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Persistent Left Superior Vena Cava in Fetuses—An Autopsy Series

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ABSTRACT

Objective: To review fetal autopsy reports with persistent left superior vena cava (PLSVC) and identify its associations. *Materials and methods*: Autopsy reports of all fetuses diagnosed with PLSVC in our center from January 2011 to December 2015 were reviewed. Fetuses less than 15 weeks gestational age along with autolyzed and damaged hearts were excluded from the study. The study group was compared with controls during this period. *Results*: Prenatal ultrasound detection rate of PLSVC was 13.06%. All the cases had associated anomalies of which 96% had extra cardiac anomalies and 67% had intrinsic cardiac defects among which septal defects were most common (39.6%). Anomalies of cardiovascular, respiratory, genitourinary and musculoskeletal, hypoplastic thymus and single umbilical artery were significantly higher in the study group. *Conclusion*: This study emphasizes on the importance of improving the technical skill for imaging the three-vessel view as PLSVC seems to have significant associations.

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KEYWORDS
Persistent left superior venacava; dilated coronary sinus; fetal autopsy; prenatal diagnosis; cardiac anomaly; extra cardiac anomaly

Introduction

Persistent left superior vena cava is observed in 0.3% of the autopsies in general population [1]. It is a marker of embryopathy and occurs due to failure of involution of left horn of the embryonic sinus venosus, left anterior and common cardinal veins. It is associated with 4–8% of congenital heart diseases [1]. Most common association is with the heterotaxy syndrome. Our aim was to review fetal autopsy cases with PLSVC to determine the frequency and types of associated anomalies.

Materials and methods

This is a five-year retrospective case control study from January 2011 to December 2015 conducted at our center which is a single tertiary fetal imaging unit. Search queries like persistent left SVC, persistent left superior vena cava, PLSVC, left SVC, left superior vena cava, dilated coronary sinus were used to retrieve data from our database. Independent searches were run by separate individuals to validate the search results. Autopsy reports of all fetuses diagnosed

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with PLSVC over this period were reviewed. Gestational age, ultrasound report, autopsy findings and karyotype reports (when available) of the fetuses were analyzed. Autolyzed and damaged hearts were excluded and fetuses between 15 and 38 weeks gestational age were included. This was considered the study group. Controls were selected from the rest of the fetal autopsies done in the same period by simple random sampling method using random numbers. The random numbers were generated without replacement. Two controls were taken for each case.

All the fetuses included in the study and control group had undergone a detailed autopsy as per the centers policy based on international guidelines. Formalin fixed fetuses (10% neutralized buffered formalin) had undergone routine external body measurements (crown heel length, crown rump length, foot length, head circumference and inter innercanthal distance), detailed external examination and internal systemic examination. Histopathology of organs was done when indicated and the 5 mm sections mounted on 75 × 25 mm slides were stained with hematoxylin- eosin stain and studied under the microscope. The final report carried detailed autopsy findings, fetogram report, and histopathological findings. Full body X-rays of all fetuses and photographic documentation of all the autopsies were archived in our central database. The data retrieval was done from the archived autopsy reports and images in both groups. The study group was divided into cardiac and noncardiac groups. Abnormal findings were grouped under the major systems—central nervous system, respiratory system, genitourinary system, gastrointestinal system, and muskuloskeletal system. Hydrops, cystic hygroma, intrauterine growth retardation, single umbilical artery, hypoplastic thymus and dysmorphic facies were identified as additional associated findings in the noncardiac group. Facial dysmorphism was confirmed with the center's geneticist. Proven and suspected syndromes based on the autopsy findings were also considered for analysis.

Prenatal ultrasound reports were noted from the center's database in cases which were diagnosed in our center. For those who were referred from outside, the prenatal ultrasound was retrieved from the available referral records.

Statistical analysis

All data were analyzed using R software version 3.2.3. The detected anomalies were represented as frequency and percentages. The comparison of detected anomalies between cases and control were done using two proportion *z*-tests. Statistical significance is kept at 5% level of significance.

Results

A total of 4563 fetal autopsies were performed during 5-year study period in which 222 cases were diagnosed with PLSVC with a frequency of 4.8%. 146 cases were those imaged in our center and 76 in other centers. In total, 29 (13.06%) were identified on prenatal ultrasound of which 28 cases were seen in our center and 1 from another center, with the rate of identification being 19.17% and 1.3%, respectively.

PLSVC drained directly into the coronary sinus in 208 (93.24%), into the left atrium in 9 (0.04%) and the remaining 5 (0.02%) cases drained into the common atrium. One case had an absent right SVC.

