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ORIGINAL ARTICLE

Significance of Fetal Aberrant Right Subclavian Artery and Comparison with Other Second Trimester Markers for Down Syndrome Screening

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Abstract The chief objectives of our study were to assess the incidence and significance of fetal aberrant right subclavian artery (ARSA) in a nonreferral cohort of south Indian antenatal woman, and to compare it with other second trimester markers of Down syndrome. This was a prospective study conducted at Edappal hospital, India. After satisfying inclusion and exclusion criteria, 2000 consecutive antenatal women, seeking prenatal care and planning delivery at the same center, were recruited in a consecutive fashion. ARSA was identified as a retrotracheal arterial vessel in the axial three vessel trachea view, coursing towards right axilla. During February 2015 to January 2016, nine cases of ARSA were identified amongst 2000 antenatal women, yielding an incidence of 0.45 % (95 % CI 0.2–0.9 %). Of these, eight cases (8/9, 89 %) were isolated with normal karyotype, and negative for 22q11 microdeletion. Down syndrome was prenatally diagnosed in four cases (4/2000, 0.2 %), with ARSA detected in one case [sensitivity—25 %, specificity—99.6 %, positive likelihood ratio (+LR)—62.5 %, negative likelihood ratio (−LR)—0.75 %; Odds ratio 82.8 %, 95 % CI 7.8–883]. Of the significant second trimester minor markers, an absent nasal bone was the most common (13/2000, 0.65 %), followed by ARSA. All the isolated cases had normal neonatal outcomes. ARSA is relatively common second trimester aneuploidy marker, associated with high global +LR but nil isolated +LR. Indication for fetal karyotype in isolated cases seems to be weak.

Keywords Aberrant right subclavian artery · Down syndrome · Aneuploidy markers · Subclavian view · Aortic arch · Three vessel trachea view

Introduction

The current protocols of prenatal screening for Down syndrome combines the attributes from maternal history, serum biochemical factors, and ultrasound markers into a mathematical algorithm that provides individualized risks, contingent to which further decisions are taken [1]. The ultrasound parameters include physical features of the fetus such as nasal bone, and vascular markers such as ductus venosus [2]. Fetal aberrant aortic arch vessels have been the latest addition to the group of ultrasound markers, based on the observation that their prevalence in aneuploid fetuses was greater than in euploid fetuses, statistically translating into significant likelihood ratios [3].

Fetal aortic arch abnormalities have been reported with an incidence of 1–2 % in the general population [4]. The commonest aortic arch anomaly is a left aortic arch (LAA) associated with an aberrant right subclavian artery (ARSA) [5]. Normally, the brachiocephalic trunk with the right subclavian artery (RSA) and the right common carotid artery (RCA) is the first branch of the aortic arch, followed by the left common carotid artery (LCA) and the left subclavian artery (LSA). The evolution of ARSA can be explained by the hypothetical double aortic arch model theory, wherein there occurs a partial regression of the aortic arch between RSA and RCA [6]. Consequently, the LAA now gives rise to RCA as the first branch followed by

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LCA, LSA, and finally the ARSA. The ARSA then takes a retroesophageal course in 80 % of cases, between the esophagus and trachea in 15 %, and less commonly anterior to the trachea or mainstem bronchus in 5 % [7].

An ARSA was first described by Hunauld in 1735 from an autopsy case [8]. Its radiological features were first described by Kommerall in 1936 in an adult roentogram [9]. The association of ARSA with Down syndrome was originally reported by Strauss in 1953 [10], and further insight into its association in mongoloid fetuses with cardiac malformations was provided by Goldstein [11]. The prenatal detection of ARSA was first reported by Chaoui et al. [12] in 2005. Since then numerous studies have investigated ARSA from different perspectives. A wide variation has been noted in the reported incidence figures, and association with Down syndrome in these studies [10, 13–16]. A recent metanalysis has estimated the incidence of ARSA in fetuses with Down syndrome to be 23.6 % (95 % CI 19.4–27.9 %), and in euploid fetuses to be 1.02 % (95 % CI 0.86–1.10 %) [17]. In contrast to the low-risk population, the association of ARSA with Down syndrome and cardiac anomalies was observed to be higher in the referral and high risk antenatal cohort [18].

