The unpredictable nature of IUFD in pregnancies that are complicated by ICP and reports of abnormal heart tracing in ICP-affected pregnancies led investigators to hypothesize that these cases of IUFD are caused by impaired fetal cardiomyocyte function that resulted in fetal cardiac arrest. Indeed, the bile acid taurocholate was shown to impair the rate of contraction, the synchronicity, and the calcium dynamics of rat cardiomyocytes in a dose dependent manner,[3] which could result in fetal dysrhythmia and in sudden IUFD.

In summary, the data in this case of IUFD that included the facts that the woman had severe ICP, that the dead fetus's monitoring suddenly became pathologic, that there was no evidence of IUGR, and that the autopsy was normal support the occurrence of a cardiac event attributed to ICP. ■

Yael Raz, MD
Eli Rimon, MD
Department of Obstetrics and Gynecology
Lis Maternity Hospital, Tel Aviv Medical Center
Sackler Faculty of Medicine
Tel Aviv University
Tel Aviv, Israel
elir@tasmc.health.gov.il

The authors report no conflict of interest.

REFERENCES

1. Garite TJ, Clark RH, Elliott JP, Thorp JA. Twins and triplets: the effect of plurality and growth on neonatal outcome compared with singleton infants. Am J Obstet Gynecol 2004;191:700-7.
2. Geenes V, Chappell LC, Seed PT, Steer PJ, Knight M, Williamson C. Association of severe intrahepatic cholestasis of pregnancy with adverse pregnancy outcomes: a prospective population-based case-control study. Hepatology 2014;59:1482-91.
3. Gorelik J, Harding SE, Shevchuk AI, et al. Taurocholate induces changes in rat cardiomyocyte contraction and calcium dynamics. Clin Sci (Lond) 2002;103:191-200.

 http://dx.doi.org/10.1016/j.ajog.2015.08.006

Indomethacin as a tocolytic harmful to preterm infant

TO THE EDITORS: Amy Hammers et al[1] recently published a critical metaanalysis of indomethacin as a tocolytic that demonstrated evidence of harmful effects to preterm infants. The investigators have used rigorous methods for metaanalysis of observational studies. They acknowledge that the selection biases are difficult to control using metaregression analysis because many important confounders are not identified. The investigators did not study randomized clinical trials (RCT) because there are only 3 reported trials with a rather limited number of patients. Bronchopulmonary dysplasia (BPD) was not a significant risk factor in the study of Hammers et al, whereas indomethacin increased the risk of BPD in metaanalysis of RCTs.

The discordance in the results between cohort studies and RCT effects may be due to a selection bias. In the metaanalyses published on the topic, there have been fewer cohorts listing BPD as an outcome, compared with neonatal outcomes, such as intraventricular hemorrhage. Of the 7 cohort studies used by Hammers et al to estimate the risk of BPD, 3 listed preterm pregnancies with or without requirement of tocolysis as control subjects. As a result, the exposed pregnancies may have under-representation of intrauterine growth restriction and preeclampsia and over-representation of spontaneous birth cases compared with control subjects; some of the studies actually showed that these differences between the groups were statistically significant. This is likely to result in an overestimate of the risk of intraventricular hemorrhage and an underestimate of the risk of BPD in the indomethacin group.[2,3] We reanalyzed the risk of BPD using the references listed by Hammer et al and included only the 4 studies that compared 2 populations that required tocolytic. We found a significant increase in the risk of BPD (odds ratio, 1.7; 95% confidence interval, 1.2−2.7). This estimate is consistent with the result of the randomized trial.[4]

The harmful consequences of indomethacin tocolytic treatment shortly before the birth of a preterm infant may overshadow the benefits of prolonging the short duration of pregnancy. For instance a follow up of a randomized trial shows evidence of adverse long-term effect in small toddlers, despite a significant increase in the duration of pregnancy in the indomethacin group. Many investigators, including those who are involved in formulating consensus guidelines, prefer to evaluate RCTs rather than retrospective observational studies. ■

Mikko Hallman, MD
PEDEGO Research Center
University of Oulu
Oulu University Hospital
Oulu, Finland
mikko.hallman@oulu.fi

Erkki Pesonen, MD
Skåne University
Department of Paediatrics
Skåne University Hospital
Lund, Sweden

Kari Teramo, MD
Obstetrics and Gynecology
University of Helsinki
Helsinki University Hospital
Helsinki, Finland

The authors report no conflict of interest.

REFERENCES

1. 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;212:505.e1-13.

