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Mini Review

PREMATURE CONSTRICTION OF FETAL DUCTUS ARTERIOSUS: ROLE OF MATERNAL INTAKE OF NON-STEROIDAL ANTI-INFLAMMATORY DRUGS (NSAIDS) AND POLYPHENOL-RICH FOODS

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ABSTRACT

The fetal ductus arteriosus is essential for fetal circulatory integrity. This crucial shunt is maintained patent by intriguing interplay of dilating and constricting mechanisms involving the production of prostaglandins, endothelial nitric oxide, elevated pulmonary arterial pressure secondary to closed lungs and constricted pulmonary arterioles. Premature constriction/closure of fetal ductus arteriosus exerts profound impacts on cardiac hemodynamics constituting a life-threatening situation and may result in intrauterine fetal demise. In this brief article, we review the clinical manifestation and echocardiographic features of premature constriction of fetal ductus arteriosus as well as discuss the most common causes of this pathological condition including maternal use of NSADs, polyphenol-rich foods.

Keywords: Ductus arteriosus; Premature constriction of fetal ductus arteriosus; Polyphenol-rich food; NSAIDs; Echocardiography

INTRODUCTION

The fetal circulation is strikingly different from adult mammalian circulation where there is virtually no mixture of deoxygenated and oxygenated blood (Mott JC, 1982). For a normal fetal circulation there must be three functional shunts namely the ductus venosus, the foramen ovale and the ductus arteriosus (DA). The DA is a large channel found normally in all

mammalian fetuses, connecting the main pulmonary trunk to the descending aorta (Gournay V, 2011). This is one of the most essential vessels of a normal fetus allowing 55% of combined cardiac output to supply the lower half of fetal body (Gournay V, 2011 and Weichert J, *et al.*, 2010). The ductus arteriosus is kept patent during fetal life by complex process regulated by both dilating and constrictive factors (Weichert J, *et al.*, 2010). Soon after birth, it is functionally closed by reversible constriction and would anatomically close within weeks to months by the active proliferation of tunica intima (Coceani F, *et al.*, 2012).

Premature constriction of fetal ductus arteriosus due to a variety of intrinsic and more importantly extrinsic causes can lead to potential noxious effects on fetal circulatory integrity and may threaten fetal viability (Zielinsky P, 2014). Severe premature constriction of the fetal DA leads to an acute increase of right ventricular afterload, pulmonary arterial hypertension, increased right ventricular pressure, right ventricular systolic dysfunction, severe tricuspid regurgitation, dilated right atrium of the fetus, lethal respiratory failure in newborns (Gewillig M, *et al.*, 2009; Hofstadler G, *et al.*, 1996 and Mielke G, *et al.*, 1998). With the phenomenal advancements in prenatal ultrasound technology, fetal echocardiography has become the most important noninvasive method in early diagnosis of premature constriction of fetal DA and its dangerous consequences (Weichert J, *et al.*, 2010 and Chao RC, 1993). With this performant technique, more and more cases of premature constriction of fetal DA have been diagnosis as well as more external substances have been identified as triggers or facilitators of this dangerous phenomenon (Weichert J, *et al.*, 2010; Zielinsky P, 2014 and Gewillig M, *et al.*, 2009). This mini review will discuss briefly about the normal regulation of fetal DA, the role of maternal intake of non-steroidal anti-inflammatory drugs or polyphenol-rich foods as initial causes of premature constriction of fetal DA.

Regulation of fetal ductus arteriosus patency

In normal cardiovascular organogenesis the ductus arteriosus originates from distal portion of the left sixth primitive aortic arch. In a normal fetal circulation, the right ventricle pumps approximately 65% of combined cardiac output. However, due to the high pulmonary vascular resistance, only 12% of right ventricular output enters the pulmonary circulation and the remaining 88% (approximately 55% of combined cardiac output) crossing the DA into

the descending aorta (Gournay V, 2011 and Weichert J, *et al.*, 2010). Hence, the DA is a vital component of the fetal circulation.

The microscopic structure of the DA is significantly different from that of the adjacent pulmonary arteries or aorta. The media of the DA is composed of longitudinal and spiral layers of smooth muscle fibers within concentric layers of elastic tissue (Gournay V, 2011; Clyman RI, *et al.*, 2001 and Richard C, *et al.*, 2004). The intima of the DA is irregular and thick composed of smooth muscle and endothelial cells (Clyman RI, *et al.*, 1998). The smooth muscle cells of DA are oxygen-sensitive, whereas the endothelium releases vasoactive substances such endothelin and nitric oxide in modulating DA tone (Hamrick SEG, *et al.*, 2010). Contraction of DA smooth muscle cells results in narrowing of the lumen and shortening of the DA (Gournay V, 2011). Patency of fetal DA is regulated by low oxygen tension and some prostanoids, predominantly prostaglandin E2 (PGE_2) and prostacyclin (PGI_2). PGE_2 and PGI_2 levels are high in the fetus because of both placental production and diminished clearance by the fetal lungs (Schneider DJ, *et al.*, 2006). In addition, the high vascular pressure within the ductal lumen secondary to the elevated pulmonary vascular resistance is essential in preventing the DA from closing (Weichert J, *et al.*, 2010).

