Association between ultra-processed foods before pregnancy and hyperemesis gravidarum: a case-control study

Abstract

Aims: Hyperemesis gravidarum (HG) is a multifactorial pregnancy disorder characterized by severe nausea and vomiting, often necessitating hospitalization. While its etiology remains incompletely understood, dietary factors may play a significant role. This study investigates the association between pre-pregnancy consumption of ultra-processed foods (UPFs) and the incidence of HG.

Methods: A hospital-based case-control study was conducted in Tehran, Iran, from April 2020 to June 2021, involving 45 newly diagnosed HG cases and 126 controls. HG diagnosis followed the American College of Obstetrics and Gynecology criteria. Pre-pregnancy UPF intake was assessed using a validated semi-quantitative food frequency questionnaire, with foods classified according to the NOVA system. Multivariable logistic regression models adjusted for potential confounders were employed to evaluate the association between UPF consumption and HG risk.

Findings: After adjusting for covariates, significant inverse associations were observed between higher UPF intake and HG risk. The multivariable-adjusted odds ratios (ORs) for the highest vs. lowest tertile of UPF consumption were as follows: total UPFs (OR: 0.31; 95% CI: 0.19–0.48; P-trend = 0.002), dairy beverages (OR: 0.18; 95% CI: 0.09–0.52; P-trend = 0.048), and processed meats/fast foods (OR: 0.13; 95% CI: 0.06–0.71; P-trend = 0.015).

Conclusion: These findings suggest that lower pre-pregnancy UPF consumption is associated with reduced odds of developing HG. Further prospective studies are needed to confirm these observations and explore potential mechanisms.

Keywords: ultra-processed foods, hyperemesis gravidarum, dietary risk factors, NOVA classification, case-control study

Introduction

Hyperemesis gravidarum (HG) is a debilitating pregnancy complication with a multifactorial etiology, characterized by severe and persistent nausea and vomiting (NVP) [1]. While NVP affects 50–80% of pregnant women, HG is a more severe condition, occurring in 0.3–3% of pregnancies and often requiring hospitalization [2,3]. However, some populations report significantly higher incidence rates [4]. The clinical consequences of HG are profound, including maternal weight loss, dehydration, electrolyte imbalances (hypokalemia, metabolic alkalosis), nutritional deficiencies, and psychological distress [5]. Fetal complications may also arise, such as low birth weight, preterm delivery, small-for-gestational-age infants, and even stillbirth [6]. Additionally, maternal risks such as preeclampsia and placental abruption have been associated with HG [7].

The exact pathogenesis of HG remains unclear, but several risk factors have been identified. These include young maternal age, nulliparity, multiple pregnancies, female fetus, family history of HG, prior HG in previous pregnancies, gestational trophoblastic disease, low pre-pregnancy BMI, obesity, Helicobacter pylori infection, hyperthyroidism, oxidative stress, and psychological factors [5]. Beyond these, pre-pregnancy lifestyle factors—such as vitamin deficiencies, alcohol consumption, sedentary behavior, and high intake of saturated fats—may further increase susceptibility to HG [8].

Processed meats, a major dietary source of saturated fats, have been implicated in various adverse health outcomes [9]. More broadly, ultra-processed foods (UPFs)—defined by extensive industrial processing—have seen a dramatic global increase in consumption over recent decades due to their convenience, long shelf life, and hyper-palatability [10,11]. The NOVA classification system categorizes foods based on processing level, with UPFs typically being energy-dense, high in added sugars, salt, and unhealthy fats, while lacking fiber and essential micronutrients [12, 13, 14]. Numerous observational studies have linked UPF consumption to non-communicable diseases, including metabolic syndrome, cardiovascular disease, and certain cancers [15, 16].

