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Maternal Antibodies to *Chlamydia trachomatis* and Risk of Gastroschisis

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Abstract

Background—Gastroschisis, a birth defect of the abdominal wall, is increasing in prevalence. The largest increase in prevalence has been observed among young mothers (<20 years). The prevalence of *Chlamydia trachomatis* (CT) infection is highest among young women and has also been increasing over time. The objective was to investigate the association between immunoglobulin G antibodies to *Chlamydia trachomatis* (CT) (anti-CT) and Chlamydial heat shock protein 60 (anti-CHP60) during pregnancy, and risk of gastroschisis among offspring.

Methods—We conducted a nested case–control study of 292 gastroschisis cases identified from the Congenital Malformations Register and 826 live born controls matched on age and birth year within the Finnish Maternity Cohort. Early pregnancy serum samples were used to categorize women by seropositivity to anti-CT and anti-CHP60. Women seronegative for anti-CT and anti-CHP60 served as the reference. We used conditional logistic regression to calculate odds ratios (ORs) and 95% confidence intervals (CIs). Effect measure modification by maternal age (<25 years, ≥25 years) was also assessed.

Results—Seropositivity to anti-CT (17.8% of cases vs. 16.0% of controls) or anti-CHP60 (23.6% of cases vs. 22.0% of controls) was not associated with gastroschisis. Although, the OR for seropositivity to anti-CT alone was slightly elevated (OR, 1.19; 95% CI, 0.73–1.94), specifically among young mothers (<25 years) (OR, 1.65; 95% CI, 0.81–3.37), the results were imprecise.

Conclusion—*Chlamydia* infection, as measured by immunoglobulin G antibodies to CT and CHP60, is not associated with gastroschisis, however, our assays were not able to distinguish recent infection.

Keywords

gastroschisis; *Chlamydia trachomatis*; antibodies; heat shock protein

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Introduction

Gastroschisis, a birth defect of the abdominal wall, has been increasing in prevalence worldwide (Castilla et al., 2008). This increase has predominantly been driven by younger mothers. In the United States from 1995 through 2005, the annual percentage increase in the prevalence of gastroschisis was 6.5% among mothers less than 20 years old while just 0.2% among mothers 35 years or older (Kirby et al., 2013). This growing disparity has led to investigations of potential risk factors known to be more common or increasing in prevalence among younger mothers.

There is a mounting body of literature suggesting that maternal genitourinary infections, including urinary tract infections (UTIs) and sexually transmitted infections, may be involved in the development of gastroschisis. Studies based on maternal report of first trimester genitourinary infections have reported increases in risk of gastroschisis among mothers with either a UTI or sexually transmitted disease (STD) (Feldkamp et al., 2008, Yazdy et al., 2014). One study showed these associations were amplified when the infection was coupled with young maternal age, indicating a synergism between infection and young age (Yazdy et al., 2014). With regard to specific types of STDs an increased risk of gastroschisis has been observed among mothers whom reported genital herpes infections (Ahrens et al., 2013) and with seropositivity to *Chlamydia trachomatis* (Feldkamp et al., 2015), and to herpes simplex virus 2 (HSV-2) (Werler et al., 2016).

C. trachomatis (CT) is the most common sexually transmitted bacterial infection (Weinstock et al., 2004). The prevalence of CT infection is highest among young women (Tao et al., 2014) and has also been increasing over time (Johnson et al., 2014). A substantial proportion of CT infections are asymptomatic which highlights the limitation of using self-reported or medically treated infection data and underscores the necessity of biospecimens to correctly classify exposure. The presence of immunoglobulin G (IgG) antibodies to CT in maternal serum can indicate past exposure to CT as these antibodies can remain detectable for months and even years after infection (Horner et al., 2013, 2016). Antibodies to Chlamydial heat shock protein 60 (CHP60) can also provide information regarding CT exposure, serving as a marker of possible chronic or persistent CT infections (Brunham and Peeling 1994; Peeling et al., 1997). A recent study of IgG antibodies to CT from mid-pregnancy serum samples demonstrated an increased risk of gastroschisis in offspring among mothers with a particular subtype of IgG antibodies to CT, IgG3, (Feldkamp et al., 2015) which are a possible marker of recent infection (Geisler et al., 2012).

The aim of this study was to examine the association between IgG antibodies to CT and CHP60 present in first trimester maternal sera samples and risk of gastroschisis using data from the Finnish Maternity Cohort (FMC), a population-wide biobank repository of pregnancies in Finland.

