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Second-trimester fetal aberrant right subclavian artery: original study, systematic review and meta-analysis of performance in detection of Down syndrome

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KEYWORDS: aberrant right subclavian artery; chromosomal abnormalities; Down syndrome; meta-analysis; systematic review; ultrasound marker

ABSTRACT

Objectives *First, to estimate the prevalence of fetal aberrant right subclavian artery (ARSA) in our population and its association with Down syndrome. Second, to determine the feasibility of ultrasound to visualize ARSA in the three planes. Finally, to carry out a systematic review of the literature on the performance of second-trimester ARSA to identify fetuses with Down syndrome.*

Methods *ARSA was assessed by ultrasound in the axial plane and confirmed in the longitudinal and coronal planes during the second half of pregnancy in women attending our unit (from February 2011 to December 2012). A search of diagnostic tests for the assessment of ARSA was carried out in international databases. Relevant studies were subjected to a critical reading, and meta-analysis was performed with Meta-DiSc.*

Results *Of the 8781 fetuses in our population (mean gestational age: 24 ± 5.4 weeks), 22 had Down syndrome. ARSA was detected in the axial view in 60 cases (0.7%) and confirmed in the coronal view in 96.7% and in the longitudinal view in 6.7% ($P < 0.001$). Seven cases with ARSA had Down syndrome and all were in the non-isolated-ARSA group. The estimates of positive likelihood ratio (LR) were 0 for isolated ARSA and 199 (95% CI, 88.9–445.2) for non-isolated ARSA. In the systematic review, six studies were selected for quantitative synthesis. The pooled estimates of positive and negative LRs for global ARSA were, respectively, 35.3 (95% CI, 24.4–51.1) and 0.75 (95% CI, 0.64–0.87). For isolated ARSA, the positive and negative LRs were 0 (95% CI, 0.0–14.7) and 0.98 (95% CI, 0.94–1.02), respectively.*

Conclusions *The prevalence of ARSA seems close to 1%. The coronal plane is the most suitable for its confirmation after detection in the axial plane. Detection of isolated or non-isolated ARSA should guide decisions about karyotyping given that isolated ARSA shows a weak association with Down syndrome.*

INTRODUCTION

Chromosomal abnormalities are present in 0.1–0.2% of all newborns. The most frequent abnormality is Down syndrome[1], the prevalence of which is affected positively by maternal age and inversely by gestational age[2].

Ultrasound screening for Down syndrome is based on the observation that most fetuses with chromosomal abnormalities have major structural malformations or minor anomalies (markers) that can be detected using ultrasound. Interest in prenatal assessment of fetal aberrant right subclavian artery (ARSA) has increased because of the known association between this condition and Down syndrome and other congenital anomalies[3–7]. Ultrasound assessment of ARSA is performed in the axial plane at the level of the three vessels and trachea view[8], although it can also be observed in the longitudinal and coronal planes (Figure 1)[9,10]; however, feasibility in non-axial planes has not been described.

Several recent studies have estimated the prevalence of fetal ARSA in healthy fetuses and in Down syndrome fetuses and assessed the usefulness of ARSA as an ultrasound marker for Down syndrome in the second trimester of pregnancy[3,5,6,11,12]. The results reflect a wide range of prevalence values in Down syndrome fetuses (8–37%)[3–6,8,9,13,14] and discrepancies in the positive likelihood ratio (LR+), depending on whether ARSA is an isolated anomaly (LR+: 0–29.6)[3,5,6,15] or a non-isolated anomaly (LR+: 12.6–42.04)[3,5,7,8,13]. The

