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ORIGINAL ARTICLE

Prenatal Diagnosis of Aberrant Right Subclavian Artery in Unselected North Indian Population: Significance and Counselling

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Abstract This study was carried out to assess the incidence and association of aberrant right subclavian artery in North Indian population and to analyse its significance as a marker of Down syndrome and to formulate an adaptable protocol for counselling and management of such pregnancies. A prospective assessment of 1024 consecutive unselected pregnancies with gestational age between 12 and 34 weeks was carried out from May 2016 to August 2017 at the author's fetal medicine centre in North India. The screening for ARSA was performed with Color Doppler using low PRF at 3 vessel trachea view in axial section followed by confirming of arterial flow pattern by pulse Doppler. Incidence of ARSA in this study was 0.58%. Thirty-three percent of cases of ARSA were associated with other anomalies whereas 66% were isolated. Trisomy 21 was found in 16.6% of cases. ARSA as a marker of Trisomy 21 has a high specificity (99%) but low sensitivity (33%, [95% CI]). Although global likelihood ratio (LR) for ARSA as a marker for Down syndrome was high, the LR for isolated ARSA was nil. Isolated ARSA can be considered a normal variant and does not warrant invasive prenatal diagnosis in the scenario of low biochemical risk. On the other hand, ARSA associated with other markers/anomalies warrants invasive prenatal diagnosis.

Keywords Prenatal · Aberrant right subclavian artery · ARSA · Genetic counselling · Down syndrome · Indian

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Introduction

The right subclavian artery normally arises as a branch of brachiocephalic artery. Sometimes, it follows an aberrant course after arising directly from the aortic arch as the fourth vessel and traversing behind the trachea, which is termed as aberrant right subclavian artery (ARSA) [1, 2]. Fetal ARSA has emerged as an important marker of Down syndrome (trisomy 21) in the literature [1–7]. However, recent research studies refute the association of isolated ARSA with Down syndrome [5] and pose a dilemma in terms of management protocol and applicability in Indian scenario. This study addresses these dilemmas by prospectively assessing the incidence, structural and chromosomal associations of ARSA in North Indian scenario and by presenting a flowchart protocol adaptable for routine practice.

Methodology

The objectives of the present study were (1) To determine the incidence of fetal aberrant right subclavian artery in an unselected North Indian population and its association with chromosomal and structural anomalies. (2) To address the difficulty in counselling and management in cases with prenatal diagnosis of ARSA. It was prospectively carried out from May 2016 to August 2017 at the author's fetal medicine centre. During this time, 1024 consecutive unselected pregnancies with gestational age between 12 and 34 weeks were screened for fetal aberrant subclavian artery (ARSA) on WS80A (Samsung Medison Ltd., Korea) ultrasound machine with help of curvilinear transducer (1–5 MHz) for transabdominal scan (Fig. 1). The screening was performed with Colour Doppler, keeping the PRF low

