Ultrasound Obstet Gynecol 2012; **39**: 191–195
Published online in Wiley Online Library (wileyonlinelibrary.com). **DOI:** 10.1002/uog.10053

Aberrant right subclavian artery: incidence and correlation with other markers of Down syndrome in second-trimester fetuses

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KEYWORDS: aberrant right subclavian artery; ARSA; Down syndrome; nasal bone; nuchal fold

ABSTRACT

Objective *To assess the incidence of aberrant right subclavian artery (ARSA) and other strong markers of Down syndrome and their correlation in a large population of second-trimester Down syndrome fetuses assessed in a tertiary referral center.*

Methods *Presence or absence of ARSA and other major ultrasound markers of Down syndrome was assessed in a population of 106 second-trimester Down syndrome fetuses referred to our unit for expert assessment and/or termination of pregnancy after karyotyping performed for positive first- or second-trimester screening or advanced maternal age or on maternal request. All cases in which the diagnosis of Down syndrome followed the ultrasound detection of major anomalies or soft markers were excluded from the study, as were all cases with a gestational age less than 14 + 0 weeks. We searched for the ARSA on the three vessels and trachea view using color or power Doppler. All fetuses underwent a thorough anatomic assessment and fetal echocardiography. The other Down syndrome markers assessed were: absent or hypoplastic nasal bone (NB−), defined as length $< 5^{th}$ centile; nuchal fold ≥ 5 mm; and mild pyelectasis (> 5 mm). In addition, the presence of major cardiac and extracardiac defects was recorded. A correlation analysis was then performed in order to investigate possible associations between markers and/or major anomalies. Postmortem or postnatal diagnostic confirmation was available in all cases.*

Results *The mean (SD) gestational age at ultrasound assessment was 20.4 (4.1) weeks. The incidence of the various variables in the population of Down syndrome fetuses was: ARSA, 25%; NB−, 43%; nuchal fold ≥ 5 mm, 16%; pyelectasis, 17%; major heart defects, 41%; atrioventricular septal defect, 25%; and extracardiac anomaly, 24%. The presence of ARSA did not correlate with any of the other variables. The only positive correlations (*$P < 0.05$*) were between NB− and pyelectasis, and between cardiac and extracardiac defects.*

Conclusions *This represents the largest Down syndrome population assessed for ARSA. In this series, the incidence of ARSA was 25%, lower than previously reported in much smaller series. Its presence did not correlate with the presence of any other marker or major anomaly, including heart defects.*

INTRODUCTION

In the normal aortic arch branching pattern, the right subclavian artery arises from the innominate artery. In a rarer variant, this vessel arises independently as a fourth vessel of the aortic arch, courses behind the trachea and then turns towards the right shoulder. The anomalous course has resulted in this variant being named 'aberrant right subclavian artery' (ARSA). Postnatally, an ARSA has been found in 1–2% of normal individuals (from neonates to adulthood) at autopsy[1], but its incidence is increased in cases of Down syndrome, with figures ranging between 2.9% and 100%[2–8].

The identification of an ARSA in fetuses with Down syndrome was reported for the first time in 2005 by Chaoui *et al.*[9]. Since then, a few other series have confirmed the feasibility of prenatal diagnosis of this benign aortic arch branching anomaly, but the reported incidence in Down syndrome fetuses varies significantly,

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Accepted: 27 June 2011

from 29% to 37%[9–13]. Furthermore, the relationships with other major or soft markers of Down syndrome have been addressed only in the first trimester[14].

The objective of this investigation was twofold: 1) to report the incidence of ARSA in a set of 106 second-trimester fetuses with Down syndrome, and 2) to ascertain whether, in this population, there was any correlation between ARSA and a series of markers of Down syndrome and major cardiac and extracardiac anomalies.

