Indomethacin in Pregnancy: Applications and Safety

Gael Abou-Ghannam, M.D.[1] Ihab M. Usta, M.D.[1] Anwar H. Nassar, M.D.[1]

[1] Department of Obstetrics and Gynecology, American University of Beirut Medical Center, Hamra, Beirut, Lebanon

Address for correspondence and reprint requests Anwar H. Nassar, M.D., American University of Beirut Medical Center, P.O. Box 113-6044/B36, Hamra 110 32090, Beirut, Lebanon (e-mail: an21@aub.edu.lb).

Am J Perinatol 2012;29:175–186.

Abstract

Preterm labor (PTL) is a major cause of neonatal morbidity and mortality worldwide. Among the available tocolytics, indomethacin, a prostaglandin synthetase inhibitor, has been in use since the 1970s. Recent studies have suggested that prostaglandin synthetase inhibitors are superior to other tocolytics in delaying delivery for 48 hours and 7 days. However, increased neonatal complications including oligohydramnios, renal failure, necrotizing enterocolitis, intraventricular hemorrhage, and closure of the patent ductus arteriosus have been reported with the use of indomethacin. Indomethacin has been also used in women with short cervices as well as in those with idiopathic polyhydramnios. This article describes the mechanism of action of indomethacin and its clinical applications as a tocolytic agent in women with PTL and cerclage and its use in the context of polyhydramnios. The fetal and neonatal side effects of this drug are also summarized and guidelines for its use are proposed.

Keywords
- indomethacin
- tocolysis
- preterm labor
- short cervix
- polyhydramnios
- fetal side effects

Preterm labor (PTL) is a major cause of neonatal morbidity and mortality worldwide.[1] Care of premature infants has dramatically improved over the years but the progress in decreasing the incidence of preterm birth (PTB) has not been remarkable.[2]

A multitude of tocolytic agents have been tried to prolong labor including β-agonists, calcium channel blockers, prostaglandin synthetase inhibitors, magnesium sulfate, and oxytocin receptor antagonists. However, no clear-cut first-line treatment has been identified.[3] In addition, there is limited evidence supporting the role of tocolytics in improving perinatal outcomes despite some success in prolonging pregnancy.[3]

Indomethacin, a prostaglandin synthetase inhibitor, has been used as a tocolytic since the 1970s[4] and recently as a first-line agent in Canada.[5] On the other hand, maternal–fetal medicine specialists in the United States would choose magnesium sulfate first, then prostaglandin synthetase inhibitors as first-line tocolytic agents.[6]

In this article, we describe the mechanism of action of indomethacin and its clinical applications as a tocolytic agent in women with PTL and cerclage and its use in the context of polyhydramnios. The fetal and neonatal side effects of this drug are also summarized and guidelines for its use are proposed.

Mechanism of Action

It is well documented that prostaglandins are involved in PTL.[7] By enhancing myometrial gap junctions and stimulating calcium intracellular influx as well as its release from the sarcoplasmic reticulum, prostaglandins result in activation of myosin light-chain kinase and muscular contraction.[7] Prostaglandin levels increase in the plasma and amniotic fluid of women in labor, and prostaglandin metabolites have also been shown to be higher in women who deliver preterm.[7]

Indomethacin is a prostaglandin inhibitor that acts by competing with arachidonic acid for cyclooxygenase (COX). This mechanism of action was confirmed by Niebyl et al,[8] who showed that when treated with indomethacin for tocolysis, the maternal serum level of prostaglandin F2α metabolite decreases.

received
March 17, 2011
accepted after revision
May 6, 2011
published online
July 22, 2011

DOI http://dx.doi.org/10.1055/s-0031-1284227.
ISSN 0735-1631.

Uterine contractility is influenced by other mechanisms, and the effect of nonsteroidal anti-inflammatory drugs (NSAIDs) is not due to inhibition of prostaglandin synthesis alone. Using myometrial strips collected at the time of cesarean delivery, Sawdy et al[9] showed almost complete and immediate inhibition of spontaneous contractions when using indomethacin. Inhibition of prostaglandins alone cannot explain this finding because time is needed for accumulated prostaglandin to decrease and COX activity to stop. This can rather be explained by the indomethacin-mediated inhibition of calcium channel currents.[9]

Another mechanism of tocolysis by indomethacin involves the nuclear factor kappa β (NFkB) protein. These proteins are involved in COX-2 and prolabor genes, such as interleukin (IL)-8 expression. NFkB activity is increased during labor and acts as an antiprogesterone.[10] In addition, both COX-2 and IL-8 genes are up-regulated before labor.[11,12] It has been shown that NFkB activity is reduced by NSAIDs.[13]

Use of indomethacin for the treatment of PTL, therefore, not only would reduce prostaglandin synthesis but also potentially would reduce the antiprogesterone effect of NFkB on the other prolabor genes such as IL-8 and IL-1β.[14]

