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Retrospective Clinical Research Report



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Abstract

Objective: Some drugs have adverse effects on glucose metabolism, but it is unknown whether prescription drugs used prior to conception influence the future risk of gestational diabetes mellitus (GDM). Our study evaluated whether the purchase of prescription drugs 6 months prior to conception was associated with the occurrence of GDM.

Methods: This cohort study enrolled women with a Finnish background who delivered between 2009 and 2015 in the city of Vantaa, Finland (N = 10,455). Data on maternal characteristics and prescription drug purchases were obtained from national health registers. The use of a unique personal identification number enabled us to combine the register data on an individual level.

Results: Six months prior to conception, women who had pregnancies complicated by GDM purchased more prescription drugs than women without GDM (1.38 ± 2.04 vs. 1.11 ± 1.80). The GDM risk was higher in women with higher numbers of prescription purchases and those with more than three deliveries.

Conclusions: Multiparous women who purchase several prescription drugs should be given personalized counseling to prevent GDM.

Keywords

Cohort study, gestational diabetes mellitus, parity, prescription drug, drug purchase, glucose homeostasis, counseling, Anatomical Therapeutic Chemical Classification System

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Introduction

Gestational diabetes mellitus (GDM) is a pregnancy complication.¹ common Globally, the prevalence of GDM is increasing, reflecting a global health concern.^{1,2} The prevalence of GDM varies between 2% (Ireland) and 32% (Norway) depending on the population studied and the diagnostic criteria employed, and estimates of 9% and 6% have been recorded for North America and Europe, respectively.^{2,3} GDM increases the risk of adverse short- and long-term health outcomes for both the women and their offspring and affects the overall wellbeing of the fetus.^{1,4–7}

According to a large US study, the five most common chronic diseases in women of childbearing age were depression (prevalence, 15%), asthma (prevalence, 8%), obesity (prevalence, 8%), thyroid diseases (prevalence, 7%), and hypertension (prevalence, 6%).⁸ Previous studies reported that 50% to 80% of non-pregnant women of childbearing age used prescription drugs, most commonly for asthma and acute respiratory diseases, contraception, depression and/or anxiety, pain, and thyroid disorders.9-11 Among women of childbearing age, the use of prescription drugs appears to be increasing.¹² Furthermore, some drugs such as corticosteroids and some antipsychotic drugs such as olanzapine increase blood glucose levels, but the influence of overall medication use prior to conception on GDM risk is unclear.^{13–16}

In Finland, the prevalence of GDM is as high as 21%,¹⁷ and national register data on pregnancies as well as the purchases of prescription drugs are comprehensive, offering a unique opportunity to evaluate the influence of prescription drug purchases on the risk of GDM.

This study evaluated whether prescription drug purchases prior to conception were associated with the occurrence of GDM in Finnish women.

Materials and methods

Study design and participants

This study was a population-based cohort study from the city of Vantaa, Finland. In 2015, Vantaa was the fourth biggest city in Finland, with approximately 44,000 women of childbearing age. The study cohort consisted of women with a Finnish background (i.e., born in Finland with Finnish or Swedish as the native language) living in Vantaa and without previously diagnosed diabetes mellitus who delivered a baby between 1 January 2009 and 31 December 2015. Multiparous women with a history of GDM in previous pregnancies were included in the study. Only women with a Finnish background were included in this study to exclude the confounding effects of ethnicity on the risk for GDM and the effects of culture on the use of drugs.

Maternal characteristics

The Finnish Institute for Health and Welfare (THL) maintains the Finnish Medical Birth Register (http://www.thl.fi/ en/statistics/parturients). This register contains maternal antenatal data from all live births and stillbirths from 22 gestational weeks or 500 g onwards including every delivery hospital in Finland. From the Finnish Medical Birth Register, we obtained data on women's age at the time of delivery, cohabitation status, pre-pregnancy weight and height, smoking history (non-smokers, smokers who quit during the first trimester, smokers who continued after the first trimester), parity, use of infertility treatments, and diagnosis of GDM. The quality of the Finnish Medical Birth Register is considered to be high.¹⁸

Pre-pregnancy body mass index (BMI) was calculated as the pre-pregnancy body weight divided by height squared (kg/m^2) . Data on height, weight, and GDM were

further completed using information from patient records in Vantaa Health Care.

Educational attainment was defined according to number of schooling years by applying a national classification, which was obtained from Statistics Finland (http:// www.stat.fi/meta/luokitukset/koulutus/001-2016/kuvaus). Data on maternal comorbidities were obtained from the Social Insurance Institution (http://www.kela.fi/web/en/reim bursements-for-medicine-expenses).

