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# Aberrant right subclavian artery at 16 to 23 + 6 weeks of gestation: a marker for chromosomal abnormality

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**KEYWORDS:** aberrant right subclavian artery; aortic arch; fetal heart; second-trimester screening; trisomy 21

## ABSTRACT

***Objectives*** *This study was carried out to determine the feasibility of defining the position of the right subclavian artery (RSA) by fetal echocardiography between 16 and 23 weeks of gestation, and the association between an aberrant right subclavian artery (ARSA) and chromosomal and cardiac defects.*

***Methods*** *We examined the position of the RSA in all patients who attended our unit for a fetal cardiac scan. The assessment was carried out using a transverse view of the fetal chest sweeping up from the level of the aortic arch, using color flow mapping. An ARSA was diagnosed when this vessel was not seen in the normal position and an arterial vessel was seen crossing behind the trachea towards the right arm, arising as a fourth branch of the aortic arch, at a lower level than normal.*

***Results*** *The course of the RSA could be identified in more than 95% of the 2799 fetuses examined between 16 and 23 + 6 weeks of gestation. An ARSA was found in 43 fetuses. The incidence was 1.5% in normal fetuses, 28.6% in fetuses with trisomy 21, 18.2% in fetuses with trisomy 18 and 8% in fetuses with other chromosomal defects. There was an association between an ARSA and cardiac defects in seven of the 43 fetuses (16%), and three of these seven fetuses had a normal karyotype.*

***Conclusions*** *Assessment of the RSA by a fetal cardiologist is possible in almost all cases. The finding of an ARSA is much more common in fetuses with chromosomal defects, in particular trisomy 21 (where the prevalence of an ARSA was 29%), compared with euploid fetuses. Moreover, the presence of an ARSA may be associated with an increased incidence of intracardiac malformations. Examination of the position of the RSA is likely to become a routine ultrasound marker for chromosomal abnormalities in the second trimester of pregnancy.* 

## INTRODUCTION

Abnormalities of the aortic arch are fairly common malformations, occurring as variants in the normal population or, alternatively, occurring in association with intracardiac anomalies. One such arch abnormality is an aberrant origin of the right subclavian artery (ARSA). This artery usually arises above the level of the aortic arch, as the first branch from the innominate (or brachiocephalic) artery, which in turn is the first vessel that arises from the aortic arch (Figure 1). However, autopsy studies[1] have shown that in about 1–2% of normal people, the right subclavian artery (RSA) arises anomalously as a fourth branch of the aortic arch. In contrast to the normal vessel, which arises at the level of the shoulders and travels almost horizontally rightwards, the aberrant vessel arises from the first portion of the descending aorta and passes behind the trachea and cranially as well as rightwards (Figure 2). It has been noted in autopsy series and in cardiac catheterization studies that there is an increased incidence of this anomaly in cases of trisomy 21, although the incidence varied between 2.8 and 100%[2–8]. However, there was an element of selection bias in some of these studies, in that those patients with Down syndrome who were subjected to catheterization or autopsy were usually known to have intracardiac congenital heart disease (CHD). It should be noted that ARSA is, in general, an asymptomatic benign finding, although esophageal compression, resulting in dysphagia, has been reported in some cases[9–12].

An ARSA is not easy to identify at routine postnatal echocardiography, so its incidence (either in the normal

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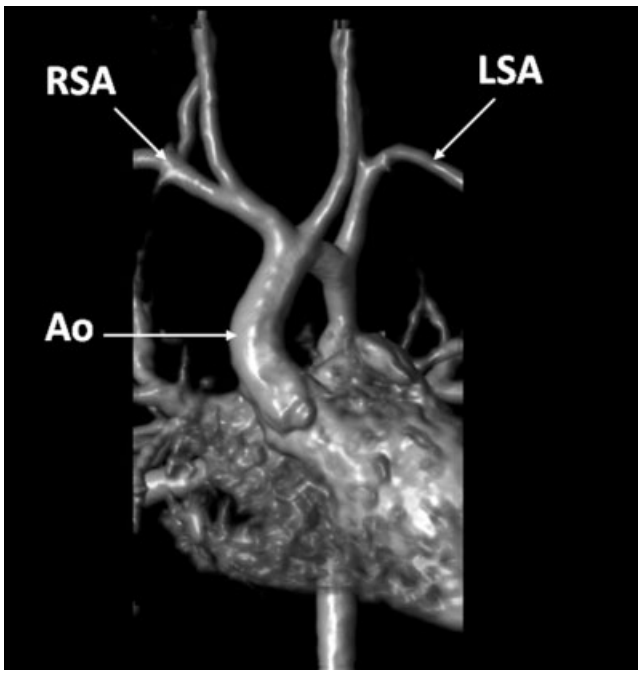


