

Acute severe reversible oligohydramnios induced by indomethacin in a patient with rheumatoid arthritis: A case report and review of the literature

**S. Topuz¹, M.D.; R. Has², Assoc. Prof.; H. Ermiş³, Prof.; A. Yıldırım³, Prof.;
L. İbrahimoğlu³, Prof.; A. Yüksel³, Prof.**

Department of Obstetrics and Gynecology, Istanbul University, School of Medicine, Istanbul (Turkey)

Summary

Although the association between oligohydramnios and indomethacin use for premature labor has been well known for many years, there have been few cases published about it. We present a case of indomethacin-induced oligohydramnios due to use in a patient for rheumatoid arthritis. A 27-year-old G2P1 woman was referred to our prenatal unit with oligohydramnios at 33 weeks of pregnancy. Ultrasonography revealed severe oligohydramnios with an amniotic fluid index of 0.9 cm. She gave a history of daily 150 mg indomethacin use for newly diagnosed rheumatoid arthritis. All possible reasons for oligohydramnios were excluded and indomethacin was discontinued. In four days the amniotic fluid was observed as normal. We concluded that the oligohydramnios caused by indomethacin occurs quickly, is dose-related and reversible. Amniotic fluid volume should be monitored while using indomethacin.

Key words: Oligohydramnios; Indomethacin; Rheumatoid arthritis.

Introduction

Oligohydramnios is associated with increased perinatal mortality and morbidity. It has a heterogeneous etiologic spectrum. Indomethacin is used in patients with preterm labor, idiopathic polyhydramnios or rheumatic diseases [1, 2]. Although the association between oligohydramnios and indomethacin has been well known for many years, there have been few cases published about it [3, 4]. We present a case of acute severe reversible oligohydramnios with no apparent ill-effect on the fetus or neonate, induced by indomethacin in a patient with rheumatoid arthritis and a review of the literature.

Case

A 27-year-old G2P1 woman was referred to our prenatal unit with oligohydramnios at 33 weeks of pregnancy. Ultrasonography revealed severe oligohydramnios with an amniotic fluid index of 0.9 cm. No structural fetal abnormality was detected in detailed scanning. The fetal biometric parameters were appropriate for 33 weeks of gestation; thus intrauterine growth restriction was not detected. Blood pressure was within normal limits and biochemical parameters were negative for preeclampsia. She was not complaining about premature rupture of the membranes and sterile speculum examination revealed no collection or pool of amniotic fluid. The pH of nitrazine paper was 4.5. Fetal well-being was assured with a reactive nonstress test. To find out the etiology of oligohydramnios, the patient's medical and obstetric history were evaluated. Two weeks before she had been prescribed indomethacin, 150-mg/day, due to

newly diagnosed rheumatoid arthritis. We discontinued indomethacin and started betamethasone, 12 mg/day, for lung maturation. The patient was scheduled to be followed with a daily nonstress test and amniotic fluid index measurement. The patency of the ductus arteriosus was confirmed with fetal echocardiography. On the following day a nonstress test was reactive and the amniotic fluid index measured 3.8 cm. On the second and third days the amniotic fluid index measured 7.8 cm and 11 cm, respectively. On the fourth day the preterm premature rupture of the membranes took place and a 2,270 g female baby with 7/8 Apgar scores was delivered vaginally. Neonatal assessment and follow-up examinations of the infant were unremarkable.

Discussion

Oligohydramnios is quantitatively defined as an amniotic fluid index (AFI) less than the fifth percentile for gestational age. Clinical conditions commonly associated with oligohydramnios are ruptured membranes, urinary tract malformation, intrauterine growth restriction, post-date pregnancy and placental insufficiency. One of the rarely seen reasons for oligohydramnios is drugs, such as prostaglandin-inhibiting agents. Oligohydramnios caused by indomethacin has some distinctive features. It is dose-related, occurs quickly but is reversible with cessation of the drug [1-3]. We think that our case is a good example to illustrate the features of oligohydramnios caused by indomethacin.

Indomethacin as a prostaglandin-inhibiting agent has been used for many years to prevent preterm labor especially in those cases with polyhydramnios and it is an

Revised manuscript accepted for publication June 10, 2003

alternative therapeutic choice in symptomatic patients with rheumatoid arthritis. In contrast to the generally favorable maternal side-effect profile, the potential for fetal and neonatal complications of indomethacin usage is worrisome. Three principal fetal side-effects of indomethacin have been of concern: oligohydramnios, constriction of the ductus arteriosus, and pulmonary hypertension.