Assessment of GDM

Since 2008 in Finland, GDM has been screened using a standard 75-g 2-hour oral glucose tolerance test (OGTT) between 24 and 28 weeks of gestation in all pregnant women, excluding those at low risk. Women at low risk are defined as follows: nulliparous age of less than 25 years with BMI of 18.5 to 24.9 kg/m^2 and no first-degree family history of diabetes, and multiparous age of less than 40 years with BMI < 25 kg/m^2 and no prior GDM or prior offspring with birthweight >4500 g (Current Care Guidelines for GDM, www.kaypahoito.fi).

In the OGTT, one or more pathological glucose levels with the following diagnostic thresholds lead to a diagnosis of GDM: fasting plasma glucose $\geq 5.3 \,\text{mmol/L}, 1$ hour glucose $\geq 10.0 \,\mathrm{mmol/L}$, and 2-hour glucose \geq 8.6 mmol/L (Current Care Guidelines for GDM, www.kaypahoito.fi). Screening of GDM is mainly performed in communal antenatal clinics in primary health care centers, and it is free of charge for women. In Finland, almost 100% of pregnant women use the communal antenatal clinics (https://thl.fi/fi/web/lapsetnuoret-ja-perheet/peruspalvelut/aitiys ja lastenneuvola/aitiysneuvola).

Data on prescription drug purchases

We obtained data on prescription drug purchases using Anatomical Therapeutic Chemical Classification System (ATC) codes 6 months prior to conception from the Prescription Register maintained by the Social Insurance Institution prescription register. ATC codes are as follows: code A, Alimentary tract and metabolism; code Blood and blood-forming organs; B, code C, Cardiovascular system; code D, Dermatological drugs; code G, Genitourinary system and reproductive hormones; code H, Systemic hormonal preparations excluding reproductive hormones and insulins; code J, Anti-infectives for systemic use; code L, Antineoplastic and immunomodulating agents; code M, Musculoskeletal system; code N, Nervous system; code P, Antiparasitic products, insecticides, and repellents; code R, Respiratory system; and code S, Sensory organs (https://www.whocc. no/atc ddd index/). The prescription register contains personal data on the number of prescription drug purchases and the date of purchase. The prescriptions consisted of drugs for both acute and chronic diseases.

We calculated the date of conception by reducing the duration of pregnancy from the day of delivery. The duration of pregnancy is reported in the Finnish Medical Birth Register based on an ultrasound examination of early pregnancy or, in its absence, the last menstrual period.

In Finland, every citizen and permanent resident has a personal identification number. With this personal identification number, register data from the Finnish Medical Birth Register, the Social Insurance Institution, and Statistics Finland were combined on an individual level. Before analyzing the results, the study participants were pseudoanonymized to prevent their identification.

The reporting of this study conforms to the STROBE guidelines.¹⁹

Ethical approval

The ethics committee of the Hospital District of Helsinki and Uusimaa, Finland

(356/13/03/03/2015, 2 November 2015), and the health authority of the city of Vantaa, Finland have approved the study. THL and The Finnish Social Insurance Institution and Statistics Finland have given permission to use register data in the study.

The study was conducted according to the World Medical Association Declaration of Helsinki. Informed consent was not required because this study was a registerbased cohort study and none of the study participants was contacted.

Statistical analyses

Data are presented as the mean and standard deviation or as counts with percentages. We made statistical comparisons between pregnancies without and with GDM using generalizing estimating equation (GEE) models with the exchangeable correlation structure and appropriate distribution and link function. We used GEE models to account for the correlation between repeated pregnancies in individual women. The models included age, prepregnancy BMI, smoking, fertility treatments, educational attainment, and comorbidity as covariates when appropriate. We applied Bonferroni adjustment to correct the levels of significance and confidence intervals (CIs) for multiple testing. We evaluated the normality of variables using graphically and the Shapiro-Wilk W test. The Stata 16.0 (StataCorp LP; College Station, TX, USA) statistical package was used for the analysis.

Results

Of 14,063 pregnancies (10,455 women), GDM was diagnosed in 16.3% of the pregnancies. Women diagnosed with GDM were older (31.4 [standard deviation {SD} 5.0] years versus 29.9 [SD 5.1] years, P < 0.001) and they had higher pre-pregnancy BMI (27.8 [SD 6.1]kg/m² versus 23.7 [SD 4.2] kg/m², P < 0.001) than women without GDM. No differences were observed in smoking habits or parity (Table 1).