**Figure 1** Postnatal magnetic resonance image demonstrating normal origin of the left (LSA) and right (RSA) subclavian arteries Ao, aorta.

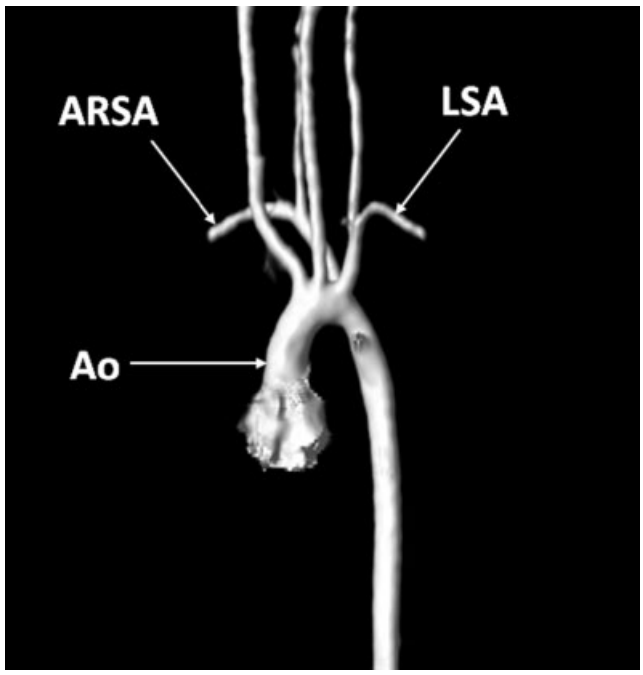


**Figure 2** Postnatal magnetic resonance image demonstrating an aberrant right subclavian artery (ARSA) arising from the descending aorta (Ao). Note that the course of an ARSA would not be seen in a standard long-axis view of the aortic arch. LSA, left subclavian artery.

population or in cases with Down syndrome) has not been addressed recently using non-invasive technology. A study published in 2005[13], however, described the identification of this artery during fetal echocardiography and re-emphasized the association of an aberrant origin with trisomy 21. Two recent prenatal ultrasound studies reported an incidence of ARSA, of about 28% and 37%, respectively, in trisomy 21 fetuses between 13 and 26 weeks of gestation[14,15].

The aim of this study was threefold: first, to determine the feasibility of the prenatal assessment of the RSA during fetal echocardiography; second, to evaluate the association between ARSA and chromosomal abnormalities; and, third, to evaluate the association between ARSA and cardiac defects prenatally.

## METHODS

The course of the RSA was investigated during fetal echocardiography in all patients who attended our Unit between March 7 2006 and December 31 2007. For this analysis, only singleton pregnancies between 16 and 23 + 6 weeks of gestation with a left aortic arch were included. All cardiac examinations were carried out by a specialist fetal cardiologist, using mainly a Voluson E8 ultrasound system (RAB 4-8-D probe; GE Medical Systems, Milwaukee, WI, USA). In order to visualize the fetal RSA, a previously described technique was followed[16]. A transverse view of the fetal thorax, at the level of the aortic arch, was obtained and the arch was confirmed to cross the midline from right to left in a normal manner; if necessary, the probe was moved to position the fetal spine at 3 or 9 o'clock, so that the subclavian artery would be either going directly up towards the transducer or directly away from it. Color flow mapping was then used to identify the horizontal course of the RSA. The normal course of this artery is tortuous, arising from the brachiocephalic trunk and crossing the upper thorax in front of the trachea towards the right arm, at the level of the clavicles. The accompanying vein can sometimes be identified anterior to the artery (Figures 3 and 4). In contrast, an ARSA arises as a fourth branch of the arch, and therefore at a lower level, close to the junction of the arterial duct with the descending aorta. Its course is diagonal and crosses the thorax posterior to the trachea, between the trachea and the spine, to reach the right arm. A wide separation can be seen between the artery and its accompanying vein, which maintains its normal position behind the clavicle (Figure 5). In some cases, pulsed Doppler of the vessel behind the trachea was used to confirm that the vessel behind the trachea was arterial, as the hemiazygous vein can, in rare cases, lie in this position.

