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An Evaluation of Nutritional and Vasoactive Stimulants as Risk Factors for Gastroschisis: A Pilot Study

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Abstract

Objective: To evaluate poor maternal nutrition, environmental exposures and vasoactive stimulants as potential risk factors for gastroschisis.

Methods: A case-control study was conducted among singleton pregnancies diagnosed in a tertiary teaching hospital in a 22-month period. Cases of gastroschisis were matched to controls at the time of diagnosis by race and maternal age. Demographics, periconceptual exposures, nutritional biomarkers and illicit drug hair analysis were evaluated. Analyses were performed using conditional logistic regression.

Results—Thirty gastroschisis cases and 76 controls were studied with no associations observed for illicit drug use or serum levels of ferritin, iron, B6, B12, folate or zinc. Neither prescription medication nor over the counter mediation use differed between cases and controls. Following adjustment for insurance, education, low BMI and nulliparity, mothers of gastroschisis cases had an increased odds of alcohol use one month prior and/or during early pregnancy compared to controls, with adjusted OR 3.19 (95% CI 1.01–11.61).

Conclusions: Our findings suggest that further investigation of vasoactive stimulants such as alcohol is warranted in the search to identify risk factors for gastroschisis.

Keywords

gastroschisis; anomaly; nutrition; alcohol

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Introduction

The prevalence of gastroschisis has been precipitously rising worldwide for over thirty years [1–4]. Although outcomes are good with advances in pediatric surgical care, gastroschisis carries a 10% mortality rate, and is associated with a 10% prevalence of other anomalies in the gastrointestinal or in another organ system [5–6]. Among survivors, there remains a significant risk of major morbidity or disability secondary to surgical complications, prolonged total parenteral nutrition, sepsis or short gut syndrome [7]. In addition, there is an increased risk of prematurity which also carries its own risk of morbidity and disability [7]. The risk for gastroschisis appears to be increased in young women from socially disadvantaged environments, with nutritional deficits serving as potential contributing factors [8–9]. Although classically described as predominantly occurring in young Caucasian women, the unexplained increase in prevalence has been observed across all age groups and races, with the largest increase (over 200% in the past decade) occurring in non-Hispanic African American women below 20 years of age [4,10]. While evidence regarding the etiology of gastroschisis is limited, it is suspected that observed racial/ethnic differences reflect differences in the distribution of nutritional or behavioral risk factors. The aim of this pilot study was to explore the role of maternal nutritional and vasoactive stimulant exposure in the development of gastroschisis among patients treated within a single facility during a 22 month time period. Using hematologic evaluation for anemia, iron stores, B vitamins and zinc, and hair analysis for illicit drugs, the aim of this study was to use objective measures of exposure assessment to examine associations with these potential risk factors and generate hypotheses that could be more fully examined in a subsequent large-scale study.

Materials and Methods

University of Oklahoma Investigational Review Board approval and an NIH Certificate of Confidentiality were obtained prior to initiation of this study. Within the University of Oklahoma Health Sciences Center (OUHSC) obstetric clinic system, over 5,000 patients are seen and 20,000 diagnostic ultrasounds are performed each year with between 26–29 cases of gastroschisis diagnosed and managed annually. As a tertiary level center, patients are referred from across the state, with the most common time of diagnosis between 16–22 weeks gestational age pregnancy.

We conducted a case-control study among patients referred to a university-based tertiary level obstetric clinic for routine mid-pregnancy ultrasound. Cases were defined as singleton pregnancies with a diagnosis of isolated fetal gastroschisis by ultrasound less than 24 weeks gestation, confirmed by a Maternal-Fetal Medicine physician between September 2010 and June 2012. At the time of diagnosis of gastroschisis, affected patients were offered enrollment, with written consent obtained. Patients who were referred for routine second trimester anatomy ultrasounds and who had a singleton normal study were recruited as controls. One to five controls were matched to each case by maternal age +/− 2 years and race/ethnicity. Controls were consented at that time of recruitment, following the normal ultrasound. Study participation was limited to patients living in the state of Oklahoma at the time of conception. Women with multiple pregnancies or a fetus known to have lethal anomalies, and/or chromosome abnormalities were excluded.