Route of Administration and Pharmacokinetics

Although the exact site of action of indomethacin has never been confirmed, the most likely target for prostaglandin synthesis inhibition seems to be the cervix and fetal membrane.[15–21] Because placing prostaglandins into the cervix or vagina can induce labor, it seems logical that indomethacin could be applied vaginally to induce tocolysis.[15] Clinically, however, oral and rectal routes are more commonly used. In most reports, treatment is usually initiated by a loading dose of either 50 mg[22] or 100 mg[9,22–27] rectal suppositories. Oral loading dose of 50 mg has also been reported in several studies.[8,28,29] In some protocols, if tocolysis was judged suboptimal after the loading dose, a repeat dose 100 mg indomethacin rectally would be used 1 to 2 hours after the initial dose.[30] Concerning maintenance treatment, most studies agree on the oral route of either 25 mg[22,25–27] or 50 mg[8,22–24,27–29] every 4 to 6 hours for 24 to 48 hours. But 50 mg indomethacin rectally for maintenance every 6 hours is also reported.[31]

Peak maternal plasma concentrations are achieved within 2 hours of initiation of treatment, although rectal administration achieves a peak level somewhat faster than oral administration.[32] Indomethacin readily crosses the placenta with fetal umbilical artery serum concentrations equilibrating with the maternal serum levels within 5 hours of dosing.[33] Metabolism of the drug is primarily done by the liver, but ~10 to 20% is excreted unchanged in the urine.[34] The half-life of indomethacin in premature infants is at least double (63 hours) that in adults.[35] The immature liver accounts for the prolonged half-life in the fetus.[8,36]

Regarding efficacy, the vaginal and oral routes have been compared in two studies. In a rat model, Fortson et al[37] showed that the vaginal route was more effective in prolonging pregnancy. Abramov et al[38] compared the efficacy of 200 mg intravaginal or intrarectal plus oral indomethacin in delaying PTL in singleton pregnancies with idiopathic PTL (< 33 weeks of gestation). Twenty-three women were randomized to each arm. Intravaginal indomethacin was more effective in delaying delivery for more than 7 days (78% versus 43%, $p = 0.03$) and was associated with a longer interval from initiation of treatment to delivery (26.5 ± 5.7 versus 12.6 ± 3.7 days, $p = 0.007$). In addition, birth weights were significantly higher in the intravaginal group with shorter duration of mechanical ventilation and neonatal intensive care unit stay.[38] The incidence of respiratory distress syndrome (RDS), neonatal septicemia, necrotizing enterocolitis (NEC), and intraventricular hemorrhage (IVH) was also lower in the intravaginal group, without reaching statistical significance. Transient fetal and maternal side effects were similar in both groups.

NSAID Use in PTL

Multiple NSAIDs such as indomethacin, nimesulide, sulindac, and celecoxib have been used for treatment of PTL. COX-2 is the isoform of COX mostly involved in PTL.[14] Therefore, the latter three drugs, being COX-2-selective inhibitors, were expected to gain more popularity than indomethacin, which is a nonselective COX inhibitor. However, when compared with indomethacin, nimesulide resulted in the same prolongation of labor and had similar side effects.[39] On the other hand, sulindac and celecoxib decreased the amniotic fluid to a lesser extent than indomethacin and were equally effective in delaying delivery.[26,40] Even with those promising results, indomethacin is still the most commonly used NSAID in the treatment of PTL.

Indomethacin versus Placebo

Although indomethacin tocolysis has been investigated since the mid-1970s, only three randomized, placebo-controlled, double-blind trials with a total of 100 women have compared it with placebo.[8,23,28] Niebyl et al,[8] in a prospective, randomized, double-blind trial, showed that compared with placebo ($n = 15$), treatment with indomethacin ($n = 15$) for 24 hours was significantly more effective in inhibition of PTL with treatment failure occurring in nine placebo-treated women versus only one in the indomethacin group ($p < 0.01$). There was no difference with respect to delivery rate 48 hours after treatment, gestational age at delivery, birth weight, and neonatal morbidity and deaths.

Zuckerman et al,[23] in a prospective, randomized, double-blind study, examined the effect of 200 to 300 mg indomethacin in women with PTL between 24 and 34 weeks of gestation. In 15 of 18 indomethacin-treated women (83.3%), PTL was arrested compared with 4 of 18 (22.2%) in the placebo group. The mean gestational age at delivery was significantly greater in the indomethacin group (36.4 versus 31.2 weeks, $p < 0.001$). It is important to note that these studies were not entirely placebo controlled. In the placebo group, some women received other tocolytic agents. Furthermore, difficulty in pooling information was encountered

because these studies used different outcomes in their reports. Niebyl et al[8] studied tocolytic failure on the basis of continued cervical dilation, rather than a prolongation of pregnancy. Finally, Panter et al[28] randomized women between 23 and 30 weeks to either indomethacin (50 mg followed by 25 mg 6 hourly for 48 hours) or placebo. Treatment with indomethacin led to prolongation of gestation for more than 48 hours in 13/16 (81%) of women compared with 10/18 (56%) in the placebo group, but these differences were not statistically significant. The incidence of perinatal mortality or severe neonatal morbidity was not significantly different between the groups.

A Cochrane meta-analysis reviewed those three studies.[41] It concluded that tocolysis with indomethacin resulted in a statistically significant reduction in the numbers of women delivering less than 37 weeks of gestation (relative risk [RR] 0.21, 95% confidence interval [CI] 0.07 to 0.62; number needed to treat 2, 95% CI 1 to 3). It also showed a reduction in delivery within 48 hours of initiation of treatment (RR 0.20, 95% CI 0.03 to 1.28) and within 7 days (RR 0.41, 95% CI 0.10 to 1.66).[41] Furthermore, there was an increase in gestational age at birth (weighted mean difference 3.53 weeks, 95% CI 1.13 to 5.92) and birth weight (weighted mean difference 716.34 g, 95% CI 425.52 to 1007.16). However, none of those studies showed a difference in neonatal outcome between treatment and control groups.

