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The effect of smoking on the risk of gestational diabetes mellitus and the OGTT profile during pregnancy



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ABSTRACT

Objective: To analyze the relationship between smoking and the risk of GDM, as well as with the OGTT profile during pregnancy.

Patients and methods: A total of 7437 pregnant women were studied. OGTT was performed at the 3rd trimester. Women were categorized as non-smokers (A), as those who ceased smoking at pregnancy (B), and as smokers (C).

Results: 5434 (73.1%) women were group A, 1191 (16%) group B and 812 (10.9%) group C. The rates of GDM among the groups were: A 33.7%, B 34.2%, C 34.2% (ns). However, the number of individuals requiring insulin treatment was significantly different: A 39.2%, B 47.5%, C 50.6% ($p < 0.001$). Regarding OGTT, fasting glucose levels were significantly higher in group C (89 ± 13 vs 86 ± 12 mg/dl) compared to A, whereas 3-h glucose values were significantly lower (104 ± 33 vs 112 ± 32 mg/dl) ($p < 0.001$). Group B demonstrated intermediate glucose concentrations. Similar findings were observed in women without GDM. In women with GDM, higher 1-h glucose levels were measured in group C (210 ± 31 vs 205 ± 28 mg/dl) compared with A ($p = 0.024$). Further, group C sub-analysis found that those who smoked more than 10 cigarettes showed significantly lower 3-h glucose levels (111 ± 31 vs 128 ± 40 mg/dl) compared to those who smoked less than 10 ($p = 0.006$). HbA1c in women with GDM was higher in group C (4.6 ± 0.6 vs $4.5 \pm 0.6\%$) compared with A ($p = 0.027$).

Conclusions: The present study did not show any correlation between smoking and GDM risk. However, OGTT profile and HbA1c differed according to smoking status in women with and without GDM.

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Abbreviations: GDM, gestational diabetes mellitus; OGTT, oral glucose tolerance test

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1. Introduction

Smoking has been traditionally considered as a risk factor for increased insulin resistance. Patients with both type 1 and type 2 diabetes mellitus (DM) who smoke present a worse metabolic profile [1–4]. Even in individuals without DM, the glycemic profile of smokers seems to be changed. A well-performed meta-analysis provided evidence that individuals who smoke present higher levels of glycosylated hemoglobin (HbA1c) compared to non-smokers. On the other hand, they have lower glucose levels at both fasting and 2 h after an OGTT with 75 g glucose load. Ex-smokers presented intermediate results [5].

Regarding Gestational DM (GDM), the type of diabetes diagnosed in the second or third trimester of pregnancy that is not clearly overt diabetes, data are scarce and conflicting so far. Most studies as well a systematic review that qualitatively synthesized several of these 10 years ago [6,7] did not prove any association between cigarette smoking during pregnancy and the risk of GDM. However, there are other data that could support that smoking increases [8] or even decreases the risk for GDM [9]. Different criteria for the diagnosis of GDM used in various studies may affect these results, as according to the criteria applied the severity of cases with GDM as well as the OGTT profile may be different. Furthermore, various studies so far have included various ethnicity populations, which may also affect the results.

Despite conflicting results regarding the definite risk of GDM, smoking does affect the metabolic profile of these women. It has been associated with worse metabolic control [10] and a higher risk of severe hypoglycemia in the third trimester in type 1 diabetic women [11]. Notably, in women diagnosed with GDM a different OGTT (oral glucose tolerance test) pattern has been described between smokers and non-smokers [12], as well as disproportionately high HbA1c levels for glycemic values.

The aim of this study is to analyze the relationship between smoking during pregnancy and the risk for GDM. Moreover, to investigate the OGTT profile in relationship with smoking status in pregnant women with and without GDM.

2. Patients and methods

2.1. Study participants

This is a retrospective study. A total of 7437 pregnant women from our prospectively collected database, created from 01.01.2000 to 31.12.2015, were studied. Research has been approved by the Institutional Review Board of the “Alexandra” Hospital in Athens, Greece. Written informed consent was obtained from all participants.

All women underwent a diagnostic 3-h 100 g OGTT during the 3rd trimester of pregnancy, specifically at 27.3 ± 3.9 gestational weeks. 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].

According to smoking status, women were categorized as non-smokers (group A), as those who ceased smoking at confirmation of pregnancy (group B), and as smokers (group C).

