Acetaminophen Use in Pregnancy and Risk of Birth Defects

Findings From the National Birth Defects Prevention Study

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OBJECTIVE: To investigate whether exposure during the first trimester of pregnancy to single-ingredient acetaminophen increases the risk of major birth defects.

METHODS: Data from the National Birth Defects Prevention Study, a population-based, case–control study, were used. Women who delivered between January 1, 1997, and December 31, 2004, and participated in the telephone interview were included. Type and timing of acetaminophen use were assigned based on maternal report. Women reporting first-trimester acetaminophen use in a combination product were excluded, resulting in a total of 11,610 children in the case group and 4,500 children in the control group for analysis.

RESULTS: The prevalence of first-trimester single-ingredient–acetaminophen use was common: 46.9% (n=5,440) among women in the case group and 45.8% (n=2,059) among women in the control group (*P*=.21). Overall, acetaminophen was not associated with an increased risk of any birth defect. Among women reporting a first-trimester infection and fever, use of acetaminophen was associated with a statistically significantly decreased odds ratio (OR) for anencephaly or craniorachischisis (adjusted OR 0.35, 95% confidence interval [CI] 0.08–0.80), encephalocele (adjusted OR 0.17, 95% CI 0.03–0.87), anotia or microtia (adjusted OR 0.25, 95% CI 0.07–0.86), cleft lip with or without cleft palate (adjusted OR 0.44, 95% CI 0.26–0.75), and gastroschisis (adjusted OR 0.41, 95% CI 0.18–0.94).

CONCLUSION: Single-ingredient–acetaminophen use during the first trimester does not appear to increase the risk of major birth defects. It may decrease the risk of selected malformations when used for a febrile illness.

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LEVEL OF EVIDENCE: II

Acetaminophen (N-acetyl-p-aminophenol), also known in Europe as paracetamol, is a commonly used over-the-counter medication. In addition to generic products, at least 90 different brand-name products containing acetaminophen are registered in the United States (www.nlm.gov). By itself, acetaminophen is marketed for pain relief (analgesic) or as a fever reducer (antipyretic). It also frequently is found in cold and flu remedies that contain decongestants and antihistamines and in some prescription pain medications, also combined with narcotics.

The pharmacokinetics of acetaminophen in pregnancy are not well-understood.[1] The usual recommended dose of acetaminophen is close to its toxic adult dose (the therapeutic index is narrow),[2] raising concern for maternal overdose and fetal toxicity. Nevertheless, acetaminophen has been the recommended drug of choice for pain and fever during pregnancy.[1,3,4] A recent study found that 65.5% of women reported its use sometime during pregnancy, and 54.2% used acetaminophen during the first trimester.[5]

Despite the frequent use of acetaminophen in pregnancy, data on the associated risk of birth defects

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For values based on Figures 1 and 2, see the appendices online at http://www.links.lww.com/AOG/A147 and http://www.links.lww.com/AOG/A148.

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are limited. Some studies looked at a broad spectrum of birth defects, and their findings have been either negative[4] or inconclusive,[3,6,7] as have other studies that focused on specific birth defects. For example, both positive and negative associations with gastroschisis have been reported.[8,9] No significant association for muscular ventricular septal defects was noted.[10]

To provide specific and current information on this commonly used medication, we examined the relationship between maternal use of single-ingredient acetaminophen during the first trimester of pregnancy and the occurrence of birth defects. We report findings from the National Birth Defects Prevention Study, a large, population-based, case–control study from multiple areas in the United States.

MATERIALS AND METHODS

The National Birth Defects Prevention Study is an ongoing, multicenter, population-based, case–control study of major birth defects ascertained from 10 centers in the United States (Arkansas, California, Georgia, Iowa, Massachusetts, New Jersey, New York, North Carolina, Texas, and Utah) designed to investigate genetic and environmental causes of birth defects. The case group includes live births, stillbirths, and pregnancy terminations with selected birth defects identified through population-based birth-defect registries. Those in the case group with a known cause for the birth defect (eg, chromosomal or genetic disorders) are excluded. Participants for the control group are selected randomly from all live births to represent the case population of each center. Details of the study and its methodology have been published previously.[11,12] Overall participation was 72% for mothers of children in the case group and 69% for mothers of children in the control group during the study period. Institutional review boards at the Centers for Disease Control and Prevention and at each participating center approved this study.

