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Iatrogenic Adverse Fetal Events – A Clinical Sequelae of Nimesulide use in Third Trimester of Pregnancy. Review of Literature along with Case Report

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Abstract: ***Objective: To describe clinical consequences after maternal intake of nimesulide, a nonsteroidal anti-inflammatory (NSAID'S) drug which is selective cyclo-oxygenase (COX) type-2 inhibitor. Methods: Case Report. Results: Reviewing clinical history of a mother who presented with ultrasonographic scan showing oligohydromnios (AFI ~ 3- 4) at 34 weeks 2 days of gestation, history revealed intake of tablet nimesulide for lower backache. On evaluation, fetal echocardiogram showed restrictive flow pattern in ductus arteriosus. Fetal surveillance by Non stress test showed abnormal fetal heart rate recording with baseline fetal tachycardia (~ 180 beats per minute) at 35weeks 2 days of gestation and biophysical profile was poor (=2) which nesseciated urgent abdominal delivery. Neonatal echocardiogram on third day of life was normal. Conclusion: Adverse fetal events observed in this case like oligohydromnios, premature ductal constriction with restrictive flow pattern, abnormalities in fetal heart rate trace denotes clinical sequelae of maternal nimesulide use, which were avoidable by spreading awareness regarding use of analgesic drugs in pregnancy.***

Keywords: Nimesulide. Oligohydromnios. Fetal heart rate. Ductal arteriosus. Adverse fetal events. Premature ductal constriction

1. Introduction

Cyclo-oxygenase (COX) exists in two isoforms. COX-1 which is considered a house keeping gene, is constitutively expressed wherever prostaglandin synthesis remains contant, whereas COX-2, a inducible form associated with inflammation, is expressed in fetal and adult kidneys of all species examined [1 –7]. Both isoforms were demonstrated in chorion-decidua and amnion at term gestation [1]. Nonsteroidal anti-inflammatory (NSAID'S) drugs which are routinely used as analgesics act by inhibiting cyclo-oxygenase enzymes. These are commonly bought analgesic tablets from medical stores in many countries even without a proper medical prescription. Use of NSAID'S in later half of pregnancy has been reported to cause adverse fetal outcomes like premature closure of Ductus arteriosus, pulmonary hypertension, oliguria leading to oligohydromnios, renal dysgenesis etc [8-12]. Renal abnormalities are peculiar when NSAID'S were admistered before 32nd week of gestation [13, 14]. These effects were not only restricted to the use of indomethacin which was used as a tocolytic agent but was also reported by inadvertent prescription of other NSAID'S like diclofenac and Nimesulide during the latter stages of pregnancy, one of which the effect of nimesulide is exemplified in this case [9, 15-17].

2. Case Report

A 26 year old woman, gravida 2 para 1, had her first visit with us at 34 weeks 4 days period of gestation with ultrasonography report documenting oligohydromnios with amniotic fliud index of 3-4. Her blood pressure records were normal and daily fetal movement count was adequate. Her previous pregnancy was uneventful and a male infant of 3200grams was delivered by caesarean section, done in view of non progression of labor at term gestation. Her index pregnancy was booked supervised at a regional private hospital and antenatal scans done at 18 weeks and 27 weeks period of gestation demonstrated normal fetal growth with no obvious gross congenital malformations and adequate liquor. As she was having abdominal overdistention, a scan done at 32 weeks 5 days period of gestation demonstrated polyhydromnios with amniotic fliud index of ~ 25-26 with normal fetal growth and no gross congenital malformations. A repeat scan done after 2 weeks showed oligohydromnios. On detail review of her history, blood sugars done at 24 weeks and blood pressure records were normal. There was no history of leaking per vagina or fever. On taking drug history, she revealed taking nimesulide tablets 50mg, for her backache for almost 8 days, which were inadvertently prescribed by local Registered Medical Practioner (RMP) and the repeat scan demonstrated oligohydromnios, which was done 6 days after last intake of nimesulide tablet. After admission her blood sugars were retested and she was diagnosed to have gestational diabetes with impaired fasting blood sugar values. She was started on diabetic diet. Fetal umbilical artery doppler study done was normal. Fetal echo done at 34 weeks 6 days period of gestation showed restrictive flow in ductus arteriosus. Daily fetal movement count was adequate and daily Non stress test was reassuring, until 35weeks 2 days of gestation, when it showed abnormal fetal heart rate recording with baseline fetal tachycardia (~ 180 beats per minute), with moderate baseline variability and no accelerations with fetal movements which were decreased. Patient was not in labor, there was no scar tenderness and her pulse and temperature were normal. On