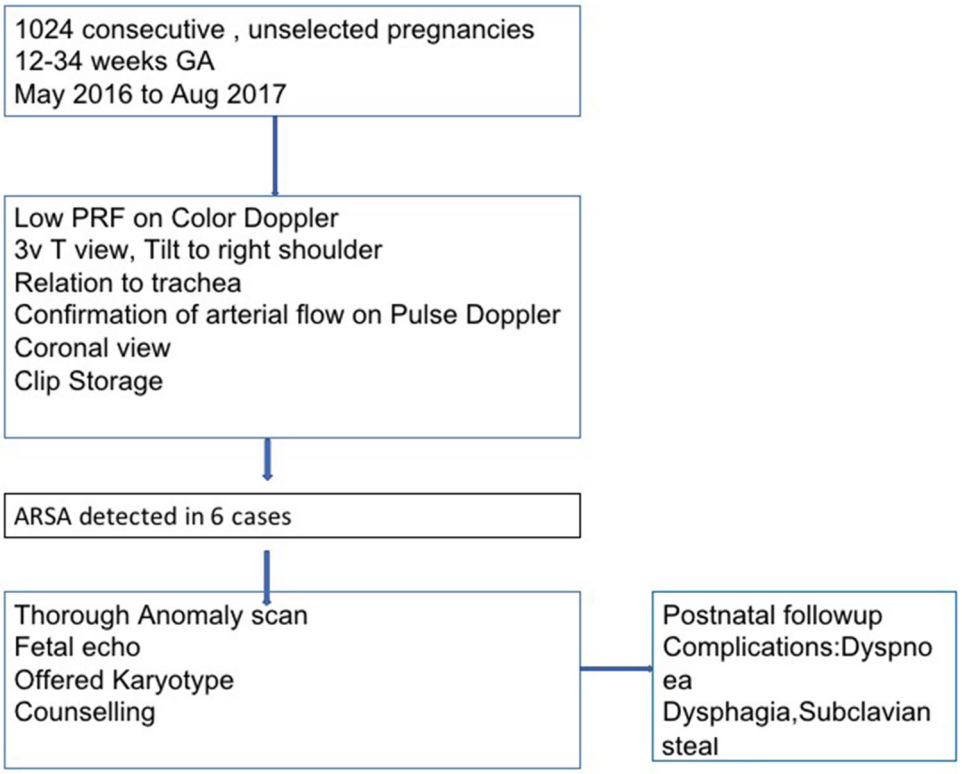

Fig. 1 Flowchart depicting recruitment, assessment and management of the cases in the study. (karyo- karyotype, NFT-nuchal fold thickness, SUA-single umbilical artery, (n) = number of cases)

(10–15 cm/s), at the level of 3 vessel trachea view and tilting the probe towards fetal right shoulder as described by Chaoui et al. [1]. The normal right subclavian artery in the axial plane was visualized as an S-shaped vessel passing anterior to the trachea at the level of the clavicle. Aberrant right subclavian artery (ARSA) arose as the last vessel from the aorta and took a course behind the trachea to the right arm. The course of ARSA was straight (Fig. 2a and b). A coronal view of the fetal thorax posterior to the trachea and anterior to the spine was obtained to show ARSA as a vessel arising from the descending aorta at the level of the aortic isthmus and following an oblique course towards the right clavicle and shoulder. Pulsed Doppler of the vessel behind the trachea was used to confirm the

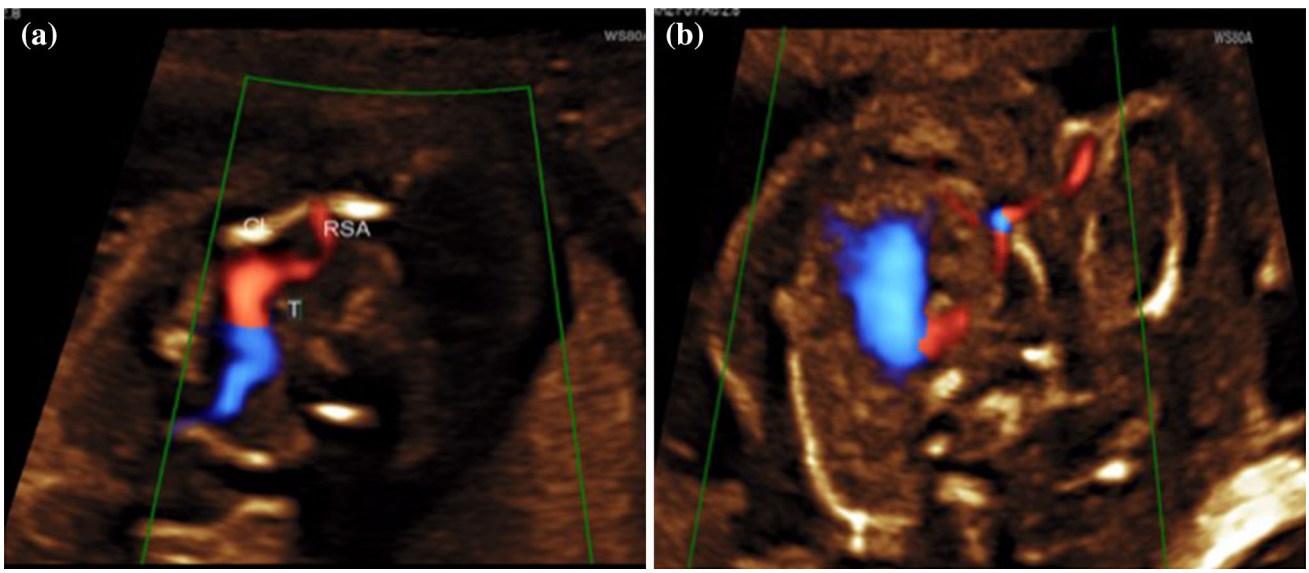

Fig. 2 **a** Normal right subclavian artery (RSA) at the level on clavicles going in front of trachea (T) with a 'S' shaped tortuous course. **b** Aberrant right subclavian artery with a retro-tracheal, straight course towards right arm

