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An Autopsy Based Cross-sectional Study of Human Fetal Heart: Clinical Implications

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ABSTRACT

Introduction: much of the knowledge about the fetal cardiac growth is derived from discrete observations in clinics through echocardiography. A trend line of changes of the different dimensions of fetal heart from the time of functioning in utero till the time of delivery obtained from autopsy studies might actually supplement the data obtained through echocardiography. These data can be of help to clinicians for planning a better therapeutic outcome for infants with congenital heart disease.

Methods:this cadaveric cross- sectional observational study was carried out in thirty spontaneously aborted human fetuses of 7th to 38th week's gestations. Autopsies were performed and the targeted morphometric parameters were measured with digital vernier calipers. Pearson's correlation (r) was used to determine the correlation coefficient. A p- value < 0.05 was considered significant.

Results: the fetal heart weight increased by 764.63 times from 0.104 grams at 7 week of gestation to 79.522 grams at 38 weeks gestation. The fetal cardiac volume increased by 56 times from 0.25 cc to 8 cc at 38 weeks as compared to 7^{th} week. The correlation coefficient (r) between heart weight and gestational age, CRL, HC were 0.8699, 0.8418 and 0.8196 respectively and were statistically significant ($p<0.01$).

Conclusions: the study indicated that RV, LV and IVS wall followed a linear growth pattern with gestational age. No significant difference of rate of growth observed between the RV and LV wall. The thickness of the RV, LV and IVS wall can serve as indirect tools for monitoring the fetal cardiac growth.

Keywords: Fetal heart; Ventricular wall; Interventricular septum; Fetal echocardiography.

Introduction

There had been a time in the past when clinical examination of the fetal heart centered around measuring heart rate and rhythm monitored in the late pregnancy with either stethoscope or maternal ECG leads. Remarkable developments in the diagnosis and management of congenital heart diseases (CHDs) which happened during the last few decades have made it possible to bring down mortality and morbidity. At the same time, the post-operative quality of life of those treated surgically has also been substantially improved. The knowledge of the fetal heart development and its correlation with the adult anatomic parameters are imperative for better management of the various CHDs. The advancements in the medical technology have not only made significant escalation in the medical research related to prenatal cardiac development but also made possible to achieve the long cherished dream of in-utero interventions. Data from fetal cardiac morphometry provides clinicians a more vivid idea relating to the evolution of the pathophysiology of many CHDs. The clinical prognosis following an intervention for CHDs can also be predicted and monitored much more accurately in the immediate and remote postoperative period. Most data with regard to the fetal cardiac development has evolved from the comprehensive and reliable fetal echocardiography studies[1–7] both ventricular dimensions, interventricular septal thickness, heart area, heart circumference, thoracic diameter, thoracic circumference and thoracic area were measured in the four-chamber view during diastole. Diameters of the pulmonary trunk and ascending aorta were obtained in the short axis and long axis view during systole. Ultrasound examinations were performed with a 5.0-MHz transvaginal and/or transabdominal phased-array sector scanner. RESULTS: The four-chamber view and the cross-over of the pulmonary artery and the aorta were adequately visualized in 44% of the fetuses at 10 weeks of gestation, in 75% at 11 weeks of gestation, in 93% at 12 weeks of gestation and in 100% of the fetuses at 13-17 weeks of gestation. Before 14 weeks of gestation transvaginal sonography was superior to the transabdominal sonography in visualization of the fetal heart and great arteries. After 14 weeks of gestation transabdominal sonography