Materials and Methods

We conducted a population-based case-control study of gastroschisis nested within the FMC (Werler et al., 2016). The FMC is a biorepository that contains serum samples from nearly

all pregnant women in Finland since 1983. Blood samples are collected during the first trimester of pregnancy to screen for congenital infections and sera are stored at the Finnish National Institute for Health and Welfare. The FMC covers more than 98% of all Finnish pregnancies with a mean gestational age at sampling of 11.1 weeks and with 90% of samples being collected by the 15th week of gestation. Informed consent was obtained from pregnant women before their blood draw for the use of samples in scientific studies. The study protocol was approved by the coordinating ethics committee of the Medical Faculty of Oulu and was approved by the FMC steering group. The permission to collect information from the registries was received from THL (National Institute for Health and Welfare) after consulting the Data Protection Ombudsman in Finland.

GASTROSCHISIS

The Congenital Malformations Register is a nationwide registry of malformations among elective terminations, spontaneous abortions, stillbirths, and livebirths. Cases of gastroschisis (1987–2012) were identified by International Classification of Diseases, 9th Revision, code from the Congenital Malformations Register and records of gastroschisis cases were reviewed by a clinical geneticist. Based on the absence or presence of other major defects, cases were classified as isolated (85%) or multiple. Controls were nonmalformed infants selected from the Medical Birth Register and matched to cases by maternal age (± 1 year), infant year of birth, and geographic region.

ANTIBODY ANALYSIS

Mothers of cases and controls were linked to the FMC using a personal identification number and subjects without an available serum sample were excluded. *C. trachomatis* specific IgG antibodies (anti-CT) and anti-CHP60 were analyzed using the major outer membrane protein peptide-based (*C. trachomatis*-IgG-ELISA plus, Medac Diagnostika, Germany) and Chlamydial recombinant CHP60 protein-based (CHP60-IgG-ELISA, Medac Diagnostika, Germany) commercially available enzyme-linked immunosorbent assay (ELISA) kits according to manufacturer's instructions. Anti-CT antibody results are expressed as unit values (AU/ml) with AU/ml ≥ 25 as a cutoff of negative result and anti-CHP60 results are expressed as an optical density (OD) index (OD value of the sample at 450 nm/OD of the negative control) with OD < 0.4 as a cutoff of negative results. We considered subjects whose test results were in the gray zone to be seropositive.

Women were initially categorized based on seropositivity for anti-CT antibodies, labeled "anti-CT," and seropositivity for anti-CHP60 antibodies, labeled "anti-CHP60." Women with seropositivity to both would have been included in each of these categories. We performed a secondary analysis in which we examined women with seropositivity to either anti-CT or anti-CHP60 antibodies, labeled "Any." These women were also further categorized into 3 mutually exclusive CT infection groups as follows; (1) Anti-CT and anti-CHP60 positive women labeled as "Both," (2) anti-CT positive and anti-CHP60 negative labeled as "anti-CT only," and (3) anti-CT negative and anti-CHP60 positive women were labeled as "anti-CHP60 only." Women that were anti-CT and anti-CHP60 negative were labeled as "no infection."

STATISTICAL ANALYSIS

Maternal characteristics, including age, gravidity, parity, and smoking during pregnancy, were obtained from the Medical Birth Register, which contains information on all livebirths and stillbirths from 22 gestational weeks or 500 grams onward (Gissler et al., 1995). The distribution of maternal characteristics among gastroschisis cases and controls was tabulated. These characteristics were also described by “anti-CT,” “anti-CHP60,” and “no infection” among controls only. We used conditional logistic regression to calculate odds ratios (OR) and 95% confidence intervals (CIs) using the “no infection” group as the reference. Using a change-in-estimate approach with a criterion of 10% change, no covariate was retained in the adjusted models. Because HSV-2 was associated with gastroschisis in this same study population, ORs were adjusted for HSV-2 positivity. Serologic measures of HSV-2 in this dataset have previously been described (Werler et al., 2016). An analysis stratified by maternal age (<25 years, ≥25 years) was performed to assess effect measure modification.

Results

A total of 427 potential cases were identified from the Malformations Register. Of these, 118 were excluded for diagnostic reasons (early embryonic defects, insufficient information, chromosomal abnormalities), and 17 were excluded due to unclear serum sampling dates or missing CT-serology data, resulting in 292 gastroschisis cases and their 826 matched controls (Fig. 1). Overall, 97 cases (33.2%) and 247 controls (29.9%) had evidence of any antibodies, either anti-CT or anti-CHP60, with 52 cases (17.8%) and 132 controls (16.0%) seropositive for anti-CT antibodies, and 69 cases (23.6%) and 182 controls (22.0%) seropositive for anti-CHP60 antibodies. A total of 24 (8.2%) cases and 67 (8.9%) controls were seropositive to both (Table 1).

