

Teratogen Update: Fetal Effects of Indomethacin Administration During Pregnancy

MARY E. NORTON*

Department of Obstetrics and Gynecology, Brigham and Women's Hospital, Boston, Massachusetts 02115

Indomethacin is a nonsteroidal anti-inflammatory analgesic used in the treatment of disorders such as rheumatoid arthritis, ankylosing spondylitis, and osteoarthritis. Prostaglandins have a significant stimulatory effect on established labor; because indomethacin is a potent inhibitor of prostaglandin synthesis, this agent is also used in the treatment of preterm labor. Like other prostaglandin synthetase inhibitors, indomethacin acts by inhibiting the activity of the cyclo-oxygenase enzyme necessary for the synthesis of prostaglandins, prostacyclin, and thromboxane. Unlike aspirin, which causes an irreversible inhibition of this enzyme, indomethacin results in a competitive and reversible inhibition.

FIRST-TRIMESTER USE AND TERATOGENICITY

Animal studies of indomethacin use and potential teratogenicity have produced conflicting results. While indomethacin has been found to cross the placenta freely during the second half of human gestation (Traeger et al., '73; Moise et al., '90), animal studies have suggested that early in pregnancy, transplacental passage of indomethacin is minimal (Klein et al., '81). Studies by Klein et al. ('81) reveal that in rats, indomethacin does not cross the placenta in pharmacologically significant quantities until close to parturition.

Most rodent studies have demonstrated no increase in the frequency of malformations in offspring of mice and rats treated during pregnancy with indomethacin in doses ranging up to 100 times those used clinically (Klein et al., '81; Kalter, '73; Randall et al., '87). Kusanag et al. ('77) treated pregnant mice with 7.5 mg/kg of indomethacin orally on days 7-15 and produced an increased incidence of fused ribs and other skeletal defects in the offspring. Gupta and Goldman ('86) reported incomplete virilization of the external genitalia in the male offspring of pregnant mice treated with 1 mg/kg of subcutaneous indomethacin on days 11-14. In rabbit studies, treatment with 8 or 16 mg/kg/day of subcutaneous indomethacin from the day of mating has been shown to cause increased resorptions of developing embryos with no increase in birth defects in the survivors (O'Grady et al., '72).

Data available on first-trimester exposure during human pregnancy suggest that this drug does not

produce malformations. Aselton et al. ('85) reported only one congenital defect in 50 women who had taken indomethacin during pregnancy. Another study reported the outcomes of 8 women treated with 700-1,200 mg of indomethacin over 3-8 days in the first trimester for ovarian hyperstimulation syndrome. Of the nine live babies in that report, one had a mild degree of hypospadias and the remainder had no reported birth defects (Katz et al., '84). In a large surveillance study in Michigan of 229,101 pregnancies from 1985 to 1992, 114 newborns had been exposed to indomethacin during the first trimester. Seven (6.1%) major birth defects were observed (5 expected), 2 of which were cardiovascular (1 expected). No anomalies were observed in 5 other categories reported (oral clefts, spina bifida, polydactyly, limb reduction defects, and hypospadias) (Briggs et al., '94).

COMPLICATIONS OF INDOMETHACIN USE IN THE SECOND AND THIRD TRIMESTERS OF PREGNANCY

Indomethacin has been used in the treatment of preterm labor since 1974 (Zuckerman et al., '74). Prostaglandins promote uterine activity by increasing myometrial gap junctions, and by stimulating an increase in intracellular calcium. In isolated human myometrial strips that contract with the addition of oxytocin or prostaglandin $F_{2\alpha}$, contractions are abolished by the addition of indomethacin (Garrioch, '78).

In the second half of pregnancy, indomethacin crosses the placenta and reaches concentrations in the fetus equal to those in the mother. In one study of human pregnancy, investigators treated 26 women at 23-37 weeks gestation with 50 mg of indomethacin and measured fetal umbilical cord indomethacin levels 6 hr later. Mean maternal and fetal levels were 218 ng/ml and 219 ng/ml, respectively, and did not vary over this gestational age range (Moise et al., '90). Because prostaglandins are important in the regulation of many organ systems and readily reach the fetus, prostaglandin

*Correspondence to: Mary E. Norton, M.D., Antenatal Diagnostic Center, Brigham and Women's Hospital, 75 Francis St., Boston, MA 02115.

Received 15 September 1997; Accepted 9 June 1997

synthetase inhibition with indomethacin has the potential to cause a number of complications in the fetus and newborn.

MATERNAL EFFECTS

In nonpregnant adults, prostaglandin synthetase inhibitors have been reported to cause gastrointestinal ulceration and perforation, as well as acute renal failure; interference with renal excretion of water, sodium, and potassium; interference with antihypertensive and diuretic therapy; acute interstitial nephritis; nephrotic syndrome; and chronic renal injury. These renal complications are generally reversible, and can be attributed to interference with the physiologic actions of prostaglandins on the kidney (Schlondorff '93). There have been several independent reports of transient renal insufficiency in pregnant women treated with indomethacin as well (Steiger et al., '93; Walker and Cantrell, '93).

Indomethacin interferes with platelet function and has been found to prolong bleeding time in preterm infants (Corazza et al., '84) and pregnant women (Lunt et al., '94). While use of aspirin in pregnancy has been associated with increased antepartum and/or postpartum hemorrhage (Briggs et al., '94), indomethacin does not appear to lead to increased bleeding during delivery (Gerson et al., '90; Lunt et al., '94). Antipyretic effects of indomethacin are theoretically possible, and may potentially mask occult maternal chorioamnionitis. While chorioamnionitis is considered a contraindication to use of indomethacin (or any other tocolytic), an increased incidence of intra-amniotic infection has not been reported with the use of this agent.

FETAL EFFECTS OF IN UTERO INDOMETHACIN EXPOSURE

Indomethacin has profound effects on platelet and neutrophil function (Friedman et al., '78), cerebral, mesenteric, and renal hemodynamics (Meyers et al., '91; Gleason, '87; Rudolph et al., '78), gastrointestinal oxygen consumption (Meyers et al., '91), renal tubular function (Rudolph et al., '78), and the functioning of the ductus arteriosus (Moise et al., '88; Clyman et al., '85), all of which have implications for the fetus. A number of fetal and neonatal complications have been reported after prenatal indomethacin exposure, potentially attributable to these effects (Table 1). In the fetus, indomethacin has been reported to cause constriction of the ductus arteriosus (Moise et al., '88) and decreased urine output (Hickok et al., '89), frequently resulting in oligohydramnios (Bivins et al., '93). In the neonate born after prenatal indomethacin exposure, reported complications have included pulmonary hypertension (Manchester et al., '76; Csaba et al., '73), persistent ductus arteriosus (Norton et al., '93), necrotizing enterocolitis (Major et al., '94), ileal perforation (Vanhaesebrouck et al., '88a), intracranial hemorrhage (Norton et al., '93; Iannucci et al., '96), cystic brain lesions (Baerts

et al., '90), and renal dysfunction (Buderus et al., '93). The likelihood of these complications may be influenced, in part, by the timing and duration of indomethacin administration during pregnancy.

A number of studies have focused on the general issue of neonatal outcome after administration of indomethacin as a tocolytic agent. In four randomized trials, the efficacy and safety of indomethacin was compared with that of intravenous β -adrenergic agonists in patients presenting with premature labor (Morales et al., '89; Besinger et al., '91; Eronen et al., '94; Kurki et al., '91). In three studies (Morales et al., '89; Eronen et al., '94; Kurki et al., '91), the use of indomethacin was limited to 48–72 hrs, while in the study by Besinger et al. ('91), mothers received long-term treatment. In two of these studies, the delay in delivery was comparable in the indomethacin and β -adrenergic agonist group (Morales et al., '89; Besinger et al., '91). By contrast, Kurki et al. ('91) reported that delivery was delayed >48 hr in 96% of patients treated with indomethacin, versus 76% of patients treated with ritodrine, a difference that was statistically significant. Likewise Eronen et al. ('94) reported that indomethacin delayed delivery 6.6 weeks versus 4.5 weeks in the β -adrenergic agonist group.

