Fetal left brachiocephalic vein in normal and abnormal conditions

E. SINKOVSKAYA*, A. ABUHAMAD*, S. HORTON*, R. CHAOUI† and K. KARL‡

*Division of Maternal-Fetal Medicine of the Department of Obstetrics & Gynecology Eastern Virginia Medical School, Norfolk, VA, USA; †Prenatal Diagnosis Center, Berlin, Germany; ‡Department of Obstetrics and Gynecology, Ludwig-Maximilians-University, Munich, Germany

KEYWORDS: anomalous pulmonary venous connection; fetal heart; left brachiocephalic vein; venous anomalies

ABSTRACT

Objectives To establish normal values of fetal left brachiocephalic vein (LBCV) dimensions during normal pregnancy and determine whether routine assessment of the LBCV may help in identifying fetuses with congenital abnormalities of this vessel.

Methods Fetal LBCV was assessed prospectively during ultrasound examinations in 431 normal singleton pregnancies. The visualization rate of the transverse view of the upper fetal chest at the level of drainage of the LBCV into the superior vena cava (SVC) by two-dimensional (2D) and 2D plus color Doppler ultrasound was evaluated. Reference ranges of LBCV diameter during non-complicated pregnancies were established. Interobserver and intraobserver measurement variability was analyzed. In addition, a retrospective review of the hospital medical records of 91 pregnancies with fetuses diagnosed with LBCV abnormalities was performed.

Results Sonographic assessment of the fetal LBCV was consistently achieved in the second and third trimesters and in some fetuses in the first trimester of pregnancy. In normal fetuses LBCV diameter increased significantly throughout pregnancy, with a mean value of 0.7 mm at 11 weeks and 4.9 mm at term. Dilation of the fetal LBCV was noted in five cases of intracranial arteriovenous malformation and six cases of supracardiac type total anomalous pulmonary venous connection. Abnormal course of the LBCV was noted in 12 fetuses. In 63 fetuses with a persistent left SVC and a right SVC the LBCV was absent.

Conclusion This is the first study describing an effective sonographic approach for the assessment of fetal LBCV dimensions during pregnancy. The normative data may provide an additional means of detecting rare anomalies of systemic and pulmonary veins during pregnancy.

INTRODUCTION

The region of the upper mediastinum in the fetus has drawn increasing interest since the three vessels and trachea view became part of the comprehensive fetal cardiac examination. In the upper mediastinum, the course of the right subclavian artery can be assessed and the size of the thymus can be measured, with implications for some defined high-risk conditions. In this anatomic region, dorsal to the thymus but slightly cranial and anterior to the transverse aortic and ductal arches, the left brachiocephalic vein (LBCV) can be imaged. The basic anatomy of the LBCV and its associated abnormalities can therefore be assessed and such information can prove valuable in certain clinical conditions.

Embryologically, the left and right brachiocephalic veins are formed behind the sternoclavicular joints by the union of the internal jugular and subclavian veins of the respective side, and unite to form the superior vena cava (SVC). While the right brachiocephalic vein (RBCV) runs vertically downwards in front of the brachiocephalic artery, the LBCV courses almost horizontally across the superior mediastinum in front of the three branches of the aortic arch (Figure 1). The LBCV joins the RBCV behind the manubrium sterni at the lower border of the first right costal cartilage.

It has been shown that the LBCV is significantly dilated in the presence of supracardiac total anomalous pulmonary venous connection (TAPVC). However, normal dimensions of the LBCV have not been established in the fetus.
METHODS

Fetal LBCV was assessed prospectively in 431 consecutive normal singleton pregnancies at 11 + 0 to 39 + 6 weeks’ gestation. Exclusion criteria were maternal age less than 18 years, maternal obesity (body mass index ≥ 30 kg/m²), intrauterine growth restriction or macrosomia, fetal congenital abnormalities and refusal to participate in the study. In addition, a retrospective review of the medical records of 91 pregnancies with fetuses diagnosed with LBCV abnormalities (size, course and absence) between January 2008 and December 2010 was performed. Digital video recordings, three-dimensional volumes and digitally stored images were used for the off-line measurement of the LBCV in this group. The prospective and retrospective cases were obtained from three centers with expertise in fetal echocardiography, which contributed equally to the data collection. A uniform protocol for the visualization and measurement of the fetal LBCV was used in all centers.

