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Maternal Medication Use and Risks of Gastroschisis and Small Intestinal Atresia

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Gastroschisis and small intestinal atresia (SIA) are birth defects that are thought to arise from vascular disruption of fetal mesenteric vessels. Previous studies of gastroschisis have suggested that risk is increased for maternal use of vasoactive over-the-counter medications, including specific analgesics and decongestants. This retrospective study evaluated the relation between maternal use of cough/cold/analgesic medications and risks of gastroschisis and SIA. From 1995 to 1999, the mothers of 206 gastroschisis cases, 126 SIA cases, and 798 controls in the United States and Canada were interviewed about medication use and illnesses. Risks of gastroschisis were elevated for use of aspirin (odds ratio = 2.7, 95% confidence interval: 1.2, 5.9), pseudoephedrine (odds ratio = 1.8, 95% confidence interval: 1.0, 3.2), acetaminophen (odds ratio = 1.5, 95% confidence interval: 1.1, 2.2), and pseudoephedrine combined with acetaminophen (odds ratio = 4.2, 95% confidence interval: 1.9, 9.2). Risks of SIA were increased for any use of pseudoephedrine (odds ratio = 2.0, 95% confidence interval: 1.0, 4.0) and for use of pseudoephedrine in combination with acetaminophen (odds ratio = 3.0, 95% confidence interval: 1.1, 8.0). Reported fever, upper respiratory infection, and allergy were not associated with risks of either defect. These findings add more evidence that aspirin use in early pregnancy increases risk of gastroschisis. Although pseudoephedrine has previously been shown to increase gastroschisis risk, findings of this study raise questions about interactions between medications and possible confounding by underlying illness. *Am J Epidemiol* 2002;155:26–31.

gastroschisis; intestinal atresia, medicine; pregnancy

Gastroschisis and defects of the small intestine are clinically distinct congenital malformations, but it is thought that they share a common etiologic mechanism. Gastroschisis, a defect of the abdominal wall through which the intestines protrude at birth, putatively results from disruption of the omphalomesenteric artery by the eighth week of gestation (1–4). Small intestinal atresia (SIA) has been induced by occlusion of the superior mesenteric artery in dogs (5).

Previous epidemiologic studies of gastroschisis have shown increased risks among mothers who have reported taking various vasoactive over-the-counter medications, including pseudoephedrine (6, 7), phenylpropanolamine (6, 7), aspirin (6–9), ibuprofen (6, 7), and acetaminophen (6). These agents vary in their pharmacologic actions, in the prevalence of their use in pregnancy, and in the amount of evidence showing increased risks of gastroschisis. However, these medications share common indications for their use, particularly upper respiratory infections. In fact, many over-the-counter products combine decongestants, antipyretics/analgesics, and other agents and are marketed according to the symptoms they relieve. At the same time, gastroschisis has been observed to occur in clusters, and some studies, but not all, have reported greater frequencies of births in certain seasons (10–12). These observations raise the question about whether an infectious agent might increase risk. Although there have been few epidemiologic studies of SIA, it has been postulated that risk factors for gastroschisis might be the same for SIA, since both defects are thought to result from abnormal fetal mesenteric vasculature (2–5). Our study was designed to examine gastroschisis and SIA risks in relation to cold and antipyretic/analgesic medications, with specific attention to rigorous ascertainment of relevant medications taken and illnesses experienced in early pregnancy.

MATERIALS AND METHODS

This case-control study was conducted from June 1995 through March 1999 in 15 cities across the United States and Canada. Study subjects were ascertained from 29 pediatric tertiary care hospitals within 5 months of birth. Institutional review board approval was obtained from each participating hospital. Gastroschisis cases were defined as newborn infants with intestines protruding through the wall of the abdomen lateral to, but not involving, the umbilicus. SIA cases were defined as atresia, stenosis, or webbing of the duodenum, jejunum, or ileum, without gastroschisis. Gastroschisis and SIA cases with known chromosomal abnormalities or Mendelian-inherited disorders were

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Abbreviation: SIA, small intestinal atresia.