In these four studies, the mean gestational age at the time of delivery was >34 weeks. Three of the studies (Morales et al., '89; Besinger et al., '91; Kurki et al., '91) found no statistical difference in neonatal outcome, although Besinger et al. ('91) reported 3 cases of primary pulmonary hypertension in the infants exposed to indomethacin versus none in the control group. Eronen et al. ('91) reported an increased incidence of respiratory distress syndrome (82% vs 29%), bronchopulmonary dysplasia (73% vs 6%), and necrotizing enterocolitis or focal intestinal perforation (27% vs 0%) in the indomethacin-exposed group.

One other randomized trial compared safety of long-term indomethacin versus oral terbutaline after treatment with intravenous tocolytics for preterm labor (Bivins et al., '93). This study of 71 patients found no difference in neonatal outcome, although these investigators did report a 27% incidence of ductal constriction and 38% incidence of oligohydramnios in the indomethacin group. In the terbutaline group, only one fetus developed oligohydramnios, in conjunction with intrauterine growth restriction. Only fetuses exposed to indomethacin were specifically investigated for evidence of ductal constriction. The timing of complications with regard to duration of indomethacin administration was random and occurred from 1 to 24 days after initiation of indomethacin treatment. Although both the ductal constriction and oligohydramnios resolved with discontinuation of therapy, the study was terminated because of this high incidence of fetal complications.

A number of retrospective reports have also addressed the issue of neonatal complications after antenatal tocolysis with indomethacin. In one report, neo-

nates who had been exposed to indomethacin in utero for 24–48 hr were compared with infants exposed to other or no tocolysis. Infants in this study delivered at a mean gestational age of 35 weeks, and there was no excess of neonatal complications in the indomethacin group (Niebyl and Witter, '86). Another retrospective report of maternal indomethacin administration found no apparent excess of neonatal complications, although this study had no control group, and a mean gestational age at delivery of 35.6 weeks (Dudley and Hardie, '85). Gerson et al. ('90) reported on long-term maternal indomethacin use (mean 43.9 days) and also found no increase in neonatal complications compared with infants exposed to other tocolytics, these infants all delivered at a mean gestational age of 33 weeks.

Two other retrospective studies have focused specifically on patients who delivered very preterm infants (≤ 30 weeks gestation, $< 1,500$ g) after indomethacin tocolysis (Norton et al., '93; Major et al., '94). Norton et al. ('93) studied infants born at ≤ 30 weeks gestation after maternal treatment for preterm labor and compared outcomes in those exposed to indomethacin versus those exposed to other tocolytics. Mothers were treated with 50–6,000 mg of indomethacin (median 425 mg) over 1–79 days (median 3 days). Most mothers received their last dose of indomethacin within 24 hr of delivery. Major et al. ('94) studied infants born at $< 1,500$ g and also compared outcomes in those exposed to indomethacin versus those exposed to other or no tocolytics. In both of these studies, neonates exposed in utero to indomethacin at 26–27 weeks gestation had a higher rate of complications as compared with infants exposed to other tocolytics at the same gestational age.

Norton et al. ('93) found that preterm infants born after in utero exposure to indomethacin experienced more necrotizing enterocolitis (29% vs 8%), intracranial hemorrhage (28% vs 9%), and patent ductus arteriosus (62% vs 44%) than do unexposed controls of the same gestational age. More indomethacin-exposed infants with a patent ductus arteriosus required surgical ligation because of either a lack of initial response or a reopening of the ductus after postnatal indomethacin therapy (50% vs 20%). Infants exposed to prenatal indomethacin also had a lower urine output and higher serum creatinine concentration during the first three days of life. Major et al. ('94) focused specifically on the risk of necrotizing enterocolitis after prenatal indomethacin exposure and found the risk to be 20% in indomethacin-exposed infants versus 7% in controls. The increased risk of necrotizing enterocolitis was not present in infants delivering > 24 hr after prenatal indomethacin exposure.

In the study by Norton et al. ('93), indomethacin was administered within the week prior to delivery in 88% of cases, while Major et al. ('94) reported that the final dose of indomethacin was given within the 4 days prior to delivery in 67% of cases. The adverse outcomes reported in these very preterm infants may be due to both their increased vulnerability and the timing of

indomethacin with regard to labor, delivery and perinatal adaptation.

Tocolytic agents, including indomethacin, are generally given for just 48 hours to allow administration of betamethasone to aid in fetal lung maturation. These medications are rarely used after 34 weeks gestation, when the risk of complications of prematurity becomes very low and the benefit of betamethasone administration is no longer apparent. This is important to consider when evaluating the safety of indomethacin and other tocolytic agents and in comparing data from various studies of these drugs. In those studies in which the mean gestational age at delivery is > 34 weeks, one would expect that indomethacin administration was discontinued, in most cases, several days to weeks prior to delivery. In those studies that focused on very preterm infants, most patients were delivered within several hours or days of indomethacin administration. It appears from the available data that when indomethacin is administered early in pregnancy (< 32 weeks) and delivery occurs near term, the neonate is unlikely to demonstrate any adverse effects. However, in those infants who fail tocolysis and deliver despite indomethacin administration, the risk of serious sequelae is significant.

Effects of indomethacin on the fetal ductus arteriosus

Animal studies have indicated that both prostacycline and prostaglandin E_2 are important in maintaining the patency of the fetal ductus arteriosus (Sideris et al., '83). Studies in both animals and humans have demonstrated constriction of the fetal ductus arteriosus after administration of prostaglandin synthetase inhibitors. In utero constriction of the ductus arteriosus can lead to tricuspid regurgitation in utero, and has been reported to result in hydrops and fetal death (Hallack et al., '91). In the neonate, antenatal indomethacin has been associated with primary pulmonary hypertension (Manchester et al., '76; Goudie and Dosselot, '79; Csaba et al., '78) and patent ductus arteriosus (Norton et al., '93), both attributed to in utero constriction of the ductus. In addition, ductal constriction in utero can lead to cardiac decompensation in the presence of ductus-dependent congenital heart disease (Menahem, '91).

Sharpe et al. ('75) found that administration of 15 mg/kg of indomethacin orally to pregnant rats and rabbits was followed by in utero constriction of the fetal ductus arteriosus. This response also occurred at lower doses (2.5 mg/kg), and the effect increased as gestation advanced. Arishima et al. ('91) confirmed these findings with doses as low as 1 mg/kg orally, and Momma and Takao ('89a) found the ductal constriction to be increased in rats when indomethacin was combined with betamethasone (1 mg/kg subcutaneously), which is often administered during tocolysis for preterm labor to aid in fetal lung maturation (Momma and Takao '89a).