Fetal echocardiography was performed according to the official guidelines and standardized cardiac planes were documented in the digital image database. Transabdominal ultrasound was performed for fetal examination of all study patients. In case of inadequate visualization owing to the position of the fetus or suboptimal imaging in the first trimester, the transvaginal approach was used. All ultrasound examinations were performed using Voluson 730 Expert and Voluson E8 ultrasound equipment (GE Healthcare, Kretz Ultrasound, Zipf, Austria) with transabdominal high-resolution 4–8-MHz and RM-6C transducers and a 5–9-MHz transvaginal transducer.

Visualization and measurement of fetal LBCV

When the fetus was in a dorsoposterior position, the LBCV was identified by first visualizing the three vessels and trachea view and then moving the transducer slightly cranially and obliquely to the left side. This plane represents a transverse oblique view of the upper fetal chest at the level of drainage of the LBCV into the SVC (Figure 2). In this plane cross-sections of the three aortic arch branches are seen dorsal to the vein and the thymus and sternum are seen anterior to the LBCV. Color Doppler ultrasound was also used to identify the vein crossing to the right side of the thorax. In order to determine the largest diameter of the vein during late systole when blood return to the veins is highest, cineloop images were reviewed until the maximum diameter was noted.

The anteroposterior diameter of the LBCV was measured in its middle part anterior to the spine using two-dimensional (2D) imaging (Figure 3). In each case the LBCV diameter was measured three times, and the average of these three measurements was used in further analysis to represent the diameter of the LBCV. All measurements were achieved in the absence of fetal breathing, since fetal breathing may alter venous return. Measurements were collected by three independent investigators. In order to evaluate interobserver reproducibility of the LBCV measurements, 50 cases were randomly retrieved and the LBCV diameter was measured by two investigators (S.H. and E.S.) using stored video clips. Both investigators were blinded to the initial measurement and each other’s measurements.

Statistical analysis

Statistical analysis was performed using the SAS 9.1.3 software (SAS, Cary, NC, USA). Normal distribution of continuous variables was assessed with the Kolmogorov–Smirnov test. Continuous variables are reported as mean ± SD or median (interquartile range (IQR)) depending on the data distribution. Categorical data were expressed by frequencies and percentages, and P < 0.05 was considered to be statistically significant. In the control group, regression analysis was used to construct reference ranges with fetal gestational age for LBCV diameter. In each fetus in the prospective and retrospective groups, the measured LBCV diameter subtracted from the respective normal mean for gestational age was used to calculate the delta value. The Kruskal–Wallis test and Dunn’s test were used to determine the significance of differences in the delta values of the LBCV diameter in the abnormal cases and normal controls.

Repeat-measurement ANOVA was used to assess intraobserver variation. Interobserver reproducibility was evaluated by calculating limits of agreement using

![Figure 1 Pathology specimen of the fetal mediastinum in frontal view](Image 50x207 to 486x782).
Fetal left brachiocephalic vein

Figure 2 Transverse oblique view of the upper fetal chest at the level of drainage of left brachiocephalic vein (LBCV) into superior vena cava in pathology specimen (a), two-dimensional ultrasound (b) and color Doppler imaging (c). BCT, brachiocephalic trunk; EsO, esophagus; L, left; LCCA, left common carotid artery; LSA, left subclavian artery; R, right; S, spine; SVC, superior vena cava; Thy, thymus; Tr, trachea.

Figure 3 Two-dimensional ultrasound image showing measurement of the anteroposterior diameter of the fetal left brachiocephalic vein in its middle part.

