

## Aberrant right subclavian artery: is a strong marker for Down syndrome and congenital heart disease?

*Aberran sağ subklavyen arter: Down sendromu ve konjenital kalp hastalığı için güçlü bir belirteç midir?*

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### Abstract

**Purpose:** The association between fetal aberrant right subclavian artery (ARSA) and Down syndrome has been known for a long time. The aim of our study was to determine the incidence of ARSA in our population and its association with Down syndrome and congenital heart diseases (CHD).

**Materials and methods:** Between 2015-2018 years, fetal echocardiography was performed in 3150 pregnant population at a tertiary referral center for prenatal diagnosis. The presence of ARSA was verified by visualization of the transverse 3-vessel trachea view by color Doppler sonography during fetal echocardiography. The frequency of ARSA and its correlation with Down syndrome were investigated in our study.

**Results:** Among the 3150 patients, an ARSA was detected in 42 fetuses (1.3%) and isolated ARSA was detected in 36 fetuses (1.14%). Of nine fetuses with Down syndrome, ARSA was positive in two (22.2%). ARSA was positive in only one of the fetuses with CHD (4.1%). The positive likelihood ratios of isolated ARSA for Down syndrome and CHD were 0.73 and 3.81, respectively.

**Conclusion:** In our case series, prenatal detection of ARSA does not appear to be a strong marker alone of Down syndrome and the isolated ARSA shows a weak association with CHD.

**Key words:** Aberrant right subclavian artery, congenital heart disease, Down syndrome.

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### Özet

**Amaç:** Fetal aberran sağ subklavyen arter (ARSA) ile Down sendromu arasındaki ilişki uzun zamandır bilinmektedir. Çalışmamızın amacı popülasyonumuzdaki ARSA insidansını ve Down sendromu ve konjenital kalp hastalıkları (KKH) ile ilişkisini belirlemektir.

**Gereç ve yöntem:** 2015-2018 yılları arasında üçüncü basamak merkezde prenatal tanı için 3150 gebeye fetal ekokardiyografi yapıldı. ARSA varlığı, fetal ekokardiyografi sırasında transvers 3 damar trakea planında renkli Doppler sonografide görüntülenmesi ile doğrulandı. Çalışmamızda ARSA'nın sıklığı ve Down sendromu ile korelasyonu araştırıldı.

**Bulgular:** 3150 hasta arasında 42 fetüste (%1,3) ARSA, 36 fetüste (%1,14) izole ARSA saptandı. Down sendromlu dokuz fetüsten iki hastada (%22,2) ARSA pozitifliği. ARSA, KKH olan fetüslerden sadece birinde pozitifliği (%4,1). İzole ARSA'nın Down sendromu ve CHD için pozitif olasılık oranları sırasıyla 0,73 ve 3,81 idi.

**Sonuç:** Olgu serimizde, prenatal ARSA'nın saptanması Down sendromu için tek başına güçlü bir marker gibi görünmemektedir ve izole ARSA, KKH ile zayıf bir ilişki göstermektedir.

**Anahtar kelimeler:** Aberran sağ subklavyen arter, konjenital kalp hastalığı, Down sendromu.

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## Introduction

Trisomy 21 is the most frequent chromosomal abnormality in live born infants [1]. Several prenatal genetic screening strategies and diagnostic tests are used for accurate prenatal identification of trisomy 21, among which ultrasonography is the key component. Ultrasound screening for trisomy 21 is based on the observation that most fetuses with chromosomal abnormalities have major structural malformations or minor "soft markers". The presence of sonographic markers increases the risk for trisomy 21 [2]. Population-based studies have shown that over 40% of babies with trisomy 21 have a major cardiac anomaly, the most common being atrioventricular septal defects (AVSD) [3]. In addition to major cardiac anomalies and septal defects, by definition of soft markers for trisomy 21, such as echogenic intracardiac focus (EIF) and aberrant right subclavian artery (ARSA), fetal cardiac examination only itself can give such worthy information about diagnosis. ARSA is one of the most widely examined markers for fetal trisomy 21 [2].