Given that UPFs are a major source of saturated fats and may promote systemic inflammation and oxidative stress—both hypothesized mechanisms in HG pathogenesis—we sought to investigate

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their potential role. To date, no study has examined the association between UPF intake and HG risk. Therefore, this case-control study aimed to evaluate whether pre-pregnancy consumption of UPFs is associated with higher odds of developing HG in Iranian women, while adjusting for key confounding variables.

Methods

Ethical Considerations and Study Design

The present study was conducted in full compliance with the ethical principles outlined in the latest version of the Helsinki Declaration. Ethical approval was obtained from the Institutional Review Board of the National Nutrition and Food Technology Research Institute at Shahid Beheshti University of Medical Sciences, Tehran, Iran (approval code: IR.SBMU.NNFTRI.REC.1399.067). Prior to participation, all enrolled subjects, including both HG cases and controls, provided written informed consent.

Study Population and Recruitment

We conducted a hospital-based case-control study between April 2020 and June 2021 in the obstetrics and gynecology departments of general hospitals across Tehran, Iran. The study population comprised 45 pregnant women diagnosed with hyperemesis gravidarum (HG) and 135 healthy pregnant controls without HG. Case identification and diagnosis were performed according to the standardized criteria established by the American College of Obstetricians and Gynecologists (ACOG) [17]. The diagnostic criteria for HG included: (1) persistent vomiting unrelated to other medical conditions; (2) biochemical evidence of acute starvation (ketonuria); and (3) documented weight loss exceeding 5% of pre-pregnancy body weight.

Inclusion and Exclusion Criteria

For the HG case group, we established rigorous inclusion criteria to ensure homogeneity of the study population. Eligible participants were women aged 18-35 years with singleton pregnancies at gestational ages below 14 weeks. Additional exclusion criteria included: history of alcohol consumption or substance use; utilization of assisted reproductive technologies; current Helicobacter pylori infection; adherence to specialized dietary regimens prior to pregnancy; presence of chronic metabolic disorders (including diabetes mellitus and cardiovascular diseases); history of swallowing disorders or eating pathologies; and current use of estrogen-containing medications.

Control group participants were selected based on the absence of current or previous HG diagnosis. For both cases and controls, we implemented additional exclusion criteria to ensure data quality: (1) reported daily energy intake values falling outside three standard deviations from the study population mean; and (2) incomplete food frequency questionnaire responses with more than 60 items left unanswered.

Data Collection Procedures

Trained research personnel collected comprehensive demographic and clinical data through structured interviews. The collected variables included: maternal age; gestational week; parity; smoking status; family history of HG; socioeconomic indicators (monthly household income, educational attainment, and occupational status); and detailed medication/supplement use history.

Anthropometric measurements were obtained following standardized protocols. Height measurements were performed by a single trained examiner using a calibrated stadiometer, with participants standing barefoot in an erect position and shoulders in neutral alignment; measurements were recorded to the nearest millimeter. Pre-pregnancy weight and waist circumference values were obtained through self-report. For participants who could not recall these measurements, we extracted the earliest available anthropometric data from prenatal medical records. Body mass index (BMI) was calculated using the standard formula: weight (kg) divided by height squared (m^2). Physical activity levels were quantified using a validated questionnaire that has demonstrated reliability in previous studies [18].

Dietary Assessment Methodology

Dietary intake data were collected by trained dietitians using a validated 168-item semi-quantitative food frequency questionnaire (FFQ) [19]. This interviewer-administered instrument, adapted from Willett's FFQ [20], assessed habitual dietary patterns during the year preceding pregnancy. The FFQ incorporated standardized portion sizes for all food items. During administration, interviewers provided visual aids and detailed explanations of portion sizes before querying consumption frequencies (daily, weekly, monthly, or yearly).

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The research team converted reported food consumption frequencies to gram quantities using standardized household measures. For composite dishes (e.g., pizza), nutrient composition was determined based on typical restaurant preparation methods. Nutrient and energy values were calculated using both the USDA Food Composition Database and the Iranian Food Composition Table. Ultra-processed foods (UPFs) were classified according to the NOVA food classification system [21], with 37 FFQ items aggregated into seven distinct categories. Daily UPF intake was expressed in grams per day.