performing biophysical profile there were sluggish fetal movements with no measurable cord free liquor pocket (B.P.P=2), indicating certain fetal asphyxia [18, 19]. Patient and her husband were counselled the necessity of urgent abdominal delivery in view of fetal distress. Intraoperative liquor was found to be minimal without any evidence of meconium. A male infant weighing 2300gms was delivered by emergency caesarean section, with Apgar scores of 7 and 9 at 1 and 5 min, with no pulmonary or cardiac complications. On pathological examination of placenta, neither signs of vascular disease nor signs of infection or abruption were noted. A neonatal echocardiogram done at 3 days of life demonstrated a structurally normal heart, with closure of ductus arteriosus and no evidence of pulmonary hypertension. Baby is doing well on routine follow-up.

3. Discussion

We are presenting a case of continuum of adverse fetal events - iatrogenic severe oligihydromnios, premature constriction of ductus arteriosus, fetal heart rate abnormalities, from inadvertent prescription of nimesulide as an analgesic, denoting sequelae of its use in third trimester of pregnancy. Initial polyhydromnios of our patient can be explainable by undiagnosed gestational diabetes mellitus.

Nimesulide (N-(4-nitro-2-phenoxyphenyl)-methane-sulphonilamide), is a nonsteriodal anti inflammatory drug, displays 30-100 fold selectivity for COX-2 compared with COX-1 [20, 21]. We carried out a MEDLINE search (January 1980 through August 2018) confined to English language and with key words nimesulide, ductal arteriosus, oligohydromnios, fetal heart rate and found no relative association of all entities together, as observed in our case. In a article by *Paladini et. Al*, reported cases of severe ductal constriction following maternal self medication of nimesulide, fetal echocardiographic changes were evident following fetal heart rate changes in 3 patients [9]. *Federico et Al*, reported a case where acute premature constriction of ductus arteriosus was diagonised by fetal echo, which was done in view of abnormatalities in fetal heart rate trace [22]. In both the above articles, there was no existence of severe oligohydromnios. Few case reports of severe oligohydromnios as a lone clinical presentation, post nimesulide maternal ingestion were reported [10].

As known COX type-2 enzyme is fundamental for nephrogenesis, and is upregulated on fetal membranes and myometrium at parturition, maternal nimesulide use can lead to its inhibition attributing to fetal renal abnormalities [11, 12].

Prostaglandin E(2) relaxes smooth muscle and tends to inhibit the closure of ductus arteriosus. Its premature constriction / closure is a well known effect of maternal indomethacin ingestion which is a potent inhibitor of prostaglandin E(2) production by human foetal membranes [15, 16]. This action is also shown by nimesulide as evident from our case and certain other studies [9, 22].

Although few consider COX-2 inhibitors relatively safe in late second and early third trimester as tocolytics [23, 24], it is beneficial to memorise, even those selective for COX type 2 inhibition such as nimesulide, is associated with risk of cardiopulmonary toxicity (premature closure of ductus arteriosus, pulmonary hypertension), renal dysfunction which may progress to renal insufficiency with oligohydrmnios etc [9, 10, 12, 22].

Considering safety of nimesulide there are controversies regarding its use not only in pregnancy but also in nonpregnant adults [10, 25]. Even though the drug is contraindicated in pregnancy and children under 12 years of age, it is been sold over –the- counter in many countries even without any medical prescription.

4. Conclusion

In women who have been taking analgesics, we suggest continuous maternal and fetal surveillance, as done in our case, for early detection of fetal distress and timely intervention henceforth avoiding further complications and for optimum outcome. The present case emphasizes the need to strengthen our healthcare practices at peripheral level, since many cases were treated by local RMP's without adequete knowledge about the drugs given in pregnancy. It is important to educate rural women to make use of government services that are available at Primary Health Centre, Rural Health Centre, Community Health Centre for better antenatal care. All practising doctors, obstetricians should judiciously use analgesics in pregnancy and they should be aware of the adverse effects of drugs.

5. Declaration

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Ethical approval: Not required

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