All the cases had associated anomalies with extra cardiac anomalies in 96% and isolated cardiac defects in 4%. Cardiovascular (67.12%) followed by musculoskeletal anomalies (50.90%) were the most common associations found on autopsy. It was found that 33.33% of

Table 1. Syndromes identified in study group.

Syndromes/association ($N = 31$)	Number of cases *n* (%)
Heterotaxy	7 (22.58)
Sirenomelia	3 (9.67)
Vacterl association	3 (9.67)
Short rib polydactyly syndrome	3 (9.67)
Klippelfiel Syndrome	2 (6.45)
Triploidy	2 (6.45)
Down's Syndrome	2 (6.45)
Trisomy 18	2 (6.45)
Joubert syndrome	1 (3.22)
Ellis Van Creveld	1 (3.22)
Caudal Regression Syndrome	1 (3.22)
Neolaxova	1 (3.22)
Vater association	1 (3.22)
Meckel Gruber Syndrome	1 (3.22)
Potter Sequence	1 (3.22)

cases had single umbilical artery and 50.90% of cases were associated with hypoplastic thymus. 50.40% of cases had facial dysmorphism. 17.11% fetuses were growth restricted and 2.25% had cystic hygroma. Overall 14% of cases had Syndromes/Associations of which heterotaxy syndrome was the most common (Table 1). Outflow tract anomalies were the common cardiovascular pathology in the heterotaxy group. Karyotyping result was available in 10 cases of which two were Down's syndrome (one pure trisomy and one robertsonian translocation 14:21), one trisomy 18, one recurrent triploidy and the rest were normal. As karyotype results for the other cases were not available, calculation of rate of aneuploidy was not possible.

For the purpose of a detailed autopsy review the cases were divided into two groups. Cardiac (Group 1) and Non cardiac (Group 2) based on the presence of intrinsic cardiac anomalies. The cardiac group comprised 67% of cases. Septal defects (39.6%) were the most common in the cardiac group followed by outflow tract defects (39.2%). Tables 2 and 3 describe few of the common cardiac and noncardiac anomalies noted in the study group. Apart from the defects described in the table, truncus arteriosus 9 (6.04%), transposition of great vessels 8 (5.36%), anomalous pulmonary venous connection 7 (4.6%) tetralogy of fallot, 4 (2.68%) along with a few other anomalies were also identified.

The control group was compared with the study group and it was found that cardiovascular, respiratory, genitourinary, musculoskeletal anomalies along with hypoplastic thymus and single umbilical artery were significantly more frequent in the group with PLSVC than in controls (Table 4).

Table 2. Common cardiac anomalies noted in the study group.*

Cardiac anomaly $N = 149$	*n* (%)
Double outlet right ventricle	38 (25.50)
Ventricular septal defect	31 (20.80)
Pulmonary artery hypoplasia/valve stenosis	24 (16.10)
Hypoplastic left heart syndrome	23 (15.43)
Atrioventricularseptal defect	22 (14.76)
Tubular aortic arch hypoplasia	20 (13.42)
Right aortic arch	16 (10.73)
Aberrent right subclavian artery	13 (8.72)
Tricuspid valve dysplasia	13 (8.72)

*Total number of cardiac anomalies will be more than the calculated percentage of cardiac association as many cases had a combination of defects.

Table 3. Common non cardiac anomalies noted in the study group.

System anomaly	*n* (%)
Central nervous system ($n = 61$)	
Both cortical and posterior fossa abnormalities	18 (29.50)
Respiratory system ($n = 110$)	
Hypoplastic lungs with segmentation defect	96 (87.27)
Gastrointestinal system ($n = 71$)	
Hepatobiliary anomalies	22 (30.98)
Genitourinary system ($n = 109$)	
Renal anomalies	74 (67.88)

Table 4. Frequency of anomalies in the study group and control group.

Anomaly	Control group *n* (%)	Study group *n* (%)	*p*-value
Central nervous system	113 (25.57%)	61 (27.48%)	0.56
Cardiovascular system	55 (12.44%)	149 (67.12%)	<0.001*
Respiratory system	60 (13.57%)	110 (49.55%)	<0.001*
Gastrointestinal system	139 (31.45%)	71 (31.98%)	0.896
Genitourinary system	91 (20.59%)	109 (49.1%)	<0.001*
Muskuloskeletal system	139 (31.45%)	113 (50.9%)	<0.001*
Thymus	125 (28.28%)	113 (50.9%)	<0.001*
Syndromes	43 (9.73%)	32 (14.41%)	0.078
Single umbilical artery	34 (7.69%)	74 (33.33%)	<0.001*

*Anomalies with significant difference between cases and controls.
**Total number of anomalies will be more than the number of cases as more than a single anomaly was identified in many cases.

