Nonsteroidal Antiinflammatory Drugs in Late Pregnancy and Persistent Pulmonary Hypertension of the Newborn

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KEY WORDS

persistent fetal circulation, pulmonary hypertension, newborn infant, epidemiology, perinatal health, nonsteroidal antiinflammatory drugs

ABBREVIATIONS

BDS—Birth Defects Study
CI—confidence interval
DA—ductus arteriosus
FO—foramen ovale
NSAID—nonsteroidal antiinflammatory drug
OR—odds ratio
OTC—over the counter
PPHN—persistent pulmonary hypertension of the newborn

All authors made substantive intellectual contributions to this study; each has contributed sufficiently in the work to take public responsibility for appropriate portions of the content; and each has seen and approved the final submission version of the manuscript.

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WHAT'S KNOWN ON THIS SUBJECT: Knowledge is limited regarding the epidemiology of persistent pulmonary hypertension of the newborn (PPHN). Previous work has implicated a host of perinatal risk factors and a few antenatal antecedents of PPHN, including maternal consumption during pregnancy of nonsteroidal antiinflammatory medications.

WHAT THIS STUDY ADDS: In contrast to results of previous studies, we found no association between PPHN and maternal consumption during late pregnancy of nonsteroidal antiinflammatory drugs in general or ibuprofen in particular.

abstract

OBJECTIVE: Persistent pulmonary hypertension of the newborn (PPHN) is a clinical syndrome of late-preterm and full-term infants associated with failure of the normal fetal-to-neonatal circulatory transition. This study was designed to test the hypothesis that risk for PPHN is increased after antenatal exposure to nonsteroidal antiinflammatory drugs (NSAIDs), with particular emphasis on late gestational exposures.

METHODS: Between 1998 and 2003, we interviewed 377 women whose infants had PPHN and 836 control mothers of infants matched to cases by hospital and birth date. Interviews captured information on prescription and over-the-counter medication use in pregnancy as well as a variety of potential confounding factors. Crude and adjusted odds ratios (ORs) and 95% confidence intervals (CIs) for third-trimester maternal NSAID use were estimated by using multivariate conditional logistic regression.

RESULTS: During the third trimester of gestation, 33 infants (8.8%) with PPHN were exposed to any NSAID compared with 80 (9.6%) controls (OR 0.8; 95% CI 0.5–1.3). We observed an elevated OR for PPHN risk among infants whose mothers consumed aspirin during the third-trimester; however, the lower 95% CI included the null. Neither nonaspirin NSAIDs at any time during pregnancy nor ibuprofen use during the third trimester was associated with an elevated risk of PPHN. Similarly, no association was observed between a mother's third-trimester acetaminophen use and the occurrence of PPHN in her newborn.

CONCLUSIONS: This large multicenter epidemiologic study of PPHN risk revealed no evidence to support the hypothesis that maternal consumption during pregnancy of NSAIDs overall or ibuprofen in particular is associated with PPHN risk. *Pediatrics* 2013;131:79–87

The pulmonary circulation of the fetus is characterized by high vascular resistance when compared with the lower pulmonary vascular resistance necessary for pulmonary gas exchange in postnatal life. As a result, the fetal circulation diverts blood that has been oxygenated by the placenta away from the fetal lungs by means of 2 channels: the ductus arteriosus (DA) and foramen ovale (FO). In the normal transition at birth from fetal-to-neonatal circulation, pulmonary vascular resistance falls, and the right-to-left DA and FO hemodynamic shunting that occurs in the normal fetus ceases. In 1 or 2 of every 1000 live births, however, there is a failure of the normal fetal-to-neonatal circulatory transition.[1–3] This disruption leads to persistent pulmonary hypertension of the newborn (PPHN), a disorder characterized by postnatal persistence of elevated pulmonary vascular resistance, right-to-left shunting of blood through the fetal channels, diminished pulmonary blood flow, and profound hypoxemia.[4–6] PPHN typically occurs in a full-term or late-preterm infant who has no associated congenital anomalies and becomes symptomatic within minutes or hours of birth with severe respiratory failure, is caused by vascular remodeling or a maladaptive pulmonary vascular response,[3,4,7,8] and is associated with substantial morbidity and mortality.[1–3,9,10]

Epidemiologic associations between PPHN and perinatal factors such as meconium aspiration, pneumonia, sepsis, nonvertex presentation, and cesarean delivery are well recognized.[11–13] Although some of these factors may be consequences of or, alternatively, share common antecedents with PPHN, pulmonary vascular remodeling observed among infants who had PPHN and died soon after birth[14] suggests that antenatal exposures might contribute to the development of PPHN.