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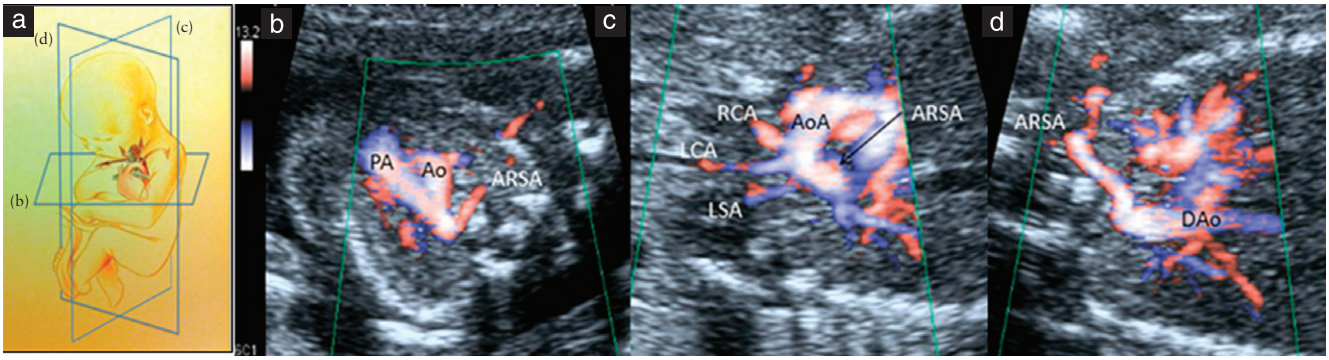

Figure 1 Schematic diagram of fetus (a) and corresponding ultrasound images of aberrant right subclavian artery (ARSA) in three views (b–d). (b) Axial view. ARSA arises close to the ductus arteriosus and follows a retrotracheal course toward the right shoulder. (c) Longitudinal view. ARSA arises distally from the aortic arch (AoA) as the fourth supra-aortic vessel, behind the left subclavian artery (LSA). (d) Coronal view. ARSA arises close to the descending thoracic aorta (DAo) and follows an oblique course toward the right shoulder. Ao, aorta; LCA, left carotid artery; PA, pulmonary artery; RCA, right carotid artery.

limitations of these studies include a lack of data on the prevalence of Down syndrome and on the presence of ARSA as an isolated/non-isolated finding. In 2013, Agathokleous *et al.* published a meta-analysis based on two population-based studies carried out to investigate second-trimester markers[16]. More recent data have been reported since then[12,14,15,17].

The aims of our study were three-fold: first, to estimate the prevalence of fetal ARSA in our population; second, to investigate the feasibility of visualization of ARSA in the three main sonographic planes; and third, to conduct a systematic review and meta-analysis to assess the performance of ARSA (isolated and non-isolated) in screening for Down syndrome.

METHODS

Population study and ultrasound visualization of ARSA

We performed a prospective study (February 2011 to December 2012) to estimate the prevalence of fetal ARSA in all women attending our fetal medicine unit for routine ultrasound examination or referred to our hospital during the second half of pregnancy for a suspected fetal anomaly. All women were evaluated by two experienced observers using a transabdominal 4–8-MHz probe (Voluson E6; GE Medical Systems, Zipf, Austria) and gave written informed consent for their inclusion. The study was approved by the Institutional Review Board of our hospital.

Fetal ARSA arises distally from the aortic arch behind the left subclavian artery and close to the aortic isthmus, rather than at the first branch of the brachiocephalic artery. In the three vessels and trachea view, application of highly sensitive color Doppler with a low-velocity range (10–15 cm/s) shows its anomalous origin on the aortic arch and its retrotracheal course toward the right shoulder (Figure 1b, Videoclip S1)[8]. Pulsed-wave Doppler can help to differentiate between ARSA and the azygos vein, which courses to the right of the trachea.

For our second objective, when ARSA was detected, images of this vessel were obtained in the longitudinal and coronal views when possible, following the methods described by Chaoui *et al.*[9] (Figure 1c) and De León-Luis *et al.* (Figure 1d, Videoclip S2)[10]. These complementary approaches, together with the use of pulsed-wave Doppler, help to confirm the diagnosis of ARSA and, especially in the coronal view, to differentiate it from neighboring vessels[9,10].

