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ORIGINAL RESEARCH

Correlation Analyses of the Consumption of Artificial Sweeteners During Pregnancy and the Incidence of Gestational Diabetes Mellitus

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Background: Pregnant women face a higher risk of developing gestational diabetes mellitus (GDM) due to the poor dietary habits. GDM can influence the health of both mothers and child. As food processing develops, pregnant women inevitably consume artificial sweeteners, among with the three most common are sucralose, aspartame, and sodium saccharin. It is a concern whether artificial sweeteners consumed during pregnancy increases GDM risk.

Purpose: To analyze the association between artificial sweetener consumption during pregnancy and the incidence of GDM.

Methods: 422 pregnant women from a Guangdong hospital were surveyed through convenience sampling. The questionnaire collected general information, artificial sweeteners consumption and other GDM related factors. According to the International Association of Diabetes and Pregnancy Study Groups (IADPSG), GDM was diagnosed was met the 75g oral glucose tolerance test (OGTT) at any time of pregnancy. The consumption of artificial sweeteners was categorized into low and high-consumption groups according to a four-point scale. A multifactorial logistic regression model was used to control for confounders and analyze the association between artificial sweetener consumption andGDM.

Results: This study included 422 pregnant women with a mean age of (32 ± 3.73) years and a GDM incidence of 13.74%. The GDM incidence was higher in the high artificial sweeteners consumption group (56.90%), than in the low consumption group (43.10%) ($p < 0.05$). Increased artificial sweetener consumption was linked to a higher GDM risk (OR=2.66,95% CI: 1.48–1.78). High artificial sweeteners consumption was a GDM risk factor in BMI-stratified analyses.

Conclusion: High consumption of artificial sweeteners, like sucralose, aspartame, and sodium saccharin, is linked to increased risk of GDM in pregnant women. Further research is required to confirm results and explore mechanism, guiding healthy eating habits during pregnancy.

Keywords: artificial sweeteners, gestational diabetes mellitus, pregnancy diet, maternal health

Introduction

Gestational diabetes mellitus (GDM) is a common complication of pregnancy, defined as the onset of glucose intolerance in mid-to-late pregnancy or for the first time during pregnancy, and is associated with increased complications and long-term health risks for both mother and child.[1] According to statistics, the global average prevalence of GDM is as high as 8.8%, with some countries and regions exceeding 20%,[2] of which the prevalence of GDM in Asia is 20.9%,[3] and the prevalence in China is 13%.[4] GDM has been found to be a major risk factor for preeclampsia, macrosomia, shoulder dystocia, and neonatal hypoglycemia.[5,6] Notably pregnant women with GDM are also at extremely high risk of developing type 2 diabetes and other cardiometabolic complications later in life after the end of pregnancy.[7–9] Even offspring affected by GDM show a 2-8-fold higher risk of obesity, metabolic syndrome, and impaired insulin secretion and sensitivity than offspring of non-GDM women.[10] Therefore, early identification of risk factors for gestational diabetes mellitus and prevention of GDM is particularly important.

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It is well known that, in addition to factors such as age, family history, frequency of delivery, and literacy, body weight and dietary habits are also important factors in the development of GDM.[11] Studies have shown that dietary management is the primary and most effective treatment for gestational diabetes mellitus.[12,13] Therefore, dietary modification has also become an important part of our efforts to regulate weight and nutrition during pregnancy and to reduce gestational diabetes.[14] Excessive consumption of sugary drinks during pregnancy has been found to increase the risk of gestational diabetes in pregnant people.[15] In order to avoid consuming too much sugar, which can lead to weight gain and various chronic diseases, people prefer to choose sugar-free foods containing various types of artificial sweeteners.

Artificial sweeteners are synthetic chemicals with high sweetness and no/low calories used as sugar substitutes. China currently allows the use of the three most common artificial sweeteners (sucralose, aspartame, saccharin). They are now widely used in ultra-processed foods and beverages, such as sugar-free drinks, snacks, dairy products, etc.[16] Whether the consumption of artificial sweeteners affects human health has attracted the attention of experts and scholars. In a French cohort study, it was found that a high consumption of artificial sweeteners was associated with an increased risk of cancer through a 10-year follow-up of the study participants.[17] Even some researchers have found a correlation between high consumption of artificial sweeteners and increased risk of cardiovascular disease.[18]

A growing number of epidemiological and animal studies have found that the metabolism of artificial sweeteners leads to significant reductions in beneficial anaerobic bacteria, causing imbalances in the gut microbiota.[19] This intestinal dysbiosis may lead to obesity, abnormal glucose tolerance and even related metabolic disorders.[20] In an animal study, aspartame was found to be metabolized to produce large amounts of gluconeogenic reaction precursors, and depletes and reduces the flora that maintains glucose homeostasis in mice,[21] leading to impaired glucose tolerance.[22] It was found that pregnant people consumed more sweeteners than non-pregnant people,[23] and that the intake of these high added sugars is associated with an increased risk of developing GDM.[24] Whether the intake of artificial sweeteners during pregnancy increases the risk of GDM due to the special physiological features and dietary characteristics of pregnancy has aroused widespread concern among experts and scholars. It was found that feeding artificial sweeteners to pregnant female rats for a period of time resulted in reduced abundance of intestinal flora and glucose intolerance.[25–27] There are fewer studies on whether intake of artificial sweeteners by pregnant mothers increases the risk of GDM in the population. Pre-pregnancy consumption of sugar-sweetened beverages has also been reported to be associated with the risk of developing GDM.[28] In a more specific study, it was found that drinking more than five sugary colas per week increased the risk of gestational diabetes by 22% compared to the rest of the population.[29] However, the study only focused on sugary cola drinks and did not cover other beverages such as fruit juices, which is a relatively homogenous category and an incomplete assessment of the food. In addition, the summary of evidence on the effects of sugary drinks or artificial sweeteners during pregnancy on mothers and offspring also suggests that the consumption of artificial sweeteners may have a negative impact on the health of mothers and offspring, and that more clinical trials are needed to prove this point.[30]

Therefore, the aim of our study was to analyze the association between consumed artificial sweeteners and Gestational Diabetes Mellitus (GDM) in a cohort of pregnant women.