The hypothesis that antenatal maternal consumption of nonsteroidal anti-inflammatory drug (NSAIDs) could lead to PPHN is based on the demonstration, in both animals[9,15,16] and humans,[17,18] of fetal or neonatal DA constriction with salicylate[9,15] or indomethacin.[16–18] Human case reports have linked the occurrence of PPHN with maternal NSAID treatment.[17,19–26] In 1996, a small epidemiologic study found an increase in PPHN risk (odds ratio [OR] = 6.2, 95% confidence interval [CI] 1.8–21.8) associated with antenatal exposure to NSAIDs, a finding that was based on just 7 exposed cases, only 4 of whom reported third-trimester use.[11] In 2001, another study reported a significant association between PPHN and the presence of NSAIDs (ie, aspirin, ibuprofen, indomethacin, naproxen) in meconium (OR 21.5, calculated from table 4 in Alano et al).[27]

METHODS

Study Design

To test the hypothesis that late pregnancy exposure to NSAIDs is associated with an increased risk of PPHN, we conducted a case-control study of risk factors for PPHN among infants identified through the Slone Epidemiology Center's Birth Defects Study (BDS), an ongoing surveillance program of risk factors for birth defects.[28] The PPHN study component was designed specifically to rigorously identify infants with PPHN and evaluate risk factors for PPHN, with particular emphasis on antenatal NSAID exposure.

Study Population

Study subjects were drawn from 97 institutions in 4 metropolitan areas (Boston, Philadelphia, San Diego, and Toronto) between 1998 and 2003. They were identified through review of admissions and discharges at major referral hospitals and clinics, logbooks in NICUs and through weekly telephone contact with collaborators at newborn nurseries in community hospitals (the latter to identify infants with PPHN who might not have been referred to major centers). Healthy newborns from the same centers also were enrolled. Institutional review board approval was obtained from all participating institutions. All mothers who were interviewed provided consent.

Designation of Case Status

All infants admitted to the newborn intensive care units (NICUs) at participating hospitals were screened by BDS nurses or respiratory therapists trained to identify infants with respiratory signs or diagnoses that made them candidates for having PPHN. To determine eligibility and identify infants who met criteria for PPHN, 1 investigator (LVM) who was masked to maternal exposure history, reviewed the medical records of all infants with diagnostic codes for asphyxia, cyanotic congenital heart disease, respiratory distress syndrome, pneumonia, meconium aspiration, transient tachypnea of the newborn, persistent fetal circulation, or pulmonary hypertension. Because we excluded infants with major congenital malformations from our analyses, those with known anomalies such as congenital heart disease or pulmonary hypoplasia were ineligible.

PPHN cases were defined as follows:

- Gestational age >34 weeks. Gestational age, as reported in the infant's medical record at the time of ascertainment, was verified by comparing the date of birth to the due date reported by the mother, which was based on her last menstrual period or early pregnancy ultrasound estimate.
- Presentation shortly after birth with severe respiratory failure, defined as the need for intubation and mechanical ventilation.
- Evidence of pulmonary hypertension as documented either by a ≥5% gradient between preductal

and postductal oxygen saturation or by echocardiographic evidence. Among those who underwent echocardiography, infants were designated as having PPHN if the cardiologist evaluating the echocardiogram assigned the diagnosis of PPHN or noted marked pulmonary hypertension or if the echocardiogram showed right-to-left hemodynamic shunting at the FO or DA or bidirectional hemodynamic shunting accompanied by leftward bowing of the ventricular septum to a degree consistent with pulmonary arterial pressure that was greater than half of the systemic pressure.

A potential case subject was excluded from eligibility for a PPHN diagnosis if he or she had evidence of any congenital cardiothoracic abnormality except for patent ductus arteriosus, patent foramen ovale, atrial septal defect, or a single, small, muscular ventriculoseptal defect.

