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Is There Epidemiologic Evidence to Support Vascular Disruption as a Pathogenesis of Gastroschisis?

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Abstract

Gastroschisis is a congenital defect of the abdominal wall that occurs most commonly in the offspring of young women. The defect is often hypothesized to result from vascular disruption in the early embryo. We measured the associations between maternal vasoactive exposures in pregnancy, as possible markers of vascular disruption, and gastroschisis risk, using data collected as part of the National Birth Defects Prevention Study. Study participants included mothers of births from 10/1997 to 12/2003 in ten states. The mothers of 514 gastroschisis cases were matched by age at delivery and state to 3,277 non-malformed controls and compared for periconceptional smoking and use of vasoconstrictors, non-steroidal anti-inflammatory drugs (NSAIDs), and vasodilators. Multivariable-adjusted odds ratios (OR) and 95% confidence intervals (CI) were estimated from conditional logistic regression. Case mothers were more likely than control mothers to smoke (OR=1.5, 95% CI=1.2-1.9) and report use of non-aspirin NSAIDs (1.4, 1.1-1.7) and anti-hypertensive vasodilators (2.6, 0.9-8.0), but not vasoconstrictive decongestants (1.0, 0.7-1.4). Cigarette smoking had little effect on gastroschisis risk in mothers less than 25 years of age, but the OR was 3.0 (1.8-5.0) for those ≥ 25 years. Likewise, ORs were greatest in the older women for use of non-aspirin NSAIDs (1.6, 1.0-2.6) and bronchodilators (3.0, 1.8-5.0). These findings suggest that, overall, vasoactive risk factors play a minor role in the etiology of gastroschisis, and do not support the vascular disruption hypothesis. However, the observation that increased ORs for some vasoactive exposures were confined to older women raises the question of whether inherent maternal factors might influence risk.

Keywords

gastroschisis; pregnancy; medications; smoking

INTRODUCTION

Gastroschisis is a congenital defect of the ventral body wall, resulting in protrusion of the intestines outside the abdominal cavity. The umbilical ring and/or abdominal wall are hypothesized to be compromised by vascular disruption of the omphalomesenteric artery, resulting in herniation of the bowel outside the abdomen [Hoyme et al., 1981]. Evidence in support of this hypothesis comes from both human embryology and clinical observations. Normal re-routing of the blood supply in the area of the developing abdominal wall results

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in an asymmetry, as the left omphalomesenteric artery undergoes apoptosis and the right side is retained [deVries, 1980; Hoyme et al., 1981]. Paired with this observation of normal development is the fact that gastroschisis occurrence is also asymmetric - almost always to the right of the umbilicus. Hoyme hypothesized that the asymmetric blood supply around the umbilical ring creates an area that is more vulnerable to vascular disruption [Hoyme et al., 1981]. Additional evidence in support of vascular disruption includes the coincidence of gastroschisis and other purported vascular disruption defects [Hoyme et al., 1983; Kilic et al., 2001; Komuro et al., 2003; Reid et al., 1986; Robertson et al., 1992] and reports of gastroschisis in the offspring of women who used cocaine, a powerful vasoconstrictor [Hume et al., 1994; Lynberg et al., 1992]. Hoyme's hypothesis has been disputed [Feldkamp et al., 2007] and alternative pathogeneses of gastroschisis have been proposed, which include defects of differentiation, folding and/or fusion in the early embryo [Feldkamp et al., 2007] and failure of the normally-herniating gut to return to the abdomen [Shaw, 1975].

However, because normal and abnormal development of the abdominal wall is not completely delineated, due in large part to limited experimental models [Feldkamp et al., 2007], it remains unclear how gastroschisis develops. One genetic survey has identified polymorphisms associated with gastroschisis [Torfs et al., 2006], but any roles those genes may have in development are, as yet, undiscovered. In the meantime, can epidemiologic observations inform this literature?