Various important characteristics of study participants are presented in Table 1. The great majority were primi-gravida, therefore the number of previous GDM cases was very low and not considered in the study. The same applies to the number of previous obstetric outcomes. There was no specific questionnaire on physical activity, because the data for this very large cohort (which includes every pregnant woman who visited the hospital) are derived from the standard hospital record. However, it can be noted that almost all women appeared to have a sedentary profile. With regard to nutritional habits, the dietitian issued to all GDM women a daily diet whose calories were based on the pre-pregnancy BMI according to IOM guidelines for weight gain.

2.2. 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%. HbA1c was determined using high pressure liquid chromatography (HPLC-HA8160 Menarini Arkay). The inter- and intra-assay coefficients of variation for HbA1c was less than 2%.

2.3. Statistical analysis

Results are presented as mean \pm SD for continuous variables, as absolute numbers and percentages in parentheses for categorical variables. Distribution of continuous parameters was tested by the 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. Stepwise logistic regression analysis followed in order to confirm the independent association of smoking with fasting and 3-h glucose plasma value. All statistical analyses were performed using the Statistical Package for Social Sciences (SPSS 22.0, Inc, Chicago, IL, USA). A p value of <0.05 was considered statistically significant.

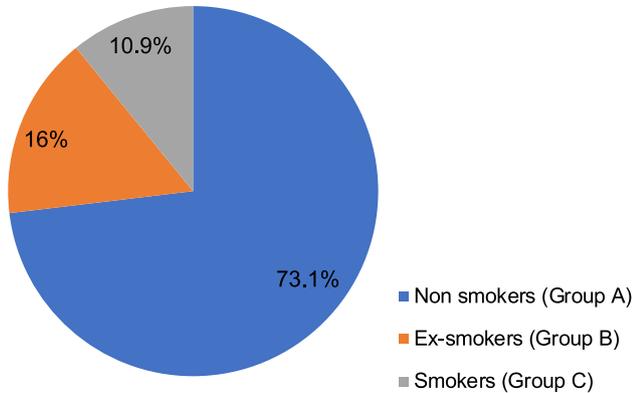
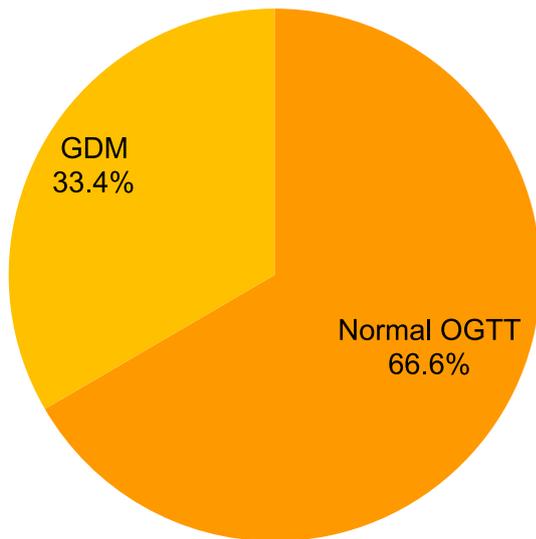
3. Results

Of the total 7437 pregnant women participating in the study, 5434 (73.1%) women were included in group A, 1191 (16%) in group B and 812 (10.9%) in group C (Fig. 1). Of those, 4955 (66.6%) women were without GDM and 2482 (33.4%) were diagnosed with GDM (Fig. 2). The rates of GDM among the 3 groups were: group A 33.7%, group B 34.2% and group C 34.2%, without statistically significant differences ($p > 0.05$) (Fig. 3).

Furthermore, no significant differences in the number of OGTT abnormal values were observed. However, the number of individuals requiring insulin treatment was significantly

