Published in final edited form as:
J Clin Gastroenterol. 2013 September ; 47(8): 700–705. doi:10.1097/MCG.0b013e318286fdb0.

Carbohydrate Intake as a Risk Factor for Biliary Sludge and Stones during Pregnancy

Alan C. Wong, MD MPH[1] and **Cynthia W. Ko, MD MS**[1]
[1]Department of Medicine, University of Washington, Seattle, Washington

Summary

Background—High carbohydrate intake has been linked to insulin resistance, obesity, and abnormal serum lipid profiles—conditions which favor gallstone formation.

Goals—The aim of this study was to evaluate the effect of dietary carbohydrate intake on incident gallbladder disease, defined as biliary sludge and stones, during pregnancy.

Study—We prospectively studied 3,070 pregnant women who underwent serial gallbladder ultrasound during pregnancy and at 4-6 weeks postpartum. All women had at least 2 study ultrasounds for comparison. A semi-quantitative food frequency questionnaire was completed by subjects in the early 3rd trimester. Multivariate logistic regression was performed to assess the risk of incident gallbladder disease across quartiles total and individual carbohydrate and individual carbohydrates (starch, sucrose, galactose, fructose, and lactose) intake.

Results—The cumulative incidence of gallbladder disease was 10.2% by 4-6 weeks postpartum. The risk of incident gallbladder disease during pregnancy was significantly higher among women in the highest quartile of total carbohydrate intake vs. those in the lowest quartile (odds ratio 2.09, 95% confidence interval 1.02-4.27). High intake of fructose was associated with increased risk even after additional adjustment for total carbohydrate intake (odds ratio 2.18, 95% confidence interval 1.23-3.86, comparing highest to lowest quartile). No association was found between the intake of starch, sucrose, lactose, or galactose and the risk of incident gallbladder disease.

Conclusions—High consumption of total carbohydrate and fructose may increase the risk of developing gallbladder disease during pregnancy. Dietary modification during pregnancy might reduce gallstone incidence during this time period.

Keywords

dietary carbohydrates; gallstones/epidemiology; fructose; pregnancy/complications

Introduction

Gallbladder disease, defined as biliary sludge and stones, is a significant cause of maternal morbidity during pregnancy. Biliary sludge consists of microscopic precipitates of cholesterol or bilirubin, and is a precursor to development of gallstones.[1] Gallbladder

Corresponding author and address for reprints Cynthia W. Ko, MD MS University of Washington Division of Gastroenterology Box 356424 Seattle, WA 98195 Phone: 206-543-4407 Fax: 206-221-1356 cwko@u.washington.edu.

Statement of Interests: The authors have no personal or financial conflicts of interest.

disease is the second most common abdominal emergency during pregnancy and the leading non-obstetrical cause of maternal re-hospitalization in the first 60 days after delivery.[2, 3] Previous studies indicate that biliary sludge and stones form in up to 31% and 5.1% of pregnant women, respectively.[4, 5] Effective strategies aimed at preventing gallstone formation are necessary to reduce the burden and cost of gallbladder disease during pregnancy.

There is increasing evidence to support a connection between dietary intake and gallstone disease. In studies of non-pregnant women, high intake of dietary carbohydrates has been linked to gallstone disease and cholecystectomy,[6-10] although not all studies support this conclusion.[11, 12] Since many of these studies evaluated symptomatic gallstone disease, further clarification on whether carbohydrate intake affects the incidence of gallstones or the risk of developing symptoms from pre-existing gallstones is needed. If carbohydrate intake is indeed associated with gallstone formation, dietary modification might be an effective method of prevention during pregnancy. Presently, the effect of carbohydrate intake on gallstone disease during pregnancy is unclear and needs further investigation. The aim of this study was to prospectively evaluate the effect of dietary carbohydrate intake on incident gallbladder sludge/stones during pregnancy. We hypothesized that high dietary carbohydrate intake would be associated with an increased risk of gallbladder sludge/stone formation during pregnancy. We evaluated the effect of total carbohydrate intake, as well as intake of individual sugars and starch.