Indomethacin versus Other Tocolytics

Several randomized controlled studies have compared indomethacin with other tocolytics alone or in combination, reporting variable success rates.[24,25,27,29,42,43] Eight trials comparing all COX inhibitors with other tocolytics were included in a Cochrane metaanalysis.[22,24,25,27,29,44–46] A reduction in the number of women delivering prior to 37 weeks of gestation was noted in the COX inhibitor group (RR 0.53, 95% CI 0.31 to 0.94; number needed to treat 8, 95% CI 4 to 50).[41] In addition, a nonsignificant reduction in the number of women delivering before 48 hours after initiation of treatment was shown (RR 0.59, 95% CI 0.34 to 1.02). However, there were no differences in the number of women delivering within 7 days or in reported maternal or neonatal outcomes.

Compared with intravenous magnesium sulfate, Morales and Madhav[24] found that indomethacin was equally effective in delaying delivery for 48 hours. In a head-to-head comparison with β-sympathomimetic drugs (ritodrine and terbutaline), indomethacin was shown to be equally effective in delaying delivery.[27,29,43] Another β-sympathomimetic drug compared with indomethacin is nylidrin, which has been shown to be more effective in delaying delivery for 48 hours and beyond 37 weeks[25]; however, it was also associated with more prematurity-related complications.[47]

The combination of ritodrine and indomethacin against ritodrine alone has been addressed in two trials.[42,48] Katz et al[42] showed a prolongation in pregnancy of 5.6 weeks in the combination group compared with 3.6 weeks for ritodrine alone ($p < 0.05$). Similarly, Gamissans et al[48] showed that the group receiving the combination had longer gestation, a higher proportion of women delivering at term, and a lower incidence of low-birth-weight neonates than the ritodrine-only group, even though these differences were not statistically significant. It is important to note that those trials are very heterogeneous. The ritodrine and indomethacin maintenance regimens differed: one study used maintenance tocolysis until 35 weeks and the other continued it until 38 weeks.

When combined with ethanol tocolysis, there were fewer women who delivered within 48 hours compared with ethanol tocolysis alone or placebo combined with ethanol. In addition, labor was delayed 14 days or more in 50% of the patients but the results were not statistically significant.[49]

Because subclinical infection has been implicated as an etiologic factor in PTB, Newton et al[50] performed a randomized double-blind trial comparing a combination therapy of magnesium sulfate, indomethacin, and ampicillin-sulbactam with single-agent tocolysis with magnesium sulfate. The investigators reported no difference between the two regimens with regard to delivery delay, incidence of PTB, and neonatal outcome.

Multiple reviews and meta-analyses have critically analyzed the numerous trials on indomethacin as a tocolytic,[30,51–54] all reaching the same conclusions, suggesting that indomethacin is the most efficacious medication. Higby et al[51] analyzed 328 studies undertaken between 1933 and 1992 on all tocolytics and concluded that prostaglandin synthetase inhibitors are the only effective agents for tocolysis. These results should be viewed with caution because the initial controlled trials were performed without the use of antenatal corticosteroid therapy to accelerate fetal lung maturity. However, most studies agreed that the potential complications associated with indomethacin use are primarily due to prolonged therapy; therefore, it appears to be an acceptable tocolytic agent for a limited duration of less than 72 hours.[52]

The most recent meta-analysis by Haas et al[53] reviewed 58 studies in a attempt to determine the optimal tocolytic agent with the highest efficacy-to-toxicity ratio in women between 28 and 32 weeks. Prostaglandin synthetase inhibitors were shown to be superior in delaying delivery for at least 48 hours and 7 days but not up to 37 weeks; calcium channel blockers were found to be superior for this outcome. Similar discontinuation rates due to side effects were found for all tocolytics, except for β-sympathomimetics, which had a higher discontinuation rate. Most importantly, the authors found no significant difference in RDS and neonatal death among all tocolytics when compared with each other and placebo.

Cerclage

Many studies have shown that women with a short cervix have asymptomatic contractions.[55,56] Therefore, it has been postulated that indomethacin, owing to its tocolytic activity, might have a role in the management of these women. In addition, cerclage placement causes inflammation with prostaglandins F1 and E2 transiently rising soon after the procedure.[57] Because inflammation is involved in the mechanisms

of PTL,[7] some authors have tried to investigate the efficacy of indomethacin after cerclage placement to decrease PTB.[57,58]

Surprisingly, in the retrospective study by Visintine et al,[58] the administration of indomethacin at the time of ultrasound-indicated cerclage was not associated with a decrease in spontaneous PTB. Randomized controlled trials that have specifically addressed the role of indomethacin use alone in the management of women with short cervices are lacking. However, when analyzing women with dilated cervices between 14 and 26 weeks in a retrospective study by Berghella et al, those with cerclage who received indomethacin had a nonsignificant decrease in PTB at less than 32 weeks (odds ratio [OR] 0.56, 95% CI 0.26 to 1.25) and less than 35 weeks (OR 0.52, 95% CI 0.23 to 1.14).[59]

