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Nonsteroidal antiinflammatory drug use among women and the risk of birth defects

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Abstract

OBJECTIVE—We examined whether the use of nonsteroidal antiinflammatory drugs (NSAIDs) in early pregnancy was associated with a range of structural birth defects.

STUDY DESIGN—Data were from the National Birth Defects Prevention Study, a multisite population-based, case-control study of risk factors for birth defects.

RESULTS—Among women in the National Birth Defects Prevention Study, 22.6% reported the use of NSAIDs in the first trimester of pregnancy, most commonly ibuprofen, aspirin, and naproxen. Of the 29 defect groups that were examined, most were not associated with NSAID use. Small-to-moderate increased risks of some oral cleft groups, some neural tube defect groups, anophthalmia/microphthalmia, pulmonary valve stenosis, amniotic bands/limb body wall defects, and transverse limb deficiencies were associated with ibuprofen, aspirin, and naproxen exposure.

CONCLUSION—The use of NSAIDs in early pregnancy does not appear to be a major risk factor for birth defects, although there were a few moderate associations between NSAIDs and specific birth defects.

Keywords

birth defect; medication in pregnancy; National Birth Defects Prevention Study; nonsteroidal antiinflammatory drug

The group of medications termed *nonsteroidal antiinflammatory drugs* (NSAIDs) includes aspirin, ibuprofen, naproxen, and several other agents. Their pharmacologic action involves prostaglandin inhibition in the adult; although they cross the placenta, their action in fetal

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tissues is not known.[1] Because NSAIDs are indicated for the treatment of symptoms of common conditions such as pain, headache, colds, and flu and because many of them are available without a prescription, they are among the most commonly taken medications both in and outside of pregnancy. A previous report showed approximately 1 in 4 women take an over-the-counter NSAID during pregnancy.[2]

Despite the widespread use of NSAIDs in pregnancy, few large-scale studies have addressed the risks or safety of such use. Reports on aspirin use in pregnancy have been based largely on nonsystematic studies with small samples or have examined all types of structural birth defects as 1 outcome, which limits the ability to draw inferences on many reproductive outcomes, particularly birth defects.[3] The absence of information falsely can suggest the lack of associations. Conversely, there may be avoidance of beneficial medications because of unsubstantiated fear of adverse outcomes. The present study sought to help close the information gap for 1 group of pregnancy outcomes: birth defects. Data on the use of NSAIDs from the National Birth Defects Prevention Study (NBDPS) were analyzed.

Materials and Methods

Study population

The study population was derived from the NBDPS; a detailed description of the study design has been published elsewhere.[4] Briefly, the NBDPS is an ongoing case-control surveillance study that was designed to identify infants with major birth defects and to evaluate genetic and environmental risk factors. Case infants for the study are identified from the state birth defect surveillance system of 10 states (Arkansas, California, Georgia, Iowa, Massachusetts, New Jersey, New York, Texas, North Carolina, and Utah). Cases include live births, stillbirths of ≥20 weeks' gestation or >500 g, or elective terminations with any of >30 eligible birth defects groups that are diagnosed in the first year of life. Each case is reviewed and confirmed by a clinical geneticist.[5] Control subjects are liveborn infants with no major birth defects who are selected from the same base population as the cases. Control subjects are selected randomly either from birth certificates or from birth hospitals with the use of a stratified random sample.[6] Our study included women with expected due dates between October 1, 1997, through December 2004. The NBDPS is a population-based study. All cases that meet study criteria and who reside in the study area are study eligible. All randomly selected control subjects are also study eligible. Participation rates represent the proportion of subjects who are study eligible who agreed to participate in the study. Of all control subjects who were asked to participate in the study, 69% agreed; of all cases who were asked to participate in the study, 72% agreed. Reasons for nonparticipation included women who were contacted and declined to participate and women who could not be located before they aged out of the study (>24 months from estimated due date). All study sites obtained institutional review board approval; all study participants provided informed consent.