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accurately demonstrated the structure of the fetal heart. The ratio of right and left ventricle (RV/ LV. Similar data from autopsy studies are sparse in literature especially with regard to the morphometry of the fetal ventricles and interventricular septum (IVS). Some studies have attempted to study the same in adult, but considering the significant hemodynamic and physiological alternations between fetal and adult circulation, it is pertinent to gather more accurate data from cadaveric fetal morphometry studies which can tally better with fetal ECHO findings and might substantiate and complement the ECHO derived data in a reliable manner. Furthermore, as most of the adult cardiac morphometric data derived from cadaveric and imaging studies have been carried out in subjects who had CHDs, they sometimes do not provide accurate reflection of the normal development. Undoubtedly, fetal ECHO is one of the best non-invasive modality for CHDs, nevertheless, some authorities have constantly emphasized the need of autopsy studies to supplement the quantitative data obtained from ECHO in prenatal diagnosis[5,8-9]. The quantitative data available from the existing autopsy studies on human ventricular development seem to be requiring more support in this context[9,10–16]. With this background we intended to study the morphology of fetal ventricular wall and fetal IVS. The objective of this study was to determine the various quantitative parameters of fetal cardiac growth such as weight, thickness of the right and left ventricular wall and the muscular part of the IVS wall as the fetus transitions through the intrauterine life to postnatal life. The study has been carried out on spontaneously aborted fetuses of gestation between 07-38 weeks.

Methods

This cross-sectional study was carried out in thirty (30) formalin (10%) fixed hearts obtained from fetuses of both genders between 7th to 38th week of gestational age collected over a period of three years between 2017-2020. Those fetuses with gross congenital anomalies were excluded from the study. The guidelines pertaining to the use of dead human organs and tissues for use of teaching and research were followed as per institutional norms. The standard methods of dissection were followed during exploration of the thoracic viscera. The position of the adjacent viscera with the contained heart in the middle mediastinum enclosed in the pericardial sac is noted. The parietal pericardium is meticulously dissected to expose the heart. The heart was then taken out and weight and volume of the heart measured (Fig: 1 & 2). The wall and septum thickness was measured at the thickest part of the corresponding wall in an oblique coronal section of the hearts which extended from the apex below, to the transverse pericardial sinus above (Fig: 2a, 2b, 2c). Crown rump length (CRL), head circumference (HC) of the fetuses was also measured. An electronic weighing machine, non-stretchable measuring tape and digital vernier calipers were used for taking the measurements. Obtained data was tabulated and analyzed with Microsoft Excel version 2019 and SPSS software. Pearson's correlation coefficient (r) was determined. A p- value less than 0.05 was considered significant.

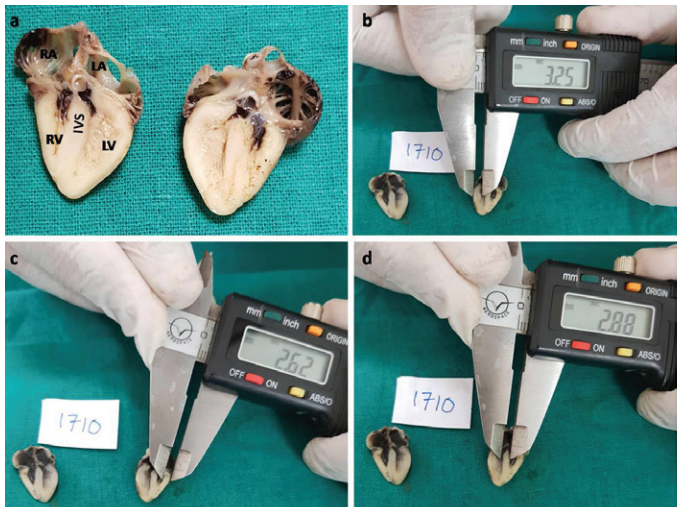

Figure 1. (a, b, c, d): a-coronal section of the fetal heart, process of measuring fetal heart parameters (b-right ventricle wall thickness, c-left ventricle wall thickness & d-interventricular wall thickness) with vernier calliper.

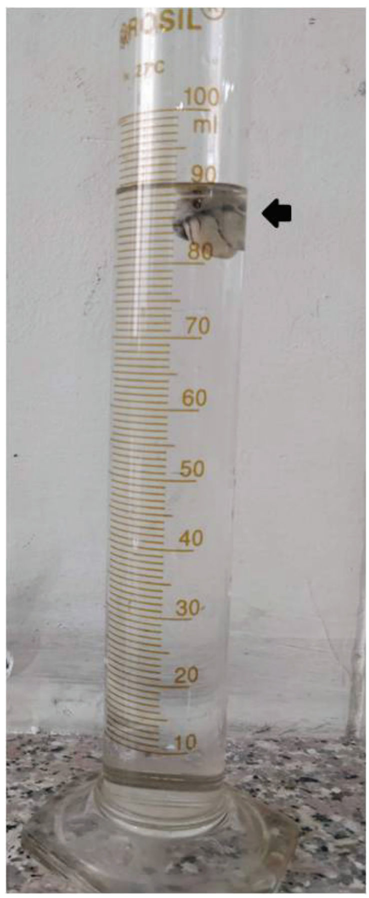

Figure 2. Method of measurement of the volume of fetal heart.