Bland–Altman analysis and coefficient of variation (CV) in %, for which the following formula was used:

\[ CV = \left( \frac{SD}{(\text{mean of measurement of Observer #1 and Observer #2})} \right) \times 100. \]

RESULTS

In the prospective group, visualization and measurement of the fetal LBCV using 2D ultrasound was successful in most cases in the mid-second and third trimesters of pregnancy (Table 1). The use of color Doppler in addition to 2D ultrasound significantly improved the identification of the vessels at the level of the fetal upper mediastinum and was associated with the highest visualization rate of the fetal LBCV within each gestational age range. Fetal body or breathing movements, anterior position of the fetal spine, small size of the vessel in early gestation and fetal crowding in late gestation contributed to our inability to obtain appropriate views of LBCV in 25/431 (5.8%) cases.

Fetal LBCV diameter was successfully measured in 13/39 (33.3%) fetuses prior to 15 + 0 weeks’ gestation and in 361/392 (92.1%) after 15 + 0 weeks. There was a significant increase in LBCV diameter with advancing gestational age:

\[ \text{diameter} = (0.1442 \times \text{GA}) - 0.8812, \]

where diameter is measured in mm and GA is gestational age in weeks (SD0.31, \( R^2 = 0.87 \); Figure 4).

Detailed analysis of fetal LBCV in the retrospective group of abnormal anatomy highlighted three types of congenital LBCV abnormality: abnormal size of the LBCV secondary to increased venous return across this vessel; abnormal course of the LBCV; and absence of the LBCV. Comparison of median delta values and IQR of the LBCV diameter in fetuses with LBCV abnormalities and normal controls is shown in Table 2.

Significant dilation of the fetal LBCV was identified in 11 fetuses, including four with vein of Galen aneurysm, one with arteriovenous malformation of the dural sinuses.

Table 1 Rate of successful visualization and measurement of left brachiocephalic vein on two-dimensional (2D) and color Doppler ultrasound (US) according to gestational age (GA) (n = 431)

<table>
<thead>
<tr>
<th>GA (weeks)</th>
<th>n</th>
<th>Visualization on 2D + color Doppler US without measurement (%)</th>
<th>Visualization and measurement on 2D-US only (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>11 + 0 to 14 + 6</td>
<td>39</td>
<td>57</td>
<td>33</td>
</tr>
<tr>
<td>15 + 0 to 18 + 6</td>
<td>58</td>
<td>91</td>
<td>85</td>
</tr>
<tr>
<td>19 + 0 to 22 + 6</td>
<td>120</td>
<td>100</td>
<td>94</td>
</tr>
<tr>
<td>23 + 0 to 27 + 6</td>
<td>107</td>
<td>100</td>
<td>96</td>
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<tr>
<td>28 + 0 to 31 + 6</td>
<td>42</td>
<td>100</td>
<td>92</td>
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<tr>
<td>32 + 0 to 35 + 6</td>
<td>51</td>
<td>98</td>
<td>87</td>
</tr>
<tr>
<td>36 + 0 to term</td>
<td>14</td>
<td>90</td>
<td>79</td>
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was absent. In 63 cases there were bilateral SVCs.

Abnormal size of LBCV group: 11.275 (2.450 to 3.531) *.

Abnormal course of LBCV group: 12. -0.019 (-0.109 to 0.090).

Absent LBCV (data for the RBCV group): 5. 0.006 (-0.217 to 0.104).

Data given as n or median (interquartile range). * Significant difference (P < 0.005). RBCV, right brachiocephalic vein.

and six with supracardiac-type TAPVC (Figure 5). In all 11 of these fetuses, the LBCV diameter was found to be significantly higher than in normal controls (P < 0.001) and it was above the 95th percentile in all 11 cases.

An abnormal course of the LBCV was noted in 12 fetuses and included cases of intrathymic and subaortic course of the vein. In six cases the intrathymic course was through the thymus instead of posterior to it, with the shape of the vessel curved instead of straight (Figure 6). Intrathymic course was not associated with any cardiac or extracardiac anomalies. In two cases of pulmonary atresia with ventricular septal defect (VSD) and with right aortic arch and four cases of isolated right aortic arch and left-sided ductus arteriosus, the LBCV coursed posterior to the aortic arch. There were no significant differences in LBCV diameter between fetuses with an abnormal course of the LBCV and fetuses in the normal control group (P = 0.7).