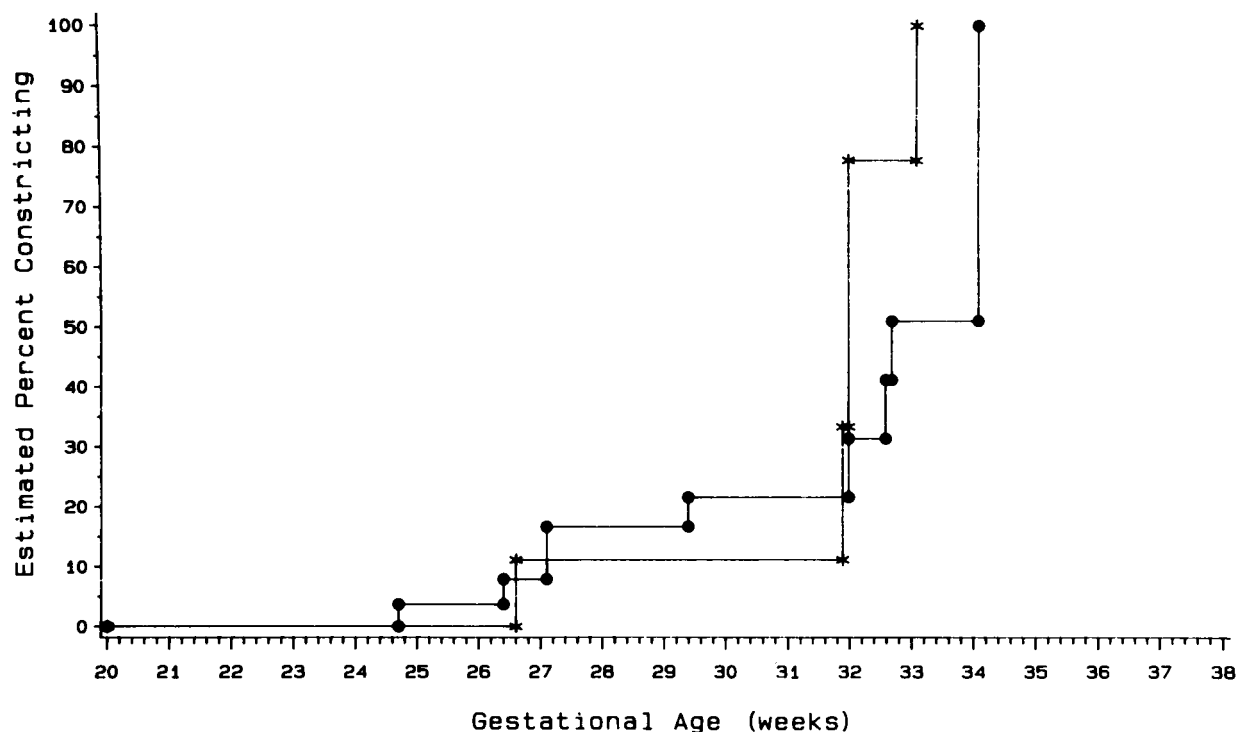


Fig. 1. Incidence of fetal ductal constriction after maternal indomethacin exposure with advancing gestational age. From Moise ('93).

It has been demonstrated in rats and sheep that chronic fetal ductal constriction and occlusion can affect the right ventricle and lead to morphologic changes in the pulmonary vasculature and can result in persistent pulmonary hypertension in the newborn (Momma and Takao, '89b; Wild et al., '89; Morin, '89). Subendocardial ischemia and papillary muscle dysfunction have been observed in fetal sheep within 48 hr of indomethacin-induced ductal constriction (Levin et al., '79).

In humans, postnatal indomethacin can cause closure of the ductus arteriosus, and is used therapeutically when this structure remains patent in preterm neonates (Heymann et al., '76). Ductal constriction can also occur in utero after maternal indomethacin administration (Moise et al., '88). Using fetal echocardiography, Moise et al. ('90) described this effect in a study of women between the gestational ages of 20 and 34 weeks. The ductus became more responsive to indomethacin later in pregnancy, with 5–10% of fetuses displaying ductal constriction at <27 weeks, 15–20% at 27–31 weeks, 50% at 32 weeks, and 100% at >34 weeks gestation (Moise, '93) (Fig. 1).

Constriction of the ductus in utero can lead to a diversion of right ventricular output either in a retrograde fashion through the tricuspid valve (tricuspid regurgitation) or into the pulmonary arteries. Eronen et al. ('91) studied 14 women at 24–34 weeks gestation treated with 50 mg of indomethacin every 6–8 hr for 72 hr. Nine of the 14 fetuses developed ductal constriction, and 3 of 14 developed tricuspid regurgitation sugges-

tive of congestive heart failure. Increased pulmonary blood flow due to in utero ductal constriction can result in pulmonary arterial hypertrophy and pulmonary hypertension (Moise et al., '88). After birth, this resultant pulmonary hypertension causes shunting of blood through the foramen ovale, bypassing the lungs, with resultant difficulty in adequate oxygenation of the neonate. Primary pulmonary hypertension has been reported in neonates after maternal indomethacin therapy for premature labor (Manchester et al., '76; Goudie and Dossetor, '79; Csaba et al., '78; Besinger et al., '91). Csaba et al. ('78) reported primary pulmonary hypertension in 5 of 10 neonates exposed to indomethacin in utero. Besinger et al. ('91) reported primary pulmonary hypertension in 3 of 25 neonates born after prolonged in utero indomethacin exposure. This complication has been reported primarily in infants delivering when indomethacin exposure occurred after 32 weeks gestation.

Norton et al. ('93) studied infants born at 24–30 weeks gestation after prenatal exposure to a broad range of doses of indomethacin (50–6,000 mg). Those infants exposed to prenatal indomethacin had an increase in patent ductus arteriosus (PDA) (66% vs 44% in infants exposed to other tocolytics). In addition, infants exposed to prenatal indomethacin were more likely to require surgical ligation of their PDA due to either a lack of response to postnatal indomethacin or a reopening of the duct after initial closure. The increase in PDA in the indomethacin-exposed infants was associ-

ated with advancing gestational age, consistent with the gestational age-dependent increase in ductal constriction which has been described. Eronen et al. ('94) also found more failure of postnatal indomethacin to close the ductus in infants who had been exposed to prenatal indomethacin, although this difference did not reach statistical significance ($P = 0.07$), and in another study found that ductal reopening occurred more often after in utero indomethacin exposure (17% vs 0%) (Eronen, '93). Studies in sheep have found that after initial constriction in vivo, the ability of the ductus to actively constrict in response to indomethacin or oxygen is limited, possibly reflecting early intimal layer ischemic damage (Clyman et al., '85). Likewise in humans, prenatal indomethacin exposure may cause in utero constriction with resultant damage to the ductus arteriosus, resulting in an increased incidence of PDA, as well as in the need for surgical ligation. Again, this increase in PDA occurs most frequently in infants exposed to indomethacin after 27 weeks gestation, consistent with the increased incidence of in utero ductal constriction that occurs with increasing gestational age (Norton et al., '93).

The effects of indomethacin on the fetal ductus occur at typical clinical doses, and the lower limit of indomethacin exposure at which this phenomenon occurs is unknown (Moise et al., '88; van den Veyver et al., '93b). Constriction of the ductus is gestational age dependent and is seldom seen at <27 weeks, with a dramatic increase in the response to 50% at 32 weeks and 100% at 34 weeks gestation (Eronen et al., '91; Moise, '93).

Effects of indomethacin on fetal gastrointestinal tract

Indomethacin has significant effects on the mesenteric circulation. Gastrointestinal complications, including intestinal perforation, are known side effects of indomethacin therapy in adults and newborn infants (Alpan et al., '85; Cassady et al., '89). Both prenatal and postnatal exposure to indomethacin have been implicated in an increased risk of necrotizing enterocolitis and isolated intestinal perforation in preterm infants (Norton et al., '93; Major et al., '94; Nagaraj et al., '81).

In animals and preterm infants, indomethacin has been shown to decrease mesenteric blood flow (Cronen et al., '82; Feigen et al., '81), block autoregulation of terminal ileum oxygen consumption (Meyers et al., '91) and increase the risk of bowel necrosis after temporary ischemia (Krasna et al., '92). Cronen et al. ('82) treated dogs with 0.25–1.25 mg/kg of indomethacin per rectum, and found a significant decrease in blood flow to the stomach as well as the mid- and terminal ileum. Feigen et al. ('81) also found that in dogs, intravenous indomethacin (2.5 mg/kg) produced severe, acute vasoconstriction in the mesenteric vascular bed. This indomethacin-induced vasoconstriction occurred at doses as low as 0.25 mg/kg IV. Krasna et al. ('92) studied the effect of indomethacin on rates of bowel necrosis in mice

TABLE 1. Reported fetal and neonatal complications after maternal indomethacin therapy for preterm labor

Fetal
Constriction of ductus arteriosus
Tricuspid regurgitation
Decreased urine output
Oligohydramnios
Hydrops
Fetal death
Neonatal
Pulmonary hypertension
Patent ductus arteriosus
Failed response of patent ductus arteriosus to medical therapy
Necrotizing enterocolitis
Ileal perforation
Intraventricular hemorrhage
Cystic brain lesions
Renal dysfunction

after temporary ischemia. These investigators occluded the superior mesenteric vessels for 15 min, and compared rates of intestinal necrosis on three groups of mice: those treated with indomethacin (0.4 µg/kg IV daily for 3 days after intestinal occlusion or sham surgery), those treated with 15 min of intestinal occlusion only, and those treated with both indomethacin and intestinal occlusion. Sixty-one percent of those treated with both developed bowel necrosis, versus 8% in the intestinal occlusion-only group and 0% in the indomethacin-only group. They concluded that in the shocked preterm infant who may have suffered temporary intestinal ischemia, exposure to indomethacin may significantly increase the risk of developing necrotizing enterocolitis.