Materials and Methods

Study Subjects

In this study, convenience sampling method was used to select pregnant women in early pregnancy in a tertiary hospital in Guangdong Province from October 2019 to October 2024 as the study population. (1) Inclusion criteria: ① Women up to 12 weeks of pregnancy; ② Possessing adequate literacy skills to understand and complete the questionnaire; ③ Having established a pregnancy health management file at the hospital and planning to continue health management and delivery at the same hospital; ④ Signing an informed consent form. (2) Exclusion criteria: ① Pregnant women already diagnosed with gestational diabetes; ② Those with severe physical illnesses (such as decompensated heart, liver, or kidney function); ③ Individuals with multiple food or drug allergies; ④ Participants lost to follow-up. A total of 435 questionnaires were distributed in this study and after excluding 13 samples with incomplete baseline information, 422 pregnant women were finally included as study participants, with a questionnaire validity rate of 97%.

Sample Size

Primary outcome is that pregnant women get gestational diabetes during pregnancy, based on our pre-laboratory data. The incidence of GDM was 19% (19/100).We estimate the desirable samples size can be calculated as,[31] $n=Z^2.\ \hat{p}(1-\hat{p})/E^2=1.96*1.96*0.19*0.81/(0.05*0.05) = 237$, $237*(1+20\%) = 285$ n: Indicates the required sample size. Z: The Z-value corresponds to the confidence level. When the confidence level is 95%, Z=1.96. $\hat{p}$: An estimate of the proportion of a population with a certain characteristic, $\hat{p} = 0.19$. E: allowable margin of error, which is half the width of the confidence interval E=0.05. Under normal circumstances, we would increase the sample size by 20%, which would require distributing 284 questionnaires. However, considering the low response rate due to the COVID-19 pandemic, we further expanded the sample size and eventually distributed 435 questionnaires. We ultimately collected 422 valid responses.

Research Tools

General Information Questionnaire

A general information questionnaire was created by the researcher after reviewing the relevant literature and in accordance with the study objectives, taking into account the demographic characteristics of pregnant women in the region. The information included: general demographic information (age, weight, education, family income, work status, health status, etc). and other information (dietary habits, smoking status, alcohol consumption, etc).

Food Additive Estimation Questionnaire

After consents to participate in the study, participants were instructed to keep a food diary to record the amount of food consumed and the composition of the food. For those foods for which the study subjects could not provide specific additive ingredients, we could obtain them by using food additive data established by nutritionists. In this study, we chose the food additives estimation questionnaire, which was developed by a number of nutritionists from Australia and the Chinese University of Hong Kong, based on the creation of a food additives database. The Food Additives Database contains information on the types of food additives contained in each specific food and the maximum permitted intake (MPI) for each food additive. When we entered the food information from the questionnaire into the database, we were able to calculate the type and amount of food additives specifically consumed by the study participants. The scale was divided into two parts, the first of which asked about past dietary habits and specific food consumption (39 questions) to estimate early life consumption of processed foods and beverages on a four-point scale. The questions are designed to be scored as 0 (less likely to be exposed) or 1 (more likely to be exposed). The total score can be used to rank participants based on early life food additive consumption. (2) The second part of the survey can be used in a semi-quantitative way to assess participants' recent food consumption by asking about the frequency of consumption of the selected food list (26 questions). Based on the additives allowed in the food list, a score can be calculated for the additive category. However, when another additive with a similar purpose was present, a lower concentration was usually used. The assessment of food additive consumption was converted through Codex Alimentarius CXS 192e International Food Standards (CODEX) by two dietitians. The total consumption of artificial sweeteners during pregnancy was finally converted by using the formula: annual consumption of food additives (mg/year) = concentration of additives in food $(mg/kg)^a/1000 \times$ daily food consumption $(g)^b \times 365$ (a: maximum permissible level of consumption in food or actual level of consumption in food b: one standard portion per day or recommended daily portion). The mean kappa coefficients for Part 1 and Part 2 were 0.61 and 0.67, respectively. Two instruments have been created and validated in two languages to reliably assess food additive consumption in the distant and near future.[32]

Quality Control

In this study, 15 pregnant women who met the inclusion criteria were conveniently selected as pre-survey respondents before the formal survey. After obtaining the consent of the study subjects, the survey instruments of various scales were used, through which the content of the general information survey and the reliability and validity of each scale could be further refined and corrected.

