Case-control Study of a Gastroschisis Cluster in Nevada

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Objective: To identify potential risk factors associated with a sudden increase in gastroschisis cases in northern Nevada.

Design: Case-control study.

Setting: Medical centers and a pregnancy care center in Reno, Nevada.

Participants: Participants (n=14) were women who gave birth to infants with gastroschisis at either of the 2 medical centers in Reno, Nevada, from April 5, 2007, through April 4, 2008. Controls (n=57) were selected from the same pregnancy center providing perinatal care to the cases and were matched 4:1 to the case mothers by maternal date of birth within 1 year.

Main Exposures: Environmental exposures and illnesses during pregnancy.

Outcome Measures: Association of gastroschisis with illnesses, medications, or environmental exposures.

Results: Gastroschisis was associated with the use of methamphetamine (odds ratio [OR], 7.15; 95% confidence interval [CI], 1.35-37.99) or any vasoconstrictive recreational drug (methamphetamine, amphetamine, cocaine, ecstasy) (OR, 4.46; 95% CI, 1.21-16.44) before pregnancy. When we limited self-reported illnesses to those occurring during the first trimester of pregnancy, chest colds (OR, 16.77; 95% CI, 1.88-150.27) and sore throats (OR, 12.72; 95% CI, 1.32-122.52) were associated with gastroschisis.

Conclusions: These findings add strength to the hypothesis that use of methamphetamine and related drugs is a risk factor for gastroschisis and raise questions about the risks associated with infections.


GASTROSCHISIS IS A BIRTH defect characterized by incomplete closure of the abdominal wall. The condition has increased in prevalence globally over the past several decades, although prevalence varies by geographic region.1-7 In the United States, the estimated prevalence of gastroschisis is 3.73 per 10 000 live births, based on data from The National Birth Defects Prevention Network.8 A recent analysis of National Birth Defects Prevention Network data confirmed that gastroschisis prevalence has increased in the United States since 1995, although the analysis included only 15 states with complete data.9 In California, the prevalence increased 3.2-fold from 1987 to 2003 to 2.57 per 10 000 live births.10 This compares with an earlier increase from 0.86 to 0.89 per 10 000 live births from 1968 to 1977.11 These data are consistent with a recent review of international data indicating that gastroschisis prevalence has increased 10- to 20-fold during the past 15 years from a baseline of approximately 1 in 50 000 births.1

While a few hypotheses about etiology have been advanced, young maternal age remains the only consistent, strong risk factor for gastroschisis. The association of gastroschisis with young maternal age has prompted many investigators to focus on potential etiological roles of life-style factors that may be more common in young women such as lack of prenatal care or use of alcohol, tobacco, or illicit drugs during pregnancy.12,13 In addition to maternal lifestyle factors, gastroschisis has been associated with use of certain vasoconstrictive medications thought to disrupt blood flow to the artery located near the right of the umbilicus, resulting in weakening of the abdominal wall and herniation of the gut.14 Still, the global increase in prevalence and the tendency to occur in clusters suggests that an environmental exposure plays a role in the etiology of gastroschisis.
We recently investigated a cluster of gastroschisis cases in Washoe County, Nevada, after local clinicians suspected an increase in the number of cases in the community. From April 5, 2007, to April 4, 2008, 14 cases of gastroschisis were identified by public health nurses and perinatologists. The rate for this period (22.6 cases per 10,000 live births) was higher than for any of the previous 16 years (average rate, 2.1 cases per 10,000 live births; range, 0.00-5.89 cases per 10,000 live births), resulting in a relative rate of 9.89 (95% confidence interval [CI], 4.92-19.88; P < .001). To identify risk factors associated with the sudden increase in gastroschisis cases, we conducted a case-control study, randomly selecting controls from the same source population as the cases.

