Unexpected resolution of first trimester fetal valve stenosis: consequence of developmental remodeling?

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Pulmonary stenosis is a common congenital heart defect, often forming part of a congenital heart disease complex, such as tetralogy of Fallot. Isolated pulmonary stenosis is usually well-differentiated postnatally and encompasses a broad spectrum of malformation, depending on the degree of involution of its supporting ventricle with the most severe morphological form being pulmonary atresia with intact ventricular septum (PAIVS). However, early pregnancy features and predictors of circulatory outcome have proven to be difficult to characterize.

The paper by Bronshtein and colleagues in this episode of the journal reports the outcome of fetuses with evidence of pulmonary stenosis in the first trimester anatomy scan. (1) Instinctively the fetal cardiologist expects valvular obstructive lesions to worsen during pregnancy as reduced forward flow often leads to poor growth of the pulmonary tree and to complete, usually muscular pulmonary atresia. This is usually accompanied by progressive involution of the right ventricular outflow tract which, combined with muscular overgrowth, may remove any evidence of the ventriculo-arterial connection. (2)

As expected, babies born with a milder phenotype in this study were not identified in the first trimester, but surprisingly the authors describe resolution of isolated elevated pulmonary valve velocities in 60% of affected fetuses by delivery, with progression of disease occurring in only a quarter.

The coexistence of tricuspid regurgitation often helps to risk -stratify fetuses with pulmonary stenosis or atresia. Although important tricuspid regurgitation is associated with reduced right ventricular filling times and a reduction in forward flow through the pulmonary trunk resulting in valvar atresia, it has been shown to improve tricuspid valve growth in PAIVS. It has also been shown to be a good predictor of a postnatal biventricular circulation in several studies, provided fetal hydrops does not occur. (3,4) However, why might there be resolution rather than progression of pulmonary valve flow abnormalities in the first trimester fetus?

The components of the right ventricular outflow tract and their early appearances may provide an important clue. The pulmonary valve is supported by an infundibulum, a conical-shaped muscular extension arising from the right ventricular outlet. The proximal part of the infundibulum comprises of the septomarginal trabeculations on the free wall and the supraventricular crest (crista), both of which are capable of a hypertrophic response secondary to activation of the Renin Angiotensin system. This anatomy therefore forms the substrate for subvalvar hypertrophy, given the right circumstances.

Developmental studies of the pulmonary valve in the human fetus show it to be thick and gelatinous with poor separation of its leaflets from the arterial wall prior to 10 post-menstrual weeks (Figure 1A) Progressive cavitation of the outflow cushions and a process of endothelial to mesenchymal transformation allow normal embryonic development of the leaflets of the semilunar valves and their accompanying arterial sinuses of both outflow tracts. (5) After cardiogenesis, from about 10 post-menstrual weeks, there is maturation and growth of the heart structures. Our anatomical studies in

this respect showed leaflet remodeling from thick gelatinous structures to more mature thin valves between 9 and 13 weeks. (6,7) (Figure 1) Furthermore, at 9 weeks the pulmonary and aortic valves were at similar levels and orientations, unlike the distinctly higher level of the pulmonary valve and angulation of the aortic valve observed later. It is plausible that a spectrum of timing of this maturational process exists, which was identified by the authors. Conceivably, immaturity of the valves and the orientations of the outflow tracts may manifest as higher than normal valvar velocities that resolve with maturation.

Increased wall thickness is also recognized in the great arteries of the first trimester fetus and remodeling occurs during the early second trimester to produce a decrease in wall thickness to total diameter ratio from 0.27 to 0.11 between 10 and 20 gestational weeks. (Figure 2) This is important information for the sonographer as color flow mapping is used as a surrogate for vessel size in first trimester echo and these appearances may give the impression of pulmonary valve stenosis and a narrow right ventricular outflow tract, rather than reflecting the normal maturational process in the human fetal heart.

Hemodynamic forces also play a role; vascular shear forces are important to ensure normal valvar development. There is a relatively high distal impedance in the immature placenta that will contribute to altered physiology in the early human heart and an inability of the right ventricle to perform its expected function of relaxation, filling and pressure generation may lead to the plate-like pulmonary valve seen sonographically in some cases of pulmonary stenosis.

Our knowledge of first trimester pathophysiology continues to increase by improved imaging of the early human heart, but studies sometimes report seemingly paradoxical observations that require knowledge of early developmental changes to aid their interpretation.

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Figure legends

Figure 1

Images of both semilunar valves. Top panel A) shows the pulmonary valve at 9 gestational weeks. The leaflets are thick and rounded in the longitudinal view (left) and redundant in the middle image. The arrow in the histological image illustrates the unclear border between the valve and the arterial wall (right image). Lower panel B) shows the aortic valve at 13 weeks for comparison. The valve leaflets are much sharper than in the first trimester (left). The closure lines are well defined in the “en face” view (middle). The arrow shows a clearer border suggesting a more developed valve structure.

Ao: aorta; LA: left atrium; LV: left ventricle; LVOT: left ventricular outflow tract; PT: pulmonary trunk; RVOT: right ventricular outflow tract

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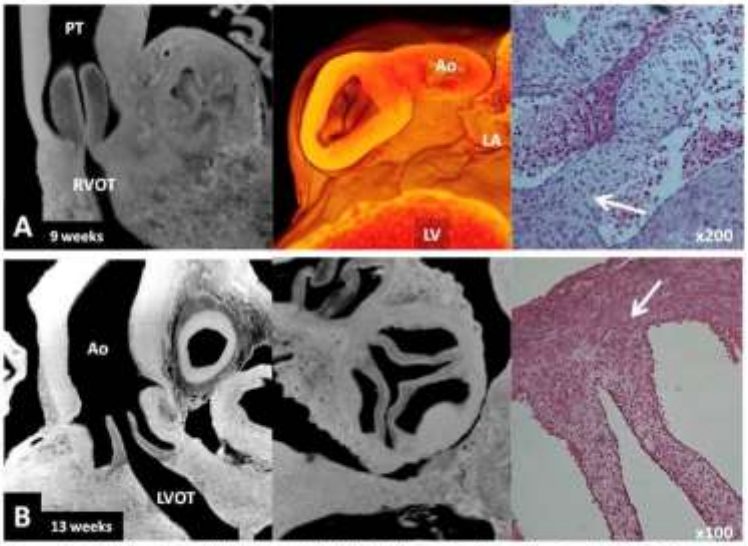
Figure 2

The increased wall thickness in comparison to the outer diameter of the pulmonary trunk at 0.27 is illustrated in the human fetal heart between 10 and 12 post-menstrual weeks. Similar measurements at 20 post-menstrual weeks show a ratio of 0.11.

PT: pulmonary trunk

Figure 1



Ao: aorta, LA: left atrium, LV: left ventricle, LVOT: left ventricular outflow tract, RA: right atrium, RVOT: right ventricular outflow tract, PT: pulmonary trunk, SID: sample ID

Figure 2