Materials and Methods

Study population

Pregnant women attending their first obstetrics clinic at Madigan Army Medical Center (Tacoma, Washington) were approached consecutively (n = 8,929). Women were excluded if they were less than 18 years of age, had poor English language comprehension, were more than 20 weeks pregnant, or had plans to move away within 3 months. Those who were eligible and interested in enrollment (n = 4,897) gave written informed consent. Enrolled subjects were offered serial fasting gallbladder ultrasound examination during each trimester of pregnancy (10-12 weeks gestation, 17-19 weeks gestation, 26-30 weeks gestation) and at 4-6 weeks postpartum. The study was approved by the Institutional Review Boards of the University of Washington and Madigan Army Medical Center.

Assessment of gallbladder sludge and stones

Gallbladder ultrasonography was performed with a standard imaging protocol using a 3.5- to 7.0-MHz rotatory sector scanning transducer (ATL Inc., Bothell, WA, or Acuson Corp., Mountain View, CA). All study ultrasounds were performed by sonographers with specialized training in gallbladder ultrasound and with women fasting or having drunk only sips of water. Findings were recorded by the sonographers, and images and findings were reviewed by one of two designated study radiologists with expertise in gallbladder ultrasound. Sludge was defined as the presence of low-level echoes that shift with position changes and without postacoustic shadowing. Stones were defined as high-amplitude echoes greater than 2 mm in diameter with postacoustic shadowing. In 10,887 scans, there were discrepancies between the radiologist's and the sonographer's readings in 70 regarding the diagnosis of sludge (kappa 0.93) and in 25 regarding the diagnosis of stones (kappa 0.98). In case of discrepancy, the radiologist's reading was accepted as correct. 1,261 women completed the first trimester ultrasound, 3,019 women completed the second trimester ultrasound, 3,041 completed the third trimester ultrasound, and 2,046 completed the 4-6 week postpartum ultrasound.

Dietary assessment

At study entry, subjects completed a questionnaire documenting their medical, obstetrical, family, and social histories. Nutrient data was collected using a food frequency questionnaire (version WHX, 1992) developed by the Nutrition Assessment Shared Resource (NASR) of Fred Hutchinson Cancer Research Center (FHCRC, Seattle, Washington).[13] This validated questionnaire was administered in the early 3rd trimester of pregnancy, and inquired about the nutritional habits of the subjects from the time of conception to the time the questionnaire was given. Using data from the food frequency questionnaires, the number of daily servings of individual foods was determined, from which estimated intake of total and individual carbohydrates were calculated according to data from the Nutrition Coordinating Center (NCC) at the University of Minnesota (Minneapolis, Minnesota). Pre-pregnancy body mass index (BMI) was calculated from self reported weight immediately before pregnancy and height measured at study intake. Reported pre-pregnancy weight was not independently validated. Weight gain during pregnancy was calculated as the difference between self-reported pre-pregnancy weight and the pre-delivery weight obtained from the subject's medical record. Fasting serum samples were obtained at 26-28 weeks gestation and tested for glucose and lipid values by the clinical laboratory at Madigan Army Medical Center.

Statistical analysis

Women with gallstones on entry ultrasound (n = 208) were excluded from analysis. Those with sludge seen on the entry ultrasound were followed to see whether progression to stones occurred. Women with new sludge, new stones, or progression of baseline sludge on entry ultrasound to stones on a subsequent ultrasound were defined as having incident gallbladder disease. Women were additionally excluded from the final data analyses if they did not complete a dietary questionnaire (n = 184), had fewer than 2 interpretable gallbladder ultrasounds (n = 1,402), or had a prior cholecystectomy (n = 33). This resulted in 3,070 subjects included in the analysis.