Cases of ARSA were registered and scanned for associated anomalies using conventional ultrasound and fetal echocardiography. Karyotyping was discussed with the parents. All maternal-perinatal data were recorded at the ultrasound examination and after birth. Special attention was paid to cases with suspicion of Down syndrome or associated structural anomalies, and postnatal karyotype was determined when suspicious features were observed in the newborn. Postnatal echocardiography was performed in all affected cases to confirm prenatal findings. Once pre- and postnatal evaluations were performed, classification as a case of isolated ARSA was made according to the lack of other ultrasound markers for chromosomal abnormalities and/or fetal structural anomalies.

Systematic review

Information sources and search strategies

We searched the major international bibliographic databases (MEDLINE, EMBASE and CINAHL) for diagnostic studies. The final review was conducted in July 2013. The articles were identified using comprehensive search criteria and a combination of MeSH and EMTREE terms with the following keywords: 'trisomy 21', 'Down syndrome' and 'fetal aberrant right subclavian artery'. These terms were combined with methodological filters developed to identify diagnostic studies[18]. The references included in the articles selected were also reviewed to search for related citations.

Selection criteria and identification of relevant documents

The search was not restricted by date of publication. Articles in languages other than English or Spanish were

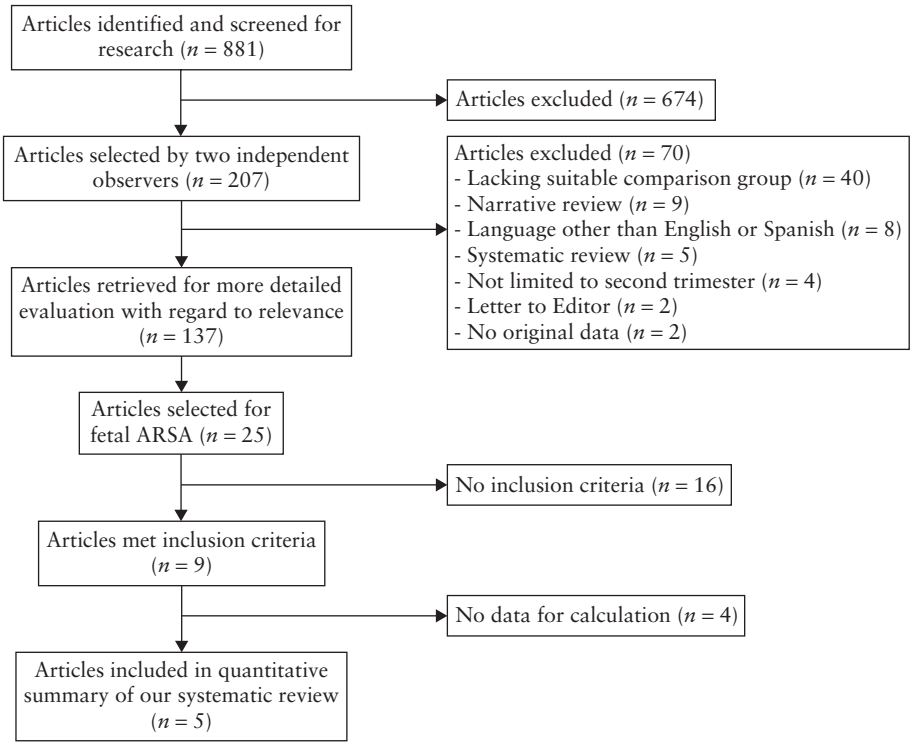

Figure 2 Flowchart describing the process of study selection in the meta-analysis.

excluded. The resulting search lists included the title and/or abstract and were used for initial identification of relevant documents. Up to five independent researchers participated in this stage following a previous published methodology and search criteria[19]. An article was considered to be relevant if at least one of the observers considered it relevant. In that case, the full text was retrieved. Interobserver agreement was 100%.