A meta-analysis by Berghella et al[60] reviewed studies[61–64] in which asymptomatic women with a short cervix < 25 mm on transvaginal ultrasonography between 14 and 27 weeks were assigned to either receive cerclage or not. In women who did not undergo cerclage, outcomes were compared between women given indomethacin and those who were not. This review showed that indomethacin did not prevent PTB before 35 weeks (RR 0.69, 95% CI 0.44 to 1.13); however, a reduction in PTB before 24 weeks of gestation was noted (RR 0.14, 95% CI 0.02 to 0.92), associated with a trend toward improved perinatal mortality.[60] It is worth mentioning that the sample size was 35% of that required to provide sufficient power to assess PTB $<$ 35 weeks. In the same meta-analysis, almost all women treated by cerclage had also received indomethacin, therefore no control group is available for comparison. This systematic review is unique in that it is the only study so far to assess the efficacy of tocolytic therapy for a short cervical length without cerclage.[60]

Finally, the possible role of indomethacin as a therapeutic and diagnostic tool was investigated.[65] A stratification protocol for treatment of short cervix was developed according to degree of shortening. When cervical length improved after indomethacin therapy, a 33% reduction in the need for cerclage in women with short cervix was reported. On the other hand, when it did not improve or it deteriorated, the woman was more likely to require a cerclage and deliver at an earlier gestational age. This protocol achieved a prolongation of gestational age beyond 34 weeks in 94% of women who were diagnosed with progressively shorter cervix between 12 and 28 weeks of gestation.

Maternal Side Effects

Indomethacin causes minimal side effects to the mother including nausea, vomiting, and dyspepsia.[66] As any prostaglandin synthetase inhibitor, indomethacin causes some gastric irritation and may exacerbate peptic ulcer disease and gastritis.[67] Hematologically, indomethacin affects the platelets and may cause a prolongation of bleeding time, but not of prothrombin time and activated partial thromboplastin.[67]

Except for a case report by Lissak et al[68] of severe hypersensitivity reaction (shortness of breath, bronchospasm, and hepatic injury), allergic reactions to indomethacin are very rare. However, cross-sensitivity between indomethacin, aspirin, and salicylates should always be kept in mind. Maternal contraindications for treatment with indomethacin include coagulation dysfunction, hepatic or renal disorder, gastrointestinal ulcerative disease, and asthma in aspirin-sensitive patients.[66]

Fetal-Neonatal Complications

Indomethacin blocks the production of vasoactive prostaglandins, which prompted some authors to evaluate its effect on uterine blood flow. Doppler studies of the umbilical and uterine vessels done by Mari et al[69] and Moise et al[70] showed that uteroplacental flow was not altered in women in PTL treated with indomethacin.

Transplacental passage of indomethacin has been shown to be minimal early in gestation,[71] although it crosses freely near term.[72] This is one reason indomethacin has always been considered an attractive tocolytic agent before 32 weeks. In contrast, Norton et al[73] reported an increased risk of neonatal complications in infants born at or before 30 weeks of gestation.

Actually, there has been a lot of debate about the possible deleterious fetal and neonatal effects of indomethacin.[74] Multiple studies have raised the issue of increased neonatal complications (oligohydramnios, renal failure, NEC, IVH, and closure of the patent ductus arteriosus [PDA]) with its use, although others have refuted such associations.

Cerebral Side Effects

There is still a lot of controversy about the actual role of indomethacin in the pathogenesis of brain injury (IVH, periventricular echogenicity, or periventricular leukomalacia [PVL]), complications mostly seen in preterm infants. Some authors suggested that indomethacin was directly implicated,[73,75–81] others found no associations between IVH and indomethacin treatment,[28,30,82–84] and some even suggested a possible protective cerebral effect of indomethacin.[85,86]

Baerts et al[77] reported that infants exposed to indomethacin and born before 30 weeks of gestation had more cystic PVL. These results were then confirmed by Norton et al,[73] who looked at preterm infants delivered at or before 30 weeks of gestation who were exposed to indomethacin matched with nonexposed infants for gestational age at delivery, gender, steroid use, and rupture of membranes. Tocolysis with indomethacin was found to be an independent risk factor for grade II to IV IVH in infants. However, this study was criticized because it included grade II IVH with the more clinically significant grades III and IV. Indeed, although grade II IVH was significantly associated with indomethacin use, grades III and IV IVH were similar between the two groups.

One study found that the risk of IVH was greater in neonates who had received indomethacin within 48 hours of delivery, although no matching for delivery indication was performed.[81] More women in the indomethacin group were delivered due to preeclampsia, and more neonates exposed to indomethacin were also exposed to other tocolytics. Clearly, pregnancies refractory to one tocolytic and requiring more

than one agent could have the characteristics that predispose to the occurrence of IVH. Furthermore, in this study women receiving long-term indomethacin for more than 72 hours as well as women with ruptured membranes were included.

A similar predisposition to IVH was noted in high-risk neonates.[31,78] Very low-birth-weight preterm infants (500 to 800 g) receiving magnesium sulfate and indomethacin for tocolysis had a twofold increased risk of grades III and IV IVH compared with those receiving magnesium sulfate only.[78] Even after controlling for gestational age, birth weight, maternal hypertension, and antenatal corticosteroid use, the association was still statistically significant (OR 2.7, 95% CI 1.17 to 6.36).[31] Finally, Friedman et al[76] showed that indomethacin tocolysis was associated with an increased risk for periventricular echogenicity (transient form of neonatal white matter injury) in the absence of long-term injury such as PVL.