Exposure

Mothers are contacted and interviewed by way of a computer-assisted telephone interview that lasts approximately 1 hour. The interview includes detailed questions about exposures

that occurred 3 months before conception through the end of pregnancy. A pregnancy calendar that is built into the computer-assisted telephone interview allows the mothers to respond about the timing of exposures in the way that she best recalls: by date, month of pregnancy, or trimester. Interviews are to be completed no earlier than 6 weeks and no later than 24 months after the estimated due date. Mothers are asked whether they had any of a list of specific illnesses or conditions (eg, cold, flu, injuries); if so, what medications, if any, were taken. The mothers were also asked about use of Advil (Pfizer Inc, New York, NY), Motrin (McNeil-PPC, Inc, Philadelphia, PA), Nuprin (Bristol-Meyers Squibb, Princeton, NJ), ibuprofen, aspirin, and Aleve (Bayer Healthcare LLC, Morristown, NJ). For each medication that was reported, mothers were asked when they took it and how often. If a woman reported that she had taken a medication and reported a start date that was in the first trimester, but could not characterize frequency of use in terms of daily or days per week or month, her use was considered to be “as needed.” All medications that were reported in the interview were coded according to the Slone Epidemiology Center Drug Dictionary (Slone Epidemiology Center, Boston, MA), which links product name to all components.

Because most structural malformations develop within the first trimester, we focused on NSAID use during this time period, which was defined as the estimated day of conception through 3 months afterward. NSAIDs included medications with the following ingredients: carboxyl acetic acid, carboxyl anthranilic acid, carboxyl propionic acid, carboxyl salicylate, enolic pyrazole, enolic oxicam, enolic pyrazolone, enolic quinazolinone, and other miscellaneous components. NSAIDS were further grouped according to component into aspirin, ibuprofen, or naproxen; there were not enough women who used other types of NSAIDs to examine them separately. Women who reported taking multiple types of NSAIDs were included in all applicable exposure groups. Because the month of consumption could not be categorized with certainty for medications that were reported “as needed,” we considered such use separately. Thus, for each medication, women were divided into 3 mutually exclusive groups: exposed in the first trimester, as needed, and unexposed at any time during pregnancy (P1-P9). In addition, we examined multiple and single component NSAID use, as well as route of exposure (oral or topical).

Outcome

Clinical geneticists at each site reviewed clinical data on potential cases with the use of standardized case definitions to ensure their study eligibility. Cases with known cause (single-gene disorders or chromosomal abnormalities) were excluded. Cases were further classified according to the presence or absence of other structural defects. Cardiac defect cases were also classified as simple if they were discrete anatomically.[7]

Over 30 structural malformation groups are included in the NBDPS. We restricted our analysis to defects with ≥100 cases, after excluding those cases with a family history of the same type of malformation, to have sufficient power to examine potential risk factors. Noncardiac case groups that were eligible for analysis included anencephaly and craniorachischisis, spina bifida, encephalocele, hydrocephaly, anophthalmia/microphthalmia, cataracts, anotia/microtia, cleft palate with or without cleft lip, cleft palate alone, esophageal atresia, intestinal atresia/stenosis (only jejunal, ileal, and multiple small-intestinal atresias),

anorectal atresia/stenosis, hypospadias (second/third degree), longitudinal limb deficiency, transverse limb deficiency, craniosynostosis, diaphragmatic hernia, omphalocele, gastroschisis, and amniotic band syndrome/limb body wall complex. For cardiovascular defects, cases were restricted to those classified as simple (ie, well-defined, pure conditions), without accompanying noncardiac defects and included dextro-rotated transposition of the great arteries, tetralogy of Fallot, ventricular septal defect (perimembraneous), ventricular septal defect (muscular-only collected for the first year of the study), pulmonary valve stenosis, aortic stenosis, hypoplastic left heart syndrome, coarctation of the aorta, and total anomalous pulmonary venous return.

Inclusion/exclusion criteria

We excluded mothers with preexisting diabetes mellitus for both cases (n = 709) and control subjects (n = 130) because of the known association of diabetes mellitus with various birth defects. We also excluded women who had missing information about their exposure to NSAIDS or were exposed only during trimesters 2 or 3 (cases, 799 women; control subjects, 282), which yielded a final study size of 14,915 cases and 5546 control subjects.