The researcher explained the purpose of the survey and the principle of confidentiality to the volunteers before filling out the questionnaire and conducted the survey anonymously after obtaining each other's consent. During the process of filling out the questionnaire, the researcher used a unified instruction to tell the research participants about the method of filling out the questionnaire and the precautions to be taken. Information was collected through face-to-face interviews during pregnancy and after delivery. A basic information questionnaire was completed by the respondents themselves, and a food additive estimation scale was used by the researchers to facilitate food quantification with the aid of retrospective dietary food molds and containers to help record the frequency and average amount of each food item consumed by the pregnant women. After the investigator completed the questionnaire, the questionnaire was quality-controlled and reviewed on-site to ensure the completeness and accuracy of the results.

Outcomes and Covariates

The primary outcome is the incidence of GDM (non-diabetes mellitus/non-hyperglycaemia at the recruitment and self-report GDM at middle or late gestational age follow-up, or confirmed GDM by the research nurse at delivery).According to the diagnostic criteria of the IADPSG,[33] GDM can be diagnosed in pregnant women at any time during pregnancy if they undergo a 75g OGTT (oral glucose tolerance test). Upon arrival at the hospital, subjects first underwent fasting venous blood collection to determine fasting blood glucose. Then 75 g of anhydrous glucose (or 82.5 g of glucose with 1 molecule of water) was dissolved in 250–300 mL of water, and the subjects drank it all within 5 minutes. Blood glucose was measured from venous blood drawn 1 hour and 2 hours after the first sip of glucose solution. And have one of the following blood glucose levels: fasting blood glucose level between 5.1 mmol/L and less than 7.0 mmol/L, blood glucose level of 10.0 mmol/L or higher one hour after, or blood glucose level between 8.5 mmol/L and less than 11.0 mmol/L two hours after. Meeting any one of these criteria is sufficient for a GDM diagnosis.

Accordingly, potential covariates were identified as below: age, region, individual income, education level, working status, pre-pregnancy BMI (calculated by self-report height and weight, categories for Asian areas follows:underweight (<18.5 kg/m^2), normal weight (18.5 ≤BMI<23kg/m^2), overweight or obese (≥23kg/m^2),[34] pre-pregnancy alcohol usage, smoking status, and dietary habits. Information on all mentioned covariates was collected at recruitment.

Statistical Analysis

IBM SPSS Statistics for Windows, Version 26.0 (IBM Corp., Armonk, NY, USA) was applied for with statistical analysis. Count data were described by frequency and percentage, measures obeying normal distribution were described by mean ± standard deviation, and non-normal measures were expressed as median and quartiles. The chi-square test was used to analyze the differences between groups in terms of maternal age, pre-pregnancy BMI, education level, family income, smoking, alcohol consumption, and whether or not they were primiparous. The study subjects were divided into two groups according to the difference in consumption of artificial sweeteners in order of high and low, namely, the high consumption group (the first 25%) and the low consumption group (the second 75%), and the population in the low consumption group of artificial sweeteners was used as the reference category. Binary logistic regression analysis was used to explore the association between total artificial sweetener consumption and gestational diabetes mellitus, stratified by age and pre-pregnancy BMI.

Results

Basic Information

The study finally included 422 pregnant women, of whom 58 had GDM, a incidence of 13.7%. The mean age of the study population was 32±3.7 years, and 107 women were of advanced maternal age (≥35 years), accounting for 25.4% of the total. The vast majority of the study population had college and undergraduate degrees, accounting for 84.4% of the total population. The median pre-pregnancy BMI of the study population was 20.5 kg/m^2,and 58 pre-pregnancy overweight and obese (≥23 kg/m^2) individuals accounted for 13.7% of the total population. Specific results are shown in Table 1.

Table 1 The Basic Situation of the Research Object Is Compared

Characteristic	All Population	Normal	Gestational Diabetes Mellitus	t/x^2	P-value
Number of observations (n/%)	422 (100.00)	364 (86.26)	58 (13.74)		
Age ($\bar{x} \pm s$)	32±3.73	32.05±3.76	33.15±3.50	1.80	0.04[a]
Age groups (n/%)				9.12	0.04[b]
<35 years	315 (74.64)	281 (77.20)	34 (58.62)		
≥35 years	107 (25.36)	83 (22.80)	24 (41.38)		
Education level (n/%)				1.37	0.47[b]
High school or below	30 (7.11)	27 (7.42)	3 (5.17)		
Bachelor	356 (84.36)	308 (84.62)	48 (82.76)		
Master or above	36 (8.53)	29 (7.97)	7 (12.07)		
Income (yuan/month)				3.36	0.19[b]
<10,000	41 (9.72)	36 (9.89)	5 (8.62)		
10,000–30,000	289 (68.48)	254 (69.78)	35 (60.34)		
>30,000	92 (21.80)	74 (20.33)	18 (31.03)		
Primiparous woman (n/%)					
No	257 (60.90)	214 (58.79)	43 (74.14)	4.95	0.03[b]
Yes	165 (39.10)	150 (41.21)	15 (25.86)		
Pre-pregnancy BMI M(P25, P75)	20.5 (18.8,22.4)	20.3 (18.7,22.0)	22.6 (20.5,24.9)	4.31[b]	<0.001[b]
Pre-pregnancy BMI (n/%)				13.42	<0.001[b]
<18.5	87 (20.62)	81 (22.25)	6 (10.34)		
18.5≤BMI<23	277 (65.64)	251 (68.96)	34 (58.62)		
BMI≥23	58 (13.74)	32 (8.79)	18 (31.04)		
Smoking status (n/%)				0.02	0.97[b]
No	415 (98.34)	358 (98.35)	57 (98.28)		
Yes	7 (1.66)	6 (1.65)	1 (1.72)		
Alcohol use (n/%)				3.97	0.04[b]
No	301 (71.33)	266 (73.08)	35 (60.34)		
Yes	121 (28.67)	98 (26.92)	23 (39.66)		
Working status (n/%)				1.17	0.60[b]
Fulltime	22 (5.21)	18 (4.95)	4 (6.90)		
Parttime	29 (6.87)	24 (6.59)	5 (8.62)		
Housewife or others	371 (87.91)	322 (88.46)	49 (84.48)		

(*Continued*)

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Table 1 (Continued).