Within the study group, hypoplastic thymus was significantly more frequent in the cardiac group (Table 5).

Discussion

Persistent left SVC (Fig. 1) is a vascular variation which can be associated with cardiac and extracardiac anomalies. Identification in prenatal ultrasound is aided by the presence of an extra vessel to the left of the pulmonary trunk in the three-vessel view.

There are various theories explaining the persistence of the left SVC. One is absence of mechanical compression needed to cause regression of the left horn of sinus venosus, anterior and common cardinal vein in the presence of AV canal defects, mitral atresia, and cortriatrium [1]. Lateralization defects in heterotaxy syndrome may have a similar mechanism. Ninety

Table 5. Frequency of anomalies noted in cardiac and non cardiac group.

Anomaly	Cardiac group ($N = 149$) *n* (%)	Non cardiac group ($N = 73$) *n* (%)	*p*-value
Central nervous system	45 (30)	16 (22)	0.209
Respiratory system	69 (46)	41 (56)	0.161
Gastrointestinal system	46 (31)	26 (36)	0.455
Genitourinary system	70 (47)	39 (53)	0.4
Muskuloskeletal system	76 (51)	37 (51)	0.99
Hypoplastic thymus	87 (58)	25 (34)	0.0008*
Single umbilical artery	50 (34)	24 (33)	0.882
Syndromes	23 (14)	8 (11)	0.532

*Hypoplastic thymus was significantly more frequent in the cardiac group compared to non cardiac group.
**Total number of anomalies will be more than the number of cases in each group as more than a single anomaly was identified in many cases.

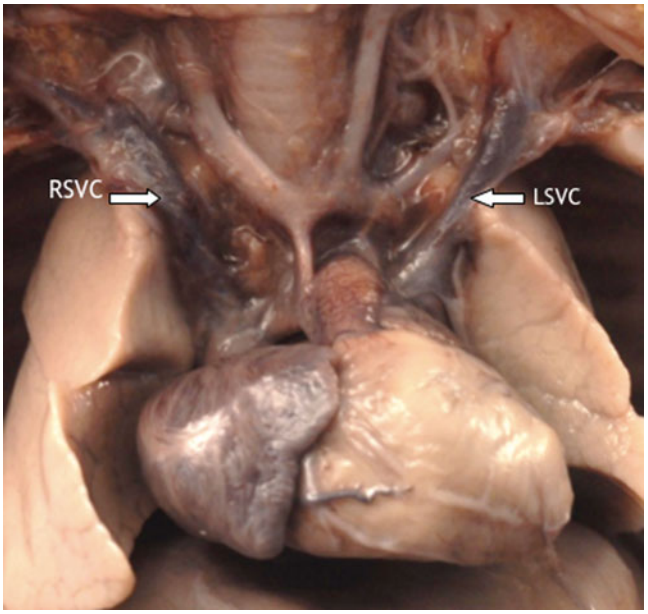

Figure 1. PLSVC with hypoplastic aortic arch.

percent of cases of PLSVC drain into the coronary sinus with the remaining 10% into the left atrium [1]. The same was confirmed in this study with the majority draining into coronary sinus (Fig. 2) and only 4% into the left atrium and 2% into the roof of the common atrium. Our autopsy study had a frequency of 4.8% in a 5-year period with a low detection rate of 13.06% on ultrasound in the cases sent for autopsy. Very few autopsy studies on PLSVC are available and hence ultrasound studies were used for comparison in order to reach a plausible conclusion (Table 6).

Our study reports associated cardiac defects in 67% of cases which is comparable with the studies by Galindo et al. and Berg et al. with a reported prevalence of 81.4% and 83%,