Results

The number of fetuses studied was between 7th to 38th weeks of gestation. Number of fetuses were 3, 25 and 2 in the 1st trimester (up to 12 weeks), 2nd trimester (13th - 26th weeks) and 3rd trimester (13th - full term) respectively. The average weight in 1st, 2nd and 3rd trimester was 29.67 grams, 284.72 grams and 1755 grams respectively. The fetal heart weight increased by 764.63 times from 0.104 at 7 week of gestation to 79.522 grams at 38 weeks gestation. The fetal cardiac volume increased by 56 times from 0.25 cc to 8 cc at 38 weeks as compared to 7th week. An increasing trend correlating with gestational age in weeks has been noted in the right ventricle (RV) wall, left ventricle (LV) wall and IVS thickness. The RV wall thickness increased by 5.81 times at 22 weeks compared to the value at 7th week; then decreased to 0.90 times at full term compared to the value at 22 weeks. The final RV wall thickness at 38 weeks was 5.25 times the thickness at 7th week. The LVW thickness increased by 7.65 times at 21 weeks compared to the value at 7th week; then decreased to 0.82 times as compared to the value at 21 weeks. The final LV wall thickness at 38 weeks was 6.28 times the thickness as compared to the thickness at 7th week. The IVS thickness increased by 7.39 times at 22 weeks compared to the value at 7th week; then again increased by 1.3 times compared to the value at 21 weeks. The final IVS thickness at 38 weeks was 9.86 times the thickness at 7th week. The IVS wall was found thickest followed by the LV & RV wall during the gestation period studied.

The correlation coefficient (r) between heart weight and gestational age, CRL, HC were 0.8699, 0.8418 and 0.8196 respectively and were statistically significant [$p<0.01$] (Fig 3). The correlation coefficient (r) between heart volume and gestational age, CRL, HC were 0.8437, 0.8233 and 0.8028 respectively and were statistically significant ($p<0.01$). The correlation coefficient (r) between the fetal weight and fetal heart weight, fetal weight and fetal heart volume, fetal heart weight and fetal heart volume, RV-LV wall thickness, RV-IVS wall thickness and LV-IVS wall thickness were 0.9505, 0.8882, 0.9578, 0.8984, 0.8645, 0.8567 respectively. All the values have been found statistically significant ($p<0.01$).