The position of the RSA was classified as normal, aberrant or not possible to identify. Only a few minutes during the fetal echocardiographic examination were allocated to the classification of the course of the RSA. All data were recorded in our database, together with maternal demographic data and other results from fetal ultrasound examinations, for subsequent analysis.

The outcomes of each pregnancy, including the presence of fetal abnormalities, cardiac defect and karyotype were collected. The karyotype was obtained from a chorionic-villous or amniotic fluid sample prenatally

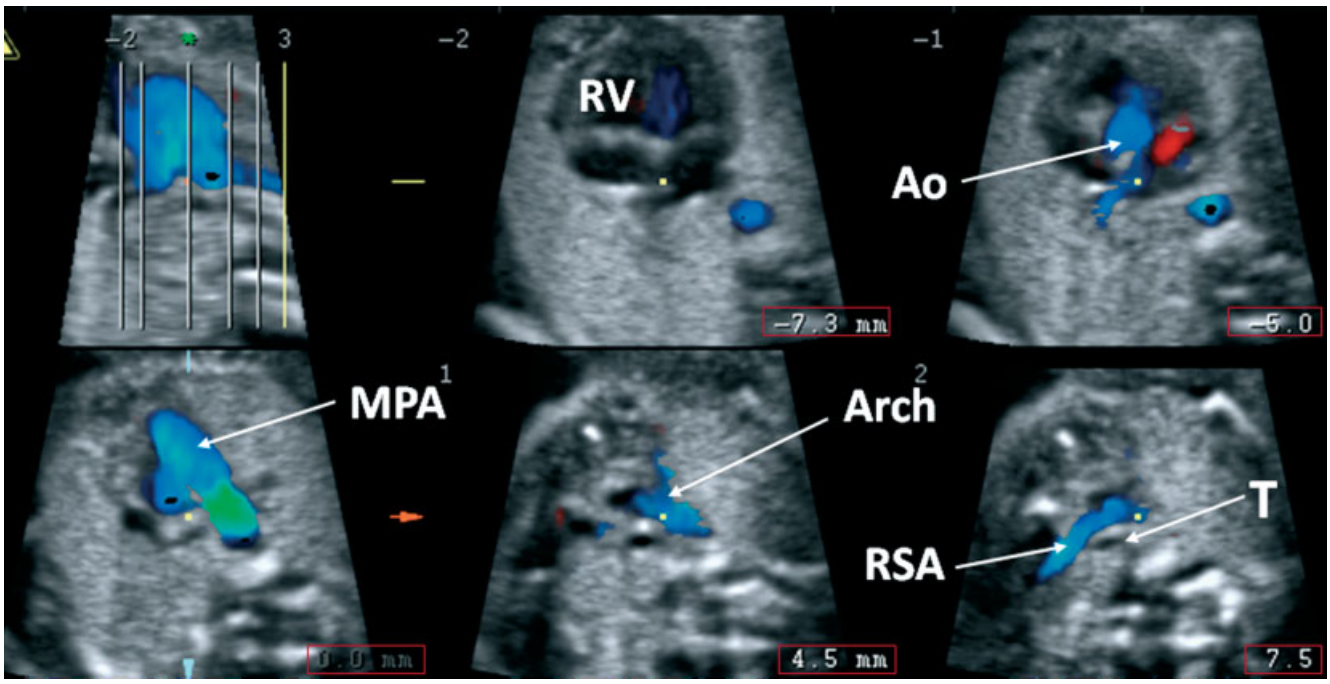


**Figure 3** Tomographic images demonstrating the relationship of the normal right subclavian artery (RSA) to the standard views. Note that the normal RSA lies 3 mm above the level of the transverse arch and 14.8 mm above the level of the four-chamber view in this 20-week fetus. Ao, aorta; MPA, main pulmonary artery; RV, right ventricle; T, trachea.