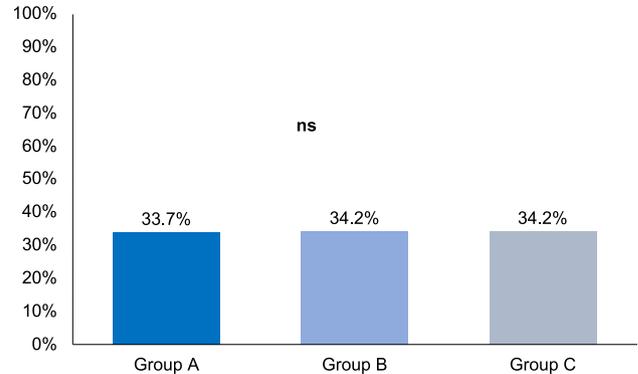
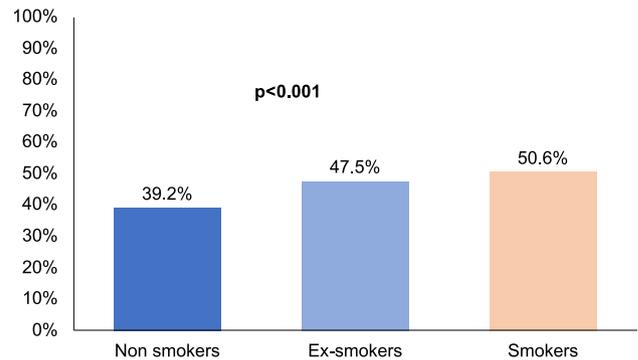
Table 1 – Characteristics of study participants.

Characteristics	Group A	Group B	Group C	p value
Age (years)	30.7 ± 5.6	31.2 ± 5.3	32.1 ± 5.6	ns
BMI (kg/m ²)	25.4 ± 5.1	25.8 ± 5.4	26.4 ± 6.1	<0.001 (A vs C)
Weight Gain (kg)	9.6 ± 5.5	11 ± 5.7	11.2 ± 6.6	<0.001 (A vs B, A vs C)
Family History of Diabetes	9.6%	13.7%	15.1%	<0.001 (in all comparisons)
Ethnicity	Caucasian 72.4% Black 16.4% Asian 11.2%	Caucasian 95.3% Black 3.9% Asian 0.8%	Caucasian 97.2% Black 2.8% Asian 0%	<0.001 (A vs B, A vs C)

**Fig. 1 – Women distribution according to smoking status.****Fig. 2 – Women distribution according to GDM diagnosis.**

different among the 3 groups: group A 39.2%, group B 47.5% and group C 50.6% ($p < 0.001$) (Fig. 4).

Regarding the OGTT profile, fasting glucose levels were significantly higher in group C (89 ± 13 vs 86 ± 12 mg/dl) compared with group A, whereas 3-h glucose values were significantly lower (104 ± 33 vs 112 ± 32 mg/dl) ($p < 0.001$). Group B demonstrated intermediate glucose concentrations (Table 2). Similar findings were observed in the sub-analysis of glucose values in women with normal OGTT (Table 3). Concerning women diagnosed with GDM, higher 1-h glucose

**Fig. 3 – Rates of GDM among the 3 groups (non-significant differences).****Fig. 4 – Women with GDM requiring insulin treatment among 3 groups.**

levels were measured in group C (210 ± 31 vs 205 ± 28 mg/dl) compared with group A ($p = 0.024$), in addition to the aforementioned findings of higher fasting and lower 3-h glucose values (Table 2). Moreover, HbA1c in women with GDM was higher in group C (4.6 ± 0.6 vs $4.5 \pm 0.6\%$) compared with group A ($p = 0.027$) (Table 2).

Further group C sub-analysis using the cutoff of 10 cigarettes per day found that those who smoked more than 10 cigarettes showed significantly lower 3-h glucose levels (111 ± 31 vs 128 ± 40 mg/dl) compared to those who smoked less than 10 ($p = 0.006$) (Table 4). Stepwise logistic regression analysis confirmed the independent association of smoking with fasting and 3-h glucose plasma value, after adjustment for BMI and gestational weight gain.

Table 2 – OGTT profile among women with GDM.

Measurements	Group A	Group B	Group C	p value
Fasting glucose (mg/dl)	94 ± 14	96 ± 15	97 ± 15	<0.001
1-h glucose (mg/dl)	205 ± 28	206 ± 30	210 ± 31	0.024
2-h glucose (mg/dl)	180 ± 33	178 ± 36	180 ± 39	ns
3-h glucose (mg/dl)	136 ± 37	130 ± 37	125 ± 30	<0.001
HbA1c (%)	4.5 ± 0.6	4.5 ± 0.6	4.6 ± 0.6	0.027

Table 3 – OGTT profile among women without GDM.