For the National Birth Defects Prevention Study, data analysis is based on a set of well-defined birth defects that are collected by birth-defects surveillance programs at each center. All records of children with birth defects are reviewed by clinical geneticists to determine study eligibility. Based on this review, each child eligible to be included in the case group is classified as isolated or multiple. To be classified as a multiple, two or more major birth defects involving different organ systems (and not part of a sequence) must be present. Children in the case group are classified into groups defined by specific and homogenous phenotypes (eg, cleft lip with or without cleft palate is separated from cleft palate alone). Children in the case group may be included in more than one birth-defect group if two or more eligible defects are present (ie, a child with a cleft palate and spina bifida will be included in the cleft palate group and the neural tube defect group and classified as a multiple). Congenital heart defects are classified by phenotype in major groups and selected subgroups.[13] For example, we looked at conotruncal defects as a group and, in addition, at its two larger subgroups separately (d-transposition of the great arteries and tetralogy of Fallot). Congenital heart defects that involved two or more structures (eg, pulmonary valve stenosis with a septal defect) were classified as associations.

Trained interviewers administered a computer-assisted telephone interview to mothers of children in the case and control groups. Every woman was queried about medication use from 3 months before conception through the entire pregnancy. From these responses, information on acetaminophen consumption was extracted using the Slone Epidemiology Center Drug Dictionary, which identifies product-specific ingredients. This information was used to classify acetaminophen exposure into single-ingredient (acetaminophen alone) and combination (acetaminophen with other products). Women reporting having used both single-ingredient acetaminophen and combination products during the first trimester were considered exposed to combination products and excluded from this analysis.

Acetaminophen consumption was queried specifically in multiple sections of the computer-assisted telephone interview, including the sections that asked about episodes of respiratory illness, urinary tract infections, and pelvic inflammatory disease and the section that queried systematically about the use of prescription and nonprescription medications. Other computer-assisted telephone interview questions queried medication use as a follow-up to any report of other fevers or illnesses, injuries, and surgeries. The information requested of each participant with regard to acetaminophen use included product name, start and stop date, duration of use, and frequency of use.

For this study, a pregnancy was considered exposed to acetaminophen if there was any maternal use from the first day of the last menstrual period through the first 12 weeks of pregnancy. The month of exposure was inferred if at least one date (ie, start or stop date) and duration (ie, number of days used) were reported. If the information was insufficient to establish whether or when exposure had occurred (eg, when women stated that they "took as needed"), the exposure was classified as uncertain and all such participants were excluded from the case and control groups.

Children were included in the case or control groups if they were born after October 1, 1997, and had an estimated date of delivery (EDD) before January 1, 2005. A total of 15,778 children in the case group and 5,958 children in the control group were available for the study. After excluding women for whom the timing of acetaminophen exposure was uncertain (n=2,749 in the case group, n=1,084 in the control group) and those who used a combination product (n=672 in the case group, n=226 in the control group) or reported having pregestational diabetes (n=747 in the case group; n=148 in the control group), a total of 11,610 children in the case group and 4,500 children in the control group were eligible. The number of children in the control group for several birth-defect categories was reduced owing to a center's not contributing these cases during a specific time period. For example, congenital cataracts became an eligible defect for children born on or after January 1, 2000, and orofacial clefts became an eligible defect for one center (Utah) for children born on or after July 1, 2004.