Characteristic	All Population	Normal	Gestational Diabetes Mellitus	t/x^2	P-value
Any disease(s) (n/%)				1.58	0.21[b]
No	170 (40.28)	151 (43.18)	19 (32.76)		
Yes	252 (59.72)	213 (56.82)	39 (67.24)		
Dietary habits (n/%)				7.28	0.03[b]
Vegetables > Meat	169 (40.05)	153 (42.03)	16 (27.59)		
Vegetables = Meat	171 (40.52)	147 (40.38)	24 (41.38)		
Vegetables < Meat	82 (19.43)	64 (17.58)	18 (31.03)		

Notes: [a]Statistical method is the *t*-test and the statistic is the t-value; [b]The statistical method is the chi-square test and the statistic is the x^2 value.
Abbreviations: BMI, body mass index; $\bar{x} \pm s$, mean±standard deviation; M(P25, P75), median (upper quartile P25, lower quartile P75).

Artificial Sweetener Consumption

The distribution of consumption as well as total amount of the three artificial sweeteners was statistically different between the two study groups ($p < 0.05$). In the GDM group, the percentage of people with high consumption of aspartame was higher than the percentage of people with low consumption (58.62%: 41.38%), the percentage of people with high consumption of sucralose was higher than the percentage of people with low consumption (58.62%: 41.38%), the percentage of those with high consumption of saccharin was higher than the percentage of those with low consumption (55.17%: 44.83%). The percentage of those with high total consumption of artificial sweeteners in the GDM group was also higher than the percentage of those with low total consumption of artificial sweeteners (56.90%: 43.10%), as shown in Table 2.

Table 2 Non-Nutritive Sweetener Consumption During Pregnancy

Characteristic	All Population	Non-Gestational Diabetes Mellitus	Gestational Diabetes Mellitus	x^2	P-value
Number of observations (n/%)	422 (100.00)	364 (86.26)	58 (13.74)		
Aspartame (n/%)				26.44	0.04
Low	300 (71.09)	276 (75.82)	24 (41.38)		
High	122 (28.91)	88 (24.18)	34 (58.62)		
Sucralose (n/%)				34.07	0.03
Low	308 (72.99)	284 (78.02)	24 (41.38)		
High	114 (27.01)	80 (21.98)	34 (58.62)		
Saccharin sodium (n/%)				26.44	0.03
Low	307 (72.75)	281 (77.20)	26 (44.83)		
High	115 (27.25)	83 (22.80)	32 (55.17)		
Total consumption (n/%)				26.21	<0.001
Low	307 (72.75)	282 (77.47)	25 (43.10)		
High	115(27.25)	82 (22.53)	33 (56.90)		

Notes: The statistical method is the chi-square test and the statistic is the x^2 value; $p < 0.05$ indicates a statistically significant difference between groups.

Univariate Analysis of GDM

After subgrouping by whether or not they had GDM and comparing the basic characteristics of the two groups of researchers, it was found that there was a statistically significant difference in the distribution of age, whether or not they were primigravida, pre-pregnancy BMI, dietary habits, consumption of alcoholic beverages, and three types of artificial sweeteners between the two populations ($p < 0.05$). The specific results are shown in Table 1.

The Association Between Artificial Sweetener Consumption and Gestational Diabetes Mellitus

Based on previous studies and the between-group differences in the data of this study, total consumption of sucralose, aspartame, saccharin, and artificial sweeteners during pregnancy was set as the independent variable, and age, whether or not the child was born at first birth, pre-pregnancy BMI, dietary habits, and consumption of alcoholic beverages were set as the confounding variables, and logistic regression analyses were conducted to analyze the results. As shown in Table 3, after adjusting for other covariates related to gestational diabetes mellitus, it was found that the total consumption of artificial sweeteners and high consumption of the other three artificial sweeteners were risk factors for the development of gestational diabetes mellitus in the logistic regression analyses of the three models using the "low consumption group" as the reference group with the following OR values (OR=2.66, 95% CI: 1.48–1.78); (OR=2.32, 95% CI: 1.15–1.47); (OR=1.49, 95% CI: 1.35–1.36); and (OR=2.97, 95% CI: 1.17–1.49).

Subgroup Analysis

Since age and pre-pregnancy BMI were the main risk factors for the development of GDM and there were significant between-group differences in the study, age and pre-pregnancy BMI were used as the basis for stratification, and subgroup analyses were conducted to analyze the associations between total consumption of artificial sweeteners and GDM, as shown in Table 4.