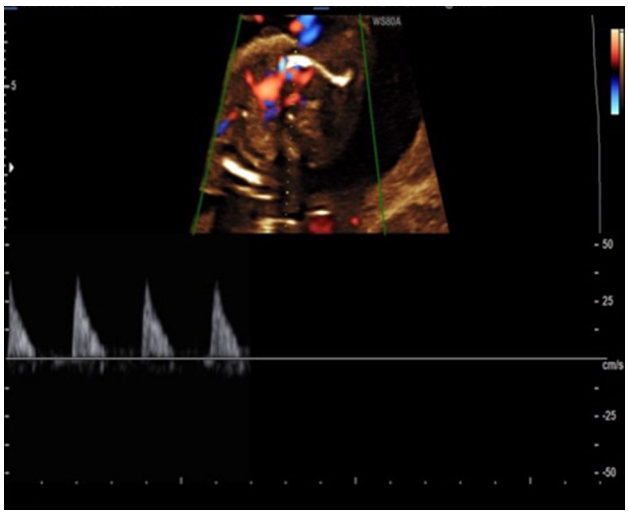

Fig. 3 Pulse Doppler on retrotracheal vessel shows arterial waveform thus excluding hemiazygous vein and confirming ARSA

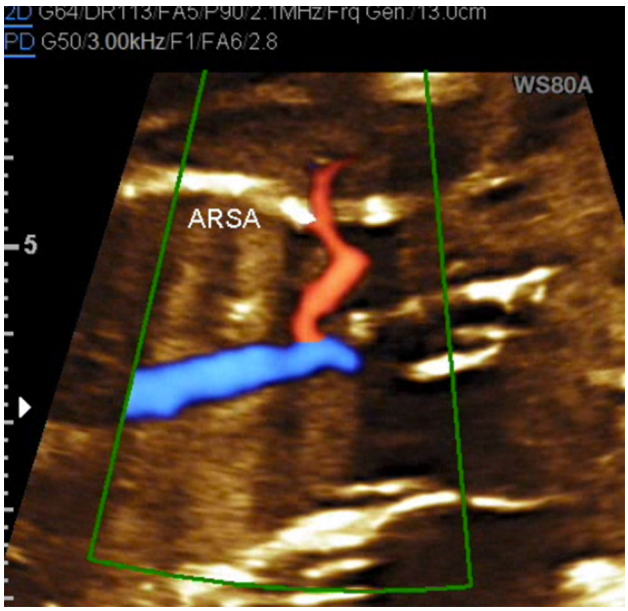

Fig. 4 ARSA in coronal view seen as the last vessel coming from the aortic arch and coursing towards the right shoulder

arterial flow pattern, as the hemiazygous vein can lie in the same position and needs to be excluded (Figs. 3 and 4) [2, 3].

All the cases with detection of ARSA were subjected to thorough anomaly scan, fetal echo and genetic counselling. Invasive test for fetal karyotype prenatally was offered and discussed with the couple.

Results

Assessment of right subclavian artery (RSA) was possible in all 1024 pregnancies recruited in the study period (100%) on transabdominal scan in axial view at level of 3 vessel view. Demonstration of ARSA in coronal view was possible with ease in the second trimester but difficult in first and third trimesters. Out of 1024 cases, ARSA was detected in 6 cases (0.58%). Two of these cases (33.33%) were associated with other structural anomalies (Cases 1 and 3, see Table 1) and 4 were isolated (66.6%). Trisomy 21 was detected in 1 out of 6 cases (16.6%) which also showed a major marker in form of increased nuchal fold thickness. Rest of the cases (83.3%) were euploid. The incidence of ARSA in Trisomy 21 in present study was 33.3%. Sensitivity of ARSA in detection of Trisomy 21 in present study was 33% (95% CI). The specificity of ARSA in Trisomy 21 detection was high (99%). The positive and negative likelihood ratios were 68.7 (10.9–42.1%) and 0.67 respectively.