The ability to acquire the quality and quantity of data needed to determine case status varied among medical centers. In response, potential PPHN cases were subsequently classified as

1. "confirmed" if they met every criterion for the case definition of PPHN;
3. "probable" if their clinical courses were highly suggestive of PPHN and their diagnostic criteria for PPHN approximated, but did not fall within, the specified ranges;
3. "possible" if their clinical courses were consistent with PPHN but appropriate diagnostic tests were never performed or were unavailable; or
4. "not a case" if their clinical or diagnostic tests were inconsistent with PPHN.

Subjects were excluded from consideration if they lacked information judged necessary to classify the subject into one of the categories above. Only confirmed and probable cases were included in the main analyses.

Selection of Controls

The control group included infants born after 34 weeks' gestation without a congenital abnormality or a respiratory problem who were matched to cases by birth hospital and calendar date of birth (±30 days). We initially selected up to 4 potential controls per case and interviewed on average 2.2 controls per case. After final classification of PPHN cases and completion of interviews, controls who were matched to confirmed and probable cases and those who had completed interviews were selected for the analyses.

Assessment of Exposure

Within 6 months of delivery, trained study nurses who were unaware of the hypothesis interviewed the mothers of the case and control infants. The telephone interview was detailed and structured and included questions on demographic characteristics, the mother's medical and obstetrical history, parents' habits and occupations, and a history of the use of all medications (prescription and over the counter [OTC]) from the period 2 months before conception throughout the entire pregnancy. The interview was computer-based, with direct entry of responses and access to dictionaries (ie, drugs and diagnoses) and instantaneous coding. Recall of specific analgesic/antipyretic products was aided by the BDS Medication Identification Booklet containing pictures of available OTC products.

Drug use and illness information were collected by using a 4-level approach for obtaining medication information (by illness, medication category, symptom, and drug prompts) that has been previously described.[29,30] This method ensures more complete reporting[29,31] and allows linkage between all medications and occurrences of illnesses.

We defined late pregnancy exposure as use of NSAIDs anytime in the third trimester. We classified NSAIDs as either aspirin or nonaspirin NSAIDs and considered specific nonaspirin NSAIDs (mainly ibuprofen). Because the third trimester is shorter among infants born preterm, thereby reducing the opportunity for exposure during this trimester, we also considered the use of NSAIDs during the month preceding the delivery (time-varying exposure), and repeated the analysis among infants born at full-term gestation (≥37 weeks postmenstrual age). Because 1 epidemiologic study found the increased PPHN risk after first trimester exposure,[11] we also evaluated the effect of NSAID use for each trimester. Finally, because low-dose aspirin is used to treat some pregnancy-related conditions and NSAID treatment is used to arrest preterm labor, we evaluated the potential effect of these indications for treatment.

Data Analysis

In this analysis, we sought to evaluate 2 principal study hypotheses: (1) maternal consumption during pregnancy of NSAIDs, but not acetaminophen, is associated with an increased risk of the infant developing PPHN and (2) the association between NSAIDs and increased PPHN risk is most evident when the NSAID consumption occurs during the third trimester.

Matched ORs and their 95% CIs were estimated for PPHN by using multivariate conditional logistic regression with separate terms for the 3 medication exposures, race/ethnicity (ie, black, Hispanic, Asian, others, and white as referent), diabetes mellitus, prepregnancy BMI (ie, 20–27, >27, unknown, and <20 as referent), hypertension, and multiple birth. Analyses were performed by using SAS for Windows, version V.8.2.

Using the same data set, we previously tested the hypothesis that selective

serotonin reuptake inhibitors increased the risk of PPHN.[30]

RESULTS

Of 843 term or near-term newborn infants we identified with diagnoses of asphyxia, cyanotic congenital heart disease, respiratory distress syndrome, pneumonia, meconium aspiration, transient tachypnea of the newborn, persistent fetal circulation, or pulmonary hypertension, 377 were classified as having confirmed or probable PPHN. They were matched to 836 controls (Table 1). The participation rate was 69% for mothers of PPHN subjects and 68% for mothers of controls. After exclusion of mothers who could not be located and invited to participate, the rates were 73% and 71%, respectively.