Epidemiologic studies have employed both hypothesis-generating [Drongowski et al., 1991; Goldbaum et al., 1990; Haddow et al., 1993; Torfs et al., 1994; Werler et al., 1992a] and hypothesis-testing {[Haddow et al., 1993; Martinez-Frias et al., 1997; Torfs et al., 1996; Werler et al., 2002] approaches with regard to gastroschisis pathogenesis. For example, an earlier 'fishing expedition' of maternal demographic, reproductive, and behavioral factors in relation to gastroschisis reported an increased risk associated with pseudoephedrine use, generating the hypothesis that the vasoconstrictive effects of this drug might disrupt fetal blood flow during development and cause gastroschisis [Werler et al., 1992a]. Subsequently, epidemiologic studies have been launched to test this vascular disruption hypothesis, focusing on maternal exposure to vasoactive agents such as cigarette smoking and vasoactive medications [Martinez-Frias et al., 1997; Werler et al., 2002]. In this paper, we first apply the hypothesis-testing approach, using data collected in the National Birth Defects Prevention Study (NBDPS) on cigarette smoking and vasoactive medication use. Secondly, we consider maternal age as an effect modifier to generate hypotheses about the pathogenesis of gastroschisis.

MATERIALS AND METHODS

The NBDPS is a population-based case-control study of birth defects, which involves mothers and their offspring from ten states. In each of the states, birth defect registries identify infants with selected major structural malformations and a random sample of live born infants without major defects as a control group. The years of births that were included in NBDPS varied by state: California, Iowa, Georgia, Massachusetts, and Texas (October 1997-December 2003); Arkansas (January 1998 - December 2003); New Jersey (January 1998 - mid-2002); New York (October 1997 - mid-2002 and 2003); and North Carolina and Utah (2003). Mothers of case- and control-infants who consent to participate in the study are interviewed by telephone within 24 months after their estimated date of delivery about pregnancy events and exposures, demographic factors, and reproductive history. The institutional review boards at the Centers for Disease Control and Prevention and each state approved the study protocol. Additional details on NBDPS study methods have previously been reported [Yoon et al., 2001].

Outcome

The case group comprised study subjects with the diagnosis of gastroschisis either as an isolated anomaly or as a part of multiple congenital anomalies. Diagnoses abstracted from medical records were reviewed by a clinical geneticist (CAM). Infants with gastroschisis who had a recognized chromosomal anomaly or a single-gene disorder were not eligible for inclusion in NBDPS. In addition, only English- and Spanish-speaking mothers were eligible. Infants who had abdominal wall disruption and phenotypes consistent with either amniotic band sequence or limb-body-wall-disruption sequence were excluded from these analyses. Control subjects were infants without a known structural defect, born during the same time period and same geographic study sites as cases. Because young maternal age is strongly associated with gastroschisis and the proportion of gastroschisis cases to controls varied across states, controls were matched to cases by mother's year of age at delivery and state. There were no cases without controls and the average was 7.3 controls per case. Thirty-six percent of the original pool of controls was excluded because there was no gastroschisis case of the same age from the same center. The median times to interview were 9.5 months for mothers of case-infants and 8.8 months for mothers of control-infants.

Exposures

The time frame of interest is two weeks before through 14 weeks after the last menstrual period, which we call the periconceptional period. Cigarette smoking was classified as any smoking during that time period. For level of cigarette smoking, we used categories of the average number of cigarettes smoked per day. For the 37% of smokers who changed the amount or quit smoking during this period, we used the largest reported number of cigarettes smoked per day during the period. For medication use, we identified over 275 products that were considered to have possible vasoactivity, including decongestants, anti-migraine triptans, non-steroidal anti-inflammatory drugs (NSAIDs), aspirin, anti-hypertensives, and bronchodilators. Exposure included any use during the periconceptional period, as defined above. Frequency of use was based on the reported number of pills (doses) per day, week, or month. "As needed" use was recorded when a woman reported use that couldn't be averaged into a number of pills per day, week or month, e.g., 'daily during some weeks but only one pill during other weeks' or 'whenever I had a headache or pain'. Number of days of use was calculated from duration and frequency of use. For example, use 3 times per week for 60 days = $3/7 \times 60 = 25.7$ days. For folic acid supplementation, exposure included use reported during the period from 14 through 44 days after the last menstrual period, which we call pregnancy month 1.