Six months prior to conception, 44% of all pregnant women had purchased at least one prescription drug. Pregnant women with pregnancies complicated by GDM purchased more prescription drugs than women without GDM (1.38 [SD 2.04] drug purchases versus 1.11 [SD 1.80] drug purchases, P < 0.001). Six months prior to conception, women with pregnancies complicated by GDM more frequently purchased prescription drugs with ATC codes A (5.5%) versus 3.9%, P = 0.004after Bonferroni correction; risk ratio [RR]= 1.11 [95% CI = 0.92-1.33]), C (3.0% versus 1.8%, P = 0.003 after Bonferroni correction; RR = 1.12 [95% CI = 0.87 - 1.42]), G (7.0%) versus 5.2%, P = 0.007 after Bonferroni correction; RR = 0.98 [95% CI = 0.82-1.18]), N (16.1% versus 12.7%, P < 0.001 after)Bonferroni correction; RR = 0.10 [95% CI = 0.99-1.24]), and R (12.7% versus 9.6%, P < 0.001 after Bonferroni correction; RR = 0.12 [95% CI = 0.98-1.27]). Figure 1 presents the purchases of prescription drugs by ATC code as a percentage of the total number of pregnancies.

There was an interaction between parity and GDM. The risk of GDM was higher in women with a higher number of purchases of prescription drugs and those with more than three previous deliveries (both P = 0.001, Figure 2).

Discussion

To the best of our knowledge, this is the first study to evaluate the relationships of the number of prescription drug purchases prior to conception and parity with GDM. It is possible that women with multiple deliveries and women with GDM also have other health related problems or other diseases requiring the use of prescription drugs. A Canadian study reported that in women,

	Pregnancies without GDM n = 11,764	Pregnancies with GDM $n = 2299$	Р
Age (years), mean (SD)	29.9 (5.1)	31.4 (5.0)	< 0.001
Cohabiting, n (%)	10,232 (87.0)	2033 (88.4)	0.057
Pre-pregnancy body mass index	23.7 (4.2)	27.8 (6.1)	<0.001
Smokers, n (%)			0.41
Non-smokers	9949 (84.6)	1920 (83.5)	
Smokers who quit during the first trimester	662 (5.6)	142 (6.2)	
Smokers who continued after the first trimester	1153 (9.8)	237 (10.3)	
Fertility treatments, n (%)	655 (5.6)	190 (8.3)	<0.001
Education years	13.4 (2.6)	13.3 (2.5)	0.015
Parity			0.27
One	5186 (44.1)	1003 (43.6)	
Тwo	4356 (37.0)	825 (35.9)	
Tree	1523 (12.9)	307 (13.4)	
Four	442 (3.8)	108 (4.7)	
Five or more	257 (2.2)	56 (2.4)	
Comorbidity, n (%)	866 (7.4)	226 (9.8)	<0.001
Thyroid disorders	86 (0.7)	14 (0.6)	0.52
Epilepsy	88 (0.8)	7 (0.3)	0.018
Mental diseases	86 (0.7)	33 (1.3)	<0.001
Rheumatoid diseases	138 (1.2)	39 (1.7)	0.040
Lung diseases	364 (3.1)	104 (4.5)	<0.001
Inflammatory bowel diseases	118 (1.0)	26 (1.1)	0.58
Cardiovascular diseases	39 (0.3)	15 (0.6)	0.023

Table 1. Baseline characteristics according to the presence of GDM in 10,455 women.

GDM, gestational diabetes mellitus; SD, standard deviation.

the use of medication increased with increases in the prevalence of chronic diseases, age, and the number of physician visits.²⁰ We did not observe any association between the number of prescription drug purchases 6 months prior to conception and parity.

In Finland, the prevalence of GDM is high, being 21% in 2019, whereas the median rate in other European countries is 6%.^{3,17} Our study finding of a GDM rate of 16% is similar to Finnish nationwide findings (16% in 2015).¹⁷ Our study observations that the maternal pre-pregnancy BMI and age were higher in women with GDM are consistent with several previous study findings.^{21–25}

We observed that almost half of the women had purchased a prescription drug

within 6 months before conception. This is in line with previous US and European studies reporting that 50% to 80% of non-pregnant women of childbearing age used prescription drugs.^{9–11} According to our study findings, the most commonly purchased prescription drugs were drugs used for infections (ATC code J), disorders of the musculo-skeletal system (ATC code M), disorders of the nervous system (ATC code N), and disorders of the respiratory system (ATC code R). These findings are in line with previous findings in which the most commonly used prescription drugs after contraceptives were anti-infectives, asthma drugs, epilepsy drugs, depression and/or anxiety drugs, analgesics, and thyroid drugs.9-11



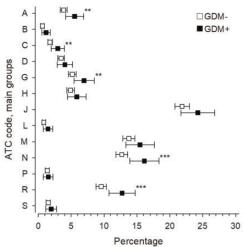


Figure 1. Prescription drug purchases by ATC codes as a percentage of the total number of pregnancies (N = 14,063) 6 months prior to conception in women without and with gestational diabetes mellitus. Whiskers represent 95% confidence intervals after Bonferroni correction. *P < 0.05, **P < 0.01, ***P < 0.001; Bonferroniadjusted probabilities.