Table 3 Logistic Regression Analysis of the Association Between Artificial Sweeteners Consumption and GDM During Pregnancy

Characteristic	Number of Cases / Non-Cases	Mould 1[a]	Mould 2[b]	Mould 3[c]
Aspartame				
Low	24/276	1.00	1.00	1.00
High	34/88	1.12 (1.05~1.77)*	1.25 (1.08~1.65)*	2.32 (1.15~1.47)*
Sucralose				
Low	24//284	1.00	1.00	1.00
High	34/80	1.12 (1.26~1.74)	1.42 (1.16~1.54)*	1.49 (1.35~1.36)*
Saccharin sodium				
Low	26/281	1.00	1.00	1.00
High	32/83	2.09 (1.12~1.96)	1.38 (1.34~1.51)*	2.97 (1.17~1.49)*
Total consumption				
Low	25/282	1.00	1.00	1.00
High	33/82	1.21 (1.04~2.99)*	1.35 (1.90~2.31)*	2.66 (1.48~1.78)*

Notes: [a]Model 1: no adjustment for any factor; [b]Model 2: Adjusted for age, education, monthly household income, work status, and pre-pregnancy BMI; [c]Model 3 was further adjusted for dietary habits, pre-pregnancy smoking, alcohol consumption during pregnancy, health status during pregnancy, and whether or not the woman was a primigravida based on model 2; *ndicates $p < 0.05$.

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Table 4 Logistic Regression Analysis of Association Between Artificial Sweeteners and Gestational Diabetes Stratified by Age and Pre-Pregnancy BMI

Characteristic	Low Total Consumption	High Total Consumption	Interaction P-value
Age			0.437
<35 years	1	1.24 (1.14~1.56)	
≥35 years	1	1.35 (1.12~1.23)	
Pre-pregnancy BMI			0.56
BMI<18.5	1	1.69 (0.96~1.24)	
18.5≤BMI<23	1	1.32 (0.86~1.32)	
BMI≥23	1	1.28 (1.32~1.54)	

Notes: Adjustment variables were age, pre-pregnancy BMI classification, education, monthly household income, work status, dietary habits, pre-pregnancy smoking, alcohol consumption during pregnancy, health status during pregnancy, and whether or not they were primigravida. No adjustment was made for the corresponding stratification variables. High total consumption was the group with artificial sweeteners total consumption >48616 g/year, and the rest was the low total consumption group.

Stratification by age showed that high total consumption of artificial sweeteners in the lower age group (<35 years) was positively associated with the risk of GDM compared with the reference group (OR=1.24, 95% CI: 1.14 ~1.56); Subgroup analyses stratified by pre-pregnancy BMI showed that high total consumption of artificial sweeteners was positively associated with the risk of GDM in the overweight and obese pre-pregnancy BMI groups compared to the reference group, respectively (OR=1.28, 95% CI: 1.32–1.54); there was no interaction between age, pre-pregnancy BMI, and total consumption of artificial sweeteners during pregnancy.

Discussion

Studies have reported that pregnant women consume even more artificial sweeteners than the general population, and that excessive consumption of sugar-sweetened beverages increases the risk of nutritional imbalances during pregnancy.[35] And it is not clear whether consuming artificial sweeteners at the higher end of the safe range during pregnancy increases the risk of gestational diabetes. Our study comparatively analyzed the effects of different consumptions of three common artificial sweeteners and total artificial sweetener consumption on gestational diabetes mellitus by investigating the daily diet of 422 pregnant women. The Food Additives Database contains information on the types of food additives contained in each specific food. When we entered the food information from the questionnaire into the database, we were able to calculate the type and amount of food additives specifically consumed by the study participants. The results showed that the prevalence of gestational diabetes mellitus was 13.7%, which is consistent with previous studies that found a 14% prevalence of GDM globally.[36] High total consumption of artificial sweeteners during pregnancy was found to be strongly associated with the risk of developing GDM after controlling for confounding factors such as age, household income, and pre-pregnancy consumption of alcoholic beverages. The present study shows that higher consumption of artificial sweeteners associated with increased the risk of GDM. Pregnant women with a high consumption of total artificial sweeteners during pregnancy were 2.6 times more likely to develop GDM than those with a low consumption, and those in the high consumption groups of aspartame, sucralose, and sodium saccharin were 2.3, 1.5, and 3 times more likely, respectively, to develop GDM than those in the low consumption group.

There have been animal experiments that have explained the potential mechanisms underlying the association between artificial sweetener consumption and metabolic alterations; after entering the gastrointestinal tract, artificial sweeteners can alter the composition and function of the intestinal flora, destroying beneficial flora and promoting the growth of harmful flora. This intestinal dysbiosis is associated with systemic inflammation and insulin resistance, resulting in poor metabolic health in individuals.[37] Sucralose has been experimentally shown to alter and regulate the composition and abundance of the gut microbiota when consumed, and its metabolites together induce metabolic disorders.[38] In addition, some artificial sweeteners have been shown to induce oxidative stress and trigger inflammatory cells, which are associated with the development of metabolic diseases such as insulin resistance and type 2 diabetes mellitus.[39]

In the present study, we found that high consumption of sucralose, aspartame, sodium saccharin, and total artificial sweeteners is correlated with increased the risk of GDM, which had not been mentioned in previous studies. A case-control study explored the relationship between sucralose and maternal metabolic health and found that higher serum sucralose levels may be associated with a better state of glycemic control.[40] However, no direct causal relationship has been demonstrated. Two studies on the effects of chronic sucralose consumption found that it caused an ecological imbalance in the gut and disrupted insulin metabolism.[41,42] This evidence supports our findings.