Statistical analyses

Frequency distributions of maternal factors, cigarette smoking, and vasoactive medications were tabulated for cases and controls. Multivariable-adjusted odds ratios for cigarette smoking and vasoactive medication use were estimated from conditional logistic regression models, stratified by mother's year of age at delivery and study center, with terms for race/ethnicity (non-Hispanic African American, Hispanic, other versus White non-Hispanic), pre-pregnancy body mass index (<18.5 , 25.0 - 29.9 , ≥ 30.0 kg/m², unknown versus 18.5 - 24.9 kg/m²), education (<12 , 12, 13-15 years, unknown versus ≥ 16 years), parity (nulliparous, missing versus parous), binge alcohol use in the periconceptional period (≥ 5 drinks on any occasion versus else), oral contraceptive use in the periconceptional period, and folic acid supplementation in pregnancy month 1 (exposed, unknown versus none). The mothers of three controls reported unknown oral contraceptive use and were grouped with the unexposed. Multivariable-adjusted odds ratios were also estimated within age categories for smoking and use of the more common vasoactive medications.

RESULTS

Study subjects included 514 mothers of offspring with gastroschisis (cases) and 3,277 mothers of offspring with no known birth defect (controls). The distributions of demographic and behavioral factors are shown for both cases and controls in Table I. Forty percent of cases were born to mothers who were less than 20 years of age. Even though controls were matched by age to cases, control mothers were older than case mothers due to increasing control-to-case ratios with increasing age (from 2.6 for ≤ 17 year olds to 19.6 for ≥ 30 year olds). California contributed the largest number of cases, with the lowest ratio of controls to cases (4.5). Due to the later start up, Utah and North Carolina represent only one year of case and control births. Gastroschisis cases were less likely to be born to mothers who are African American, obese, college-educated (due in part to younger ages), and folic acid users in pregnancy month 1. Compared to controls, almost twice as many case mothers reported binge drinking or use of oral contraceptives in the periconceptional period.

Table II presents distributions of smoking and vasoactive medication use in the periconceptional period for cases and controls, and adjusted odds ratios and 95% confidence intervals. Any cigarette smoking increased the risk of gastroschisis 1.5-fold, but a clear dose-effect relationship was not observed. Decongestant use was reported by similar proportions of case and control mothers and the odds ratio was 1.0. Likewise, use of bronchodilators was not associated with gastroschisis risk. An odds ratio of 1.4 was observed for use of NSAIDs. Although the crude odds ratio for aspirin use was 1.5 (data not shown), adjustment for state and maternal age reduced the estimate to 1.1. Use of anti-hypertensive medication was reported by slightly more case than control mothers, but confounding occurred, resulting in a 2.6-fold increased risk that was not statistically significant. With only 5 cases exposed to anti-hypertensive medications and 1 case exposed to triptans, further analyses were not explored. NSAIDs, decongestants, aspirin, and bronchodilators were taken by enough study women to allow analyses of levels of intake, including the number of pills taken per day and the number of days of use (Table III). No clear patterns were observed for increasing gastroschisis risk with increasing number of pills per day or number of days of use across any of the four medication groups.

Because young maternal age is so strongly associated with gastroschisis occurrence, odds ratios for smoking and use of NSAIDs, decongestants, aspirin, and bronchodilators were estimated within age categories. Table IV shows that cigarette smoking was not associated with risk of gastroschisis in the youngest mothers, but was associated with a 3-fold increased risk in mothers ≥ 25 . Odds ratios for 25-29 and ≥ 30 year olds were 2.7 (1.4-5.0) and 4.3 (1.7-11.1), respectively. This trend of increasing smoking effects across age groups was statistically significant ($p < .001$). A similar pattern was observed for bronchodilator use, with a 3.7-fold increased risk in ≥ 25 year olds. For NSAIDs, the odds ratio estimate was greatest (1.6) in this older group, but was also elevated (1.4) in the youngest mothers; the lower bound of both estimates was 1.0.