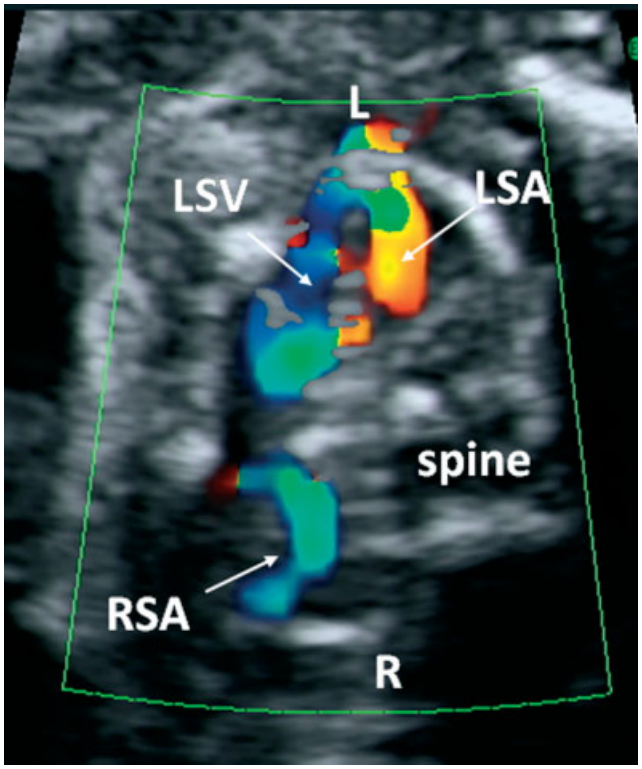


**Figure 4** Just above the level of the aortic arch, the right (RSA) and left (LSA) subclavian arteries are seen in their normal position on color flow mapping. In order to distinguish the arteries from the arm veins, which run close to each other, the color map must be as expected, with flow away from the aortic arch in both vessels. Also, a long course of vessel extending outside the confines of the thorax must be seen, which will ensure distinction from the branch pulmonary arteries that lie just below the arch. L, left; LSV, left subclavian vein; R, right.

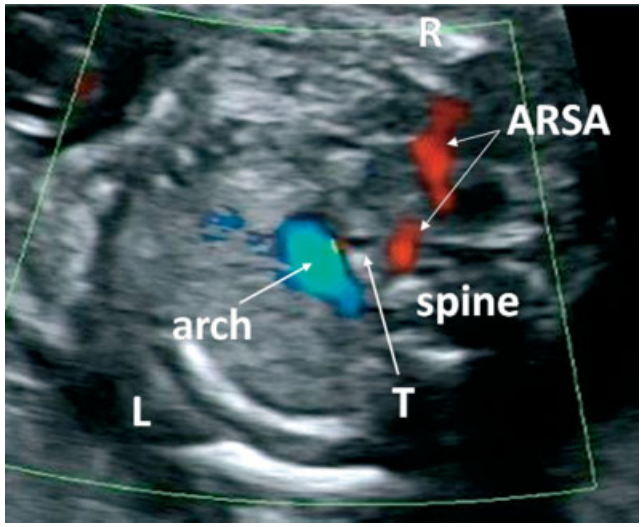


**Figure 5** An aberrant right subclavian artery (ARSA) arises from the descending aorta behind the trachea and below the level of the aortic arch at the level of the arterial duct, in contrast to a normal right subclavian artery that would arise above the arch. L, left; R, right; T, trachea.

or from a blood-test sample of a neonate with suspicious features of a chromosomal anomaly. In cases where no karyotype was obtained prenatally, the karyotype was considered normal if the newborn appeared clinically normal to the local examining pediatrician.

