Aberrant Right Subclavian Artery—To Test or Not to Test, That Is the Question

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Abstract

Objectives This study aimed to determine if isolated fetal aberrant right subclavian artery (ARSA) is associated with an increased risk of chromosomal abnormalities and to see whether or not invasive testing should be considered.

Methods We conducted a retrospective study from January 2017 to December 2021. All prenatally diagnosed cases of ARSA were reviewed and their clinical data were collected. Amniocentesis was advised after genetic counseling in every case of ARSA.

Results One hundred and thirteen patients of ARSA were diagnosed at 21.2 ± 2.4 weeks of gestational age. Eighty-eight fetuses had isolated ARSA. Eighty-three patients underwent amniocentesis. Of those, six had Down syndrome and one had Turner syndrome. Four fetuses with genetic abnormalities had no other ultrasound findings; however, the association of isolated ARSA with chromosomal abnormalities was not statistically significant (p-value $= 0.998$). Ten patients underwent termination of pregnancy including seven with chromosomal abnormalities and three fetuses with other structural anomalies. The mean age of postnatal follow-up was 2.2 years. Mild respiratory distress was seen in one fetus. No neonatal intensive care unit admissions were present.

Conclusion Isolated ARSA by itself does not significantly increase the risk of associated chromosomal abnormalities. The detection of fetal ARSA, however, mandates a detailed fetal ultrasound. Invasive testing can be deferred in cases of isolated ARSA. Larger prospective studies are required to see the role of cell-free DNA as an optimal alternative option.

Keywords
- amniocentesis
- ARSA
- Down syndrome
- trisomy 21

Introduction

Aberrant right subclavian artery (ARSA) is the most common aortic arch anomaly with an incidence of 1 to 2.3%. It arises directly from the aorta, as its fourth branch distal to the left subclavian artery and courses behind the trachea toward the right shoulder.[1–3] The aortic arch normally gives rise to three branches, the right brachiocephalic trunk, the left common carotid, and left subclavian artery. The right subclavian artery (RSA) and right common carotid arises from right brachiocephalic trunk (►**Fig. 1**)

Three vessel trachea view with low pulse repeatation frequency (PRF) settings has made the diagnosis of ARSA relatively easy with the vessel seen originating at the

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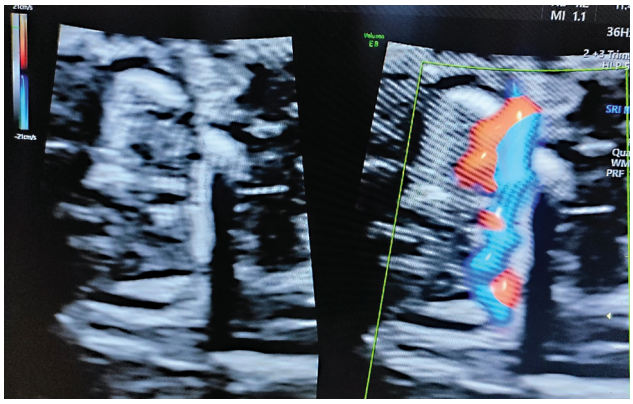

Fig. 1 Normal path of right subclavian artery in **S**-shaped manner.

junction of aortic and ductal arch traversing behind the trachea.[3] Confirmation of the diagnosis can be achieved by additional coronal views allowing direct visualization of ARSA coming from aorta toward the right shoulder (►**Fig. 2**).

The incidence of ARSA in trisomy 21 ranges from 28.5 to 37.5%.[4] Previous studies have showed high diagnostic performance of ARSA in detecting trisomy 21, with positive likelihood ratio (LR) ranging from (LR+) 0 to 29.6 for isolated anomaly and (LR+) 12.6 to 42.04 for nonisolated anomaly. The estimated pooled global positive LR (LR+) and negative LR (LR–) for ARSA were 35.3 (95% confidence interval [CI], 24.4–51.1) and 0.75 (95% CI, 0.64–0.87), respectively.[5–9]

However, a few recent studies have challenged this association, thereby creating a dilemma toward the utility of ARSA in diagnosing trisomy 21.[1,3] This study addresses these disputes by retrospectively evaluating the structural and chromosomal abnormalities associated with fetal ARSA along with its clinical outcome.