Because of concerns about potential misclassification due to recall, we also stratified the analyses by the time to interview. However, these analyses did not explain the observed results (data not shown).

DISCUSSION

In this analysis of over 500 cases with gastroschisis, we sought to determine whether there is support for a vascular disruption pathogenesis by evaluating exposures to vasoactive agents. Our overall findings are mixed: slight to moderate increased risks were observed for cigarette smoking and use of anti-hypertensives and NSAIDs, but neither use of

decongestants nor bronchodilators was associated with gastroschisis risk. When levels of exposures were considered, risks were not highest for those more heavily exposed to cigarettes or any of the vasoactive medications. These findings suggest that, overall, vasoactive risk factors play a minor role in the etiology of gastroschisis, and do not provide additional support for the vascular disruption hypothesis.

However, the observed pattern of risks for vasoactive exposures in older versus younger mothers is more intriguing in terms of the pathogenesis of gastroschisis. Despite the comparatively larger risk of gastroschisis and greater prevalence of smoking in younger women, cigarette smoking had no effect on risk in women under 20; on the other hand, it increased the risk in older women, ranging from 1.3-fold in 20 to 24 year olds to 4.3-fold in ≥ 30 year olds. A similar modifying effect of age on the association between cigarette smoking and gastroschisis risk was observed in recent study in Utah [Feldkamp et al., 2008a]. Such effect modification might be consistent with a vascular disruption hypothesis, but in the mother, rather than the fetus. Specifically, longer duration of smoking (assuming older smokers have smoked for more years) might contribute to uterine vascular damage, as has been observed in experimental models [Suzuki et al., 1980], and maternal vascular damage might in turn lead to the development of gastroschisis. Elevated risks in older women were also associated with use of NSAIDs (borderline significance) and bronchodilators, raising the possibility that chronic use of some vasoactive medications, or chronic conditions for which they are taken, might cause vascular damage similar to that hypothesized for cigarette smoking.

Proposed explanations for the higher prevalence of gastroschisis in younger women have focused on exposures that are more common in that group, such as cigarette smoking, illicit drug use, and genitourinary infections. While each of these exposures has been linked to gastroschisis [Draper et al., 2008; Feldkamp et al., 2008a; Feldkamp et al., 2008b; Goldbaum et al., 1990; Haddow et al., 1993; Morrison et al., 2005; Torfs et al., 1994], the magnitude of the associations are not strong enough to explain the more than 10-fold greater risk in teenage women compared to those aged 30 years or more. Our findings of increased gastroschisis risks associated with cigarette smoking and vasoactive medication use in older, but not younger, women does not help unravel the enigma as to why gastroschisis occurs most commonly in young women. Is there an underlying (endogenous) factor in young women that is responsible for their greater risk of gastroschisis, which at the same time offers these younger women protection from exogenous risk factors? One possible endogenous factor is uterine vasculature (vessels or blood flow), which affects placental sufficiency. Previously, gastroschisis and other birth defects have been hypothesized to arise from vascular disruption of fetal vessels, but vascular disruption of maternal vessels might play a role. Could very young mothers have immature uterine vasculature and older mothers who are exposed to chronic vasoactive agents have damaged uterine vasculature, each of which is associated with increased gastroschisis risk? Parity might serve as a marker of immature uterine vasculature, but the age-independent effect of nulliparity on gastroschisis risk was only 1.3 in this study, similar to what others have reported [Byron-Scott et al., 1998; Goldbaum et al., 1990; Werler et al., 1992b]. Thus, nulliparity alone is unlikely to explain the inverse association with age.

