

Case-control study of self reported genitourinary infections and risk of gastroschisis: findings from the national birth defects prevention study, 1997-2003

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ABSTRACT

Objective To assess the association between genitourinary infections in the month before conception to the end of the first trimester and gastroschisis.

Design Case-control study with self reported infections from a computer assisted telephone interview.

Setting National birth defects prevention study, a multisite, population based study including 10 surveillance systems for birth defects in the United States.

Participants Mothers of 505 offspring with gastroschisis and 4924 healthy liveborn infants as controls.

Main outcome measure Adjusted odds ratios for gastroschisis with 95% confidence intervals.

Results About 16% (n=81) of case mothers and 9% (n=425) of control mothers reported a genitourinary infection in the relevant time period; 4% (n=21) and 2% (n=98) reported a sexually transmitted infection and 13% (n=67) and 7% (n=338) reported a urinary tract infection, respectively. Case mothers aged <25 years reported higher rates of urinary tract infection alone and in combination with a sexually transmitted infection compared with control mothers. In women who reported both types of infection, there was a greater risk of gastroschisis in offspring (adjusted odds ratio 4.0, 95% confidence interval 1.4 to 11.6).

Conclusion There is a significant association between self reported urinary tract infection plus sexually transmitted infection just before conception and in early pregnancy and gastroschisis.

INTRODUCTION

Gastroschisis is a congenital malformation in which abdominal organs prolapse through a defect in the fetal abdominal wall, leading to considerable morbidity and mortality during infancy. The causes and mechanisms of this condition are largely unclear, but some evidence implicates environmental or maternal factors. Such evidence includes the rapidly increasing occurrence of gastroschisis in several countries worldwide¹⁻⁵ at a rate and magnitude unlikely to be caused by changes in gene frequency. In addition, gastroschisis is more common in infants born to women aged under 20.⁶⁻¹⁰

Although its average birth prevalence is about 1 in 2700 births,¹¹ gastroschisis occurs at a rate up to six times higher in infants of mothers under 20 years compared with mothers aged 25 or older.¹² This group of younger women also accounts for much of the increasing trends.^{4,13,14}

Several studies of gastroschisis have tried to identify an environmental risk factor that could account for these epidemiological findings—a factor that is increasing internationally and that might be particularly pronounced or harmful among younger women. Researchers have identified epidemiological associations with smoking,^{7,8,10,15,16} alcohol use,^{10,17} and use of common medications, such as paracetamol, aspirin, ibuprofen, pseudoephedrine, and phenylpropanolamine.^{18,19} It is unclear, however, if these findings reflect causal effects or explain the rising rates of gastroschisis.

We examined genitourinary infections as potential risk factors for gastroschisis. These infections include both urinary tract infections and sexually transmitted infections, which are common among sexually active young women.^{20,21} The frequent and increasing rates of genitourinary infections among women make this a reasonable focus of investigation. The investigation was conducted as part of the national birth defects prevention study.^{22,23}

METHODS

Study design

The national birth defects prevention study is a multisite, population based, case-control study of genetic and environmental risk factors for birth defects supported and coordinated by the US Centers for Disease Control and Prevention (CDC). Cases are identified through 10 population based surveillance programmes in 10 states (Arkansas, California, Georgia, Iowa, Massachusetts, New Jersey, New York, North Carolina, Texas, and Utah), according to mother's residence. Liveborn infants, stillbirths, and terminations of pregnancy are eligible. Concurrently, liveborn infants are selected randomly from the same birth

population to serve as controls, without any matching. Details of study methods have been published.²² Once enrolled in the study, mothers of affected and control infants take part in a computer assisted telephone interview in English or Spanish. During the interview, trained staff systematically collect data on demographics, use of medication, illnesses, occupation, lifestyle, and other exposures from three months before pregnancy through to the end of pregnancy. Participation rates were 72% for case mothers and 69% for control mothers.