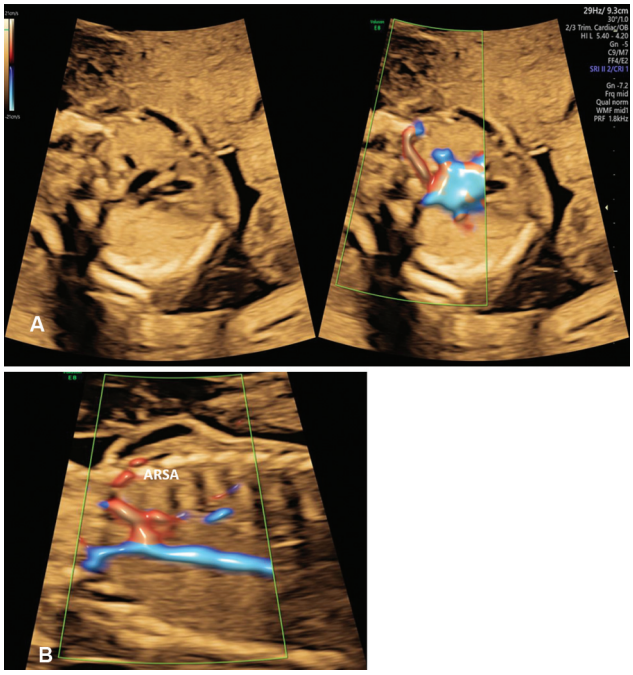

Fig. 2 (**A**) Axial section at three-vessel trachea view showing aberrant right subclavian artery (ARSA) behind the trachea. (**B**) Coronal section showing ARSA arising directly from aorta.

The aim of this study is to assess whether isolated fetal ARSA is associated with Down syndrome or any other chromosomal abnormalities and to see whether or not invasive testing should be considered.

Materials and Methods

After approval from institutional ethical board and taking informed consent, this retrospective study was conducted at CIMAR Fertility Centre, Kochi and Edappal Hospital, Kerala, from January 2017 to December 2021. All prenatally diagnosed cases of ARSA were reviewed and their clinical data were collected.

The antenatal screening of ARSA was done as described by Chaoui et al, in 2005[6] at the three-vessel trachea view with simultaneous two-dimensional and color Doppler images at low PRF settings. Normally, the RSA is seen at the level of clavicle running anterior to trachea in an S-shaped fashion. ARSA has a relatively straighter course traversing behind the trachea toward the right arm, originating from the V in the three-vessel trachea view. The terminology of isolated ARSA was used when no other associated structural anomalies were seen.

As per hospital protocol, upon detection of ARSA, dedicated fetal echocardiography was done using International Society of Ultrasound in Obstetrics and Gynaecology (ISUOG) guidelines and detailed anomaly scan was done to look for any additional abnormalities using transabdominal and/or transvaginal route on GE VolusionS8, E8, and E10 machine. Genetic counseling with invasive amniocentesis was offered to all patients. Genetic testing is done by either karyotyping, comparative genomic hybridization (CGH) Microarray and/or exome sequence.

Results

One hundred and thirteen patients with ARSA were detected from January 2017 to December 2021. The mean gestational age was 21.2 ± 2.4 weeks and the mean maternal age at diagnosis was 28.9 ± 5.4 years. Five patients (4.4%) were diagnosed in first trimester, 2 patients (1.75%) in third trimester, and remaining 106 patients (93.85%) in second trimester during anomaly scan. Of total 113 patients, 83 patients underwent amniocentesis, while the remaining 30 patients refused, of which one agreed for noninvasive prenatal testing (NIPT) and 6 patients underwent genetic sonogram for further evaluation. The fetuses for whom karyotyping was not done had no complaints in postnatal life thus excluding any major chromosomal anomalies. Eighty-eight of one hundred and thirteen cases had isolated ARSA, while remaining 25 patients had either associated cardiac, extracardiac anomalies, or had high risk in combined testing.

Of 83 patients who underwent amniocentesis chromosomal rearrangements were seen in nine patients. Six patients with ARSA had Down syndrome, one had high risk on combined testing (1:90), while three had low screening risk but had few additional soft markers like echogenic

Table 1 All cases of ARSA with associated chromosomal abnormalities

Sl. no.	GA (wk)	Maternal age (y)	Indication	Associated abnormalities	Diagnosis	Management
1	25	23	Second opinion for multiple soft markers	TR with EIF	Trisomy 21	Terminated
2	16	25	Early anomaly	None	Trisomy 21	Terminated
3	22	19	Anomaly scan	None	Trisomy 21	Terminated
4	16	28	Anomaly scan	Absent nasal bone	Trisomy 21	Terminated
5	20	21	Anomaly scan	EIF	Trisomy 21	Terminated
6	21	25	2nd opinion CT T21 high risk	None	Trisomy 21	Terminated
7	26	32	Anomaly scan	None	Turner syndrome	Terminated
8	20	27	Anomaly scan	None	Inversion of chromosome 9	2 years old normal child
9	20	29	Anomaly scan	TR with EIF	Inversion of chromosome 9	3.5 years old, normal child