To be included in the review, a study had to report on the prevalence of fetal ARSA in healthy fetuses and/or in Down syndrome fetuses in the second trimester of pregnancy. A more restrictive search was carried out to select studies using data based on ARSA validity indicators (Figure 2).

Data extraction and assessment of methodological quality

Studies considered to be relevant were critically assessed by a group of at least three evaluators who used the Critical Appraisal Skills Programme (CASP) criteria for diagnostic studies[20]. The quality of the studies was classified as acceptable, medium or high, according to the criteria outlined in the Osteba Critical Reading guidelines[21].

For a study to be selected, it had to fulfil the screening criteria on the evaluation forms. Studies that were considered to be both relevant and methodologically sound were then examined by two independent observers who extracted the following ultrasound data: sensitivity (absolute and relative frequencies), specificity (absolute and relative frequencies) and LR for isolated, non-isolated and global ARSA.

Statistical summary of data (meta-analysis)

The meta-analysis was performed to provide a quantitative summary of the performance of ARSA in screening for Down syndrome. Using metaregression to estimate the relative diagnostic odds ratio associated with the covariate (risk indicator), we explored sources of heterogeneity, such as differences in Down syndrome in the populations studied. These differences represent the change in diagnostic performance of the test under study per unit increase in the covariate.

The analysis was performed using Meta-DiSc, a software program for meta-analysis of studies evaluating diagnostic screening tests. Meta-DiSc was developed by the Clinical Biostatistics Unit, Ramón y Cajal Hospital, Madrid[22].

RESULTS

Population study and ultrasound visualization of ARSA

During the study period, we examined 8781 fetuses, 4.8% of which were referred to our unit. Mean maternal age was 32.1 ± 4.3 years. The right subclavian artery was visible in the axial plane in 98% of cases (including cases of normal and aberrant artery). We detected 60 cases of ARSA (prevalence, 0.7%; 95% CI, 0.5–0.8%). The mean gestational age was 24 ± 5.4 weeks at diagnosis and 38 ± 2.3 weeks at delivery.

All cases of ARSA were detected in the axial view. The feasibility of visualization of ARSA in the complementary planes was significantly higher in the coronal view than in the longitudinal view (96.7% *vs* 6.7%; $P < 0.001$).

Table 1 Details of ultrasound findings and outcome in fetuses with non-isolated aberrant right subclavian artery (ARSA)

Case	*Cardiac anomalies*	*Extracardiac anomalies*	*Karyotype*	*Outcome*
1	None	Cystic hygroma, single umbilical artery	Normal	Full term
2	None	Umbilical vein varix	NP	Full term
3	None	Mild bilateral ventriculomegaly	Trisomy 21	Full term
4	None	Short long bones, increased nuchal fold	Normal	Full term
5	Hypoplastic left ventricle	None	Dup22q11.2	Full term*
6	None	Bilateral pyelectasis, talipes, increased nuchal fold	Trisomy 21	TOP
7	None	Thymic hypoplasia, short long bones	Normal	Full term
8	None	Cystic hygroma	Trisomy 21	Full term
8	None	Hypoplastic nasal bone	NP	Full term
9	None	Frontal edema	NP	Full term
10	None	Bilateral pyelectasis, increased nuchal fold	NP	Full term
11	None	Severe IUGR, hyperechogenic bowel	Normal	Preterm birth
12	None	Frontal edema, increased nuchal fold	Normal	Full term
13	None	Single umbilical artery	NP	Full term
14	None	Esophageal atresia	NP	Full term
15	AV canal defect	Agenesis of ductus venosus, cystic hygroma, hydrops fetalis	NP	TOP
16	None	Increased nuchal fold, omphalocele, reversed a-wave in DV	Trisomy 21	Intrauterine demise
17	AV canal defect	None	Trisomy 21	TOP
18	Pericardial effusion, tricuspid regurgitation, intracardiac foci	Hypoplastic nasal bone	Trisomy 21	Full term
19	Tricuspid regurgitation	None	NP	Unknown
20	None	Frontal edema	NP	Full term
21	None	Hypoplastic nasal bone, hyperechogenic bowel, reversed a-wave in DV	Trisomy 21	TOP

*Neonatal death. AV, atrioventricular; DV, ductus venosus; IUGR, intrauterine growth restriction; NP, not performed; TOP, termination of pregnancy.