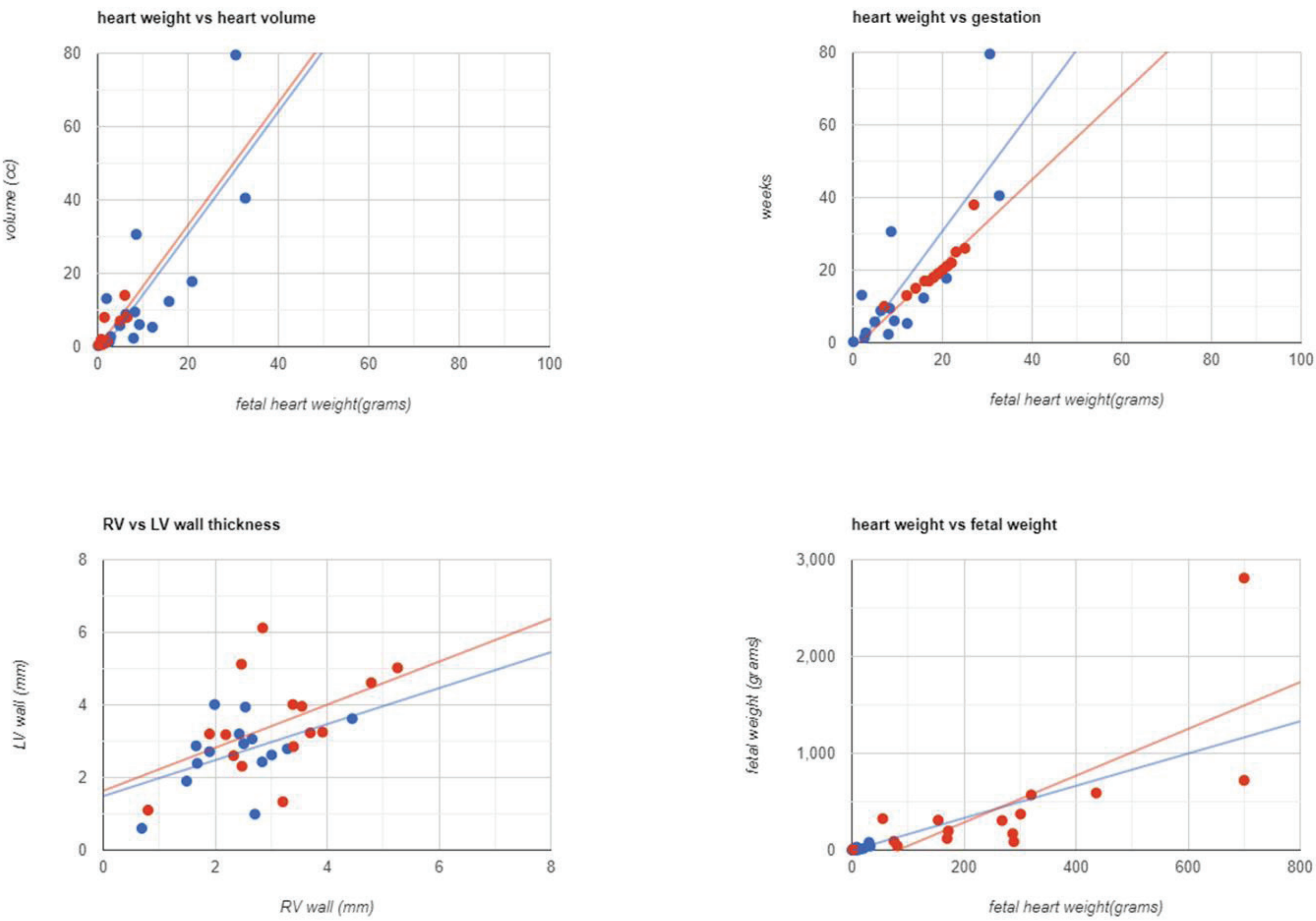

Figure 3. Dot plot showing the correlation between fetal weight and fetal volume, fetal weight with gestation, fetal weight with crown rump length (CRL), fetal volume with CRL.

Discussions

The heart develops from the midline splanchnopleuric mesoderm and positioned ventral to the primitive foregut. During 4th week of development, the ventricles develop from the ventral side of the looping primary heart tube and move to the left and posterior aspect. The right ventricle develops to the right of the left ventricle which is a prerequisite for the appropriate connection with the developing atria. It is postulated that the sidedness of the ventricles is influenced by the very important transcription factors retinoic acid and TBX5 dependent signaling pathways. The determination of sides in ventricles development differs from that of atria development. Atrial development is more in line with the general asymmetry of the left and right sidedness of the body as determined by several transcription factors such as PITX2; Nodal, Lefty and Cited-217. The muscular interventricular septum (IVS) is actually a wall formed secondary to the rapid expansion of the adjacent right and left ventricles. An apical cleft above the muscular portion between the free rim of muscular ventricular septum and the fused endocardial cushion enables communications between the two ventricles in the initial period[18]. The closure of the interventricular foramen subsequently takes place by proliferation of the mesenchyme lying close to the endocardial cushion and thus the normal IVS without any communicating channel in it is formed[19]. Anomalies in the development of the IVS leads to congenital lesions such as of muscular type of ventricular septal defect (VSD) caused by single or multiple perforations in the muscular IVS. Similarly, membranous type of VSD due to faulty fusion of the atrioventricular cushions with the right and left bulbar ridges and single common ventricle due to failure of development of the either the membranous and / or muscular IVS can also occur. The inter-atrial septum development occurs mostly secondary to the rapid enlargement of the developing atria. The persistence of inter-atrial communications is a requirement in the fetal period. Though in normal circumstances, it is the ductus arteriosus and not the inter-ventricular communication persistence which is relevant in fetal life, the inter-ventricular communications are very much required for survival of the fetus in some congenital conditions such as tetralogy of Fallot[20].

