OBSTETRICS

Antenatal exposure to indomethacin increases the risk of severe intraventricular hemorrhage, necrotizing enterocolitis, and periventricular leukomalacia: a systematic review with metaanalysis

Amy L. Hammers, MD; Luis Sanchez-Ramos, MD; Andrew M. Kaunitz, MD

OBJECTIVE: The purpose of this study was to provide an updated summary of the literature regarding the effects of tocolysis with indomethacin on neonatal outcome by systematically reviewing previously and recently reported data.

STUDY DESIGN: All previously reported studies pertaining to indomethacin tocolysis and neonatal outcomes along with recently reported data were identified with the use of electronic databases that had been supplemented with references that were cited in original studies and review articles. Observational studies that compared neonatal outcomes among preterm infants who were exposed and not exposed to indomethacin were included in this systematic review. Data were extracted and quantitative analyses were performed on those studies that assessed the neonatal outcomes of patients that received antenatal tocolysis with indomethacin.

RESULTS: Twenty-seven observational studies that met criteria for systematic review and metaanalysis were identified. These studies included 8454 infants, of whom 1731 were exposed to antenatal indomethacin and 6723 were not exposed. Relative risks with 95% confidence intervals were calculated for dichotomous outcomes with the use of random and fixed-effects models. Metaanalysis revealed no statistically significant differences in the rates of respiratory distress syndrome, patent ductus arteriosus, neonatal mortality rate, neonatal sepsis, bronchopulmonary dysplasia, or intraventricular hemorrhage (all grades). However, antenatal exposure to indomethacin was associated with an increased risk of severe intraventricular hemorrhage (grade III-IV based on Papile's criteria; relative risk, 1.29; 95% confidence interval, 1.06—1.56), necrotizing enterocolitis (relative risk, 1.36; 95% confidence interval, 1.08—1.71), and periventricular leukomalacia (relative risk, 1.59; 95% confidence interval, 1.17—2.17).

CONCLUSION: The use of indomethacin as a tocolytic agent for preterm labor is associated with an increased risk for severe intraventricular hemorrhage, necrotizing enterocolitis, and periventricular leukomalacia.

Key words: intraventricular hemorrhage, necrotizing enterocolitis, periventricular leukomalacia

Cite this article as: Hammers AL, Sanchez-Ramos L, Kaunitz AM. Antenatal exposure to indomethacin increases the risk of severe intraventricular hemorrhage, necrotizing enterocolitis, and periventricular leukomalacia: a systematic review with metaanalysis. Am J Obstet Gynecol 2015;212:●●●●.

Preterm birth represents an important perinatal health problem across the globe, not only in terms of associated mortality rates but also with regard to short- and long-term morbidity and financial costs.[1,2] In the Unites States, the preterm birth rate reached its peak in 2006 (12.8%). However, despite a gradual decline for the seventh straight year in 2013 (11.4%),[3] the United States ranks as 1 of the top 10 countries in the world with the highest number of preterm births.[4] In the United States, premature birth accounts for nearly 35% of deaths in the first year of life at an estimated annual cost that exceeds $26 billion. In addition, preterm birth contributes to substantial neurobehavioral impairment.[5]

Major recent progress has been made toward the early diagnosis,[6] prediction,[7-9] and prevention of spontaneous preterm birth.[10-13] However, the mainstay of therapy for the treatment of acute preterm labor continues to be the employment of pharmacologic agents with the aim of arrest of or decrease of uterine contractility and thereby delaying preterm birth. Although tocolytic agents have been shown to delay delivery for 48 hours to 7 days,[14,15] their use has not led to an improvement in neonatal outcomes. Nonetheless, this short prolongation of pregnancy allows for the maternal transfer to a tertiary center and

From the Department of Obstetrics and Gynecology, University of Florida College of Medicine—Jacksonville, Jacksonville, FL.

Received June 27, 2014; revised Oct. 8, 2014; accepted Oct. 28, 2014.

The authors report no conflict of interest.

Corresponding author: Amy Hammers, MD. amy.hammers@jax.ufl.edu

0002-9378/$36.00 • • http://dx.doi.org/10.1016/j.ajog.2014.10.1091

the administration of corticosteroids to enhance fetal lung maturity.[16]

A variety of pharmacologic agents that have been used, most off-label, to suppress uterine contractility include betamimetics,[17-21] magnesium sulfate,[22-25] oxytocin receptor antagonists,[15,26-29] calcium channel blockers,[30-34] cyclooxygenase inhibitors,[35-41] and nitric oxide donors.[42-46] Each of these agents has a unique mechanism of action and side-effects. A recent metaanalysis suggested that the calcium channel blocker nifedipine appears to meet several characteristics of an ideal tocolytic agent.[30] A systematic review and network metaanalysis[47] and a metaanalysis with decision analysis[48] concluded that calcium channel blockers and prostaglandin inhibitors had the highest probability of delaying delivery and improving neonatal and maternal outcomes.