Crude and adjusted odds ratios (ORs) with 95% confidence intervals (CIs) were calculated using logistic regression to assess the risk for each phenotype associated with reported exposure to acetaminophen using the same a priori covariates for all birth-defect groups: maternal age (younger than 20 years, 20–24 years, 25–29 years, 30 years or older), education (less than 12 years, 12 years, more than 12 years), preconception body mass index in kg/m^2 (lower than 18.5, 18.5–24.9, 25.0–29.9, 30.0 or higher), gestational diabetes (yes, no), fever (yes, no), smoking in the first trimester (yes, no), folic acid use from 3 months before conception through the first trimester (none, intermittent or less than 12 days per month, and continuous or 12 or more days per month), race/ethnicity (non-Hispanic white, non-Hispanic African American, Hispanic, other), and parity (0, 1, 2, 3, 4 or more).

For each phenotype examined, children in the case group were stratified into all cases (combining isolated cases and cases with multiple congenital anomalies) and into isolated cases. To examine potential confounding or effect modification associated with first-trimester infection or fever, stratified analyses also were performed for the following subgroups: 1) women who reported no history of either infection or fever, 2) women who reported infection without fever, and 3) women who reported infection and fever. Stratified analysis by infection and fever status was performed on all children in the case group for each phenotype (ie, isolated and multiple congenital anomalies). The distribution of maternal variables by case-group and control-group status was evaluated using the χ^2 statistic. All analyses were conducted using SAS 9.1 (SAS Institute Inc., Cary, NC, 2002–2003).

RESULTS

Table 1 shows the distribution of selected characteristics among mothers of children in the case and control groups. Compared with mothers of children in the control group, mothers of those in the case group were more likely to be non-Hispanic white, primigravidae, cigarette smokers, overweight, or obese and were interviewed more than 18 months after the EDD.

The prevalence of single-ingredient–acetaminophen use was 46.9% among mothers of children in the case group and 45.8% among mothers of those in the control group (P=.21). Among women younger than 20 years of age, reported use was higher in mothers of children in the case group than in mothers of those in the control group (42.8% compared with 37.0%, P=.02). The use of single-ingredient acetaminophen was highest among women between 25 and 29 years of age (49.4% in mothers of children in the case group, 48.3% in mothers of children in the control group) and among non-Hispanic white women (55.3% in mothers of children in the case group, 55.9% in mothers of children in the control group). Use was lowest among Hispanic women (32.9% in mothers of children in the case group, 30.2% in mothers of children in the control group [data not shown]).

Figure 1, Appendix 1 [available online at http://www.links.lww.com/AOG/A147] summarizes graphically the adjusted ORs for birth defects associated with acetaminophen use by phenotype. The adjusted ORs were very close to and statistically indistinguishable from unity for all phenotypes (Fig. 1, Appendix 1 [available online at http://www.links.lww.com/AOG/A147]). Among mothers of children in the case and control groups reporting no infection or fever during the first trimester, both elevated and decreased ORs were seen, none of which were statistically significant (Fig. 2, Appendix 2 [available online at http://www.links.lww.com/AOG/A148]).

A different pattern of risk for single-ingredient–acetaminophen exposure was evident for women who reported first-trimester infection without fever compared with those who reported neither infection nor fever (Fig. 2, Appendix 2 [available online at http://www.links.lww.com/AOG/A148]). Elevated ORs were observed among many phenotypes, but CIs included 1.0 in all but one phenotype: a statistically significantly decreased OR was observed for choanal atresia.

Among women who reported having both first-trimester infection and fever, the results were quite

Table 1. Maternal Characteristics for Children in the Case and Control Groups in the National Birth Defects Prevention Study, 1997–2004