ARSA was isolated in 39 (65%) cases and was non-isolated in 21 (35%) cases. We detected five (8.3%) cases with cardiac defects and 16 (26.7%) had additional extracardiac anomalies (Table 1). No cases of Down syndrome were detected in fetuses with isolated ARSA.

Among the 8781 fetuses explored, we detected 22 cases of Down syndrome (1/400; 95% CI, 1/263–1/625). In 17 of the 60 cases of ARSA, the parents opted for fetal karyotyping, which revealed six cases of trisomy 21. One case of trisomy 21 was diagnosed after birth. The fetus had mild bilateral ventriculomegaly and intrauterine growth restriction (the parents declined prenatal karyotyping). The sensitivity and specificity of ARSA, as a marker of trisomy 21, were 31.8% and 99.3%, respectively. In our population, the overall LR+ of ARSA was 52.6 (95% CI, 27.0–102.5). For isolated ARSA, the LR+ was 0 (95% CI, 0.0–14.7) and for non-isolated ARSA, it was 199 (95% CI, 88.9–445.2). These results show that no association was detected between isolated ARSA and Down syndrome (Tables 2 and 3).

The interobserver agreement described previously by our group for the detection of normal right subclavian artery or ARSA showed a kappa index of 1 between two experienced observers (C. Bravo, F. Gámez, T. Álvarez, L.J. Ortiz-Quintana, J. De León-Luis, unpubl. data).

Systematic review

The initial search revealed a list of 25 articles, which were reviewed by two independent observers. Only nine articles met the inclusion criteria (Table 2). Finally, five studies of the selection and our own work were selected for the quantitative synthesis of this systematic review (Figure 2; Table 3).

The quality of all the studies was acceptable according to the CASP criteria. However, none of the articles included the assessment of interobserver agreement. In three articles, the populations had a high risk for Down syndrome (those referred for a comprehensive ultrasound scan or echocardiography after a previously positive combined screening result, cases of advanced maternal age, those with previous abnormal ultrasound findings and those with risk factors for congenital heart disease or other risk factors for Down syndrome)[5,12,13].

Table 3 summarizes the sensitivity and specificity of ARSA of each of the six articles included in the meta-analysis (i.e. the five published articles[3,5,12–14] and the present study). The results of the meta-analysis show that ARSA, as an ultrasound marker of Down syndrome, has low sensitivity (29.3%) and high specificity (99.2%) (Table 4).

Diagnostic performance indicators for ARSA and isolated ARSA are shown in Table 4 and include theresults of our study (Figure 3). The pooled estimates of global LR+ and negative LR (LR–) for ARSA were, respectively, 35.3 (95% CI, 24.4–51.1) and 0.75 (95%CI, 0.64–0.87). For isolated ARSA, the LR+ and LR– values were 0 (95% CI, 0.0–14.7) and 0.98 (95% CI, 0.94–1.02), respectively.

Diagnostic performance was similar between the studies, according to the risk group, with no significant changes in the relative diagnostic odds ratio (0.48; 95% CI, 0.09–2.60; $P = 0.48$).