In assessing the role of indomethacin in the pathogenesis of IVH, Souter et al[81] studied the pulsatility index in the fetal middle cerebral artery and found that it increased with indomethacin use. In a pig model, indomethacin decreased fetal cerebral blood flow, and hypothetically it may lead to cerebral hypoperfusion injury, resulting in PVL.[87] On the other hand, Parilla et al[22] reported that indomethacin does not seem to affect cerebral blood flow significantly and therefore might cause IVH through another mechanism. Like most NSAIDs, indomethacin inhibits platelet aggregation. It has been postulated that the lack of platelet aggregation associated with fluctuations in intracranial pressure during labor would lead to the increased risk of IVH.[82,88] Merrill et al[74] stipulated that the rapid postnatal volume expansion, in the face of indomethacin-induced oliguria, may increase cerebral capillary pressure. They concluded that these mechanisms, individually or collectively, may be at work in the pathogenesis on IVH in preterm infants receiving NSAIDs.

Contrary to the reports summarized above, multiple retrospective, case-control studies of infants born before 32 weeks of gestation found no relationship between indomethacin tocolysis and IVH.[28,82–84,88] In one study, the incidence of grade III or IV IVH was even decreased (13.3 to 5.3%) in the indomethacin group, though this did not reach statistical significance.[89] It is worth mentioning that both groups received magnesium sulfate and betamethasone before delivery.

The possible association between indomethacin and IVH could simply be due to confounding variables, mainly gestational age at delivery, with increased risk at earlier gestational age. In addition, it has been suggested by Macones et al[30] that the possible association between indomethacin and cerebral ultrasound abnormalities may be related to the fact that indomethacin was given for PTL refractory to first-line tocolytics in most studies. As pointed to before, this could be due to a more severe condition such as subclinical infection that may also predispose to IVH.[30] In addition, subclinical infections are strongly and independently associated with major neonatal complications.

Multiple studies have demonstrated a possible protective effect of indomethacin on cerebral circulation, especially during the first 72 hours of life of very low-birth-weight neonates.[85,90,91] In a randomized trial, the postnatal use of indomethacin in very low-birth-weight infants has been shown by Ment et al[85] to significantly decrease the incidence and severity of IVH. Furthermore, preexisting IVH did not worsen with indomethacin treatment.[86] Actually, indomethacin leads to an increase in cerebral vascular resistance that stabilizes cerebral hemodynamics in preterm infants.[92] Therefore, it could be possible that antenatal administration of indomethacin provides prophylactic effects similar to the ones demonstrated in neonates.[92]

In animal studies, indomethacin was shown to decrease cerebral blood flow when administered to fetal pigs during hypoxia/hypercapnia[87]and to help germinal matrix maturation,[93] modifications that should be protective from IVH.

Multiple meta-analyses have been published to address those contradictory results. First, Loe et al[94] reviewed 28 studies including 6008 infants and concluded that indomethacin tocolysis does not increase the risk of IVH (OR 1.02, 95% CI 0.55 to 1.89). This conclusion should be taken with caution as this analysis did not define clear diagnostic criteria for neonatal outcomes and did not evaluate PVL. In addition, it only included three randomized clinical trials, failed to mention two published observational studies, and included one study with data on postnatal indomethacin. In the Cochrane review,[41] when comparison was done between any COX inhibitor and any tocolytic, the RR for IVH (grade III/IV) was 0.61 (95% CI 0.08 to 4.40). For β-sympathomimetic agents, the RR was inestimable because there were no IVH cases in the β-sympathomimetic group and for magnesium sulfate, an RR of 0.61 (95% CI 0.08 to 4.40) was observed.

Finally, 21 retrospective and observational studies were grouped by Amin et al[95]in a meta-analysis that thoroughly looked at all the known possible neonatal side effects of indomethacin. Indomethacin was significantly associated with PVL but not with severe IVH.

According to these studies, the debate remains whether indomethacin is an independent risk factor for cerebral injury in preterm infants.

Renal Abnormalities

Indomethacin had been shown to cause renal disorders that include decreased amniotic fluid, structural malformations, and acute or chronic renal failure in severe cases.[43,47,73,74,80,81,89,96–108] It is known to decrease plasma renin activity by inhibiting the renin-angiotensin system.[81] Pomeranz et al[109] suggested that the suppression of the renin-angiotensin system activity is of critical importance in the production of these complications.

In addition, indomethacin is a potent vasoconstrictor of fetal blood vessels, including the renal arteries.[81] It decreases renal blood flow and could lead to renal dysfunction.[110] Oligohydramnios is one of the most common complications of prolonged indomethacin use, due to a decrease in fetal urine production,[43,99–105,111] even though it has been shown to be transient and reversible with cessation of the drug.[104,112,113] A study on pregnant rhesus monkeys receiving indomethacin for more than 48 hours revealed that it

could lead to oliguria and oligohydramnios, as well as incomplete nephrogenesis in the fetuses.[114]

A retrospective study by Hendricks et al[104] showed that 26 of 67 subjects receiving long-term indomethacin therapy developed an ultrasound documented decrease in the volume of amniotic fluid. On the contrary, Wurtzel[115] showed that long-term indomethacin therapy had no effect on fetal renal function.