In 68 fetuses with a persistent left SVC, the LBCV was absent. In 63 cases there were bilateral SVCs and no bridging vein as LBCV was found. In five cases there was a left SVC with an absent right SVC and the RBCV drained blood from the right jugular vein to the left SVC (Figure 7). In all five cases the RBCV diameter was within the normal limits for the LBCV-generated norms at the respective gestational age (P = 0.9).

Reproducibility of LBCV diameter measurements

Repeated measurement ANOVA demonstrated that there was no significant difference in the three separate measurements of the LBCV diameter by the same observer (P = 0.84). There was no significant change with gestational age in the intraobserver agreement of LBCV diameter measurement (r = 0.09, P = 0.43).

Mean difference and 95% limits of agreement between paired measurements of LBCV diameter performed by Observer #1 (E.S.) and by Observer #2 (S.H.) were close to zero, with no significant difference. There was no significant change with gestation in the interobserver agreement for measurement of LBCV diameter (r = 0.14, P = 0.56). The interobserver CV for LBCV diameter measurement was 5.9%.

DISCUSSION

This is the first study describing a sonographic approach for the prenatal assessment of the fetal LBCV. The LBCV or innominate vein is formed by the confluence of the left jugular and left subclavian veins, crosses the mediastinum ventral to the great vessels and drains into the SVC. This study shows that the fetal LBCV can be consistently and reliably visualized and measured on 2D ultrasound in the second and third trimesters of pregnancy, and in some fetuses in the first trimester. The diameter of the LBCV increases significantly throughout normal pregnancy, with a mean value of 0.7 mm at 11 weeks and 4.9 mm at term. The LBCV diameter measurements were highly reproducible and in about 95% of cases differences between measurements by the same observer or the measurements by two different observers were within 10% of each other.

In this study we evaluated several conditions that show abnormality of the LBCV including dilation, abnormal course and absence of the vein. A dilated LBCV was found in association with increased perfusion, as observed in association with intracranial arteriovenous malformations. Typically in vein of Galen aneurysm, volume overload leads to dilation of both jugular veins and subsequently dilation of the LBCV and SVC. Arteriovenous fistulae, such as the vein of Galen aneurysm, may be easily identified as a ‘cystic’ intracerebral structure on 2D ultrasound, but other intracranial fistulae, such as arteriovenous malformation of the dural sinus, may not be easily seen and the detection of dilated LBCV in the upper mediastinum may help in seeking for the underlying etiology.

Our study has demonstrated that fetuses with supracardiac-type TAPVC were found to have increased venous return across the LBCV, which resulted in significant dilation of this vessel. Anomalies of pulmonary venous connections can occur as isolated anomalies or as part of complex cardiac malformations. However this diagnosis is difficult to make in the fetus and...
Figure 5 Ultrasound images in transverse oblique view of the upper fetal chest at the level of drainage of left brachiocephalic vein (LBCV) into superior vena cava, demonstrating dilated LBCV in a fetus with a supracardiac form of total anomalous pulmonary venous connection (a) and in a fetus with vein of Galen aneurysm (b). Eso, esophagus; L, left; R, right; S, spine; SVC, superior vena cava; Tr, trachea.

Figure 6 Two-dimensional ultrasound (a) and color Doppler (b) images showing an abnormal course of the left brachiocephalic vein (LBCV) through the thymus. Note the bent shape of the vessel. L, left; R, right; S, spine; SVC, superior vena cava; Thy, thymus.

most cases have been missed prenatally. Recently with improvements in ultrasound technology, a few series and case presentations have reported on the accurate detection of anomalies of pulmonary venous connections in the fetus, either in isolation or as part of heterotaxy syndrome. According to the anatomic site of anomalous connection there are four types of TAPVC: supracardiac, cardiac, infracardiac and mixed type. The supracardiac type is the most common and accounts for about 45% of all cases of TAPVC. In this condition the four pulmonary veins merge behind the left atrium into a confluence vein, which connects via a vertical vein to the LBCV, draining into the SVC. Blood flow from both lungs and from the left jugular vein drains across the LBCV, leading to its significant dilation. In rare occasions in supracardiac TAPVC the drainage can also be directly to the right SVC or to the azygos system of veins.