Table 2 Population studies meeting inclusion criteria with reports on the prevalence of aberrant right subclavian artery (ARSA) and Down syndrome (DS)

Study	*GA (weeks)*	*Total pop. (fetuses)*	*Prev. ARSA*	*Prev. DS*	*Prev. ARSA and DS*	*Isolated ARSA*	*Isolated ARSA/ DS with ARSA*
Chaoui 2005[28]	15–34	908	14 (1.5)	NR	1 (0.1)	NR	0
Borenstein 2008[13]*	16–24	183	4 (2.2)	3 (1.6)	1 (0.5)	NR	NR
Zalel 2008[3]*	13–26	924	13 (1.4)	8 (0.9)	3 (0.3)	6 (46)	0
Entezami 2009[29]	13–36	7773	125 (1.6)	NR	9 (0.1)	78 (62)	0
Borenstein 2010[5]*	16–23 + 6	2670	43 (1.6)	28 (1)	8 (0.3)	NR	1 (12.5)
Gul 2012[17]	17–33	4125	17 (0.4)	NR	1 (0.02)	9 (53)	1 (100)
Willruth 2012[12]*	16–28	1337	14 (1)	11 (0.8)	1 (0.07)	9 (64.2)	0
Rembouskos 2012[15]	1st tri.–24	6219	89 (1.4)	NR	6 (0.09)	20 (22.5)	1 (16.6)
Yazicioglu 2013[14]*	2nd tri.	2081	23 (1.1)	20 (1)	7 (0.3)	9 (39)	0
Our study*	15–37	8781	60 (0.7)	22 (0.2)	7 (0.08)	39 (65)	0

Only the first author is reported for each study. Data are given as range, *n* or *n* (%). *Studies included in the meta-analysis. NR, not reported; pop., population; Prev., prevalence; tri., trimester.

Table 3 Validity indicators of aberrant right subclavian artery (ARSA) as an ultrasound marker for Down syndrome in the studies included in the meta-analysis

Study	*Type of risk*	*Total pop. (fetuses)*	*First-trimester screening*	*Sens. (%)*	*Spec. (%)*	*ARSA LR+*	*ARSA LR−*	*Isolated ARSA LR+*	*Non-isolated ARSA LR+*
Borenstein 2008[13]	High	183	Yes	33.3	99.4	59	0.6	—	—
Zalel 2008[3]	Low	924	Yes	37.5	98.5	26.6	0.6	0	87.2
Borenstein 2010[5]	High	2670	Yes	28.6	98.8	24.1	0.7	—	—
Willruth 2012[12]	High	1337	Unknown	9	99.2	11.5	0.9	0	30
Yazicioglu 2013[14]	Low	2081	Yes	35	99.2	45	0.6	0	102.9
Our study	Low	8781	No	31.8	99.1	52	0.7	0	198.7

Only the first author is reported for each study. LR+, positive likelihood ratio; LR−, negative likelihood ratio; pop., population; Sens., sensitivity; Spec., specificity.

Table 4 Validity indicators for global aberrant right subclavian artery (ARSA) as an ultrasound marker for Down syndrome

Variable	*ARSA*	*Isolated ARSA*
Number of studies	6	4
Sensitivity (95% CI)	0.293 (0.203–0.398)	0.0 (0.0–0.059)
Specificity (95% CI)	0.992 (0.991–0.993)	0.995 (0.994–0.996)
LR+ (95% CI)	35.3 (24.4–51.1)	0.0 (0.0–14.7)
LR− (95% CI)	0.75 (0.64–0.87)	0.98 (0.94–1.02)
Presence of heterogeneity	No	No

LR+, positive likelihood ratio; LR−, negative likelihood ratio.

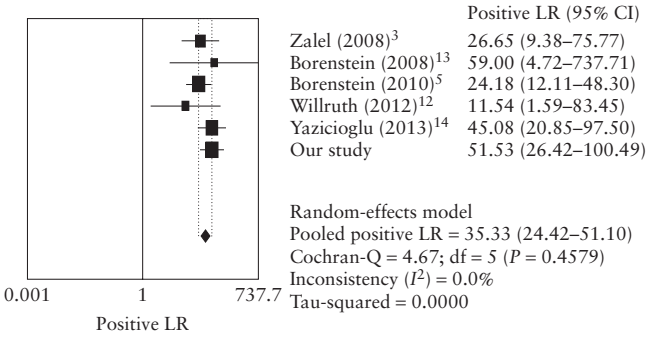

Figure 3 Graph of the positive likelihood ratio (LR) of aberrant right subclavian artery (ARSA) in the second trimester according to the results of the meta-analysis.