Demographic, prenatal, and perinatal factors associated with PPHN in this study population have been previously described.[29] Those that were considered potential confounding factors in analyses of the relationships among analgesics and PPHN are presented in Table 2. Factors associated with increased risk of PPHN included maternal race/ethnicity (ie, Black or Asian), BMI >27, maternal diabetes mellitus or asthma, cesarean delivery, male infant gender, birth weight <2500 or >4000 g, gestational age <37 or >41 weeks, and large for gestational age designation. Reduced PPHN risk was observed for infants whose mothers had received >15 years of education.

Among matched control subjects, overall rates of exposure at any time during pregnancy were 71.7% for acetaminophen, 28.3% for ibuprofen, 6.9% for aspirin, and 5.4% for other NSAIDs. Exposure to analgesics varied during pregnancy, and the observed patterns differed both by medication and pregnancy trimester (Fig 1). In the first trimester, acetaminophen use increased and the use of other analgesics dropped considerably. At the end of the first trimester, acetaminophen use was 51% and ibuprofen, aspirin, and intake of other NSAIDs had fallen to 6%, 2.3%, and 0.7%, respectively. Acetaminophen and ibuprofen exposure remained relatively constant throughout the remainder of pregnancy. In the third trimester, however, aspirin and other NSAID use fell to 1.7% and 0.45%, respectively. Although third-trimester acetaminophen use was somewhat lower for those in the Toronto and San Diego centers than in the Boston or Philadelphia centers, the third trimester patterns of consumption of aspirin, ibuprofen, and other NSAIDs were relatively consistent across all 4 centers (data not shown).

We first considered all infants irrespective of gestational age at birth. Figure 2 shows ORs and 95% CIs for conditional logistic regression, by pregnancy month of exposure. Table 3 presents the results of conditional logistic regression analyses for matched data associated with third-trimester exposure. The crude third-trimester estimates were 1.82 for aspirin, 0.65 for ibuprofen, and 0.8 for acetaminophen; all the 95% CI bounds included the null. Additional analyses involved a series of sequential models that adjusted for potential confounders, late preterm birth (gestational age 34–37 weeks), and cesarean delivery. Although prematurity and cesarean delivery cannot be true confounders because they occur after prenatal NSAID exposure and possibly after the pathologic features of the outcome, we explored whether they accounted for any of the observed associations as intermediate variables or were proxies for unmeasured confounders. ORs remained largely unchanged for ibuprofen and acetaminophen but decreased for aspirin to 1.19 (0.50–2.87). When the analyses were restricted to infants born at or beyond 37 weeks of gestation (Table 4), the adjusted OR for ibuprofen was 0.42 (0.20–0.89), for aspirin was 1.47 (0.52–4.12), and for acetaminophen was 0.90 (0.64–1.27). Analysis of time-varying exposures that considered drug use during the gestational month preceding delivery rather than during the third trimester did not yield meaningfully different results (data not shown).

TABLE 1 Categorization of the Study Population: Control Subjects and Subjects Referred as Potential PPHN Cases, 58% of Whom Were Designated Confirmed or Probable PPHN Cases[a]

Case or Control Status	Frequency	Percent of Eligible Study Population
Controls	9032	85.99
Matched control subjects	836	7.91
PPHN cases	377	
Confirmed PPHN	337	3.20
Probable case	40	0.36
Potential PPHN cases	268	
Ascertained PPHN	5	0.10
Possible case	28	0.27
Indeterminate case	37	0.36
Not a case	198	1.81

[a] The final study population consisted of 377 PPHN cases and 836 matched controls.