Some studies in preterm infants have suggested that postnatal indomethacin given for treatment of PDA increases the risk of necrotizing enterocolitis and isolated ileal perforations (Nagaraj et al., '81; Alpan et al., '85; Cassady et al., '89). There are case reports of similar complications after in utero indomethacin exposure (Vanhaesebrouck et al., '88a), and recent evidence indicates that prenatal indomethacin may in fact increase the rate of necrotizing enterocolitis as well as isolated intestinal perforations in preterm infants (Norton et al., '93; Major et al., '94; Eronen et al., '94). Three controlled studies have found the incidence of necrotizing enterocolitis to be 20–29% in preterm infants exposed in utero to indomethacin, versus 8–9% in unexposed controls (Norton et al., '93; Eronen et al., '94; Major et al., '94). Most infants in these three studies were exposed to 450 mg of indomethacin over a 48-hr period, although the range included 50–6,000 mg over several weeks. Neither total dose nor duration of exposure was associated with an increased risk of necrotizing enterocolitis. However, those infants delivered within 48 hr of maternal indomethacin administration had an increased incidence of necrotizing enterocolitis, while those born >48 hr after maternal indomethacin did not. As suggested by animal studies, it appears that

preterm infants, who may suffer temporary hypoxic insults during labor, delivery, and the early perinatal period, have a great increase in the risk of significant sequelae of those hypoxic insults (i.e., necrotizing enterocolitis) when they have been exposed to indomethacin just prior to delivery. The stresses of preterm labor and delivery may be less well-tolerated without the benefit of regulatory prostaglandins.

Renal effects of indomethacin

The kidney synthesizes several prostaglandins important in the regulation of renal function. These prostaglandins (primarily PGI₂ and PGE₂) affect modulation of renal blood flow, glomerular filtration rate, renin release, the concentration mechanism and excretion of sodium and potassium. In adults, these prostaglandin-mediated effects are primarily important only during activation of vasoconstrictor systems. Nephrogenesis in the premature infant is not complete until 36 weeks gestation, however, and studies in rats have suggested that prostaglandins may also play a role in renal development (Pace-Asciak, '75).

In animals, long term administration of indomethacin has resulted in structural as well as functional abnormalities. Structural renal changes, including enlargement of the Golgi bodies and an increase in inclusion bodies in the cytoplasm and rough endoplasmic reticulum of the podocytes, have been observed in the rat after administration of 4 mg/kg of intraperitoneal indomethacin for ≥ 8 days (Sessa et al., '73). In another study, eight pregnant rhesus monkeys were treated with indomethacin according to the following schedule: days 150–165, the dose was 10–15 mg/kg/day; thereafter, the dose was increased to 21–28 mg/kg/day until delivery (days 171–187). Treatment with indomethacin was associated with oligohydramnios in 7 of 8 monkeys, with a 50% fetal mortality rate. In the fetuses who died, the mean weight of the kidneys was 38% less than average (Novy, '78).

Transient renal dysfunction has been reported as a complication of indomethacin in adults, newborns, preterm infants, and fetuses (Seyberth et al., '83; Gersony et al., '83; Goldenberg et al., '89; Gleason, '87). A dramatic decline in hourly fetal urine output was demonstrated by Kirshon et al. ('88) as soon as 5 hr after the beginning of maternal indomethacin treatment (25 mg orally every 4 hr) (Fig. 2). This response was not correlated with maternal serum indomethacin levels, and completely resolved 24 hr after indomethacin was discontinued. Decreases in fetal urine output have been reported with the long-term and short-term use, defined as greater than or less than 48 hrs, (Kirshon et al., '88, '91), and occur in up to 82% of cases (Hickok et al., '89). The mechanism may be an alteration in prostaglandin-mediated tubular function, as renal blood flow does not appear to be changed (Mari et al., '90). Although Goldenberg et al. ('89) reported a single case suggesting that this response is dose dependent, the rapid reversibility of the phenomenon, irre-

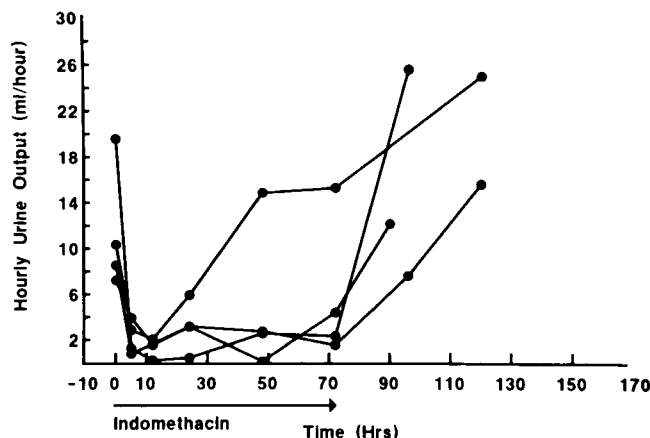


Fig. 2. Fetal urine output in four patients before, during and after indomethacin therapy (25 mg orally q6h). From Kirshon et al. ('88).

spective of the total maternal dose, is consistent with the pharmacokinetic action of indomethacin: an enzyme inhibition process without a dose-response association (Brash et al., '81).

When indomethacin is administered shortly before delivery, the renal effects can persist into the newborn period. A number of studies have documented an increased serum creatinine and decreased urine output during the first 3 days of life in preterm infants born after maternal treatment with indomethacin in the 24 hr preceding delivery (Norton et al., '93; Vanhaesebrouck et al., '88b).

The decrease in fetal urine output seen following maternal indomethacin administration can result in oligohydramnios (Besinger et al., '91; Goldenberg et al., '89; Uslu et al., '92; Itskovitz et al., '80; Vanhaesebrouck et al., '88a; Novy, '78; Gleason, '87; Kirshon et al., '91), with an incidence in reported series of 10–38% (Morales et al., '89, Bivins et al., '93). Although both the decreased urine output and oligohydramnios are usually reversible (Goldenberg et al., '89), several cases of severe and sometimes irreversible renal insufficiency have been described in human neonates exposed to indomethacin during fetal life (Cantor et al., '80; Itskovitz et al., '80; Veersema et al., '83; Vanhaesebrouck et al., '88a; Simeoni et al., '89; Gubler et al., '91; Restaino et al., '91; Jacqz-Aigrin et al., '93; Buderus et al., '93). In one case series, van der Heijden et al. ('94) described six infants exposed in utero to 150–400 mg of indomethacin daily for 2–11 weeks prior to delivery who were born with persistent anuria and unusual renal cystic lesions. These fetuses were exposed at 23–32 weeks gestation and were born at 29–37 weeks gestation. All six infants died of renal failure.

Cerebrovascular effects of indomethacin

Indomethacin has been shown to have a significant effect on cerebral hemodynamics in the fetus and neonate, as well as in adults. Altshuler et al. ('79) demonstrated that in rats and mice, maternal treat-

ment with 4 mg/kg of indomethacin during the last 3 days of gestation caused an increased incidence of neuronal necrosis in the diencephalon of live born fetuses. At 2 mg/kg, this neuronal necrosis was not observed.

In humans, Baerts et al. ('90) reported an increase in cystic brain lesions in infants born before 30 weeks gestation after prenatal indomethacin treatment when compared with infants treated with other or no tocolytics. At least two studies in preterm infants have linked maternal indomethacin treatment with an increased risk of intracranial hemorrhage in the neonate. Norton et al. ('93) found a 28% incidence of intracranial hemorrhage in preterm infants born after in utero indomethacin exposure versus 9% in gestational age-matched controls. Iannucci et al. ('96) also found the incidence of significant intracranial hemorrhage to be increased in very preterm infants whose mothers had received tocolysis with indomethacin. This finding contrasts with data that indomethacin may protect against neonatal intraventricular hemorrhage when given postnatally (Ment et al., '88).