Studies which have simultaneously compared ARSA with the other second trimester minor markers, particularly in the nonselected mixed risk antenatal women are limited. With the current information of ARSA in background, the primary objective of our study was to pragmatically assess the screening performance of ARSA in a nonreferral mixed risk, south Indian antenatal population recruited in a consecutive fashion. The secondary objective was to compare ARSA with the other second trimester markers of Down syndrome. The antenatal cohort attending the fetal medicine unit of a tertiary care private health care institution, and delivering at the same facility, constituted the study population.

Materials and Methods

This was a prospective single center, observational and descriptive study, conducted in the department of Feto-maternal medicine of Edappal hospital, Malappuram, Kerala. Our institution is a tertiary care private health care facility, with its Fetal Medicine unit catering to both the antenatal women of the institution as well as those referred to it, primarily from north Kerala. We routinely look for all the second trimester minor markers of aneuploidies, between 15 and 20 weeks of gestation. The mid trimester scans are performed as per ISUOG guidelines [19].

After approval from the institutional ethics board, all consecutive nonreferral antenatal women with singleton pregnancy, seeking prenatal care from our institution, during the period 1st February 2015 till 31st January 2016, were recruited for the study. The gestational window of 16 + 0–24 + 6 weeks was selected as all antenatal women of our hospital undergo ultrasound scans during this period. The exclusion criteria included those antenatal women who were referred for reasons such as expert opinion for previously detected fetal abnormalities, and fetal echocardiography.

Informed consent was obtained from all individual participants of the study. All ultrasound scans were performed using transabdominal 1–5 MHz curvilinear transducer (C1-5-D, GE Voluson E8, Vienna, Austria) by trained fetal medicine consultants. The criteria for prenatal diagnosis of fetal ARSA were those suggested by Chaoui et al. (Fig. 1) [11]. The steps involved were:

1. The axial three vessel trachea (3VT) view of fetal heart was obtained.
2. The color Doppler mode of the ultrasound machine was put on with Pulse repetion frequency reduced to 1.2–2.5 kHz.
3. The ARSA was identified as a retro-tracheal vessel having a relatively straight course towards right axilla in the axial 3VT view, with arterial waveform on spectral analysis. If detected, its presence was confirmed in at least one other orthogonal view (coronal or longitudinal). Care was taken not to confuse with azygous vein which has a postero-anterior course in the axial 3VT view. Demonstration of ARSA in two planes, and agreement amongst minimum three observers was required for confirmation of diagnosis, prior to documentation. If the visualization of normal RSA or ARSA was not possible during the cardiac examination, then a review was done for repeat cardiac assessment at a later visit, usually within one week.
4. If ARSA was not found, the demonstration of normal RSA and LSA in an axial plane cranial to the transverse aortic arch was done (subclavian view). The two arteries appear as ‘bicycle handle bar’ at this level [19].

All cases with ARSA underwent fetal karyotype, via G banding of cultured cells obtained from amniocentesis. If the karyotype was normal, fluorescent in situ hybridization (FISH) for detection of monosomy 22q11.2 microdeletion was performed. Postnatal evaluation was done for all neonates, though this did not involve imaging, due to poor detection rates of postnatal ultrasound for ARSA, and performing other modalities such as MRI or contrast CT was not justified in otherwise healthy infants.

The collected data was analyzed using MedCalc, version 15.0 (MedCalc Software, Ostend, Belgium). Descriptive statistics was carried out with continuous variables expressed as median and inter-quartile ranges, and

