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Impact of smoking on gestational diabetes mellitus and offspring birthweight in primiparous women

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Abstract

Introduction: Smoking has been shown to affect glucose homeostasis and increase the risk for type 2 diabetes mellitus. Further, gestational diabetes mellitus (GDM) and smoking are known to influence offspring birthweight. The effect of smoking on glucose homeostasis in pregnancy is less studied and the findings are inconsistent. The aim of this study was to evaluate the effect of smoking on risk for GDM and to evaluate the impact of smoking and GDM on offspring birthweight.

Material and methods: This is an observational cohort study encompassing 4111 Finnish primiparous women from the city of Vantaa, Finland, who delivered a singleton child between 2009 and 2015. Data were obtained from Finnish national registers. Study participants had complete oral glucose tolerance test results and were divided into three groups according to smoking status: non-smokers (I), smokers who quit during first trimester (II), and smokers who continued after first trimester (III).

Results: Prevalence of GDM was 19.8%, 24.3%, and 26.6% in non-smokers, those who quit, and those who continued after the first trimester, respectively (P = .004 for differences between groups). The odds ratio for GDM in smokers who continued after the first trimester compared with non-smokers was 1.65 (95% CI 1.09-2.57) after adjustments for age, prepregnancy body mass index, education, and cohabitation. In women without GDM, offspring birthweight was lowest in those who continued smoking after the first trimester (P = .010 for differences between groups). In women with GDM, smoking status did not influence offspring birthweight.

Conclusions: Smoking during pregnancy is associated with an increased risk for GDM. Offspring birthweight is lowest in women who continue smoking after the first trimester. If pregnancy is complicated by GDM, offspring birthweight is not influenced by smoking.

KEYWORDS

birthweight, gestational diabetes mellitus, offspring, primiparous, smoking

Abbreviations: BMI, body mass index; CI, confidence intervals; GDM, gestational diabetes mellitus; OR, odds ratio; SD, standard deviation; T2D, type 2 diabetes mellitus.

1 | INTRODUCTION

Gestational diabetes mellitus (GDM) is defined as any kind of abnormal glucose metabolism first detected, or with first onset, during pregnancy.[1] The prevalence of GDM worldwide has been rising dramatically during the last decades, making it a serious global health issue.[2,3] An optimal glucose metabolism during pregnancy is crucial for normal fetal development and growth. GDM, and especially untreated maternal hyperglycemia, during pregnancy is associated with exaggerated fetal growth known as macrosomia.[1]

Some widely accepted risk factors for GDM are advancing maternal age, maternal obesity, and a genetic predisposition for type 2 diabetes mellitus (T2D) or GDM.[4] Moreover, maternal short stature, maternal low birthweight, and a lower socioeconomic status have also been recognized to increase the risk for GDM.[3,4] In studies on non-pregnant women, smoking has been shown to affect glucose homeostasis and increase the risk for T2D.[5,6] Interestingly though, the effects of smoking on glucose homeostasis in pregnancies are less studied and the findings are somewhat conflicting: some studies show an increased risk for GDM among smokers,[7-9] some a decreased risk,[10] and some studies report no association at all.[3,11-13]

The prevalence of smoking during pregnancy has been estimated to vary between 10.5% and 13% in the early 2000s in USA and Sweden.[14] In Finland, the prevalence of smoking among pregnant women has remained stable at 15% between the years 1991-2015.[15] Smoking during pregnancy is of major concern because it is known to increase the risk for severe pregnancy complications such as preterm birth, perinatal mortality, and stillbirth.[14] Moreover, smoking is inversely associated with offspring birthweight.[14] Offspring size at birth, in turn, is recognized to have long-lasting effects on health over the lifespan.[16]

In 2016, we initiated a long-term follow-up study in the city of Vantaa, Finland, to assess short- and long-term health effects of glucose metabolism on the pregnant women and their offspring. It is of interest to study risk factors for GDM, especially those that are modifiable, to aim for a more efficient screening and prevention of GDM in the future. The objective of this study was to evaluate the effects of smoking on glucose homeostasis, and further, to evaluate the combined effects of smoking and GDM on offspring birthweight in primiparous women.

Key message

Smoking during pregnancy increases risk for gestational diabetes mellitus (GDM) but decreases offspring birthweight. If the pregnancy is complicated by GDM, offspring birthweight is not influenced by smoking.