Local cerebral blood flow is believed to be controlled in part by prostaglandins synthesized by the cerebral microvasculature (Moncada et al., '79; Wolfe, '79). In adults, indomethacin has been shown to cause a reduction in cerebral blood flow of 40–50% (Wennmalm et al., '81). Preterm infants treated for PDA with 0.1–0.2 mg/kg of IV indomethacin after delivery have also been demonstrated to have a fall in cerebral blood flow (Cowan, '86), as well as decreases in oxygen delivery, blood volume, and the reactivity of blood volume to changes in arterial CO₂ tension (Edwards et al., '90). These effects seem to be greater in the presence of increased arterial PCO₂ (Wennmalm et al., '81; Cowan, '86), and studies have suggested that they are due to a drug-induced cerebral vasoconstriction.

Following maternal indomethacin use, the fetal middle cerebral artery pulsatility index can be increased in association with ductal constriction and tricuspid regurgitation (van den Veyver et al., '93b). The described changes in cerebral oxygen delivery as well as the disruption of cerebrovascular control might compromise cellular oxygen availability, particularly in regions of the brain where the arterial supply is precarious (Edwards et al., '90). In addition, indomethacin inhibits platelet aggregation, and studies have indicated an association between intracranial hemorrhage and hemostatic disorders (Friedman et al., '78; McDonald et al., '84). Maternal ingestion of other nonsteroidal anti-inflammatory drugs (NSAIDs) has been associated with an increased incidence of intracranial hemorrhage in preterm infants (Rumack et al., '81). In the fetus exposed to indomethacin during the 24 hr prior to delivery, disruption of cerebrovascular control, and the fluctuation in intracranial pressure during active labor combined with platelet dysfunction may contribute to an increased risk of intracranial hemorrhage.

Respiratory effects of indomethacin

A recent randomized trial has linked antenatal indomethacin with an increased risk of bronchopulmonary dysplasia and respiratory distress syndrome (Eronen et al., '94). Two other retrospective trials did not find an increase in respiratory complications in preterm infants after antenatal indomethacin (Norton et al., '93; Major et al., '94). Eronen et al. ('94) theorized that the inhibition of cyclooxygenase by indomethacin leads to an increased availability of leukotrienes with vasoconstrictor and proinflammatory properties (Shore et al., '89). In addition, laboratory and animal data indicate a significant decrease in alveolar luminal volume and a delay in the development of lamellar bodies and surfactant components after exposure to indomethacin, which may contribute to an increased risk of respiratory complications (Acarregui et al., '90; Bustos et al., '78). In the two studies in which respiratory distress syndrome was not increased (Norton et al., '93; Major et al., '94), the majority of indomethacin-exposed infants had also received antenatal corticosteroids, while most infants in the study by Eronen et al. ('94) had not. Possibly this treatment was sufficient to overcome any adverse effect of indomethacin on surfactant production.

Clinical efficacy of indomethacin for preterm labor

A number of retrospective and/or uncontrolled series have been reported on use of indomethacin as a tocolytic agent, in which the authors have concluded that this drug is safe and effective (Zuckerman et al., '74, '84; Dudley and Hardie, '85; Niebyl and Witter, '86; Gamisans et al., '78; Katz, '83; Gerson et al., '90). Fewer prospective, randomized, controlled trials have been reported (Niebyl et al., '80; Morales et al., '89; Kurki et al., '91; Besinger et al., '91; Bivins et al., '93; Eronen et al., '94), and results of these trials have been conflicting. Kurki et al. ('91) and Eronen et al. ('94) both randomized women in preterm labor to indomethacin versus nylidrin, a β -adrenergic agonist. Delivery was delayed longer in the indomethacin-treated women than in those treated with nylidrin.

Other randomized trials have not found indomethacin to have greater efficacy than β -adrenergic agents. One small prospective, randomized, placebo-controlled trial found that while contractions were arrested more quickly in patients treated with indomethacin, delivery occurred at the same gestational age in the indomethacin- and placebo-treated groups (Niebyl et al., '80). Morales et al. ('89) randomized 106 women in preterm labor to indomethacin versus ritodrine and found no difference in the number of women who had delivery delayed for >48 hr or for >1 week. These investigators did report significantly fewer maternal side effects and lower costs with indomethacin than with ritodrine. Besinger et al. ('91) randomized patients to indomethacin versus ritodrine for long term treatment of preterm labor, and found an equivalent delay in delivery of

greater than one week and an equivalent gestational age at delivery. Bivins et al. ('93) randomized women to long-term tocolysis with indomethacin or terbutaline after successful intravenous tocolysis and found an equal number of women delivered at >34 weeks in both groups.

In conclusion, while some investigators have concluded that indomethacin may be superior to β -adrenergic agonists in the treatment of preterm labor, most of the available data do not demonstrate improved efficacy of this agent. The most obvious benefits are the decreased maternal side effects and maternal costs of administration, as indomethacin can be given orally and does not require monitoring necessary with β -adrenergic agonists.

SUMMARY

Indomethacin freely crosses the placenta and can interfere with fetal prostaglandin production and alter the normal physiology of the fetal cardiovascular system (Moise et al., '90). It has long been recognized that indomethacin should be avoided in pregnant women at >32 weeks gestation, as the risk of pulmonary hypertension in the neonate is significant. More recent data have demonstrated that pulmonary hypertension results from in utero ductal constriction, which occurs in close to 100% of fetuses exposed to indomethacin at >32 weeks gestation. Neonatal complications due to in utero indomethacin exposure are uncommon—provided that delivery is successfully delayed—and occurs well after indomethacin treatment has been discontinued. When discontinued at ≥ 1 week or more prior to delivery, neonatal complications from indomethacin are not expected, as it causes a reversible enzyme inhibition. However, when treatment for preterm labor fails and delivery occurs within 48 hr of maternal indomethacin administration, the risks to the fetus of numerous complications of prematurity appear to be increased.

Although the statement is frequently made that a short course of indomethacin is safe, there are no data demonstrating a difference in outcome between short- and long-term treatment. Complications of indomethacin use appear to be idiosyncratic and have been reported in patients receiving a single dose, while series of patients on long-term indomethacin have demonstrated no increase in neonatal complications when indomethacin is discontinued several weeks prior to delivery, and delivery occurs near term. Most neonatal complications appear to be due to effects of prostaglandin synthetase inhibition that occur proximate to preterm delivery, robbing the immature fetus of these protective mechanisms during the many cardiovascular changes and stresses of labor and delivery. Especially under pathophysiologic conditions, the function and integrity of various organs may become dependent on vasodilatory prostaglandins. When given immediately prior to delivery, antenatal indomethacin appears to have profound effects during perinatal transition which may increase the risk of neonatal complications.

The major justification for tocolysis is to decrease the risk of neonatal complications associated with prematurity. However, infants exposed to indomethacin have a higher risk of complications than their unexposed controls when tocolysis fails (Norton et al., '93; Eronen et al., '94). Eronen et al. ('94) found that preterm infants exposed to antenatal indomethacin required more intensive care and had more serious morbidity despite increased gestational ages. It does not appear that the efficacy indomethacin as a tocolytic is sufficient to outweigh the risk of complications when treatment fails.

The use of indomethacin may be appropriate in situations in which preterm delivery is unlikely, such as prophylactic use prior to cerclage placement or intraabdominal surgery performed during pregnancy. Pregnant patients receiving indomethacin should be monitored for the development of fetal ductal constriction or oligohydramnios. Antenatal indomethacin should be avoided when delivery seems imminent, after 32 weeks gestation, or when ductus dependent congenital heart disease is present.

GENETIC COUNSELING

Indomethacin, when taken in the first trimester of pregnancy, does not seem to increase the risk of fetal malformations. However, use of indomethacin later in pregnancy may increase the risk of fetal or neonatal complications, or both. Risks to the fetus include constriction of the ductus arteriosus and tricuspid regurgitation, potentially leading to heart failure, hydrops, and fetal demise. Complications that may be increased in the infant exposed to indomethacin in utero include pulmonary hypertension, patent ductus arteriosus, renal dysfunction, necrotizing enterocolitis, intestinal perforation, intracranial hemorrhage, and cystic brain lesions. The chance of developing any of these complications is influenced in part by the gestational age at administration of indomethacin and timing of indomethacin in relationship to timing of delivery. Maternal ingestion of indomethacin increases the risks to the fetus and neonate when taken after 32 weeks pregnancy, or within several days of preterm delivery.

