 39.2%, spring = 32.4% and autumn = 32.4% ($P < 0.0001$). The odds ratio for being diagnosed with GDM was much higher during summer 1.65 (95% CI: 1.43–1.90), with spring and autumn following with 1.23 (95% CI: 1.08–1.39) compared to winter. Glucose levels during OGTT were measured: significantly increased blood glucose values were observed at 60, 120 and 180 min in summer, which remained significant after adjustment for age, gestational age, BMI, weight gain during pregnancy and blood pressure. Prospective Study B: At temperatures above 25°C, the average glucose 60-min and 120-min levels were increased. The relative risk for abnormal glucose values at 60 min, when the environmental temperature increased over 25°C, was 2.2 (1.5–3.3).

Conclusions: GDM prevalence in Greece presents seasonal variation, with higher risk during summer due to post glucose load level variations. These variations could be attributed to differences in environmental temperature.

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Introduction

Gestational diabetes mellitus (GDM) is the type of diabetes diagnosed in the second or third trimester of pregnancy that is not clearly overt diabetes (1). GDM carries important risks for both the mother and the neonate. The results of the hyperglycemia and adverse pregnancy outcome (HAPO) study, including in total more than 25 000 multinational pregnant women, indicated strong and continuous associations of maternal glucose levels with increased fetal hyperinsulinemia and birth

weight, both over the 90th percentile, as well as other adverse maternal, fetal and neonatal outcomes, such as pre-eclampsia, cesarean delivery, shoulder dystocia and neonatal hypoglycemia, even within ranges below those diagnostic of diabetes (2). These results revealed the necessity for appropriate diagnosis of GDM and proper management of these pregnant women (3).

Apart from careful consideration of the diagnostic criteria used for GDM, other parameters have also been

discussed in the literature. The effect of different seasons on the prevalence of gestational diabetes has also been addressed by a few studies, with conflicting results. In 1994, a prospective study from Brazil was the first to show an increased frequency for GDM diagnosis during summer (4), but thereafter no such seasonal or monthly variation was confirmed (5, 6). However, other experimental studies revealed continuously that post-load blood glucose levels were higher at higher ambient temperatures (7, 8, 9). Very recently, a large cohort study from Australia showed that the prevalence of GDM indeed varies according to seasons, with possible overdiagnosis in summer or underdiagnosis in winter (10), while another study from Sweden suggested again seasonal variation in the incidence of GDM diagnosis, with a peak in the summer (11). At the same time, a huge retrospective cohort study of 60 306 eligible South Australian live-born singletons during 2007–2011 reported an increased GDM prevalence in the summer, based on the estimated date of conception (12).

Two observational studies were conducted. The aim of retrospective Study A was to investigate a probable effect of seasons on the diagnosis of GDM, while the aim of prospective Study B was to look at the specific impact of the environmental temperature on the diagnosis of this clinical entity.

Patients and methods

Research has been approved by the Institutional Review Boards of the 'Alexandra' Hospital in Athens, Greece. Written informed consent was obtained from all participants.

Study A

Study A retrospectively considered 7618 pregnant women of Greek origin who underwent a 3-h 100g OGTT during the 3rd trimester of pregnancy between 2000 and 2012. For the diagnosis of GDM, the ADA 2000 (Carpenter and Coustan) criteria were used, i.e. detection of two or more abnormal values lead to diagnosis of GDM, glucose at fasting ≥ 5.3 mmol/L (95 mg/dL), 1 h ≥ 10.0 mmol/L (180 mg/dL), 2 h ≥ 8.6 mmol/L (155 mg/dL), 3 h ≥ 7.8 mmol/L (140 mg/dL) (13). Seasonal and monthly GDM prevalence, as well as mean seasonal glucose levels during OGTT (at 0, 60, 120 and 180 min) were estimated. Data for mean month temperature during the duration of the study were obtained from the Hellenic National Meteorological Service (14). The equations for glucose

concentrations in different units are 1 mmol/L = 18 mg/dL and 1 mg/dL = 0.05556 mmol/L.

Study B

Study B prospectively included 768 pregnant women of Greek origin, who were examined in the 3rd trimester of gestation over an 18-month period (January 2013–June 2014). In this study, the temperature was recorded every day at 09:00 h. All the participants underwent an oral glucose tolerance test (OGTT) with 75 g of glucose in a controlled climate room. The diagnosis of GDM was based on the new IADPSG criteria (15), subsequently adopted by World Health Organization (WHO) criteria, i.e. glucose at fasting ≥ 5.1 mmol/L (92 mg/dL), 1 h ≥ 10.0 mmol/L (180 mg/dL), 2 h ≥ 8.5 mmol/L (153 mg/dL) (16).