2 | MATERIAL AND METHODS

This is an observational cohort study from the city of Vantaa, which is part of the Helsinki metropolitan area, with 220 000 inhabitants. During a 7-year follow-up, between 1 January 2009 and 31 December 2015, 7750 primiparous women without a history of diagnosed diabetes mellitus gave birth. Of these, 4111 Finnish women (born in Finland with Finnish or Swedish as native language) and aged ≥18 years delivered their first singleton child at term between gestational weeks 37 and 42. All of these women had complete data from a standard 2-hour 75-g oral glucose tolerance test (OGTT). We included only those women who had complete OGTT results, so as to have a reliable diagnosis of GDM in the current pregnancy. This was a register-based study with no patient involvement. No identifiable personal data were available to the researchers.

Since 2008, the Finnish Current Care Guidelines for GDM recommend screening of all pregnant primiparous women for GDM between gestational weeks 24 and 28 using a standard 2-hour 75-g OGTT, except in low-risk women, ie women aged under 25 years, with a prepregnancy body mass index (BMI) between 18.5 and 25 kg/m^2, and with no family history of diabetes mellitus.[17] If the pregnant primiparous woman is considered to be at high risk for GDM, that is, with a prepregnancy BMI >35 kg/m^2, glucosuria in early pregnancy, a family history of T2D, use of oral corticosteroid medication, or a history of polycystic ovarian syndrome, the screening for GDM will have been performed already between gestational weeks 12 and 16.[17] If the early screening result is not diagnostic, the OGTT will be repeated between gestational weeks 24 and 28.

Diagnostic criteria used for the diagnosis of GDM were defined according to the Finnish Current Care Guidelines for GDM as one or more pathological glucose values in a standard 2-hour 75-g OGTT with thresholds as follows: fasting plasma glucose ≥5.3 mmol/L, 1-hour glucose ≥10.0 mmol/L, and 2-hour glucose ≥8.6 mmol/L.[17]

Data on maternal-fetal characteristics were obtained from the Finnish Medical Birth Register, which is maintained by the Finnish Institute for Health and Welfare. The register receives information about all live and stillbirths from gestational weeks 22 or with a birthweight ≥500 g, from all Finnish maternity hospitals (http://www.thl.fi/en/statistics/parturients). From this source we obtained the following information about the primiparous women: pregestational weight, height, previous pregnancies (including miscarriages, induced abortions, and ectopic pregnancies), infertility treatments, information about current pregnancies and deliveries, hospitalization for hypertension during pregnancy, and smoking during pregnancy. More specifically, smoking status was self-reported and documented in a structural form at hospitals at time of delivery. According to pre-defined smoking categories on the form, the women were divided into three groups with the following definitions: non-smokers (I), smokers who quit during the first trimester of pregnancy (II), and smokers who continued after the first trimester of pregnancy (III). Additionally, the following information on the offspring was collected: sex, birth length, birthweight, and head circumference.

Offspring birthweights were calculated as Z-scores (according to sex and gestational age) within the study cohort.

Incomplete information about GDM, maternal height, and prepregnancy weight was completed using information from individual patient records from Vantaa Health Care.

Statistics Finland provided information about educational attainment, according to years of schooling (Official Statistics of Finland: http://stat.fi/til/vkour/index_en.html).

2.1 | Statistical analyses

Data in the table are presented as means with range or standard deviations (SD) or as counts with percentages. Offspring birthweight was calculated as Z-scores (according to sex and gestational age) within the study cohort. Statistical comparisons between the three groups according to smoking status were performed using analysis of variance, and chi-squared tests. Adjusted differences between the groups were evaluated using analysis of covariance and logistic models. Models included age, prepregnancy BMI, education, and cohabiting as covariates. Hommel's adjustment has been applied to correct levels of significance for multiple testing (at significance level 0.05). The normality of the variables was evaluated graphically and by using the Shapiro-Wilk W test. Stata 16.0 (StataCorp LP) statistical package was used for the analysis.