Two trials evaluated amniotic fluid volume in short-term use (48 hours) of indomethacin.[24,26] When compared, both indomethacin and celecoxib were shown to decrease amniotic fluid index (AFI).[26] However, follow-up was limited to 72 hours. Similarly, Morales and Madhav[24] compared 48-hour courses of magnesium sulfate and indomethacin and found that the latter resulted in oligohydramnios in 2 of 49 patients, both of which resolved within 48 hours of stopping therapy. Contrary to previous results, Sandruck et al[112] showed that short-term use of indomethacin tocolysis in singleton and twin pregnancies lead to nonsignificant change in amniotic fluid volume over time. In addition, amniotic fluid volumes were evaluated every 24 hours for 7 days after the cessation of the treatment, and there was no evidence that the nonsignificant decrease in amniotic fluid persisted for prolonged periods once the medication was stopped.

When quantitative assessment of AFI was done by Savage et al,[116] they suggested a low frequency of oligohydramnios (AFI $<$ 5 cm; 7.3%). Furthermore, no association between oligohydramnios and dose regimen, duration of therapy, or gestational age during therapy was found.

Indomethacin has also been implicated in more severe renal complications such as neonatal renal failure.[28,35,73,81,96,98,99,106,107,117,118,119] Acute renal failure has been shown to be reversible but can also lead to chronic renal failure and end-stage renal disease in severe cases.[98,99]

Infants exposed to antenatal indomethacin and delivered at less than 31 weeks had higher serum creatinine levels and lower urine output compared with the unexposed group.[73] These effects were not related to the total dose of indomethacin or the time from the last dose of indomethacin until delivery. The randomized controlled trial by Panter et al[28] revealed statistically significant oliguria in the first 24 hours of life in the group of babies that received indomethacin.

Chronic renal failure has been reported in five neonates whose mothers received indomethacin at gestational age 21 to 25 weeks for up to 16 weeks,[99] although acute renal failure that resolved spontaneously within 2 months was encountered in a member of a twin pregnancy where indomethacin was used for tocolysis and polyhydramnios.[109] Nishikubo et al[106] reported three cases of renal failure in very low-birth-weight infants with persistent high creatinine following prolonged indomethacin use (3 to 14 days). One of the infants even required peritoneal dialysis, and a mortality due to renal failure and sepsis was also reported. Confirming these findings, it was shown that very low-birth-weight babies of less than 31 weeks of gestation delivered within 48 hours of indomethacin exposure were more likely than unexposed infants to have renal impairment at 72 hours of age.[81] However, this study was criticized for using long-term indomethacin and for failing to match for delivery indications.

When indomethacin was compared with other COX inhibitors (sulindac and nimesulide), it was shown that all drugs caused almost similar significant reduction in fetal urine production as well as AFI over the 48-hour treatment period, both of which were similarly reversible to pretreatment levels within 72 hours of discontinuing therapy.[113] The long half-life of indomethacin in premature infants could explain the effect of indomethacin lasting after birth, if administered close to delivery. In addition, some authors suggest that indomethacin leads to a long-standing alteration of fetal renal perfusion persisting even after clearance of the drug from the fetomaternal circulation.[81]

Keeping in mind the association between indomethacin and oligohydramnios, obstetricians should monitor AFI regularly in women receiving treatment for prolonged periods. If used only for 48 hours, the effect on the amniotic fluid is reversible. If oligohydramnios develops and does not resolve within 24 to 48 hours after the discontinuation of treatment, one should search for other causes of oligohydramnios. Antenatal administration of indomethacin close to delivery may cause renal impairment in very low-birth-weight infants and should be practiced with caution. Finally, it would also be important to inform the pediatric team about the use of indomethacin in utero, in case the neonate develops renal failure at birth.

Patent Ductus Arteriosus

After oligohydramnios, the main concern about using indomethacin as a tocolytic is its effect on the ductus arteriosus. There are two important effects that should be elaborated here. First, antenatal indomethacin leads to premature closure of the PDA in utero.[31,73,75,77,81,83,120–123] Second, although debated, indomethacin decreases the sensitivity of the ductus to indomethacin, rendering it less effective postnatally in cases where the PDA persisted.[47,73,75,81,124–129]

Multiple studies established the direct effect of indomethacin on PDA in utero. When comparing indomethacin with sulindac and nimesulide, it was shown that ductal Doppler pulsatility index was less reduced over a 48-hour treatment with indomethacin than the two other agents, and was reversible once the treatment was withheld.[113] Räsänen and Jouppila[130] compared indomethacin and sulindac and confirmed that both have ductal effects. The effect was noted only after 4 hours from starting indomethacin, whereas it took 24 hours for sulindac to affect the PDA. Most studies linking premature closure of the ductus to indomethacin included fetuses with gestational age beyond 28 weeks, when the PDA is more sensitive to indomethacin.[81,83,113,121,130] The incidence of ductal constriction after indomethacin use has been reported to range from 28 to 50%, with an increased risk at gestational age beyond 31 weeks[83,121,122] or with a longer regimen.[31,83,121]

Some studies have also reported tricuspid regurgitation in conjunction with ductal constriction with indomethacin therapy;[28,120,122,131] similar to ductal constriction, tricuspid regurgitation has been reported to be transient and reversible.[131] Respondek et al[132] reviewed 305 studies that included 107 fetuses exposed to indomethacin. Fetal echocardiography

data analysis concluded that 74% had normal results, 10% had tricuspid regurgitation, and 6% had ductal constriction.