Assay

Venous samples were collected in BD Vacutainer spray-coated K2EDTA Tubes. Plasma glucose levels were measured not more than 10 min later by an enzymatic, colorimetric method in a Cobas Integra/400 autoanalyzer (Roche Laboratory Systems). The intra- and inter-assay CV with this method of glucose measurement in our laboratory is less than 3.2%.

Statistical analysis

Results are presented as mean \pm s.d. for continuous variables, as absolute numbers and percentages in parentheses for categorical variables. Distribution of continuous parameters was tested by Kolmogorov–Smirnov test. Differences in continuous variables were tested using parametric or non-parametric tests, as appropriate. Differences in categorical variables were tested using χ^2 test with Yates Correction. ANOVA analysis and MANOVA models were also performed in order to confirm the findings. For each month (Table 1) and each season (Table 2), the odds of the absolute numbers of women with and without GDM were calculated. The month (January) and season (winter) with the lowest odds were considered the baseline odds. For every other month or season, the odds ratio (OR) was calculated as the odds of the month (season) to the baseline odds. The 95% confidence intervals were also calculated from a relevant statistical formula. The association between temperature and glucose levels was at first investigated with Pearson's correlation coefficients and linear regression analysis. Following this, the discrimination

Table 1 Prevalence, relative prevalence and odds ratio of GDM per month (Retrospective Study A).

Month	GDM (%)	RP	OR (95% CI)	MMT (°C)
Jan	32.7	1	Relative to January	9.5
Feb	36.4	1.11	1.21 (0.94–1.56)	10.5
March	36.9	1.13	1.24 (0.97–1.58)	12
April	41.2	1.26	1.42 (1.11–1.82)	16
May	38.3	1.17	1.31 (1.03–1.65)	21
June	44.7	1.36	1.60 (1.26–2.04)	25
July	49.2	1.50	1.88 (1.49–2.38)	28
Aug	49.9	1.52	1.84 (1.42–2.37)	28
Sept	39.5	1.21	1.41 (1.11–1.79)	24
Oct	38.9	1.19	1.29 (1.02–1.65)	20
Nov	37.4	1.14	1.25 (0.98–1.59)	16
Dec	32.8	1.00	1.02 (0.79–1.32)	11.5

MMT, mean month temperature.

ability of temperature on abnormal glucose levels at 0, 60 and 120 min was investigated using receiver-operating characteristics (ROC) analysis curves with the intention of finding the best cutoff temperatures that provide the best tradeoff between sensitivity and specificity. This method culminates in 2×2 contingency tables that can provide the ORs with their 95% confidence intervals (CI), which is the ratio of the odds of the number of abnormal to normal glucose levels above and below the cutoff temperature. The significance of the effect of temperature on glucose levels was reexamined after adjustment for the effects of age and BMI with the use of stepwise logistic regression models. All statistical analyses were performed using the Statistical Package for Social Sciences (SPSS 22.0). A *P* value of <0.05 was considered statistically significant.

Results

Study A

GDM prevalence, relative prevalence (RP) and odds ratio (OR, 95% CI) per month, using January as a reference point, as well as mean monthly temperatures are shown in [Table 1](#).

GDM prevalence, RP and odds ratio (OR, 95% CI) per season, using winter as a reference point are shown

Table 2 Prevalence, relative prevalence and odds ratio of GDM per season (Retrospective Study A).

Season	GDM (%)	RP	OR (95% CI)
Winter	28.1	1	Relative to winter
Spring	32.4	1.15	1.23 (1.08–1.39)
Summer	39.2	1.4	1.65 (1.43–1.90)
Autumn	32.4	1.15	1.23 (1.08–1.39)

in [Table 2](#). There was no statistical difference in fasting glucose blood levels with respect to the seasons. However, significantly increased blood glucose values were observed at 60, 120 and 180 min in summer vs winter, while spring and autumn values were intermediate (ANOVA: $P < 0.0001$). The effect of seasons on glucose levels at 60, 120 and 180 min remained an independent significant factor after adjustment for age, gestational age, BMI, weight gain during pregnancy, systolic and diastolic blood pressure (MANOVA model, $P < 0.0001$).

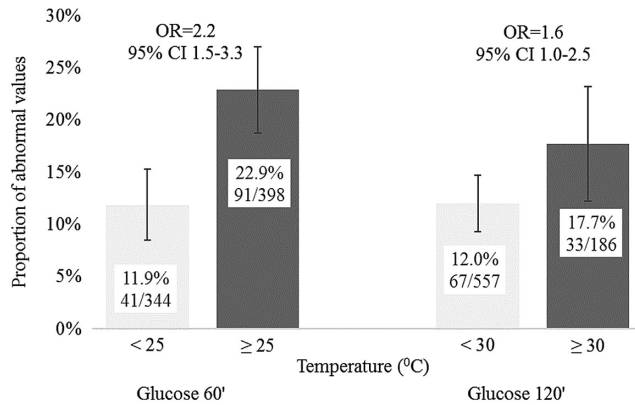
In *Study A*, daily changes of environmental temperature (ET) were not recorded; therefore, our findings on seasonal variation in the diagnosis of gestational diabetes could not be directly related to environmental temperature fluctuations. For this reason, we proceeded with prospective *Study B*.