2.2 | Ethical approval

The present study has been approved by the ethics committee of the Hospital District of Helsinki and Uusimaa (356/13/03/03/2015, 2 November 2015), as well as by the health authority of the city of Vantaa, Finland. Finnish Institute for Health and Welfare and Statistics Finland gave their permission to use register data for this study. As this is an observational register-based study, the study participants do not need to provide any Statement of Informed Consent, as outlined by the Hospital District of Helsinki and Uusimaa, and the health authority of Vantaa city. The study participants were not contacted. Data cannot be shared for both legal and ethical reasons. Data from the Finnish Institute for Health and Welfare, Statistics Finland, and the Finnish Social Insurance Institution can only be used for the purpose stated in the license granted, scientific research on society by the license applicant, and can therefore not be shared with third parties.

3 | RESULTS

3.1 | Characteristics of study participants

Characteristics of the 4111 study participants, grouped according to smoking status into three groups, are shown in Table 1. The overall prevalence of smoking was 15.1%. Of the primiparous women, 8.1% were smokers who quit smoking during the first trimester and 7.4% of the women were smokers who still continued smoking after the first trimester. Age differed between the groups, with non-smokers being the oldest (mean age 30.0 [SD 4.5] years) ($P < .001$ for differences between groups). Similarly, educational attainment differed between the groups with a higher educational attainment in the group of non-smokers ($P < .001$ for differences between groups). Prepregnancy BMI was significantly lower in non-smokers compared with the two groups of smokers, but did not differ between smokers who either quit or continued smoking after the first trimester.

TABLE 1 Differences in characteristics of the primiparous women (N = 4111) according to smoking status

	Smoking status			
	Non-smokers (I) N = 3475	Smokers who quit during the first trimester (II) N = 305	Smokers who continued after the first trimester (III) N = 331	*P*-value[a]
Age (y), mean (SD)	30.0 (4.5)	27.5 (4.7)	26.5 (5.5)	<.001 [I/II, I/III, II/III]
Height (cm), mean (range)	166 (6)	166 (6)	166 (6)	.30
Prepregnancy weight (kg), mean (SD)	67.8 (13.6)	70.6 (14.8)	72.5 (17.0)	<.001 [I/II, I/III]
Cohabiting, n (%)	2919 (84)	235 (77)	228 (69)	<.001 [I/II, I/III, II/III]
Education years, mean (SD)	14.2 (2.3)	12.7 (2.1)	11.2 (2.1)	<.001 [I/II, I/III, II/III]
Prepregnancy BMI (kg/m^2), mean (SD)	24.6 (4.6)	25.7 (5.0)	26.3 (5.6)	<.001 [I/II, I/III]
Previous pregnancies, n (%)	638 (18)	77 (25)	103 (31)	<.001 [I/II, I/III]
Fertility treatment, n (%)	384 (11)	10 (3)	8 (2)	<.001 [I/II, I/III]
Hypertensive disorders[b]	224 (6)	27 (9)	17 (5)	.15
Cesarean delivery, n (%)	800 (23)	74 (24)	71 (22)	.75

Abbreviations: BMI, body mass index; SD, standard deviation.

[a]*P*-value for differences between groups; Hommel's multiple comparison procedure was used to correct significance levels for post hoc testing ($P < .05$).

[b]Hospitalization for hypertension during pregnancy.