DISCUSSION

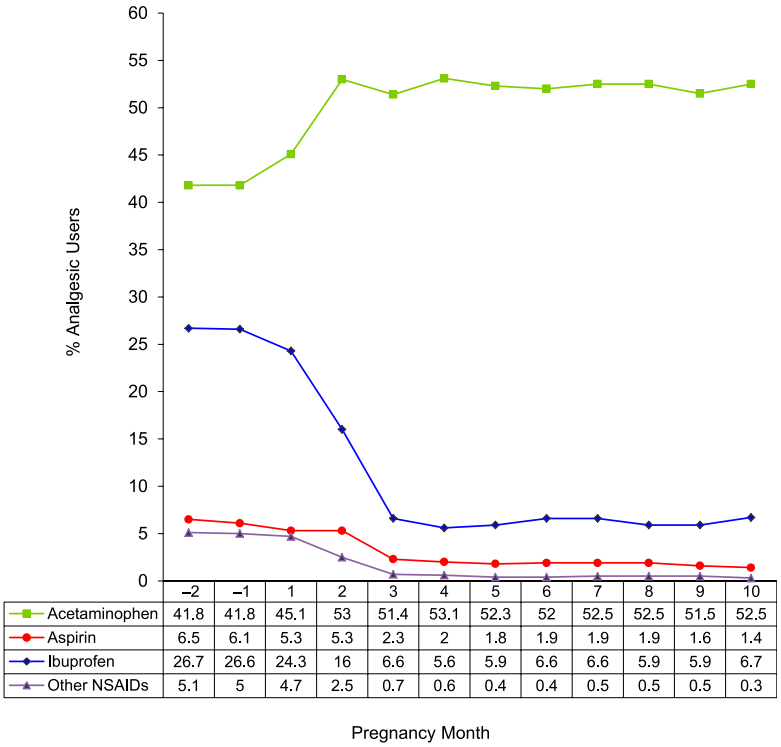
Despite biological plausibility, supportive laboratory work, and some epidemiologic evidence, in the current multicenter study, we found no consistent support for the hypothesis that a mother's NSAID consumption during pregnancy increases the risk of her infant developing PPHN. Although the risk associated with aspirin exposure increased as gestation progressed (maximum OR 2.34; 95% CI 0.94–5.88),

TABLE 2 Demographic, Pregnancy, and Neonatal Factors and Their Relationship With PPHN

Variable	PPHN *N* (%)	Matched Controls *N* (%)	Crude Matched OR (95% CI)	Adjusted I[a] OR (95% CI)	Adjusted II[b] OR (95% CI)
Demographic factors					
Maternal race					
White	217 (57.6)	606 (72.5)	Reference	Reference	Reference
Black	70 (18.6)	75 (9.0)	3.0 (1.9–4.7)	2.5 (1.5–4.1)	2.5 (1.4–4.5)
Asian	32 (8.5)	42 (5.0)	2.3 (1.4–3.8)	2.5 (1.4–4.4)	2.9 (1.5–5.7)
Hispanic	45 (12.0)	91 (11.0)	1.4 (0.9–2.1)	1.2 (0.8–2.0)	1.1 (0.6–1.9)
Other	13 (3.5)	22 (2.6)	2.0 (1.0–4.1)	1.7 (0.8–3.7)	2.7 (1.0–7.0)
Maternal age					
≤25	99 (26.3)	208 (24.9)	Reference	Reference	Reference
25–30	104 (27.6)	241 (28.8)	1.0 (0.7–1.4)	1.3 (0.9–1.9)	1.0 (0.6–1.7)
30–35	112 (29.7)	261 (31.2)	1.0 (0.7–1.4)	1.2 (0.8–1.9)	1.0 (0.6–1.6)
>35	62 (16.5)	126 (15.1)	1.1 (0.8–1.7)	1.5 (0.9–2.4)	1.2 (0.7–2.0)
Maternal education					
<13	135 (35.8)	228 (27.3)	Reference	Reference	Reference
13–15	106 (28.1)	234 (28.0)	0.8 (0.6–1.1)	0.8 (0.5–1.1)	0.9 (0.6–1.4)
>15	136 (36.1)	374 (44.7)	0.6 (0.5–0.9)	0.7 (0.5–1.0)	0.8 (0.5–1.3)
Parity					
Primiparous	250 (66.3)	561 (67.1)	Reference	Reference	Reference
Multiparous	127 (33.7)	275 (32.9)	1.0 (0.8–1.3)	1.2 (0.9–1.6)	1.0 (0.7–1.4)
BMI					
<20	38 (10.1)	152 (18.2)	Reference	Reference	Reference
20–27	197 (52.3)	497 (59.5)	1.5 (1.0–2.3)	1.5 (1.0–2.3)	1.3 (0.8–2.0)
>27	134 (35.5)	174 (20.8)	3.0 (1.9–4.6)	2.5 (1.6–4.0)	1.7 (1.0–2.9)
Unknown	8 (2.1)	13 (1.6)	2.2 (0.8–5.9)	2.0 (0.7–5.5)	0.9 (0.2–3.2)
Pregnancy factors					
Maternal smoking					
Never	226 (60.0)	494 (59.1)	Reference	Reference	Reference
Before pregnancy	84 (22.3)	206 (24.6)	0.9 (0.7–1.2)	0.9 (0.6–1.3)	0.9 (0.6–1.4)
During pregnancy	67 (17.8)	136 (16.3)	1.1 (0.8–1.5)	1.1 (0.7–1.6)	1.1 (0.7–1.7)
Multiple gestation					
Singleton	365 (96.8)	819 (98.0)	Reference	Reference	Reference
Multiple	12 (3.2)	17 (2.0)	1.6 (0.8–3.5)	1.3 (0.6–2.9)	0.4 (0.1–1.0)
Infant gender					
Female	138 (36.6)	426 (51.0)	Reference	Reference	Reference
Male	239 (63.4)	410 (49.0)	1.9 (1.4–2.4)	1.6 (1.2–2.2)	1.5 (1.1–2.1)
Asthma					
Yes vs No	46 (12.2)	62 (7.4)	1.7 (1.2–2.6)	1.6 (1.0–2.5)	2.0 (1.2–3.4)
Hypertension					
Yes vs No	66 (17.5)	90 (10.8)	1.8 (1.3–2.6)	1.3 (0.9–1.9)	1.3 (0.8–2.1)
Diabetes mellitus					
Yes vs No	37 (9.8)	35 (4.2)	2.4 (1.5–3.8)	1.6 (0.9–2.8)	1.2 (0.6–2.3)
NSAIDs third trimester					
Yes vs No	37 (9.8)	87 (10.4)	1.0 (0.6–1.5)	0.8 (0.5–1.3)	0.6 (0.4–1.1)
Perinatal factors					
Delivery					
Vaginal	146 (38.7)	677 (81.0)	Reference		Reference
Cesarean delivery	231 (61.3)	159 (19.0)	7.5 (5.5–10.4)		7.0 (4.9–10.1)
Gestational age (wk)					
<37	60 (15.9)	42 (5.0)	3.8 (2.5–5.8)		3.6 (2.0–6.5)
37-41	227 (60.2)	670 (80.1)	Reference		Reference
>41	90 (23.9)	124 (14.8)	2.2 (1.6–3.0)		2.1 (1.4–3.1)
Birth wt (g)					
<2500	29 (7.7)	29 (3.5)	2.4 (1.4–4.1)		1.1 (0.5–2.4)
2500–4000	275 (72.9)	704 (84.3)	Reference		Reference
>4000	73 (19.4)	102 (12.2)	2.0 (1.4–2.8)		1.7 (1.1–2.6)