The chi-squared test was used to examine whether there was a significant difference in the incidence of ARSA between the chromosomally normal and abnormal fetuses.

## RESULTS

We attempted to assess the RSA in 2799 patients and this was considered successful in 2670 (95.4%).

The median gestational age was 20 + 3 (range, 16 + 0 to 23 + 6) weeks. Fetal echocardiography was performed for the following indications: increased nuchal translucency following first-trimester screening (49.9%); a family history of cardiac defects (10.6%); an extracardiac fetal defect (8.3%); risk re-assessment following second-trimester biochemistry tests or lack of screening for chromosomal defects (7.3%); maternal condition, including diabetes, epilepsy and others (5.8%), suspected cardiac defect (5.3%), or maternal medication (4.2%); abnormal second-trimester ultrasound marker (2.6%); and other reasons (6%).

An ARSA was found in 43 out of the 2670 fetuses in which the RSA was successfully assessed. Within this group of 43 fetuses, 28 (65.1%) were chromosomally or clinically normal and 12 (27.9%) had an abnormal karyotype (eight with trisomy 21, two with trisomy 18, one with monosomy chromosome X and one with partial monosomy chromosome). Three (7%) fetuses were lost to follow-up, but no structural abnormalities for these fetuses had been detected upon scanning. Chromosomal abnormalities were diagnosed by prenatal or postnatal karyotyping or by clinical assessment of the newborn. In 236 (8.8%) cases the outcome of pregnancy remains unknown because of either the lack of fetal karyotype data or postnatal follow-up data. In Table 1, the RSA assessment according to the fetal karyotype or outcome is summarized.

The incidence of ARSA was significantly lower in the normal fetuses (chromosomally or known normal outcome) compared with the trisomy 21 fetuses ($P < 0.001$). Similarly, ARSA was more common in the fetuses with trisomy 18 ($P < 0.001$) and all other chromosomal abnormalities ($P = 0.002$) compared with the normal fetuses.

In the group of 2670 fetuses in which the RSA was successfully assessed, a cardiac defect was found in 120, 113 (94%) of which had a normal RSA. Therefore, in the group of 43 fetuses with an ARSA, seven (16.3%) had an intracardiac defect. Of these seven fetuses, three had a normal karyotype. In these three fetuses, the diagnosis was tetralogy of Fallot with pulmonary atresia in two and coarctation of the aorta in one. In the four fetuses with a karyotype anomaly, there was an atrioventricular septal defect in one fetus with trisomy 21, a ventricular septal defect and an atrioventricular septal defect in one each of two fetuses with trisomy 18, and tetralogy of Fallot in one case with partial monosomy of chromosome 3. One further case with trisomy 21 was found to have a ventricular septal defect, in addition to ARSA, after birth.

In the 12 fetuses with ARSA and a chromosomal anomaly, 11 had one or multiple other markers of chromosomal anomaly. In one fetus, however, the ARSA was the only abnormal finding.

**Table 1** Outcome of pregnancy and position of the right subclavian artery (RSA) in fetuses in which the RSA was successfully assessed

| | | *RSA position* (n *(%)*) | |
|---|---|---|---|
| *Outcome* | n | *Normal* | *Aberrant* |
| Normal karyotype | 932 | 918 (98.5) | 14 (1.5) |
| Normal clinical assessment | 1438 | 1424 (99.3) | 14 (0.97) |
| Trisomy 21 | 28 | 20 (71.4) | 8 (28.6) |
| Trisomy 18 | 11 | 9 (81.8) | 2 (18.2) |
| Other chromosomal defects | 25 | 23 (92) | 2 (8) |
| No follow-up data | 236 | 233 (98.7) | 3 (1.2) |
| Total | 2670 | 2627 | 43 |

## DISCUSSION

There were three main findings of this study. First, it was possible to assess the position of the RSA during mid-trimester fetal echocardiography, and successful evaluation was achieved in more than 95% of cases. The analysis was restricted to the gestational age range between 16 and 23 + 6 weeks in order to evaluate the usefulness of assessment of the RSA around the typical time for routine scanning. Since the conclusion of the study, RSA assessment has become part of our normal fetal echocardiographic examination, giving an even higher successful evaluation rate than was achieved in the present study. Second, ARSA was much more common in chromosomally abnormal than normal fetuses; and, third, in the karyotypically normal fetus, the presence of ARSA appears to coincide with an increased risk of CHD.