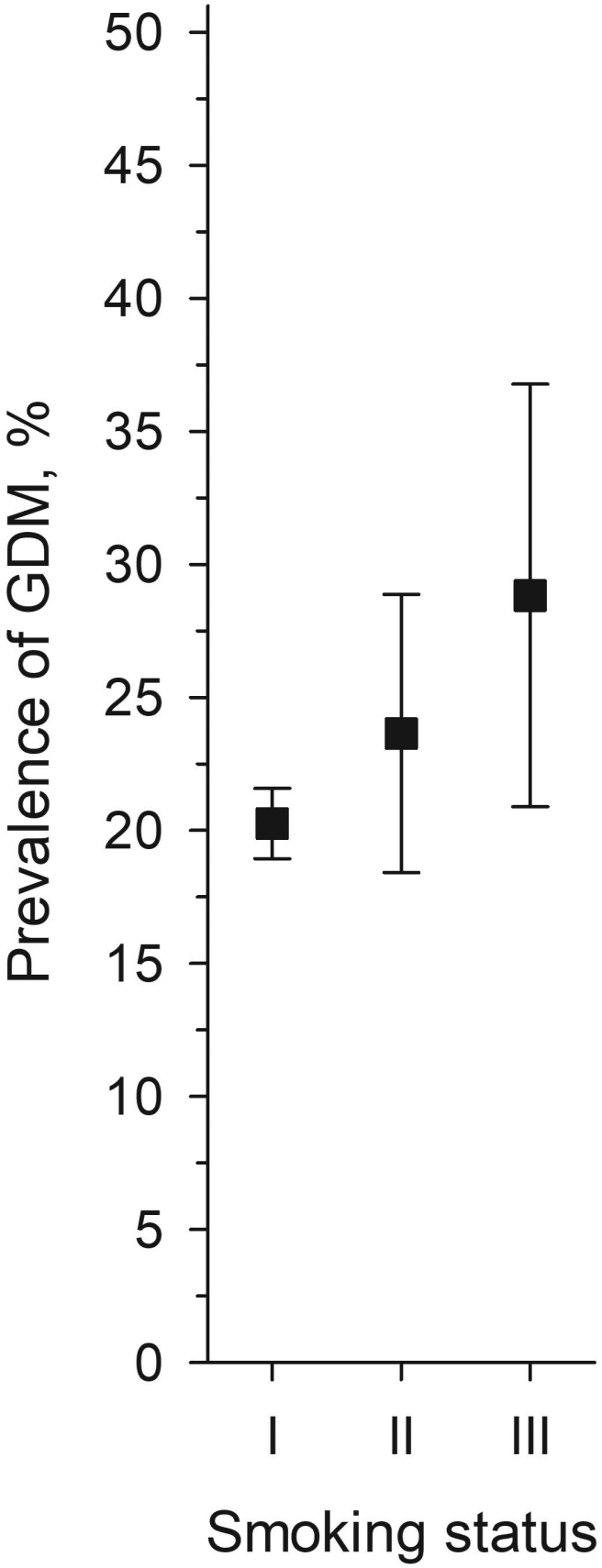

FIGURE 1 Prevalence of gestational diabetes mellitus (GDM) according to smoking status. Prevalence of GDM according to smoking status after adjustments for age, prepregnancy body mass index, education, and cohabiting. The three groups were defined as follows: non-smokers (I), smokers who quit during the first trimester (II), and smokers who continued after the first trimester (III). Whiskers represent 95% confidence intervals

3.2 | Smoking status and prevalence of GDM

The overall prevalence of GDM in the study cohort was 20.7%. In the group of non-smokers, the prevalence was 19.8%, whereas, in both groups of smokers the prevalence was higher: 24.3% in those who quit, and 26.6% in those who continued after the first trimester, respectively (P = .004 for differences between groups). The differences between groups also remained significant after adjustments for age, prepregnancy BMI, education, and cohabiting (P = .028) (Figure 1).

Similarly, the odds ratio (OR) for GDM in the group of smokers who continued after the first trimester compared with non-smokers was 1.65 (95% CI 1.09-2.47) after adjustments for age, prepregnancy BMI, education, and cohabiting. The OR for GDM in smokers who quit during the first trimester compared with non-smokers was 1.24 (95% CI 0.90-1.72), after adjustments for the same confounders.

3.3 | Smoking status and its effect on OGTT values

The effect of smoking status on glucose concentrations after an OGTT in the three groups was evident both on fasting glucose concentrations (P = .013) and 1-hour postprandial glucose concentrations (P = .002), after adjustments for age, prepregnancy BMI, education, and cohabiting (Figure 2). Smoking status did not affect 2-hour postprandial glucose concentrations (P = .10), after adjustments for the same confounders (Figure 2).

3.4 | Effect of smoking status and GDM on offspring birthweight

Figure 3 shows the impact of maternal smoking status and GDM and their interaction on offspring birthweight, adjusted for maternal age and prepregnancy BMI. Independently, GDM did not affect offspring birthweight across the three groups, whereas smoking did, and the interaction between GDM and smoking was significant. In primiparous women without GDM, offspring birthweight was lower in the group of smokers who continued after the first trimester. However, in primiparous women with GDM, smoking did not influence offspring birthweight, not even in the group of smokers who continued after the first trimester.