Statistical analysis

We first examined the distribution of characteristics between various exposure groups among control subjects, and also the distribution of characteristics between cases and control subjects. Descriptive characteristics included interview site, maternal race/ethnicity, maternal age at delivery, maternal body mass index, maternal highest education level achieved, folic acid supplementation during the period 1 month before conception through the first month of the first trimester, maternal smoking (from 1 month before conception through the end of the first trimester), sex of infant, binge drinking, gestational diabetes mellitus, fever (from 3 months before pregnancy through the end of first trimester), time between birth and interview, multiple births, and parity. Fever was ascertained through questions regarding the occurrence of fever that was associated with certain illnesses (such as respiratory tract infections and urinary tract infections) and through explicitly asked questions about fever independent of any other illnesses. Confounders that were selected were those that were associated with exposure among the control subjects or associated with the outcome (study site, race/ethnicity, folic acid, smoking, binge drinking, and fever in the first trimester). We used logistic regression to estimate crude and adjusted odds ratios (ORs) and their 95% confidence intervals (CIs).

Results

Overall, there were 3173 women (15.5%) who had been exposed to NSAIDs during the first trimester who reported their frequency of use and 1452 women (7.1%) who reported using NSAIDs “as needed” during a time period that included the first trimester. Of the women who reported their exposure frequency, 703 (22%) reported using aspirin; 2451 (77%) reported using ibuprofen; 475 (15%) reported using naproxen, and 39 (1.2%) reported using other NSAIDs. Of the women who reported using NSAIDs as needed, 218 (15%) reported aspirin use; 1240 (85%) reported ibuprofen use; 249 (17%) reported naproxen use, and 5 (0.34%) reported the use of other NSAIDs. In total, 693 of exposed women (15%) reported

using >1 type of NSAID (aspirin, ibuprofen, or naproxen). There were 15,836 women (77%) who were not exposed to NSAIDs at any time during pregnancy.

Table 1 shows the characteristics of women according to NSAID-exposure groups, among control subjects only. Exposed women were fairly similar, regardless whether they reported their frequency of use but were more likely to take folic acid supplements, to drink alcohol or smoke during pregnancy, and to have a shorter time span between birth and interview than unexposed women.

Table 2 shows the patterns of NSAID exposure among cases and control subjects. Sixteen percent of all cases and 14% of all control subjects were exposed to NSAIDs during the first trimester. Approximately one-half as many case and control mothers reported NSAID use as needed (7.3% and 6.6%, respectively). Because most exposure to NSAIDs, regardless of case/control status and frequency of exposure, was through oral route and was single component use, we decided to focus on oral, single component NSAID exposure for the remainder of the analysis.

Table 3 shows the distribution of oral, single component aspirin, ibuprofen, and naproxen use for specific defect groups and control subjects. Women whose NSAID information was missing were included in the total number of cases but not in the exposed or unexposed group counts. Exposure rates were generally similar for most specific defect case groups and control subjects, with some exceptions. ORs and 95% CIs (both crude and adjusted for study site, race/ethnicity, and first trimester folic acid supplementation, smoking, alcohol, and fever) were calculated. We presented results for which adjusted ORs were <0.70 or >1.5 for at least 1 of the NSAID types.