Maternal Characteristic	Case Group (n=11,610)	Control Group (n=4,500)	P*
Age (y)			.58
Younger than 20	1,388 (12.0)	525 (11.7)	
20–24	2,738 (23.6)	1,043 (23.2)	
25–29	2,918 (25.1)	1,178 (26.2)	
30 or older	4,566 (39.3)	1,754 (39.0)	
Race/ethnicity			.04
Non-Hispanic white	6,795 (58.5)	2,595 (57.7)	
Non-Hispanic African American	1,123 (9.7)	504 (11.2)	
Hispanic	2,818 (24.3)	1,088 (24.2)	
Other	838 (7.2)	296 (6.6)	
Missing	36 (0.3)	17 (0.4)	
Education (y)			.20
Less than 12	2,159 (18.6)	793 (17.6)	
12	2,961 (25.5)	1,123 (25.0)	
More than 12	6,320 (54.5)	2,514 (55.9)	
Missing	170 (1.5)	70 (1.6)	
Previous pregnancies			.01
0	3,740 (32.2)	1,337 (29.7)	
1	3,261 (28.1)	1,338 (29.7)	
2	2,189 (18.9)	914 (20.3)	
3	1,247 (10.7)	473 (10.5)	
4 or more	1,134 (9.8)	427 (9.5)	
Missing	39 (0.3)	11 (0.2)	
Alcohol (first trimester)			.68
No	8,865 (76.4)	3,432 (76.3)	
Yes	2,551 (22.0)	1,001 (22.2)	
Missing	194 (1.7)	67 (1.5)	
Smoking (first trimester)			.01
No	9,382 (80.8)	3,724 (82.8)	
Yes	2,086 (18.0)	721 (16.0)	
Missing	142 (1.2)	55 (1.2)	
Periconception folic acid use			.93
No	2,688 (23.2)	1,047 (23.3)	
Intermittent	5,303 (45.7)	2,036 (45.2)	
Continuous	3,333 (28.7)	1,310 (29.1)	
Missing	286 (2.5)	107 (2.4)	
Preconception BMI (kg/m^2)			.02
Less than 18.5	676 (5.8)	256 (5.7)	
18.5 to 24.9	6,008 (51.7)	2,434 (54.1)	
25.0 to 29.9	2,492 (21.5)	940 (20.9)	
30.0 or higher	1,935 (16.7)	666 (14.8)	
Missing	499 (4.3)	204 (4.5)	
Time to interview (mo)			<.001
6 or less	2,109 (18.2)	1,572 (34.9)	
7–12	5,052 (43.5)	1,905 (42.3)	
13–18	2,827 (24.3)	686 (15.2)	
19–24	1,494 (12.9)	285 (6.3)	
Missing	128 (1.1)	52 (1.2)	
Center			<.001
Arkansas	1,445 (12.4)	479 (10.6)	
California	1,860 (16.0)	746 (16.6)	
Iowa	1,188 (10.2)	513 (11.4)	
Massachusetts	1,988 (17.1)	697 (15.5)	
New Jersey	751 (6.5)	279 (6.2)	
New York	742 (6.4)	357 (7.9)	
Texas	1,456 (12.5)	550 (12.2)	
CDC/Atlanta	1,286 (11.1)	439 (9.8)	
North Carolina	381 (3.3)	237 (5.3)	
Utah	513 (4.4)	203 (4.5)	

BMI, body mass index; CDC, Centers for Disease Control and Prevention.
Data are n (%) unless otherwise specified.
* χ^2 test.

varied (Fig. 2, Appendix 2 [available online at http://www.links.lww.com/AOG/A148]). Significantly decreased ORs were seen for anencephaly or craniorachischisis, encephalocele, anotia or microtia, all oral facial clefts, cleft lip with or without cleft palate, and gastroschisis.

DISCUSSION

Confirming earlier findings,[5] the first-trimester use of single-ingredient acetaminophen was common in this population-based study. We found that single-ingredient–acetaminophen use did not present a measurably increased risk of birth defects. The few modestly increased or modestly decreased ORs are consistent with random fluctuations. However, among women reporting illnesses, including febrile illnesses (which are common indications for the use of acetaminophen products), the use of single-ingredient acetaminophen was associated with a reduced risk of several birth defects.