Discussion

Demonstration of right subclavian artery whether normal or aberrant, were possible in all cases in this study (100%) in the axial view at level of 3 vessel view. This demonstration was feasible by transabdominal scan in the entire range of gestation (12–34 weeks) included in this study. No difficulty was encountered even at 12–14 weeks

Table 1 Karyotype, associated structural abnormalities and outcomes in the cases with ARSA

Case	GA, associated structural anomalies	Karyotype	Outcome, current age
Case 1	14 weeks, SUA, absent nasal bone	Normal	Male, 37 weeks (SGA) 2.3 kg, healthy, 6 months, no complications
Case 2	18 weeks, no associated anomalies	Normal	Female, 2.8 kg, healthy, 8 months
Case 3	19 + 1 weeks, increased nuchal fold thickness, mild pyelectasis, clinodactyly	Trisomy 21	Termination of pregnancy (TOP)
Case 4	20 weeks 6 days, none	Normal	Male, 2.5 kg, healthy, 10 months, no complications
Case 5	32 weeks, none, symmetric FGR	Denied	Postnatal Karyotype normal, 1 month old female
Case 6	18 + 1 weeks, none	Normal	Ongoing

GA gestational age, *SUA* single umbilical artery, *TOP* termination of pregnancy, *T21* trisomy 21, *FGR* fetal growth restriction

gestation in demonstrating RSA or ARSA trans abdominally and 340 patients in this gestation were screened. One of 340 fetuses screened in the first trimester had ARSA (Case 1, Table 1). Invasive testing for fetal karyotype for excluding Trisomy 21 was offered in this case after counselling. Previous studies usually limited their inclusion to either 20–34 or 11–13^{+6} weeks [1–3].

Incidence of ARSA in the unselected population was 0.58%. In the literature, most studies report incidence of ARSA to be 1–2% [2–4]. One reason of lower incidence of ARSA in present study can be due to lower incidence of Down syndrome − 0.34% (n = 3 out 1024) compared to incidence of approximately 1% in other studies with high incidence of ARSA. Song et al. [5] and De Leon Luis et al. [6] have reported incidence similar to the current study. Incidence of ARSA in cases with Down syndrome was 0.09%, which is comparable to other studies in the literature [2–6]. Low sensitivity and high specificity of ARSA as a marker for Down syndrome reiterates that presence of ARSA does not always mean fetus is affected with Down syndrome but provokes the need to screen for other markers to confirm or exclude Down syndrome. Global positive likelihood ratio (LR) for ARSA as a marker for Down syndrome is high, but positive LR as an isolated ARSA is nil or 0. This means that when ARSA is present in isolation, the fetus is unlikely to have Down syndrome. This underscores the conclusion of recent studies that invasive testing is not mandatory in presence of isolated ARSA [4, 6], which is in contradiction to previous studies [2]. Previous studies stated high likelihood of isolated ARSA with Down syndrome and LR was stated to be as high as 3.9 in a Meta-analysis [7]. Invasive testing can be offered to the couple as a part of non-directive genetic counselling. Prospective studies with a larger population are awaited before this debate gets answered for certainty. Until then, it is better not to miss and at the same time avoid unnecessary invasive related complications. So, if the couple wishes, cell free fetal DNA can be considered in isolated cases of ARSA followed by invasive testing if the former shows high risk. However, caution needs to be exercised in interpreting 'isolated' ARSA. Term 'isolated' should be reserved for no identifiable marker for Down syndrome or detectable structural malformation on ultrasound at that gestation. A slight deviation from this definition would lead to increase in number of isolated cases of ARSA in Down syndrome foetuses, which would be the case with Zalel et al. [8], where persistent left superior vena cava with ARSA was included as an isolated ARSA case. The statistical outcome of the South Indian study [9] was compared to that of present study in the Table 2. The incidence, sensitivity, specificity, positive global and isolated LR was more or less similar in both the Indian studies. Association of isolated ARSA with 22q11 deletion and other trisomies is not well established in the literature [10]. However, 22q11del must be tested when ARSA is associated with conotruncal cardiac defects [11].