Adjusted ORs for single component, oral ibuprofen, aspirin, and naproxen exposure in the first trimester are presented in Table 4 for the 9 defect types for which an elevated risk was seen. When specific defect types were considered, risk estimates were not consistent across the 3 types of NSAID exposure for these defects. However, ibuprofen, aspirin, and naproxen were each associated with increased risks for neural tube defects, albeit different neural tube defect types. Similarly, one or another of the oral cleft types was associated with ibuprofen, aspirin, and naproxen, although the cleft type varied by exposure. Amniotic band/limb body wall complex was associated with both aspirin and ibuprofen exposure. For pulmonary valve stenosis, the risk was confined to naproxen use. The strongest and most consistent associations were observed for anophthalmia/microphthalmia, with adjusted ORs of 3.0 (95% CI, 1.3–7.3), 1.9 (95% CI, 1.1–3.3), and 2.8 (95% CI, 1.1–7.3), for aspirin, ibuprofen, and naproxen exposure, respectively. The OR that compared any NSAID exposure to nonexposure for the anophthalmia/microphthalmia group was 2.1 (95% CI, 1.3–3.5). A possible 2-fold increased risk of transverse limb deficiencies was observed for naproxen use, with a lower 95% CI of 1.0. For all the birth defects that are presented in Table 4 with enough power to examine the “as needed” exposure group, relative risk estimates for women with “as needed” use were nearly identical to women who were classified as exposed.

We also ran this analysis that was restricted only to cases with isolated defects (Table 4) and found that the effect estimates were nearly identical to those for the nonrestricted cases, with

the exception of anophthalmia/microphthalmia, for which the increased risk seemed confined to associated cases only. Most NSAID-exposed anophthalmia/microphthalmia cases had a variety of accompanying birth defects; the adjusted OR for any NSAID exposure and risk of anophthalmia/microphthalmia that was restricted to the 14 nonisolated cases was 2.8 (95% CI, 1.4–5.5). Because other NBDPS investigators have shown both fever and genitourinary infection to increase anophthalmia/microphthalmia risk,[8] we estimated the OR for NSAID use after excluding women with such histories during the first trimester of pregnancy; the elevated ORs for non-isolated anophthalmia/microphthalmia and exposure to any NSAID during the first trimester remained (OR, 2.4; 95% CI, 1.5–3.8).

Comment

This multisite, population-based, case-control study found that 22.6% of women in the NBDPS reported the use of NSAIDs in the first trimester of pregnancy, of which 70% reported the frequency of their use and 30% reported using NSAIDs “as needed.” The most commonly reported NSAID exposures were aspirin, ibuprofen, and naproxen. Although most defects that were examined were not associated with NSAID use, small-to-moderate increased risks were estimated for ibuprofen, aspirin, and naproxen use in relation to anophthalmia/microphthalmia, amniotic bands/limb body wall defects, pulmonary valve stenosis, possibly transverse limb deficiencies, oral clefts, and neural tube defects, although the type of oral cleft and neural tube defect that was associated with exposure that varied across specific drugs. For example, ibuprofen use was associated with spina bifida; aspirin use was associated with anencephaly/craniorachischisis and encephalocele, and naproxen use was associated with encephalocele. Although we evaluated women who reported using NSAIDs “as needed” separately to examine whether the association may differ in this group, given the larger potential likelihood of exposure misclassification, we found no evidence of this difference in our analysis.

The NBDPS data have been used previously to examine the relationship between NSAIDs and muscular ventricular septal defects. Similar to this study, the authors found no association between NSAIDs and muscular ventricular septal defects during the first trimester (adjusted OR, 1.0; 95% CI, 0.64–1.6) or 1 month before pregnancy to birth (adjusted OR, 0.99; 95% CI, 0.67–1.5).[9] However, that study did not examine birth defects other than muscular ventricular septal defects. Other previous analyses of NBDPS data that used earlier versions of the data set have seen associations between nonaspirin NSAIDs and gastroschisis among older women[10] and between NSAIDs and amniotic bands and terminal transverse limb defects.[11] In the present study, we also reported a borderline increase in terminal transverse limbs with the use of naproxen and in amniotic bands with the use of aspirin and ibuprofen. Similar to our results, a previous study,[12] which used prospectively reported registry data, found an association between cleft lip with or without cleft palate and naproxen. That study was based on 4 exposed cases; this current study is based on 45 cases and thus able to produce a more stable effect estimate. Therefore, for oral clefts, neural tube defects, and amniotic bands/limb body wall complex, increased risks were observed for isolated defects, which suggests an effect on the development of those particular structures. In contrast, the association for anophthalmia/microphthalmos was confined to cases with accompanying defects and did not appear to be attributed to associations with neural tube

defects, oral clefts, or amniotic bands. Of the 14 NSAID-exposed anophthalmia/microphthalmos cases, 7 had unilateral craniofacial anomalies that were suggestive of possible hemifacial microsomia. Early pregnancy ibuprofen exposure was associated with a possible increased risk of hemifacial microsomia in a previous study (OR, 1.7; 95% CI, 0.9–3.0).[13]

