Associations Between Maternal Fever and Influenza and Congenital Heart Defects

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Objective To examine associations between maternal reports of prenatal fever or influenza and congenital heart defects (CHDs), and to evaluate whether those associations varied with antipyretic use.

Study design We analyzed case infants with CHD (n = 2361) and control infants without CHD (n = 3435) from the Baltimore-Washington Infant Study (1981-1989). Participating mothers were asked whether they experienced a "fever of 101°F or higher," had "influenza (flu)," or used an antipyretic agent (ie, acetaminophen, salicylate, or nonsteroidal anti-inflammatory drug) during the period extending from 3 months before pregnancy through the end of the third month of pregnancy. We used logistic regression to compute ORs and 95% CIs while controlling for potential confounders.

Results There were significant associations between fever and influenza and specific CHDs, namely right-sided obstructive defects (fever: OR, 2.04; 95% CI, 1.27 to 3.27; influenza: OR, 1.75; 95% CI, 1.16 to 2.62) and atrioventricular septal defects in infants with Down syndrome (fever: OR, 1.92; 95% CI, 1.10 to 3.38; influenza: OR, 1.66; 95% CI, 1.04 to 2.63). Maternal antipyretic use in the setting of fever or influenza tended to decrease these associations.

Conclusions Prenatal maternal fever or influenza may be associated with right-sided obstructive lesions in all infants and with atrioventricular septal defects in infants with Down syndrome. The use of antipyretics might attenuate such associations. *(J Pediatr 2011;158:990-5)*.

Despite numerous advances in the treatment of congenital heart disease during the past 30 years, congenital heart defects (CHDs) continue to be a leading cause of morbidity and mortality in children.[1] Identification of risk factors for CHDs and subsequent efforts to prevent congenital heart disease remain important priorities for research.[2]

Examination of maternal exposures during pregnancy has offered some clues as to potential risk factors for CHD. Maternal febrile illness and hyperthermia have been associated with a variety of birth defects, especially defects of the central nervous system.[3-10] Associations of maternal fever and hyperthermia with CHD are less clear-cut, however.[11-20] The association between CHD and some viral illnesses, particularly rubella, has been well documented,[21,22] yet analyses of the role of influenza in the risk of CHD have yielded inconsistent findings.[13,16,17,23] Previous reports of the associations between maternal fever or influenza and CHD are summarized in Table I. Whether the variations in findings across studies reflect differences in study populations, methods, sampling variation, types of infections, or frequency and severity of febrile illness is unclear.

In the present study, we aimed to evaluate possible associations between reports of maternal fever and/or influenza during pregnancy and CHD. Furthermore, in an effort to ascertain whether any possible associations between maternal fever and/or influenza and CHD might be due to fever, we also examined the effects of antipyretic therapy on those associations.

Methods

Cases and controls in this study were participants in the Baltimore-Washington Infant Study (BWIS), a population-based, case-control study among live births to residents of Maryland, Washington, DC, and northern Virginia between 1981 and 1989. The BWIS data collection methods have been described in detail previously.[24] Cases were infants born with structural CHD confirmed by echocardiography, catheterization, surgery, or autopsy by 1 year of age; premature infants with patent ductus arteriosus as an isolated heart defect and infants with arrhythmias in the absence of structural heart defects were excluded from the BWIS. Controls consisted of a random sample of live-born infants without birth defects born in the region and frequency-matched to cases on month, year, hospital of birth, and age at interview. During the study period, 4390 cases and 3572 controls were enrolled. Barriers to eligibility for a mother to be interviewed included a physician's refusal to have the subject's mother contacted, failure to locate the mother, adoption, language barrier, death of

AVSD	Atrioventricular septal defect
BMI	Body mass index
BWIS	Baltimore-Washington Infant Study
CHD	Congenital heart defect

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Table I. Summary of published studies evaluating associations of fever and influenza with CHD