Case classification

At each site a clinical geneticist reviewed case records. For this analysis, one investigator (CAM) also further reviewed and classified all cases. We also included cases in which fetuses were diagnosed prenatally and stillborn or the pregnancy was terminated, except in Massachusetts and New Jersey. Cases of gastroschisis were classified as isolated or multiple, and both types were included in the study. In isolated cases gastroschisis was the single major defect, though minor defects might also have been present. Intestinal atresia in cases of gastroschisis was considered a sequence defect (that is, the atresia is secondary or resulted from the gastroschisis) and these cases were classified as isolated. In multiple cases there was at least one additional unrelated major malformation, such as a congenital heart defect or a renal malformation.²³ We excluded cases of gastroschisis with phenotypes consistent with amniotic band sequence or limb-body wall disruption sequence.

Exposure assessment

Women were considered as exposed if they reported a genitourinary infection at any time in the month before conception to the end of the first trimester. The specific questions that explored genitourinary infections were: "Did you have any of the following illnesses: a kidney, bladder, or urinary tract infection?" or "Did you have pelvic inflammatory disease or PID?" and "Did you have any other diseases or illnesses that we have not already talked about such as sexually transmitted diseases?" Two investigators (MLF and LDB) who were blinded to case or control status reviewed the answers to the latter question to identify any mention of a genitourinary infection.

We divided genitourinary infections into urinary tract infections, such as bladder or kidney infections, or sexually transmitted infections, such as chlamydia, human papillomavirus, genital herpes, trichomoniasis, gonorrhoea, bacterial vaginosis (included in the sexually transmitted infection group as it often co-occurs with other sexually transmitted infections), or an unspecified sexually transmitted infection. Any woman who reported pelvic inflammatory disease was considered to have a sexually transmitted infection because most cases of pelvic inflammatory disease are thought to be caused by chlamydia or gonorrhoea.²⁴

We examined urinary tract infections and sexually transmitted infections together and separately.

Specifically, we created four exposure groups: either urinary tract infection or sexually transmitted infection, both types of infection (intersection), urinary tract infection only, and sexually transmitted infection only. We created the joint exposure group to assess whether women reporting both types of infection during the period of interest had a greater risk of having an affected pregnancy compared with women who reported only a sexually transmitted infection or only a urinary tract infection. Reporting the combined infection might reflect an exposure to a greater dose of pathogen or to a more severe infection. The unexposed group comprised women who reported neither type of infection during the period of interest. We excluded women for whom we did not have enough information for a definite placement in any group.

We carried out further analyses to assess whether the use of antibiotics to treat urinary tract infections or sexually transmitted infections was associated with gastroschisis. We also examined fever associated with urinary tract infections or pelvic inflammatory disease. We were not able to determine whether a fever occurred with a reported sexually transmitted infection as this was not specifically asked about in the telephone interview.

Inclusions, exclusions, and final study group

We included participants with estimated due dates from 1 October 1997 to 31 December 2003. We used estimated dates rather than dates of birth or delivery to control for differences in length of gestation (because of preterm birth and terminations) between cases and controls.

The initial group comprised mothers of 539 affected offspring and 5008 control infants. We excluded 24 affected offspring because of limb-body wall disruption sequence phenotype (20 cases), suspected omphalocele (three cases), and pentalogy of Cantrell (one case). We also excluded mothers with pregestational diabetes (one case and 26 controls) and nine case and 57 control mothers because of uncertainty about the presence or timing of a genitourinary infection during the period of interest. The final study group comprised mothers of 505 offspring and 4924 control infants.

Statistical analysis

As potential covariates we considered maternal age (continuous), smoking and alcohol consumption during the period around conception (yes or no), maternal race or ethnicity (Hispanic or non-Hispanic), maternal education (0-12 years or >12 years), body mass index (BMI) before pregnancy (continuous variable), first pregnancy (yes or no), gestational diabetes (yes or no), illicit drug use (yes or no), month of conception, and study centre (10 sites). We assessed the distribution of these variables by case-control status with Pearson's χ^2 test. We examined effect modification by maternal age by stratifying by maternal age groups and then using the Breslow-Day statistic and also used logit plots to test for evidence of interaction.

