Editorial

Dextro-transposition of great vessels: difficult to detect prenatally, one of the most dangerous and one of the best prognosed

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Epidemiology

Dextro-transposition of the great arteries (d-TGA) states about 5–7% of all congenital heart diseases (CHD), 2–3 times more in boys, approximately about 20–30 cases per 100,000 live birth and could be also detected in twin pregnancies (1-4). The difference in prevalence varies between countries and regions between 10 to 47 cases per 10,000 births (5). The explanation of these differences might be lack of the proper data, probably from the cases which were not detected prenatally and postnatally.

D-TGA is a ductus arteriosus (DA) dependence malformation and it is also dependent from foramen ovale (FO). It means that without these two fetal cardiovascular connections a newborn very quickly after delivery becomes hypoxemic and acidotic. Routine intakes of intravenous prostaglandin E1 (PGE) to keep arterial ductal open are mandatory and possible in all centers; but emergency Raskind procedure [balloon atrial septostomy (BAS)] in the case of closed or restricted FO is also a crucial procedure to improve neonatal oxygenation and prevent preoperative multi-organ damage and death and is performed only in referral centers. Prenatal detection of d-TGA allows transfer in utero for delivery to these tertiary care centers which have a catheter theatre to performed BAS in critical CHD. Although this advantage is obvious for any newborn with d-TGA lesion, only 3 publications to date have shown better outcomes of infants with diagnoses of prenatal *vs.* postnatal d-TGA (6-8).

Prenatal detection

The percentage of prenatal diagnosis of d-TGA has been growing for many years but it still remains below 50% and is much less often detected prenatally than hypoplastic left heart syndrome (HLHS) despite very similar prevalence (3,5,9). In many European countries prenatal detection rate is below 40%, in some even less than 10% (5). In Poland in 1999 Prof. Respondek-Liberska funded an award for prenatally detected d-TGA, and in 2004 we had the first winner. Why so late? Why is the detection of d-TGA less efficient than HLHS? Such proportion between d-TGA and HLHS comes from the four-chamber view, which affects ventricular morphology less markedly or frequently in fetus with d-TGA (*Figures 1,2*), thereby making prenatal detection more difficult (5,10). Prenatal detection of CHD which has an abnormal four chamber view, for example HLHS is much higher, is the basic element in fetal heart screening study in all recommendations in the world (11-13). The next and more difficult step is evaluation of the fetal heart outflow tracts and the three-vessel view, which is much more difficult and crucial to detect d-TGA.

In addition, a prenatal diagnosis is more common for lesions that are not isolated (coexisting with chromosomal abnormalities or noncardiac defects) (10). D-TGA is very rarely associated with genetic syndromes, such as Down, Turner, Noonan, Williams or Marfan syndromes. Heterotaxy seems to be the only genetic syndrome with a

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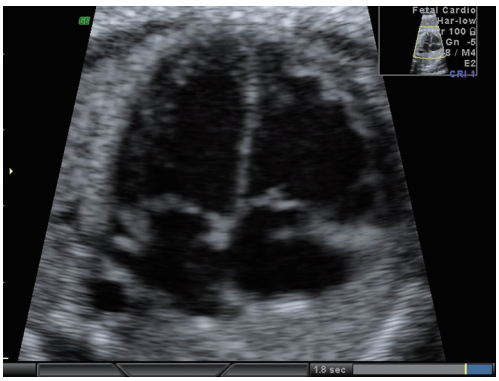

Figure 1 Normal four-chamber view.

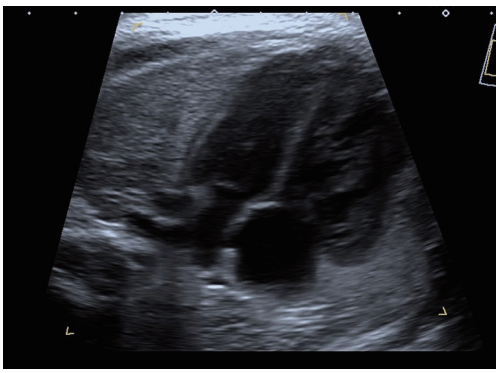

Figure 2 Four-chamber view in fetus with dextro-transposition of the great artery (d-TGA).

strong relation to d-TGA (14). Prevalence of extracardiac anomalies in d-TGA patients is also very rare, sometimes kidney diseases and cerebral abnormalities may appear (14,15). Normal four chamber view (*Figure 2*), non-coexisting chromosomal syndromes and extracardiac malformations place d-TGA in one of the less prenatally detected CHD when compared to other critical CHD (range, 8–42%) (8,9,16).