On univariate analysis, we used t-tests to compare continuous variables and chi-square tests for categorical variables. We used Spearman's rank correlation coefficient to examine the correlation between carbohydrate intake and BMI at entry, age, and serum lipid and glucose levels. Multivariate logistic regression analysis was performed to assess the risk of incident gallbladder disease across quartiles of intake of total carbohydrate and individual carbohydrates (starch, sucrose, galactose, fructose, lactose) after adjustment for various categorical (Hispanic origin, history of diabetes, and smoking) and continuous variables (age, pre-pregnancy BMI, weight gain during pregnancy, parity; dietary intake of caffeine, alcohol, calories, total carbohydrates, protein, fat, fiber, cholesterol, fatty acids; and fasting serum HDL, LDL, triglyceride, cholesterol, glucose levels). Two-sided *P* values less than 0.05 were considered statistically significant. Analyses were performed with SPSS, version 17 (Chicago, Illinois).

Results

The cumulative incidence of new sludge, new stones, or progression of baseline sludge to stones was 7.1% by the second trimester, 8.8% by the third trimester, and 10.2% by weeks postpartum. 160 women (5.2%) developed only sludge, while 154 women (5.0%) developed new stones by the postpartum examination. In univariate analysis, women of Hispanic origin had a higher risk of forming new sludge or stones than non-Hispanic women (Table 1). Women who formed new sludge or stones had a higher pre-pregnancy BMI and gained less weight during pregnancy. Those who formed new sludge or stones had significantly higher triglyceride (p=0.02) and glucose (p=0.007) levels and significantly lower high density

lipoprotein (HDL) cholesterol levels (p=0.004). A personal history of diabetes, low density lipoprotein (LDL) cholesterol levels, and dietary intake of calories, fat, fiber, total carbohydrates, starch, sucrose, lactose, and galactose were not significantly different between women with or without incident sludge or stones (Tables 1 and 2). Total carbohydrate and sucrose intake had a borderline association with entry body mass index, but were not associated with serum lipids or glucose (Supplementary Digital Content, Table 1). Total carbohydrate intake had a slight negative correlation with age at study entry. Fructose intake was inversely correlated with age and serum HDL cholesterol, while starch intake had a modest negative correlation with serum glucose.

Multivariate models were developed to study the relationship between incident gallbladder disease and total or individual carbohydrate intake (Table 3). In these models, we adjusted for age, Hispanic origin, weight-related variables, history of diabetes, smoking, parity, and total caloric, caffeine, and alcohol intake. We also adjusted for dietary intake of protein, fat, fiber, cholesterol, and fatty acids, as well as for serum lipid and glucose levels. The effects of total carbohydrates, starches, and individual sugars (sucrose, fructose, lactose, and galactose) were examined in separate models. In the analyses of starch and individual sugars, we also adjusted for total carbohydrate intake.

These models demonstrated an increased odds of incident gallbladder disease among those in the highest quartile of total carbohydrate intake (OR 2.09, 95% CI 1.02-4.27) and fructose intake (OR 2.18, 95% CI 1.23-3.86) when compared to their respective lowest quartiles of intake. (Table 3). Intake of sucrose, lactose, and galactose were not significantly associated with incident sludge/stones, but there was a non-significant increase in risk of incident gallbladder disease with increasing starch intake.

Discussion

In this prospective study, we found high total carbohydrate and fructose intake to be associated with increased risk of incident gallbladder sludge and stones during pregnancy. These associations persisted despite adjustment for numerous potential confounding factors, such as pre-pregnancy BMI, weight gain during pregnancy, and serum lipid and glucose levels. The strength of the association for high carbohydrate or fructose intake was greater than the effect of race or ethnicity, which were not significant risk factors for sludge or stones in our previous studies, but is less than the association we have previously seen for obesity (OR 4.45, 95%CI 2.59-7.64 comparing BMI ≥30 vs. <25).[5]

Among the individual carbohydrates examined in this study, fructose was found to be uniquely associated with incident gallbladder disease independent of total carbohydrate intake. The mechanism by which fructose promotes gallbladder disease is unclear, although excessive fructose intake has been shown to produce conditions that favor gallstone formation. Fructose promotes hepatic insulin resistance in humans,[14, 15] a condition that enhances cholesterol gallstone formation in mice.[16] Fructose bypasses phosphofructokinase, the rate limiting enzymatic step imposed on glucose, and its metabolites are funneled into fatty acid synthesis, resulting in hepatic lipogenesis, hypertriglyceridemia, and visceral fat deposition.[14, 17-19] Prolonged consumption of a fructose rich diet results in elevation of serum leptin[20], a satiety hormone that has been associated with gallbladder disease during pregnancy.[5] Excessive fructose intake might contribute to the metabolic syndrome,[17, 21-23] and gallstones, in turn, are linked to the metabolic syndrome.[24] Thus, insulin resistance and the metabolic syndrome are potential pathways connecting fructose intake to gallstone formation. It is unclear why other individual carbohydrates were not associated with gallstone formation, although we hypothesize that they have differing effects upon glucose or lipid metabolism and insulin sensitivity.