Since the first description of ultrasonographic imaging of fetal heart in 1972 by Winsberg *et al*., researchers have started working on the various quantitative parameters related to growth of the fetal heart and studied its utilization as prenatal growth assessment tool[21,22,6,23]. In 1992, Cooper *et al*. highlighted the probable correlation between thickened fetal inter-ventricular septum and asymmetrical septal hypertrophy observed at birth in fetuses of gestation between 31 - 34 weeks[24]. The mean thickness of the IVS was found to be between 3 mm – 4 mm in fetus of 32-35 weeks by Tan *et al*. and Vielles's *et al*.[5]. Zielinsky *et al*. on the other hand described increased asymmetrical IVS thickness in fetuses of diabetic mothers with a mean IVS thickness of 7.12 + 1.6 mm at 32 weeks[25,26]. Our observation of fetal heart parameters are in line with the observation by Mandorla S *et al*. who studied fetal heart by M- mode ultrasound in fetuses of 19th weeks to term gestation and opined that the atrial and ventricular wall thickness increases linearly with gestational age. John Sutton *et al*. in his observation on 55 spontaneously aborted human fetuses of gestational age from 8th to 40th weeks commented that the rate of growth of right and left ventricular wall follows a linear pattern with gestation age. They also stated that there is no significance difference between the rate of growth of right and left ventricular wall thickness[27]. It seems from the existing literature that the right and left ventricles grow more or less at the same rate throughout the period of gestation right from the time of completion of cardio genesis to full term. The notion of right ventricular growth dominance in the developing human fetal heart is also not supported by most observational studies[28]. Cavalcanti J S *et al*. also had similar observations with regard to IVS wall growth during fetal period[29]. As opposed to the data derived from the existing echocardiography studies, there is limited data available from fetal heart autopsy which could substantiate and correlate the existing ECHO data[20]. A good set of data gathered from autopsy is expected to reflect more accurately the growth of the fetal heart and at the same time expected to improvise the existing knowledge of prenatal heart development. Erstwhile literature has provided data in the form of quantitative measurements of the different cardiac chambers and segments of inter-ventricular or inter-atrial septum. But a prenatal trend line is still lacking with regard to fetal heart weight, volume, thickness of RV, LV and IVS which can corroborate and correlate well with the gestational age. We analysed the changes in targeted morphometric parameters of foetal heart in the aborted fetuses from 7th to 38th week. At first glance from the parameters, the more rapid growth of the fetal heart in the 2nd and 3rd trimester of pregnancy can be made out. All the samples we studied were formalin fixed fetal hearts. Erstwhile studies reported that there is minimal alteration in measurement of the cardiac parameters between 1-3 percent before and after fixations. Therefore though the measurements obtained in formalin fixed hearts may not be as accurate as in living state, however it can be assumed that the measurements will not differ significantly from living state. During the early and late stages of gestation some measurements deviated from the linearity. Nevertheless, most of the parameters measures followed a linear pattern throughout the gestation. Both RV & LV wall thickness increased with gestation, and LV wall thickness has been consistently found greater than the RV wall at any given point.

Conclusion

The present study highlights the growth pattern of the RV wall, LV wall and the IVS wall during the vital intra-uterine period of late first trimester until birth. By simple assessment of the growth of the RV, LV and IVS wall, we indirectly tried monitoring the growth of the ventricle as it transitions the entire duration of fetal period. Though there was no significant difference of rate of growth observed between the RV and LV wall, we found that the growth of RV, LV and IVS wall follows a linear pattern with gestational age. The ventricular growth increased linearly up to 20-21 weeks, and then rate slowed down thereafter till 39 weeks. This quantitative study of the growth of RV, LV and IVS wall thickness in fetuses should not only help in understanding the pathogenesis of VSD, but will also be useful as baseline data supplementing the data derived from echocardiography examination of fetal heart.

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Mini Curriculum and Author's Contribution

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