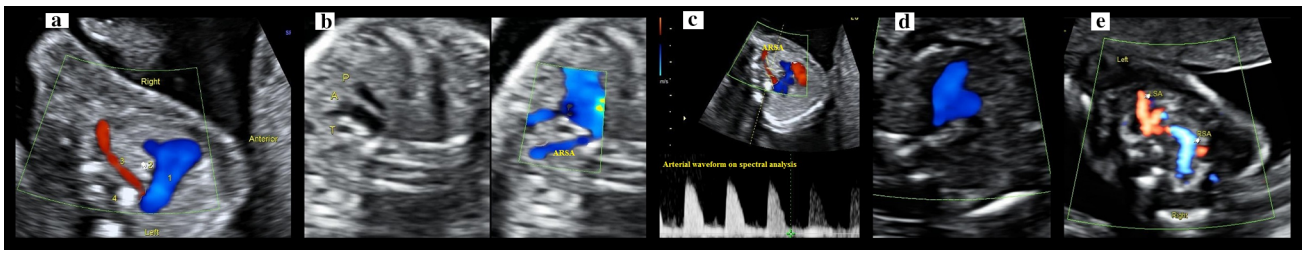

Fig. 1 *Gray scale*, *color Doppler*, and *spectral Doppler* images of ARSA and normal subclavian arteries. **a** Axial three vessel trachea view showing (*1*) Color confluence of aortic and ductal arches, (*2*) Trachea, (*3*) ARSA, and (*4*) Spine. **b** Coronal plane, combined *gray scale* and *color Doppler* demonstration of ARSA. **c** *Spectral Doppler* confirmation of the ARSA with the arterial waveform. **d** Normal three vessel trachea view with absence of ARSA. **e** Axial plane cranial to the transverse aortic arch view showing the *right* and *left* subclavian artery forming a bicycle *handle bar* sign *A* aorta, *ARSA* aberrant right subclavian artery, *LSA* left subclavian artery, *P* pulmonary artery, *RSA* right subclavian artery, *T* trachea

categorical data as percentages with confidence intervals (set at 95 %).

Results

A total of 2000 antenatal women were recruited in the study from February 2015 till January 2016, satisfying the inclusion and exclusion criteria. Visualization of the 3VT, and subclavian views were achieved in all cases. Fetal ARSA was noted in nine cases in the second trimester (incidence = 9/2000, 0.45 %; 95 % CI 0.2–0.9 %). Of these, eight cases (8/9, 89 %) were isolated (Table 1). The median maternal age of the nine cases was 29 years (IQR, [23–34]), while the median completed gestational age at diagnosis was 22 weeks (IQR, [22–24]).

From the total 2000 antenatal women studied, a total of five cases had aneuploidies (5/2000, 0.25 %). Down syndrome was prenatally diagnosed in four out of these five cases (4/2000, 0.2 %). An ARSA was found in association with one case of Down syndrome [sensitivity—25 %, specificity—99.6 %, positive likelihood ratio (+LR)—62.5 %, negative likelihood ratio (−LR)—0.75 %; odds ratio 82.8 %, 95 % CI 7.8–883). An increased nuchal translucency was the predominant finding associated with Down syndrome (3/4, 75 %) as shown in Table 2. All cases of ARSA were associated with a left ductus arteriosus.

Table 3 compares the incidence of the other second trimester minor and major markers in the study population. Of the significant second trimester minor markers, an absent nasal bone was the most frequent (13/2000, 0.65 %), followed by an ARSA. Major anomalies were present in 1.6 % of the cases, with cardiac defects being most common (9/2000, 0.45 %). Down syndrome was associated with one case of cardiac anomaly (Table 2).

Fetal testing for monosomy 22q 11.2 microdeletion was done in eight cases of ARSA (excluding the one with Down syndrome), with normal results in all. All cases diagnosed with chromosomal abnormalities (5/2000, 0.25 %), and major anomalies underwent termination of pregnancy. In the rest of the cases, normal neonatal outcomes were observed.

Discussion

Our study showed that the incidence of fetal ARSA in a nonreferral, mixed risk, south Indian antenatal population during the midtrimester ultrasound was 0.45 %. After absent nasal bone, an ARSA was found to be the second most common significant minor marker of chromosomal abnormalities. The association of ARSA with Down syndrome was also quantified in the same population, providing an insight into its performance as a screening parameter.

The incidence of prenatally detected ARSA is affected by the composition of the antenatal population being studied, and whether the population is a referral or a nonreferral one [18, 21–24]. For instance, the incidence of ARSA was detected to be high in a group that was referred primarily for fetal echocardiography [25]. A referral population will have inherent characteristics (such as advanced maternal age) that will result in bias for estimates of ARSA, and its association with Down syndrome and cardiac defects. ARSA is known to have independent association with both the groups of Down syndrome as well as fetal cardiac lesions [25–27]. The largest study done on nonselected antenatal population, estimated the incidence of fetal ARSA to be 0.4–1.9 % [22]. The incidence of ARSA in our study was well within this range. The nature of our study population ensured that ARSA was being assessed from the context of screening, as it was essentially a nonreferral mixed risk one.