[a] Adjusted for other covariates within demographic and pregnancy factors.

[b] Adjusted for all the covariates in the table.



	–2	–1	1	2	3	4	5	6	7	8	9	10
Acetaminophen	41.8	41.8	45.1	53	51.4	53.1	52.3	52	52.5	52.5	51.5	52.5
Aspirin	6.5	6.1	5.3	5.3	2.3	2	1.8	1.9	1.9	1.9	1.6	1.4
Ibuprofen	26.7	26.6	24.3	16	6.6	5.6	5.9	6.6	6.6	5.9	5.9	6.7
Other NSAIDs	5.1	5	4.7	2.5	0.7	0.6	0.4	0.4	0.5	0.5	0.5	0.3

FIGURE 1
Trends in analgesic use during pregnancy. These data reflect the use of selected analgesics among matched control subjects by pregnancy month. The denominator at each time point reflects women pregnant at that gestational month.

the lower confidence bound did not exclude the null. Unexpectedly, among infants born at or beyond 37 weeks' gestation, maternal ibuprofen consumption in the third trimester of pregnancy was associated with an ~50% reduced risk of PPHN (OR 0.42; 95% CI 0.20–0.89).

Our negative findings for NSAIDs as a risk factor for PPHN are puzzling given the biological plausibility for such an association. NSAIDs inhibit prostaglandin synthesis, inducing fetal ductus arteriosus constriction,[16–18,21] increasing pulmonary blood flow, and remodeling the pulmonary vasculature,[9,32,33] resulting in postnatal pulmonary hypertension.[34] Furthermore, the pattern of pulmonary vascular morphologic changes described in animals exposed in utero to prostaglandin inhibitors[9,32] is similar to that found in a subset of infants with PPHN.[14] On the other hand, in utero constriction of the DA with prostaglandin inhibitors also appears to produce local hypoxia and remodeling of the vessel, changes that decrease ductal responsiveness and contractility after birth[35] resulting in patent ductus arteriosus, would not lead to PPHN, however.