The protocol for fetal ARSA compatible In Indian scenario is depicted in flowchart below (Fig. 5).

For all cases where ultrasound detects ARSA, thorough search of other markers and/or malformations is mandatory in expert hands. In cases of truly Isolated ARSA, invasive testing is not mandatory but can be offered. Non-Invasive prenatal screening by cell free fetal DNA can also be considered in these isolated cases. For all those cases with other detectable markers or malformations, invasive testing for fetal karyotype is mandatory to confirm/exclude Down syndrome. If ARSA is detected at 12–14 weeks scan, an early anomaly scan along with biochemical screening (Dual marker) should be carried out. Parents should be counselled about the increased association of ARSA with Trisomy 21 in presence of other markers and hence, the importance of detailed second trimester anomaly scan even if ARSA appears to be isolated at 12–14 weeks scan. If ARSA is associated with any other marker (e.g. absent

Table 2 Comparison of statistical parameters of current study with that of other studies in literature

Study	GA (weeks)	N =	Incidence of ARSA	Incidence of ARSA in T21	Sensitivity	Specificity	LR +	LR −	LR + isolaged ARSA
Chaoui et al. [2]	15–34	908	1.5%	0.1%	NR	NR	NR	NR	Reported 1 case of 21 in isolated ARSA
Borenstein [11]	16–23 + 6	2670	1.6%	0.3%	28.6	98.8	24.1	0.7	NR
Willruth et al. [4]	16–28	1337	1	0.07%	9	99.2	11.5	0.9	0
De Leon Luis [6]	15–37	8781	0.7	0.08%	31.9	99.1	52	0.7	0
Song et al. [5]	20–34	7547	0.4	No T21 with ARSA	–	–			NR
Seenesh et al. [9]	16–24	2000	0.45	NR	25%	99.6	62.5	0.7	0
Current study	12–34	1024	0.58	0.09%	33%	99.5	68	0.67	0

NR not recorded

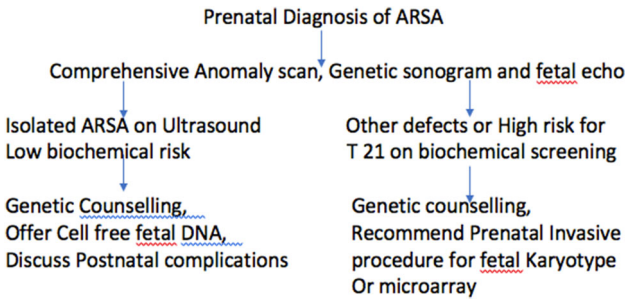

Fig. 5 Protocol for management of fetal ARSA

nasal bone, increased nuchal translucency) of trisomy 21 or any structural anomaly, invasive testing to confirm fetal karyotype must be offered.

Though small, there is a risk of dysphagia lusoria, dyspnoea and subclavian steal syndrome due to its aberrant course behind the trachea and oesophagus leading to compression of these structures. These symptoms can manifest at any age postnatally. Ligation and transposition of aberrant vessel to the right carotid artery via open or endoscopic approach is required in symptomatic cases [12]. None of the cases in this study had this complication so far. However, all cases with prenatal diagnosis of ARSA who continue the pregnancy need to be counselled about these minor postnatal complications, which was done in this study.

Conclusion

Though ARSA has emerged as an important prenatal marker for Down syndrome, isolated ARSA is unlikely to be a major warning marker for trisomy 21. Nonetheless, all cases with prenatal diagnosis of ARSA should be referred to fetal medicine specialist for thorough anomaly scan and genetic sonogram and adjusted biochemical risks for trisomies should be reviewed. In the presence of other markers of trisomy 21 or structural anomalies, invasive testing for fetal karyotype/microarray should be done. Truly isolated ARSA can be considered a normal variant present in 1–2% of euploid population and potential postnatal complications should be discussed.

Compliance with Ethical Standards

Ethical Approval Ethical committee of Paras hospitals approved this study.

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