Compared with control mothers, case mothers were more likely to be nulliparous (60.3% vs. 48.2%) and more likely to smoke during pregnancy (19.9% vs. 17.4%). Among controls only, women seropositive for anti-CT antibodies were more likely to be ≥25 years of age. Smoking during pregnancy was more common among “anti-CT” or “anti-CHP60” mothers compared with those with no infection. The percentage of mothers with HSV2 IgG antibodies was highest among those seropositive for anti-CT antibodies. The percentage of control subjects classified as no CT infection increased over the study period (Table 2).

The presence of anti-CT antibodies was slightly more common among cases than among controls (17.8% vs. 16.0%), as was the presence of anti-CHP60 antibodies (23.6% vs. 22.0%). The conditional OR for the associations between seropositivity from anti-CT antibodies and anti-CHP60 antibodies with gastroschisis was null after adjustment for IgG antibodies to HSV-2. In the secondary analysis with finer categories of antibody profiles, the OR for “anti-CT only” was slightly elevated (1.30; 95% CI, 0.81–2.10). Adjustment for IgG antibodies to HSV-2 attenuated this finding to 1.19 (95% CI, 0.73–1.94). The ORs for the other categories were essentially null (Table 3).

Results stratified by maternal age (<25, ≥25) are presented in Table 4. Among young mothers, the OR for “anti-CT” and gastroschisis was 1.17 (95% CI, 0.70–1.95). Among older mothers (≥25 years), this OR was 0.96 (95% CI, 0.56–1.63). In the secondary analysis,

an elevated OR was observed for “anti-CT only” and gastroschisis among younger mothers (OR, 1.65; 95% CI, 0.81–3.37), although this estimate was based on only 14 cases.

Discussion

Seropositivity to anti-CT antibodies or anti-CHP60 antibodies was not associated with an increased risk of gastroschisis in this population-based case-control study. The OR for the presence of anti-CT antibodies without anti-CHP60 antibodies suggested a 30% increased risk of gastroschisis, before adjustment for HSV-2 seropositivity. This observed association between serologic evidence of past CT infection and gastroschisis is similar to that of a case-control study based on maternal report that reported an OR of 1.33 (95% CI, 0.14–12.82) (Elliott et al., 2009). However, in our study, some of the 1.3-fold increased risk appeared to be due to confounding by HSV-2 infection. Two other studies reported ORs of similar magnitude for self-reported STDs during the first trimester in relation to gastroschisis although neither of these studies distinguished between specific types of STDs (Feldkamp et al., 2008; Yazdy et al., 2014).

Our findings stand in contrast to the one other study to our knowledge that evaluated CT serology in relation to the risk of gastroschisis. Feldkamp et al. examined CT IgG subtypes 1 and 3 and reported a near fourfold increase of gastroschisis for the presence of IgG3 antibodies. They also reported no association for the more common IgG1 subtype. They state that IgG3 is reflective of a more recent CT exposure as IgG3 antibodies only remain elevated for a short period after CT exposure. In the present study, we did not distinguish between IgG1 and IgG3 and our assay could not distinguish recent infection from past infection. Additionally, our assay would have captured other IgG subtypes, such as IgG2 and IgG4, which are known to have a low response to CT infection (Geisler et al., 2012), and may explain the absence of a strong association.

It has previously been hypothesized that observed associations between genitourinary infections and gastroschisis may operate through a pathway involving immune response. Antibodies to CHP60, which are reflective of chronic CT infection, have been found to be more predictive of outcomes such as tubal factor infertility and pelvic inflammatory disease, than other markers of CT infection, although findings have been contradictory. It has been hypothesized that the superior prediction of CHP60 stems from human heat shock protein synthesis being upregulated during pregnancy and women with a history of *Chlamydia* infection and immunity to CHP60 may develop autoimmunity to *human* heat shock protein resulting in adverse pregnancy outcomes (Witkin, 1999; Belhia et al., 2010). The presence of antibodies to CHP60 was not associated with an overall increased risk of gastroschisis in our study.