On the other hand, few studies have demonstrated that antenatal exposure to indomethacin is not associated with premature PDA constriction.[82,89,116,133] In the review by Loe et al,[94] no association between indomethacin and PDA constriction was found (OR 1.25, 95% CI 0.64 to 2.54). In one study, the frequency of PDA closure was reported to be 6.5% with indomethacin use, irrespective of gestational age, dose, or duration of treatment.[116] However, the majority of women included were less than 31 weeks of gestation. Another study reported an incidence of ductal constriction of 11%, but the authors performed fetal echocardiography 24 hours after the end of the treatment, which could have given time for some constriction to resolve.[28] In addition, all babies were less than 30 weeks of gestation, when the PDA is less susceptible to indomethacin effect.[28]

To increase the controversy, betamethasone has been incriminated in the toxicity associated with indomethacin on the PDA.[134] This finding has not been confirmed by others.[116]

A second effect of indomethacin on the PDA is on its sensitivity. When an infant is born premature, the closure of the PDA might be delayed. The usual treatment is fluid restriction and postnatal indomethacin. However, several authors reported that antenatal indomethacin exposure renders the PDA less sensitive to postnatal indomethacin,[47,73,75,81,124–129] thus increasing the need for surgical correction.[47,73,128,129] A small randomized controlled trial that compared indomethacin with a β-sympathomimetic agent prenatally has shown that the number of infants requiring indomethacin postnatally for PDA closure was the same in both groups.[47] However, surgical ligation was needed in half of the infants whose mothers received indomethacin and in none of those receiving the β-sympathomimetic. Moreover, a prospective study, showed OR of 10.5 for surgical treatment of PDA in premature neonates with in utero exposure to indomethacin.[124] It is important to note that the relation between antenatal indomethacin exposure and postnatal failure of medical therapy for PDA has been shown to be time dependent[121] and, in animal studies, dose dependent.[135] In the various meta-analyses, there is agreement that indomethacin treatment at less than 34 weeks of gestation for tocolysis does not increase the risk of PDA.[94,95]

Necrotizing Enterocolitis

As for the association between NEC with indomethacin, there is also a lot of disagreement. Some authors suggest that antenatal indomethacin is an independent risk factor for the development of NEC.[4,73,80,96] Possible postulated mechanisms for NEC and intestinal perforation are decreased mesenteric blood flow and alterations of the defense mechanism of the neonatal gastrointestinal tract.[136,137,138,139] On the other hand, others concluded that there was no direct association between indomethacin and NEC in premature infants.[28,31,89,140–142]

In the study by Norton et al,[73] infants exposed to indomethacin antenatally and delivered at less than 30 weeks of gestation had an increased risk of developing NEC. However, this risk was not increased by an increased dose, prolonged treatment, or a shorter time from the last dose of indomethacin until delivery. Contrarily, Major et al[96] reported that neonates born weighing less than 1500 g and exposed to indomethacin developed NEC more often than those not exposed, but the risk was higher among infants whose mothers had received over 48 hours of indomethacin treatment and those who were delivered within 24 hours of the last dose. Finally, compared with nylidrin, indomethacin-exposed neonates had higher rates of NEC, especially if delivered within 5 days of the start of the treatment (27% versus 0%).[47]

Contrary to those results, Vermillion and Newman[89] reported no increase in NEC in premature infants, even if delivered within 48 hours after indomethacin exposure. The same results were found when comparing magnesium alone with magnesium and indomethacin.[78] Those results were supported by Panter et al,[28] where neither NEC nor other neonatal morbidities were greater in the indomethacin treatment group. Even when looking at the higher-risk group of infants (birth weight less than 1500 g), NEC was not shown to be associated with indomethacin exposure.

Meta-analyses agree that indomethacin use at less than 34 weeks is not a direct risk factor for the development of NEC (OR 2.43, 95% CI 0.73 to 8.03)[143] and (OR 1.4, 95% CI 0.91 to 2.3).[95] However, NEC was increased by antenatal indomethacin when analysis was restricted to retrospective cohort studies with recent exposure to indomethacin (OR 2.2, 95% CI 1.1 to 4.2), or only observational studies matched for antenatal steroid exposure and gestation at birth.[95]

Respiratory Complications

Last, respiratory complications have also been linked to exposure to indomethacin in utero.[18,133] Indomethacin stimulates proinflammatory mediators in the lung and inhibits surfactant production, which could lead to an increase in the incidence of RDS and bronchopulmonary dysplasia (BPD).[144] A small, randomized, controlled pilot study that recruited 34 women (39 babies), with 16 (19 babies) on indomethacin treatment and 18 (20 babies) on placebo, found increased neonatal morbidity associated with indomethacin treatment, which was not attributable to either NEC or IVH but to a higher incidence of chronic lung disease.[28] The trend toward more chronic lung disease was present even though over 80% of mothers received a complete course of corticosteroid treatment. This finding is consistent with the results of the trial comparing indomethacin with nylidrin,[47] where BPD occurrence was significantly higher in the indomethacin group. A very important confounder in the latter study was that corticosteroid use was very low (8% and 13% in the indomethacin and nylidrin groups, respectively). The same confounder was found in another study where no antenatal corticosteroids were administered; the study showed a positive association between indomethacin and RDS.[133] Contrary to these findings, different retrospective trials showed no significant association between BPD and indomethacin.[81,82,142]