Findings from this current analysis are generally consistent with earlier reports for cigarette smoking [Feldkamp et al., 2008b; Goldbaum et al., 1990; Haddow et al., 1993; Torfs et al., 1994; Werler et al., 1992b], and non-steroidal inflammatory medications [Torfs et al., 1996; Werler et al., 1992a]. However, no overall association was observed, in the present study, for aspirin or decongestant use, contrary to earlier reports [Drongowski et al., 1991; Martinez-Frias et al., 1997; Torfs et al., 1996; Werler et al., 1992a; Werler et al., 2002]. These discrepancies are difficult to reconcile because methodological issues, such as

reporting error due to longer intervals between birth and interview and differences in data collection methods, should apply equally to all drugs within a given study. All studies of medication use and gastroschisis have involved retrospective data collection, with a range of 1 to 60 months between the interview and date of delivery. Assuming that recall accuracy decreases as this interval increases, the present findings might be more vulnerable to recall error because interviews were conducted up to 24 months after date of delivery. However, positive associations were reported for aspirin use from studies with both longer [Drongowski et al., 1991] and shorter intervals [Martinez-Frias et al., 1997; Torfs et al., 1996; Werler et al., 1992a; Werler et al., 2002]. Another explanation for the equivocal findings for decongestant and aspirin use might be misclassification of type of medication. There is a vast array of analgesic and cold products that varies according to the number and types of agents; recall of exact product names can be difficult, but information on specific products is sometimes necessary to determine exposure. For example, because the Tylenol brand of products contains acetaminophen alone or in combination with decongestants or other active ingredients, a report of 'Tylenol' might miss important exposures. Recall of the timing of medication use is likely misclassified, particularly for decongestants and analgesics, which are typically taken intermittently. If misclassification of reported timing of use is similar for cases and controls, it could also explain the equivocal findings.

In addition, cigarette smoking and use of the medications studied herein have been shown to be vasoactive in adults, but their vasoactivity in uterine or fetal vessels in early gestation has not been established. Observed associations of these exposures in association with gastroschisis risk could reflect other, non-vascular, pathogenetic processes.

Our analysis was limited by the small number of exposed subjects for some comparisons, especially within age strata. We controlled for many different demographic, reproductive, and medical factors, but there is a possibility of confounding by unidentified factors. For medication use, confounding by the underlying condition for which the medication was taken is a concern, and was not considered in this analysis. One possibility is asthma, for which both vasoconstricting and anti-inflammatory medication use were previously shown to increase the risk of gastroschisis in the NBDPS, using data through 2002 [Lin et al., 2008]. With the addition of 2003 births, as presented in this study, we found that use of bronchodilators decreased in cases and increased in controls, reducing the overall odds ratio towards 1.0. Nevertheless, the observed elevated odds ratios for NSAID and bronchodilator use in older mothers may represent underlying associations with conditions of chronic inflammation, which has been suggested as a cause of gastroschisis [Feldkamp et al., 2008b]. If inflammation is in the causal pathway for gastroschisis, it could explain the elevated risks associated with smoking, genitourinary infection [Feldkamp et al., 2008b], and use of amphetamines [Draper et al., 2008], each of which has been associated with markers of inflammation or immune response [Connor, 2004; Leitich, 2005; Yanbaeva et al., 2007].

In conclusion, this is the largest study of gastroschisis and vasoactive exposures to date, allowing age-specific analyses that raise new questions about pathogenesis. Findings suggest that the increased risk of gastroschisis in very young women is not due to vasoactive exposures. The observation that some vasoactive exposures increased risks only in older mothers raises the hypothesis that cumulative exposure over childbearing years might result in uterine vascular damage and adversely affect fetal development of the abdominal wall.

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Table 1

Maternal demographic and behavioral factors among infants with gastroschisis (cases) and infants with no major birth defects (controls), National Birth Defects Prevention Study, 1997-2003