We first computed crude (unadjusted) risk estimates associated with each exposure group. We then used logistic regression to adjust for potential confounders. To determine the best model, we examined the association between each covariate and the risk for gastroschisis and included in the full model those covariates that were associated with risk (univariate $P < 0.25$) and did not show collinearity with each other.²⁵ The overall model fit was assessed with both

the variance inflation factor for collinearity and the likelihood ratio test.²⁶

Among most women, human papillomavirus does not elicit cytological signs of infection because it evades an effective immune response locally or systemically²⁷ so the opportunity for a fetal effect is probably limited. Therefore, we reanalysed the data after excluding women who reported infection with human papillomavirus or who had an abnormal smear result, precancerous findings, or cancer during the period around conception. All analyses were conducted with SAS 9.1 (SAS Institute, Cary, NC, 2002-3).

Table 1 | Characteristics of case and control mothers participating in national birth defects prevention study, 1997-2003. Figures are numbers (percentages) of women

	Gastroschisis (n=505)	Controls (n=4924)	P value*
Maternal age (years):			
<20	240 (47.5)	712 (14.5)	<0.001
20-24	173 (34.3)	1110 (22.5)	
25-29	56 (11.1)	1321 (26.8)	
≥30	36 (7.1)	1781 (36.2)	
Smoking†:			
Yes	180 (35.9)	941 (19.2)	<0.001
No	321 (64.1)	3963 (80.8)	
Race or ethnicity†:			
Non-Hispanic white	267 (53.0)	2956 (60.2)	<0.001
Non-Hispanic black or African American	40 (7.9)	577 (11.7)	
Hispanic	159 (31.5)	1107 (22.5)	
Other	38 (7.5)	272 (5.5)	
Maternal education (years)†:			
<12	160 (32.2)	821 (16.8)	<0.001
12	188 (37.8)	1212 (24.8)	
>12	149 (30.0)	2856 (58.4)	
BMI before pregnancy†:			
<18.5	49 (9.9)	279 (5.9)	<0.001
18.5-24.9	343 (69.4)	2681 (56.8)	
25.0-29.9	79 (16.0)	1043 (22.1)	
≥30	23 (4.7)	719 (15.2)	
Alcohol consumption†:			
Yes	203 (40.8)	1849 (37.9)	0.206
No	295 (59.2)	3033 (62.1)	
First pregnancy:			
Yes	253 (49.9)	1438 (29.2)	<0.001
No	252 (50.1)	3481 (70.8)	
Gestational diabetes†:			
Yes	7 (1.4)	179 (3.6)	0.008
No	497 (98.6)	4738 (96.4)	
Study centre:			
Arkansas	66 (13.1)	582 (11.8)	<0.001
California	119 (23.6)	682 (13.9)	
Georgia	46 (9.1)	545 (11.1)	
Iowa	56 (11.1)	558 (11.3)	
Massachusetts	45 (8.9)	638 (13.0)	
New Jersey	45 (8.9)	572 (11.6)	
New York	28 (5.5)	457 (9.3)	
North Carolina	7 (1.4)	157 (3.2)	
Texas	76 (15.0)	601 (12.2)	
Utah	17 (3.4)	132 (2.7)	

* χ^2 test for difference in distribution within each covariate.

†Values for each covariate might not add up because of missing exposure information.

RESULTS

The groups differed in several maternal characteristics, including age, smoking, race or ethnicity, maternal education, BMI before pregnancy, first pregnancy, gestational diabetes, and study centre (table 1).

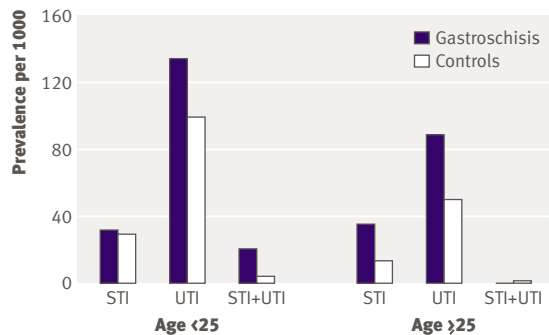
Overall, 16% (n=81) of case mothers and 9% (n=425) of control mothers reported a genitourinary infection; 4% (n=21) and 2% (n=98) reported a sexually transmitted infection and 13% (n=67) and 7% (n=338) reported a urinary tract infection, respectively.

The figure shows that younger mothers (under 25) tended to report higher rates of genitourinary infection than mothers aged 25 and over. This difference was particularly noticeable for the combination of infections (no case mothers aged 25 and over reported both a sexually transmitted infection and a urinary tract infection).