Detailed demographic, behavioral and medical information were obtained by interview at enrollment. Patients self-reported their age at conception, race/ethnicity, level of education and insurance status. Pregnancy history was documented by the medical record and at enrollment by history number of prior pregnancies, history of bleeding during the current pregnancy, vitamin use before and during pregnancy, and whether the pregnancy was planned. Patients also reported any use of alcohol, tobacco, illicit drugs (cocaine, marijuana, methamphetamine, and opiates), or over the counter or prescribed medications in the month prior to or during pregnancy. The patient's body mass index (BMI) was documented in kg/m^2at the time of a positive pregnancy test from their prenatal record. Because only four participants (1 case and 3 controls) had a BMI < 18.5, we evaluated low BMI by examining BMI ≤ 19.0.

A 25cc maternal blood sample was obtained at enrollment and analyzed for complete blood count, iron, ferritin, folate, B6, B12, homocysteine, zinc, and complete metabolic profile. Also at enrollment, a hair sample containing approximately 90 hair strands was collected by a certified research nurse cutting the hair as close to the scalp as possible per testing lab instructions (Omega Laboratory, Ohio). Testing for illicit drug use was performed on the most recent 1.5 inches. The Standard 5-Panel tests for Amphetamines (Amphetamines, Methamphetamine, and Ecstasy), Cocaine, Opiates (Codeine, Morphine, and Heroine metabolite), Phencyclidine (PCP), and Marijuana indicated presence or absence of detection.

Cochran-Mantel-Haenszel tests were estimated to evaluate differences in periconceptual characteristics between cases and controls adjusted for the matching characteristics of maternal age and race/ethnicity. Conditional logistic regression models were used to calculate odds ratios (OR) and exact 95% confidence intervals (CI) accounting for the matched design. Adjusted models also controlled for insurance (Medicaid/No Insurance vs. Private), education (greater than high school vs. high school or less), low body mass index (≤ 19 vs. >19), and nulliparity (0 vs. ≥ 1 live births). Analyses were conducted using Statistical Analysis Software (SAS) v.9.4 (Cary, NC).

Results

Between September 2010 and June 2012, 38 gastroschisis cases were diagnosed <24 weeks, and 31 of these consented to participate. Seventy-six controls matched for age and race were recruited over the same time interval. There was one case without available matched controls; thus, 30 cases were included in the analyses.

The study population was diverse in ethnicity (68% Caucasian, 24% Hispanic, 5% African American, and 4% Native American). The population was also diverse with regard to education and insurance status, with no differences observed between groups. Seventy-three percent of case and control pregnancies were unplanned, with mean age at conception of 20.9 +/−4.5 (range 15–33 years) for cases and 22.7 +/−4.5 (range 16–34) for controls. A lower proportion of cases were obese (13% vs. 33%) compared to controls, but the association between body mass index and gastroschisis did not achieve statistical significance (Table 1). Similarly, although anemia and B12 deficiency occurred more often

in cases, no statistically significant differences in nutritional biomarkers were identified between groups (Table 2).

Table 3 illustrates the comparison of substance use among gastroschisis cases compared to controls. Nearly half of controls and 40% of cases were taking oral contraceptives at conception. Tobacco use was high in both groups with a statistically non-significant tendency towards more first trimester tobacco use among gastroschisis cases. The use of prescription narcotics or anti- anxiety medications around conception was striking in both groups, but did not differ between cases and controls. Use of over the counter medications was also substantial, particularly with Tylenol followed by ibuprofen. Self-reported use of alcohol was profound in both groups, with greater prevalence among gastroschisis cases (36.7% vs. 18.4%; unadjusted OR 2.63, 95% CI 0.86–8.57). Following adjustment for insurance, education, low BMI and nulliparity, in addition to maternal age and race which were addressed in the matched analysis, the association between alcohol use and gastroschisis persisted and became statistically significant (adjusted OR 3.19 (95% CI 1.01–11.61). Although recalled history of exposure showed no significant difference in illicit drug exposure in the periconceptual period (Table 3), hair analysis for any illicit drug at enrollment surprisingly indicated a lower prevalence of exposure among gastroschisis cases (3.3%) compared to 13.2% of matched controls (unadjusted OR 0.24 95% CI 0.01–1.83).

Discussion

This pilot study was designed to explore hypotheses concerning potential risk factors for gastroschisis, with the prospect of informing the development of more definitive studies that could reveal potential targets for preventive measures. We identified an association between periconceptual consumption of alcohol and pregnancies complicated by isolated gastroschisis. If confirmed, programs addressing preconception alcohol abstinence may assist in reversing the rising gastroschisis prevalence.