LITERATURE CITED

- Acarregui, M.J., J.M. Snyder, M.D. Mitchell, and C.R. Mendelson (1990) Prostaglandins regulate surfactant protein A (SP-A) gene expression in human fetal lung in vitro. *Endocrinology* 127:1105-1013.
- Alpan, G., F. Eyal, I. Vinograd, R. Udassin, G. Amir, P. Mogel, and B. Glick (1985) Localized intestinal perforations after enteral administration of indomethacin in premature infants. *J Pediatr.* 106:277-281.
- Altshuler, G., H.F. Krous, D.H. Altmiller, and G.L. Sharpe (1979) Premature onset of labor, neonatal patent ductus arteriosus, and prostaglandin synthetase antagonists—A rat model of a human problem. *Am J Obstet Gynecol.* 135:261-265.
- Aselton, P.A., H. Jick, A. Milunsky, J.R. Hunter, and A. Stergachis (1985) First-trimester drug use and congenital disorders. *Obstet Gynecol.* 65:451-455.

- Baerts, W., W.P. Fretter, W.C. Hop, H.C. Wallenburg, R. Spritzer, and P.J. Sauer (1990) Cerebral lesions in preterm infants after tocolytic indomethacin. *Dev. Med. Child. Neurol.* 32:910-918.
- Besinger, R.E., J.R. Niebyl, W.G. Keyes, and T.R.B. Johnson (1991) Randomized comparative trial of indomethacin and ritodrine for the long-term treatment of preterm labor. *Am J Obstet Gynecol.* 164:981-988.
- Bivins, H.A., R.B. Newman, D.A. Fyfe, B.A. Campbell, and S.L. Stramm (1993) Randomized trial of oral indomethacin and terbutaline sulfate for the long-term suppression of preterm labor. *Am. J. Obstet. Gynecol.*, 169:1065-1070.
- Brash, A.R., D.E. Hickey, T.P. Graham, M.T. Stahlman, J.A. Oates, and R.B. Cotton (1981) Pharmacokinetics of indomethacin in the neonate. *N. Engl. J. Med.*, 305:67-72.
- Briggs, G.G., R.K. Freeman, and S.J. Yaffe (eds) (1994) *Drugs in pregnancy and lactation*, Williams & Wilkins, Baltimore, pp 443-452.
- Buderus, S., B. Thomas, H. Fahnenstich, and S. Kowalewski (1993) Renal failure in two preterm infants: Toxic effect of prenatal maternal indomethacin treatment? *Br. J. Obstet. Gynaecol.*, 100: 97-98.
- Bustos, R., G. Ballejo, G. Guissi, R. Rosas, and J.C. Isa (1978) Inhibition of fetal lung maturation by indomethacin in pregnant rabbits. *J. Perinat. Med.*, 6:240-245.
- Cantor, B., T. Tyler, R.M. Nelson, and G.H. Stein (1980) Oligohydramnios and transient neonatal anuria. A possible association with the maternal use of prostaglandin synthetase inhibitors. *J. Reprod. Med.*, 24:220-223.
- Cassady, G., D.T. Crouse, J.W. Kirklín, M.J. Strange, C.H. Joiner, G. Godoy, G.T. Odrezin, G.R. Cutter, J.K. Kirklín, and A.D. Pacifico (1989) A randomized controlled trial of very early prophylactic ligation of the ductus arteriosus in babies who weighed 1000 g or less at birth. *N. Engl. J. Med.*, 320:1511-1516.
- Clyman, R.L., D. Campbell, M.A. Heymann, and F. Mauray (1985) Persistent responsiveness of the neonatal ductus arteriosus in immature lambs: A possible cause for reopening of patent ductus arteriosus after indomethacin-induced closure. *Circulation*, 71:141-145.
- Corazza, M.S., R.F. Davis, A. Merritt, R. Bejar, and W. Cvetnic (1984) Prolonged bleeding time in preterm infants receiving indomethacin for patent ductus arteriosus. *J. Pediatr.*, 105:292-296.
- Cowan, F. (1986) Clinical and laboratory observations: Indomethacin, patent ductus arteriosus, and cerebral blood flow. *J. Pediatr.*, 109:341-342.
- Cronen, P.W., H.S. Nagaraj, J.S. Janik, D.B. Groff, J.C. Passmore, and C.E. Hock (1982) Effect of indomethacin on mesenteric circulation in mongrel dogs. *J. Pediatr. Surg.*, 17:474-478.
- Csaba, I.F., Sulyok, E., and T. Ertl (1978) Clinical note: Relationship of maternal treatment with indomethacin to persistence of fetal circulation syndrome. *J. Pediatr.*, 92:484.
- Dudley, D.K.L., and M.B. Hardie (1985) Fetal and neonatal effects of indomethacin used as a tocolytic agent. *Am. J. Obstet. Gynecol.*, 151:181-184.
- Edwards, A.D., J.S. Wyatt, C. Richardson, A. Potter, M. Cope, D.T. Delpy, and E.D.R. Reynolds (1990) Effects of indomethacin on cerebral haemodynamics in very preterm infants. *Lancet*, 335:1491-1495.
- Eronen, M. (1993) The hemodynamic effects of antenatal indomethacin and a beta-sympathomimetic agent on the fetus and the newborn: A randomized study. *Pediatr. Res.*, 33:615-619.
- Eronen, M., E. Pesonen, T. Kurki, O. Ylikorkala, and M. Hallman (1991) The effects of indomethacin and a β -sympathomimetic agent on the fetal ductus arteriosus during treatment of premature labor: A randomized controlled trial. *Am. J. Obstet. Gynecol.*, 164:1441-1446.
- Eronen, M., E. Pesonen, T. Kurki, K. Teramo, O. Ylikorkala, and M. Hallman (1994) Increased incidence of bronchopulmonary dysplasia after antenatal administration of indomethacin to prevent preterm labor. *J. Pediatr.*, 124:782-788.
- Feigen, L.P., L.W. King, J. Ray, W. Beckett, and P.J. Kadowitz (1981) Differential effects of ibuprofen and indomethacin in the regional circulation of the dog. *J. Pharmacol. Exp. Ther.*, 219:679-684.
- Friedman, Z., V. Whitman, M.J. Maisels, W., Jr. Berman, K.H. Marks, and E.S. Vessell (1978) Indomethacin disposition and indomethacin-induced platelet dysfunction in premature infants. *J. Clin. Pharmacol.*, 18:272-279.
- Gamissans, O., E. Canas, V. Cararach, J. Ribas, B. Puerto, and A. Edo (1978) A study of indomethacin combined with ritodrine in threatened preterm labor. *Eur. J. Obstet. Gynecol. Reprod. Biol.* 8:123-128.
- Garrioch, D.B. (1978) The effect of indomethacin on spontaneous activity in the isolated human myometrium and on the response to oxytocin and prostaglandin. *Br. J. Obstet. Gynaecol.*, 85:47-52.
- Gerson, A., S. Abbasi, A. Johnson, M. Kalchbrenner, G. Ashmead, and R. Bolognese (1990) Safety and efficacy of long term tocolysis with indomethacin. *Am. J. Perinatol.*, 7:71-74.
- Gersony, W.M., G.J. Peckham, R.C. Ellison, O.S. Miettinen, and A.S. Nadas (1983) Effects of indomethacin in premature infants with patent ductus arteriosus: Results of a national collaborative study. *J. Pediatr.*, 102:895-906.
- Gleason CA (1987) Prostaglandins and the developing kidney. *Semin. Perinatol.*, 11:12-21.
- Goldberg, R.N., D. Chung, S.L. Goldman, and E. Bancalari (1980) Brief clinical and laboratory observations: The association of rapid volume expansion and intraventricular hemorrhage in the preterm infant. *J. Pediatr.*, 96:1060-1063.
- Goldenberg, R.L., R.O. Davis, and R.C. Baker (1989) Indomethacin-induced oligohydramnios. *Am. J. Obstet. Gynecol.*, 160:1196-1197.
- Goudie, B.M., and J.F.B. Dossetor (1979) Effect on the fetus of indomethacin given to suppress labor. *Lancet*, 2:1187-1188.
- Gubler, M.C., A.J. van der Heijden, C. Carlus, and M. Lacoste (1991) Persistent anuria in 6 neonates exposed to indomethacin during pregnancy. *J. Am. Soc. Nephrol.*, 2:307.
- Gupta, C. and A. Goldman (1986) The arachidonic acid cascade is involved in the masculinizing action of testosterone on embryonic external genitalia in mice. *Proc. Natl. Acad. Sci. USA*, 83:4346-4349.
- Hallak, M., A.A. Reiter, N.A. Ayres, and K.J. Moise (1991) Indomethacin for preterm labor: Fetal toxicity in a dizygotic twin gestation. *Obstet. Gynecol.*, 78:911-913.
- Heymann, M.A., A.M. Rudolph, and N.H. Silverman (1976) Closure of the ductus arteriosus in premature infants by inhibition of prostaglandin synthesis. *N. Engl. J. Med.*, 295:530-533.
- Hickok, D.E., K.A. Hollenbach, S.F. Reilley, and D.A. Nyberg (1989) The association between decreased amniotic fluid volume and treatment with nonsteroidal anti-inflammatory agents for preterm labor. *Am. J. Obstet. Gynecol.*, 160:1525-1531.
- Iannucci, T.A., R.E. Besinger, S.G. Fisher, J.G. Gianopoulos, and P.G. Tomich (1996) Effect of dual tocolysis on the incidence of severe intraventricular hemorrhage among extremely low-birth-weight infants. *Am. J. Obstet. Gynecol.*, 175:1043-1046.
- Itskovitz, J., H. Abramovich, and J.M. Brandes (1980) Oligohydramnios, meconium and perinatal death concurrent with indomethacin treatment in human pregnancy. *J. Reprod. Med.*, 24:137-140.
- Jacqz-Aigrin, E., M. Guillonnet, C. Boissinot, F. Bavoux, J.F. Hartmann, and P. Blot (1993) Effets maternels et neonatals de l'indomethacine administree pendant la grossesse. *Arch. Fr. Pediatr.*, 50:307-312.
- Kalter, H. (1973) Nonteratology of indomethacin in mice. *Teratology*, 7:19.
- Katz, Z., M. Lancet, R. Borenstein, and J. Chemke (1984) Absence of teratogenicity of indomethacin in ovarian hyperstimulation syndrome. *Int. J. Fertil.*, 29:186-188.
- Kirshon, B., K.J. Moise, N. Wasserstrum, C.-N. Ou, and J.C. Huhta (1988) Influence of short term indomethacin therapy on fetal urine output. *Obstet. Gynecol.*, 72:51-53.
- Kirshon, B., K.L. Moise, G. Mari, and R. Willis (1991) Long-term indomethacin therapy decreases fetal urine output and results in oligohydramnios. *Am. J. Obstet. Gynecol.* 8:86.
- Klein, K.L., W.J. Scott, K.E. Clark, and J.G. Wilson (1981) Indomethacin-placental transfer, cytotoxicity, and teratology in the rat. *Am. J. Obstet. Gynecol.*, 141:448-452.