Strengths of this study included detailed clinical classification of outcomes and ability to control for a wide number of covariates. Our study is limited by the retrospective design and self-reported exposures, which could lead to differential misclassification between cases and control subjects. The use of NSAIDs during pregnancy was self-reported by the mother between 6 weeks and 24 months after expected due date. It is possible that mothers had trouble recalling their use of NSAIDs in pregnancy. Further, the data were collected after the outcome of pregnancy was known, and it is possible that women with offspring who had a birth defect were more or less likely to recall their use of NSAIDs than women who served as control subjects. Another potential limitation results from multiple comparisons. However, although it is possible that chance is the explanation for some of the observed associations, the fact that 20 of the 168 comparisons that were made were statistically significant suggests that at least some of them may not be due to chance.

In summary, the use of NSAIDs in early pregnancy does not appear to be a major risk factor for birth defects, although there were a few moderate associations between NSAIDs and anophthalmia/microphthalmia, amniotic bands/limb body wall defects, pulmonary valve stenosis, oral clefts, and neural tube defects. Because these associations have not been reported previously from other datasets (with the exception of naproxen and cleft lip with or without cleft palate), further studies with detailed data on timing, frequency, dose, and indication are necessary.

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TABLE 1

Descriptive characteristics of exposure groups during first trimester among nonmal formed control subjects in the National Birth Defect Prevention Study, 1997–2004

Variable	Exposed to NSAIDs, n (%)[a]	Exposed to NDAIDs, as needed, n (%)[b]	Unexposed, n (%)[c]
Site			
Arkansas	80 (10)	95 (26)	508 (12)
California	106 (14)	0	632 (14)
Georgia	69 (8.9)	57 (16)	454 (10)
Iowa	147 (19)	43 (12)	442 (10)
Massachusetts	133 (17)	0	589 (13)
New Jersey	11 (1.4)	85 (23)	463 (11)
New York	49 (6.3)	48 (13)	390 (8.9)
Texas	109 (14)	16 (4.4)	511 (12)
North Carolina	39 (5.0)	20 (5.5)	215 (4.9)
Utah	37 (4.7)	3 (0.82)	195 (4.4)
Maternal race/ethnicity			
Non-Hispanic white	539 (69)	266 (72)	2541 (58)
Non-Hispanic black	77 (9.9)	53 (14)	489 (11)
Hispanic	125 (16)	35 (9.5)	1062 (24)
Asian/Pacific Islander	13 (1.7)	7 (1.9)	143 (3.3)
Native American/Alaskan	6 (0.77)	0	20 (0.45)
Other	20 (2.6)	6 (1.6)	124 (2.8)
Missing	0	0	20 (0.45)
Maternal age at delivery, y			
<20	85 (11)	49 (13)	474 (11)
20–34	588 (75)	263 (72)	3323 (76)
≥35	107 (14)	55 (15)	602 (14)
Maternal body mass index			
Underweight	57 (7.3)	26 (7.1)	225 (5.1)
Normal	411 (53)	206 (56)	2393 (54)
Overweight	171 (22)	69 (19)	930 (21)
Obese	124 (16)	59 (16)	643 (15)
Missing/out of range	17 (2.2)	7 (1.9)	208 (4.7)
Maternal highest education level, y			
0–12	303 (39)	132 (36)	1844 (42)
>12	470 (60)	235 (64)	2513 (57)
Missing	7 (0.90)	0	42 (0.95)
Any use of folic acid, B1-P1	416 (53)	193 (53)	2232 (41)
Preterm birth			