METHODS

CASES AND CONTROLS

We defined cases as women who gave birth to infants with gastroschisis at either of the 2 major medical centers in Reno, Nevada (Washoe County) from April 5, 2007, through April 4, 2008. Gastroschisis cases were diagnosed by perinatologists (R.N.S., E.O.) who had provided perinatal care, or, for women without prenatal care (n=1), by the pediatric surgeon performing gastroschisis repair. For most of the cases, the defect was diagnosed (International Classification of Diseases, Ninth Revision [ICD-9] code 658.8X/756.79) at 15 to 20 weeks' gestation by ultrasound, performed either primarily or as a follow-up referred because of an elevated maternal serum alpha-fetoprotein screening test. Cases were referred to the Washoe County Health District by medical center social workers or by perinatologists after the infants' births for routine follow-up by public health nurses.

Control mothers were selected at random from the same pregnancy care center that provided perinatal care to most (85.7%) of the cases. From a list of all women receiving care at the pregnancy center, we created an initial sampling frame by restricting the list to women who had given birth since April 5, 2007. We then created a list of potential controls for each case mother by including women whose dates of birth were within 1 year of the case mothers. Potential control mothers were telephoned randomly until interviews were scheduled, with 4 women for each case. Women with disconnected telephones were removed from the list. Women with working telephone numbers were called up to 4 times before being removed from the list owing to no answer, busy signal, answering machine, or inability to reach the mother (eg, someone answered the telephone but reported that the mother was not home or unavailable).

From April 5, 2007, through April 4, 2008, a total of 14 case mothers were identified and interviewed. Of 389 women called from the lists of potential controls, 77 (19.8%) were reached by telephone. Most of the women who were not reached had disconnected telephones (34.4%) or were not available after 4 telephone calls (45.8%). Of the women who were reached by telephone, only 4 (5.2%) refused to participate, although 16 (21.9%) did not answer the door at the time of the scheduled interview and were replaced. Of the 57 women interviewed as controls, 26 (45.6%) required assistance of a Spanish interpreter. This compares with 2 (14.3%) of the case mothers. Most of the case mothers were young (median age, 18 years; range, 16-36 years), white (92.9%), and Hispanic (71.4%) (Table 1).

INTERVIEWS

Case mothers were interviewed by the same public health nurse (L.L.) in their homes (n=13) or by telephone (n=1). Interviews with Spanish-speaking mothers were conducted with the assistance of an interpreter. Control mothers were interviewed in their homes (n=51), at their workplace (n=1), in an office in the county health department (n=2), or by telephone (n=3) by either the senior epidemiologist (L.E.) or the public health nurse (L.L.). To reduce interviewer bias, the epidemiologist and public health nurse interviewed 1 case mother together before commencing interviews with control mothers. Appointments were made with control mothers so that each interviewer had the assistance of the same Spanish interpreter when needed.

The median time from the infant's date of birth until the interview was 94 days (range, 14-244 days) for cases and 187 days (range, 49-386 days) for controls. The longer interim period for controls reflects the fact that, as a public health investigation, initial efforts were focused on interviewing cases to identify a potential environmental risk factor that explains the cluster. Controls were selected after all cases had been ascertained.

All women were given information about the gastroschisis cluster and encouraged to ask questions, either about the birth defect or the public health investigation. After answering all questions, the interviewers read aloud the consent forms to the mothers, assuring them that they could stop the interview at any time or refuse to answer any question. Interviews were begun after consent forms were signed. Approval of an institutional review board was not required because the case-control study was conducted as a public health investigation for the purpose of identifying a specific cause of the cluster of gastroschisis cases.

QUESTIONNAIRE

The questionnaire used for collection of data included questions informed by previously hypothesized risk factors such as use of certain prescription medications or recreational drugs, use of tobacco or alcohol, certain lifestyle factors, reproductive history, and presence of infections.14,16-21 We also included questions about demographics, educational and residential history, family birth defects, military service, medical history, immunization history, occupational history, dietary information related to raw meats, dairy products, or imported foods, and household, hobby, and work exposures. A copy of the questionnaire is available on request.