Existing epidemiologic evidence linking antenatal NSAID exposure and PPHN is limited and based on smaller studies lacking the power and methodologic rigor of the current study. The link between maternal NSAID consumption during pregnancy and PPHN is based largely on a series of case reports. The only previous epidemiologic study showing a positive association between antenatal NSAID exposure and PPHN[11] was based on only 26 infants whose mothers reported NSAID intake at any

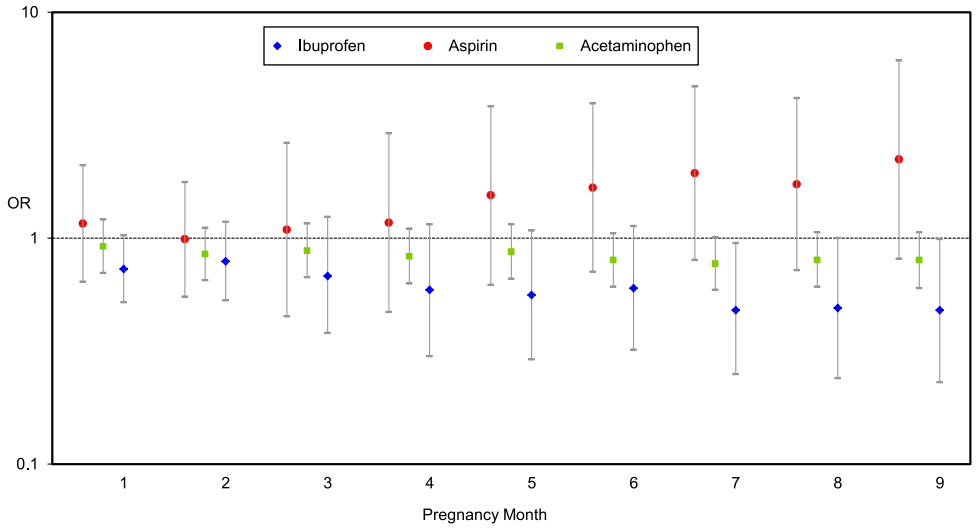


FIGURE 2
Association between PPHN and antiinflammatory drug use by pregnancy month. Conditional logistic regression for matched data showing ORs and 95% CIs adjusted for maternal race, diabetes, pre-pregnancy BMI, and gestational hypertension.

TABLE 3 Association Between PPHN and Selected Analgesics Used During the Third Trimester

	PPHN, *N* (%)	Controls, *N* (%)	Crude OR (95% CI)	Adjusted OR[a] (95% CI)	Adjusted OR[b] (95% CI)	Adjusted OR[c] (95% CI)
Ibuprofen	18 (4.8)	64 (7.7)	0.65 (0.38–1.12)	0.56 (0.31–1.02)	0.58 (0.32–1.05)	0.56 (0.28–1.11)
Aspirin	15 (4.0)	19 (2.3)	1.82 (0.92–3.62)	1.69 (0.77–3.69)	1.66 (0.74–3.74)	1.19 (0.50–2.87)
Acetaminophen	191 (50.7)	475 (56.9)	0.80 (0.63–1.03)	0.86 (0.66–1.12)	0.87 (0.66–1.14)	0.86 (0.63–1.17)

Conditional logistic regression for matched data.

[a] Adjusted for race, diabetes, pre-pregnancy BMI, hypertension, and multiple births.

[b] Adjusted for preterm birth, in addition to variables noted in [a].

[c] Adjusted for cesarean delivery, in addition to variables noted in [a] and [b].

TABLE 4 Association Between PPHN and Selected Analgesics Used During the Third Trimester

	PPHN, *N* (%)	Controls, *N* (%)	Crude OR (95% CI)	Adjusted OR[a] (95% CI)	Adjusted OR[b] (95% CI)
Ibuprofen	15 (4.7)	62 (7.8)	0.55 (0.30–0.99)	0.40 (0.21–0.78)	0.42 (0.20–0.89)
Aspirin	12 (3.8)	17 (2.1)	2.01 (0.91–4.46)	2.34 (0.94–5.88)	1.47 (0.52–4.12)
Acetaminophen	159 (50.2)	456 (57.3)	0.83 (0.63–1.09)	0.86 (0.64–1.16)	0.90 (0.64–1.27)

Conditional logistic regression for matched data. Restricted to term births (≥37 wk).