Upon stratification by maternal age, the association between anti-CT antibodies and gastroschisis was driven by young mothers below 25 years. In our data, past infection (IgG antibodies to CT) did in fact increase with age among control mothers. The lack of an association between past infection and gastroschisis among older women may be partly explained by the higher prevalence of anti-CT antibodies among control women. We were

unable to circumvent this issue and assess the joint effect of young maternal age and infection due to the age-matched design.

In the present study, 16% of control women tested positive for IgG antibodies to CT which is in line with estimates of prevalence among European asymptomatic women (Wilson et al., 2002), but is much lower than that reported among control women in the Feldkamp study. The difference may be due to our use of the MEDAC test, which has previously been shown to capture approximately one-third of those that test seropositive according to whole elementary body based ELISA. The ELISA captures antibodies against a wide range of antigenic structures, part of which may be nonspecific, although cross-reactivity with other *Chlamydia* species was not problematic (Geisler et al., 2012). The racial composition of the two studies also varied and racial variation among serovars in response to CT have previously been observed (Workowski et al., 1992; Geisler et al., 2012).

Consistent with previous studies from Finland, we observed a decrease in the seroprevalence of CT over the study period (Lyytikäinen et al., 2008). Although an increase in diagnoses of *Chlamydia* infections has been observed, this decrease in seroprevalence may be explained by early detection and treatment (Brunham et al., 2005) or alternatively an increase in repeated infections, which are only captured as unique *Chlamydia* infections in intervals longer than 3 months. CT is associated with infertility and spontaneous abortion. Therefore, prevalence among mothers of live born controls in our study likely underestimates the prevalence in the general population.

The major strength of the present study is the use of the world's largest repository of serum samples from pregnant women. These samples were collected in early pregnancy, a time frame that parallels the development of gastroschisis, and, therefore, represents the appropriate etiologic window. The use of serum samples to measure IgG antibodies to both CT and CHP60 can provide a more detailed assessment of CT infection history. CT IgG antibodies decrease with time since infection, with evidence of a decrease in antibodies six months after infection followed by a plateau, but have been observed to remain detectable years after infection and are, therefore, useful in identifying a past infection. Samples from the Finnish Maternity Cohort have previously been used to report on a well-established association between IgG antibodies to CT and ectopic pregnancy (Rantsi et al., 2016), providing support for the validity of using these samples for classification of CT exposure. Additional strengths include the medical record review of gastroschisis cases by a clinical geneticist and the use of the Medical Birth Register for control selection, which captures nearly all birth in Finland.

Our study is not without limitations. Antibodies to CHP60 are not necessarily specific to *C. trachomatis* because it shares antigenic epitopes between *Chlamydia* species along with other bacteria and eukaryotic cells, which may be a source of exposure misclassification. Additionally, we did not have complete information on UTIs or all other STDs. Previous studies have shown that women with antibodies to CT have concomitant seropositivity to HPV-16, HSV-2, and *Treponema pallidum*, more often than would be expected (Kibur et al., 2000). In the case of HSV-2, for which we did have serologic data, our findings were attenuated upon adjustment. It is unclear how adjustment for seropositivity to other

infections would impact our findings, although none of the subjects in our dataset would be suspected to be positive for *Treponema pallidum*. Other potential confounders for which we lacked information included treatment for CT infection and other risk-taking behaviors.

CONCLUSIONS

Seropositivity for antibodies to CT or CHP60 was not associated with an increased risk of gastroschisis. It is important to note that adjustment for seropositivity to genital herpes attenuated all associations for anti-CT antibodies. Optimally, future studies would use CT serological assays that could accurately measure recent and repeated *Chlamydia* infection and concomitant genitourinary infections and the risk of gastroschisis. However, precise measurement of these exposures requires longitudinal design, which is prohibitive for studies of a rare outcome like gastroschisis.

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FIGURE 1.
Diagram of cases and matched control study population.

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Seropositivity to IgG antibodies to *Chlamydia trachomatis* and CHP60 among Gastroschisis Cases and Controls, Finnish Maternity Cohort, 1987 to 2012

TABLE 1

		Cases (<i>n</i> = 292)		Controls (<i>n</i> = 826)	
		CT IgG		CT IgG	
		+	-	+	-
		Total		Total	
CHP60 IgG	+	24	45	69	67
		182		115	
	-	28	195	223	65
		644		579	
Total		52	240	292	132
		826		694	

Demographic and Reproductive Characteristics by Case and Control Status and by *Chlamydia* Exposure Category among Controls Only, 1987 to 2012