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excluded. Two control groups were used for both case groups. Malformed controls were infants with major structural malformations other than gastroschisis, SIA, or other gastrointestinal defects. Nonmalformed controls were infants with medical conditions requiring hospital admission (e.g., infections, prematurity, hyperbilirubinemia, transient tachypnea, meconium aspiration, seizures, and gastrointestinal problems). Because gastroschisis, but not SIA, is strongly associated with young maternal age, mothers of malformed and nonmalformed controls were matched to the age (+2/–4 years) of gastroschisis mothers, but not SIA mothers. Eligibility for all cases and controls required permission from the infant's physician for the mother to be contacted about the study. Mothers were sent a letter describing the study and a medication identification booklet containing color pictures of cold and antipyretic/analgesic products to help women differentiate among similarly named products (e.g., Tylenol vs. Tylenol Flu (McNeil PPC, Inc., Fort Washington, Pennsylvania)). After informed consent was obtained, a nurse-interviewer administered the standardized questionnaire by telephone within 6 months after delivery. The interviewer was not blinded to case/control status to avoid her appearing to be insensitive to the families' situations, which might have undermined her rapport. Information was collected on demographic factors; reproductive, illness, and medication histories; and cigarette and beverage consumption. Detailed questions were asked about occurrences of allergies, colds, influenza, bronchitis, sinus problems, headaches, and asthma and whether medications were taken for those illnesses. Medication use was also elicited by prompts of specific drugs. Details on medication use were obtained, including the specific product, start and stop dates of use, frequency, duration, form (liquid, pill), amount taken per day, and reason for use. For each medication reported, women were asked to retrieve the bottle, if available, to accurately identify the product. If the bottle or package was not available for cold or antipyretic/analgesic medications, the woman was asked to identify the product in the Medication Identification Booklet (Slone Epidemiology Unit, Boston University School of Public Health, Boston, Massachusetts). Each reported product was linked to the Slone Epidemiology Unit Drug Dictionary, which identifies individual ingredients in multiple component products.

Use of pseudoephedrine, phenylpropanolamine, aspirin, ibuprofen, and acetaminophen was examined. In addition, we also examined use of antihistamines, guaifenesin, and dextromethorphan because they are often taken with decongestants and antipyretics/analgesics. Exposure was defined as any reported use of a medication from the first day of the last menstrual period through 84 days after the last menstrual period (lunar months 1–3), the developmentally relevant time period for both defects. For each drug, use was compared with no use during lunar months 1–3. Use of combination products was also examined. Potential confounding by reported indication for medication use and by reported presence of fever was assessed.

Logistic regression was used to estimate odds ratios and 95 percent confidence intervals. Models for gastroschisis risk were conditional on the match and included terms for pseudoephedrine, phenylpropanolamine, aspirin, ibuprofen, acetaminophen, antihistamines, guaifenesin, dextromethorphan, fever, upper respiratory infection, and allergy. Adjustments were also made for the potential confounding effects of family income (<$15,000, $15,000–$24,999, $25,000–$34,999, $35,000–$64,999, and ≥$65,000), maternal years of education (<12, 12, 13–15, and ≥16), illicit drug use, and cigarette smoking (none, 1–19, and ≥20 cigarettes per day). Unconditional logistic regression models were used for SIA risk estimation, controlling for the same set of factors as described for gastroschisis and maternal age (<20, 20–21, 22–23, 24–25, 26–27, 28–29, and ≥30 years). We did not estimate odds ratios for exposures with fewer than five exposed cases or controls because of the instability of such estimates.

RESULTS

There were 206 gastroschisis and 126 SIA cases, representing 79 and 75 percent, respectively, of eligible cases. There were 382 malformed and 416 nonmalformed controls, representing 73 percent and 68 percent, respectively, of eligible controls.

Table 1 shows the frequency of medications used and illnesses that occurred during lunar months 1–3 for cases and controls. Because frequencies varied little between the two control groups, we combined them for odds ratio estimation, as presented in table 2. Maternal use of pseudoephedrine, aspirin, and acetaminophen was more frequent among gastroschisis cases than among controls. Risk estimates for aspirin (odds ratio = 2.7) and acetaminophen (odds ratio = 1.5) were statistically significant, whereas the 1.8-fold increased risk for pseudoephedrine was of borderline significance. For SIA, pseudoephedrine use doubled risk with borderline significance, but use of other medications did not increase risk. Reported fever, upper respiratory infection, and allergy did not appear to affect risks of either defect, nor did they act as confounders of medication risk estimates.