Because during this special period of pregnancy, all the systems in the pregnant woman's body will undergo a series of changes to adapt to the growth and development needs of the fetus, in which the intestinal flora will also undergo significant changes.[43] Gut microbes are significantly different in women with GDM compared to healthy pregnant women.[44] The number of beneficial flora such as Actinobacteria spp. and Bifidobacteria spp. decreased significantly, while harmful flora such as Enterobacteriaceae and Rumatococcaceae increased in GDM women.[45] Moreover, these changes in the intestinal flora are largely involved in the pathologic process of GDM and are highly likely to indicate disturbances in the body's metabolism of glucose and fat, among other things.[46] A study found that high consumption of artificial sweeteners induced impaired glucose metabolism in pregnant rats, further increasing the occurrence of gestational diabetes mellitus.[47] This study's findings indicate that the incidence of GDM was higher in the group with higher consumption of the three artificial sweeteners and their total consumption compared to the group with normal consumption. However, in a comparison of the effects of sugar-sweetened beverages and sugar-free beverages on gestational diabetes during pregnancy, it was found that the consumption of sugar-free beverages did not increase the risk of GDM.[28] This finding differs from the results of the present study, and the reason for this difference is that, in addition to the differences in genetics and lifestyle and dietary habits of the different populations, it is more important that the foods included in the two studies are not exactly the same. The former only compared the effects of consuming two different beverages during pregnancy and the different frequencies of consumption on GDM, while in the present study not only the beverages consumed by pregnant women during pregnancy were collected, but also other foods consumed during pregnancy.

Despite our recommendation to avoid artificial sweeteners where possible, our studies have found that pregnant women still consume them to a greater or lesser extent from beverages, dairy products, candies, and other foods. The consumption of artificial sweeteners during pregnancy should be approached with caution, and more experimental and clinical studies are still needed to validate the association and mechanism of influence between the consumption of artificial sweeteners during pregnancy and GDM.

Strengths and Limitations

The strength of this study lies in the fact that for the first time, a specific food additive consumption questionnaire was used for the assessment of the dose of artificial sweeteners in different foods consumed by pregnant women during pregnancy, with a special container to uniformly measure the food-specific consumption. We used food measurement containers to help participants recall specific food intake, which can effectively reduce recall bias. The association between the consumption of artificial sweeteners during pregnancy and GDM was explored in detail, which provides a certain foundation for subsequent studies. The food additive consumption questionnaire has good reliability and validity and can be applied to other regional population studies.

However, there are many shortcomings in this study: first, common confounders were controlled for in the study, residual confounding bias could not be completely ruled out. We controlled for common confounders in our study through a variety of statistical methods, for confounding bias that may still exist. More confounders need to be included for control in future studies. Second, the study population was only collected from a tertiary hospital in Guangdong

Province, which is a small collection area with a small sample size, and there may be differences in geographic regions and dietary habits, so more clinical data may be needed to support a wider dissemination of the study.

Conclusion

In conclusion, excessive consumption of artificial sweeteners during pregnancy is associated with increased the risk of developing gestational diabetes mellitus (GDM), and it is particularly important to develop a more scientific and precise dietary management program for pregnant women during pregnancy to improve their health during pregnancy. Women during pregnancy are advised to be cautious about the consumption of artificial sweeteners, especially common sugar-free beverages, yogurt, ice cream, and pastries. More experimental and clinical studies on the effects of artificial sweeteners on maternal health are needed in the future to validate these results and guide healthy eating habits in the pregnant population.

Ethics Approval and Consent to Participate

This study has been reviewed and approved by the Foshan First People's Hospital. The ethical acceptance number is CLRS 2022-55, and our study was conducted following the Declaration of Helsinki. Before the study commenced, all participants provided informed consent and voluntarily chose to participate, with the right to withdraw from the study at any point. All data collected were anonymized and used exclusively for our research.

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Disclosure

The authors report no conflicts of interest in this work.