Questions about illnesses and medication use during pregnancy focused on the 6-month period beginning 1 month before the last menstrual period and extending 3 months after the last menstrual period. The interviewers marked this period on individualized calendars for each woman and referred to the calendar throughout the interview. Women were asked if they had any of 29 health conditions (Table 2) including "any other illness" during the 6-month period outlined on the calendar and, if so, the date of onset, the duration of illness, and whether any medications were taken. To facilitate memory about medication use during this period, women were asked specifically (ie, by name) about 8 cold medicines, 5 asthma medications, 12 pain medications, 12 antibiotics, 4 antidepressants, 5 weight reduction medications, and 5 vitamins. For recreational drugs, women were asked whether they had used, in the year before pregnancy, any of the following: amphetamines, cocaine, marijuana, Ritalin (Novartis Pharmaceuticals, Basel, Switzerland), 3,4-methylenedioxyxymethamphetamine (MDMA, or ecstasy), and methamphetamine. Women with positive answers were asked whether they continued to use them during pregnancy.
After all interviews were completed, we reviewed available medical records of cases (n=12) and controls (n=50) to identify physician-diagnosed illnesses and prescribed medications during pregnancy. When available, information about use of tobacco, alcohol, or recreational drugs was noted from the medical records.

STATISTICAL ANALYSIS

We used conditional logistic regression, stratifying by case and matched control groups, to determine whether illnesses, medications, and other exposures were associated with gastroschisis. Conditional logistic regression was performed using Cox proportional hazards modeling (PROC PHREG) in SAS version 9.1 (SAS Inc, Cary, North Carolina).

RESULTS

Case infants had lower mean birth weight (4.6 pounds) than controls (7.1 pounds) and were more likely to be premature (50% vs 5.3%). Most case and control mothers identified themselves as white (92.9% and 89.5%) and Hispanic (71.4% and 68.4%), with similar education (mean, 10.4 and 10.5 years, respectively) (Table 1). Only 46% of the controls reported that they were born in the United States compared with 64.3% of the cases. Case and control mothers were similar in most characteristics, including mean height, age at menarche, weight gain during pregnancy, use of birth control at conception, previous pregnancies, and change of residence during pregnancy; however, case and control mothers differed in characteristics related to lifestyle and illnesses during pregnancy (Table 2).

Gastroschisis was associated with the use of methamphetamine (odds ratio [OR], 7.15; 95% CI, 1.35-37.99) or any vasoconstrictive recreational drug (methamphetamine, amphetamine, cocaine, ecstasy) (OR, 4.46; 95% CI, 1.21-16.44) before pregnancy, but it was not statistically significantly associated with use of tobacco or alcohol at the time of pregnancy.

We compared interview data on methamphetamine use with medical record information and found under-reporting in both places. Of women who reported methamphetamine use before pregnancy (controls, 5; cases, 5),
0% of controls and 50% of cases had matching medical record information. For those whose medical record noted methamphetamine use (controls, 3; cases, 5), 0% controls and 40% cases had matching interview information. Odds ratios using any of these indicators (ie, methamphetamine use by report, methamphetamine use by medical record note, or methamphetamine use by either of these) were similar (report OR, 7.15; 95% CI, 1.35-37.99; medical record OR, 7.86; 95% CI, 1.50-41.10; either OR, 6.94; 95% CI, 1.77-27.17).

Gastroschisis was also associated with several illnesses reported by mothers to have occurred within the 6-month period beginning 1 month before their last menstrual period (Table 2). The highest ORs were for sore throat (OR, 15.94; 95% CI, 1.83-138.97) and bladder infection (OR, 10.49; 95% CI, 1.05-104.37). When we limited self-reported illnesses to those occurring during lue- 
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cold, or sore throat during the same period yielded an OR of 4.64 (95% CI, 1.23-17.56).