2. Ment LR, Ådén U, Lin A, et al. Gene-environment interactions in severe intraventricular hemorrhage of preterm neonates. Pediatr Res 2014;75:241-50.

3. Klinger G, Sokolover N, Boyko V, et al. Perinatal risk factors for bronchopulmonary dysplasia in a national cohort of very-low-birthweight infants. Am J Obstet Gynecol 2013;208:115.e1-9.

4. Eronen M, Pesonen E, Kurki T, Teramo K, Ylikorkala O, Hallman M. Increased incidence of bronchopulmonary dysplasia after antenatal administration of indomethacin to prevent preterm labor. J Pediatr 1994;124:782-8.

 http://dx.doi.org/10.1016/j.ajog.2015.08.022

REPLY

The thoughtful comments of Drs Hallman, Personen, and Teramo regarding our recently published metaanalysis are appreciated.[1] We are aware of the ongoing interest of these researchers on the adverse effects of antenatal exposure to indomethacin, including an elevated risk for bronchopulmonary dysplasia (BPD).[2]

While attempting to replicate their subgroup analysis of our data, excluding comparison groups not receiving tocolytics, we noted an abstraction error that resulted in an incorrect pooled effect estimate for the BPD outcome. In our report, the data as reported by Van Overmeire et al[3] were transposed inadvertently, resulting in an incorrect pooled relative risk of BPD of 1.12 (95% confidence interval, 0.79−1.59).

We have revised our metaanalysis overall and, in particular, for the BPD outcome, and we conclude that the use of indomethacin as a tocolytic agent is associated not only with an increased risk for severe intraventricular hemorrhage, necrotizing enterocolitis, and periventricular leukomalacia but also for BPD (relative risk, 1.37; 95% confidence interval, 1.19−1.60; Table).

Based on our previous metaanalysis of published randomized trials[4] and our current metaanalysis of observation studies,[1] we fully agree that the use of indomethacin antenatally to prevent preterm birth causes important neonatal adverse effects that, in fact, include an elevated risk of bronchopulmonary dysplasia. ■

TABLE

Risk for bronchopulmonary dysplasia associated with the antenatal maternal exposure to indomethacin (corrected data)

Study	Group (n/N)		Relative risk (95% confidence interval)
	Exposed	Not exposed	
Van Overmeire	18/38	9/38	2.00 (1.03-3.88)
Ojala	3/82	2/94	1.72 (0.29-10.04)
Gerson	3/24	4/33	1.03 (0.25-4.19)
Al-Alaiyan	2/15	4/15	0.50 (0.11-2.33)
Soraisham	61/75	75/148	1.35 (1.16−1.57)
Sood	22/63	106/565	1.86 (1.27−2.72)
Vermillion	19/75	39/150	0.97 (0.61−1.56)
M-H pooled RR			1.37 (1.19−1.59)

Heterogeneity $X^2 = 7.66$ (degrees of freedom = 6; P = 0.264).

RR, relative risk; *CI*, confidence interval; *M-H*, Mantel-Haenszel.

Hammers. Reply. Am J Obstet Gynecol 2015.

Amy L. Hammers, MD
Luis Sanchez-Ramos, MD
Andrew M. Kaunitz, MD
Department of Obstetrics and Gynecology
University of Florida College of Medicine − Jacksonville
Jacksonville, FL
Hammers.amy@gmail.com

The authors report no conflict of interest.

REFERENCES

1. 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 meta-analysis. Am J Obstet Gynecol 2015;505:e1-13.

2. Eronen M, Pesonen E, Kurki T, Teramo K, Ylikorkala O, Hallman M. Increased incidence of bronchopulmonary dysplasia after antenatal administration of indomethacin to prevent preterm labor. J Pediatr 1994;124:782-8.

3. Van Overmeiere B, Slootmaekers V, De Loor J, et al. The addition of indomethacin to betamimetics for tocolysis: any benefit for the neonate? Eur J Obstet Gynecol Reprod Biol 1998;77:41-5.

4. Loe SM, Sanchez-Ramos L, Kaunitz AM. Assessing the neonatal safety of indomethacin tocolysis: a systematic review with meta-analysis. Obstet Gynecol 2005;106:173-9.

 http://dx.doi.org/10.1016/j.ajog.2015.08.023

Prenatal aneuploidy screening using cell-free DNA

TO THE EDITORS: We sincerely thank the Society for Maternal-Fetal Medicine Publication Committee for its recent article that addressed noninvasive prenatal testing (NIPT).[1] The document provides invaluable information and guidance for practitioners. A concept that was not addressed was test accuracy, which is itself a discrete measure of screening