Fetal anhydramnios following maternal non-steroidal anti-inflammatory drug use in pregnancy

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Abstract

We present a case report of transient fetal anhydramnios following maternal non-steroidal anti-inflammatory drug use in pregnancy. This reduction in liquor volume resolved following cessation of the medication with no obvious ill-effect on neonatal outcome. The case report is followed by a comprehensive summary of the relevant literature.

Keywords

Fetomaternal medicine, ultrasound, drugs (medicines)

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Introduction

We present a case of transient fetal anhydramnios following maternal non-steroidal anti-inflammatory drug (NSAID) use in pregnancy.

Case report

This 33-year-old multiparous woman was cared for in our maternal medicine service due to a background of Sjögren's syndrome. This was diagnosed in 2012, whereupon she was found to be Ro antibody positive. Of note, anti-cardiolipin antibodies and lupus anticoagulant were negative. She also suffered from fibromyalgia with consequent chronic back pain which required a nerve block in this pregnancy.

Ultrasound was performed at 18, 20 and 31 weeks with normal liquor volume recorded. She presented for a growth scan at 32⁺₆, indicated due to her medical history. The fetus was found to be appropriately grown, though no cord free pool of liquor was found. The kidneys appeared ultrasonographically normal with positive end-diastolic flow on umbilical artery Doppler examinations. There was no history of rupture of membranes, and speculum examination with Amnisure ROMTM test was negative. It was then revealed that she had been taking the NSAID mefenamic acid 500 mg tds, prescribed by her dentist three days prior for relief of toothache. This was ceased immediately and a fetal ultrasound examination the following day revealed oligohydramnios (deepest vertical pool 1.4 cm) with some fluid within the urinary bladder. Four days later liquor volume was normal on ultrasound examination, and this remained so at weekly review thereafter.

She laboured spontaneously at 40 weeks' gestation, and membranes were artificially ruptured to accelerate labour. Liquor volume was documented as normal with meconium grade I noted. She delivered a healthy male infant weighing 3.85 kg. Both mother and baby were discharged home well on day two. Baby had normal urine output, and neonatal renal ultrasound was normal.

Discussion

NSAIDs are among the most widely used medications in the world.¹ NSAIDs often form the basis of first-line therapy for numerous conditions that also manifest during pregnancy, with self-medication often practised by pregnant women. A Norwegian prospective cohort study

found that 7.2% of pregnant women in their population used an NSAID during pregnancy.² Patients with rheumatologic disorders or other inflammatory conditions may often continue or initiate NSAID therapy during pregnancy.³ NSAIDs may also be used in the management of women presenting with symptoms and signs suggestive of threatened preterm labour.^{4,5}

NSAIDs cross the placenta and may therefore cause fetal and/or neonatal adverse outcomes. Their effect depends on the particular NSAID used, its dose and duration of treatment, gestational age at administration and the interval between administration and delivery.⁶ In particular, use of indomethacin during the third trimester has been associated with impaired renal function, premature closure of the ductus arteriosus, intracranial haemorrhage and necrotising enterocolitis.⁷

The mechanism by which NSAIDs induce renal dysfunction is likely to be related to their interference with prostaglandin synthesis, by reversibly inhibiting the two major isoforms of the enzyme cyclooxygenase (COX-1 and COX-2).⁸ The blockade of prostaglandin synthesis by NSAIDs and the decreased activation of prostaglandin receptors reduce renal perfusion. This leads to reduction in the production of fetal urine, the main source of amniotic fluid, particularly from the second trimester onwards.

The first reported case of oligohydramnios in association with maternal NSAID use was in 1980 by Cantor et al.⁹ Further individual cases have been reported in the literature with the majority of cases transient and reversible upon cessation of the drug with no deleterious neonatal effects.^{10–12} However, impaired renal function may be manifested as acute renal failure with or without oliguria, chronic renal failure, neonatal proteinuria and hyperkalaemia. Indeed, case reports have documented neonatal renal compromise ranging from transient renal failure^{13,14} to chronic renal dysfunction with persistent anuria.^{15–17} It has been reported that preterm neonates born to mothers who used NSAIDs during pregnancy have a 7.38-fold

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Table 1. Reported cases published to date on effects of non-steroidal anti-inflammatory drugs (NSAIDs) on fetal liquor volume (LV) or renal ultrasound findings.