Maternal factor	Cases N=514		Controls N=3,277*	
	#	%	#	%
Age (years)				
≤17	75	(14.6)	196	(6.0)
18-19	131	(25.5)	354	(10.8)
20-24	203	(39.5)	1094	(33.4)
25-29	66	(12.8)	866	(26.4)
≤30	39	(7.6)	767	(23.4)
Center				
Arkansas	67	(13.0)	410	(12.5)
California	120	(23.3)	542	(16.5)
Georgia	47	(9.1)	409	(12.5)
Iowa	56	(10.9)	381	(11.6)
Massachusetts	48	(9.3)	382	(11.7)
New Jersey	47	(9.1)	329	(10.0)
New York	28	(5.4)	238	(7.3)
North Carolina/Utah	24	(4.7)	98	(3.0)
Texas	77	(15.0)	488	(14.9)
Race/ethnicity				
Non-Hispanic White	270	(52.5)	1783	(54.4)
Non-Hispanic African American	43	(8.4)	427	(13.0)
Hispanic	161	(31.3)	894	(27.3)
Asian/Pacific Islander	16	(3.1)	83	(2.5)
Native American/Alaskan Native	5	(1.0)	13	(0.4)
Other	18	(3.5)	71	(2.2)
Missing	1	(0.2)	6	(0.2)
Body Mass Index (kg/m ²)				
Underweight < 18.5	51	(9.9)	223	(6.8)
Normal weight (18.5-24.9)	348	(67.7)	1732	(52.9)
Overweight (25-29.9)	80	(15.6)	683	(20.8)
Obese ≤ 30	23	(4.5)	470	(14.3)
Missing	12	(2.3)	169	(5.2)
Education (years)				
<12	160	(31.1)	696	(21.2)
12	195	(37.9)	950	(29.0)
13-15	118	(23.0)	884	(27.0)
≤16	32	(6.2)	719	(21.9)
Missing	9	(1.8)	28	(0.9)
Periconception alcohol use				

Maternal factor	Cases N=514		Controls N=3,277*	
	#	%	#	%
≤ 5 drinks on any occasion	89	(17.3)	314	(9.6)
< 5 drinks on any occasion	118	(23.0)	849	(25.9)
None	299	(58.2)	2081	(63.5)
Missing	8	(1.6)	33	(1.0)
Periconception oral contraceptive use				
Yes	40	(7.8)	149	(4.5)
No	474	(92.2)	3125	(95.4)
Missing	0		3	(<0.1)
Folic acid supplementation in pregnancy month 1				
Yes	191	(37.2)	1461	(44.6)
No	308	(59.9)	1746	(53.3)
Missing	15	(2.9)	70	(2.1)

* Controls are matched to cases by maternal age at delivery and state of residence.

Table II

Cigarette smoking and vasoactive medication use among mothers of infants with gastroschisis (cases) and mothers of infants with no major birth defects (controls), National Birth Defects Prevention Study, 1997-2003

Periconception exposure	Cases N=514		Controls N=3277		OR	(95% CI)*
	#	%	#	%		
Cigarette smoking						
Any	186	36.2	725	22.1	1.5	1.2-1.9
≤1 /day	10	1.9	31	0.9	1.8	0.8-3.9
2-14 /day	105	20.4	419	12.8	1.3	1.0-1.7
15-24 /day	45	8.7	190	2.8	1.4	0.9-2.0
25+ / day	11	2.1	42	1.3	1.7	0.8-3.5
Medication						
NSAIDs	151	30.1	755	23.0	1.4	1.1-1.7
Decongestants	47	9.1	323	9.9	1.0	0.7-1.4
Aspirin	33	6.4	143	4.4	1.1	0.7-1.7
Bronchodilators	21	4.1	99	3.0	1.2	0.7-2.0
Anti-hypertensives	5	1.0	22	0.7	2.6	0.9-8.0
Anti-migraine triptans	1	0.1	8	0.2	--	---
Unknown vasoactive**	20	3.9	84	2.6	1.2	0.7-2.2

* Odds ratios and 95% confidence intervals, adjusted for maternal age at delivery and state of residence by stratification and for race/ethnicity, BMI, education, alcohol use, oral contraceptive use, folic acid supplementation.

** Includes women who reported use of unknown analgesic or cough/cold product, or whose timing of vasoactive medication was unknown.