Since pseudoephedrine, aspirin, and acetaminophen can be taken together in combination products, we examined their use according to the number and type of components (table 3). Most pseudoephedrine use is in a combination product, usually with acetaminophen. Both aspirin and acetaminophen were taken most often as single-component products, and acetaminophen combination products most often included pseudoephedrine. Table 4 presents the odds ratios for single and combination pseudoephedrine, aspirin, and acetaminophen use. Single-component pseudoephedrine does not appear to increase risks of either gastroschisis or SIA, based on small numbers. Single-component acetaminophen was associated with a slightly increased risk of gastroschisis, of borderline significance, but such use was not associated with an increase in risk of SIA. Single-component aspirin use was associated with a more than threefold increase in risk of gastroschisis. Use of combination products that included pseudoephedrine was associated with increases in risks of both gastroschisis and SIA. Most combination products contained both pseudoephedrine and acetaminophen; such use was associated with a 4.2-fold increase in risk of gastroschisis and

TABLE 1. Medication use and illnesses during lunar months 1–3 among cases and controls, United States and Canada, 1995–1999

Exposure	Cases				Controls			
	Gastroschisis		SIA*		Malformed		Nonmalformed	
	No.	%	No.	%	No.	%	No.	%
Pseudoephedrine	35	17	27	21	45	12	43	10
Phenylpropanolamine	8	4	2	2	14	4	13	3
Aspirin	13	6	5	4	13	3	12	3
Ibuprofen	30	15	15	12	48	13	47	11
Acetaminophen	120	58	72	57	184	48	202	49
Antihistamines	26	13	18	14	48	13	56	14
Guaifenesin	12	6	9	7	19	5	24	6
Dextromethorphan	17	8	12	10	23	6	33	8
Fever	16	8	12	10	24	6	28	7
Upper respiratory infection	56	27	44	35	101	26	95	23
Allergy	31	15	22	18	66	17	64	15

* SIA, small intestinal atresia.

TABLE 2. Odds ratios for medication use and illnesses, United States and Canada, 1995–1999

Exposure	Gastroschisis		SIA*	
	OR*	95% CI*,†	OR	95% CI†
Pseudoephedrine	1.8	1.0, 3.2	2.0	1.0, 4.0
Phenylpropanolamine	1.2	0.5, 3.1	0.5	0.1, 2.7
Aspirin	2.7	1.2, 5.9	0.5	0.2, 1.8
Ibuprofen	1.1	0.7, 1.8	0.9	0.5, 1.7
Acetaminophen	1.5	1.1, 2.2	1.0	0.6, 1.6
Antihistamines	0.6	0.3, 1.2	0.9	0.4, 1.8
Guaifenesin	0.7	0.3, 1.5	0.7	0.3, 2.0
Dextromethorphan	1.1	0.3, 4.5	0.8	0.1, 9.7
Fever	1.0	0.5, 2.0	1.4	0.6, 3.3
Upper respiratory infection	0.9	0.6, 1.5	1.3	0.7, 2.3
Allergy	0.8	0.5, 1.3	0.9	0.5, 1.7

* SIA, small intestinal atresia; OR, odds ratio; CI, confidence interval.

† Odds ratios adjusted for maternal age (SIA only), education, income, medication use, illness, illicit drug use, and cigarette smoking.

a threefold increase in risk of SIA. Use of other pseudoephedrine- or acetaminophen-containing combination products was less common; risks were estimated for gastroschisis only, and odds ratios were increased, but were not statistically significant. Users of multiple-component products did not ingest higher doses of pseudoephedrine or acetaminophen than did single-component users.

Although we did not find maternal reports of upper respiratory infection, allergy, or fever to be associated with gastroschisis or SIA risk, the increased risks of gastroschisis and SIA observed for pseudoephedrine and acetaminophen taken in combination form raised the question of confounding by underlying infectious illness, particularly by a specific microorganism, that could not be accurately measured from maternal report. Because gastroschisis can occur in clusters (perhaps reflecting an infectious etiology), we used an alternative approach to examine the possibility of confounding by infectious disease. If we assume that cases in the cluster group would more likely have an infectious etiology than

TABLE 3. Medication use according to the number of components, United States and Canada, 1995–1999

Medication (type)	Cases				Controls			
	Gastroschisis		SIA*		Malformed		Nonmalformed	
	No.	%	No.	%	No.	%	No.	%
Pseudoephedrine								
Single	6	3	10	8	20	5	16	4
Combination	29	14	17	14	25	7	27	7
With acetaminophen	23	11	14	11	21	6	21	5
Without acetaminophen	6	3	3	2	4	1	6	1
Aspirin								
Single	12	6	4	3	10	3	11	3
Combination	1	0.5	1	1	3	1	1	0.2
Acetaminophen								
Single	90	44	55	44	155	41	167	40
Combination	30	15	17	14	29	8	35	8
With pseudoephedrine	23	11	14	11	21	6	21	5
Without pseudoephedrine	7	3	3	2	8	2	14	3

* SIA, small intestinal atresia.