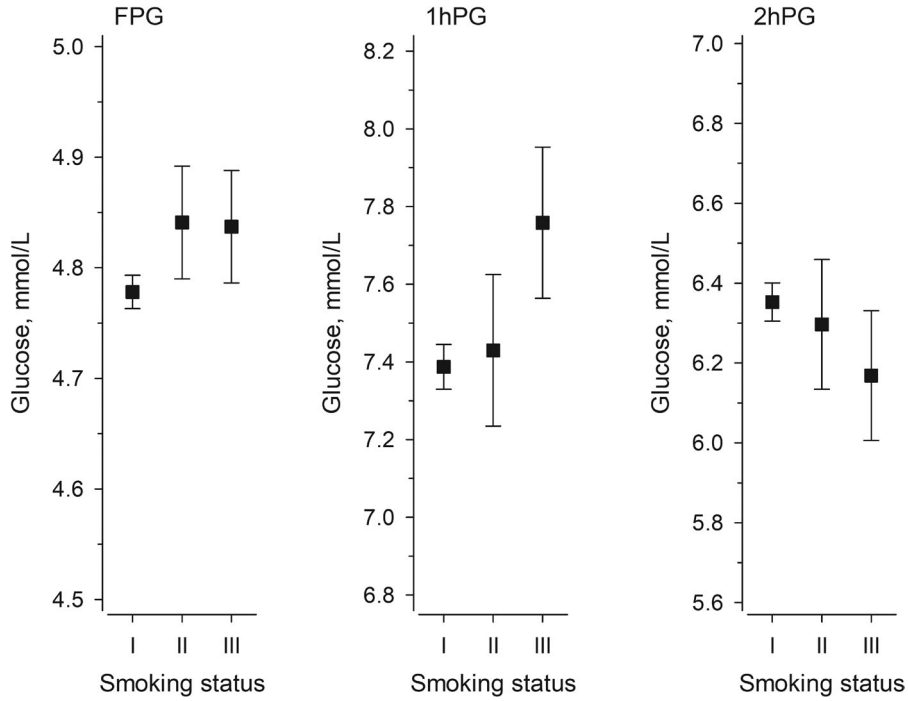

FIGURE 2 The effect of smoking status on oral glucose tolerance test (OGTT) values. The effect of smoking status on OGTT values. The three different groups were defined as follows: non-smokers (I), smokers who quit during the first trimester (II), and smokers who continued after the first trimester (III). Models were adjusted for age, prepregnancy body mass index, education, and cohabiting. Whiskers represent 95% confidence intervals. Abbreviations: 1hPG, 1-hour plasma glucose; 2hPG, 2-hour plasma glucose; FPG, fasting plasma glucose

4 | DISCUSSION

The overall prevalence of GDM in the study cohort was 20.7% and overall GDM prevalence was associated with smoking status. Non-smokers had significantly lower fasting and 1-hour glucose concentrations compared with smokers who continued smoking after the first trimester. However, 2-hour glucose concentrations did not differ between smokers and non-smokers. In primiparous women without GDM, offspring birthweight was lower in those who continued smoking after the first trimester compared with non-smokers. However, in women with GDM, smoking status did not influence offspring birthweight.

The prevalence of GDM in the study cohort of 21% must be considered high, as the highest reported nationwide prevalence of GDM during the same study period was 16%.[18] The high prevalence is likely because the cohort consisted of women with complete data from OGTT, who are regarded as being at high-risk for GDM. The 15% prevalence of smokers in the beginning of pregnancy is in line with findings from Finland in general.[15]

The relation between smoking and T2D has been widely studied and a positive association between smoking and risk of T2D has been verified in two recent systematic reviews.[5,6] Further, WHO has newly endorsed smoking as a modifiable risk factor in prevention of T2D.[19] The association between smoking and GDM is, however, more controversial. Several epidemiological studies have assessed the relation showing positive,[7-9] negative,[10] and neutral[3,12] relations. A systematic review from 2008 reported no significant association between smoking and GDM,[11] however, the number of included studies was low and most of them were based on unadjusted measurements. In 2018, nonetheless, Wang et al published a meta-analysis with the same findings.[13]