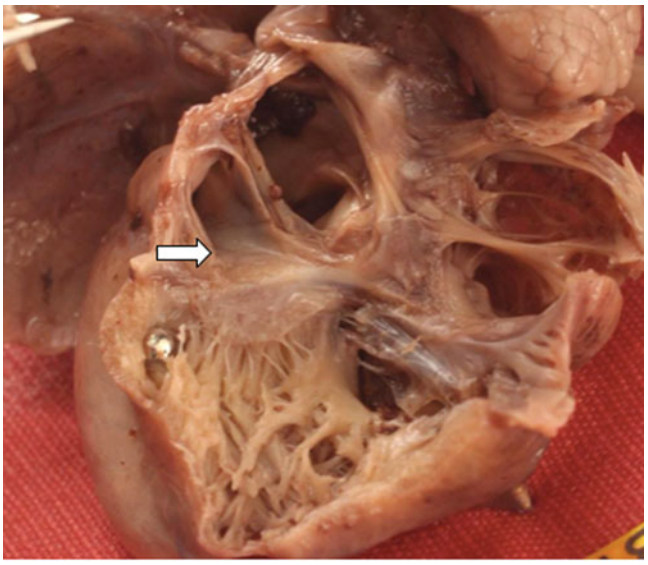

Figure 2. Dilated coronary sinus.

Table 6. Comparison of our study with other similar studies.

Anomaly	Our study $N = 222$	Esmer et al. [1]* $N = 31$	Galindo et al. [2] $N = 55$	Berg et al. [3]* $N = 82$
Isolated PLSVC	None	25.8%	5.5%	9%
Cardiac	67%	48.4%	81.4%	83%
Extra cardiac	96%	54.8%	NA	7%
Isolated Cardiac	4%	NA	NA	23%
Heterotaxy	3.15%	NA	41%	45%
Common associated cardiac defect	Outflow tract and septal defects	NA	Outflow defects	Septal defects
Frequency of PLSVC	4.8% (Autopsy frequency)	NA	0.2% (Normal hearts) 9% (Associated Cardiac defects)- Ultrasound incidence	NA

*Ultrasound studies that include autopsy findings.

respectively [2,3]. Septal defects were found to be the most common cardiac anomaly which is similar to the findings reported by Berg et al. [3] and Esmer et al. [1], whereas in the study by Galindo et al outflow tract anomalies were found to be more common [1–3]. Role of PLSVC in the pathogenesis of cardiac anomalies has been widely studied. Dilated coronary sinus in PLSVC contributing to the development of Hypoplastic left heart syndrome (HLHS) has been speculated in a study by Taweevisit et al. [4]. Similar conclusions were reached in a study by Agnoleti et al. [5] where they found that the overall frequency of obstructive lesions of the left heart with relative hypoplasia of left ventricle was higher in patients with PLSVC than in those without. Cases of hypoplastic left heart syndrome and isomerism of atrial appendages were excluded from their study. In another study by Kula et al. [6] a statistically significant association was present between PLSVC and other congenital cardiac anomalies. The combination of cardiac anomalies found with PLSVC have been attributed to disorders in development of secondary heart field by Postema et al. [7]. Thus association of cardiac defects with PLSVC cannot be ruled out as a co incidence and many such studies need to be done in order to shed light on the embryopathology of the anomaly.

Association of noncardiac findings with PLSVC was high in our study. This could reflect that this is an autopsy series and most of the fetuses had multisystem anomalies. Comparison with control group clearly negates the possibility of a coincidence. Also in the study in pediatric population by Postema et al. [7] 87% of PLSVC cases had CHD and 60% had noncardiac anomalies. This led to conclusion that LSVC is a powerful marker for both cardiac and extra-cardiac anomalies by the authors.

The percentage of heterotaxy syndrome in our study group was less (3%) in contrast to the studies by Berg et al. and Galindo et al. where they reported a frequency of 45.5% and 41%, respectively [2,3]. However our study reflects the percentages in a pure prenatal autopsy series.

The true frequency of syndromes /association could not be studied in this series due to nonavailability of karyotype reports for all the cases. Hence the actual significance of PLSVC in syndromic fetuses remains unknown. However, in a study by Du et al. [8] the frequency of PLSVC was lower among the chromosomally or clinically normal fetuses compared with chromosomally abnormal fetuses. Hence the study concluded that persistent left superior vena cava is more common among chromosomally abnormal than normal fetuses.

Limitations

The limitations of this study is that it is from a single tertiary referral center and does not include the live born with PLSVC. Hence possibility of a skewed dataset is recognized and it might not represent the scenario in general population.

Summary

The frequency of PLSVC was found to be 4.8% in this fetal autopsy series. Overall 96% had extra cardiac anomalies and 67% of cases had associated intrinsic cardiac defects. As prenatal detection rate is very low, we emphasize on the importance of three-vessel view in fetal cardiac screening by ultrasound. Future studies can combine liveborn and autopsy cases for a better understanding of PLSVC and its associations.

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Declaration of interest

The authors declare no conflicts of interests.

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