

## IDIOPATHIC: PRENATAL CLOSURE OF THE DUCTUS ARTERIOSUS CAUSING FETAL HYDROPS

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### Abstract

Spontaneous premature closure of the human fetal ductus arteriosus is an uncommon event that often results in significant morbidity and mortality. We present a case of a neonate with prenatal previously not detected intrauterine closure of the ductus arteriosus in a 21-year-old, G3P1A2L1 mother with type 2 consanguinity at 39 weeks of gestation, with previous scans showing placenta previa grade 1 at 21weeks and Doppler study showing pericardial effusion at 36weeks. Caesarean section was performed in view of absent progression of labour. A male newborn weighing 4100gm, required bag and mask and intubation. With an excellent neonatal outcome. Finally we suggest that fetal echo in third trimester & maternal education programs to avoid self-medication and provide training for good diet is necessary.

### Introduction

Intrauterine ductus arteriosus closure is a rare occurrence which has not been fully explored. It is usually hard to diagnose<sup>1</sup> and both its incidence and prognosis are unknown<sup>2</sup>. Prostaglandin inhibitors such as indomethacin are effective tocolytic agents and may be used to prevent premature labor<sup>3</sup>. However, it is well established that indomethacin can cause premature constriction and can lead to closure of the fetal ductus arteriosus<sup>4</sup>. This can lead to serious fetal and neonatal complications including hydrops fetalis, oligohydramnios, hyperbilirubinemia, pulmonary hypertension, necrotizing enterocolitis and intraventricular hemorrhage<sup>5,6</sup>. Recent data based on serial fetal echocardiography suggest that about 50% of all fetuses whose mothers are undergoing indomethacin treatment for preterm labor develop constriction of the ductus arteriosus, with the proportion of ductal constriction after 34 weeks of gestation increasing exponentially<sup>7,8</sup>. With the advent of new oxytocin antagonist tocolytics it is still very open to debate whether the benefits of indomethacin treatment at <32 weeks of gestation outweigh the potential risks<sup>9</sup>. Diclofenac is a non-steroidal antiphlogistic drug closely related to indomethacin. Diclofenac forms part of many prescriptions that are commonly – and in some cases uncritically – used for pain relief. Until now, there has been little evidence regarding the side effects of diclofenac ingestion during pregnancy.

To the best of our knowledge this is the first case of complete mature intrauterine closure of the ductus arteriosus, most likely idiopathic in nature, following

mother on enoxaparin for 6months in view of history of two medical termination of pregnancy at three and half months and five months with regular followup to doctor without any other significant medication.

### Case Presentation

The male newborn was 55 cms long, HC is 37.5cms, AG is 40.5cms, and weighed 4100 grams. Immediately after the birth, baby was limp, blue and frail, with no respiration or cardiac output. The infant was stimulated and his mouth and nose were cleared. He was also provided with AMBU bag and mask ventilation with chest compression. Then infant was orally intubated and bag and tube ventilation was continued. Adrenaline was injected into the umbilical vein and the infant's heart started beating; the initial heart rate was 100 beats per minute and later it was > 120-140 beats per minute. With assisted ventilation, the infant turned pink and started responding to stimuli. APGAR was 2,5 and 9 at 1,5 and 10mins respectively. His finger was probed in and his life parameters were assessed– the oxygen saturation was 70%->86%->93-95%, HR 140-149', RR 77 and the temperature is 96°F. As the baby's condition was serious, he was transported to tertiary centre (Masai Children's Hospital in Kolhapur).

Infant was hospitalised in the Neonatal Intensive Care Unit, where the mechanical ventilation was continued. The baby had peripheral edema. On auscultation of lungs, noticed decreased breath sounds in bilateral lower lobes. The heart rate was 120-130 beats per minute, while the respiratory rate was 70 breaths/min. The saturation was between 85% and 88 % (the values were comparable on all four limbs).Chest x-ray was done which showed bilateral

pleural effusion. Then echocardiogram performed with in 4 hours, showed pericardial effusion with patent foramen ovale with ballotable valvula foraminis ovalis with right to left flow, the right atrium enlarged with normal valves, severe tricuspid regurgitation, moderate mitral regurgitation and right ventricle with abnormal hypertrophic muscularis without acceleration of blood flow. No detectable flow was shown at the ductus arteriosus.

The baby needed catecholamines and was treated with Furosemide. Baseline investigations along with blood culture was sent and first line antibiotics were started. On the second day of his life, 24 hrs investigations (CRP, I.Ca<sup>2+</sup>, Sr.bili) along with LFT and coagulation profile was sent, which showed raised SGOT and SGPT along with deranged coagulopathy. Fresh frozen plasma transfusion was given. When his general condition improved, inotropes and ventilation were gradually weaned and stopped on 4 day of his life, then he was taken on CPAP followed by cyclical CPAP for next 36hrs and gradually on low flow nasal device and off oxygen on next 24hours and simultaneously feeds were increased gradually. Follow up echocardiogram showed a considerable improvement in comparison to the echo performed on the day one of the infant's life. ASD/PFO with left-to right shunt had no features of pulmonary hypertension, persistent right ventricular hypertrophy was identified – the right ventricle wall was 4.5mm (n=1,4-3,6mm), dyskinetic movements of the Interventricular septum were also identified. An ECG revealed regular sinus rhythm, right axis deviation and some features of right ventricular hypertrophy. General condition being good, the baby was shifted to mother side and discharged. Baby weight at the time of discharge is 3384 grams. The final diagnosis is a cardiovascular disorder which begun in the prenatal period i.e., premature ductus arteriosus closure causing fetal hydrops.

