Analysis of Nonsteroidal Antiinflammatory Drugs in Meconium and Its Relation to Persistent Pulmonary Hypertension of the Newborn

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ABBREVIATIONS:

PPHN	persistent pulmonary hypertension of the newborn
NSAID	nonsteroidal antiinflammatory drug
GC/MS	gas chromatography/mass spectrometry
PDA	patent ductus arteriosus
OR	odds ratio
CI	95% confidence interval
NO	nitric oxide
ECMO	extracorporeal membrane oxygenation

FROM ABSTRACT

Objective.
The objective of this study was to detect fetal exposure to nonsteroidal antiinflammatory drugs (NSAIDs) by meconium analysis and to determine the relationship between fetal exposure to NSAIDs and the development of persistent pulmonary hypertension of the newborn (PPHN).

Methods.
In a case-control study of the inborn and outborn nurseries of a large urban medical center, meconium was collected from 101 newborn infants (40 with the diagnosis of PPHN based on clinical or echocardiographic criteria and 61 randomly selected, healthy, term infants [control]) and analyzed for NSAIDs (ibuprofen, naproxen, indomethacin, and aspirin) by gas chromatography/mass spectrometry. The risk of developing PPHN was determined in infants who were exposed antenatally to NSAID.

Results.
Infants with PPHN (n = 40) had a mean gestation of 38.9 weeks and birth weight of 3524 g, which were similar to those of the control group (n = 61).

However, the incidence of low Apgar scores at 1 minute and 5 minutes was significantly higher in the PPHN group than in the control group.

The diagnoses associated with PPHN were primary PPHN (25%), meconium aspiration syndrome (35%), respiratory distress syndrome (20%), low Apgar score/asphyxia (12.5%), and pneumonia/sepsis (8%).

Mean duration of ventilator support for the PPHN group was 11 days. Nitric oxide (NO) was given to 19 infants (47.5%) for a mean duration of 25.4 hours. Fourteen of the 19 infants who were treated with NO (74%) required extracorporeal membrane oxygenation, and 2 died.

The overall incidence of positive NSAID in meconium in the study population (n = 101) was 49.5%: 22.8% were positive for ibuprofen, 18.8% for naproxen, 7.9% for indomethacin, and 43.6% for aspirin.

There was poor agreement between maternal history of NSAID use and NSAID detection in meconium.

PPHN was significantly associated with
1) The presence of at least 1 NSAID in meconium, or
2) The presence in meconium of aspirin, ibuprofen, or naproxen.

By logistic regression analysis, low Apgar scores at 1 and 5 minutes and the antenatal exposure to aspirin, naproxen, and ibuprofen were significantly associated with PPHN and treatment with inhaled NO or extracorporeal membrane oxygenation.

Conclusion.
We confirm by meconium analysis the results of previous studies that demonstrated that the use of NSAIDs during pregnancy, particularly aspirin, ibuprofen, and naproxen, is high; is grossly underestimated by maternal history; and is significantly associated with PPHN.

Thus, the easy access to over-the-counter NSAIDs of pregnant women should be reevaluated, and the potential dangers of these drugs to the newborn infant should be more effectively promoted.

THESE AUTHORS ALSO NOTE:

"Persistent pulmonary hypertension of the newborn (PPHN) has been associated with antenatal exposure to nonsteroidal antiinflammatory drugs (NSAIDs)."

"NSAIDs (ibuprofen, indomethacin, naproxen, and aspirin) are cyclooxygenase inhibitors that can reduce or inhibit arachidonic acid release and block the synthesis of prostaglandins and thromboxane, which are involved in maintaining ductal patency and regulation of pulmonary vasculature."

In animal studies, surgical occlusion of the ductus arteriosus or exposure to NSAIDs causes a structural remodeling of the peripheral pulmonary vascular bed, resulting in pulmonary arterial hypertension.

"The occurrence of PPHN in infants has been linked to antenatal NSAID exposure in the mother."

Postmortem studies of infants whose mothers received NSAIDs during pregnancy showed pulmonary arteriolar muscularization.

The true incidence of maternal use of NSAIDs is not known because most studies have relied on maternal history, which have been shown to be quite inaccurate. This might be because of a recall problem or the failure of the mother to recognize the presence of NSAIDs in multiingredient over-the-counter medications.

Meconium drug analysis is a new method for identifying in utero exposure of infants to a number of illicit and legal drugs, and it has been shown to be sensitive and specific.

METHODS
The authors used a GC/MS (gas chromatography/mass spectrometry) assay method to analyze the NSAIDs (aspirin, ibuprofen, indomethacin, and naproxen) in meconium.