Epidemiologic data support in part an environmental teratogen theory for gastroschisis. Several studies have consistently found maternal tobacco use to be an independent risk factor for gastroschisis [9,11–12]. The associations of potentially vasoactive illegal substances, such as cocaine, methamphetamine, marijuana, and gastroschisis have shown conflicting results. Animal studies clearly support a vascular disruptive effect on the fetus with cocaine or methamphetamine [13]. However, most studies of the association between cocaine or methamphetamine and gastroschisis have been retrospective and questionnaire based, even though self-reporting of illicit drugs is known to be inaccurate [14]. A novel hair analysis study by Morrison, et al objectively evaluated preconception drug use by hair analysis in 22 gastroschisis cases and found 18% to be positive [15]. Given hair analysis can determine exposure for the past 90 days, the author was able to date the exposure to the preconception period or early first trimester [16]. A multicenter study on illicit drug use detected by hair analysis found the association with gastroschisis held only in those mothers of young age [17]. The typical rates for hair growth is one-half inch/month; thus, hair testing reveals drug use in a 90 day window in contrast to a urine or blood drug screen which will only detect use in the past 24–72 hours. In our study, we proceeded with hair drug testing at the time of gastroschisis diagnosis or at the time of routine second trimester ultrasound in

controls which provided exposure information as early as 4 weeks gestational age (Omega Laboratory, Ohio). These measures, however, would not accurately detect exposure before or during the earliest stages of organogenesis, if this were the etiologically relevant window of exposure. We did not find an increased frequency of illicit drug use among our gastroschisis mothers, and in fact the opposite was true in comparison to controls. It is possible that there are other vasoactive substances of abuse being used that were not detected by the method of hair analysis used in this study.

A low BMI has been reported as a risk factor for gastroschisis by other investigators, which we did not confirm in our study population [18]. We did, however, observe an increased odds ratio for low BMI and an odds ratio for high BMI that was in the direction of a protective effect against gastroschisis, although the point estimates lacked precision. A study within the National Birth Defects Study population also reported a protective association for BMI>30 kg/m^2 [OR 0.2(95% CI 0.1–0.3)] but did not observe a positive association with low BMI [19].

Animal studies have shown that exposure of mice to a low protein, low zinc diet in combination with carbon monoxide exposure, to mimic tobacco, resulted in a 47% increased risk of gastroschisis [20]. An age-matched case control study investigated this combination in human pregnancies by assessing low BMI (<22kg/m^2), low dietary protein intake (<72 grams), low dietary zinc intake (<10 mg) and high carbon monoxide (CO) exposure (smoking >1 pack of cigarettes per day or daily Marijuana), and found positive associations with gastroschisis for each on univariate analysis [9]. When examining multiplicative interactions, the authors reported a joint effect for low BMI and high CO exposure (OR 26.5, 95% CI 7.85–89.4) when compared to mothers with normal to high BMI who were not smokers. This combined effect exceeded the independent effects of low BMI (OR 19.7, 95% CI 4.3–89.6) or high CO exposure (OR 16.8, 95% CI 2.5–113.4) but the point estimates were imprecise [9]. A joint effect of low zinc and high CO on gastroschisis was also observed (OR 1.9 (95% CI 1.6–2.2) when compared to non-smoking mothers without low zinc intake, but the magnitude did not exceed the independent effects of the two exposures. This study was limited by its design, with information on exposures 3 months prior to the index pregnancy obtained by questionnaire completed 3–6 months after delivery. Our extensive nutritional biomarker assessment did not confirm such associations between zinc and gastroschisis. In our study, given only 1 case and 1 control were both underweight (BMI≤ 19) and smokers before or during the first three months of pregnancy, we did not have a sufficient sample size to adequately explore this or other interactions.

We identified a positive association with alcohol use reported one month prior to pregnancy or during the first trimester. Our findings are supported by the identified association of periconceptual use of alcohol with gastroschisis in the National Birth Defects Prevention Study (OR 1.40; CI 1.17–1.67) [21]. Despite our efforts to incorporate objective quantitative measures for exposure assessment, hair analysis for alcohol was unfortunately not available at time of this study to confirm the association with self-reported exposure. Despite lack of quantitative verification of the periconceptual alcohol exposure, this finding if confirmed may provide a link in the chain of explanation for the increasing prevalence of gastroschisis.