The incidence of ARSA in the normal population has been reported to be about 0.5–2% in prenatal and postmortem studies[1,4,15–17]. The results of this study confirm the findings of other, smaller, studies with an incidence of ARSA of 1.5% in chromosomally normal fetuses. In the group without karyotype confirmation, but otherwise normal, the incidence of ARSA was also about 1%.

The incidence of ARSA in the trisomy 21 population reported by pathological and postnatal studies varies between 2.8 and 100%[2–8] and therefore the real incidence remains unclear. However, prenatal studies reported a prevalence of ARSA of 28–37% in affected fetuses in the second trimester of pregnancy[13–15] and about 8% in the first trimester[16]. In our population, the incidence of ARSA was found to be 28.6% in 28 fetuses with Down syndrome. According to our data, the presence of ARSA in the 16- to 23-week gestational age-range increases the risk for trisomy 21 by about 20-fold, and for trisomy 18 by about 12-fold.

The incidence of ARSA is 1.5% in those with a normal karyotype, but 3% in the group with CHD and a normal karyotype, suggesting an increased association of this finding with CHD of about double, consistent with the report of Zapata *et al.*[1]. However, the group we studied was referred for fetal echocardiography (nearly 50% had an increased nuchal translucency) and therefore was at increased risk for CHD. This is evidenced by the rate

of CHD of 4%, compared with the expected rate in an unselected population of about 0.6–0.8%. This may have biased this aspect of our results.

One limitation of our study is that there was no outcome in 8% of cases. In addition, there was no way of confirming our diagnosis of ARSA, or indeed a normal RSA, as the course of the RSA is not readily detectable by echocardiography in postnatal life. However, an ARSA was confirmed in two of the newborns with a prenatal diagnosis of an intracardiac defect, who underwent cardiac surgery. Further tests, such as magnetic resonance imaging, which is the best method of visualizing the RSA after birth, are not justifiable in an asymptomatic newborn.

The karyotype of about one-third of the cases that were assessed using fetal echocardiography was known to the examiner, so this may have introduced some bias in detection.

A further limitation is the possibility of 22q11 deletion, which was not sought in the majority of cases where the fetal karyotype was available. The Di George deletion is also a condition that may not be clinically obvious in the neonate and therefore overlooked. Although, to our knowledge, isolated ARSA is not a condition that is associated with 22q11 deletion, it is grouped as an 'arch anomaly', some of which do have a known association with this deletion, for example, an interrupted aortic arch. One publication[18] suggests that, at least in the setting of associated conotruncal malformations, a left arch with an aberrant left subclavian artery had a high association (85%) with 22q11 deletion.

Zalel *et al.*[15] found that all their fetuses with an ARSA and chromosomal defects had other markers suggestive of chromosomal anomaly. However, one of our 12 fetuses had no other markers, so the absence of other markers cannot be relied upon to exclude trisomy 21 in particular.

The advantages of our study are the large number of fetuses examined, the large number of chromosomal defects and the assessment by a specialist fetal cardiologist.

Moreover, this is, to our knowledge, the largest number of cases reported to date. However, this was a highly selected group which was examined by specialists. We believe that identifying the position of an RSA is not difficult for the fetal cardiologist and is fairly easy for sonographers with experience in evaluating the fetal heart. However, the results obtained here may be difficult to reproduce in a screening setting and certainly will require a period of training for those less skilled in fetal cardiac scanning.

We have now incorporated the assessment of RSA into our routine fetal echocardiographic examination, and in the presence of an isolated ARSA we discuss the option of an invasive test with the parents. Data on the position of the RSA in an unselected low-risk population are not yet available; however, we believe that if such studies confirm our findings, the assessment of the position of the RSA may become a useful marker for chromosomal defects, especially if used in combination with other ultrasound markers.

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