RESULTS
A total of 101 infants were enrolled in the study: 40 in the PPHN group and 61 in the control group.

The neonatal profiles of infants in the PPHN and control groups were similar except for significantly lower 1- and 5-minute Apgar scores in the PPHN group.

Other diagnoses that are associated with PPHN include:
Meconium aspiration
Idiopathic or primary PPHN
Respiratory distress syndrome
Low Apgar score/asphyxia
Pneumonia
Group B streptococcal sepsis

"Among the 40 infants with PPHN, 10 infants required only hood oxygen, but at 100% concentration, and the infants exhibited marked lability in oxygen saturation, particularly during the first 24 hours of life. Thirty infants required a ventilator; the mean duration of ventilator support was 11 days. Nineteen of these infants (47.5%) required inhaled nitric oxide (NO), and 14 infants (75%) subsequently were placed on an extracorporeal membrane oxygenator (ECMO) and 2 died." **[These are serious problems].**

"PPHN was significantly associated with a low 1- or 5-minute Apgar score and the presence of NSAIDs in meconium, particularly aspirin and ibuprofen."

"Only a few infants (n = <10) had 2 or more NSAIDs in their meconium, which precluded further analysis on whether fetal exposure to >1 NSAID further increased the risk for PPHN."

In 101 meconium samples:
49.5% were found to be positive for NSAIDs
43.6% positive for aspirin (other forms of salicylate were not assessed)
7.9% positive for indomethacin
22.8% positive for ibuprofen
18.8% positive for naproxen

In contrast, by maternal history, only:
1% had a history of aspirin use
1.6% of indomethacin use
12.8% of ibuprofen use
11.7% of naproxen use

"Thus, the degree of agreement between exposure to NSAIDs as detected by meconium analysis or maternal history was very low."

There was a significant association between the concentrations of ibuprofen in meconium and PPHN.

There was a significant association between the concentrations of naproxen in meconium and the use of ECMO (extracorporeal membrane oxygenation) or NO (nitric oxide).

DISCUSSION

PPHN occurs at a rate of approximately 1 per 600 to 1500 live births.

The role of NSAIDs as a predisposing factor to the development of PPHN has been previously suggested in several studies, and this study "has confirmed these observations."

"The use of NSAIDs during pregnancy is common because the exposure of the public to these medications through the print and television media is widespread."

"Although the labels on these drugs provide adequate warning of the potential harm to the fetus if these drugs are used during pregnancy, it is likely that the warnings are ignored."

NSAIDs are one of the most widely used agents during pregnancy.

"The NSAIDs are used for their antiinflammatory, analgesic, or antipyretic properties and are available over the counter."

Indomethacin is the only exception and usually is available only by prescription, which may explain why the low fetal exposure to indomethacin in this study.

"NSAIDs may unknowingly be taken by mothers through multiingredient, over-the-counter medications."

"For example, Pepto Bismol contains bismuth subsalicylate, which, if hydrolyzed and absorbed in the gastrointestinal tract, results in significant serum salicylate levels."

Low-dose aspirin has been used for the prevention of hypertension in pregnancy.

NSAIDs readily cross the placenta and have a long half-life in the fetus.

"Of the various NSAIDs identified in meconium, aspirin, ibuprofen, and naproxen were significantly associated with the development of PPHN."

"Severe PPHN, which required ECMO treatment, was significantly associated with naproxen or ibuprofen."

The rate of pregnant women's reporting the use of NSAIDs during pregnancy was low, which is likely attributable to problems of drug recall or the difficulty in recognizing NSAIDs that are marketed under various trade names or as part of multiingredient pain medications.

This study reinforces the usefulness of meconium analysis as a sensitive test to identify drugs that the fetus may have been exposed to during gestation.

"Drugs are deposited in meconium through bile secretion or through fetal swallowing of drugs in the amniotic fluid."

"Because meconium is formed as early as the 12th week of gestation and normally is not excreted by the fetus until after birth, meconium analysis offers a wide window for detecting fetal exposure to drugs."

CONCLUSION

The authors "confirm by meconium analysis what has been suggested by previous studies:

That NSAID use during pregnancy is significantly underestimated by maternal history and that the association between NSAID use during pregnancy, particularly aspirin, ibuprofen, and naproxen and PPHN is high."

"Thus, the easy access of over-the-counter NSAIDs to pregnant women should be reevaluated, and the potential dangers of these drugs to the newborn infant should be more effectively promoted."