Despite being a common cardiac malformation, TAPVC is not commonly diagnosed in prenatal series. We believe that targeted evaluation of LBCV diameter may help in the detection of the most common form of supracardiac type of TAPVC. However, the impact on LBCV diameter of site of drainage, presence of obstruction at the site of drainage as well as evolution with gestational age, requires further investigation.
An abnormal course of the LBCV in the fetus is rare. In the retrospective part of this study, six fetuses were found to have presented with an abnormal course of the LBCV through the thymus. The clue to the presence of intrathymic course of the LBCV is the bent shape of this vessel. Abnormal subaortic course of LBCV (ASLBV) in children was recently reported by Nagashima et al.\textsuperscript{12} with an incidence of 0.57\% in association with congenital heart disease and in less than 0.02\% as an isolated finding.\textsuperscript{25}

The authors also reviewed 200 cases of ASLBV from the literature and revealed that in most cases, the course is left lateral to the aortic arch, traversing from the left to the right side, anterior to the trachea, anterior and superior to the pulmonary trunk, and crossing posterior to the ascending aorta. The vein then joins the SVC near the insertion of the azygos vein. In this review it was also noted that an ASLBV is often associated with conotruncal and aortic-arch anomalies, including association with deletion 22q11. Interestingly, 66\% of patients had a right-sided aortic arch. In our series subaortic course of the LBCV was identified in two cases of pulmonary atresia with VSD and four fetuses in combination with a right aortic arch.

Embryologically, the development of the LBCV creates a bridge to the jugular vein to drain the blood directly to the right SVC, and is followed by regression of the left SVC. Absence of this ‘bridging’ vein is typically seen with a persistent left SVC. In our case series, 68 fetuses were diagnosed with a persistent left SVC. None of the 63 fetuses with bilateral SVC had a bridging LBCV. However in five cases with agenesis of the right SVC, an RBCV was identified and the course of this vein was between the right jugular vein and the left SVC. These findings cannot confirm the observations of Huhta et al.,\textsuperscript{6} who reported in 1982 on a bridging vein in 11/20 (55.0\%) of children with bilateral left SVC.

To our knowledge this is the first study to evaluate prospectively the fetal LBCV during pregnancy. We have developed a technique of sonographic visualization of the fetal LBCV and established reference ranges for LBCV diameter in the normal gestation.\textsuperscript{13} These normative data may provide an additional means to help in the detection of anomalies of systemic and pulmonary veins during pregnancy. This is the first study to describe a sonographic approach to the prenatal assessment of the fetal LBCV. Further prospective studies in a clinical setting are needed to confirm the clinical applicability of fetal LBCV assessment in prenatal diagnosis with regard to vascular abnormalities. Our initial results are, however, promising and we suggest

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\textit{Figure 7} Ultrasound images in three vessels and trachea view and transverse oblique view of the upper fetal chest at the level of the left brachiocephalic vein in a fetus with bilateral superior vena cava (SVC) (a, b) and in a fetus with unilateral left-sided SVC (c, d). Ao, aorta; L, left; PA, pulmonary artery; R, right; RBCV, right brachiocephalic vein; S, spine.
that imaging of the LBCV should be incorporated in fetal echocardiography.

ACKNOWLEDGMENT

Thanks to Dr Anna Klassen from the Department of Human Anatomy, Orenburg State Medical Academy of Federal Agency for Healthcare and Social Development, Orenburg, Russia, for providing the pathology specimen illustrations.

REFERENCES

QUERIES TO BE ANSWERED BY AUTHOR & EDITOR

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Queries to Author:

AQ1 Please check that all affiliations are correct and complete

AQ2 Au: I have changed “Interobserver and intraobserver variations were analyzed” to ‘Interobserver and intraobserver measurement variability were analyzed’, ok? (OS)

AQ3 Au: “v. Galen aneurysm” expanded to ‘vein of Galen aneurysm’, is that correct? (OS)

AQ4 Au: “The region of the upper mediastinum in the fetus recently drew increasing interest since the three-vessels-trachea view became part of the comprehensive fetal cardiac examination” reworded to ‘The region of the upper mediastinum in the fetus has drawn increasing interest since the three vessels and trachea view became part of the comprehensive fetal cardiac examination’, ok? (OS)

AQ5 Au: “and the size of the thymic gland can be measured in some defined high-risk conditions” changed to ‘and the size of the thymic gland can be measured, with implications for some defined high-risk conditions’, is that correct? (OS)

AQ6 Author query: ‘thymic gland’ changed to ‘thymus’; OK?