Study B

ET was not correlated with glucose 0-min levels ($r = -0.037$, $P > 0.05$), but it was significantly correlated with glucose 60-min levels ($r = 0.119$, $P < 0.01$) and glucose 120-min levels ($r = 0.076$, $P < 0.05$). ROC analysis revealed that temperature has significant discrimination ability on abnormal glucose levels at 60 min ($P < 0.01$) and 120 min ($P < 0.05$). Linear regression analysis showed that at temperatures above 25°C, the average glucose 60-min levels were increased by 0.05067 mmol/L (0.912 mg/dL) for each degree increase in temperature. At temperatures above 30°C, the average glucose 120-min levels were increased by 0.02817 mmol/L (0.507 mg/dL) for each degree increase in temperature.

The percentages of abnormal glucose values above and below these cutoff values and the related ORs are shown in [Fig. 1](#). According to these results, three groups of pregnant women were formed, specifically: <24.9°C (group 1), 25–29.9°C (group 2) and >30°C (group 3). A stepwise logistic regression model showed that the temperature effect remains significant on glucose 60-min levels even after adjusting for age and BMI, but on glucose 120 min, the effect regresses to non-significance.

The mean glucose values and the prevalence of abnormal glucose values were recorded at 0, 60 and 120 min of OGTT and are presented in [Table 3](#). There was no statistical difference in the levels of fasting glucose. However, a statistically significant difference was observed among the three groups regarding the 60-min glucose levels. This finding was confirmed regarding the mean values of glucose and the percentages of abnormal values ($P < 0.001$). The relative risk between groups 2 and

**Figure 1**

Percentages and 95% CI of abnormal glucose levels above and below the temperature cutoff values of 25°C for glucose 60 min and 30°C for glucose 120 min ORs (and their 95% CI) for the related 2×2 contingency tables.

3 compared to group 1 was 1.8 (1.2–2.9) and 2.6 (1.7–4.2), respectively. Regarding the value of glucose at 120 min., a statistically significant difference was observed between group 3 and groups 1 and 2.

Discussion

The aim of this paper was to investigate the effect of seasons on the diagnosis of GDM, as well as the specific impact of the ET on the diagnosis of this clinical entity. Results showed that GDM prevalence in Greece presents seasonal variation, with higher risk for diagnosis during summer. This was due to post glucose load levels variation. At temperatures above 25°C, the average glucose 60 min and 120 min levels are increased.

The risk for GDM diagnosis during summer was significantly increased (~70%) compared to winter. In 1994, a prospective study from Brazil showed first such an

increased frequency for GDM diagnosis during summer (4). Thereafter, no such seasonal or monthly variation was confirmed by few studies, which followed (5, 6). Very recently, a large cohort study from Australia (10) using the WHO criteria for the diagnosis for GDM (16) was published and is in accordance with our retrospective results, although at the time, we used the Carpenter and Coustan criteria. They found that the prevalence of GDM varies indeed according to seasons, with higher prevalence in summer. This variation was due to post load 1-h and 2-h glucose values and not due to fasting glucose values (10). At the same time period, another study from Sweden suggested again seasonal variation in the incidence of GDM diagnosis, with a peak in the summer (11). Specifically, 11 538 women underwent a 75-g OGTT during the 28th week of gestation. The 2-h glucose levels increased by 0.009 mmol/L (0.162 mg/dL) for every degree increase in temperature, while summer was associated with increased 2-h glucose levels and increased frequency of GDM compared to other seasons (OR: 1.51, 95% CI: 1.24–1.83, *P* value <0.001). At the same time, a huge retrospective cohort study of 60 306 eligible South Australian live-born singletons during 2007–2011 reported an increased GDM prevalence in the summer (12). In this study, it is highlighted that seasonal variation may also reflect seasonality of environmental factors during conception (12).

Daily changes of ET were not recorded in *Study A*; therefore, our findings could not be directly related to ET fluctuations. In order to investigate if the observed variations could be attributed to differences in ambient temperature (despite steady room temperature during the OGTT procedure) or other environmental and nutritional factors, we proceeded with a prospective study. The strength of the prospective part is that it includes a simultaneous measurement of ET. Thus, these data provide evidence that the increase of ambient temperature over

Table 3 Glucose levels in various temperature groups (Prospective Study B). The mean values in each measurement (0, 60 and 120 min) were subjected to ANOVA with temperature group as the between-subjects factor. The cross tabulations of the three temperature groups against the absolute frequencies of normal and abnormal values in each measurement were subjected to chi-square tests.