Several other studies have looked at dietary carbohydrates and gallstones in men and non-pregnant women, but they are heterogeneous in their definition of gallstone disease, method of dietary assessment, and results. In subset analyses including only women, an Australian case-control study found high sugar intake to be associated with gallstones detected by ultrasound, cholecystography, or intraoperative visualization[10], while an Indian case-control study found high intake of total and refined carbohydrates to be associated with gallstones detected intraoperatively or by radiological methods.[9] In Italy, a large cross-sectional study showed that high carbohydrate intake was associated with previously undiagnosed gallstones detected by ultrasound among females,[7] while two other European studies had mixed results.[8, 12] Two prospective studies using data from the Nurses' Health Study (NHS) also had conflicting results. In the first study, intake of carbohydrate and sucrose was not associated with cholecystectomy or imaging-confirmed symptomatic gallstones that did not require cholecystectomy.[11] In the second study, high consumption of carbohydrate, starch, sucrose, and fructose was positively associated with the risk of cholecystectomy.[6] The opposing results from the NHS based studies might be due to differences in statistical power as the latter study had longer patient follow-up duration and more identified cases (4 years, 612 cases vs. 16 years, 5771 cases).

There is limited data on the effect of dietary carbohydrates on gallstone disease during pregnancy. To our knowledge, only two small studies have addressed this specific issue. A cross sectional study of 512 pregnant women found no association between sucrose intake and gallstones.[25] A prospective study of 128 pregnant women also found no association between gallstones and the intake of total carbohydrates.[26] This latter study was limited by the use of subjects' self reported history and symptoms to identify gallstone cases.

Excessive intake of dietary carbohydrates has been linked to dyslipidemia and obesity—both of which are thought to contribute to gallstone formation. In a controlled study of lean and obese women, de novo lipogenesis was 2 to 3 fold higher in subjects who were overfed with a predominantly carbohydrate diet.[27] High carbohydrate and low fat diets have also been shown to result in elevation of serum triglyceride and a decrease in HDL cholesterol levels, changes which have been linked to gallstone risk.[28, 29] Some, but not all, studies examining the effect of diet on weight loss have suggested that carbohydrate rich diets result in higher body mass when compared to lower carbohydrate diets.[30]

In pregnant women, a physiologic rise in serum estrogen, progesterone, human placental lactogen, and cortisol results in insulin resistance and a shift towards a diabetogenic state.[31, 3233, 34] High carbohydrate intake during pregnancy might magnify the negative effects of this insulin resistance by stimulating additional insulin release. We have previously shown that insulin resistance is associated with incident gallbladder disease during pregnancy.[35] Insulin resistance is believed to promote the conditions necessary for cholesterol gallstone formation, and diabetes is a risk factor for prevalent gallstones.[36] Insulin resistance and hyperinsulinemia potentially affect biliary cholesterol saturation and gallbladder motility–both key pathogenic factors in the development of cholesterol gallstones.[37, 38, 39, 40] Therefore, limiting the consumption of carbohydrates during pregnancy might reduce the risk of gallstone formation, especially in those who possess other known risk factors.

The strengths of this study include its large size, prospective design, and specific focus on the pregnant population. Our prospective identification of incident gallbladder disease allows for a better understanding of the effect of dietary carbohydrates on the natural history of gallstone formation. Whereas many previous studies used total carbohydrate and/or refined sugar intake as their only dietary measure, this study also analyzes the effect of starches and individual mono- and disaccharides on gallbladder disease.