ARSA is the most common benign congenital abnormality of the aortic arch [4]. 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). It is detected by applying color Doppler at the level of the three-vessel-trachea view during fetal echocardiography [5-7]. Several studies have revealed that the prevalence of ARSA to be 8–37% in fetuses with trisomy 21 [5-12].

In this study, we report our experience of the detection of ARSA in an unselected population of pregnant women attending a routine morphology scan at a single university hospital and the relationship between ARSA and trisomy 21 in our cases in the light of literature and thereby to investigate its importance as a soft marker for the prenatally detection of trisomy 21.

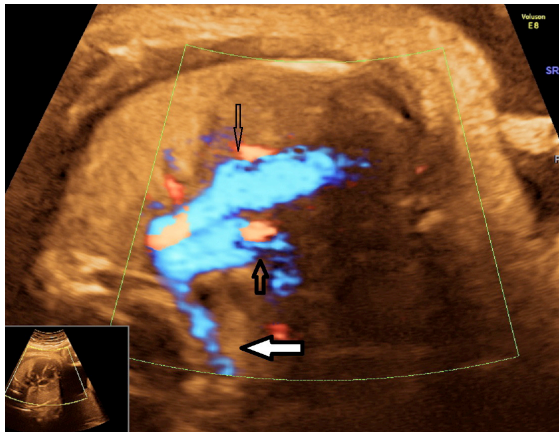
## Materials and methods

This retrospective study was conducted at the maternal fetal medicine unit in Izmir Katip Celebi University School of Medicine, Atatürk Education and Research Hospital during the period between September 2015 and January 2018. The Medical Ethics Committee of Pamukkale University School of Medicine Ethics Committee approved the trial (Registration number: 60116787-020/11863). For this analysis, only singleton pregnancies with ultrasound examination at 18 or more weeks of gestation were included. In our pregnant population, low risk and high risk group ratio were 9.01% (284/3150) and 90.9% (2866/3150) for Down syndrome, 10.8% (342/3150) and 89.2% (2808/3150) for congenital heart disease, respectively.

All fetuses underwent a thorough anatomic assessment and fetal echocardiography between 18<sup>th</sup> and 22<sup>nd</sup> of pregnancies.

The indications for the second trimester detailed fetal anomaly scan were advanced maternal age ( $\geq 35$  years), risks based on previous history, abnormal sonographic findings in preceding examinations, chromosomal abnormalities, maternal wish for targeted ultrasound examination. Detailed ultrasound examination in the second trimester included screening for a soft marker, structural abnormalities, anatomical evaluation and fetal echocardiography. Adequate fetal cardiac examination was defined if fetal cardiac four chamber view, ventricular outflow tracts, three vessels and three vessels-trachea views are viewed properly. We recorded fetal echocardiography findings and presence or absence of ARSA during fetal cardiac examination of all patients. All fetal cardiac examinations are performed by the same physician who is an expert on fetal cardiac examination by ultrasonography. The ultrasound device used was a Voluson E6 system (GE Healthcare, Milwaukee, WI) with a RAB 4–8-MHz transabdominal probe. The assessment of the ARSA was adopted from the description of Chaoui et al. [5]. After the visualization of the three vessels-trachea view, Doppler velocity is adjusted downward to the range of 15–25 cm/s and the probe was tilted to cranium. ARSA was detected as a vessel curving anterior to the

trachea and superior vena cava into the right shoulder (Figure 1).



**Figure 1.** Aberrant right subclavian artery depicted by color Doppler ultrasonography in axial view. ARSA arises close to the ductus arteriosus and follows a retrotracheal course toward the right shoulder. Thick arrow: aorta; thin arrow: pulmonary artery; white arrow: ARSA

Patients with ARSA and with abnormal sonographic findings, advanced maternal age and abnormal prenatal screening test results were recommended to undergo amniocentesis

after genetic counseling. Additionally, when isolated ARSA was detected in patients during detailed fetal echocardiography, calculation of adjusted ultrasound risk assessment was made again and genetic counseling was given according to result of patient-specific risk for Down syndrome.