We found smoking to be associated with an increased risk for GDM. Comparisons between the above-mentioned studies with mixed findings regarding the relation between smoking and GDM must be considered carefully. Most importantly, smoking status of the pregnant women has mostly been self-reported and assessed in different manners depending on the study. Second, diagnostic criteria for GDM vary between studies, and finally, analyses have been performed with different confounding factors. It is, for example, of great importance to recognize the confounding effects of socioeconomic factors and weight gain after smoking cessation in early pregnancy,[20] as both excessive weight gain[21] and socioeconomic deprivation, which smoking can be related to, are known to increase the risk for GDM.[3] In a meta-analysis by Wang et al assessing the effect of smoking cessation in early pregnancy, the authors concluded that most of the included studies adjusted for BMI or gestational weight gain, which might attenuate the increased risk for GDM.[13] On the other hand, in a cohort study showing no effect of smoking on GDM, Anna et al controlled, among other variables, for age and socioeconomic status, but not for obesity.[3] One can only speculate how the selection of possible confounders affects the relation between smoking and gestational diabetes.

Chronic cigarette smoking increases insulin resistance through a direct effect on insulin-mediated glucose uptake as well as on pancreatic β-cell function and insulin secretion.[6] Acute effects on glucose homeostasis and elevated postprandial glucose concentrations can, at least to some extent, be caused by a decreased gastric emptying in

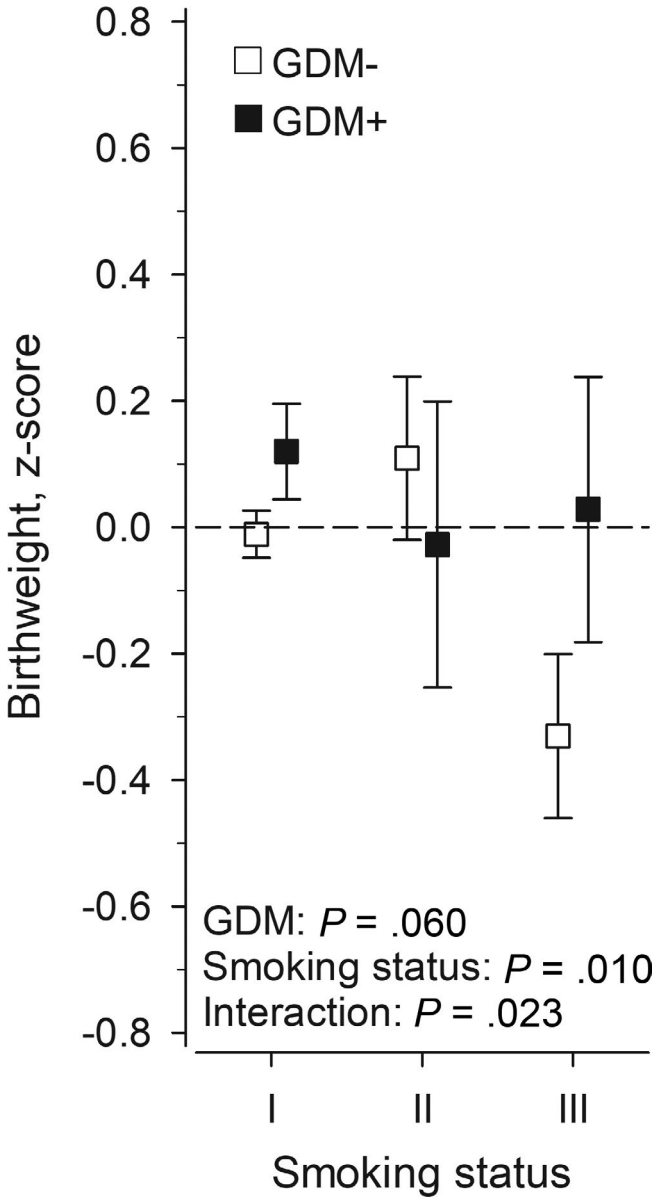

FIGURE 3 Impact of smoking status and gestational diabetes mellitus (GDM) on offspring birthweight. The impact of smoking and GDM and their interaction on offspring birthweight in three different groups depending on smoking status, adjusted for age, prepregnancy body mass index, education, and cohabiting. The three groups were defined as follows: non-smokers (I), smokers who quit during the first trimester (II), and smokers who continued after the first trimester (III). Offspring birthweight was calculated as Z-scores according to sex and gestational age. Whiskers represent 95% confidence intervals

smokers.[22] A study from the 1980s showed that smokers had higher 1-hour postprandial glucose concentrations compared with non-smokers, but lower 2-hour postprandial glucose concentrations.[23] A recent meta-analysis also reported 2-hour postprandial concentrations to be lower in smokers compared with non-smokers.[24] Likewise, also in pregnant women with GDM, 1-hour postprandial concentrations have been shown to be higher and 2-hour postprandial concentrations lower in women who smoked at the beginning of their pregnancy compared with non-smokers.[25] None of these previous studies have reported any difference in fasting glucose concentrations.