METHODS

This was a retrospective analysis including all fetuses diagnosed with Down syndrome and seen at our department for expert assessment and/or termination of pregnancy in the second trimester since 2005. Cases in which the diagnosis of trisomy 21 followed an invasive procedure carried out in our department or elsewhere because of cardiac and extracardiac anomalies and/or soft markers were excluded from the analysis, to avoid any selection bias. The indication for karyotyping in the group of 106 fetuses included in the study is reported in Table 1. It should be borne in mind that in our region there is as yet no official recommendation for screening test to be used for trisomy 21, and the standard combined first-trimester screening test (nuchal translucency + biochemistry) is not applied routinely. This results in karyotyping being performed for a variety of indications. In Italy, the National Health Service cut-off leading to invasive testing is 1 : 250 at birth.

Since the original description of ARSA in the fetus[9], at our unit we have checked for its presence in all cases undergoing fetal echocardiography and expert assessment for known Down syndrome, according to the procedure described here and in a way similar to that in other reports[13]. (1) We obtained the three-vessel view and located the transverse aortic arch, using an insonation angle $< 45°$ with respect to the location of the ARSA, if present, i.e. with the fetal spine at the 3 or 9 o'clock position; (2) we switched on color/power Doppler with reduced pulse repetition frequency (velocity range, 15–30 cm/s); (3) we tried to locate the course of the right subclavian artery in its normal position, in the upper mediastinum where it courses in front of the trachea and towards the right arm; (4) if this failed, scrolling downwards, the ARSA appeared at the level of the three-vessel view, and was seen coursing behind the trachea (Figures 1a and b). Care was taken not to mistake an azygos connection with the superior vena cava (Figure 1c) for the ARSA: the former has an anteroposterior course, and is on the right of the trachea, whereas the ARSA courses behind the trachea and has an oblique course towards the right arm (Figures 1a and b).

Table 1 Indication for karyotyping in the sample population of 106 Down syndrome cases

Indication	n *(%)*
Positive first-trimester screening	38 (35.8)
Positive triple test	28 (26.4)
Advanced maternal age (> 35 years)	26 (24.5)
Maternal decision	14 (13.3)

We retrieved from our database and analyzed the files of the 106 Down syndrome fetuses included in the study. The following binary variables were recorded and included in the statistical analysis: ARSA; absent or hypoplastic nasal bone (NB−), defined as length $< 5^{th}$ centile; nuchal fold ≥ 5 mm[15,16]; mild pyelectasis (> 5 mm); major cardiac defects; major extracardiac defects. In our center we have always recorded in the database only the second-trimester markers of Down syndrome with high likelihood ratios (NB−, nuchal fold ≥ 5 mm, major cardiac and extracardiac anomalies). Pyelectasis was included in this study because it was also recorded in the database. All other markers described in the literature over the last two decades (e.g. cardiac hyperechogenic foci, choroid plexus cysts, single umbilical artery, femur and humeral lengths, iliac wing angle) were not assessed and, hence, were not recorded in our database. We decided not to include hyperechogenic ileus in the analysis because its assessment is mainly subjective and relates to some extent to the type of scanner and transducer emission frequency.

Postmortem or postnatal diagnostic confirmation was available in all cases. At necropsy, the presence of ARSA was checked by carefully dissecting the upper mediastinal region following removal of the sternal plate. After exposure of the aortic arch, the branching of the ARSA was identified and the retrotracheal course of the vessel verified (Figure 2). Postnatally, in asymptomatic cases, the presence of ARSA was confirmed echocardiographically by checking the course of the vessel behind the trachea from the upper suprasternal planes, whereas symptomatic cases underwent computed tomography angiography or X-ray angiography.

A correlation analysis was performed (SPSS 14.0, SPSS Chicago, IL, USA), to ascertain whether there was any significant correlation between occurrence of ARSA and any of the other variables, or between any two variables.