Measurements	Group A	Group B	Group C	p value
Fasting glucose (mg/dl)	83 ± 8	83 ± 8	84 ± 8	<0.001
1-h glucose (mg/dl)	147 ± 29	148 ± 30	148 ± 30	ns
2-h glucose (mg/dl)	120 ± 23	120 ± 23	117 ± 23	ns
3-h glucose (mg/dl)	101 ± 23	99 ± 24	93 ± 23	<0.001
HbA1c (%)	4.2 ± 0.5	4.2 ± 0.5	4.2 ± 0.5	ns

Table 4 – Subgroup analysis of the OGTT profile in smokers with GDM according to number of cigarettes.

Measurements	<10 cigarettes/day	>10 cigarettes/day	p value
Fasting glucose (mg/dl)	96 ± 14	100 ± 15	ns
1-h glucose (mg/dl)	209 ± 31	215 ± 29	ns
2-h glucose (mg/dl)	179 ± 40	183 ± 30	ns
3-h glucose (mg/dl)	128 ± 40	111 ± 31	0.006

4. Discussion

The aim of this study was to analyze the relationship between smoking during pregnancy and the risk for GDM. Moreover, to investigate the OGTT profile in relationship with smoking status in pregnant women with and without GDM. The results did not show any correlation between smoking and GDM diagnosis based on the Carpenter-Coustan criteria. However, OGTT profile and HbA1c differed according to smoking status in women with and without GDM. Smokers with GDM presented increased fasting glucose levels and HbA1c levels, requiring more often insulin therapy.

The present results add to the evidence of most previous studies which did not find any correlation of smoking with GDM, based on the Carpenter-Coustan criteria. Indeed, most previous studies had not proven any association between cigarette smoking during pregnancy and the risk of GDM [6,7]. A systematic review that qualitatively synthesized 12 observational studies 10 years ago resulted in a crude odds ratio of 1.03 (99% CI 0.85–1.25) for GDM. Only 4 of the studies included presented adjusted measurements of association, and no significant association was found when these were analyzed alone (OR 0.95; 99% CI 0.85–1.07) [7]. A study which indicated a positive association between smoking and risk of GDM [8] used the National Diabetes Data Group criteria, providing specifically an adjusted odds ratio of 1.9 (95% confidence interval: 1.0, 3.6). In contrast, a Hispanic cohort showed that smoking during pregnancy was associated with a 54%

reduction in odds of GDM (OR = 0.46, 95% CI 0.22, 0.95). However, this association was no longer statistically significant after adjustment for age, parity and study site (OR = 0.47, 95% CI 0.23, 1.00) [9].

However, the number of individuals requiring insulin treatment was significantly higher in the group of smokers with GDM. Smoking-induced insulin resistance may explain this phenomenon. Smoking has been consistently described as a risk factor for increased insulin resistance [1]. Our results are in accordance with a previous study in women with GDM, where insulin treatment differed again between groups, with active smokers having a higher rate of insulin therapy than non-smokers (50.7% vs. 43.3%), although insulin doses did not differ between these groups [12]. Smoking-induced insulin resistance is probably also responsible for the higher fasting glucose levels in smokers both with and without GDM. The higher rate of insulin treatment in smokers also related to the higher 1-h plasma glucose after OGTT, which mirrors the higher postprandial values of these patients. These findings were independent of BMI and gestational weight gain.

On the other hand, 3-h glucose values were significantly lower in smokers, with ex-smokers demonstrating intermediate glucose concentrations, a phenomenon present also in women with normal OGTT. The number of cigarettes seem to further affect this finding, as further subgroup analysis found that those who smoked more than 10 cigarettes showed significantly lower 3-h glucose levels than those who smoked less than 10. This was independent of BMI and

gestational weight gain. Accelerated gastric emptying and increased glucose absorption is a likely contributor to this OGTT pattern present in smokers [5]. This pattern, along with the intermediate pattern of ex-smokers has been also described in a few previous studies, in both pregnant and non-pregnant women [5,12,14]. Higher HbA1c values among smokers are possibly due to increased erythrocyte lifespan, faster deoxyhemoglobin glycosylation and changes in the permeability of the erythrocyte membrane, as results of smoking. This finding is also in accordance with previous reports, both in pregnant and in non-pregnant women [5,12,14].