Table 2 shows odds ratios for gastroschisis by exposure group, first stratified by maternal age and then pooled to examine maternal age specific estimates. The variations were not significantly different with Breslow-Day or logit plot assessment. Crude odds ratios were higher: 2.0 (95% confidence interval 1.6 to 2.6) for sexually transmitted infection or urinary tract infections; 1.7 (1.0 to 3.0) for sexually transmitted infection only; 1.9 (1.5 to 2.6) for urinary tract infection only; and 6.8 (2.6 to 17.5) for sexually transmitted infection and genitourinary infection.

Table 3 shows a moderately increased risk for gastroschisis with exposure to genitourinary infection, particularly for the combination of infections, after adjustment for potential confounders. The risk also seemed relatively high for gastroschisis associated with other malformations (multiples), although the confidence intervals are wide and overlap those among isolated cases.

For most exposures, the pathogen was not documented. Among women who reported a urinary tract infection plus a sexually transmitted infection, the most common pathogen, *Chlamydia*, was reported by 18% of mothers of control infants and 43% of case mothers. Results were unchanged when we excluded case mothers who reported human papillomavirus infection (data not shown). We also examined any association with fever or antibiotic use. To the extent that such information was available, fever or antibiotic use for genitourinary infection was not associated with an increased risk of gastroschisis.



Prevalence of genitourinary infection (per 1000) among case mothers and control mothers, stratified by maternal age, national birth defects prevention study, 1997-2003 (STI=sexually transmitted infection, UTI=urinary tract infection)

DISCUSSION

In this population based study, we found that genitourinary infections just before or during early pregnancy were associated with a moderately increased risk of gastroschisis in offspring. The risk was highest in women who had had both a urinary tract infection and a sexually transmitted infection, and infection was more commonly reported by women aged under 25 than by those aged 25 and older. These findings, if confirmed, suggest a role for genitourinary infection as a risk factor for gastroschisis, especially among younger women.

Limitations and strengths

Participation rates were similar among case and control mothers, but we cannot exclude selective participation leading to bias. Reliability of information on exposure involved several issues. The use of a computer assisted interview probably reduced, but could not have excluded, selective, imprecise, or biased reporting. For example, we would have classified women with subclinical infection as unexposed, leading to underestimation of the risk for gastroschisis. In the United States, subclinical urinary tract infections are estimated to occur in 2-14% of pregnant women,^{28,29} and in family planning clinics for chlamydia screening, sexually transmitted infections ranged from 3.0% to 20.3%.³⁰ Reporting of a genitourinary infection might have varied depending on whether a woman had an affected child (recall bias by case-control status), although the direction and magnitude of such bias would have been

difficult to anticipate. We initially assessed effect modification by maternal age using the Breslow Day test, which, because of the small sample size, might not be valid. Logit plots confirmed the findings and we could not detect effect modification by maternal age in any genitourinary infection group.

The limitations in sample size, participation rates, and reporting reliability mean we should be cautious in interpreting our results. Specifically, the effect estimates provide a direction for the effect but are imprecise, and the findings might be spurious or due to chance.

The cases of birth defects were actively ascertained through population based programmes. Homogeneity of case reporting and classification was improved by common case definitions and final clinical review by a single clinical geneticist.

Theories behind the association

Evaluation of the plausibility of the association between genitourinary infections and gastroschisis is challenging on several levels, mainly because of the limited knowledge on aetiology and pathogenesis. Even normal closure of the ventral body wall is not well understood. The ventral body wall closes by 37 days after conception,³¹ but its genetic determinants and developmental processes are largely unknown. The pathogenesis of gastroschisis is also still being debated.³² One theory implicates vascular disruption. More recently, an abnormality in lateral fold closure leading to herniation via the vitelline duct was proposed as an alternative mechanism in at least some cases.³² These discussions are relevant to the potential role of infection in that a primary defect in wall closure might be influenced by infections earlier in pregnancy compared with a vascular disruption, which might occur after body wall closure.