RESULTS

The study population of 106 trisomy 21 fetuses had a mean gestational age at ultrasound assessment of 20 + 4 (range, 15–30) weeks. The incidences of the Down syndrome markers investigated are given in Table 2. Among the 27 fetuses with ARSA, this was the only abnormality seen on ultrasound in eight (29.6%) cases, whereas it was associated with one, two, three or four of the other variables (NB−, nuchal fold ≥ 5 mm, pyelectasis, cardiac or extracardiac defects) in seven (25.9%), eight (29.6%), three (11.1%) and one (3.7%) cases, respectively. However, the presence of ARSA did not correlate with any of the other variables. The only positive correlations ($P < 0.05$) were between NB− and pyelectasis, and between cardiac and extracardiac defects. With respect to its possible relationship with congenital heart disease (CHD), the incidence of ARSA was 22.2%

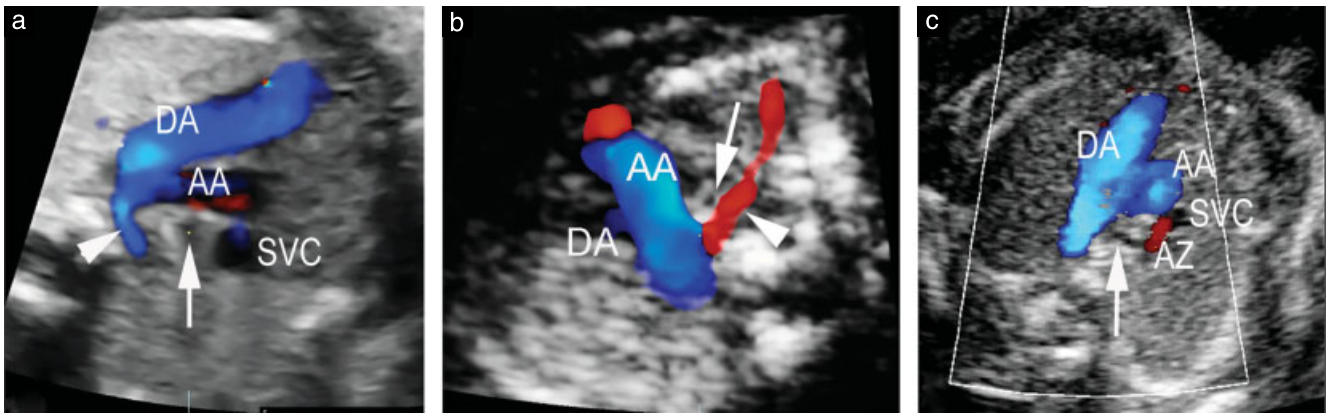

Figure 1 Aberrant right subclavian artery (ARSA) can be identified by color/power Doppler with reduced pulse repetition frequency if the insonation angle is favorable (< 30°). (a) ARSA (blue, arrowhead) in a fetus lying on its right side. (b) ARSA (red, arrowhead) in a fetus lying on its left side. (c) Azygos drainage into the superior vena cava (SVC) may sometimes be mistaken for an ARSA. However, the connection between the azygos vein and the SVC does not pass behind the trachea and its course is parallel to the ductal and aortic arches, rather than at 90° as for the ARSA. Arrows indicate the trachea. AA, aortic arch; AZ, azygos vein; DA, ductus arteriosus.