Our data suggests that a carbohydrate rich diet is associated with gallstone formation, potentially through effects on insulin resistance. However, serum insulin and leptin, possible mediators of dietary carbohydrates' effects on gallstone disease, were not measured for all participants in this study, so we could not account for their effects in our models. While we adjusted for many potential confounding factors, other variables such as physical activity and family history of gallstones remain unaccounted for. Our analyses also did not adjust for a personal history of hormonal contraceptive use. However, we have previously shown that there is no association between the use of hormonal contraceptives and the risk of incident gallbladder sludge/stones in this cohort of patients.[5] Finally, dietary data was collected at a single point in time and might not reflect changes in dietary habits over the course of pregnancy.

In conclusion, we have shown that a diet rich in total carbohydrates and fructose is associated with formation of biliary sludge and stones during pregnancy. These associations persisted despite adjustment for various potential confounding factors. Our results add to the body of literature examining diet and gallstone disease by specifically targeting a population that is at elevated risk. Dietary intervention might be an effective strategy to reduce the incidence of biliary disease among pregnant women.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

Acknowledgments

Grant Support: This work was funded in full by the National Institutes of Health, grant DK046890.

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Table 1

Selected Characteristics of Study Subjects

	No new sludge/stones n = 2756	New sludge only n = 160	New stones n=154	P – value *
Mean age, y (mean ± SD)	25.2 ± 4.9	24.9 ± 4.2	25.9 ± 5.2	0.51
Hispanic Origin, n (%)	288 (10.4)	27 (16.9)	29 (18.8)	0.001
BMI pre-pregnancy, *kg/m*^{2} (mean ± SD)	24.4 ± 4.9	26.0 ± 6.6	28.0 ± 6.8	<0.0001
History of diabetes, n (%)	49 (1.8)	2 (1.3)	1 (0.6)	0.17
Weight gain during pregnancy, *kg* (mean ± SD)	14.6 ± 6.2	13.8 ± 7.4	11.4 ± 6.6	<0.0001
Any smoking during pregnancy, n (%)	561 (20.4)	36 (22.5)	23 (14.9)	0.49
Parity, n (%)				
0	916 (33.4)	58 (36.3)	58 (37.9)	0.24
1	865 (31.5)	42 (26.2)	43 (28.1)	
≥2	965 (35.1)	60 (37.5)	52 (34.0)	
Total cholesterol, *mg/dL* (mean ± SD) **	239 ± 43	241 ± 40	237 ± 46	0.93
HDL cholesterol, *mg/dL* (mean ± SD) **	66 ± 16	64 ± 17	61 ± 16	0.002
LDL cholesterol, *mg/dL* (mean ± SD) **	131 ± 41	134 ± 36	131 ± 42	0.68
Triglyceride, *mg/dL* (mean ± SD) **	209 ± 78	214 ± 74	226 ± 78	0.01
Glucose, *mg/dL* (mean ± SD) **	74 ± 8	74 ± 7	76 ± 10	0.02

*T-tests for continuous variables and chi-square tests for categorical variables, comparing women without sludge/stones to women with either sludge and/or stones.

**Serum cholesterol, HDL, LDL, triglyceride, and glucose obtained during fasting at 26-28 weeks gestation.

Table 2

Dietary Intake of Cases and Controls

Dietary intake (mean ± SD)	**No new sludge or stones n = 2756**	**New sludge n = 160**	**New stones n=154**	**P – value** *
Total carbohydrate, *g/day*	258 ± 128	268 ± 101	249 ± 124	0.92
Fructose, *g/day*	33 ± 24	36 ± 22	35 ± 25	0.06
Starch, *g/day*	98 ± 56	100 ± 47	90 ± 51	0.34
Sucrose, *g/day*	42 ± 25	43 ± 20	41 ± 26	0.93
Lactose, *g/day*	30 ± 22	30 ± 20	27 ± 20	0.63
Galactose, *g/day*	0.5 ± 0.6	0.5 ± 0.5	0.4 ± 0.5	0.16
Protein, *g/day*	89 ± 47	88 ± 37	85 ± 54	0.43
Fat, *g/day*	87 ± 49	84 ± 39	84 ± 53	0.34
Fiber, *g/day*	17 ± 9	17 ± 8	16 ± 8	0.82
Caffeine, *mg/day*	40 ± 67	50 ± 81	51 ± 89	0.05
Alcohol, *g/day*	0.1 ± 0.7	0.5 ± 4.7	0.6 ± 6.7	0.17
Cholesterol, *mg/day*	315 ± 210	293 ± 150	323 ± 331	0.61
Saturated fatty acids, *g/day*	33 ± 19	32 ± 16	31 ± 19	0.28
Mono-unsaturated fatty acids, *g/day*	31 ± 18	30 ± 14	30 ± 20	0.40
Poly-unsaturated fatty acids, *g/day*	16 ± 10	16 ± 8	16 ± 11	0.41
Trans fatty acids, *g/day*	5 ± 3	5 ± 3	5 ± 4	0.66