Critical *vs.* planned d-TGA

D-TGA is defined as a critical CHD, but the definition varies between pediatric and fetal cardiologists (17). A contemporary, prenatal definition of critical CHD is the one which requires urgent intervention/treatment in the first 24 h of life to prevent death. Such cardiac intervention may be not only life saving for the infant but also decrease subsequent morbidity (18-24). Prenatal diagnosis of critical CHD, which requires surgical or catheter intervention in the first hours or even minutes of life, allows for delivery at a specialized center and can reduce preoperative morbidity and mortality (18). Pediatric cardiologists include in critical CHD all lesions that require prostaglandin infusion after birth or surgery within the first month of life (25). From the prenatal cardiology point of view, if the malformation is detected prenatally and prostaglandin infusion has started immediately after birth, there is no critical situation. The situation is different when we do not have a prenatal diagnosis in ductal dependent lesion and prostaglandin infusion is crucial for survival of the newborn.

Current prenatal CHD classification systems distinguish between critical d-TGA and planned d-TGA. Fetal cardiologists define critical CHD as a defect requiring intervention in the first hours, sometimes minutes of life, despite infusion of prostaglandin. Such an example is d-TGA with a restrictive or closed FO. In this case prostaglandin is not sufficient and without immediate Rashkind procedure the baby deceases. That explains why not all of the patients with prenatal diagnosis of d-TGA receive optimal care if a patient with a prenatal diagnosis of d-TGA is born outside a cardiac center capable of performing a BAS (26,27). Missing the detection of a restrictive FO could result in delivering a critical newborn that rapidly decompensates before receiving the appropriate cardiac intervention (28). Planned d-TGA involves planned surgery after prostaglandin perfusion and Rashkind procedure later than 24 h after birth (19,20,22).

The incidence of restrictive FO in newborns with d-TGA is about 38–50%, and its prenatal detection is still difficult (29). The contemporary challenge for a fetal cardiologist is to distinguish between critical and planned d-TGA before the delivery to forewarn the perinatologist and pediatric cardiologist about the necessity of urgent Rashkind procedure.

Differentiating planned d-TGA with sufficient FO from critical d-TGA with restrictive atrial septum is still challenging after many years of studying (30). Most studies have concluded that the assessment of the atrial septum is useful (29,31). Pulmonary flow is growing during the pregnancy which may cause the restriction of the FO (32,33). Therefore, the assessment of the FO in the twentieth weeks of pregnancy could be insufficient to accurately predict the newborns' condition after delivery (22,33). Changes in the FO in fetuses with d-TGA may occur late in pregnancy (34). Therefore, the routine assessment of the FO conducted in four-week intervals has been recommended from the time of diagnosis to the time of delivery (18,22,28,29,34,35).

Fetal echocardiogram examination a few days before delivery seems to be the most important to determine which babies could require Rashind procedure (17,22,28). Another tool which could help to differentiate between planned and critical d-TGA could be the maternal hyperoxygenation test (36). Schidlow and Donofrio conclude that maternal hyperoxygenation may help identify fetuses with CHD at risk for perinatal compromise, also in d-TGA fetuses (36).

Ductus arteriosus, the second shunt which is crucial for d-TGA in newborns should also be assessed for abnormal flow in fetuses with d-TGA (29). Because the physiology of the flow in DA is different in d-TGA heart in comparison to normal fetal cardiac physiology, the single evaluation of the DA flow at mid-gestation of pregnancy does not predict the same physiological condition in the third trimester (37). For this reason, it should be mandatory to perform serial fetal echocardiography in the d-TGA, and the assessment of the DA, like the FO, just before the delivery could be the most important. FO findings which raise suspicions of urgent Rashkind procedure after birth are: hypermobile septum, angle of FO valve <30°, lack of swinging motion of septum or "tethered" septum, bowing of FO valve >50% and intact FO (28,31). Abnormal ductus arteriosus with additional restrictive FO, small with moderate/severe restriction or reversed, bidirectional or accelerated flow should also raise a suspicion of an instable baby after birth (29,34). Max velocity "s" wave >41 cm/s in pulmonary vein Doppler proximal to the left atrium is another fetal echocardiography parameter useful in predicting urgent Rashkind procedure after birth (38).