Variable	Exposed to NSAIDs, n (%)[a]	Exposed to NDAIDs, as needed, n (%)[b]	Unexposed, n (%)[c]
Very preterm (<32 wk)	8 (1.0)	2 (0.54)	63 (1.4)
Preterm (32–36 wk)	70 (9.0)	30 (8.2)	343 (7.8)
Term (37–45 wk)	702 (90)	335 (91)	3992 (91)
Smoking			
Any smoking B1-P3	218 (28)	100 (27)	725 (16)
No smoking B1-P3	555 (71)	267 (73)	3648 (83)
Missing	7 (0.90)	0	26 (0.59)
Sex of infant			
Male	391 (50)	183 (50)	2223 (51)
Female	388 (50)	184 (50)	2172 (49)
Binge drinking, B1-P3			
No drinking	405 (52)	180 (49)	2853 (65)
Binge drinking (≥4 drinks)	138 (18)	58 (16)	466 (10)
Drinking, but not binge	224 (29)	117 (32)	1025 (23)
Gestational diabetes mellitus (yes)	36 (4.7)	8 (2.2)	188 (4.3)
Fever			
B3-1	41 (6.5)	26 (8.8)	218 (6.0)
P1–3	88 (14)	44 (15)	375 (10)
Time between birth and interview, mo			
≥18	44 (5.7)	16 (4.4)	338 (7.7)
<18	730 (94)	351 (96)	4037 (92)
Singleton	754 (97)	350 (95)	4268 (97)
Parity			
0	352 (45)	172 (47)	1748 (40)
1	244 (31)	106 (29)	1512 (34)
≥2	184 (24)	89 (24)	1131 (26)

B, months before conception; *NSAIDs*, nonsteroidal antiinflammatory drugs; *P* = months after conception.

[a] n = 780 women;

[b] n = 367 women;

[c] Includes women who were not exposed to any NSAIDs during entire pregnancy; n = 4399 women.

TABLE 2

Patterns of NSAID use for cases and control subjects in the National Birth Defect Prevention Study, 1997–2004

Variable	All cases combined, n (%)[a]	Control subjects, n (%)[b]
Exposed to NSAIDs	2393 (16.0)	780 (14.0)
Oral route	2388 (99.8)	778 (99.7)
Other routes	5 (0.2)	2 (2.6)
Single component	2241 (93.6)	731 (93.7)
Multiple components	146 (6.1)	48 (6.2)
Oral, single component	2239 (93.6)	730 (93.6)
NSAIDs as needed	1085 (7.3)	367 (6.6)
Oral route	1083 (99.8)	367 (100)
Other routes	2 (0.18)	0
Single component	1023 (94.3)	349 (95.1)
Multiple components	62 (5.7)	18 (4.9)
Oral, single component	1021 (94.1)	349 (95.1)

NSAIDs, nonsteroidal antiinflammatory drugs.

[a] n = 14,915 women;

[b] n = 5546 women.

TABLE 3

Distribution of aspirin, ibuprofen, and naproxen exposure (oral single agents only) among case groups in the National Birth Defect Prevention Study, 1997–2004