Premature constriction of the ductus arteriosus may occur during fetal life and can have profound and diversified effects on fetal pulmonary circulation and the right heart. This used to be considered be rare phenomenon (Gewillig M, *et al.*, 2009). The first report on constriction of DA was in a newborn, whose mother treated with isoniazid and streptomycin, presented with tricuspid insufficiency, severe heart failure and acidosis at birth and the DA was confirmed to be closed (Arcilla RA, *et al.*, 1969). The accurate incidence of premature constriction of fetal DA is still unknown. However, in the era of fetal echocardiography, increasing number of publications addressing this issue suggest the true incidence may be far underestimated. Echocardiographic features of progressive ductal constriction in the fetus comprise severe right heart dilation, significant right ventricular myocardial hypertrophy, tricuspid regurgitation with increased peak velocities, increased systolic and diastolic velocities of ductal flow, decreased pulsatility index, reversed end-diastolic ductus venosus flow (Gewillig M, *et al.*, 2009; Sridharan S, *et al.*, 2009 and Hayes DA, 2016).

Premature constriction of fetal DA can be idiopathic (Enzensberger C, *et al.*, 2012) or may occur in context of congenital heart disease such as d-transposition of great arteries partially due to abnormally higher oxygen concentration in blood crossing the DA which can be lethal if the foramen ovale is restrictive (Maeno YV, *et al.*, 1999). The most common causes of premature constriction of fetal DA are the maternal use of non-steroidal anti-inflammatory drugs (NSAIDs) and polyphenol-rich foods and/or beverages (Zielinsky P, 2014).

Role of maternal intake of NSAIDs and polyphenol-rich foods

As previously mentioned, prostaglandins, whose production is dependent of two enzymes which act in different states, cyclooxygenase-1 (COX-1) and cyclo-oxygenase-2 (COX-2) are potent dilators that keep the fetal DA patent. NSAIDs inhibit cyclooxygenases and consequently decrease endogenous prostaglandins (Momma K, *et al.*, 1987). The first reports in 1979 by Wilkinson *et al.* describing persistent pulmonary hypertension and abnormal prostaglandin levels in preterm infants after maternal treatment with naproxen (Wilkinson AR, *et al.*, 1979) might be attributed to premature constriction of fetal DA. In 1983, Momma *et al.*, conducted an experiment testing 24 different NSAIDs and demonstrated that all sixteen acidic NSAIDs but only two out of the eight basic NSAIDs constricted the fetal ductus in a dose-dependent relationship in rats (Momma K, *et al.*, 1983).

Among NSAIDs, indomethacin may be the most well-known drug that causes premature constriction of fetal DA. The fetal DA may start to constrict only few hours after maternal ingestion of indomethacin and the constriction may revert after few hours or last for weeks. The ductal sensitivity to indomethacin increases with gestational age (Zielinsky P, 2014). Beside indomethacin, a variety of other NSAIDs including diclofenac (Rein AJ, *et al.*, 1999), aspirin (Sharpe GL, *et al.*, 1975 and Schiessl B, *et al.*, 2005), metamizole, ibuprofen (Schiessl B, *et al.*, 2005), dipyrone, fluoxetine, nimesulide, piroxicam, and cetoprofen (Lopes LM, *et al.*, 216) have been identified as culprits. Rofecoxib, an elective cyclooxygenase-2 inhibitor has also shown a constrictive ductal effect on rat fetuses. The combined administration of dexamethasone and rofecoxib caused severe constriction of fetal DA (Takami T, *et al.*, 2005). Sulindac, a prostaglandin inhibitor drug utilized in premature labor, was confirmed to have a mild and transient constriction fetal DA (Momma K, *et al.*, 1989). Of note, the effect on

constriction of NSAIDs seems to be synergistically augmented by dexamethasone (Takami T, *et al.,* 2005 and Momma K, *et al.,* 1989). In a single referral center experience over a period of 26 years, the Brazilian authors reported 45 consecutive cases of premature constriction/closure of fetal DA from 26,000 referrals for fetal echocardiography. 29/45 cases (64.4%) were associated with maternal ingestion of single or multiple doses of NSAIDs (Lopes LM, *et al.,* 2016). In a meta-analysis evaluating the constrictive effect of fetal DA in third trimester of pregnancy, it was demonstrated that the risk of ductal closure was 15-fold higher in the group of women exposed to NSAIDs compared with those receiving placebo (Koren G, *et al.*, 2006). This finding was of clinical importance, because of the widespread use of indomethacin and its transplacental distribution, applied to the mother for the treatment of premature labor. A baseline echocardiography should be performed prior to indomethacin administration (Weichert J, *et al.*, 2010).