References

1. American Diabetes Association. Classification and diagnosis of diabetes: standards of medical care in diabetes—2020. *Diabetes Care*. 2020;43 (Supplement_1):S66–S76. doi:10.2337/dc20-S002.
2. Li X, Zheng J, Ma X, et al. The oral microbiome of pregnant women facilitates gestational diabetes discrimination. *J Genet Genomics*. 2021;48 (1):32–39. doi:10.1016/j.jgg.2020.11.006
3. Lee KW, Ching SM, Ramachandran V, et al. Prevalence and risk factors of gestational diabetes mellitus in Asia: a systematic review and meta-analysis. *BMC Pregnancy Childbirth*. 2018;18(1):494. doi:10.1186/s12884-018-2131-4
4. Zheng CY, Li AH. Effects of health missionary combined with individualized dietary care on self-efficacy and pregnancy outcomes of gestational diabetes mellitus patients. *Diabetes New World*. 2023;26(19):118–121. doi:10.16658/j.cnki.1672-4062.2023.19.118
5. Bryson CL, Ioannou GN, Rulyak SJ, Critchlow C. Association between gestational diabetes and pregnancy-induced hypertension. *Am J Epidemiol*. 2003;158(12):1148–1153. doi:10.1093/aje/kwg273
6. Homayouni A, Bagheri N, Mohammad-Alizadeh-Charandabi S, et al. Prevention of gestational diabetes mellitus (GDM) and probiotics: mechanism of action: a review. *Curr Diabetes Re*. 538–545; doi:10.2174/1573399815666190712193828
7. Tobias DK, Stuart JJ, Li S, et al. Association of history of gestational diabetes with long-term cardiovascular disease risk in a large prospective cohort of US women. *JAMA Intern Med*. 2017;177(12):1735–1742. doi:10.1001/jamainternmed.2017.2790
8. Ajmera VH, Gunderson EP, VanWagner LB, Lewis CE, Carr JJ, Terrault NA. Gestational diabetes mellitus is strongly associated with non-alcoholic fatty liver disease. *Am J Gastroenterol*. 2016;111(5):658–664. doi:10.1038/ajg.2016.57
9. Bellamy L, Casas JP, Hingorani AD, Williams D. Type 2 diabetes mellitus after gestational diabetes: a systematic review and meta-analysis. *Lancet Lond Engl*. 2009;373(9677):1773–1779. doi:10.1016/S0140-6736(09)60731-5
10. Damm P, Houshmand-Oeregaard A, Kelstrup L, Lauenborg J, Mathiesen ER, Clausen TD. Gestational diabetes mellitus and long-term consequences for mother and offspring: a view from Denmark. *Diabetologia*. 2016;59(7):1396–1399. doi:10.1007/s00125-016-3985-5
11. Yao Y, Jin QQ, Cheng QH. Research on the association rules of risk factors for gestational diabetes mellitus. *Chin Health Stat*. 2023;40(4):559–562. doi:10.11783/j.issn.1002-3674.2023.04.018
12. Bowers K, Tobias DK, Yeung E, Hu FB, Zhang C. A prospective study of prepregnancy dietary fat intake and risk of gestational diabetes. *Am J Clin Nutr*. 2012;95(2):446–453. doi:10.3945/ajcn.111.026294
13. American Diabetes Association. Management of diabetes in pregnancy: standards of medical care in diabetes-2020. *Diabetes Care*. 2020;43(Suppl 1):S183–S192. doi:10.2337/dc20-S014.
14. Ponzo V, Fedele D, Goitre I, et al. Diet-gut microbiota interactions and gestational diabetes mellitus (GDM). *Nutrients*. 2019;11(2):330. doi:10.3390/nu11020330
15. Li G, Yin P, Chu S, et al. Correlation analysis between GDM and gut microbial composition in late pregnancy. *J Diabetes Res*. 2021;2021:8892849. doi:10.1155/2021/8892849