Genitourinary infections have been inconsistently associated with an increased risk for major birth defects.³³⁻³⁶ One recent study reported a significant association between gynaecological infection reported before the current pregnancy and risk of gastroschisis.³⁷ The timing and type of infection was not described. A genitourinary infection could affect prenatal development in different ways, either directly or through immune and inflammatory responses. Modulators of risk include the dose of the pathogen, as well as

Table 2 | Crude odds ratios with 95% confidence intervals for risk of gastroschisis according to genitourinary infection and stratified by maternal age, national birth defects prevention study, 1997-2003

	Maternal age				Crude odds ratio	Adjusted odds ratio*	P value†
	<20	20-24	25-29	≥30			
STI or UTI	1.3 (0.9 to 2.0)	1.5 (1.0 to 2.4)	1.2 (0.5 to 3.1)	2.8 (1.1 to 7.4)	2.0 (1.6 to 2.6)	1.4 (1.1 to 1.9)	0.5158
STI only	1.3 (0.6 to 3.0)	0.7 (0.2 to 2.3)	1.4 (0.2 to 10.8)	4.9 (1.1 to 21.9)	1.7 (1.0 to 3.0)	1.2 (0.7 to 2.2)	0.1884
UTI only	1.3 (0.8 to 2.0)	1.5 (0.9 to 2.5)	1.2 (0.4 to 3.4)	2.3 (0.7 to 7.6)	1.9 (1.5 to 2.6)	1.4 (1.0 to 1.9)	0.8063
STI plus UTI	2.3 (0.5 to 10.5)	9.1 (2.0 to 41.0)	—‡	—‡	6.8 (2.6 to 17.5)	3.9 (1.4 to 10.8)	0.5286

STI=sexually transmitted infection; UTI=urinary tract infection.

*Mantel-Haenszel odds ratio, adjusted for maternal age.

†Breslow-Day test for heterogeneity of maternal age group.

‡No reports of both infections.

Table 3 | Adjusted odds ratios with 95% confidence intervals for isolated, multiple, and all cases of gastroschisis according to genitourinary tract infection, national birth defects prevention study, 1997-2003

	No (%) of controls	Isolated (n=466)		Multiple (n=39)		All (n=505)	
		No (%) of cases	Odds ratio* (95% CI)	No (%) of cases	Odds ratio† (95% CI)	No (%) of cases	Odds ratio* (95% CI)
Unexposed	4499 (91.3)	397 (85.2)	Reference	27 (69.2)	Reference	424 (83.9)	Reference
STI or UTI‡	425 (8.6)	69 (14.8)	1.3 (1.0 to 1.8)	12 (30.8)	3.1 (1.5 to 6.2)	81 (16.0)	1.5 (1.1 to 1.9)
STI only	87 (1.7)	13 (2.8)	1.3 (0.7 to 2.4)	1 (2.6)	1.2 (0.2 to 9.1)	14 (2.8)	1.3 (0.7 to 2.3)
UTI only	327 (6.6)	51 (10.9)	1.3 (0.9 to 1.8)	9 (23.1)	3.1 (1.4 to 6.7)	60 (11.9)	1.4 (1.0 to 2.0)
STI plus UTI	11 (0.22)	5 (1.1)	2.9 (0.9 to 9.5)	2 (5.1)	12.9 (2.4 to 69.1)	7 (1.4)	4.0 (1.4 to 11.6)

STI=sexually transmitted infection; UTI=urinary tract infection.

*Adjusted for maternal age, BMI before conception, smoking, and Hispanic ethnicity.

†Adjusted for maternal age only.

‡Sum of STI only, UTI only, and STI plus UTI.

individual susceptibility. For example, the increased risk among younger women might be an age related differential response to infection. This response, in turn, might vary by pathogen. Chlamydia infections seem to cause a considerable immune response,^{38,39} which might partly explain the risk of subsequent infertility,^{39,40} whereas human papillomavirus tends to be cleared without sequelae by most women without a concurrent measurable immune response.²⁷ In our study exclusion of human papillomavirus infections (and its correlates) from the analysis did not alter our findings.