Abbreviations: ARSA, aberrant right subclavian artery; CT, combined test; EIF, echogenic intracardiac focus; GA, gestational age; TR, tricuspid regurgitation.

intracardiac focus (EIF), absent nasal bone (NB), and tricuspid regurgitation (TR). Lastly, the remaining two patients had isolated ARSA, with no other associated abnormalities and low risk on combined tests (►**Table 1**). The association of feta ARSA with Down syndrome was, however, not significant (p-value = 0.998).

Three fetuses had other chromosomal abnormalities besides Down syndrome, one had Turner syndrome that was associated only with isolated ARSA, while other two had normal variants (inversion of chromosome 9) of which one was associated with EIF and TR.

Table 2 Distribution of various structural abnormalities with ARSA

Soft markers	
Absent/hypoplastic NB	6
Bilateral pelvicalyceal dilatation	4
Increased NF	2
Echogenic bowel	2
CP cyst	3
Cardiovascular anomalies	
AVSD	1
Coarctation of aorta with left SVC	1
Dilated and tortuous pulmonary artery	1
Skeletal abnormalities	
Bilateral club foot	2
CNS anomalies	
Partial/complete agenesis of corpus callosum	2
Facial abnormalities	
Retrognathia	1

Abbreviations: ARSA, aberrant right subclavian artery; AVSD, atrioventricular septal defect; CNS, central nervous system; CP, choroid plexus; NB, nasal bone; NFT, nuchal fold thickness; SVC, superior vena cava.

Various structural anomalies were seen in association with ARSA, most common being soft markers ($n = 17$; ►**Table 2**) followed by cardiovascular anomalies ($n = 3$), limb abnormalities ($n = 2$), central nervous system malformations ($n = 2$), and facial abnormalities ($n = 1$; ►**Table 2**).

Ten patients opted for the termination of pregnancy as a result of trisomy 21 (6), Turner syndrome (1), complete corpus callosum (CC) agenesis with bilateral club foot (1), partial agenesis of CC with hypoplastic NB (1), and absent NB with increased nuchal fold thickness (1). Intrauterine fetal demise occurred in one fetus having ARSA along with coarctation of aorta and left superior vena cava and one fetus with ARSA and atrioventricular septal defect expired at 18 months of age.

Postnatal follow-up was done in all infants except for those who did not progress to term. The mean age of follow-up was 2.2 years. Only one patient with isolated ARSA had complaints of respiratory distress with stridor, which resolved spontaneously thereafter.

Discussion

In this retrospective study, the presence of Down syndrome was seen in 6.6% of the cases with ARSA. ARSA is considered one of the major soft markers for Down syndrome along with absent NB, increased nuchal fold, and ventriculomegaly.[10] The incidence of Down syndrome in our study was in agreement with studies done previously ranging from 7 to 30%.[2,4–9,11–15]

The technique for prenatal visualization of normal/aberrant RSA has been described by several groups in the past. In studies by Borenstein et al[7] and Rembouskos et al,[13] identification of RSA was successfully done in 84 and 85% of cases in the first trimester ultrasound and 95 and 98% of cases in the second trimester, respectively. In our experience, though

assessment of ARSA is not as simple as other major soft markers (increased NF, absent NB, and ventriculomegaly), with special skill and proper learning curve the assessment of RSA was possible in all our cases.

Four cases of isolated ARSA with no other ultrasound findings had associated chromosomal malformations in our study. In all four cases, maternal age was less than 35 years. One case of trisomy 21 had high combined risk (1/90) while remaining three cases including two of Down syndrome and one of Turner syndrome that were totally isolated had no other abnormalities.

Similar results have been mentioned before in literature (►**Table 3**). In the study conducted by Chaoui et al,[6] Gul et al,[13] and Esmer et al[8] (total 8 cases), the maternal age was more than 35 years in 6/8 cases and the remaining 2 cases had high combined risk. Both Borenstein et al[7] and Paladini et al[2] reported total nine cases of chromosomal aberrations with isolated ARSA. In our study, there was no associated risk factor other than isolated ARSA.