On regular followups currently baby is developing normally and being active and cheerful.

### Discussion

*In utero*, closure of the fetal ductus arteriosus can occur spontaneously, but it is mostly caused by pharmacological agents. Embryologically, the ductus arteriosus forms from the sixth aortic arch. During embryonic development, this connection forms between the first portion of the pulmonary artery and isthmus of aorta, where the aortic isthmus turns into the descending aorta. The function of the ductus arteriosus is to incorporate the output of the right ventricle into the systemic circulation instead of the lungs, which are inactive in this period of life. PDA closure begins with progressive constriction of the vessel walls, which initially leads to very high flow velocities from the

pulmonary trunk towards the descending aorta, which can be measured on Doppler ultrasound.<sup>10</sup>

The most widely described drug, indomethacin will cause immediate constriction and possibly closure; in others the ductus can remain open despite repeated doses.<sup>11</sup> Now-a-days, events of idiopathic DA constriction or closure are attributed to maternal consumption of PP-rich foods in the late stages of pregnancy. The biological activity of PP is related to anti-inflammatory and antioxidant effects, which interfere with prostaglandin metabolism.<sup>12-17</sup> Chocolate and Mediterranean fruits and vegetables are rich in (epi) catechins, (epi)gallic catechins, (pro)anthocyanins, and other flavonoids, which are even more potent than indomethacin.<sup>13,14</sup> Several other pharmacological agents have been known to cause ductal constriction; for example, betamethasone, applied to enhance fetal lung maturation, can cause transient reversible ductal constriction<sup>18</sup>.

In cases of severe constriction or complete closure, the ductus arteriosus can no longer serve as a conduit of right ventricular outflow into the descending aorta and a much higher volume of blood will be directed towards the pulmonary arteries, which will lead to pulmonary hypertension. Ductal closure can lead to dilatation of the right ventricle, tricuspid insufficiency and potentially development of fetal hydrops and fetal death. It has been argued that the pronounced difference in effect, in one case<sup>19</sup> even observed in twins in which one infant suffered from ductal closure and the other's ductus remained open, is caused by different pathways of breakdown of the drug: by deacetylation or by demethylation.<sup>20</sup> In some cases ductal closure can be reversed by withdrawing the inciting agent. Studies have demonstrated that dilatatory prostaglandins such as prostaglandin E are necessary to maintain the patency of the ductus arteriosus *in utero*<sup>21,22</sup>. Momma *et al.* demonstrated that by application of non-steroidal anti-inflammatory drugs (NSAIDs) the active process of maintaining the ductus arteriosus patency *in utero* could be interrupted and a constriction and/or closure can be promoted<sup>23</sup>. Diclofenac is an NSAID and acts by inhibiting cyclooxygenase, an enzyme that metabolizes arachidonic acid in the formation of prostaglandins<sup>24</sup>. Diclofenac (Voltaren) is frequently used as a painkiller; however, to the best of our knowledge, prenatal diagnosis of premature *in utero* closure of the ductus arteriosus following diclofenac treatment has not been reported to date. Though most reports deal with indomethacin, there has been some evidence to show that diclofenac – which as an NSAID acts in a very similar way – can have a similar effect on the fetal ductus arteriosus. In a recent report, over-the-counter NSAIDs, nimesulide and acetaminophen, were shown to cause ductal closure in a fetus<sup>25</sup>. Rein *et al.* reported a case of constriction of the fetal ductus arteriosus following maternal treatment with diclofenac

for back pain at 36 weeks of gestation that was diagnosed by fetal echocardiography<sup>26</sup>.

There are a few more case reports describing closure of the ductus arteriosus following maternal treatment with diclofenac diagnosed retrospectively by echocardiography of the neonates<sup>27-29</sup>. Thus the diagnosis of premature closure of the ductus arteriosus *in utero* could be established only by the postnatal findings. There are several reports on spontaneous constriction and closure of the ductus arteriosus *in utero*<sup>30-31</sup>.

It is very difficult for doctors to suspect premature ductus arteriosus closure; it is even impossible to detect it by means of routine ultrasound examinations. This is why it seems to be essential to perform echocardiogram tests during the third trimester (if the results of the earlier ultrasound heart imaging were normal) in the case of abnormal images of the infant's four heart cavities, which Prof. Maria Respondek-Liberska emphasises in her numerous publications. Ultrasound echocardiogram imaging is dominated by cardiomegaly, dilated pulmonary artery, tricuspid regurgitation and pulmonary valve regurgitation, lack of detectable flow through the ductus arteriosus and sometimes hydrops fetalis.

## SUMMARY

The article presents the case of a neonatal ductus arteriosus closure detected in the postnatal period. The importance of performing a foetal echocardiogram in any abnormal ultrasound imaging of the four heart cavities must be emphasised. In the presented case, our attention was also drawn towards early closure of ductus arteriosus (in less than 4hrs), which are often described while discussing prenatal ductus arteriosus closure.

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