The strengths of our study include the large number of participants, the homogeneous cohort of women of Greek origin and the measurement of HbA1c simultaneously with the performance of OGTT. To our knowledge, this is the largest study so far to evaluate the OGTT profile with regard to smoking habits in pregnant women both with and without GDM. A limitation of the study could be that “Alexandra” Hospital in Athens, Greece is a referral center for high risk pregnant women. Therefore, the cases of GDM included were selected among women with greater severity of GDM and this may not reflect the general population of women with GDM. The clinical implications of the study are important. Physicians dealing with pregnant women should be aware of these possible effects, in order to take smoking habits into consideration before any diagnostic assessment and therapeutic action for GDM. Of course, consultation for smoking cessation, in general and especially during pregnancy, should constitute an essential part of routine clinical management.

In conclusion, the present study did not show any correlation between smoking and GDM risk based on the Carpenter-Coustan criteria. However, OGTT profile and HbA1c differed according to smoking status in women with and without GDM. Smokers with GDM presented increased HbA1c levels, increased fasting glucose levels, lower 3 h post-OGTT glucose levels and required more often insulin therapy.

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Declaration of Competing Interest

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

Appendix A. Supplementary material

Supplementary data to this article can be found online at <https://doi.org/10.1016/j.diabres.2019.107901>.

REFERENCES

- [1] Will JC, Galuska DA, Ford ES, Mokdad A, Calle EE. Cigarette smoking and diabetes mellitus: evidence of a positive association from a large prospective cohort study. *Int J Epidemiol* 2001;30:540–6.
- [2] Cho NH, Chan JC, Jang HC, Lim S, Kim HL, Choi SH. Cigarette smoking is an independent risk factor for type 2 diabetes: a four-year community-based prospective study. *Clin Endocrinol (Oxf)* 2009;71:679–85.
- [3] Willi C, Bodenmann P, Ghali WA, Faris PD, Cornuz J. Active smoking and the risk of type 2 diabetes: a systematic review and meta-analysis. *JAMA* 2007;298:2654–64.
- [4] Hofer SE, Rosenbauer J, Grulich-Henn J, Naeke A, Fröhlich-Reiterer E, Holl RW, et al. Smoking and metabolic control in adolescents with type 1 diabetes. *J Pediatr* 2009;154:20–3.
- [5] Soulimane S, Simon D, Herman WH, Lange C, Lee CM, Colagiuri S, et al. HbA1c, fasting and 2 h plasma glucose in current, ex- and never-smokers: a meta-analysis. *Diabetologia* 2014;57:30–9.
- [6] Terry PD, Weiderpass E, Ostenson CG, Cnattingius S. Cigarette smoking and the risk of gestational and pregestational diabetes in two consecutive pregnancies. *Diab Care* 2003;26(11):2994–8.
- [7] Wendland EM, Pinto ME, Duncan BB, Belizan JM, Schmidt MI. Cigarette smoking and risk of gestational diabetes: a systematic review of observational studies. *BMC Preg Childb* 2008;8:53.
- [8] England LJ, Levine RJ, Qian C, Soule LM, Schisterman EF, Yu KF, et al. Glucose tolerance and risk of gestational diabetes mellitus in nulliparous women who smoke during pregnancy. *Am J Epidemiol* 2004;160:1205–13.
- [9] Moore Simas TA, Szegda KL, Liao X, Pekow P, Markenson G, Chasan-Taber L. Cigarette smoking and gestational diabetes mellitus in Hispanic woman. Cigarette smoking and gestational diabetes mellitus in Hispanic woman. *Diab Res Clin Pract* 2014;105:126–34.
- [10] Hummel M, Baumgarten A, Hummel S, König S, Ziegler AG. Smoking behavior during pregnancy of women with type 1 or gestational diabetes. *Dtsch Med Wochenschr* 2007;132:1153–8.
- [11] Robertson H, Pearson DW, Gold AE. Severe hypoglycaemia during pregnancy in women with Type 1 diabetes is common and planning pregnancy does not decrease the risk. *Diab Med* 2009;26:824–6.
- [12] Aulinas A, Colom C, García Patterson A, Ubeda J, María MA, Orellana I, et al. Smoking affects the oral glucose tolerance test profile and the relationship between glucose and HbA1c in gestational diabetes mellitus. *Diab Med* 2016;33:1240–4.
- [13] American Diabetes Association. Gestational diabetes mellitus. *Diab Care* 2000;23:S77–9.
- [14] Janzon L, Berntorp K, Hanson M, Lindell SE, Trelle E. Glucose tolerance and smoking: a population study of oral and intravenous glucose tolerance tests in middle-aged men. *Diabetologia* 1983;25:86–8.