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## 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 state 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 rare congenital malformation that occurs in about 1 in 2700 births. Several studies have tried to identify an environmental risk factor that could account for the rapidly increasing occurrence of

gastroschisis in several countries worldwide,<sup>1-5</sup> especially in infants of mothers under 20 years compared with mothers aged 25 or older.<sup>6</sup> Researchers have identified epidemiological associations with smoking, alcohol use, and use of common medications. 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 as they are common among sexually active young women, and the frequent and increasing rates of infections among women make this a reasonable focus of investigation. The investigation was conducted as part of the national birth defects prevention study.<sup>7,8</sup>

### 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. Cases are identified through 10 population based surveillance programmes in 10 states, 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.<sup>7</sup> Once enrolled in the study, mothers of affected and control infants take part in a computer assisted telephone interview. During the interview, trained staff systematically collect data on demographics, use of medication, illnesses, occupation, lifestyle, and other exposures from three months before pregnancy

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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. One investigator also further reviewed and classified all cases. We also included cases that were diagnosed prenatally and resulted in a stillbirth or termination of pregnancy, except in two states. Cases of gastroschisis were classified as isolated or multiple (where there was at least one other unrelated major malformation). See [bmj.com](http://bmj.com).

### 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. We divided genitourinary infections into urinary tract infections or sexually transmitted infections. Any woman who reported pelvic inflammatory disease was considered to have a sexually transmitted infection.<sup>9</sup> We examined urinary tract infections and sexually transmitted infections together and separately.

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.

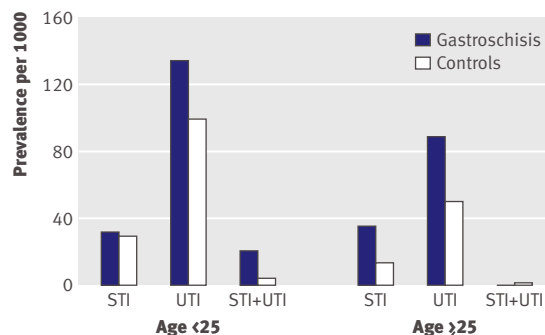
### Inclusions, exclusions, and final study group

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 infants and 5008 control infants. After exclusions the final study group comprised mothers of 505 affected offspring and 4924 control infants.

### Statistical analysis

As potential covariates we considered maternal age, smoking and alcohol consumption during the period around conception, maternal race or ethnicity, maternal education, body mass index (BMI) before



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

pregnancy, first pregnancy, gestational diabetes, illicit drug use, month of conception, and study centre. We assessed the distribution of these variables by case-control status and 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 and then used logistic regression to adjust for potential confounders. We included in the full model those covariates that were associated with risk (univariate  $P < 0.25$ ) and did not show collinearity with each other. See [bmj.com](http://bmj.com).

### 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. See [bmj.com](http://bmj.com). Overall, 16% ( $n=81$ ) of mothers of affected infants 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.

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

	Isolated ( $n=466$ )			Multiple ( $n=39$ )		All ( $n=505$ )	
	No (%) of controls	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.

**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

Crude odds ratios were: 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. The variations were not significantly different with Breslow-Day or logit plot assessment

The table 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 (multiple), 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. To the extent that such information was available, fever or antibiotic use for genitourinary infection was not associated with an increased risk of gastroschisis.

**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. We assessed effect modification by maternal age and could not detect any effect modification 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; 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. One recent study reported a significant association between gynaecological infection reported before the current pregnancy and risk of gastroschisis.<sup>10</sup> The timing and type of infection was not described. Chlamydia infections seem to cause a considerable immune response, whereas human papillomavirus tends to be cleared without sequelae by most women without a concurrent measurable immune response. 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,<sup>11</sup> particularly among women aged 15-25.<sup>12</sup> Weinstock et al estimated that nearly a half of all new sexually transmitted infections are acquired by this age cohort.<sup>13</sup> Urinary tract infections are also common during pregnancy, probably share common risk factors with sexually transmitted infections and also are more common among adolescent girls who are sexually active.<sup>14</sup>

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.<sup>15</sup> 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. *C trachomatis* might be a candidate for future research as it is known to cause both urinary tract infections and sexually transmitted infections.

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## Long term prognosis in preschool children with wheeze: longitudinal postal questionnaire study 1993-2004

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### ABSTRACT

**Objectives** To follow a population of preschool children with and without parent reported wheeze over a period of 6-11 years to determine prognosis and its important predictive factors.

**Design** Longitudinal series of five postal surveys based on the international study of asthma and allergies in childhood questionnaire carried out between 1993 and 2004.

**Setting** Two general practice populations, south Manchester.

**Participants** 628 children aged less than 5 years at recruitment and those with at least six years' follow-up data.

**Main outcome measures** Parent completed questionnaire data for respiratory symptoms and associated features.

**Results** Of 628 children included in the study, 201 (32%) had parent reported wheeze at the first observation (baseline), of whom 27% also reported the symptom on the second occasion (persistent asthma). The only important

baseline predictors of persistent asthma were exercise induced wheeze (odds ratio 3.94, 95% confidence interval 1.72 to 9.00) and a history of atopic disorders (4.44, 1.94 to 10.13). The presence of both predictors indicated a likelihood of 53.2% of developing asthma; if only one feature was present this decreased to 17.2%, whereas if neither was present the likelihood was 10.9%. Family history of asthma was not predictive of persistent asthma among children with preschool wheeze.

**Conclusion** Using two simple predictive factors (baseline parent reported exercise induced wheeze and a history of atopic disorders), it is possible to estimate the likelihood of future asthma in children presenting with preschool wheeze. The absence of baseline exercise induced wheeze and a history of atopic disorders reduces the likelihood of subsequent asthma by a factor of five.

### INTRODUCTION

Although most cases of asthma begin in early childhood, it has been difficult to predict which preschool