Group	n	Temperature (°C)	Glucose (mg/dL)			Percentage (%) of abnormal values		
			0 min	60 min	120 min	0 min	60 min	120 min
1	355	<24.9	89 ± 10	143 ± 35	117 ± 29	33.5	11.9	11.9
2	220	25–29.9	89 ± 9	148 ± 34	117 ± 31	33.2	19.8	12.3
3	193	>30	89 ± 13	155 ± 37	125 ± 36	31.6	26.3	17.7
P value			ns	**	*	ns	**	ns

*Significant at the 0.05 level; **significant at the 0.01 level. ns, non-significant.

25°C is associated with a gradual increase of post-load mean glucose values, as well as with an increase in the percentage of abnormal glucose values. Furthermore, we showed numerically in an equation that a temperature increase over 25°C by one degree raises the glucose 60-min levels by an average of 0.05067 mmol/L (0.912 mg/dL), while over 30°C, the glucose 120 min levels by an average of 0.02817 mmol/L (0.507 mg/dL). There was no such association regarding glucose 0 min levels. Contrarily, we observed a significant association primarily regarding glucose 60-min levels in temperatures higher than 25°C and, to a lesser extent, regarding glucose 120-min levels, although this effect becomes apparent at higher temperatures (>30°C). The temperature effect on glucose 120-min levels loses its significance after adjusting for age and BMI.

These findings are in accordance with the results of previous experimental studies, which showed that post-load blood glucose levels were higher at higher ambient temperatures (5, 17). Higher post-prandial glucose levels observed when patients are exposed at higher ambient temperatures could be attributed to alterations of the blood flow pattern. Exposure to high temperature induces the possible opening of arterio-venous thermoregulatory anastomoses. This could lead in turn to increased blood flow and venous blood arterialization and therefore decreased glucose tissue extraction (6, 17, 18). The technique of heated-hand presents a similar effect. In a detailed study, the mean transit time for blood through the forearm was estimated at 1 min. with usual circumstances, but when the hand was heated this time was just 0.3 min. The irreversible fractional removal of glucose was 2.9% and 1.9%, respectively (9).

Besides body surface exposure, increases in core body temperature seem to contribute to the redistribution of blood flow. In fact, core body temperature represents a much more powerful thermal regulator for cutaneous blood flow compared to skin temperature (6, 9, 17, 18). Obesity, a major contributor to GDM, could result in blood flow alterations. This could be the result of cutaneous circulation redistribution due to bigger fat volume, as well as smaller changes of core body temperature because of the decreased exposure of the core body due to the fat. Another very likely contribution of obesity to the variation in post-load glucose levels could be the reduced extraction of glucose from the blood stream due to insulin resistance. It should be noted that in the clinical conditions of this study, the effect of ambient temperature on glucose values in the OGTT of pregnant women after adjustment for BMI and body weight gain remained significant at least

at 60 min. Studies suggest that the peak of the arterio-venous difference in glucose levels coincides with the peak of the glucose curve (19). Hyperdynamic circulation during pregnancy could further contribute to the influences of ambient temperature on glucose levels (17). Of course, other factors such as the duration of daylight hours and the possible effect on activity or hormones, such as vitamin D, as well as seasonal variations in food intake, physical activity and weight gain could affect the seasonality of the GDM diagnosis. These parameters can affect maternal physiology, as well as fetal development at multiple levels and through various molecular and biochemical mechanisms and result in the development of the disease.

The temperature-induced differences in post-load glucose levels found during OGTT are less likely to be of clinical relevance in the diagnosis of people with unequivocal diabetes. Indeed, the diagnosis of type 2 diabetes has been shown in UKPDS to be more likely in the winter months (20). Another study from Greece showed that HbA1c may also be higher in winter (21). However, these temperature-induced differences could be of high importance in epidemiological and research studies, particularly in tropical countries and especially with respect to the classification of impaired glucose tolerance (IGT). Furthermore, the differences certainly are of significance for the diagnosis of GDM in pregnant women, especially for those whose post-load OGTT results are in the upper limits of normal ranges in winter, but would appear as GDM in summer.

The limitations of the study include the fact that 'Alexandra' Hospital is a referral center for high-risk pregnant women. The large number of women with GDM in the examined cohort is possibly due to that.

In conclusion, GDM prevalence in Greece presents seasonal variation, with higher risk during summer due to post-glucose load level variations. In particular, ambient temperature over 25°C is linked to an increase of post glucose values. These findings suggest the need to take into consideration high ETs during interpretation of OGTT results and diagnosis of GDM.

Declaration of interest

The authors declare that there is no conflict of interest that could be perceived as prejudicing the impartiality of this study.

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