TABLE 4. Odds ratios for medication use by type of product, United States and Canada, 1995–1999

Medication (type)	Gastroschisis		SIA*	
	OR*	95% CI*,†	OR	95% CI†
Pseudoephedrine	1.8	1.0, 3.2	2.0	1.0, 4.0
Single	0.7	0.2, 2.1	1.1	0.5, 2.9
Combination	2.5	1.0, 6.2	4.2	1.3, 14.1
Without acetaminophen	3.4	1.0, 11.3		
Aspirin				
Single	3.2	1.4, 7.1		
Combination				
Acetaminophen	1.5	1.1, 2.2	1.0	0.6, 1.6
Single	1.5	1.0, 2.1	1.0	0.6, 1.6
Combination	1.7	0.8, 4.0	0.7	0.2, 2.3
Without pseudoephedrine	2.0	0.8, 5.2		
Pseudoephedrine and acetaminophen (with or without others)	4.2	1.9, 9.2	3.0	1.1, 8.0

* SIA, small intestinal atresia; OR, odds ratio; CI, confidence interval.

† Odds ratios adjusted for maternal age (SIA only), education, income, medication use, illness, illicit drug use, and cigarette smoking.

would cases in the noncluster group, then confounding by infectious disease would be minimized in the noncluster group. For gastroschisis, we arbitrarily defined a cluster as ascertainment of at least three cases from the same geographic area born within a 30-day interval. There were 71 cases in the cluster group and 134 cases in the noncluster group (the ascertainment date was unclear for one case). Odds ratios for medication use and illnesses are presented for each group in table 5. The prevalences of medication use and illnesses were generally similar among cases in the cluster and the noncluster groups, with the exception of aspirin use, which was nearly twice as common among cluster cases. In the noncluster group, the risk estimates for any pseudoephedrine use and any acetaminophen use approached the null, but estimates for pseudoephedrine in combination with acetaminophen and for any aspirin use remained elevated. No clear pattern of risk was observed for reported illnesses within each group.

Although SIA is not known to occur in clusters, we identified 37 cases that fit our criteria as having occurred in a cluster. Among the noncluster group, there were nine cases exposed to pseudoephedrine in combination with acetaminophen, for a risk of estimate of 2.7 (95 percent confidence interval: 1.2, 5.8).

DISCUSSION

Findings on risks of gastroschisis from this study confirm, to a certain extent, those from previous studies. Specifically, aspirin use has consistently been shown to increase gastroschisis risk in both animals (13) and humans (6–9). Our study confirmed that association with an observed 2.7-fold increased risk for any use and 3.2-fold risk for single-component use, which were not altered by control for other medication use or reported illnesses. The effects of aspirin on fetal vasculature are not known, but both vasoconstriction and vasodilation can result from aspirin intake at varying doses in adults (14). Findings on other medications in this study are less consistent, however. For example, ibuprofen, which shares some pharmacologic actions with aspirin, was not observed to increase gastroschisis risk, in contrast to an earlier report (7). On the other hand, acetaminophen is not known to affect adult vasculature (14), but overall use was associated with a slightly increased risk of gastroschisis, as reported in one other study (6). While decongestants such as pseudoephedrine and phenylpropanolamine are vasoconstrictive (14) and have been observed in previous studies to increase gastroschisis risk (6, 7), we found that pseudoephedrine use overall was only modestly associated with gastroschisis risk (not statistically significant) and that phenylpropanolamine did not increase risk. However, this study was the first to examine use of combination products. We found that single-component pseudoephedrine use was not associated with an increased risk (although this finding was based on few users) and that multiple-component pseudoephedrine use was associated with such a risk. The majority of multiple-component products contained both pseu-

TABLE 5. Medication use and illnesses in relation to risk of gastroschisis according to "cluster" group, United States and Canada, 1995–1999