- Krasna, I.H., and H. Kim (1992) Indomethacin administration after temporary ischemia causes bowel necrosis in mice. *J. Pediatr. Surg.*, 27:805-807.
- Kurki, T., M. Eronen, R. Lumme, and O. Yikorkala (1991) A randomized double-dummy comparison between indomethacin and nylidrin in threatened preterm labor. *Obstet. Gynecol.*, 78:1093-1097.
- Kusanag, T., T. Ihara, and M. Mizutani (1977) Teratogenic effects of non-steroidal anti-inflammatory agents in mice. *Congen. Anom.*, 17:177-185.
- Levin, D.L., D.E. Fixler, F.C. Morriss, and J. Tyson (1978) Morphologic analysis of pulmonary vascular bed in infants exposed in utero to prostaglandin synthetase inhibitors. *J. Pediatr.*, 92:478-483.
- Levin, D.L., L.J. Mills, and A.G. Weinberg (1979) Hemodynamic, pulmonary vascular and myocardial abnormalities secondary to pharmacologic constriction of the fetal ductus arteriosus: A possible mechanism for persistent fetal circulation and transient tricuspid insufficiency in the newborn infant. *Circulation* 60:360-364.
- Lione, A., and A.R. Scialli (1995) The developmental toxicity of indomethacin and sulindac. *Reprod Toxicol.*, 9:7-20.
- Lunt, C.C., A.J. Satin, W.H. Barth, Jr., and G.D. Hankins (1994) The effect of indomethacin tocolysis on maternal coagulation status. *Obstet. Gynecol.*, 84:820-822.
- Major, C.A., D.F. Lewis, J.A. Harding, M.A. Porto, and T.J. Garite (1994) Tocolysis with indomethacin increases the incidence of necrotizing enterocolitis in the low-birth-weight neonate. *Am. J. Obstet. Gynecol.* 170:102-106.
- Manchester, D., H.S. Margolis, and R.E. Sheldon (1976) Possible association between maternal indomethacin therapy and primary pulmonary hypertension of the newborn. *Am. J. Obstet. Gynecol.*, 126:467-469.
- Mari, G., K.J. Moise, R.L. Deter, B. Kirshon, and R.J. Carpenter (1990) Doppler assessment of the renal blood flow velocity waveform during indomethacin therapy for preterm labor and polyhydramnios. *Obstet. Gynecol.*, 75:199-201.
- McDonald, M.M., M.L. Johnson, C.M. Rumack, B.L. Koops, M.A. Guggenheim, C. Babb, and W.E. Hathaway (1984) Role of coagulopathy in newborn intracranial hemorrhage. *Pediatrics*, 74:26-31.
- Menahem, S. (1991) Administration of prostaglandin inhibitors to the mother; the potential risk to the fetus and neonate with duct-dependent circulation. *Reprod. Fertil. Dev.*, 3:489-494.
- Ment, L.R., C.C. Duncan, R.A. Ehrenkranz, C.S. Kleinman, K.J.W. Taylor, D.T. Scott, P. Gettner, E. Sherwonit, and J. Williams (1988) Randomized low-dose indomethacin trial for prevention of intraventricular hemorrhage in very low birth weight neonates. *J. Pediatr.*, 112:948-955.
- Meyers, R.L., G. Alpan, E. Lin, and R.I. Clyman (1991) Patent ductus arteriosus, indomethacin, and intestinal distension: Effects of intestinal blood flow and oxygen consumption. *Pediatr. Res.*, 29:569-574.
- Moise, K. (1993) Effect of advancing gestational age on the frequency of fetal ductal constriction in association with maternal indomethacin use. *Am. J. Obstet. Gynecol.*, 168:1350-1353.
- Moise, K.J., Jr., J.C. Huhta, D.S. Sharif, C.-N. Ou, B. Kirshon, N. Wasserstrum, and L. Cano (1988) Indomethacin in the treatment of premature labor: Effects on the fetal ductus arteriosus. *N. Engl. J. Med.*, 319:327-331.
- Moise, K.J., Jr., C.-N. Ou, B. Kirshon, L.E. Cano, C. Rognerud, and R.J. Carpenter, Jr. (1990) Placental transfer of indomethacin in the human pregnancy. *Am. J. Obstet. Gynecol.*, 162:549-554.
- Momma, K., and A. Takao (1989a) Increased constriction of the fetal ductus arteriosus with combined administration of indomethacin and betamethasone in fetal rats. *Pediatr. Res.*, 25:69-75.
- Momma, K., and A. Takao (1989b) Right ventricular concentric hypertrophy and left ventricular dilatation by ductal constriction in fetal rats. *Circ. Res.*, 64:1137-1146.
- Moncada, S., and J.R. Vane (1978) Pharmacology and endogenous roles of prostaglandin endoperoxidases, thromboxane A₂ and prostacycline. *Pharmacol. Rev.*, 30:293-331.
- Morales, W.J., S.G. Smith, J.L. Angel, W.F. O'Brien, and R.A. Knuppel (1989) Efficacy and safety of indomethacin versus ritodrine in the management of preterm labor: A randomized study. *Obstet. Gynecol.*, 74:567-572.
- Morin, F.C. III (1989) Ligating the ductus arteriosus before birth causes persistent pulmonary hypertension in the newborn lamb. *Pediatr. Res.*, 25:245-250.
- Nagaraj, H.S., A.S. Sandhu, L.N. Cook, J.J. Buchino, and D.B. Goff (1981) Gastrointestinal perforation following indomethacin therapy in very low birth weight infants. *J. Pediatr. Surg.*, 16:1003-1007.
- Niebyl, J.R., D.A. Blake, R.D. White, K.M. Kumor, N.H. Dubin, J.C. Robinson, P.G. Egner (1980) The inhibition of premature labor with indomethacin. *Am. J. Obstet. Gynecol.*, 136:1014-1019.
- Niebyl, J.R., and F.R. Witter (1986) Neonatal outcome after indomethacin treatment for preterm labor. *Am. J. Obstet. Gynecol.*, 155:747-749.
- Norton, M.E., J. Merrill, B.A.B. Cooper, J.A. Kuller, and R.I. Clyman (1993) Neonatal complications after the administration of indomethacin for preterm labor. *N. Engl. J. Med.* 329:1602-1607.
- Novy, M.J. (1978) Effects of indomethacin on labor, fetal oxygenation, and fetal development in rhesus monkeys. *Adv. Prostaglandin Thromboxane Res.*, 4:283-300.
- O'Grady, J.P., B.V. Caldwell, F.J. Auletta, and L. Speroff (1972) The effects of an inhibitor of prostaglandin synthesis (indomethacin) on ovulation, pregnancy, and pseudopregnancy in the rabbit. *Prostaglandins*, 1:97-106.
- Pace-Asciak, C. (1975) Activity profiles of prostaglandin 15- and 9-hydroxydehydrogenase and 13-reductase in the developing rat kidney. *J. Biol. Chem.*, 250:2795-2800.
- Persaud, T.V.N. (1975) Prolongation of pregnancy and abnormal fetal development in rats treated with indomethacin. *IRCS Med. Sci. Libr. Compend.*, 3:300.
- Powell, J.G., and R.L. Cochrane (1978) The effects of the administration of fenopropfen or indomethacin to rat dams during late pregnancy with special reference to the ductus arteriosus of the fetuses and neonates. *Toxicol. Appl. Pharmacol.*, 45:783-796.
- Randall, C.L., R.F. Anton, and H.C. Becker (1987) Effect of indomethacin on alcohol-induced morphological anomalies in mice. *Life. Sci.*, 41:361-369.
- Restaino, I., B.S. Kaplan, P. Kaplan, H.K. Rosenberg, C. Witzleben, N. Roberts (1991) Renal dysgenesis in a monozygotic twin association with in utero exposure to indomethacin. *Am. J. Med. Genet.* 39:252-257.
- Robert, A., and T. Asano (1977) Resistance of germfree rats to indomethacin-induced intestinal lesions. *Prostaglandins* 14:333-341.
- Rudolph, A.M., and M.A. Heymann (1978) Hemodynamic changes induced by blockers of prostaglandin synthesis in the fetal lamb in utero. *Adv. Prostaglandin Thromboxane Res.*, 4:231-237.
- Rumack, C.M., M.A. Guggenheim, B.H. Rumack, R.G. Peterson, M.I. Johnson, and W.R. Braithwaite (1981) Neonatal intracranial hemorrhage and maternal use of aspirin. *Obstet. Gynecol.*, 58(suppl):52S-56S.
- Schlondorff, D. (1993) Renal complications of nonsteroidal anti-inflammatory drugs. *Kidney Int.*, 44:643-653.
- Sessa, A., P.M. Allaria, F. Conte, A. Cioffi, and G. D'Amico (1973) Ultra-structural changes of the glomeruli of the rat induced by indomethacin. *Nephron*, 10:238-245.
- Seyberth, H.W., W. Rascher, R. Hackenthal and L. Wille (1983) Effect of prolonged indomethacin therapy on renal function and selected vasoactive hormones in very-low-birth-weight infants with symptomatic patent ductus arteriosus. *J. Pediatr.*, 103:979-984.
- Sharpe, G.L., K.S. Larsson, and B. Thalme (1975) Studies on closure of the ductus arteriosus. XII. In utero effect of indomethacin and sodium salicylate in rats and rabbits. *Prostaglandins*, 9:585-596.
- Shore, S.A., K.F. Austen, and J.M. Drazen (1989) Eicosanoids and the lung. In: *Lung Cell Biology*. Vol. 41. Massaro D, ed. Marcel Dekker, New York, pp. 1011-1089.
- Sideris, E.B., K. Yokochi, T. van Helder, F. Cocceani, and P.M. Olley (1983) Effects of indomethacin and prostaglandin E₂, I₂ and D₂ on the fetal circulation. *Adv. Prostaglandin Thromboxane Leukotriene Res.*, 12:477-482.
- Simeoni, U., J. Messer, P. Weisburd, J. Haddad, and D. Willard (1989) Neonatal renal dysfunction and intrauterine exposure to prostaglandin synthesis inhibitors. *Eur. J. Pediatr.*, 148:371-373.