16. Ayoub-Charette S, McGlynn ND, Lee D, et al. Rationale, design and participants baseline characteristics of a crossover randomized controlled trial of the effect of replacing SSBs with NSBs versus water on glucose tolerance, gut microbiome and cardiometabolic risk in overweight or obese adult SSB consumer: strategies to oppose SUGARS with non-nutritive sweeteners or water (STOP sugars NOW) trial and ectopic fat sub-study. *Nutrients*. 2023;15(5):1238. doi:10.3390/nu15051238
17. Debras C, Chazelas E, Srour B, et al. Artificial sweeteners and cancer risk: results from the NutriNet-santé population-based cohort study. *PLoS Med*. 2022;19(3):e1003950. doi:10.1371/journal.pmed.1003950
18. Debras C, Chazelas E, Sellem L, et al. Artificial sweeteners and risk of cardiovascular diseases: results from the prospective NutriNet-santé cohort. *BMJ*. 2022:378:e071204. doi:10.1136/bmj-2022-071204.
19. EFSA Panel on Additives and Products or Substances used in Animal Feed (FEEDAP), Rychen G, Aquilina G, et al. Safety and efficacy of sodium saccharin when used as a feed flavour for piglets, pigs for fattening, calves for rearing and calves for fattening. *EFSA J*. 2018;16(3). doi:10.2903/j.efsa.2018.5208
20. Hui Z, Xinxuan W. Human health risks of artificial sweeteners. *J Food Sci Technol*. 2018;36(6):15–20.
21. Yoon HS, Cho CH, Yun MS, et al. Akkermansia muciniphila secretes a glucagon-like peptide-1-inducing protein that improves glucose homeostasis and ameliorates metabolic disease in mice. *Nat Microbiol*. 2021;6(5):563–573. doi:10.1038/s41564-021-00880-5
22. Kraal L, Abubucker S, Kota K, Fischbach MA, Mitreva M. The prevalence of species and strains in the human microbiome: a resource for experimental efforts. ahmed N, ed. *PLoS One*. 2014;9(5):e97279. doi:10.1371/journal.pone.0097279
23. Cioffi CE, Figueroa J, Welsh JA. Added sugar intake among pregnant women in the United States: national health and nutrition examination survey 2003-2012. *J Acad Nutr Diet*. 2018;118(5):886–895.e1. doi:10.1016/j.jand.2017.10.021
24. Shin D, Lee KW, Song WO. Dietary Patterns during Pregnancy Are Associated with Risk of Gestational Diabetes Mellitus. *Nutrients*. 2015;7 (11):9369–9382. doi:10.3390/nu7115472
25. Stupak A, Gęca T, Kwaśniewska A, et al. Comparative analysis of the placental microbiome in pregnancies with late fetal growth restriction versus physiological pregnancies. *Int J Mol Sci*. 2023;24(8):6922. doi:10.3390/ijms24086922
26. Yang R, Li X, Ying Z, et al. Prematurely delivering mothers show reductions of lachnospiraceae in their gut microbiomes. *BMC Microbiol*. 2023;23 (1):169. doi:10.1186/s12866-023-02892-z
27. Yu HR, Tsai CC, Chan JYH, et al. A higher abundance of actinomyces spp. in the gut is associated with spontaneous preterm birth. *Microorganisms*. 2023;11(5):1171. doi:10.3390/microorganisms11051171
28. Donazar-Ezcurra M, Lopez-Del Burgo C, Martinez-Gonzalez MA, Basterra-Gortari FJ, de Irala J, Bes-Rastrollo M. Soft drink consumption and gestational diabetes risk in the SUN project. *Clin Nutr Edinb Scotl*. 2018;37(2):638–645. doi:10.1016/j.clnu.2017.02.005
29. Chen L, Hu FB, Yeung E, Willett W, Zhang C. Prospective study of pre-gravid sugar-sweetened beverage consumption and the risk of gestational diabetes mellitus. *Diabetes Care*. 2009;32(12):2236–2241. doi:10.2337/dc09-0866
30. Goran MI, Plows JF, Ventura EE. Effects of consuming sugars and alternative sweeteners during pregnancy on maternal and child health: evidence for a secondhand sugar effect. *Proc Nutr Soc*. 2019;78(3):262–271. doi:10.1017/S002966511800263X
31. Wei-jun Z, Fan H. Sample size calculation method for the cross-sectional survey. *Preventive Med*. 2020;32(6):647–648. doi:10.19485/j.cnki.issn2096-5087.2020.06.028
32. Trakman GL, Lin W, Wilson-O'Brien AL, et al. Development and validation of surveys to estimate food additive intake. *Nutrients*. 2020;12(3). doi:10.3390/nu12030812
33. International association of diabetes and pregnancy study group recommendations on the diagnosis and classification of hyperglycemia in pregnancy.
34. Bajaj SS, Zhong A, Zhang AL, Stanford FC. Body mass index thresholds for asians: a race correction in need of correction? *Ann Intern Med*. 2024;177(8):1127–1129. doi:10.7326/M24-0161
35. Cioffi CE, Figueroa J, Welsh JA. Added sugar intake among pregnant women in the United States: national health and nutrition examination survey 2003-2012. *J Acad Nutr Diet*. 2018;118(5):886–895.e1. doi:10.1016/j.jand.2017.10.021
36. Wang H, Li N, Chivese T, et al. IDF diabetes atlas: estimation of global and regional gestational diabetes mellitus prevalence for 2021 by international association of diabetes in pregnancy study group's criteria. *Diabet Res Clin Pract*. 2022;183:109050. doi:10.1016/j.diabres.2021.109050
37. Suez J, Korem T, Zeevi D, et al. Artificial sweeteners induce glucose intolerance by altering the gut microbiota. *Nature*. 2014;514(7521):181–186. doi:10.1038/nature13793
38. Shi Z, Chen G, Cao Z, et al. Gut microbiota and its metabolite deoxycholic acid contribute to sucralose consumption-induced nonalcoholic fatty liver disease. *J Agric Food Chem*. 2021;69(13):3982–3991. doi:10.1021/acs.jafc.0c07467
39. Aguayo-Guerrero JA, Méndez-García LA, Manjarrez-Reyna AN, et al. Newborns from mothers who intensely consumed sucralose during pregnancy are heavier and exhibit markers of metabolic alteration and low-grade systemic inflammation: a cross-sectional, prospective study. *Biomedicines*. 2023;11(3):650. doi:10.3390/biomedicines11030650
40. Liu Y, Li X, Wu Y, Su Q, Qin L, Ma J. The associations between maternal serum aspartame and sucralose and metabolic health during pregnancy. *Nutrients*. 2022;14(23):5001. doi:10.3390/nu14235001
41. Méndez-García LA, Bueno-Hernández N, Cid-Soto MA, et al. Ten-week sucralose consumption induces gut dysbiosis and altered glucose and insulin levels in healthy young adults. *Microorganisms*. 2022;10(2):434. doi:10.3390/microorganisms10020434
42. Ahmad SY, Friel J, Mackay D. The effects of non-nutritive artificial sweeteners, aspartame and sucralose, on the gut microbiome in healthy adults: secondary outcomes of a randomized double-blinded crossover clinical trial. *Nutrients*. 2020;12(11):3408. doi:10.3390/nu12113408
43. Gorczyca K, Obuchowska A, Kimber-Trojnar Ż, Wierzchowska-Opoka M, Leszczyńska-Gorzelak B. Changes in the gut microbiome and pathologies in pregnancy. *Int J Environ Res Public Health*. 2022;19(16):9961. doi:10.3390/ijerph19169961
44. Ma S, You Y, Huang L, et al. Alterations in gut microbiota of gestational diabetes patients during the first trimester of pregnancy. *Front Cell Infect Microbiol*. 2020;10:58. doi:10.3389/fcimb.2020.00058
45. Hu P, Chen X, Chu X, et al. Association of gut microbiota during early pregnancy with risk of incident gestational diabetes mellitus. *J Clin Endocrinol Metab*. 2021;106(10):e4128–e4141. doi:10.1210/clinem/dgab346
46. Hu R, Liu Z, Geng Y, et al. Gut microbiota and critical metabolites: potential target in preventing gestational diabetes mellitus? *Microorganisms*. 2023;11(7):1725. doi:10.3390/microorganisms11071725
47. Tsai MJ, Li CH, Wu HT, et al. Long-term consumption of sucralose induces hepatic insulin resistance through an extracellular signal-regulated kinase 1/2-dependent pathway. *Nutrients*. 2023;15(12):2814. doi:10.3390/nu15122814