Sylwestrzak and Respondek-Liberska proposed assessment of the atrial septum after the thirtieth week of pregnancy using M-mode to predict the necessity of postnatal BAS in fetuses with simple d-TGA (39). They conclude that FO index could be useful to predict postnatal hemodynamic instability in fetuses with d-TGA. FO index was calculated as a maximal length of both atria in diastole, measured in a transverse plane divided by maximal excursion of the FO flap tracing in the same transverse plane (39). Patey *et al.* using spectral-tissue Doppler and speckle-tracking echocardiographic parameters, proposed a novel cardiac index, left ventricular rotation-to-shortening ratio in late pregnancy fetuses with d-TGA. Their study showed high sensitivity and specificity for prediction of BAS required quickly after delivery. They suggest the correlation between hypoxemia and unique hemodynamic loading conditions on cardiac remodeling and functional changes in fetuses with d-TGA (40). All these fetal echocardiographic parameters will assist to determine which newborn with d-TGA will required Rashkind procedure within the first day of life and which will require only prostaglandin infusion and a planned surgery in the first week of life.

Prognosis

To provide optimal care for newborns with critical d-TGA diagnosed prenatally, we should create a special delivery room which should have all equipment to maintain oxygenation and systemic perfusion until the appropriate procedures can be done (18). If the baby is unstable, the BAS should occur in the delivery room or in the intensive care unit as soon as possible after delivery. In babies who are noted to have a restrictive or closed ductus arteriosus, pulmonary hypertension may occur. In these instances, 100% oxygen and inspired nitric oxide may be beneficial (18). Creating a special delivery room in tertiary centers for babies with critical CHD may result in less morbidity and mortality in these patients (18,19). One twin with d-TGA is a very rare case, d-TGA in twins very often exists in the case of conjoined twins (4). There are not many studies about this, so the case series presented by Hu *et al.* are unique in publications (4). They showed that prognosis of isolated d-TGA in one twin is promising with appropriate management which should be like management with single pregnancy with d-TGA. The only difference is that after delivery before you start the prostaglandin infusion you must make an echocardiographic exam to assure which baby has d-TGA (4).

The study of van Velzen *et al.* is one of these which have proofed lower first-year mortality in prenatally diagnosed d-TGA than in those without prenatal diagnosis. In their study group presurgical mortality was present only in postnatal detected d-TGA cases (16). The percentage of patients reaching to adulthood after the arterial switch operation (ASO) in d-TGA reaches 90% of patients and is much higher than an average percentage for critical CHD, which is about 69% for patients who survive to 18 years of age (25,41). Familial recurrence risk is low, and children diagnosed prenatally have better cognitive skills in comparison to children diagnosed after birth in whom preoperative acidosis and profound hypoxemia are more common (41,42). Earlier ASO may have a neurodevelopmental benefit and may reduce hospital morbidity, complications, and cost. One study suggests that the third day of life is the best time for ASO (43). It is recommended to deliver a baby with d-TGA in hospitals

that perform the ASO (43). Many parameters of prenatally and early postnatally restricted FO are known and the prediction of urgent BAS after birth is still difficult in many cases. In this reason the recommendations from the American Heart Association (AHA) from 2014 state that, given that there is currently no good fetal measure to determine postnatal FO closure with a high specificity and sensitivity, all babies with d-TGA should be treated as if the FO will close at delivery, and for this reason, all neonates with d-TGA should be delivered in the hospital where there is an operating theatre and team available to perform the septostomy (44). Prenatal detection, selection between critical and planned d-TGA and appropriate management in tertiary centers allow very good, long-term prognosis in fetuses, children, and adult people with congenital d-TGA.

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