These findings should be interpreted in light of the study's limitations and strengths. First, because the study produced many comparisons (by phenotype, type of medication, and infection/fever status), some associations may be the result of chance. Second, many associations, both positive and negative, were weak and could be the result of bias or residual confounding. Biases, including toward the null, could be caused by several factors. For example, exposure was assigned based on maternal self-reports. For a common medication such as acetaminophen, exposure misclassification may occur because of poor recollection of timing before

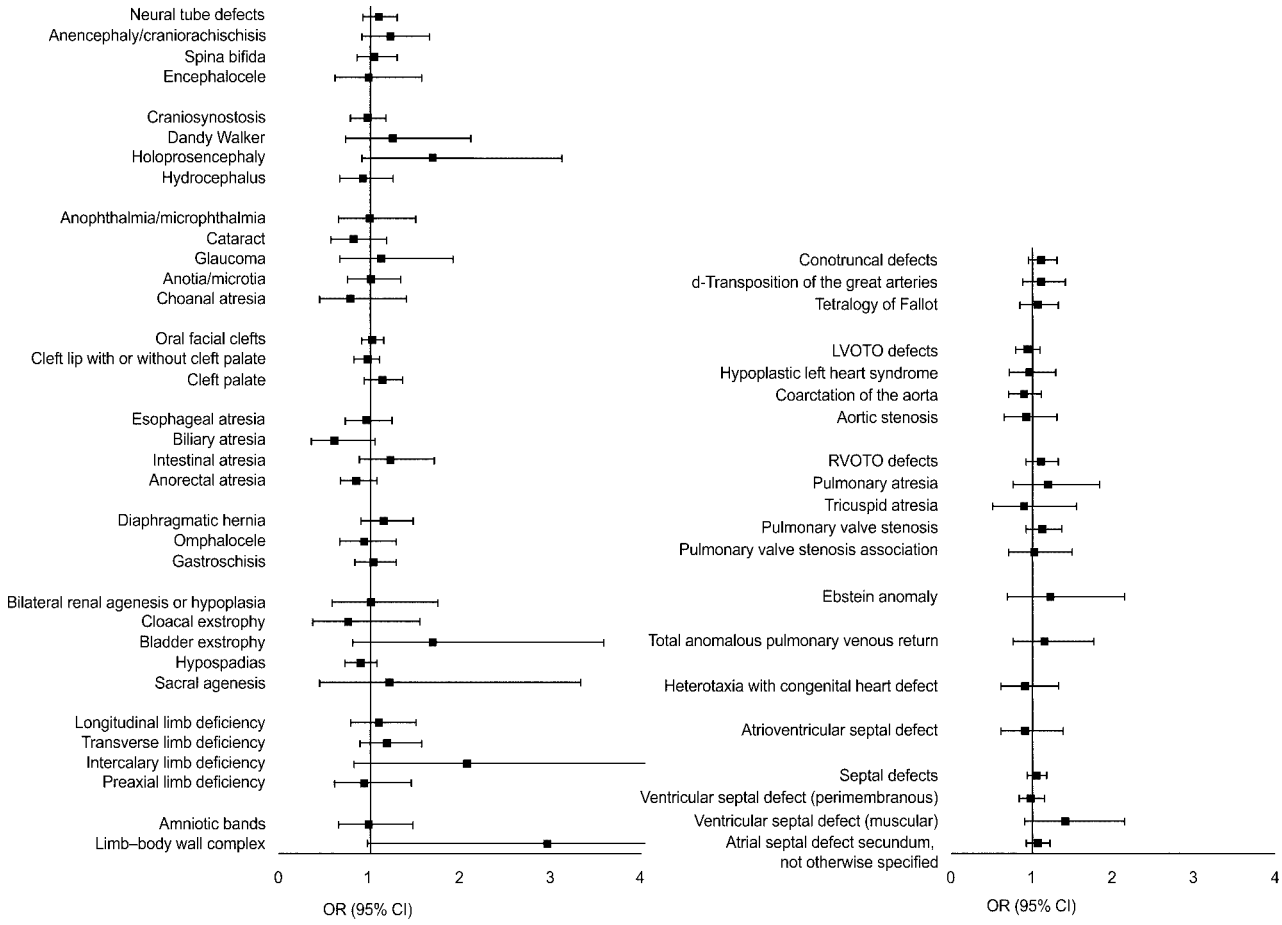

Fig. 1. Adjusted odds ratios (ORs) with 95% confidence intervals (CIs) for single-ingredient–acetaminophen use during the first trimester by birth defect, National Birth Defects Prevention Study, 1997–2004. LVOTO, left ventricular outflow tract obstruction; RVOTO, right ventricular outflow tract obstruction.