		Aspirin, n (%)		Ibuprofen, n (%)		Naproxen, n (%)		
Malformation/birth defect	**n**[a]	**Exposed (n = 550)**	**As needed (n = 160)**	**Exposed (n = 2431)**	**As needed (n = 1230)**	**Exposed (n = 474)**	**As needed (n = 249)**	**Unexposed, n (%)**[b]
Non-heart								
Anencephaly and craniorachischisis	285	2 (4.2)	1 (0.35)	33 (11.6)	25 (8.8)	4 (1.4)	4 (1.4)	204 (71.6)
Spina bifida	602	19 (3.2)	2 (0.33)	87 (14.5)	40 (6.6)	9 (1.5)	1 (0.17)	425 (70.6)
Encephalocele	113	4 (3.5)	0	9 (8.0)	9 (8.0)	5 (4.4)	1 (0.88)	82 (72.6)
Hydrocephaly	259	2 (0.77)	2 (0.77)	28 (10.8)	13 (5.0)	8 (3.1)	2 (0.77)	187 (72.2)
Anophthalmia/microphthalmia	123	8 (6.5)	0	19 (15.5)	2 (1.6)	7 (5.7)	1 (0.81)	87 (70.7)
Cataracts	157	3 (1.9)	2 (1.3)	18 (11.5)	10 (6.4)	2 (1.3)	1 (0.64)	114 (72.6)
Anotia/microtia	349	10 (2.9)	2 (0.57)	31 (8.9)	15 (4.3)	7 (2.0)	1 (0.29)	271 (77.7)
Cleft lip ± cleft palate	1423	34 (2.4)	12 (0.84)	188 (13.2)	87 (6.1)	45 (3.2)	15 (1.1)	1003 (70.5)
Cleft palate	764	30 (3.9)	5 (0.65)	98 (12.8)	52 (6.8)	23 (3.0)	14 (1.8)	551 (72.1)
Esophageal atresia	373	8 (2.1)	0	42 (11.3)	26 (7.0)	8 (2.1)	6 (1.6)	270 (72.4)
Intestinal atresia stenosis	232	4 (1.7)	2 (0.86)	26 (11.2)	11 (4.7)	2 (0.86)	2 (0.86)	177 (76.3)
Anorectal atresia/stenosis	540	15 (2.8)	5 (0.93)	59 (10.9)	38 (7.1)	11 (2.0)	13 (2.4)	384 (71.1)
Hypospadias: 2nd/3rd degree[c]	1081	26 (2.4)	12 (1.1)	99 (9.2)	82 (7.6)	21 (1.9)	15 (1.4)	811 (75.0)
Longitudinal limb deficiency	230	3 (1.3)	3 (1.3)	28 (12.2)	19 (8.3)	5 (2.2)	1 (0.43)	172 (74.8)
Transverse limb deficiency	359	8 (2.2)	3 (0.84)	41 (11.4)	19 (5.3)	11 (3.1)	2 (0.56)	268 (74.7)
Craniosynostosis	633	16 (2.5)	6 (0.95)	72 (11.4)	29 (4.6)	9 (1.4)	7 (1.1)	469 (74.1)

Malformation/birth defect	n[a]	Aspirin, n (%)		Ibuprofen, n (%)		Naproxen, n (%)		Unexposed, n (%)[b]
		Exposed (n = 550)	As needed (n = 160)	Exposed (n = 2431)	As needed (n = 1230)	Exposed (n = 474)	As needed (n = 249)	
Diaphragmatic hernia	432	10 (2.3)	4 (0.93)	46 (10.7)	27 (6.3)	8 (1.9)	5 (1.2)	309 (71.5)
Omphalocele	235	4 (1.7)	3 (1.3)	24 (10.2)	14 (6.0)	5 (2.1)	5 (2.1)	168 (71.5)
Gastroschisis	621	18 (2.9)	4 (0.64)	84 (13.5)	34 (5.5)	15 (2.4)	9 (1.5)	426 (68.6)
Amniotic band syndrome and limb body wall	181	8 (4.4)	3 (1.7)	30 (16.6)	11 (6.1)	5 (2.8)	1 (0.55)	119 (65.8)
Heart								
D-transposition of great arteries	328	10 (3.1)	5 (1.5)	33 (10.1)	19 (5.8)	11 (3.4)	5 (1.5)	244 (74.4)
Tetralogy of Fallot	552	19 (3.4)	5 (0.91)	68 (12.3)	36 (6.5)	12 (2.2)	4 (0.72)	397 (71.9)
Ventricular septal defect[d]								
Perimembraneous	823	17 (2.1)	8 (0.97)	89 (10.8)	49 (6.0)	15 (1.8)	11 (1.3)	605 (73.5)
Muscular	162	3 (1.9)	1 (0.62)	21 (13.0)	6 (3.7)	7 (4.3)	2 (1.2)	117 (72.2)
Pulmonary valve stenosis	519	13 (2.5)	5 (0.96)	61 (12)	41 (7.9)	19 (3.7)	11 (2.1)	372 (71.7)
Aortic stenosis	158	4 (2.5)	0	23 (14.6)	10 (6.3)	3 (1.9)	3 (1.9)	106 (67.1)
Hypoplastic left heart	276	7 (2.5)	5 (1.8)	28 (10.1)	16 (5.8)	5 (1.8)	4 (1.5)	209 (75.7)
Coarctation of the aorta	291	6 (2.1)	3 (1.0)	29 (10.0)	13 (4.5)	3 (1.0)	2 (0.69)	222 (76.3)
Total anomalous pulmonary venous return	130	3 (2.3)	0	9 (6.9)	5 (3.9)	2 (1.5)	2 (1.5)	102 (78.5)
Control subjects	5546	129 (2.3)	35 (0.63)	594 (10.7)	309 (5.6)	121 (2.2)	70 (1.3)	4399 (79.3)
Male control subjects	2797	64 (2.3)	20 (0.72)	304 (10.9)	155 (5.5)	52 (1.9)	31 (1.1)	2223 (79.5)