- Steiger, R.M., E.L. Boyd, D.R. Powers, M.P. Nageotte, and C.V. Towers (1993) Acute maternal renal insufficiency in premature labor treated with indomethacin. *Am. J. Perinatol.*, *10*:381-383.
- Traeger, A., H. Noschel, and J. Zaumseil (1973) [Pharmacokinetics of indomethacin in pregnancy and parturient women and in their newborn infants.] *Zentralbl. Gynakol.*, *95*:635-641.
- Uslu, T., F.S. Ozcan, and C. Aydin (1992) Oligohydramnios-induced by maternal indomethacin therapy. *Int. J. Clin. Pharmacol.*, *30*:230-232.
- Van den Veyver, I.B., and K.J. Moise, Jr. (1993a) Prostaglandin synthetase inhibitors in pregnancy. *Obstet. Gynecol. Surv.*, *48*:493-502.
- Van den Veyver, I.B., K.J. Moise, Jr., C.N. Ou, and R.J. Carpenter, Jr. (1993b) The effect of gestational age and fetal indomethacin levels on the incidence of constriction of the fetal ductus arteriosus. *Obstet. Gynecol.*, *82*:500-503.
- van der Heijden, B.J., C. Carlus, F. Narcy, F. Bavoux, A.-L. Delezoide, and M.-C. Gubler (1994) Persistent anuria, neonatal death and renal microcystic lesions after prenatal exposure to indomethacin. *Am. J. Obstet. Gynecol.*, *171*:617-623.
- Vanhaesebrouck, P., M. Thiery, J.G. Leroy, P. Govaert, C. de Praeter, and S. Coppin (1988a) Oligohydramnios, renal insufficiency and ileal perforation in preterm infants after intrauterine exposure to indomethacin. *J. Pediatr.*, *113*:738-743.
- Vanhaesebrouck, P., M. Thiery, J. Vandewall, P. Defoort, and G. Vanmaele (1988b) Serum creatinine levels in preterm infants after intrauterine exposure to indomethacin. *Med. Sci. Res.*, *16*:93.
- Veersema, D., O.A. deJong, and J.A.M. van Wijck (1983) Indomethacin and the fetal renal nonfunction syndrome. *Eur. J. Obstet. Gynecol. Reprod. Biol.*, *16*:113.
- Walker, M.P., and C.J. Cantrell (1993) Maternal renal impairment after indomethacin tocolysis. *J. Perinatol.*, *13*:461.
- Wennmalm, A., S. Eriksson, and J. Wahren (1981) Effect of indomethacin on basal and carbon dioxide stimulated cerebral blood flow in man. *Clin. Physiol.*, *1*:227.
- Wild, L.M., P.A. Nickerson, and F.C. Morin III (1989) Ligating the ductus arteriosus before birth remodels the pulmonary vasculature of the lamb. *Pediatr. Res.*, *25*:251-257.
- Wolfe, L.S. (1979). The role of prostaglandins in the central nervous system. *Annu. Rev. Physiol.*, *41*:669-684.
- Zuckerman, H., U. Reiss, and I. Rubinstein (1974) Inhibition of human premature labor by indomethacin. *Obstet. Gynecol.*, *44*:787-792.
- Zuckerman, H., E. Shalev, G. Gilad, and E. Katzuni (1984) Further study of the inhibition of premature labor by indomethacin. Part II. Double-blind study. *J. Perinat. Med.*, *12*:25.