To the best of our knowledge, few studies have evaluated the relation between smoking and glucose concentrations after an OGTT during pregnancy.[7,25] Compared with non-smokers, we discovered that primiparous women who continued smoking after the first trimester, had higher fasting glucose concentrations and higher 1-hour glucose concentrations. Women who stopped smoking after the first trimester, also had higher fasting glucose concentrations but not higher 1-hour glucose concentrations. The 2-hour concentrations showed a trend towards lower concentrations in smokers compared with non-smokers. Considering that the OGTT is mostly performed during the latter part of the second trimester, this could suggest that the adverse effects of smoking on glucose homeostasis could be reversible to some extent already during pregnancy. This idea gets support from a previous study, as chronic cigarette smokers were shown to have lower insulin sensitivity compared with non-smokers, which improved, but did not normalize after 1-2 weeks of smoking cessation.[26]

As a well-accepted phenomenon,[14] we also found offspring birthweight to be lowest in women who continued smoking after the first trimester compared with non-smokers. A low offspring birthweight in smokers is thought to be caused by restricted fetal oxygenation and nutrition transfer due to binding of nicotine and carbon monoxide to uterine artery blood flow and fetal hemoglobin.[14] Moreover, a possible interaction between maternal metabolic genes and cigarette smoking with regard to fetal growth has also been reported.[14] The adverse effects of smoking are, at least to some degree, believed to be reversible during pregnancy as the birthweights of offspring born to women who stopped smoking early in pregnancy are similar to those of offspring of non-smokers.[27] Similarly, according to our findings, offspring birthweight was not lower in those women who stopped smoking during the first trimester of their pregnancy.

One previous study evaluated the relation between smoking status, glucose homeostasis and offspring birthweight.[7] Similar to our findings, smoking seemed to affect parameters of glucose homeostasis in the direction of GDM as they showed glycated hemoglobin to be higher in heavily smoking pregnant women. Zaren et al also reported offspring birthweight to be low in heavily smoking mothers. However, in contrast to our findings, they reported offspring birthweight to be low also in those smoking mothers with higher glucose concentrations.[7] Interestingly, these women were thinner and shorter, which could, at least partly, be a confounding factor and affect the size of their newborn as maternal anthropometry is known to affect offspring size at birth.[28] In our study cohort, women who smoked had a higher prepregnancy BMI. This could, possibly, be explained by a lower degree of educational attainment, which in turn, is inversely associated with BMI.[29]

The study has several strengths. It is comprehensive and encompasses all adult Finnish primiparous women from the city of Vantaa with complete data from a standard 2-hour 75- g OGTT who delivered their first child during a 7-year follow-up period. The diagnosis

of GDM is trustworthy, it is based upon a standardized 2-hour 75-g OGTT and the diagnostic criteria have remained the same during the study period. Further, only primiparas were included in this study to exclude the confounding effects of previous GDM or multiparity on the risk for GDM. Finally, data from the Finnish Medical Birth Register can be considered of high quality.[30]

The study also has some limitations. Information about smoking status was self-reported and the number of cigarettes smoked per day was unknown. Also, we had no information on smoking status before pregnancy. Moreover, we lacked information about some well-known risk factors for GDM such as gestational weight gain and family history of diabetes. Finally, the study cohort included only women born in Finland and speaking either Finnish or Swedish, therefore generalization of the results globally might be restricted.

5 | CONCLUSION

Smoking during pregnancy is associated with an increased risk for GDM. Offspring birthweight is lowest in those women who continue smoking after the first trimester of pregnancy. However, if the pregnancy is complicated by GDM, offspring birthweight is not influenced by smoking. Smoking cessation should be highly encouraged in all pregnancies, taking the possible reversible adverse effects of smoking on both glucose homeostasis and offspring birthweight into account. Further studies are needed to evaluate the possible mechanisms and interaction between smoking and GDM on offspring birthweight, also taking socioeconomic factors and pregnancy weight gain into account.

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CONFLICT OF INTEREST

None.

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