Exposure	Cluster (n = 71)				Noncluster (n = 134)			
	No.	%	OR*	95% CI*,†	No.	%	OR	95% CI†
Pseudoephedrine	14	20	1.3	0.5, 3.1	21	16	1.3	0.7, 2.4
Acetaminophen	45	63	1.9	1.0, 3.6	75	56	1.3	0.9, 2.0
Pseudoephedrine and acetaminophen (with or without others)	9	13	2.1	0.7, 6.3	14	10	2.4	1.0, 5.7
Aspirin	6	9	3.9	1.0, 15.5	7	5	3.6	1.3, 10.1
Fever	7	10	1.7	0.5, 5.7	9	7	0.8	0.3, 1.9
Upper respiratory infection	17	24	0.7	0.3, 1.6	39	29	0.8	0.5, 1.4
Allergy	10	14	0.8	0.3, 1.8	21	16	1.2	0.7, 2.0

* OR, odds ratio; CI, confidence interval.

† Odds ratios (95% confidence intervals) adjusted for education, income, medication use, illness, illicit drug use, and cigarette smoking.

doephedrine and acetaminophen, and this combination product was associated with an approximate 4.2-fold increased risk of gastroschisis.

It is possible that an interaction between pseudoephedrine and acetaminophen might affect the development of gastroschisis and SIA, but differences in women who take these combination products, such as their underlying illnesses, might also affect risk. We hypothesized that use of pseudoephedrine/acetaminophen combination products was a marker for an infectious agent that itself increased gastroschisis risk. Although we adjusted for reported upper respiratory illnesses, measurements of specific infectious agents are difficult to obtain in observational studies, leaving open the opportunity for uncontrolled confounding. We therefore used an alternative approach to examine the possibility of confounding by underlying infection by identifying clusters of gastroschisis cases, under the hypothesis that cases that occur in clusters more likely have an infectious etiology. If medication use is confounded by infectious disease, then risk estimates for medications would approach the null among the noncluster group. For gastroschisis, estimates for any pseudoephedrine use and any acetaminophen use did, indeed, approach the null within the noncluster group. However, increased risks of gastroschisis and SIA were observed for use of pseudoephedrine in combination with acetaminophen within both the cluster and the noncluster groups. A similar pattern was observed for aspirin use and gastroschisis risk. The persistence of an elevated risk among the subgroup of cases least likely to be caused by an infectious illness suggests that the observed association for specific fever/pain and cold medications may not be confounded by maternal illness. However, since reported fever and upper respiratory illness were not associated with cluster status among cases, it is possible that such reporting might be inaccurate and/or that the cluster grouping may not be indicative of an upper respiratory infectious illness.

To our knowledge, this was the first study to examine medication use in early pregnancy in relation to SIA risk. As discussed for gastroschisis, it is biologically plausible that vasoactive effects of pseudoephedrine, phenylpropanolamine, aspirin, and ibuprofen might affect the development of SIA by fetal vascular disruption, but only multiple-component pseudoephedrine (primarily combined with acetaminophen) was associated with an increased SIA risk. While the combination of acetaminophen and pseudoephedrine was associated with a threefold increase in risk, acetaminophen use overall did not appear to affect risk.

Our findings have limitations. Selection bias might be a concern because our study was not population based. To include sufficient numbers of cases in less than 4 years, study subjects were ascertained at large tertiary pediatric care centers across the United States and Canada. However, the findings on pseudoephedrine and aspirin in this hospital-based study confirm those observed by Torfs et al. (7) in their population-based study. In addition, higher proportions of ascertained controls than of cases were ineligible for the study because physicians were either not able to be contacted or they denied permission for the family to be approached. However, it is unlikely that medication use in pregnancy would be related to successful contact of and approval by physicians. In addition, proportions of mothers whom we were unable to contact or who refused to participate were similar among cases and controls, but represented approximately 20–30 percent of the women approached. Although it is unlikely that medication use is related to successful contact and interview of mothers, if it were, these findings might not be generalizable to all women.

Information was retrospectively collected in this study, raising the possibilities of both random and differential misclassification of exposure. Several steps were taken to minimize these possibilities. The interval between birth and interview was less than 6 months for all study subjects, and the interview used standardized, detailed questions to identify medications and illnesses during early pregnancy. If there were nondifferential reporting of medication use, the observed odds ratios would underestimate true effects. Concern about differential classification (e.g., recall bias) led us to use two separate control groups: One comprised infants with malformations and the other infants without malformations. While the nonmalformed group included infants with medical conditions requiring hospitalization in the first few months of life and, thus, was not "normal," maternal recall of early pregnancy events and exposures may be closer to that of mothers of healthy infants than to that of mothers of malformed infants. It is noteworthy that the rigorous, systematic inquiry of our standardized interview resulted in strikingly similar reported prevalences of medication use and other vasoconstrictive exposures in the two control groups, suggesting similar recall accuracy.