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or during pregnancy, exact product ingredients, dose of exposure, and length of exposure. Women also may have difficulty remembering specific products consumed that contain either single-ingredient acetaminophen or combination products, and mothers of children in the case group may recall past events and exposures differently than mothers of children in the control group (recall bias). We attempted to reduce exposure misclassification by excluding women who reported using acetaminophen products "as needed," precisely because the timing of exposure could not be assigned with any certainty. Recall bias, if present, could vary by type and severity of birth defect and is difficult to prove or disprove. Assuming that single-ingredient acetaminophen does not increase or decrease the risk for birth defects, the finding (Fig. 1, Appendix 1 [available online at http://www.links.lww.com/AOG/A147]) that most adjusted ORs were close to the null value (and approximately equally distributed on either side of the null) suggests that mothers of children in the case group did not systematically recall their exposure differently compared with mothers of children in the control group. Although mothers of children in the control group were interviewed closer to their EDD than were mothers of children in the case group, differences were not seen in exposure prevalence by time from birth to interview (data not shown). Because acetaminophen is used in combination products (eg, for flu or upper respiratory infections), we also examined whether women could distinguish between single-ingredient and combination products, and we found that this was true throughout the pregnancy and to the same degree in mothers of children in the case and control groups (data not shown). A second potential source of bias is differential participation between mothers of children in the case and control groups. Although overall participation was similar