[a]Women who were missing nonsteroidal antiinflammatory drug information were included in the total number of cases but not in the exposed or unexposed group counts;

[b]n = 15,836 subjects;

[c]Male control subjects were used only in this analysis.

TABLE 4

Association of selected defects and nonsteroidal antiinflammatory drug exposure[a]

	Adjusted odds ratio (95% CI)[b]		
Birth defect	**Aspirin**	**Ibuprofen**	**Naproxen**
Non-heart			
Anencephaly/craniorachischisis			
Total	2.0 (1.0–3.9)	1.3 (0.85–2.0)	0.84 (0.30–2.3)
Isolated	2.2 (1.1–4.3)	1.3 (0.84–2.0)	0.69 (0.22–2.2)
Spina bifida			
Total	1.6 (0.93–2.7)	1.6 (1.2–2.1)	0.77 (0.35–1.7)
Isolated	1.6 (0.94–2.9)	1.6 (1.2–2.1)	0.48 (0.18–1.3)
Encephalocele			
Total	2.1 (0.75–6.1)	1.2 (0.58–2.5)	2.5 (0.89–7.3)
Isolated	2.8 (0.99–8.1)	1.0 (0.42–2.4)	3.5 (1.2–10)
Anophthalmia/microphthalmia			
Total	3.0 (1.3–7.3)	1.9 (1.1–3.3)	2.8 (1.1–7.3)
Isolated	0.94 (0.13–7.0)	1.0 (0.40–2.6)	c
Cleft lip ± cleft palate			
Total	1.1 (0.72–1.7)	1.3 (1.1–1.6)	1.7 (1.1–2.5)
Isolated	1.2 (0.76–1.8)	1.4 (1.1–1.7)	1.8 (1.2–2.7)
Cleft palate			
Total	1.8 (1.1–2.9)	1.3 (0.99–1.7)	1.4 (0.84–2.5)
Isolated	1.7 (1.0–2.9)	1.3 (0.99–1.8)	1.6 (0.90–2.8)
Transverse limb deficiency			
Total	1.2 (0.58–2.5)	1.3 (0.88–1.9)	2.0 (1.0–3.8)
Isolated	1.3 (0.62–2.7)	1.2 (0.84–1.8)	1.9 (0.95–3.7)
Amniotic bands/limb body wall			
Total	2.5 (1.1–5.6)	2.2 (1.4–3.5)	1.6 (0.55–4.4)
Isolated	2.5 (1.1–5.7)	2.2 (1.4–3.5)	1.6 (0.56–4.5)
Heart			
Isolated pulmonary valve stenosis[d]	1.1 (0.47–2.6)	1.3 (0.91–1.9)	2.4 (1.3–4.5)

CI, confidence interval.

[a] Exposed vs unexposed (as needed excluded);

[b] Adjusted for site, race/ethnicity, folic acid, smoking, binge drinking, and fever in the first trimester;

[c] Too few cases to estimate adjusted odds ratios;

[d] Analysis limited to term births only.