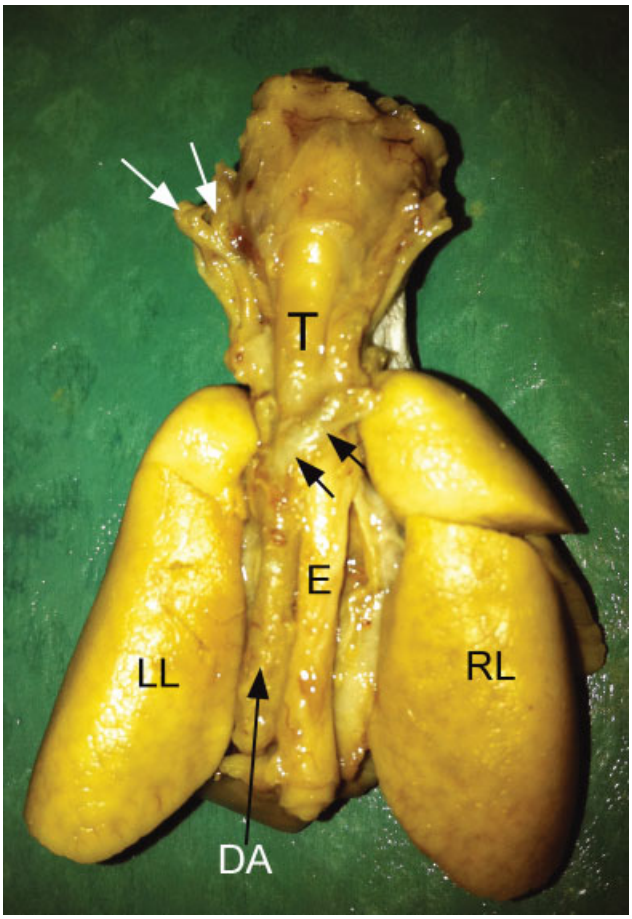

Figure 2 Pathologic specimen of heart and lungs of a fetus with Down syndrome and aberrant right subclavian artery (ARSA). The specimen is seen from the posterior aspect. The ARSA (double black arrow) is seen departing from the aorta and coursing behind the trachea (T) and esophagus (E). The double white arrow indicates the neck vessels. DA and single black arrow, descending aorta; LL, left lung; RL, right lung.

(14/63) in Down syndrome fetuses with no heart defects vs 30.2% (13/43) in those with CHD (no significant difference).

Table 2 Incidence of various sonographic markers of Down syndrome in 106 known trisomy 21 fetuses

Marker	*Incidence* (n *(%)*)
Aberrant right subclavian artery	27 (25)
Nasal bone absent/hypoplastic*	46 (43)
Nuchal fold ≥ 5 mm	17 (16)
Mild pyelectasis (> 5 mm)	18 (17)
Major heart defects	43 (41)
Atrioventricular septal defect	27 (25)
Extracardiac anomaly	25 (24)

*Length < 5th centile (4.5 mm).

DISCUSSION

To the best of our knowledge, this study reports the largest series to date (106 cases) of fetuses with Down syndrome assessed retrospectively for the presence/absence of ARSA. The rate of ARSA in our Down syndrome population was 25% (27/106). This figure is slightly smaller than the 29–37% found in previous reports in fetuses[9–14], but greater than those in adults with Down syndrome. This difference may be explained by the assessment of ARSA being less straightforward after birth than it is prenatally.

Table 3 compares our findings with the other fetal series confirming the apparently strong relationship in the fetus of ARSA with Down syndrome; in most of them the number of Down syndrome fetuses was small, not exceeding 20 cases. Taking into consideration our 25% incidence of ARSA in Down syndrome fetuses and the 29% incidence of Borenstein *et al.*[13], and bearing in mind that in the latter study the incidence of ARSA in a large group of fetuses with normal karyotype, albeit not a low-risk population, was 1.5%, it might be speculated that detecting an ARSA prenatally would increase the risk of Down syndrome by around 16–20-fold.

Another important issue to consider is that, at least in our series, the ARSA seemed to be an independent marker

Table 3 Incidence of aberrant right subclavian artery (ARSA) in the sample population of 106 Down syndrome cases and comparison with the literature

			ARSA (n (%))	
Reference	n	*GA (weeks)*	*Normal karyotype*	*Down syndrome*
Chaoui *et al.*[9] (2005)	54	18–33	0/40 (0)	5/14 (36)
Chaoui *et al.*[10] (2005)	905	15–34	13/905 (1.4)	—
Chaoui *et al.*[11] (2006)	14	< 14	—	4/14 (29)
Zalel *et al.*[12] (2008)	932	13–26	13/924 (1.4)	3/8 (37)
Borenstein *et al.*[13] (2010)	2670	16–23	28/2398 (1.2)	8/28 (29)
Total			54/4267 (1.3)	20/64 (31.2)
This series	106	15–30	—	27/106 (25.5)

Table 4 Incidence of major second-trimester ultrasound markers of Down syndrome in this study and comparison with the literature