Oligohydramnios associated with indomethacin use is common, dose-related, and reversible, but there is a report of neonatal renal insufficiency and death after prolonged administration [5]. Possible mechanisms of oligohydramnios include effects on fetal urine production, respiratory function, fetal membranes fluid production, and increase in antidiuretic hormones [6]. Goldenberg *et al.* [3] published a case of reversible indomethacin-induced oligohydramnios in a patient with preterm labor. They showed that the severity of oligohydramnios was directly related to the dose of indomethacin. They observed that ten days after discontinuation of indomethacin the amniotic fluid volume was normal. Holmes *et al.* [7] and Locatelli *et al.* [8] observed similar effects of indomethacin on amniotic fluid volume by using cyclooxygenase-2 inhibitor nimesulide in a patient with preterm labor. After using nimesulide for 25 days the amniotic fluid index measured 1.9 cm. With cessation of nimesulide the amniotic fluid index was observed to be above 5 cm. Our findings in a different indication of indomethacin use were similar to the findings of these authors. In our case, the patient had been using indomethacin, 150 mg/day, for 15 days and at the initial evaluation the amniotic fluid volume was nearly consistent with anhydramnios. After exclusion of all possible reasons for oligohydramnios and discontinuation of indomethacin, we observed that the amniotic fluid reaccumulated quickly and the amount increased linearly. On the fourth day the amniotic fluid was normal. Mamopopoulos *et al.* [9] published their experience about maternal indomethacin therapy in the treatment of polyhydramnios. They noticed that the majority of fluid reduction occurred within the first week of treatment. Subsequently, a smaller but steady reduction of fluid had been observed. The oligohydramnios observed as a response to indomethacin appears secondary to prostaglandin inhibition with a reduction in auto-regulation of glomerular filtration, renal blood flow and renin release [10]. Another mechanism proposed includes the enhanced effect of indomethacin on fetal respiratory movements, resulting in an increase in amniotic fluid reabsorption via the lungs [11]. Finally, indomethacin could also act on the fetal membranes, amnion and chorion, which are known to contain large amounts of prostaglandins [11]. The precise mechanism of indomethacin therapy in reducing amniotic fluid is unclear and it is indistinct how long these changes take to occur. Physicians caring for patients taking these medications should check the amniotic fluid index frequently.

Closure of the ductus arteriosus due to maternal indomethacin use appears to be gestational-age depen-

dent. Ductal constriction occurs before formation of prostacyclin and prostaglandin E₂, which maintain ductal vasodilatation. The likelihood of ductal constriction increases after 32 weeks of pregnancy [12]. Prior to 32 weeks, the incidence of ductal constriction is 5 to 10%. At 32 to 35 weeks, the incidence has been shown to increase to 50% after 48 hours of indomethacin exposure. Although potentially serious, ductal constriction is usually transient and responds to discontinuation of the drug. However, persistent ductal and right heart failure that did not reverse after the drug was stopped have been reported [13]. Therefore, indomethacin should be discontinued before 32 weeks' gestation if possible.

Primary pulmonary hypertension in the neonate is a potentially fetal illness that has also been associated with prolonged (more than 48 hours) indomethacin therapy [14]. Primary neonatal pulmonary hypertension has not been reported with 24 to 48 hours of therapy, but the incidence may be as high as 5 to 10% with long-term therapy [15]. In our case oligohydramnios caused by indomethacin was not detrimental to the fetus. Despite the use of indomethacin for more than 48 hours and the therapy being prolonged beyond 32 weeks of gestation, neither closure of the ductus arteriosus nor primary pulmonary hypertension was observed.

Other complications, including necrotizing enterocolitis, small bowel perforation, jaundice and intraventricular hemorrhage have been observed when indomethacin was used outside of the standardized protocols - when the duration of treatment was not limited and/or the drug was employed after 32 weeks [16]. Niebly and Witter [17], Dudley and Hardie [18] and Gartner *et al.* [19] have performed follow-up studies of children treated in utero with indomethacin and did not find significant long-term effects. None of the mentioned neonatal side-effects were observed in our case.

Rheumatoid arthritis is a rare clinical situation where a pregnant patient may use indomethacin. It is an autoimmune disease with a prevalence of approximately 2% and has a predisposition for women in their childbearing ages. However it is occasionally first diagnosed during gestation. With the exception of rheumatoid arthritis, autoimmune diseases are associated with an increased risk of poor pregnancy outcome. Rheumatoid arthritis appears to have no adverse effects on pregnancy. On the contrary pregnancy seems to have some favorable effects on rheumatoid arthritis. Many patients with rheumatoid arthritis have experienced remissions including extra-articular symptoms during pregnancy and most of these patients required no more medication. This remission, however, was short lived with more than 90% of the women relapsing within six to eight months postpartum [20]. Although not the first choice, indomethacin is widely used in those patients whose symptoms persist or worsen during pregnancy and whose symptoms are resistant to salicylates. Our patient did not benefit from the pregnancy as expected and her symptoms still persisted despite salicylates. Therefore she was prescribed indomethacin, but amniotic fluid volume was not monitored.