GDM, gestational diabetes mellitus; ATC, Anatomical Therapeutic Chemical Classification; code A, alimentary tract and metabolism; code B, blood and blood-forming organs; code C, cardiovascular system; code D, dermatological drugs; code G, genitourinary system and reproductive hormones; code H, systemic hormonal preparations excluding reproductive hormones and insulins; code J, anti-infectives for systemic use; code L, antineoplastic and immunomodulating agents; code M, musculoskeletal system; code N, nervous system; code P, antiparasitic products, insecticides, and repellents; code R, respiratory system; code S, sensory organs.

We observed relationships of parity, i.e., more than three deliveries, and a higher number of prescription drug purchases prior to conception with a high rate of GDM. When counseling these women, the counseling given by healthcare professionals should focus on the modifiable risk factors for GDM such as weight gain between pregnancies and inter-pregnancy

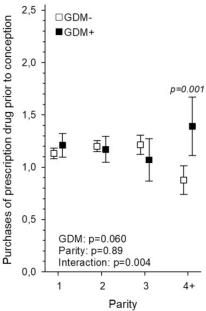


Figure 2. Relationship between parity and the mean number of prescription drugs purchases 6 months prior to conception according to the presence of GDM (adjustment for age, pre-pregnancy body mass index, smoking, fertility treatments, and educational attainment, and comorbidity). Whiskers represent 95% confidence intervals.

GDM, gestational diabetes mellitus.

interval.²⁶ We found no association between the number of prescription drug purchases and parity.

When we compared the number of prescription drug purchases and classified them into the main ATC groups, women with GDM had more purchases for ATC codes A, C, G, N, and R. The increased number of purchases of drugs used for disorders of the alimentary tract and metabolism might reflect the fact that women with GDM prior to pregnancy bought more drugs than women without GDM. Several drugs cause side effects of the upper gastrointestinal tract. Furthermore, metformin belongs to ATC main group A, and in some cases, metformin is used to treat polycystic ovary syndrome, which is a risk factor for GDM.²⁷ Women who purchased prescription drugs for cardiovascular diseases probably have more risk factors for GDM such as being overweight or obese.²⁸ Furthermore, some drugs used for cardiovascular diseases (ATC code C), such as ß-blockers, thiazide diuretics, and statins, have a negative influence on glucose homeostasis.²⁹ ATC code G includes prescription drugs used for infertility. Women with a history of fertility problems share some risk factors with women with GDM, such as advanced age and obesity, which might explain the difference in the number of purchases of ATC code G drugs.^{30,31} Drugs used for disorders for the nervous system include opioids, antimigraine drugs, antiepileptics, antipsychotics, anxiolytics. sedatives, and antidepressants. According to previous study findings, second-generation antipsychotic treatment is associated with severe metabolic alterations and weight gain.¹⁴⁻¹⁶ Among antidepressants, mirtazapine and tricyclics have high risks of inducing weight gain.^{14,15} Thus, glucose metabolism and body weight should be carefully monitored in women of childbearing age who receive these drugs.

Regarding the strengths of this study, the study cohort encompassed all Finnish women from the city of Vantaa, Finland who gave birth over a 7-year period. In addition, data on prescription drug purchases was comprehensive. The prescription register maintained by the Social Insurance Institution includes prescriptions from the public and private sectors. All data on prescription drug purchases was register-based, not self-reported. A unique personal identification number enables the combination of different register data on an individual level.

Concerning the study limitations, we had information on the purchases of prescription drugs, but because this was a registerbased study, we were missing information about drug doses and the duration of use, as well as whether the drugs were used as prescribed. Furthermore, we had the information on the ATC code of the purchase of prescription drug, but we did not know the indication for the use of drugs. We were also missing information on the use of drugs that can be purchased without a prescription. Because the size of the study cohort was limited, we were unable to evaluate the influence of any individual drug. We were missing data on some wellknown risk factors for GDM such as dietary and physical activity habits as well as the family history of diabetes. Furthermore, because all study participants were women with a Finnish background, the generalizability of our study observations is limited.

In conclusion, prescription drug purchases prior to conception are common. Women with more than three deliveries and those who used several drugs should be given personalized counseling on the modified risk factors for GDM to prevent GDM in subsequent pregnancies.

Authors' contributions

MKL wrote the manuscript. MKL, HK, MG, and JGE contributed to study design, data collection, and data research. HK performed the statistical analyses. MKL, HK, MG, PP, and JGE contributed to the interpretation of the results and discussion, reviewed the paper critically, and approved the final version of the manuscript.

Data availability statement

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 and scientific research on society by the license applicant, and it can therefore not be shared with third parties.

Declaration of conflicting interests

The authors declare no conflicts of interest.

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