In addition, exposure to specific medications was determined by examining the components of combination products. In other words, we did not rely on the women's recall of specific ingredients of cough, cold, and antipyretic/analgesic products, but rather we asked them to identify in the medication identification booklet the products they took. Therefore, the higher prevalences of pseudoephedrine and acetaminophen use among cases relative to controls, but similar rates of other cough and cold components, suggest that recall bias is unlikely to account for our findings.

Finally, sociodemographic factors, medications, illnesses, and behaviors were controlled as potential confounders, resulting in little change in risk estimates. There remains the possibility of confounding by other factors, particularly infectious agents, that were not accurately ascertained in this study.

Medications for colds, coughs, and pain are commonly used in early pregnancy. Our findings suggest that many of those medications do not increase risks of gastroschisis and SIA, but suggest that others might affect risks. Specifically, aspirin use appears to increase risk of gastroschisis, acetaminophen is modestly associated with an increased risk, and ibuprofen has no effect. Use of pseudoephedrine alone did not increase risk, but use of multiple-component pseudoephedrine, particularly pseudoephedrine in combination with acetaminophen, was associated with increases in risk of both gastroschisis and SIA. We were not able to delineate the nature of observed increased risks for multiple-component medications further.

Several questions are raised by these findings, including whether the less common use of single-component pseudoephedrine is without risk, whether medications taken in combination form interact to affect fetal development, and whether an infectious agent (independently or synergistically with pseudoephedrine and acetaminophen) affects risk. Given the widespread use of many these medications, these questions deserve attention in laboratory research settings.

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REFERENCES

1. Hoyme HE, Higginbottom MC, Jones KL. The vascular pathogenesis of gastroschisis: intrauterine interruption of the omphalomesenteric artery. J Pediatr 1981;98:228–31.
2. Van Allen MI. Fetal vascular disruptions: mechanisms and some resulting birth defects. Pediatr Ann 1981;10:219–33.
3. Hoyme HE, Jones KL, Dixon SD, et al. Prenatal cocaine exposure and fetal vascular disruption. Pediatrics 1990;85:743–7.
4. Martin ML, Khoury MJ, Cordero JF, et al. Trends in rates of multiple vascular disruption defects, Atlanta 1968–1989: is there evidence of a cocaine teratogenic epidemic? Teratology 1992;45:647–53.
5. Louw JH, Barnard CN. Congenital intestinal atresia: observations on its origin. Lancet 1955;2:1065–7.
6. Werler MM, Mitchell AA, Shapiro S. First trimester maternal medication use in relation to gastroschisis. Teratology 1992; 45:361–7.
7. Torfs CP, Katz EA, Bateson TF, et al. Maternal medications and environmental exposures as risk factors for gastroschisis. Teratology 1996;54:84–92.
8. Drongowski RA, Smith RK, Coran AG, et al. Contribution of demographic and environmental factors to the etiology of gastroschisis: a hypothesis. Fetal Diagn Ther 1991;6:14–27.
9. Martinez-Frias ML, Rodriguez-Pinilla E, Prieto L. Prenatal exposure to salicylates and gastroschisis: a case-control study. Teratology 1997;56:241–3.
10. Lynberg MC, Cordero JF, Khoury MJ. Increasing prevalence at birth of gastroschisis in metropolitan Atlanta, 1968–1990. (Abstract). Teratology 1992;45:453.
11. Penman DG, Fisher RM, Noblett HR, et al. Increase in incidence of gastroschisis in the South West of England in 1995. Br J Obstet Gynaecol 1998;105:328–31.
12. Goldbaum G, Daling J, Milham S. Risk factors for gastroschisis. Teratology 1990;42:397–403.
13. Szabo KT. Congenital malformations in laboratory and farm animals. Berkeley, CA: Academic Press, Inc, 1989.
14. Goodman GA. The pharmacologic basis of therapeutics. Ninth ed. New York, NY: McGraw-Hill Book Co, 1996.