There is strong evidence that prostaglandins are involved intimately in the initiation and progression of term and preterm labor in humans.[49-53] Prostaglandins affect myometrial contractility by direct effect with their own receptors[50,51] by an increase in the sensitivity of the myometrium to oxytocin[52] and by regulation of myometrial gap junctions.[49] They also stimulate the influx of intracellular calcium that activates the enzyme myosin light chain kinase that results in myometrial contractility.[53]

Indomethacin, a cyclooxygenase inhibitor that decreases uterine contractility by blocking the conversion of arachidonic acid to prostaglandin, has been used as a tocolytic agent since 1974.[54] Many obstetricians continue to use indomethacin as a first-line tocolytic agent, which is an indication that is supported by the American College of Obstetricians and Gynecologists.[55] A number of studies have raised concerns about the safety of indomethacin because it crosses the placenta and inhibits prostaglandin synthesis in fetal organs.[56,57] Case reports and observational studies have suggested that indomethacin may cause adverse neonatal outcomes that include necrotizing enterocolitis (NEC), intraventricular hemorrhage, periventricular leukomalacia, and other cardiac, pulmonary, and renal abnormalities.[58-61] Accordingly, indomethacin's role as a current option by obstetricians in the treatment for possible preterm labor is controversial. Since 2005, 2 systematic reviews with metaanalyses that assessed neonatal outcomes after indomethacin tocolysis, while using similar sources, have reported conflicting results.[58,59] The first of these reports included both observational studies and randomized trials; the subsequent report included only observational studies. Subsequent to these publications, more recent observational and prospective studies that assessed indomethacin tocolysis have been published.[62-67] The goal of this current study was to review these new studies, to reanalyze studies that were included in the 2 previous reviews, and to pool the data to determine more accurately the neonatal effects of indomethacin exposure, thus providing needed guidance regarding the use of this medication for tocolysis.

Materials and Methods

This systematic review and metaanalysis was conducted according to the Metaanalysis of Observational Studies in Epidemiology (MOOSE) guidelines.[68] Searches were conducted for published literature from January 1966 to March 2014. The key words *indomethacin* and *tocolysis* were used in the search independently and then in conjunction with the following other key words: *bronchopulmonary dysplasia*, *intraventricular hemorrhage*, *patent ductus arteriosus*, *necrotizing enterocolitis*, and *neonatal mortality*. Prospective and retrospective observational studies and clinical trials that evaluated tocolysis with indomethacin as an exclusive agent or in combination with other tocolytics for preterm labor vs a comparison group without tocolytics or with a different tocolytic agent were identified. In addition to including those studies that were assessed in the previous systematic reviews, we identified more recent observational studies and clinical trials that evaluated neonatal outcomes with the use of indomethacin for tocolysis in patients with preterm labor using the following computerized databases: PubMed, MEDLINE, and Cochrane. All of the included studies assessed ≥ 1 of the following neonatal outcomes: intraventricular hemorrhage (IVH) that was graded by Papile's classification based on head ultrasound scanning, NEC that was based on Bell's staging criteria or x-ray findings of pneumatosis intestinalis and/or intestinal perforation, patent ductus arteriosus (PDA) that was diagnosed by echocardiography, bronchopulmonary dysplasia (BPD) that was based on oxygen requirements of the neonate at 36 weeks postmenstrual age, respiratory distress syndrome (RDS) that was based on clinical and/or chest x-ray findings, periventricular leukomalacia (PVL) that was diagnosed on head ultrasound scanning or other imaging, neonatal sepsis that was evidenced by positive cultures and/or clinical symptoms, or neonatal death that represented death during initial hospitalization after birth. Because each report did not assess all outcomes of interest, specific outcome metaanalyses were performed that were based on a variable number of studies that were related to that outcome. Studies were excluded if they lacked a comparison group, lacked assessment of neonatal outcomes of interest, or lacked sufficient quantitative data for extraction.

Each study was scored for quality by the primary author and a second obstetrician with the use of the Newcastle-Ottawa Quality Assessment scale.[69] Data that were collected from each study included first author, study design, publication year, control group definition, gestational age at birth of subjects, neonatal outcomes that were measured, number of subjects in the study and control group, other tocolytics that were used, neonatal birthweight and gender, and the administration of steroids for fetal lung maturity. Raw data were extracted by the primary author using 2×2 tables for each neonatal outcome that was measured in the antenatal indomethacin exposure group and in the comparison group. Two other independent researchers then confirmed these data.

Metaanalyses were performed for each neonatal outcome with a Stata