Statistical Analysis

All statistical analyses were performed using SPSS software (version 20.0; SPSS Inc., Chicago, IL). We employed two-tailed hypothesis tests throughout the study, with a predetermined significance level of $\alpha = 0.05$. The normality of continuous variables was assessed through multiple approaches: visual inspection of histograms and Q-Q plots, supplemented by formal Kolmogorov-Smirnov testing.

Descriptive statistics were calculated for all study variables. Categorical variables were summarized as frequencies and percentages, while continuous variables were reported as either mean ± standard deviation (for normally distributed data) or median with interquartile range (for non-normally distributed data). Group comparisons were performed using Mann-Whitney U tests for continuous variables and chi-square tests for categorical variables.

UPF intake values were categorized into tertiles based on the distribution observed in the control group. We employed multiple binary logistic regression models to examine the association between UPF intake and HG risk. Two progressively adjusted models were constructed: Model 1: Adjusted for age and UPF-derived energy intake; Model 2: Additionally adjusted for gestational week, family history of HG, previous HG episodes, BMI, total fiber intake, and physical activity level (in MET-hours/day). Trend analyses were conducted by treating the categorical tertile variables as continuous predictors in the logistic regression models. All regression results are presented as odds ratios (OR) with corresponding 95% confidence intervals (CI).

Findings

Following rigorous data quality control measures, we excluded participants with extreme energy intake values, defined as log-transformed total energy intake exceeding ±3 standard deviations from the mean. This resulted in the exclusion of 3 HG cases and 5 control participants. Additionally, we excluded 2 HG cases and 3 controls who had incomplete dietary data, having skipped 60 or more items on the FFQ. These exclusions yielded final participation rates of 90% among HG cases and 93% among controls, with 45 cases and 126 controls included in the final analysis.

The general characteristics of the study participants are presented in Table 1. The mean age of participants was comparable between groups, with HG cases averaging 25.3 years (SD=3.3) and controls averaging 25.5 years (SD=3.6), confirming the successful implementation of our frequency-matching design. Notably, we observed significantly higher rates of both familial HG history ($p<0.05$) and previous pregnancy HG episodes ($p<0.05$) among cases compared to controls. However, the groups showed no significant differences in gestational week, parity, fetal sex distribution, pre-pregnancy anthropometric measurements (including BMI and waist circumference), educational attainment, employment status, pre-pregnancy physical activity levels, or smoking history.

Detailed dietary intake patterns are presented in Table 2. Our analysis revealed significant differences in median consumption levels between groups across multiple dietary components. HG cases demonstrated significantly higher intake of several ultra-processed food categories including: total energy derived from UPFs ($p<0.01$), total fat ($p<0.05$), saturated fat ($p<0.05$), cookies and cakes ($p<0.05$), processed meats ($p<0.01$), dairy beverages ($p<0.05$), fast foods ($p<0.01$), and oils and sauces ($p<0.05$). Conversely, control participants showed significantly higher consumption of dietary fiber ($p<0.01$), vitamin B6 ($p<0.05$), and total protein ($p<0.05$) compared to HG cases.

The associations between UPF consumption and HG risk are presented in Table 3. In fully adjusted models, we observed significant inverse associations between UPF intake and HG risk. Comparing the highest to lowest tertiles of consumption: total UPF intake showed an OR of 0.31 (95% CI: 0.19-0.48; p-trend=0.002); dairy beverages showed an OR of 0.18 (95% CI: 0.09-0.52; p-trend=0.048); and processed meats and fast foods showed an OR of 0.13 (95% CI: 0.06-0.71; p-trend=0.015). These associations demonstrated consistent and statistically significant dose-response trends. Importantly, we found no significant associations between HG risk and consumption of non-dairy

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beverages, cookies and cakes, potato chips and salty snacks, oils and sauces, or sweets in either crude or adjusted regression models.