* t-test comparing women without sludge/stones to women with either sludge and/or stones.

Table 3

Risk of incident gallbladder disease according to quartiles of carbohydrate intake

Nutrient	Quartile 1 (lowest) (n = 767)	Quartile 2 (n = 768)	Quartile 3 (n = 767)	Quartile 4 (highest) (n = 768)
Total carbohydrate, g/day				
Range of intake (mean ± SD)	12-174 (134 ±30)	175-236 (206 ±17)	237-317 (273±24)	318-1594 (421±132)
Cases, n	80	65	81	88
Controls, n	687	703	686	680
Odds ratio * (95% confidence interval)	1.00 (reference)	1.08 (0.71 – 1.64)	1.48 (0.91 – 2.42)	2.09 (1.02 – 4.27)
Fructose, g/day				
Range of intake (mean ± SD)	0.5-17 (12±4)	18-27 (23±3)	28-41 (34±4)	42-246 65±27)
Cases, n	63	82	74	95
Controls, n	704	686	693	673
Odds ratio * (95% confidence interval)	1.00 (reference)	1.62 (1.09 – 2.41)	1.40 (0.90 – 2.19)	2.18 (1.23 – 3.86)
Starch, g/day				
Range of intake (mean ± SD)	0.8-62 (47±11)	63-87 (75±7)	88-119 (102±9)	120-678 167±65)
Cases, n	92	65	70	87
Controls, n	675	703	697	681
Odds ratio * (95% confidence interval)	1.00 (reference)	0.84 (0.57 – 1.24)	0.99 (0.63 – 1.55)	1.79 (0.98 – 3.28)
Sucrose (g/day)				
Range of intake (mean ± SD)	1-25 (19±5)	26-37 (31±3)	38-53 (45±4)	54-329 (74±26)
Cases, n	72	80	88	74
Controls, n	695	688	679	694
Odds ratio * (95% confidence interval)	1.00 (reference)	1.21 (0.82 – 1.78)	1.19 (0.78 – 1.83)	1.01 (0.57 – 1.78)
Lactose (g/day)				
Range of intake (mean ± SD)	0-13 (8±3)	14-23 (18±3)	24-40 (32±5)	41-156 (60±20)
Cases, n	80	76	71	87
Controls, n	687	692	696	681
Odds ratio * (95% confidence interval)	1.00 (reference)	1.08 (0.74 – 1.58)	0.96 (0.63 – 1.48)	1.38 (0.78 – 2.44)
Galactose (mg/day)				
Range of intake (mean ± SD)	3-160 (90±40)	161-334 (250±50)	335-639 (460±90)	640-10,100 (1250±810)
Cases, n	94	61	87	72
Controls, n	673	707	680	696
Odds ratio * (95% confidence interval)	1.00 (reference)	0.59 (0.40 – 0.86)	0.90 (0.62 – 1.29)	0.69 (0.45 – 1.06)

* Multivariate model adjusting for age; Hispanic origin; pre-pregnancy BMI; weight gain during pregnancy; history of diabetes; smoking; parity; total caloric intake, intake of caffeine, alcohol, protein, fat, fiber, cholesterol, and fatty acids; and serum glucose and lipid levels. Models for individual carbohydrates were also adjusted for total carbohydrate intake.