Several theories of gastroschisis pathogenesis have been proposed, including the defect resulting from some type of vascular disruption or instead due to an innate abnormal anterior abdominal wall closure. A mouse model has linked thrombosis and abdominal wall defects with higher estrogen exposure in the first trimester [22]. Alcohol is known to increase estrogen levels in perimenopausal women, and those who are young and primiparous have higher first trimester estrogen levels [23,24]. In contrast, those with high BMI have lower estrogen levels. These findings align with an etiologic hypothesis proposed that would involve early estrogen thrombophilia, racial differences in thrombosis, and byproducts of thrombosis interfering with signaling in early development [25]. Rather than gastroschisis resulting from a vascular disruption due to some type of vasoconstrictive insult, an alternative theory would support it results from a negative impact of a teratogen on mesencyhmal cell progression for completion of the body wall [26]. An epigenetic role of preconceptual alcohol exposure in fetal alcohol syndrome has been proposed [27]. Although beyond the scope of our study, given the varied epidemiology of gastroschisis and it being determined by the 4^{th} week post fertilization, exploration of such in the etiology of gastroschisis is encouraged in future studies.

In a recent survey of 5628 nulliparous pregnant patients, 34% reported binge alcohol consumption during the 3 months before pregnancy with 23% of these binging during the first 15 weeks of pregnancy and over 60% reporting some drinking pre or post conceptually for the pregnancy duration [28]. This study also relied on self-reported measures of alcohol intake, but given the potential for underreporting of alcohol and tobacco, does support the importance of preconception education and health [23]. The American College of Obstetrics and Gynecology continues to advise against any alcohol use in pregnancy citing the potential for anomalies and for neurocognitive effects, and the Healthy People 2020 objectives include increasing alcohol abstinence pre and post conceptually up to 98% [29,30].

We showed discouraging evidence that, regardless of age, women in our clinic population lacked knowledge of risks of an unhealthy lifestyle pre or periconceptually. With 73% of the pregnancies unplanned and approximately half the study population on oral contraceptives at conception, one can also surmise lack of appropriate understanding on the importance of medication adherence.

Strengths of our study include the use of objective measures of nutritional and illicit drug exposures. Weaknesses of our study include small sample size characteristic of a pilot study and the potential for recall bias when assessing self-reported alcohol, tobacco and illicit drug use. Alcohol use was asked only by a yes or no response and not quantified in amount, duration or frequency. It is also possible that the controls do not accurately represent the exposure distribution in the source population if factors influencing referral were related to the exposure. This may have introduced selection bias. The small size of our study sample limited the precision of our measures of association and reduced statistical power, which may have resulted in a higher probability of false-negative conclusions. The small sample size also limited our ability to evaluate adjustment for additional covariates in the multivariable models. Given the sample size achieved for these pilot data, conclusions drawn from our study are best qualified as hypothesis generating observations. Furthermore, some exposures were ascertained by recollection, which is subject to recall bias. Although we

utilized quantitative biomarkers for nutritional exposures and illicit drug use, no quantitative means of assessing periconceptual exposure to tobacco and alcohol were available. Additionally, given the timing of these biomarkers were based on sonographic diagnosis; they do not capture early exposures occurring before pregnancy or within in the first four weeks of development. There has also been recent evidence for an association of gastroschisis occurrence with sexually transmitted diseases, and urinary tract infections published, but unfortunately we did not inquire on number of sexual partners, sexually transmitted diseases, or urinary tract infection in our study [31]. All may reflect risky behaviors that most certainly may be augmented by uninhibited behavior with alcohol, and therefore should be evaluated in future study.

The dramatic upswing of prevalence internationally, without limitation by race/ethnicity, age, educational or financial means demonstrates that gastroschisis has global negative public health implications. Exposure assessment in studies of rare congenital anomalies such as gastroschisis have been limited by the difficulty of obtaining appropriately timed specimen collection for biomarker analyses when outcomes are typically not identified until the second trimester or later in gestation. With improvement in first trimester anatomy evaluation and diagnosis of gastroschisis and the more recent availability of hair analysis for alcohol exposure assessment, there is an opportunity to proceed with future studies using quantitative exposure biomarkers for perinatal alcohol exposure. Our findings suggest that further investigation of vasoactive stimulants such as alcohol is warranted in the search to identify risk factors for gastroschisis.

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Table 1.

Periconceptional Characteristics of Gastroschisis Cases and Matched Controls.