Number of pills per day and number of days of use of vasoactive medications among mothers of infants with gastroschisis (cases) and mothers of infants with no major birth defects (controls), National Birth Defects Prevention Study, 1997-2003

Table III

		Cases N=514		Controls N=3277		
Periconception Use		#	%	#	%	OR(95%CI)*
NSAIDs						
Pills per day						
1-2		102	19.8	490	15.0	1.4 (1.1-1.8)
≥3		5	1.0	18	0.6	1.9 (0.6-5.6)
“As needed”		43	8.4	247	7.5	1.3 (0.9-2.0)
Duration						
1-31 days		95	18.5	476	14.5	1.3 (1.0-1.7)
≥32 days		52	10.1	262	8.0	1.5 (1.0-2.2)
Decongestants						
Pills per day						
1-2		34	6.6	215	6.6	1.0 (0.7-1.5)
≥3		9	1.8	78	2.4	0.8 (0.4-1.6)
“As needed”		3	0.6	25	0.8	1.9 (0.5-6.7)
Duration						
1-31 days		36	7.0	256	7.8	0.9 (0.6-1.4)
≥32 days		10	2.0	62	1.9	1.1 (0.5-2.2)
Aspirin						
Pills per day						
1-2		26	5.1	105	3.2	1.2 (0.7-2.0)
≥3		1	0.2	6	0.2	-
“As needed”		6	1.2	31	1.0	1.4 (0.5-3.7)
Duration						
1-31 days		25	4.9	93	2.8	1.2 (0.7-2.0)
≥32 days		8	1.6	50	1.5	1.1 (0.5-2.5)
Bronchodilators						
Pills per day						
1-2		11	2.1	61	1.9	1.1 (0.5-2.2)

Periconception Use	Cases N=514		Controls N=3277		OR(95%CI) [*]
	#	%	#	%	
≥3	4	0.8	16	0.5	1.6 (0.5-5.0)
“As needed”	6	1.2	22	0.7	1.2 (0.4-3.2)
Duration					
1-31 days	9	1.8	41	1.3	1.6 (0.7-3.7)
≥32 days	12	2.3	56	1.7	1.0 (0.5-2.0)

* Odds ratios and 95% confidence intervals, adjusted for maternal age at delivery and state of residence by stratification and for race/ethnicity, BMI, education, alcohol use, oral contraceptive use, folic acid supplementation.

Table IV

Cigarette smoking and vasoactive medication use by maternal age category among mothers of infants with gastroschisis (cases) and mothers of infants with no major birth defects (controls), National Birth Defects Prevention Study, 1997-2003

Periconception exposure	Cases		Controls		OR(95%CI) *
	#	%	#	%	
Age≤19					
Smoke	66	32.0	151	27.5	1.1 (0.7-1.7)
NSAIDs	63	30.6	125	22.7	1.4 (1.0-2.1)
Decongestants	16	7.8	35	6.4	1.0 (0.5-1.9)
Aspirin	17	8.3	28	5.1	1.3 (0.7-2.6)
Bronchodilator	7	3.4	18	3.3	0.7 (0.3-1.9)
Age 20-24					
Smoke	79	38.9	315	28.8	1.3 (0.9-1.9)
NSAIDs	50	24.6	235	21.5	1.2 (0.8-1.8)
Decongestants	16	7.9	103	9.4	0.8 (0.4-1.4)
Aspirin	12	5.9	51	4.7	1.1 (0.5-2.3)
Bronchodilator	6	3.0	42	3.8	0.8 (0.3-1.9)
Age 25 +					
Smoke	41	39.1	258	15.8	3.0 (1.8-5.0)
NSAIDs	37	35.2	395	24.2	1.6 (1.0-2.6)
Decongestants	15	14.3	185	11.3	1.2 (0.7-2.3)
Aspirin	4	3.8	64	3.9	0.9 (0.3-2.7)
Bronchodilator	8	7.6	39	2.4	3.7 (1.5-8.8)

* Odds ratios and 95% confidence intervals, adjusted for maternal age at delivery and state of residence by stratification and for race/ethnicity, BMI, education, alcohol use, oral contraceptive use, folic acid supplementation.