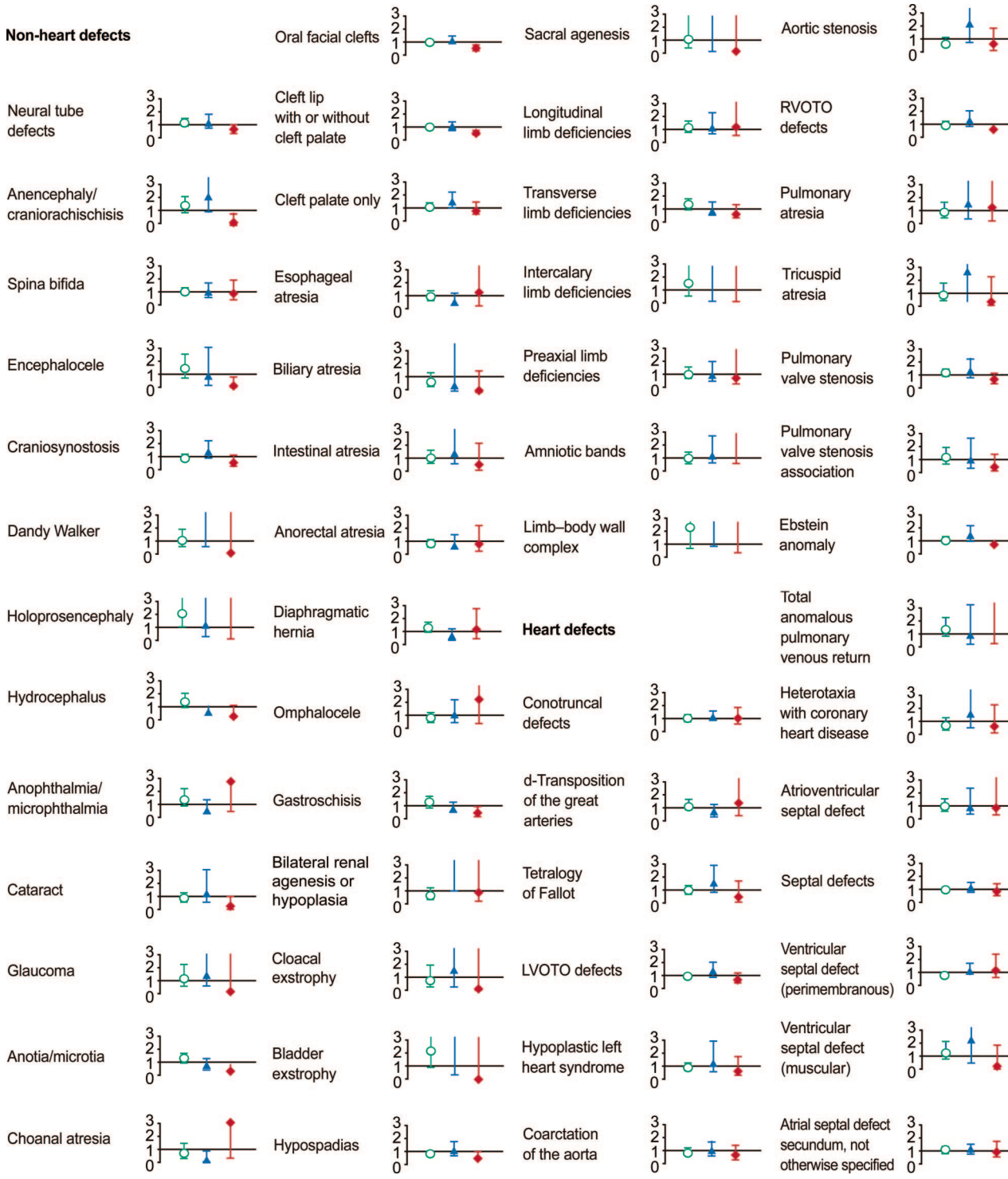

Fig. 2. Adjusted odds ratios (ORs) with 95% confidence intervals (CIs) for single-ingredient–acetaminophen use during the first trimester by birth defect, stratified by reported infection or fever (*green circle,* no infection or fever; *blue triangle,* infection but no fever; *red diamond,* infection and fever), National Birth Defects Prevention Study, 1997–2004. LVOTO, left ventricular outflow tract obstruction; RVOTO, right ventricular outflow tract obstruction.

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among mothers of those in the case (72%) and control (69%) groups in the National Birth Defects Prevention Study, participation bias cannot be excluded.

Confounding was an important consideration in the design of the study and analysis. Control for confounding was based on multivariable regression that used a standard set of covariates. We found little difference between crude and adjusted ORs, suggesting that these factors had little affect on effect estimates. In addition, stratification was used to examine the potential contribution of confounding by indication (underlying illness). Despite these approaches, it is still possible that residual confounding or effect modification may have influenced the findings.

The study has several strengths. The National Birth Defects Prevention Study is a large, multicenter, population-based study. Cases of birth defects are ascertained by intensive birth-defect surveillance methods, which reduces potential selection bias due to incomplete ascertainment. Considerable effort is put into characterizing the phenotypes clinically, and records of each child in the case group are reviewed centrally by experienced clinical geneticists. Exposure assessment is based on a standardized collection instrument using a computer-assisted telephone interview administered by trained interviewers. The Slone Drug Dictionary provided detailed data on medications. In addition, this study had a large sample size for most phenotypes compared with many previous studies, was population-based, all pregnancy outcomes were included, single-ingredient–acetaminophen use was distinguished from combination products, over-the-counter–medication use was included, which may be missed by using prescription-record linkage, and specific birth-defect phenotypes were analyzed separately rather than in broad groups.[3,4,6,7]

Our study adds in several ways to the knowledge on the teratogenic risk of acetaminophen in early pregnancy. First, there is little evidence that single-ingredient acetaminophen increases the risk of a broad range of birth defects. Findings in earlier, smaller studies suggesting an increased risk for gastroschisis[8,9] were not confirmed in this study (531 cases, adjusted OR 1.03, 95% CI 0.83–1.28). Second, compared with no use, the use of single-ingredient acetaminophen during a febrile infection was associated with a decreased risk of some birth defects. Hyperthermia has been associated with an increased risk of birth defects in both animals and humans,[14,15] particularly for neural tube defects.[16,17] Although it requires confirmation, our finding is intriguing and suggests a possible beneficial effect of single-ingredient acetaminophen on birth-defect risk when used in a specific clinical context, that is, during a febrile illness in the first trimester of pregnancy.

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