	Indication	GA (weeks)	NSAID	Duration	Liquor volume	Neonatal outcome
Topuz et al. ¹² (case report)	Rheumatoid arthritis	33	Indomethacin 150 mg	Not documented	Oligohydramnios – Normal LV 4/7 post cessation	Not documented
Fieni et al. ¹³ (case report)	PTL (DCDA twins)	27	Ketoprofene 100 mg bd	72 h	Anhydramnios/morpho- logical renal changes on ultrasound	Renal impairment x3-8/12
Pomeranz et al. ¹⁴ (case report)	PTL (DCDA twins)	32	Indomethacin 100 mg daily	2 weeks	No change in LV	Twin 1: renal impairment x2/12
Alessandri et al. ¹⁵ (case report)	PTL	35	Niflumic acid 750 mg	4 days	Anhydramnios	'transient renal failure'
Phadke et al. ¹⁶ (case series n = 3)	PTL	35 and 36	Diclofenac	Not recorded	Oligohydramnios	Anuric renal failure x3 (x1 NND)
Savage et al. ²² (cohort n = 124)	PTL/asymptomatic cer- vical shortening	16–32	Indomethacin (50–200 mg)	2–112 days (median 30)	Oligohydramnios (9/124)	No long-term renal sequelae
Sandruck et al. ¹⁹ (cohort n = 61)	PTL	27–32	Indomethacin 100 mg stat (then 50 mg 6 h)	48 h	Oligohydramnios (2/61)	Not reported
Locatelli et al. ²⁰ (cohort n = 7)	PTL	21–27	Nimeluside 100 mg bd	5–16 days (median 8)	Oligohydramnios (7/7)	No case of permanent renal damage
Norton et al. ²¹ (case control n = 57)	PTL	25–30	Indomethacin (100–6000 mg)	1–79 days (median 3)	LV not recorded	Transient oliguria/raised creatinine

PTL: preterm labour; DCDA: dichorionic diamniotic twins; NND: neonatal death; GA: gestational age.

higher risk of developing acute renal failure compared to controls.¹⁸ Type, dose and duration of NSAID used varied between these reports.

In the past, NSAIDs were used for management of preterm labour. Cohort studies on individuals using NSAIDs in this setting have revealed conflicting results. Sandruck et al.¹⁹ looked at the effect of short-term indomethacin use on amniotic fluid and concluded that it does not significantly change its volume (two cases of reversible oligohydramnios; 3.3%; 95% CI, 0.03%, 11.3%). Meanwhile, others report reversible oligohydramnios with transient renal failure from the use of both nimeluside and indomethacin.^{20,21} Savage et al.²² reviewed the long-term antenatal use of indomethacin and found a low incidence of oligohydramnios (7.3%) with no association between development of oligohydramnios and dosing regimen, duration of therapy or gestational age at cessation of therapy.²² These findings are summarised in Table 1. A Cochrane review could not adequately assess adverse effects on the fetus due to insufficient data.²³

The case we describe shows a temporal association between the period of mefenamic acid use and the development of anhydramnios, with liquor volume normalising within days of its cessation. No adverse neonatal consequences were observed.

Considering the potential association between NSAIDs and oligohydramnios, obstetricians should monitor amniotic fluid volume regularly in women receiving treatment for prolonged periods. Though rare, long-term consequences of NSAID use do occur, and postnatal liaison with neonatology colleagues is therefore recommended.

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Ethical approval

Verbal consent was obtained from the patient for publication.

Guarantor

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Case report and literature review performed by SC. The remaining authors provided clinical care to the patient and contributed to the editing of the report.