Table 1 General characteristics of participants with hyperemesis gravidarum and controls

Characteristic*	HG women n=45	Control women n=126	*P* Value†
Age, year	25 (23-27)	25 (23-28)	0.679
Familial history of HG, No (%)	26 (57.8)	10 (7.9)	<0.001
History of HG in previous pregnancy, No (%)	8 (17.8)	2 (1.6)	<0.001
Female fetus, No (%)	26 (57.8)	55 (43.7)	0.103
Pregnancy week	11 (10-12)	11 (9-12)	0.154
Parity			
Nulliparous	35 (77.8)	90 (71.4)	0.979
Multiparous	10 (22.2)	26 (20.6)	
Education, No (%)			
Primary/secondary school	26 (57.8)	80 (63.5)	
Bachelor's degree	16 (35.6)	35 (27.8)	0.441
Master's/Doctoral degree	3 (6.7)	11 (8.7)	
Pre-pregnancy smoking, No (%)			
Smokers	1 (2.2)	0	
Non-smokers	44 (97.8)	125 (99.2)	0.206
Ex-smokers	0	1 (0.8)	
Monthly family income, No (%)			
< 300 US $	28 (62.2)	97 (77)	0.055
≥ 300	17 (37.8)	29 (23)	
Pre-pregnancy physical activity (MET/h/d)	28.2 (16.5-85.1)	45.1 (22.7-69.2)	0.697
Pre-pregnancy anthropometric measurements			
BMI (kg/m2)	22.7 (21.7-25.9)	22.9 (21.4-25)	0.284
Waist circumference (cm)	82 (80-84)	80 (79-83.6)	0.202

* Values are mean ± SD unless otherwise noted
† Using Mann Whitney test or $\chi 2$ test, as appropriate.
BMI, body mass index; HG, hyperemesis gravidarum; MET, metabolic equivalent

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Table 2 Energy, nutrient intakes and dietary UPF intakes among hyperemesis gravidarum cases and controls*

	HG women n=45	Control women n=126	*P* Value†
Dietary factors			
Energy intake (kcal/d)	1925 (1745-2276)	1800 (1443-2320)	0.301
Total energy intake of UPF (kcal/d)	364.4 (196.4-552.9)	134.2 (70.3-225.1)	<0.001
Carbohydrate (g/d)	284.8 (230.8-314.8)	284.2 (208.6-341.9)	0.911
Protein (g/d)	55.8 (47.4-64.8)	67.2 (47.3-93.5)	0.007
Fat (g/d)	71.4 (54.7-88.5)	55.7 (42.1-74.4)	<0.001
Saturated fat (g/d)	21.8 (17.8-27.1)	19.8 (12.2-28.7)	0.046
Saturated fat intake of UPF (g/d)	3.64 (2.21-5.61)	1.03 (0.45-1.81)	<0.001
Dietary fiber (g/d)	12.8 (11.5-14.8)	18.9 (12.6-25.3)	<0.001
Vitamin B6 (mg/d)	0.88 (0.65-1.2)	1.18 (0.69-1.57)	0.014
UPF groups			
Total UPF	170.76 (108.95-290.69)	78.56 (43.45-155.34)	<0.001
Non-dairy Beverages	41.34 (3.98-75.01)	18.40 (4.03-70.21)	0.260
Cookies and cakes	50.68 (21.03-84.42)	26.01 (13.72-44.23)	0.004
Dairy beverages	10.26 (2.79-36.36)	3.86 (2.18-10.52)	0.006
Potato chips and salty snacks	3.64 (1.02-8.16)	2.12 (1.29-4.80)	0.297
Processed meat and fast food	6.89 (0.33-16.9)	1.53 (0.14-4.27)	0.001
Oil and sauces	8.48 (1.54-15.25)	2.69 (0.92-6.58)	0.001
Sweets	10.48 (3.54-17.25)	6.26 (4.60-10.02)	0.168