DISCUSSION

The key findings of this study are that the prevalence of fetal ARSA may be lower than 1% and that the coronal plane can be used to confirm ARSA after visualization in the axial plane. In addition, detection of ARSA should be followed by an exhaustive fetal anatomy scan to rule out other anomalies, given that isolated ARSA alone does not seem to justify routine invasive testing for Down syndrome.

In our population, the prevalence of ARSA was 0.7%. Prevalence may be affected by factors such as early screening and the prevalence of Down syndrome[3,5,13,14]. It seems reasonable that the real prevalence of ARSA in the population is lower than 1%, considering that several population-based studies with a higher prevalence of ARSA have also reported a high prevalence of Down syndrome (close to 1/100)[3,5,12,14] (Table 2). The prevalence of ARSA could be close to that of our report, as ours is the largest population screened to date (8781 fetuses) and the 95% CI for the prevalence of Down syndrome was between 1/263 and 1/625. This prevalence could be representative of a low-risk population – our mean maternal age was 32.1 years – and is similar to that reported by Snijders *et al.*[2] (1/559 cases at 20 weeks and 1/659 cases at 40 weeks).

ARSA should be visualized in the axial plane and this has been reported to be feasible in more than 83% of cases, even during the first trimester[13,15]. In our study, acquisition of images of ARSA in longitudinal views

proved to be more challenging, probably because the oblique course of the vessel makes it difficult to visualize ARSA, the aortic arch and the supra-aortic arteries in the same plane[23]. In order to avoid false-positive results caused by mistaken identification of the azygos vein, we recommend confirmation of ARSA in the coronal plane, given that this view provides an image of the full course of the aberrant vessel[10]. Pulsed-wave Doppler is also useful for this purpose in any of the three planes, given that the azygos vein has the typical venous waveform.

The results of the meta-analysis performed to determine the sensitivity and specificity of ARSA to detect Down syndrome in the second trimester demonstrate that ARSA enables correct diagnosis of healthy fetuses, with a low false-positive rate, albeit at the expense of low sensitivity (Table 4).

The LR+ and LR− values of ARSA obtained in this meta-analysis (Table 4) are significantly higher than those published recently by Agathokleous *et al.* (21.48 (95% CI, 11.48–40.19) and 0.71 (95% CI, 0.57–0.88), respectively)[16]. These differences can be explained by the higher number of studies in our analysis.

When ARSA is detected as an isolated or non-isolated marker, the prevalence of Down syndrome in these subgroups varies considerably (0% and 33%, respectively). This discrepancy is explained by the presence of three studies, other than ours, that report no cases of isolated ARSA in Down syndrome fetuses[3,12,14].