For genitourinary infection to be a plausible contributor to the rising rates of gastroschisis, particularly among younger women, the infection has to be common, must be increasing in prevalence, and ought to be either more common or more harmful among younger women. Alternatively, infection could be a correlate of the true causal factor that has the same features. Several studies have suggested that rates of sexually transmitted infections are increasing in many parts of the world,⁴¹ particularly among women aged 15-25.⁴² Weinstock et al estimated that nearly a half of all new sexually transmitted infections are acquired by this age cohort.²⁰ Among younger women in the US, the most common cause of sexually transmitted infection is *Chlamydia trachomatis*, which has a peak prevalence among people aged 25 and younger.²⁴ In England, according to data from genitourinary infection clinics, sexually transmitted infections caused by *C trachomatis* increased 46% during 1988-98, and among women the increase was greatest among adolescents aged 16-19.⁴¹ In the country of Georgia, the prevalence of asymptomatic chlamydia infection among pregnant women was 73%, again with highest rates, particularly of subclinical infection, among younger women.⁴³

Urinary tract infections are also common during pregnancy,^{35,44} either as symptomatic cystitis or asymptomatic bacteriuria. During pregnancy, the incidence of cystitis is estimated at 1-4%⁴⁵ and asymptomatic bacteriuria at 2-14%.^{28,29} In addition, urinary tract infections and sexually transmitted infections probably have common risk factors. These include having a new sexual partner in the previous 12 months, frequency of sexual intercourse in the past

30 days,^{21,46} being aged 15 or younger at first infection,⁴⁷ and having chlamydia.⁴⁸ Urinary tract infections are more common among adolescent girls who are sexually active⁴⁹ and are viewed as a common indicator of their sexual debut.⁵⁰

A possible model of the relation between genitourinary infection and gastroschisis involves an infection associated with early sexual activity, and the related risk for gastroschisis might be amplified among adolescents and younger women. Susceptibility among these women might be due to several factors, including the immune response to new pathogens, new partners, and changes in partners.⁵¹ Our finding that the risk was highest for exposure to both types of infection, particularly among younger women, suggests a combined role of infection and early sexual activity. This finding is consistent with but does not prove a role for dose of pathogen in the risk for gastroschisis. Alternatively, contributors to risk could include the type of pathogen(s) or the inflammatory or immune response to the infections. The prevalence of self reported chlamydia was higher in the group of women who reported both types of infection compared with the control group. Although we could not confirm the pathogen in the infections reported in our study, infection by *C trachomatis* might be a candidate for future research as it is known to cause both urinary tract infections and sexually transmitted infections. The role of immune or inflammatory response to infections is also unclear. Definitive answers will probably require biological specimens collected during pregnancy—but close to conception—to identify the presence of pathogen(s) and any inflammatory response. To our knowledge, this has not yet been accomplished and might be particularly challenging in retrospective case-control studies.

It is important to replicate and validate these findings, particularly with reliable markers of infection and inflammation. From a clinical and public health perspective, it will be crucial to assess whether reducing genitourinary infection in the population through clinical and public health programmes leads to a reversal of the increasing trends of gastroschisis internationally.

WHAT IS ALREADY KNOWN ON THIS TOPIC

Gastroschisis is increasing worldwide and disproportionately affects pregnancies in young women

These epidemiological patterns suggest a role for underlying environmental cause(s) such as infection, nutrition, or medication use

In young women who are sexually active, urinary tract infections and sexually transmitted infections are common and increasing in prevalence

WHAT THIS STUDY ADDS

Women reporting a genitourinary tract infection in early pregnancy (particularly both a sexually transmitted infection and a urinary tract infection) were more likely to have a child with gastroschisis

The findings are suggestive but not conclusive because of the imprecise risk estimates and the reliance on self reported events

From a public health perspective, it is crucial to assess whether reducing these common infections reverses the increasing trend of gastroschisis internationally

We thank the participants of the national birth defect prevention study. The findings and conclusions in this report are those of the authors and do not necessarily represent the official position of the Centers for Disease Control and Prevention.

Contributors: MLF conceived and designed the project, developed the analytical strategy, wrote the manuscript, and is guarantor. JR and JK assisted with analysis and manuscript preparation. SK and AW assisted with data cleaning and analysis. CAM was responsible for case classification and manuscript preparation. JCC assisted with project design and manuscript preparation. LDB provided guidance of project design and assisted with analysis and manuscript preparation.

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