Characteristic	Case (n=30) n (%)	Control (n=76) n (%)	p
Parity			
Nulliparous	18 (60.0)	28 (36.8)	0.11
Parous	12 (40.0)	48 (63.2)	
Education			
<12 years	8 (26.7)	22 (29.0)	0.95
12 years	13 (43.3)	26 (34.2)	
>12 years	9 (30.0)	28 (36.8)	
Insurance			
Private	8 (26.7)	13 (17.1)	0.10
Medicaid/No Insurance	22 (73.3)	62 (81.6)	
Missing	0 (0.0)	1 (1.3)	
Conception BMI (kg/m^2)			
≤ 19	3 (10.0)	3 (4.0)	0.16
>19–24	12 (40.0)	32 (42.1)	
25–29	11 (36.7)	17 (22.4)	
≥30	4 (13.3)	24 (31.6)	
1^{st} Trimester Bleeding			
Yes	4 (13.3)	10 (13.2)	0.80
No	26 (86.7)	66 (86.8)	
Prenatal Vitamin Use			
Prior to conception	2 (6.7)	9 (11.8)	0.27
After positive pregnancy test	12 (40.0)	29 (38.2)	
After 6 weeks of gestation	15 (50.0)	26 (34.2)	
None	1 (3.3)	11 (14.5)	
Missing	0 (0.0)	1 (1.3)	
Planned Pregnancy			
Yes	8 (26.7)	20 (26.3)	0.99

Characteristic	Case (n=30) n (%)	Control (n=76) n (%)	p
No	22 (73.3)	55 (72.4)	
Missing	0 (0.0)	1 (1.3)	

[a]Cochran-Mantel-Haenszel test for association

Table 2.

Comparison of Nutritional Biomarkers in Gastroschisis Cases and Matched Controls

Exposure	Cases (n=30) n (%)	Controls (n=76) n (%)	Unadjusted OR[a] (95% CI)	Adjusted OR[b] (95% CI)
Hemoglobin<11(g/dL)				
<11	5 (17.9)	9 (11.8)	1.63 (0.39–6.23)	1.79 (0.37–8.70)
≥11	23 (82.1)	65 (87.8)	Referent	Referent
Missing	2 (6.7)	2 (2.6)		
Iron (mcg/dL)				
<65	13 (43.3)	26 (34.2)	1.40 (0.55–3.58)	1.44 (0.54–3.91)
≥65	17 (56.7)	50 (65.8)	Referent	Referent
Ferritin (mcg/L)				
<13	9 (30.0)	27 (35.5)	0.69 (0.23–1.88)	0.78 (0.24–2.38)
≥13	21 (70.0)	49 (64.5)	Referent	Referent
Folate (ng/mL)				
<3.6	0 (0.0)	0 (0.0)		*c*
≥3.6	30 (100)	76 (100)	*c*	
Vitamin B6 (mcg/L)				
<5	2 (6.7)	6 (7.9)	0.81 (0.07–5.53)	1.81 (0.11–22.32)
≥5	24 (80.0)	60 (79.0)	Referent	Referent
Missing	4 (13.3)	10 (13.2)		
Vitamin B12 (ng/L)				
<200	3 (10.0)	6 (7.9)	1.32 (0.19–7.13)	1.24 (0.17–8.40)
≥200	27 (90.0)	70 (92.1)	Referent	Referent
Homocysteine (mcmol/L)				
<4	0 (0.0)	0 (0.0)	*c*	*c*
≥4	30 (100.0)	76 (100.0)		
Zinc (mcg/mL)				
<0.60	0 (0.0)	1 (1.3)	*c*	*c*
≥0.60	30 (100.0)	72 (94.7)		
Missing	0 (0.0)	3 (4.0)		

[a] Conditional logistic regression used to estimate odds ratios (OR) and exact 95% confidence intervals

[b] Adjusted for insurance (Medicaid/No Insurance vs. Private), education (greater than high school vs. high school or less), low body mass index (≤ 19 vs. >19), and nulliparity (0 vs. ≥ 1 live births)

[c] Not calculable

Table 3.

Comparison of Substance Use Exposures in Gastroschisis Cases and Matched Controls.