Case mothers were more likely than control mothers to report the use of medications for chest cold, head cold, or sore throat combined (OR, 9.1; 95% CI, 1.78-46.58). Use of pseudoephedrine specifically was reported by both case and control mothers (21.4% and 12.3%, respectively; OR, 1.82; 95% CI, 0.45-7.40). Because most women could not remember the names of over-the-counter medications for upper respiratory tract–related illnesses, we created a variable, cold medications, that was positive if a woman reported taking any medication besides Tylenol for these illnesses. More case mothers (42.9%) than control mothers (26.3%) reported taking cold medications, although the difference was not statistically significant (OR, 2.26; 95% CI, 0.62-8.22). However, case mothers were 12 times more likely than control mothers to report use of these medications in early pregnancy (lunar months 1-3) (OR, 12.0; 95% CI, 1.25-115.36).

Because pseudoephedrine, an ingredient of methamphetamine, is commonly used for cold and upper respiratory infections, we also considered whether mothers reported at least 1 of these exposures (ie, methamphetamine use, chest cold, sore throat). Case mothers were almost 8 times more likely than control mothers to have a self-reported chest cold or sore throat in the first trimester of pregnancy or to have used methamphetamine before pregnancy (OR, 7.97; 95% CI, 1.57-40.36).

Medical record reviews did not yield additional information about most illnesses, especially those that did not require treatment with prescribed medications. Medical record notes did not mention colds or sore throats, although they did include reports of tests or prescriptions for certain infections. We evaluated the correlation between medical record notes and interview data for bladder, vaginal, and yeast infections, which generally require prescription medications. For these conditions combined, medical records matched patient reports for 74.0% of the controls and 58.3% of the cases.

The medical records had more reliable information than interviews about prescribed medications; thus, we were able to assess the relationships between specific medications and gastroschisis. We did not find any associations between gastroschisis and specific prescribed medications or classes of medications (eg, antibiotics).

**COMMENT**

The results of our investigation of a gastroschisis cluster in Washoe County, Nevada, support the hypothesis that vasoconstrictive drug use may be an important risk factor for gastroschisis. In this population, gastroschisis was associated with the use of any vasoconstrictive recreational drug (amphetamine, cocaine, ecstasy, methamphetamine) before pregnancy, and especially with methamphetamine use. We also found that gastroschisis was associated with chest colds and sore throats in the first trimester of pregnancy. These associations could be related to the use of over-the-counter vasoconstrictive medications such as pseudoephedrine and aspirin, often used for these conditions, and associated with gastroschisis in other populations. Alternatively, the associations may signify viral or bacterial infections with a role in the etiology of gastroschisis.

We found an association between gastroschisis and self-reported urinary tract infection, which has been described in another population. That study, using data from national birth defects prevention surveillance, found a greater risk of gastroschisis (OR, 4.0; 95% CI, 1.4-11.6) in children of mothers who reported a urinary tract infection in combination with a sexually transmitted infection. We were unable to assess the influence of sexually transmitted infections because few mothers reported these. Furthermore, when we limited analysis to urinary tract infections in the first trimester of pregnancy, the OR could not be estimated owing to low numbers.

The association of gastroschisis with methamphetamine use supports the hypothesis that gastroschisis is the result of a vascular disruptive event that occurs after closure of the abdominal wall. However, a recent review of hypotheses about the development of gastroschisis noted that disruption of the artery thought to lead to gastroschisis in vascular disruption would result in necrosis of the gut rather than the abdominal wall. Under an alternative hypothesis suggested by the authors, gastroschisis could be a malformation caused by any early exposure that prevents complete closure of the abdominal wall, including infections, medications, and immunologic events. Although the biologic mechanisms are not fully understood, the association of infection with other birth defects lends plausibility to this hypothesis.

We did not find statistically significant associations between gastroschisis and use of marijuana, tobacco, or alcohol, which have been implicated in other studies, although more cases than controls used alcohol (64.3% vs 49.1%) and tobacco (42.9% vs 24.6%) before pregnancy. Interestingly, marijuana was used more frequently by controls than by cases (19.3% vs 7.1%).

Western states lead the nation in use of methamphetamine, with Nevada reporting the highest use. For example, based on national data collected by the Substance Abuse and Mental Health Services Administration from 2002 to 2004, an average of 0.6% of persons aged 12 years or older in the United States used methamphetamine in the 12 months prior to the survey, compared with 2.2% of the same age group in Nevada. For young adults (ages, 18 to 25 years), methamphetamine use was even higher (1.6% for the nation, 4.3% for Nevada).