	This series	*Literature comparison*	
Ultrasound marker	*(% (n))*	*% (n)*	*Refs*
Nasal bone absent/hypoplastic*	43 (46/106)	37.0 (55/152)	13–16
Nuchal fold ≥ 5 mm	16 (17/106)	33.5 (107/319)	19–21
Mild pyelectasis (> 5 mm)	17 (18/106)	17.6 (56/319)	19–21
Major malformation	64 (68/106)	21.4 (75/350)	19–21

*Length < 5th centile (4.5 mm). Refs, references.

of Down syndrome, showing no correlation with the various other signs considered (NB−, nuchal fold ≥ 5 mm, pyelectasis, major CHD, major extracardiac anomaly). This is a point worth emphasizing because, if confirmed, it would include ARSA among the three most powerful independent ultrasound indicators of Down syndrome, together with NB− and nuchal fold ≥ 5 mm. In our series, among 27 cases with Down syndrome and ARSA, the latter was the only sonographic abnormality detected in eight (29.6%) cases. Considering our entire population, this means that in 7.5% (8/106) of cases, Down syndrome could have been diagnosed only through the recognition of ARSA.

We found no correlation between ARSA and CHD; an ARSA was present in 22.2% (14/63) of Down syndrome fetuses with no CHD and in 30.2% (13/43) of those with CHD (not significant). In contrast, in the series of both Chaoui *at al.*[9] and Zalel *et al.*[12], there seemed to be an association between ARSA and absence of CHD, though with exceedingly low numbers. Our impression is that there are still too few data to draw any definite conclusions, both prenatally and postnatally, with postnatal studies in addition being heavily biased by their sample characteristics (either postmortem or catheterization).

Also worth noting is the incidence in our sample population of the other markers evaluated in this study: NB−, nuchal fold ≥ 5 mm, pyelectasis, major CHD and major extracardiac anomalies. Table 4 compares our rates with those of other series published in the literature. Our figures are in fair agreement with those of other studies as far as NB− and pyelectasis are concerned, but much less so with respect to nuchal fold and major congenital anomalies. Regarding the discrepancy in incidence of nuchal fold ≥ 5 mm in our series compared with the others (16% vs 33.5%), we believe that a likely explanation is that the studies from which we obtained the combined value in Table 4 were conducted during a time period in which first-trimester combined screening was not used as widely as it is now. Since an enlarged nuchal fold is nothing other than a previously enlarged NT, it is likely that in our series a significant proportion of these pregnancies had been terminated prior to second-trimester assessment, due to increased implementation of the combined screening procedure. Regarding the incidence of major anomalies in our series compared with the others (64% vs 21%), we suggest two possible factors that may account for this discrepancy. The first and more likely one is that our unit is a fetal medicine and cardiology one, so assessment of the fetal heart is rather comprehensive and even small inlet ventricular septal defects are searched for; the second is that some of our cases were seen in the relatively advanced second-trimester period (22–24 weeks). It is well known that the double bubble sign, which identifies duodenal atresia, is not visible in most cases before this period. This may have led to an underestimation of the true incidence of this anomaly in the other series[17,18], considering that these focused on the genetic sonogram, which is usually carried out at 15–18 weeks of gestation[19–21]. Other series from fetal heart experts, as well as our past experience in Down syndrome fetuses seen at our center for reasons other than a diagnosis of CHD, confirms the high prevalence of CHD in Down syndrome, if detailed fetal echocardiography is performed[18,22].

In conclusion, we have reported the incidence of ARSA in a large series of Down syndrome fetuses in which karyotyping had been performed not because of the detection of major anomalies and/or Down syndrome markers but for other reasons (Table 1), and, in this relatively unbiased Down syndrome fetal population, the incidence of ARSA was 25%. Furthermore, we have shown that ARSA is apparently independent from other sonographic major and minor Down syndrome signs, being the only sonographic sign of Down syndrome in 7.5% of the cases in our series. Considering that the incidence of ARSA was shown recently to be 1.5% in normal fetuses[13], we believe that this finding should be considered among the three most powerful ultrasound indicators of Down syndrome in the second trimester, together with the NB and the nuchal fold.

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