We recorded maternal demographic data, fetal cardiac examination including the assessment of ARSA, detailed ultrasound examination and the karyotype for each pregnancy [2]. If the karyotype was not analyzed prenatally and the newborn appeared clinically normal to the examining pediatrician, the karyotype was considered normal.

IBM Statistical Packages for Social Services version 25 was used. Mean (the standard deviation) was given for normally distributed values, while the median (minimum-maximum) was given for not normally distributed values. Sensitivity, specificity, positive predictive value (PPV), negative predictive value (NPV), Positive likelihood ratio (+LR) and Negative likelihood ratio (-LR) of ARSA and isolated ARSA for Down syndrome were calculated by 2x2 table (Table 1). Descriptive statistical analysis was used accordingly.

**Table 1.** Sensitivity, specificity, positive predictive value (PPV), negative predictive value (NPV), Positive likelihood ratio (+LR) and Negative likelihood ratio (-LR) of ARSA and isolated ARSA for Down syndrome and congenital heart disease (°)

|                              | <b>Sensitivity (%)</b> | <b>Specificity (%)</b> | <b>PPV (%)</b> | <b>NPV (%)</b> | <b>+LR (n)</b> | <b>-LR (n)</b> |
|------------------------------|------------------------|------------------------|----------------|----------------|----------------|----------------|
| ARSA (n=42)                  | 22.2                   | 98.7                   | 4.7            | 99.7           | 18.3           | 0.78           |
| Isolated ARSA (n=36)         | 11.1                   | 84.1                   | 16.6           | 77.1           | 0.73           | 1.04           |
| <b>ARSA° (n=42)</b>          | <b>4.16</b>            | <b>99.0</b>            | <b>2.31</b>    | <b>97.0</b>    | <b>4.1</b>     | <b>0.96</b>    |
| <b>Isolated ARSA° (n=36)</b> | <b>4.16</b>            | <b>98.8</b>            | <b>2.77</b>    | <b>99.2</b>    | <b>3.81</b>    | <b>0.97</b>    |

## Results

Over the study period, total 3150 pregnant women were screened, an ARSA was found in 42 fetuses (1.3%) and nine patients had trisomy 21 (0.28%). The median maternal age in our study population was 26 (minimum age: 19, maximum age: 41 years) and the mean (SD) gestational age at ultrasound assessment was 20.4 (2.3).

Of those nine patients with trisomy 21, ARSA was detected in two (22.2%). On the other hand, 4.76% of the fetuses with ARSA had also trisomy 21. Forty fetuses with ARSA were chromosomally or morphologically normal. Among the 42 cases of ARSA, 36 were isolated and 6 were associated with a cardiac anomaly and/or an extracardiac finding and/or a soft marker. Only one of the fetuses with isolated ARSA had trisomy 21. The karyotype was obtained from an amniotic fluid sample prenatally and amniocentesis was performed because of advanced maternal age and test screening positive for Down syndrome in this case. In the remaining one case with ARSA and trisomy 21, there were additional markers such as duodenal atresia, hypoplastic nasal bone and increased nuchal fold thickness.

Among five fetuses with non-isolated ARSA and normal karyotype, extracardiac anomalies were present in four fetuses. These included single umbilical artery (1 case), umbilical vein varix (1 case), renal agenesis (1 case) and borderline ventriculomegaly (1 case). In one case, ARSA was accompanied by other cardiac malformation, including atrioventricular septal defect (AVSD) and EIF. One of the fetuses with ARSA and trisomy 21 was live-born and termination of pregnancy was done to the other which had isolated ARSA.

In our pregnant population, CHD rate was 0.76% (24/3150). These included 2 AVSD, 4 VSD, 1 hypoplastic left heart, 1 transposition of great arteries, 1 tetralogy of fallot, 5 tricuspid regurgitation (TR), 6 EIF, 1 Ebstein anomaly, 1 pulmonary stenosis, 1 coarctation of aorta and 1 cardiac rhabdomyoma. Four of these fetuses with CHD were in the high-risk group and 20 were in the low-risk group. While 3 of the fetuses with Down syndrome were found in the high-risk group, six were in the low-risk group. The incidence of CHD was 44.4% (4/9) in Down

syndrome fetuses. These included 2 AVSD, 1 EIF and 1 TR. With respect to its possible relationship with CHD, the incidence of ARSA was 11.1% (1/9) in Down syndrome fetuses with no heart defects vs 11.1% (1/9) in those with CHD (no significant difference).