Our case shows that indomethacin use in a pregnant patient with any indications should be monitored for maternal and fetal adverse effects. The use should not be prolonged beyond the 32nd week of pregnancy. On the other hand while searching for the etiology of oligohydramnios, indomethacin use should also be kept in mind and should be stopped.

References

- [1] Kirshon B., Mari G., Moise K.J.: "Indomethacin therapy in the treatment of symptomatic polyhydramnios". *Obstet. Gynecol.*, 1990, 75, 202.
- [2] Lange I.R., Harman C.R., Ash K.M., Manning F.A., Menticoglou S.: "Twin with hydramnios: Treating premature labor at source". *Obstet. Gynecol.*, 1989, 160, 552.
- [3] Goldenberg R.L., Davis R.O., Baker R.C.: "Indomethacin-induced oligohydramnios". *Am. J. Obstet. Gynecol.*, 1989, 160, 1196.
- [4] Kirshon B., Moise K., Wasserstrum N.: "Influence of short-term indomethacin therapy on fetal urine output". *Obstet. Gynecol.*, 1988, 72, 51.
- [5] Van Der Heijden B.J., Carlus C., Nancy F. *et al.*: "Persistent anuria, neonatal death and renal micro cystic lesions after prenatal exposure to indomethacin". *Am. J. Obstet. Gynecol.*, 1994, 171, 617.
- [6] De Witt W., Von Mourik I., Wiesenhaan P.F.: "Prolonged maternal indomethacin therapy associated with oligohydramnios. Case reports". *Br. J. Obstet. Gynaecol.*, 1988, 95, 303.
- [7] Holmes R.P., Stone P.R.: "Severe oligohydramnios induced by cyclooxygenase-2 inhibitor nimesulide". *Obstet. Gynecol.*, 2000, 96, 810.
- [8] Locatelli A., Vergani P., Bellini P., Strobelt N., Ghidini A.: "Can a cyclo-oxygenase type-2 selective tocolytic agent avoid the fetal side effects of indomethacin?". *Br. J. Obstet. Gynaecol.*, 2001, 108 (3), 325.
- [9] Mamopoulos M., Assimakopoulos E., Reece A., Andreou A., Zheng X.Z., Mantelarakis S.: "Maternal indomethacin therapy of polyhydramnios". *Am. J. Obstet. Gynecol.*, 1990, 162, 1225.
- [10] Clive D., Stoff J.S.: "Renal syndromes associated with non-steroidal anti-inflammatory drugs". *N. Engl. J. Med.*, 1984, 310, 563.
- [11] Cabrol D., Landesman R., Muller J., Uzan M., Sureau C., Saxena B.: "Treatment of polyhydramnios with prostaglandin synthetase inhibitor (indomethacin)". *Am. J. Obstet. Gynecol.*, 1987, 157, 422.
- [12] Moise K.: "Effect of advancing gestational age on the frequency of fetal ductal constriction in association with maternal indomethacin use". *Am. J. Obstet. Gynecol.*, 1994, 168, 1350.
- [13] Mohen D., Newharn J.P., Orsogna L.D.: "Indomethacin for the treatment of polyhydramnios: A case of constriction of the ductus arteriosus". *Aust NZ J. Obstet. Gynecol.*, 1992, 32, 243.
- [14] Manchester D., Margolis H., Sheldon R.: "Possible association between maternal indomethacin therapy and primary pulmonary hypertension of the newborn". *Am. J. Obstet. Gynecol.*, 1976, 126, 467.
- [15] Besinger R.E., Niebly J.R., Keyes W.G. *et al.*: "A randomized comparative trial of indomethacin and ritodrine for the longterm treatment of preterm labor". *Am. J. Obstet. Gynecol.*, 1991, 164, 981.
- [16] Norton M.E., Merrill J., Cooper B.A.B. *et al.*: "Neonatal complications after the administration of indomethacin for preterm labor". *N. Eng. J. Med.*, 1993, 329, 1602.
- [17] Niebly J.R., Witter F.R.: "Neonatal outcome after indomethacin treatment for preterm labor". *Am. J. Obstet. Gynecol.*, 1986, 155, 747.
- [18] Dudley D.K.L., Hardie M.J.: "Fetal and neonatal effects of indomethacin used as a tocolytic agent". *Am. J. Obstet. Gynecol.*, 1985, 151, 181.
- [19] Gardner M., Skelly S., Owen J. *et al.*: "Neonatal complications associated with prenatal use of indomethacin". *Am. J. Obstet. Gynecol.*, 1995, 172, 414.
- [20] Klipple G.L., Cecere F.A.: "Rheumatoid arthritis and pregnancy". *Rheum. Dis. Clin. North. Am.*, 1989, 15, 213.

Address reprint requests to:
S. TOPUZ, M.D.
Erzurum Sitesi, Palandöken sk.
Yazıcı apt. No: 14/1 Daire 4
Altunizade - Istanbul (Turkey)