*Values are median (Q1-Q3)
†Based on Mann Whitney test
HG, hyperemesis gravidarum

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Table 3 Adjusted odds ratio (OR) estimates and 95% confidence intervals (CIs) for hyperemesis gravidarum according to the tertile of UPF groups*

	Tertiles of intakes			*P* for Trend
	1st	2nd	3rd	
Total Ultra-processed food intakes				
No. Cases/No. Controls	4/42	9/42	32/42	
Base Model†	0.23 (0.02-2.14)	1.36 (0.47-3.92)	1.00 (Ref.)	0.383
Full Model‡	0.31 (0.19-0.48)	0.88 (0.12-4.41)	1.00 (Ref.)	0.002
Non-dairy Beverages				
No. Cases/No. Controls	12/42	12/42	21/42	
Base Model†	2.65 (0.85-8.28)	1.69 (0.58-4.93)	1.00 (Ref.)	0.093
Full Model‡	0.87 (0.14-5.54)	1.02 (0.17-6.08)	1.00 (Ref.)	0.854
Cookies and cakes				
No. Cases/No. Controls	10/42	9/42	26/42	
Base Model†	2.68 (0.81-8.87)	0.80 (0.27-2.32)	1.00 (Ref.)	0.177
Full Model‡	1.36 (0.22-7.48)	0.20 (0.04-1.02)	1.00 (Ref.)	0.726
Dairy beverages				
No. Cases/No. Controls	7/42	11/42	27/42	
Base Model†	0.98 (0.37-2.61)	0.28 (0.09-0.86)	1.00 (Ref.)	0.659
Full Model‡	0.18 (0.09-0.52)	0.22 (0.11-1.06)	1.00 (Ref.)	0.048
Potato chips and salty snacks				
No. Cases/No. Controls	13/42	7/42	25/42	
Base Model†	2.49 (0.85-7.33)	0.48 (0.16-1.44)	1.00 (Ref.)	0.185
Full Mode ‡	2.82 (0.65-8.19)	0.60 (0.13-2.89)	1.00 (Ref.)	0.188
Processed meat and fast food				
No. Cases/No. Controls	5/42	11/42	29/42	
Base Model†	0.34 (0.11-1.10)	0.75 (0.28-1.99)	1.00 (Ref.)	0.432
Full Model‡	0.13 (0.06-0.71)	0.44 (0.09-1.37)	1.00 (Ref.)	0.015
Oil and sauces				
No. Cases/No. Controls	10/42	6/42	29/42	
Base Model†	1.23 (0.43-3.56)	0.48 (0.16-1.46)	1.00 (Ref.)	0.810
Full Model‡	0.31 (0.06-1.57)	0.16 (0.02-1.06)	1.00 (Ref.)	0.217
Sweets				
No. Cases/No. Controls	15/42	7/42	23/42	
Base Model†	0.95 (0.23-3.95)	1.25 (0.36-4.35)	1.00 (Ref.)	0.160
Full Model‡	1.14 (0.17-7.67)	0.84 (0.11-6.5)	1.00 (Ref.)	0.809

* logistic regression model
†adjusted for age and energy intake from UPF (Kcal/d)
‡adjusted for age, pregnancy week, BMI (Kg/m^2), energy intake from UPF (Kcal/d), fiber intake (g/d), vitamin B6 (mg/d), familial history of HG (yes/no), history of HG in previous pregnancy, parity, and physical activity (MET/h/d)
BMI, body mass index; HG, hyperemesis gravidarum; MET, metabolic equivalent; UPF, Ultra-processed food

Discussion

The current study presents novel findings regarding the association UPF consumption and HG risk. Our analysis revealed a significant association between UPF intake and HG odds after adjusting for potential confounders. While certain UPF categories demonstrated protective associations with HG risk, the overall dietary pattern characterized by higher UPF consumption appeared to be associated with increased risk, particularly when considering the parallel findings of reduced fiber and nutrient intake among HG cases. The differential effects observed across UPF subcategories

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emphasize the importance of examining both food processing methods and nutrient composition when investigating dietary risk factors for HG [22]. This study represents the first investigation of the UPF-HG association in a developing nation, building upon previous work that identified seafood, water, and vegetables as potential protective dietary factors [22].