[a] Adjusted for race, diabetes, pre-pregnancy BMI, hypertension, and multiple births.

[b] Adjusted for cesarean delivery, in addition to variables noted in [a].

time during pregnancy and just 4 mothers (1 case and 3 controls; 1% for each) who reported taking NSAIDs during the last trimester of pregnancy. That exploratory study found elevated ORs (OR 3.6, 95% CI 1.2–11 among all subjects and OR 8.1, 95% CI 2.3–28 among the inborn subjects) despite relying on maternal recall, finding unexpectedly low prevalence of NSAID use, and including early pregnancy exposures of questionable biological relevance. At the other extreme, studies based on serum[36] or meconium[27] salicylate levels found a surprisingly high prevalence of exposure (50%) and an extremely low concordance between biological samples and maternal recall (only 2 of 6 positive mothers in one study[36] and 1 of 44 in another[27] reported ingestion of aspirin). The authors of these studies attributed their findings to maternal failure to recall or recognize salicylates in multiingredient OTC medications.[27] Of note, in the meconium-based study, 33% of the "randomly selected healthy controls" were born by cesarean delivery, and 59% had meconium-stained amniotic fluid, which raises the possibility of biased control selection. Moreover, this study did not replicate the previously established associations between PPHN and postmaturity, cesarean delivery, meconium staining of the amniotic fluid, male gender of the infant, or African American ethnicity.[10–13,37,38] One recent study of the association between selective serotonin reuptake inhibitors and PPHN risk from 5 Nordic countries observed no association between NSAID use and PPHN.[39]

The main limitation of the current study is the reliance on maternal recall for information about exposure status. Several factors suggest, however, that recall bias is an unlikely explanation for our study results. First, if medication use in general was more likely to be recalled by mothers of cases than controls, an elevated risk associated with acetaminophen would be expected; this was not observed. Furthermore, there was no evidence of public perception of increased risk of PPHN associated with maternal intake of aspirin or reduced PPHN risk associated with ibuprofen consumption. We recognize that there is no gold standard for identifying exposure to OTC medications in pregnancy and carefully conducted maternal interviews are considered a reasonable way to capture such exposures. Nonetheless, misclassification is a potential source of bias, particularly for the medications under study. It is unlikely, however, that random misclassification (ie, unrelated to the outcome) would explain the differences observed between aspirin and nonaspirin (ie, acetaminophen, ibuprofen) products.

The failure of the current study to detect an association between maternal NSAID intake during pregnancy and neonatal PPHN runs counter to evidence in laboratory animals and human case reports. However, differential effects of various specific NSAIDs (eg, increased PPHN risk associated with aspirin but not other NSAIDs) is biologically plausible. The apparent reduction in PPHN risk with antenatal exposure to ibuprofen is particularly intriguing, however, and is not explained by the drug's propensity to cause DA closure. The role of inflammation in the pathogenesis of pulmonary hypertension is receiving increasing recognition,[40–44] and we speculate that the protective effect of antenatal exposure to ibuprofen in PPHN, if real, is more likely to be attributable to its antiinflammatory properties than to a direct effect on the pulmonary vasculature. If antenatal ibuprofen exposure mitigates perinatal inflammation, it might reduce the occurrence of PPHN.

CONCLUSIONS

The current study represents the largest epidemiologic study of risk factors for PPHN and was designed specifically to evaluate the hypothesis that antenatal NSAID exposure is associated with an increased risk of an infant developing PPHN. Strengths of the study are its large and geographically diverse population, thorough review and diagnostic categorization of PPHN cases, and structured interviews conducted within 6 months of each baby's birth by highly experienced interviewers using rigorous methods for medication identification.

In this large case-control study of PPHN, we found no support for the previous hypothesis that antenatal exposure to NSAIDs increases the risk of PPHN. Multivariable analyses of third-trimester exposures, adjusting for other risk factors, revealed an increase in risk of the occurrence of PPHN associated with antenatal exposure to aspirin intake, with confidence limits that did not exclude the null and an unexpected reduction in PPHN occurrence associated with third-trimester maternal intake of ibuprofen.

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