It is possible that the association of gastroschisis with methamphetamine use was influenced by selection bias. For example, we were not able to reach 34% of the eligible controls owing to disconnected phone numbers. If methamphetamine users are less likely to have working telephones, the control group might not have been representative of the source population, resulting in a spurious association. However, the prevalence of telephone service in the source population may have been low because of its expense, which is suggested by the high prevalence of women receiving government financial assistance or who are ineligible for assistance owing to lack of required immigration paperwork. For example, only 45.6% of the controls reported that they were born in the United States.
United States, compared with 64.3% of the cases. This difference was reflected in the number of controls requesting an interpreter (45.6%) compared with the cases (14.3%).

Another limitation is that we were unable to assess the timing of methamphetamine exposure with respect to the pregnancy. Many women who reported use of any drugs were unable to remember when they stopped using them. Because we expected that women would be reluctant to admit drug use during pregnancy, we included any drug use prior to pregnancy as the exposure. We compared medical record and interview data for methamphetamine use and found underreporting in both places. However, when methamphetamine use was based on interview data alone, medical record data alone, or a combination of the two, the ORs were not materially different.

The study was subject to the common limitations of case-control studies involving birth defects, especially maternal recall bias and interviewer bias. In maternal recall bias, mothers of children with birth defects may be more likely to recall earlier exposures in an attempt to identify potential causes of the birth defect. In this study, we did not limit controls to mothers of healthy infants; 1 control infant had a cleft palate, and approximately 21% of the control mothers reported that their doctor told them there was a problem with the infant at the time of the first ultrasound. A comparison between interview and medical record data showed differential agreement for controls and cases; for example, medical records matched subject reports for 74.0% of the controls and 58.3% of the cases for conditions most likely to result in medical care (bladder, vaginal, and yeast infections). However, the medical records only documented visits to the pregnancy center; thus, visits to other medical providers would not appear in the medical record.

Interviewer bias is a potential problem when interviewers are not blinded to case and control status. Blinding was not possible in this study because of its role as part of a public health investigation. Although interviewers were not blinded to case and control status in this study, they consulted frequently about interview skills to reduce bias. The interviewers and Spanish interpreter attended a short training session before beginning interviews.

Although the sample size was relatively small compared with other studies, the study had considerable strengths. Ascertainment of cases at birth ensured complete information on all cases of the cluster. Furthermore, 2 of the study staff conducted all of the interviews, using the same interpreter for all Spanish-speaking mothers. The selection of controls from the same source population that gave rise to the cases resulted in a comparison group that was similar to the cases on all socioeconomic factors. In previous studies, socioeconomic status has been identified as a risk factor for gastroschisis.7

We had hoped to find a common source of exposure that could explain the clustering of gastroschisis cases in Washoe County, Nevada, during the period under investigation. However, methamphetamine use, sore throat, and chest colds were the only statistically significant risk factors for gastroschisis in this cluster. It is possible that methamphetamine users in this group were exposed to a “bad batch” of drug because the manufacturing processes are changing frequently to reduce production cost and improve potency. It is also possible that a particular strain of virus or bacteria was present in the community during this period. However, our findings add considerable strength to the hypothesis that use of methamphetamine and related drugs is a risk factor for gastroschisis.

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Author Contributions: Dr Elliott had full access to all of the data in the study and takes responsibility for the integrity of the data and the accuracy of the data analysis. Study concept and design: Elliott, Loomis, Slotnick, and Todd. Acquisition of data: Elliott, Lottritz, Todd, Slotnick, and Oki. Analysis and interpretation of data: Elliott and Loomis. Drafting of the manuscript: Elliott. Critical review of the manuscript for important intellectual content: Elliott, Loomis, Lottritz, Slotnick, Oki, and Todd. Statistical analysis: Elliott. Administrative, technical, or material support: Lottritz, Slotnick, and Todd. Study supervision: Elliott, Slotnick, and Todd.

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