HG remains a serious pregnancy complication that frequently necessitates hospitalization during the first trimester, underscoring the importance of identifying preventive strategies [3]. Our findings support the growing evidence that nutritional status plays a critical role in HG development [22-24]. The utilization of UPF as a marker of dietary quality has become increasingly valuable in nutritional epidemiology for examining diet-disease relationships [12]. In our analysis, participants in the lowest tertile of total UPF consumption showed 69% lower odds of HG compared to those in the highest tertile. Notably, higher intakes of dairy beverages and processed meats/fast foods were also associated with reduced HG risk, suggesting complex relationships that warrant further investigation.

The mechanisms linking UPF consumption with HG risk may involve several pathways. While the exact etiology of HG remains unclear, existing evidence indicates that systemic inflammation markers are elevated in HG patients [25]. Previous research has demonstrated that diets with higher proportions of UPFs exhibit greater pro-inflammatory potential [26], with one study specifically showing that increased industrial food processing correlates with higher dietary inflammatory index scores in pregnant women [26]. Such pro-inflammatory diets may promote oxidative stress and enhance lipid peroxidation, processes that have been implicated in various pregnancy complications including HG [27,28]. The well-documented imbalance between pro-oxidants and antioxidants in HG pathogenesis [27] may be exacerbated by UPF consumption, as these products typically contain high levels of saturated fats and pro-oxidant components while being deficient in antioxidant compounds [12]. Additionally, industrial processing methods, including mechanical and thermal treatments, may further compromise the antioxidant properties of foods [29], potentially contributing to the observed associations.

Our findings regarding specific UPF categories provide important insights. The dairy beverages (including various ice creams and flavored milks) and processed meats/fast foods (such as burgers, sausages, and pizza) examined in our study were characteristically high in total and saturated fats while being relatively low in antioxidant density. These nutritional characteristics may help explain their distinct associations with HG risk. Given the widespread consumption of UPFs globally, pregnant women may be particularly vulnerable to the potential adverse effects of processing-related ingredients and nutrient imbalances.

The current study possesses several notable strengths, including high participation rates and rigorous methodology to minimize information bias. All dietary assessments were conducted by trained dietitians blinded to participant case status, and we controlled for numerous potential confounding variables in our analyses. However, certain limitations must be acknowledged. The case-control design carries inherent risks of recall and selection bias, though we mitigated this concern by focusing on newly-diagnosed HG cases. Our sample size, while adequate for initial exploration, became relatively small when divided into tertiles of UPF consumption, potentially limiting statistical power. Although we employed a validated FFQ that has demonstrated reliability in Iranian populations, some degree of dietary misclassification is inevitable in nutritional epidemiology. Additionally, cultural considerations precluded assessment of alcohol consumption, which may represent a potential confounder.

Conclusion

In summary, our findings indicate that pre-pregnancy dietary patterns characterized by lower consumption of UPFs, particularly dairy beverages and processed meats/fast foods, are associated with reduced odds of developing HG in Iranian women. These results suggest that limiting processed foods in the pre-conception period may play an important role in HG prevention. Healthcare providers, particularly dietitians working with women of reproductive age, should consider these findings when providing dietary counseling. Future research should employ larger longitudinal designs and examine comprehensive dietary patterns rather than isolated nutrients or food groups to better elucidate the mechanisms linking pre-pregnancy diet with HG risk. Such investigations would significantly advance our understanding of this challenging condition and inform evidence-based preventive strategies.

Abbreviations

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