## Discussion

Our study has shown that the incidence of ARSA in whole screened pregnant population is 1.3% in high risk and low risk pregnancies between 18 and 22th weeks of pregnancy (42/3150). Two studies were reported the incidence of ARSA as 1.4% in the normal population [5, 10]. Similarly, Borenstein et al. [9] have shown that the prevalence of ARSA in low-risk population is 1.2%. Our incidence of ARSA in normal population was almost about similar with Yazicioglu et al. [11] and Bronstein et al. [9] taking into account the population and studied pregnancy period. Although the detection rate of ARSA does not study very well in first trimester screening which it might increase with advanced gestational age, overall incidence numbers are given between 16 and 33 weeks of pregnancy in medical literatures.

Postnatally, autopsy studies [4] have shown that an ARSA has been found in about 1-2% of healthy people, whereas it has been noted in autopsy series and in cardiac catheterization studies that the incidence of ARSA is increased in cases of Down syndrome, with incidence ranging between 2.8 and 100% [13-19]. But, this frequency ranges from 29% to 37% in prenatal series [5, 9, 10]. We also showed that the incidence of ARSA in Down syndrome was 22.2% and rate of Down syndrome in whole ARSA group was also 4.7%. In our series, the incidence of ARSA in Down syndrome was lower than previously reported in other series. Similarly, Paladini et al. [6] have shown that the rate of ARSA in Down syndrome population was 25% in the largest series, which was lower than previously reported in much smaller series.

Several studies reported that ARSA to be described more common in fetuses with Trisomy 21 [2, 5, 6]. Two studies reported that the presence of ARSA during fetal echocardiography increased the Down syndrome risk about 16 to 20-fold [6, 9]. In addition, another study reported that the presence of ARSA increased the risk by about 45-fold [11]. But, when ARSA is detected

as an isolated or non-isolated marker, the incidence of Down syndrome in these groups varies considerably. Some studies reported the LR+ for an isolated ARSA as '0.00'. [8, 10, 11, 20, 21]. In the literature, Down syndrome fetuses with isolated ARSA have been described and the 95% CI of the LR+ for isolated ARSA ranges from 0 to 14. In our study, the LR+ for an isolated ARSA was 0.73. Similar with the case series, we also think that isolated ARSA is not actually a powerful marker for prenatal detection of Down syndrome.

Paladini et al. [6] reported that was no correlation between ARSA and CHD. Similarly, in our study, an ARSA was present in 20% (1/5) of Down syndrome fetuses with no CHD and in 25% (1/4), of those with CHD (not significant). So, presence of ARSA did not correlate with the presence of heart defects.

Limitations of our study include the fact that its retrospective design and a short period time for the study.

The strengths of our study were that it is a single-center study in a tertiary referral center; fetal echocardiography was performed by an experienced and certified specialist, and a relatively high number of cases.

In conclusion; in our series, the incidence of ARSA in Down syndrome was 22%, lower than previously reported in other series. The rate of ARSA in fetuses with CHD was 2.3%. Its presence did not correlate with the presence heart defects. In terms of respect to its possible relationship with CHD and Down syndrome, isolated ARSA as the single positive marker might not be a powerful marker. Further studies are warranted in larger groups of patients to show the importance of this finding in unselected pregnancies.

**Conflict of interest:** No conflict of interest was declared by the authors.

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**Ethics committee approval:** The Medical Ethics Committee of Pamukkale University School of Medicine Ethics Committee approved the trial (date: 26.08.2020 and number: 60116787-020/11863).

#### **Contributions of the authors to the article**

All authors constructed the main idea and hypothesis of the study. S.K. developed the theory and organized the material method section. All authors made the evaluation of the data in the results section. E.D. wrote the discussion section of the article. All authors reviewed the article, made the necessary corrections and approved. In addition, all authors discussed the entire study and confirmed its final version.