Exposure	Case (n=30) n (%)	Control (n=76) n (%)	Unadjusted OR[a] (95% CI)[*]	Adjusted OR[a,b] (95% CI)
First Trimester Tobacco Use				
Yes	12 (40.0)	21 (27.6)	1.45 (0.54–5.91)	1.98 (0.64–6.49)
No	18 (60.0)	54 (71.1)	Referent	Referent
Missing	0 (0.0)	1 (1.3)		
Tobacco Use History				
Current	3 (10.0)	16 (21.1)	0.56 (0.10–2.29)	1.04 (0.15–5.50)
Former	11 (36.7)	15 (19.7)	1.76 (0.56–5.72)	3.30 (0.81–15.13)
None	15 (50.0)	45 (59.2)	Referent	Referent
Missing	1 (3.3)	0 (0.0)		
Alcohol				
Yes	11 (36.7)	14 (18.4)	2.63 (0.86–8.57)	3.19 (1.01–11.61)
No	19 (63.3)	62 (81.6)	Referent	Referent
Reported Illicit Drug Use				
Marijuana				
Yes	7 (23.3)	21 (27.6)	0.60 (0.16–1.89)	0.60 (0.14–2.18)
No	23 (76.7)	54 (71.1)	Referent	Referent
Missing	0 (0.0)	1 (1.3)		
Methamphetamine				
Yes	2 (6.7)	3 (4.0)	1.92 (0.13–28.26)	2.95 (0.18–50.79)
No	28 (93.3)	73 (96.1)	Referent	Referent
Cocaine				
Yes	1 (3.3)	3 (4.0)	0.77 (0.01–10.5)	1.60 (0.02–34.62)
No	29 (96.7)	73 (96.1)	Referent	Referent
Heroin				
Yes	0 (0.0)	2 (2.6)	*c*	*c*
No	30 (100.0)	74 (97.4)		
Hair Test for Illicit Drug Use				
Yes	1 (3.3)	10 (13.2)	0.24 (0.01–1.83)	0.27 (0.01–2.27)
No	29 (96.7)	62 (81.6)	Referent	Referent
Missing	0 (0.0)	4 (5.3)		
Reported Prescription Medication				
Narcotics				
Yes	13 (43.3)	17 (56.7)	0.83 (0.34–2.00)	1.06 (0.37–3.06)
No	17 (56.7)	38 (50.0)	Referent	Referent
Missing	0 (0.0)	1 (1.3)		
Xanax				
Yes	7 (23.3)	16 (21.1)	1.24 (0.39–3.65)	1.24 (0.34–4.13)
No	23 (76.7)	60 (79.0)	Referent	Referent

Exposure	Case (n=30) n (%)	Control (n=76) n (%)	Unadjusted OR[a] (95% CI)*	Adjusted OR[a,b] (95% CI)
Oral Contraceptive Pills				
Yes	12 (40.0)	37 (48.7)	0.70 (0.26–1.87)	0.83 (0.29–2.35)
No	18 (60.0)	36 (47.4)		Referent
Missing	0 (0.0)	3 (4.0)		
Over the Counter (OTC) Medication				
Any OTC Use				
Yes	23 (76.7)	60 (79.0)	0.82 (0.29–2.53)	1.02 (0.34–3.39)
No	7 (23.3)	14 (18.4)	Referent	Referent
Missing	0 (0.0)	2 (2.6)		
Aspirin				
Yes	1 (3.3)	5 (6.6)	0.47 (0.01–5.37)	0.63 (0.01–6.84)
No	29 (96.7)	69 (90.8)	Referent	Referent
Missing	0 (0.0)	2 (2.6)		
Tylenol				
Yes	18 (60.0)	54 (71.1)	0.70 (0.27–1.89)	0.68 (0.25–1.94)
No	11 (36.7)	22 (29.0)	Referent	Referent
Missing	1 (3.3)	0 (0.0)		
Ibuprofen				
Yes	6 (20.0)	12 (15.8)	1.32 (0.39–3.99)	1.25 (0.36–3.91)
No	24 (80.0)	64 (84.2)	Referent	Referent
Sudafed				
Yes	3 (10.0)	7 (9.2)	1.01 (0.15–5.45)	1.03 (0.15–5.82)
No	27 (90.0)	69 (90.8)	Referent	Referent
Benadryl				
Yes	3 (10.0)	11 (14.5)	0.65 (0.11–2.82)	0 61 (0 10–2 81)
No	27 (90.0)	65 (85.5)	Referent	Referent

[a] Conditional logistic regression used to estimate odds ratios (OR) and exact 95% confidence intervals

[b] Adjusted for insurance (Medicaid/No Insurance vs. Private), education (greater than high school vs. high school or less), low body mass index (≤ 19 vs. >19), and nulliparity (0 vs. ≥ 1 live births)

[c] Not calculable