AQ7 Au: Could you give the dates for the prospective part of the study? (OS)

AQ8 Au: “kg/m2” added for BMI, ok? (OS)

AQ9 Au: “fetal growth restriction (IUGR)” changed to ‘intrauterine growth restriction’, ok? (OS)

AQ10 Au: “Uniformed protocol for visualization and measurement of…” changed to ‘A uniform protocol for the visualization and measurement of…’, ok? (OS)

AQ11 Au: “Fetal echocardiography was performed according to the official guidelines…”, whose guidelines did you use? (OS)

AQ12 Au: “When the fetus was in a dorsoposterior position first visualizing the three-vessel-trachea view and then moving the transducer slightly cranially and oblique to the left side identified the LBCV” reworded to ‘When the fetus was in a dorsoposterior position, the LBCV was identified by first visualizing the three vessels and trachea view and then moving the transducer slightly cranially and obliquely to the left side’, ok? (OS)

AQ13 Au: “Measurements were collected by three independent investigators”, I assume that this is across the study rather than in each individual fetus, could we clarify this here? (OS)

AQ14 Au: “median (range)” changed to ‘median (interquartile range (IQR))’ as seems to be reported, ok? (OS)

AQ15 Author query: Does this mean that the K–W test was used for abnormal cases, and the Dunn’s test for normal ones? If so, could we add ‘, respectively’ to the end of the sentence? (OS)

AQ16 Author query: ‘Repeated measurements ANOVA were used’ changed to ‘Repeat-measurement ANOVA was used’; is that OK?

AQ17 Au: I have added units of mm for delta LBCV diameter, is that correct? (OS)

AQ18 Au: “data for RBCV”, ‘data for’ added here, is that correct? (OS)

AQ19 Au: “In all 11 fetuses with abnormalities” changed to ‘In all 11 of these fetuses’, ok? (OS)

AQ20 Au: “and no bridging vein as LBCV was found”, I’m sure that this makes sense to anyone with a medical knowledge of anatomy, but this does not seem quite clear to me. Would something like the following be correct: ‘and no bridging vein such as the LBCV was found’? (OS)

AQ21 Au: “three separated measurements of the LBCV” changed to ‘three separate measurements of the LBCV’ here (i.e. just ‘d’ removed), ok? (OS)

AQ22 Au: “Repeated measurement ANOVA demonstrated that there was no significant difference in the three separate measurements of the LBCV diameter by the same observer (p=0.84)”. I am not familiar with the use of repeat measures ANOVA to assess reproducibility in this way. However, from my understanding of ANOVA models, I suspect that an intraobserver variance component will have been assessed. If so, would something along the lines of the following perhaps be more accurate here: ‘Repeated measurement ANOVA demonstrated that the intraobserver variance component, formed by the three separate measurements of LBCV diameter by the same observer in each case, was not significant overall (p=0.84)? (OS)
Queries to Author:

AQ23 Au: Could you provide the actual mean difference (perhaps with 95%CI) and 95% limits of agreement here? (OS)

AQ24 Au: “This study shows that the fetal LBCV can be reliably visualized and measured on two-dimensional ultrasound in the first, second and third trimesters of pregnancy” changed to “This study shows that the fetal LBCV can be consistently and reliably visualized and measured on 2D ultrasound in the second and third trimesters of pregnancy, and in some fetuses in the first trimester” to match better the results presented, ok? (OS)

AQ25 Au: “the retrospective part of” and “were found to have” added here, ok? (OS)

AQ26 Author query: Please confirm that CHD is congenital heart disease.

AQ27 Author query: Would something on the lines of ‘... should be incorporated in the standard fetal echocardiographic scan.’ Be appropriate here?

AQ28 Have the editors’ names for Ref. 11 been given correctly?
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