An interesting question then is raised: Is the any situation where the premature constriction of fetal DA might render beneficial? To our best knowledge, only when hydrops fetalis occurs in a fetus suffering severe Ebstein's anomaly of tricuspid valve with circular shunt physiology, the constriction of fetal DA would have beneficial effect. In this specular situation, the diminutive and malfunctioning right ventricle is unable to pump blood through the pulmonic valve due to severe tricuspid regurgitation and higher pulmonary arterial pressure caused by abnormally retrograde blood flow from aorta through the ductus arteriosus. This pressure is higher than systolic pressure generated by the already weakened right ventricle leading continuous pulmonary regurgitation. Constriction/closure of fetal DA triggered by NSADs (indomethacin) would reduce the retrograde blood flow, lower pulmonary arterial pressure, and stop pulmonary regurgitation. The right ventricle then can pump blood it receives to pulmonary arteries and cut the circular shunt. Unfortunately, the trial has been just started with initial positive results but no data have been published.

Besides NSAIDs, a variety of substances contained in teas or herbs have recently been identified to exert premature constriction on the fetal DA. Administration of herbal teas to pregnant ewes has been reported to cause ductal closure in fetal lambs (Zielinsky P, et al., 2007). In 2009, Sridharan *et al.,* reported two cases of premature constriction of fetal DA associated with the maternal consumption of camomile tea (made from the leaves of the

Camellia sinensis plant). In the first case, the constriction was reverted after discontinuation of camomile tea intake. In the second case, patient underwent delivery by Caesarian section in the same day with good neonatal outcome (Sridharan S, et al., 2009). Hayes presented a case of premature constriction of fetal DA with severe right ventricular hypertension and a right ventricular aneurysm associated with prolonged maternal use of polyphenol-rich preparation as topical treatment for striae gravidarum (Hayes DA, *et al.*, 2016). Interestingly, Rakha in 2017 reported a case of premature constriction of fetal DA due to a high maternal ingestion of fresh orange which was totally reversed 2 weeks after eliminating oranges from the maternal diet (Rakha S, 2017). The proposed mechanism of premature constriction of fetal DA is cyclooxygenase-2 and prostaglandin inhibition by polyphenols in herbal tea (Zielinsky P, 2014). Several thousand molecules having a polyphenol structure (i.e, several hydroxyl groups on aromatic rings) have been identified in higher plants, and several hundred are found in edible plants (Manach C, *et al.*, 2004). The principal alimentary sources with higher concentration in polyphenols are herbal teas, mate tea, dark chocolate, fruits, natural juices, vegetables, olive and soy oils and red wine (Zielinsky P, 2014). Given the fact that herbal tea, especially *Camellia sinensis* leaf tea which has been widely used in Asia and are expanded to other parts of the world secondary to the increased interest in its antioxidant effect (Manach C, *et al.*, 2004), there might be more cases of premature constriction on the fetal DA reported in future. Some authors even suggested that a conclusive dietary orientation for pregnant women is warranted (Weichert J, *et al.*, 2010).

Until present, the incidence of premature constriction of fetal DA seems to be low ranging from 0,17% to 1,3% of all referred fetal echocardiographic examminations (Gewillig M, *et al.*, 2009 and Lopes LM, *et al.*, 2016). The most important causes are maternal intake of NSAIDs and polyphenol-rich foods. However, in a systemic analysis of 45 cases, other substances were also involved. These included maternal use of nasal vasoconstrictor, caffeine, isoxsuprine, scopolamine and fluoxetine, exposure to a home pest control agent (Lopes LM, *et al.*, 2016). With the rapid advancements in ultrasound technology as well as standardized guidelines of prenatal ultrasound and increased awareness of premature constriction of fetal DA, we would predict that more and more cases will be reported and more causative substances identified.

CONCLUSION

The patency of fetal ductus arteriosus is essential for fetal circulatory integrity. This vital connecting vessel is kept patent by intriguing interplay of dilating and constricting mechanisms involving the production of prostaglandins, endothelial nitric oxide, elevated pulmonary arterial pressure secondary to closed lungs and constricted pulmonary arterioles. Premature constriction/closure of fetal DA exerts profound impacts on cardiac hemodynamics constituting a life-threatening situation and may result in intrauterine fetal demise. The most common causes of this pathological condition are maternal use of NSADs, polyphenol-rich foods although other substances have been sporadically reported. The rapid development and standardization in prenatal diagnosis, the refinement of ultrasound technology as well as the increased awareness of premature constriction of fetal DA as a potentially lethal process will definitely contribute to early detection, appropriate management well as identification of more causative factors.

ABBREVIATIONS

DA: Ductus Arteriosus; NSAIDs: Non-steroidal Anti-inflammatory Drugs

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