CHD	Publication	Fever		Influenza		Comments
		Exposure odds	OR (95% CI)	Exposure odds	OR (95% CI)	
All defects						
	Botto et al (2001)[13]	**93/736**	**1.8 (1.4-2.4)**	65/736	2.1 (0.8-5.5)	
	Zhang and Cai (1993)[15]	10/94	1.4 (0.7-2.9)			URI with fever
	Cleves et al (2008)[18]	33/3443	1.7 (1.0-3.0)			UTI with fever
	Acs et al (2005)[23]			**105/4375**	**1.7 (1.3-2.3)**	
Cardiac outflow defects (conotruncal)						
All	Botto et al (2001)[13]	12/125	1.3 (0.7-2.4)			
	Adams et al (1989)[17]	8/75	1.6 (0.8-3.0)	8/75	1.7 (0.9-3.3)	90% CI
	Cleves et al (2008)[18]	6/805	1.6 (0.6-4.0)			UTI with fever
dTGA	Botto et al (2001)[13]	7/58	1.9 (0.9-4.3)	5/58	2.1 (0.8-5.5)	
	Cleves et al (2008)[18]	2/292	1.4 (0.3-6.2)			UTI with fever
TOF	Botto et al (2001)[13]	3/48	0.6 (0.1-2.5)	1/48	0.5 (0.1-3.6)	
	Cleves et al (2008)[18]	2/350	1.3 (0.3-5.6)			UTI with fever
Atrial septal defects (all types)						
	Botto et al (2001)[13]	3/24	1.6 (0.4-5.6)	1/24	1.0 (0.1-7.4)	
	Cleves et al (2008)[18]	7/536	2.2 (0.9-5.8)			UTI with fever
	Tikkanen et al (1991)[19]		***P* < .01**			
AVSDs without Down syndrome						
	Botto et al (2001)[13]	2/12	2.4 (0.5-10.9)	1/12	2.0 (0.3-15.3)	
	Cleves et al (2008)[18]	1/88	2.7 (0.4-20.7)			UTI with fever
	Tikkanen et al (1991)[19]		*P* > .05			
Ebstein anomaly						
	Botto et al (2001)[13]	1/8	2.6 (0.6-12.0)	1/8	3.0 (0.4-23.9)	
Right-sided obstructive defects						
All	Botto et al (2001)[13]	**12/79**	**2.2 (1.2-4.2)**	**8/79**	**2.5 (1.1-5.3)**	
	Cleves et al (2008)[18]	**9/635**	**2.5 (1.1-5.8)**			UTI with fever
Tricuspid atresia	Botto et al (2001)[13]	**3/9**	**5.2 (1.3-20.2)**	3/9	7.9 (0.3-29.6)	
Pulmonary valve stenosis	Cleves et al (2008)[18]	**7/448**	**3.0 (1.2-7.6)**			UTI with fever
Left-sided obstructive defects						
All	Botto et al (2001)[13]	**17/89**	**2.7 (1.5-4.7)**	**12/89**	**2.9 (1.5-5.7)**	
	Cleves et al (2008)[18]	4/615	1.3 (0.5-3.9)			UTI with fever
HLHS	Botto et al (2001)[13]	4/30	2.3 (0.8-6.9)	2/30	1.6 (0.4-6.7)	
	Cleves et al (2008)[18]	1/193	1.0 (0.1-7.6)			UTI with fever
	Tikkanen et al (1991)[19]		***P* < .001**			
Aortic stenosis	Botto et al (2001)[13]	4/12	6.9 (1.0-14.8)	2/12	4.0 (0.9-17.9)	
Aortic coarctation	Botto et al (2001)[13]	**8/42**	**2.7 (1.2-6.0)**	**7/42**	**3.8 (1.6-8.8)**	UTI with fever
	Cleves et al (2008)[18]	3/310	2.1 (0.6-7.1)			

dTGA, d-transposition of the great arteries; *TOF*, tetralogy of Fallot; *HLHS*, hypoplastic left heart syndrome; *URI*, upper respiratory infection; *UTI*, urinary tract infection.
Bold type indicates significance at $\alpha = 0.05$.

the mother, or legal problems.[25] Of the 3763 interview-eligible case mothers, 3377 (90%) participated. Of the 3572 control mothers in the random selection list participating in the interviews, 78% were first choice, 17% were second choice, and the remainder were third or fourth choice. Interviews were conducted from 1 month to 22 months after birth, with 80% of case mothers and 74% of control mothers interviewed by 7 months after birth and <10% of each group interviewed beyond 12 months after birth.

For our analysis, which was performed with an exemption from the Institutional Review Board of the Centers for Disease Control and Prevention, we excluded (1) cases of muscular ventricular septal defect, because ascertainment of such cases was incomplete; (2) cases of patent ductus arteriosus, because this abnormality is not considered a true malformation; (3) cases with other syndromes or noncardiac anomalies, except for cases of atrioventricular septal defect (AVSD) associated with Down syndrome; (4) cases and controls whose mothers reported pregestational diabetes; and (5) products of multiple gestation.

Participating mothers were asked a series of detailed questions regarding exposures during defined time periods before and during their pregnancy (ie, the 3 months before pregnancy and during the first, second, and third trimesters). For maternal fever, mothers were asked if they had experienced a "fever of 101°F or higher" (≥38.3°C). For influenza, mothers reported whether or not they had "influenza (flu)." Finally, mothers were asked about all medications, prescribed or not, that they had used for any purpose before or during pregnancy. For our analysis, we studied maternal reports of fever (including with or without a report of influenza), influenza (including with or without a report of fever), and fever/influenza (report of either fever or influenza or both). We included as antipyretic agents all medications containing acetaminophen, salicylates, and/or nonsteroidal anti-inflammatory drugs. The exposure period of interest was the "periconceptional" period,