In our cohort of antenatal women, the incidence of fetuses with Down syndrome was 0.2 %, with an ARSA in 25 % of them. However, the +LR of isolated ARSA for Down syndrome was found to be nil. The prevalence of

Table 1 Salient features of cases of ARSA diagnosed from the study population (n = 9/2000)

Case no.	Maternal age in years	Gestational age at diagnosis (weeks + days)	Additional ultrasound findings	Combined test risk*	Karyotype	22q11.2** microdeletion	Neonatal outcome
1	28	25 + 6	None	1:86849	46 XX	Absent	Normal***
2	29	22 + 4	None	1:69963	46 XX	Absent	Normal
3	36	23 + 6	None	1:1113	46 XY	Absent	Normal
4	24	21 + 6	None	Not done#	46 XY	Absent	Normal
5	21	16	None	Not done#	46 XX	Absent	Normal
6	30	25 + 4	None	Not done#	46 XY	Absent	Normal
7	22	23 + 1	None	Not done#	46 XX	Absent	Normal
8	33	21 + 5	None	1:22424	46 XX	Absent	Normal
9	35	19 + 4	Increased NT	Not done#	47 XX		
			Absent nasal bone		Tri 21	Not done	Termination of pregnancy
			Hyperechoeic bowel				

NT nuchal translucency, *Tri* trisomy

* Combined test for Down syndrome risk encompassing NT, Nasal bone presence, biochemical assay of PAPP-A and free beta unit of hCG, and maternal age

** 22q11.2 microdeletion detection via fluorescent in situ hybridization

*** Normal outcome refers to birth of a healthy newborn, either via normal labor or cesarean section, with birth weight greater than 2500 g

Both first and second trimester screening not done, as couple refused

Table 2 Cases of aneuploidies diagnosed from the study population following detection of ultrasound findings

Sr no.	Maternal age in years	Gestational age (weeks + days)	Ultrasound findings	Aneuploidy
1	19	18 + 2	Increased NT (3.6 mm), DORV, VSD	Tri 21
2	40	19 + 6	None	Tri 21
3	35	18 + 6	Increased NT (3.8 mm)	Tri 21
4	34	19 + 4	Increased NT (3.6 mm), Absent nasal bone, Hyperechoeic bowel, ARSA	Tri 21
5	35	12 + 4	Increased NT (4 mm)	Tri 18

ARSA aberrant right subclavian artery, *DORV* double outlet right ventricle, *Tri* trisomy, *VSD* ventricular septal defect

ARSA in fetuses with Down syndrome has been widely reported to be between 2.9 and 100 %, with reasonably high global +LR, but scaling down to low isolated +LR [17]. This suggests that while the association of ARSA with Down syndrome is significant, in isolated occurrence its utility is questionable. This has been reflected in a recent metanalysis, where a wide difference was noted between the +LR of ARSA as an isolated anomaly (+LR: 0–29.6), and as a nonisolated anomaly (+LR: 12.6–42.04) [22]. The screening performance of ARSA is therefore debatable. Additionally based on these findings, there seems to be insufficient evidence to advise karyotype in isolated ARSA [22, 23, 28, 29]. However, presence of a normal ARSA can be considered as a protective factor, by virtue of its −LR [17]. Our study reiterated the importance of nuchal translucency led screening protocol for Down syndrome, as it was observed in 75 % of the positive cases.

Our study could not demonstrate an association between ARSA and fetal cardiac defects, despite the incidence of later being in the reported range of 0.4–1.5 % [30]. This could be due to overall fewer cases of cardiac diseases in our study, as referrals were excluded. This observation notwithstanding, an ARSA is known to occur with fetal cardiac lesions, most common being atrioventricular septal defects, and a persistent left superior vena cava [13, 25]. In our study, eight cases were additionally tested for monosomy 22q11.2 microdeletion, which was found to be negative in all. Testing for 22q11 deletion was justified due to the reported occurrence of this chromosomal abnormality with ARSA, albeit less frequently [27, 31, 32]. Due to the known association of fetal ARSA with cardiac and extracardiac anomalies, and genetic syndromes, a detailed examination of the fetal anatomy needs to be performed following detection of ARSA in a screening prenatal

Table 3 Distribution of minor markers of aneuploidies (soft markers) and major abnormalities in the study population (n = 2000)