TABLE 2

	Case status				Antibody type, controls only			
	Gastroschisis cases (n = 292)		Controls (n = 826)		Anti-CT (n = 132)		Anti-CHP60 (n = 182)	
	n	%	n	%	n	%	n	%
Maternal age								
<20	52	17.8	134	16.2	20	15.2	31	17.0
20–24	104	35.6	320	38.7	43	32.6	77	42.3
25	136	46.6	372	45.0	69	52.3	74	40.7
Gravidity								
0	123	42.1	318	38.5	42	31.8	61	33.5
3	53	18.2	124	15.0	23	17.4	40	22.0
Parity								
0	176	60.3	398	48.2	62	47.0	84	46.2
3	12	4.1	54	6.5	11	8.3	20	11.0
Smoking in pregnancy	58	19.9	144	17.4	29	22.0	41	22.5
HSV-2 IgG								
Nonreactive	178	61.0	538	65.1	68	51.5	106	58.2
Reactive	114	39.0	288	34.9	64	48.5	76	41.8
Year of birth								
1987–1991	35	12.0	94	11.4	21	15.9	27	14.8
1992–1996	48	16.4	140	16.9	30	22.7	35	19.2

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	Case status						Antibody type, controls only					
	Gastroschisis cases (n = 292)			Controls (n = 826)			Anti-CT (n = 132)		Anti-CHP60 (n = 182)		None (n = 579)	
	n	%		n	%		n	%	n	%	n	%
1997–2001	60	20.5		169	20.5		32	24.2	38	20.9	118	20.4
2002–2006	70	24.0		196	23.7		28	21.2	37	20.3	141	24.4
2007–2012	79	27.1		227	27.5		21	15.9	45	24.7	173	29.9

TABLE 3

ORs and 95% CIs for the Association between *Chlamydia* Exposure Category and Gastroschisis, Crude and Adjusted for HSV-2 Seropositivity

	Cases (<i>n</i> = 292)		Controls (<i>n</i> = 826)		Conditional OR (95% CI)	
	<i>n</i>	%	<i>n</i>	%	Crude	Adjusted ^a
Anti-CT	52	17.8	132	16.0	1.14 (0.80–1.62)	1.05 (0.73–1.52)
Anti-CHP60	69	23.6	182	22.0	1.07 (0.78–1.48)	1.03 (0.74–1.43)
Secondary analysis						
Any	97	33.2	247	29.9	1.15 (0.86–1.54)	1.09 (0.81–1.46)
Anti-CT only	28	9.6	65	7.9	1.30 (0.81–2.10)	1.19 (0.73–1.94)
Anti-CHP60 only	45	15.4	115	13.9	1.13 (0.77–1.67)	1.10 (0.75–1.63)
Anti-CT and anti-CHP60	24	8.2	67	8.1	1.04 (0.63–1.71)	0.96 (0.58–1.60)
None	195	66.8	579	70.1	1.00 (reference)	1.00 (reference)

^a Adjusted for seropositivity to HSV-2.

Odds Ratios and 95% Confidence Intervals for the Association between *Chlamydia* Exposure Category and Gastroschisis, Stratified by Maternal Age

TABLE 4

	Maternal age < 25				Maternal age ≥ 25			
	Cases (n = 156)		Controls (n = 454)		Cases (n = 136)		Controls (n = 372)	
	n	%	n	%	n	%	n	%
Anti-CT	26	16.7	63	13.9	26	19.1	69	18.5
								Conditional OR ^a (95% CI)
								0.96 (0.56–1.63)
Anti-CHP60	37	23.7	108	23.8	32	23.5	74	19.9
								Conditional OR ^a (95% CI)
								1.15 (0.70–1.90)
Secondary analysis								
Any antibody	51	32.7	134	29.5	46	33.8	113	30.4
								Conditional OR ^a (95% CI)
								1.07 (0.69–1.65)
Anti-CT only	14	9.0	26	5.7	14	10.3	39	10.5
								Conditional OR ^a (95% CI)
								0.93 (0.47–1.85)
Anti-CHP60 only	25	16.0	71	15.6	20	14.7	44	11.8
								Conditional OR ^a (95% CI)
								1.19 (0.65–2.17)
Anti-CT + anti-CHP60	12	7.7	37	8.1	12	8.8	30	8.1
								Conditional OR ^a (95% CI)
								1.06 (0.49–2.31)
None	105	67.3	320	70.5	90	66.2	259	69.6
								Conditional OR ^a (95% CI)
								1.00 (reference)

^a Adjusted for seropositivity to HSV-2.