In two meta-analyses by Loe et al[94] and Amin et al,[95] indomethacin was not associated with BPD. Indomethacin was associated with a nonsignificant increase in RDS risk when restricting analysis to studies with recent exposure to the drug (OR 2.2, 95% CI 0.94 to 5.12) but was protective against RDS when including studies matched for gestational age and antenatal steroid use (OR 0.69, 95% CI 0.39 to 1.2), although the association was not significant.[95]

Perinatal Mortality

Overall, indomethacin was not associated with increased mortality in neither of the meta-analyses.[94,95]

Conclusion of Neonatal Effects

Indomethacin has been implicated in increased risk of neonatal complications. But what would happen without indomethacin? Macones and Robinson[145] developed hypothetic cohorts of women with PTL at 24, 26, 28, 30, and 32 weeks of gestation. They described a model through which they were able to estimate the incidence of the major neonatal adverse events (RDS, grade III or IV IVH, sepsis, and death) with and without indomethacin. Indomethacin was considered an adequate tocolytic for prolonging labor enough to achieve maximum benefit from corticosteroids.[145] They concluded that between 26 and 32 weeks, it is acceptable to use indomethacin for PTL because it results in a lower total number of adverse neonatal outcomes compared with no tocolysis. On the other hand, at 24 weeks, the risks of its use outweigh the benefits.

Other Uses of Indomethacin: Polyhydramnios

Due to its ability to decrease amniotic fluid volume, indomethacin has been used for the treatment of symptomatic polyhydramnios.[146] Cabrol et al[147] were the first to report on eight women with symptomatic polyhydramnios who were treated with 2.2 to 3.0 mg of indomethacin/kg/d for 2 to 11 weeks. A significant reduction in amniotic fluid volume, fundal height, and umbilical perimeter were noted in all women. Since then, multiple cases have been reported worldwide.[148–168] Mamopoulos et al[148] reported on 15 women treated for 4 weeks with indomethacin and showed that the majority of fluid reduction occurred within the first week of treatment. Abhyankar and Salvi[163] reported 12 cases of symptomatic polyhydramnios (cardiorespiratory embarrassment, abdominal pain, or PTL) treated with indomethacin at a dose of 2.2 to 3 mg/kg/d (75 mg twice daily). They documented that 11 women were relieved from their abdominal discomfort and respiratory embarrassment. Polyhydramnios decreased both clinically and on ultrasound in 10 of the 12 women. In addition, full-term delivery was achieved in five women, and the remaining six carried to 34 to 36 weeks. Vigil-de Gracia et al[165] conducted a prospective trial on eight symptomatic women between 24 and 25 weeks of gestation with an AFI greater than 24 cm. Indomethacin was used every 6 hours until symptoms disappeared and AFI became less than 24 cm. A success rate of 100% at correcting symptomatic polyhydramnios was reported with a maximum of 6 days of treatment. Similarly, Cabrol et al[166] reported 22 women who received indomethacin at a dose of 3 mg/kg/d and showed a significant decrease in AFI, with early PTB prevented in all. Rosen et al[152] also reported indomethacin use in twin gestations and confirmed that the reduction in amniotic fluid volume was due to a decrease in fetal urine production.

Most reported cases focused on idiopathic polyhydramnios, but indomethacin has been also used in the context of polyhydramnios associated with diabetes mellitus.[166] Kriplani et al[167] reported the successful use of indomethacin in the treatment of polyhydramnios secondary to a placental chorioangioma. Finally, polyhydramnios associated with fetal cytomegalovirus infection has been successfully treated by volume-reduction amniocentesis combined with maternal indomethacin therapy.[168] The optimal dose of indomethacin for the treatment of polyhydramnios is not known, but most reports use 25 mg orally every 6 hours[146,148] or calculate the dose as 2 to 3 mg/kg/d.[146–148,166] Fetal echocardiography is recommended within the first 24 hours after therapy and weekly thereafter.[146,165] If severe constriction of the ductus arteriosus or tricuspid regurgitation is noted, the treatment should be discontinued. Lesser degrees of ductal constriction can be managed by decreasing the dose of the medication.[146]

In conclusion, indomethacin is effective in the therapeutic management of severe symptomatic polyhydramnios. Caution should be exercised to balance between the decrease in amniotic fluid and the side effects that this medication could have on the fetus. Further studies are needed to dictate the optimal dose and duration of treatment.

Conclusions

Indomethacin has been used as a tocolytic agent since the 1970s. When used between 28 and 32 weeks, it is more effective than placebo and other tocolytics in delaying delivery for at least 48 hours and 7 days but not beyond 37 weeks. Even though maternal side effects are minimal, neonatal side effects are multiple and increase when this drug is used beyond 32 weeks of gestation. It is recommended to use it for 48 hours or less and at the lowest possible dose to allow time for corticosteroid treatment but minimize neonatal complications. Monitoring AFI by ultrasound and PDA by fetal echocardiography is advisable in women receiving indomethacin. In addition, infants who were exposed to indomethacin shortly before birth should be monitored for possible IVH, NEC, and RDS. Other uses of indomethacin for the treatment of polyhydramnios or in association with cerclage have been investigated, but more studies are needed to come up with proper guidelines and recommendations in that context.

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