References

1. Singh G. Gastrointestinal complications of prescription and over-the-counter nonsteroidal anti-inflammatory drugs: a view from the ARAMIS database. *Arthritis, Rheumatis and Aging Medical Information System*. *Am J Ther* 2000; 7: 115–121.
2. Nezvalova-Henriksen K, Spigset O and Nordeng H. Effects of ibuprofen, diclofenac, naproxen, and piroxicam on the course of pregnancy and pregnancy outcome: a prospective cohort study. *BJOG* 2013; 120: 948–959.
3. Ostensen M. Drugs in pregnancy. *Rheumatological disorders*. *Best Pract Res Clin Obstet Gynaecol* 2001; 15: 953–969.
4. Loe SM, Sanchez-Ramos L and Kaunitz AM. Assessing the neonatal safety of indomethacin tocolysis: a systematic review with meta-analysis. *Obstet Gynecol* 2005; 106: 173–179.
5. Groom KM, Shennan AH, Jones BA, et al. TOCOX: a randomised, double-blind, placebo-controlled trial of rofecoxib (a COX-2-specific prostaglandin inhibitor) for the prevention of preterm delivery in women at high risk. *BJOG* 2005; 112: 725–730.
6. Cuzzolin L. Drug-related perinatal damage from the pharmacological point of view. *J Pediatr Neonat Individual Med* 2014; 3: e030253.
7. Abou-Ghannam G, Usta IM and Nassar AH. Indomethacin in pregnancy: applications and safety. *Am J Perinatol* 2012; 29: 175–186.
8. Antonucci R, Zaffanello M, Puxeddu E, et al. Use of non-steroidal anti-inflammatory drugs in pregnancy: impact on the fetus and newborn. *Curr Drug Metab* 2012; 13: 474–490.
9. Cantor B, Tyler T, Nelson RM, et al. Oligohydramnios and transient neonatal anuria: a possible association with maternal use of prostaglandin synthetase inhibitors. *J Reprod Med* 1980; 24: 220–223.
10. Shen O, Rabinowitz R, Lavie O, et al. Good fetal outcome following prolonged indomethacin induced anhydramnios. *J Perinat Med* 1995; 23: 233–236.
11. Hickock DE, Hollenbach KA, Reilley SF, et al. The association between decreased amniotic fluid volume and treatment with non-steroidal anti-inflammatory agents for preterm labor. *Am J Obstet Gynecol* 1989; 160: 1525–1530.
12. Topuz S, Has R, Ermis H, et al. Acute severe reversible oligohydramnios induced by indomethacin in a patient with rheumatoid arthritis: a case report and review of the literature. *Clin Exp Obstet Gynecol* 2004; 31: 70–72.
13. Fieni S, Gramellini D and Vadora E. Oligohydramnios and fetal renal sonographic appearances related to prostaglandin synthetase inhibitors. A case report. *Fetal Diagn Ther* 2004; 19: 224–227.
14. Pomeranz A, Korzets Z, Dolfen Z, et al. Acute renal failure in the neonate induced by the administration of indomethacin as a tocolytic agent. *Nephrol Dial Transplant* 1996; 11: 1139–1141.
15. Alessandri JL, Abossolo T, Reynaud I, et al. Non-steroidal anti-inflammatory agents and pregnancy. A study of renal and digestive toxicity of niflumic acid in the perinatal period. *J Gynecol Obstet Biol Reprod* 1994; 23: 813–818.
16. Phadke V, Bhardwaj S, Sahoo B, et al. Maternal ingestion of diclofenac leading to renal failure in newborns. *Pediatr Nephrol* 2012; 27: 1033–1036.
17. Van der Heijden BJ, Carlus C, Narcy F, et al. Persistent anuria, neonatal death and renal microcystic lesions after prenatal exposure to indomethacin. *Am J Obstet Gynecol* 1994; 171: 617–623.
18. Cuzzolin L, Fanos V, Pinna B, et al. Postnatal renal function in preterm newborns: a role of diseases, drugs and therapeutic interventions. *Pediatr Nephrol* 2006; 21: 931–938.
19. Sandruck JC, Grobman WA and Gerber SE. The effect of short-term indomethacin therapy on amniotic fluid volume. *Am J Obstet Gynaecol* 2005; 192: 1443–1445.
20. Locatelli A, Vergani P, Bellini P, et al. Can a cyclo-oxygenase type-2 selective tocolytic agent avoid the fetal side effects of indomethacin. *BJOG* 2001; 108: 325–326.
21. Norton ME, Merrill J, Cooper BA, et al. Neonatal complications after the administration of indomethacin for preterm labor. *New Engl J Med* 1993; 329: 1602–1607.
22. Savage NH, Anderson BL and Simhan HN. The safety of prolonged indomethacin therapy. *Am J Perinatol* 2007; 24: 207–213.
23. King JF, Flenady V, Cole S, et al. Cyclo-oxygenase (COX) inhibitors for treating preterm labour. *Cochrane Database Syst Rev* 2005; Issue 2. Art. No.: CD001992. DOI: 10.1002/14651858.CD001992.pub2.