However, few recent studies by Pico et al[14] and Ranzini et al[3] reported no association of isolated ARSA and Down syndrome. Pico et al reported 108 cases of ARSA of which 54 were isolated. Fetal karyotyping was performed in 59/108 (54%) fetuses. Chromosomal abnormalities were seen in 22 cases of which 11 had other ultrasound findings, 10 had ultrasound findings with congenital heart disease (CHD), and 1 case had only CHD. In the study by Ranzini et al,[3] there were total 43/79 cases of isolated ARSA and 11 cases of chromosomal malformations. Seven of eleven cases had trisomy 21 and 4/11 cases had other chromosomal abnormalities. All 11 cases had associated ultrasound abnormalities and 6/7 cases of Down syndrome had high adjusted priori risk.

Interestingly, of the six cases with Down syndrome and one with Turner syndrome no other structural abnormalities were seen. Only one case of Down syndrome had a significant marker, that is, unossified NB, which means even though the association of ARSA with Down syndrome was not significant, if we had overlooked ARSA, five of seven cases in this group would not have had invasive testing and would have undiagnosed Down syndrome neonate at birth. Hence, the diagnosis of ARSA significantly modified the risk of patients in this group thereby enabling timely detection.

Previous studies conducted by Shah, Ranzini et al, and Martínez-Payo et al[1,3,16] that also had nonsignificant results did not find any single cases of isolated ARSA with Down syndrome. However, in our study we had two truly isolated cases associated with Down syndrome and one with Turner syndrome, still the result came not significant (p-value $= 0.998$). Thus, this study provides a better understanding of correlation of ARSA with chromosomal abnormalities as it removes the assumption which may arise that previous researchers might be dealing with low-risk population. Larger prospective trials may be needed to assess the cost-effectiveness of routine evaluation of the ARSA but till then its effect and utility as significant marker for Down syndrome are reconfirmed with this study.

In our study, ARSA was associated with other structural abnormalities in 25/113 cases, which is slightly less as compared with the reports published by Ranzini et al (36/79) and Pico et al (54/108).[3,14] This can be due to variation in the study population.

Lastly, 22q11.2 deletion has been associated with ARSA in literature; however, we could not find any such case, suggesting low incidence in our population.

Only one patient had few episodes of respiratory distress with mild stridor that resolved by itself. No neonatal intensive care unit admissions were reported in any case. Unlike right aortic arch with aberrant left subclavian artery and double aortic arch that forms a vascular ring around tracheoesophageal axis, ARSA patients are usually asymptomatic.

Table 3 Comparison of various studies with chromosomal abnormalities and ARSA

Author	Year	Isolated ARSA and chromosomal abnormalities	Maternal age (y)	NT	Combined risk
Chaoui et al[6]	2005	1	42	$<$ 95th centile	NK
Borenstein et al[7]	2010	1	NK	NK	NK
Paladini et al[2]	2012	8	NK	NK	NK
Gul et al[13]	2012	1	37	NK	1/39
Rembouskos et al[12]	2012	2	NK	$>$ 95th centile	1/402
Esmer et al[8]	2013	6	37 39 29 38 42 35	$\leq$ 95th percentile $\leq$ 95th percentile $\leq$ 95th percentile $\leq$ 95th percentile $\leq$ 95th percentile $\leq$ 95th percentile	NP Positive Positive NP Positive Positive
Our study	2022	4	25 19 25 32	$\leq$ 95th percentile $\leq$ 95th percentile $\leq$ 95th percentile $\leq$ 95th percentile	Low risk Low risk 1/90 Low risk

Abbreviations: ARSA, aberrant right subclavian artery; NK, not known; NP, not performed.

There are some limitations in this study including its retrospective nature which did not allow us to calculate the incidence of ARSA in study population. Also being a tertiary center, a greater number of high-risk cases are being dealt with accounting association of isolated ARSA with chromosomal malformations. Despite these limitations, this study has various strengths. One is an adequate sample size that gave us the broader picture of cases with ARSA. Second, all the scans were performed by our experienced and competent fetal medicine specialists and these patients were kept on close follow-up and delivered at our own hospital, thereby ruling out the possibility of any associated missed abnormalities.

Conclusion

ARSA can be identified relatively easily with proper learning curve and should be screened in every fetus. The presence of ARSA should mandate an advanced ultrasound to look for any associated structural anomalies with simultaneous close follow-up. Isolated cases of ARSA can be associated with trisomy 21, but this association was not significant and therefore invasive testing can be deferred in these patients and cell-free DNA testing can suffice. Presence of multiple soft markers, however, should command invasive testing. More prospective studies are needed so that standardized protocol is established

Conflict of Interest
None declared.

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