Given the differences in the association between isolated and non-isolated ARSA and Down syndrome, it is necessary to investigate the differences in LR between both groups. Only three of the studies included in the meta-analysis and ours provide sufficient data to estimate the LR in these conditions (Table 3). The results of the LR+ of ARSA suggest that Down syndrome is 35 times more frequent in fetuses with ARSA than in healthy fetuses. Nevertheless, if ARSA is the only ultrasound finding, the results show a weak association with Down syndrome. In fact, Down syndrome fetuses with isolated ARSA have been described in the literature, although the study data are insufficient to calculate validity indicators or the articles are case series. Indeed, the 95% CI of the LR+ for isolated ARSA in this meta-analysis ranges from 0 to 14; therefore, this conclusion must be interpreted with caution. From the clinical point of view, the definition of isolated ARSA is highly relevant to be able to unify the results of the studies. According to the majority of previous studies on the topic[3,14,17], the definition of isolated ARSA has been made based on the exclusion of classical ultrasound markers of aneuploidy and/or structural malformations. A slight deviation from this definition, such as excluding minor anomalies from the non-isolated cases, would increase the number of isolated cases of ARSA in Down syndrome fetuses. That could be the case in the study of Zalel *et al.*[3] in which, if we consider a fetus affected with persistent left superior vena cava as an isolated ARSA case, the overall sensitivity and specificity of this marker would be 1.6% (95% CI, 0–8.8%) and 99.5% (95% CI, 99.4–99.6%), respectively, and the LR+ would be 3.2 (95% CI, 1–22). Despite this increase in the LR+ for isolated ARSA, the strength of the association is still low, even after inclusion of over 15 000 fetuses in the meta-analysis. In light of these considerations, the detection of an isolated ARSA should be interpreted with extreme caution, especially when it is known that several case series have described a considerable number of isolated cases of ARSA associated with Down syndrome[6,24]. Further studies are needed to elucidate this matter. Encouraging authors to calculate and publish all their data in detail (isolated ARSA and Down syndrome prevalence, definition of isolated ARSA) would contribute to a better estimation of the significance of this marker. The usefulness of systematic fetal karyotyping in cases of isolated ARSA remains questionable until the relationship between isolated fetal ARSA and Down syndrome can be established with more confidence. Our meta-analysis showed no significant differences according to risk group between studies conducted in different populations.

Among the articles selected, only ours analyzed interobserver agreement. Interobserver reliability is a key aspect in studies on diagnostic tests; indeed, it is one of the items used to assess the quality of the test. We believe that it should be taken into account when designing future studies of the diagnostic performance of ARSA in order to ensure the quality of the validity indicators.

ARSA has been associated with other genetic disorders, especially the 22q11 microdeletion involved in conotruncal cardiac anomalies[25,26]. We previously detected a case of ARSA associated with a 17p11.2 microduplication (Potocki–Lupski syndrome)[27]. Despite the association between ARSA and certain genetic conditions, the decision to include routine investigation of these genetic disorders in cases of ARSA should be based on the presence of cardiac anomalies. Again, further studies are needed before current management can be modified.

Our study had some limitations. First, first-trimester screening for Down syndrome was unavailable for our catchment area, influencing the *a-priori* prevalence of ARSA. Moreover, as ultrasound assessment for ARSA was not performed in the first trimester, it is possible that cases of fetal aneuploidy with ARSA were missed due to spontaneous miscarriage or termination of pregnancy after prenatal diagnosis. Second, prenatal detection of the 22q11 microdeletion was performed routinely only in fetuses with conotruncal heart defects, not in cases of ARSA. As this genetic disorder can manifest late in early childhood, some cases could have gone undetected. Finally, postnatal echocardiography was only performed in cases of ARSA detected prenatally, thus potentially introducing bias.

We minimized any likely publication bias by conducting an exhaustive search of relevant documents in all the main information sources available. As for selection of documents, any potential shortcomings were resolved by means of independent selection of articles by two observers, between whom agreement was total. Study quality and data extraction were assessed in duplicate to avoid errors in data tabulation and analysis.

In conclusion, the prevalence of ARSA is close to 1%. ARSA detected in the axial plane can be confirmed in the coronal plane. Given that ARSA multiplies the risk of Down syndrome 35-fold, it could serve as a useful ultrasound marker of Down syndrome in the second trimester and facilitate discussion of karyotyping with parents. The difference in LR+ between isolated and non-isolated ARSA means that invasive tests should be discussed in isolated cases. In any case, detection of ARSA should be followed by fetal echocardiography and a comprehensive anatomy scan to rule out other anomalies.

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SUPPORTING INFORMATION ON THE INTERNET

The following supporting information may be found in the online version of this article:

Videoclips S1 and S2 Aberrant right subclavian artery on ultrasound imaging: axial view (Videoclip S1) and coronal view (Videoclip S2)