Sr no.	Scan findings	Isolated	Associated with major abnormalities	Associated with minor abnormalities	Aneuploidies	Total
1	Absent nasal bone	11	0	2	1	13 (0.65 %)
2	ARSA	8	0	1	1	9 (0.45 %)
3	BL ventriculomegaly	0	6	0	0	6 (0.3 %)
4	Increased NFT	4	0	2	0	6 (0.3 %)
5	Hyperechoeic bowel	6	0	1	1	7 (0.35 %)
6	SUA	45	2	0	0	47 (2.4 %)
7	Short FDL	60	3	0	0	63 (3.2 %)
8	Choroid plexus cyst	44	0	1	0	45 (2.3 %)
9	BL pelviectasis	29	0	0	0	29 (1.5 %)
10	Increased NT	1	1	3	4	5 (0.25 %)
11	Cardiac anomalies	6	1	2	1	9 (0.45 %)
12	Other system major anomalies	–	–	–	0	22 (1.1 %)

ARSA aberrant right subclavian artery, *BL* bilateral, *FDL* femoral diaphyseal length, *NT* nuchal translucency, *NFT* nuchal fold thickness, *SUA* single umbilical artery

Total no. of major anomalies in the study population—31 (1.6 %); Total no of aneuploidies—5 (0.25 %)

Screening performance: Absent nasal bone [sensitivity—25 %, specificity—99.4 %, positive likelihood ratio—41.8 %, negative likelihood ratio—0.75 %; Odds ratio 5.1 (95 % CI 5.3–568.3)]

ARSA [sensitivity—25 %, specificity—99.6 %, positive likelihood ratio—62.5 %, negative likelihood ratio—0.75 %; Odds ratio 82.8 %, 95 % CI 7.8–883]

ultrasound [20, 28, 33, 34]. Diagnosis of an ARSA should also be accompanied by counseling regarding the future possibility of respiratory problems from vascular rings [35].

In our study, the incidence of other second trimester minor markers was simultaneously assessed. Based on their robust likelihood ratios, absent nasal bone, nuchal fold thickness, cerebral lateral ventriculomegaly and ARSA are considered as the significant second trimester markers of Down syndrome [36]. In our study, absent nasal bone was the most common marker, followed by ARSA. The pattern of distribution was identical to a large data that focused on diagnosed cases of Down syndromes [15]. This suggests a relatively common distribution of ARSA, even in low risk antenatal women. In our study, the global +LR of ARSA was found to be higher than absent nasal bone.

From the aforementioned discussion, it is evident that ARSA is a relatively common second trimester soft marker. Its association with Down syndrome and cardiac abnormalities is well established. Its incidence is next only to absent nasal bone in the second trimester fetuses. Though it has an inconsistent +LR as an isolated marker, it has been demonstrated to have independent occurrence [16]. The −LR for Down syndrome studies, including ours, suggests that its absence has a significant protective impact against Down syndrome. All this supports the addition of ARSA in mid trimester genetic sonogram and target scan. To accomplish this, the subclavian view should be added to the axial 3VT view, as the latter alone is not sufficient to diagnose uncommon aortic arch branching patterns [20, 28]. A high rate of successful visualization of ARSA is possible in the second trimester [27]. A successful assessment of RSA was obtained in 82.4–85.3 % of the cases in the first trimester and in 95.4–100 % in the second trimester [17].

Our study was a prospective evaluation, designed to recruit women in a consecutive fashion excluding referrals. Hence, it was able to introspect ARSA from a screening perspective, rather than focusing on estimating the strength of association with Down syndrome, which has already been accomplished comprehensively. Assessment of monosomy 22q.11 microdeletion was also done in our study, based on the supporting available evidence for its inclusion in diagnostic workup. Visualization of ARSA was achievable in 100 % cases. A simultaneous comparison with the incidence of the other second trimester minor markers was unique to our study. The chief limitation of the study was a lack of a large sample size. We recommend larger prospective studies that will assess the impact of addition of ARSA on aneuploidy screening via the sequential addition of its likelihood ratio. Its association with cardiac and extracardiac anomalies needs to be explored further.

To conclude, fetal ARSA is relatively common in second-trimester fetuses, and is a potential clue to underlying fetal aneuploidies, cardiac, and noncardiac anomalies.

Though characterized by high global +LR, as an isolated marker, its diagnostic yield is weak and inconsistent. Despite this, ARSA can be added to second trimester genetic and anomaly screening protocols, as it serves dual benefits from its association with chromosomal abnormalities and fetal cardiac anomalies.

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Compliance with Ethical Standards

Conflict of interest None.

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