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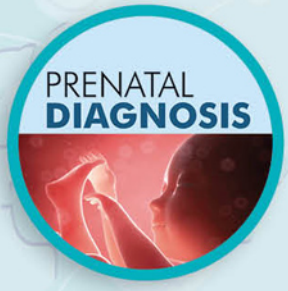

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ORIGINAL ARTICLE

WILEY PRENATAL DIAGNOSIS

Prenatal diagnosis and clinical implications of an apparently isolated right aortic arch

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Abstract

Objective: To define the associations of a prenatally diagnosed, apparently isolated right aortic arch (RAA) with chromosomal or genetic abnormalities and tracheal compression.

Methods: This was a retrospective study of apparently isolated RAA assessed by fetal cardiologists and fetal medicine specialists at Kings College Hospital, London between 2000 and 2017.

Results: The search identified 138 cases of apparently isolated RAA. Invasive testing was performed in 75, and chromosomal or genetic anomalies were identified in 16 (22%), and the most common was 22q11 microdeletion. An aberrant left subclavian artery was seen in 51% of cases. Symptoms of a vascular ring were present in 24 of 97 (25%) children who were reviewed after birth. Bronchoscopy was performed in 33 children, and significant tracheal compression was diagnosed in 28, including 18 of 19 symptomatic and 10 of 14 asymptomatic children.

Conclusions: An apparently isolated RAA is associated with a high incidence of chromosomal or genetic abnormalities and a high incidence of tracheal compression in symptomatic and asymptomatic patients. Prenatal counselling for genetic associations and postnatal airway assessment in the context of the vascular anatomy is recommended.

1 | INTRODUCTION

A Right aortic arch (RAA) is found in combination with many forms of congenital heart disease, and in such cases, the prognosis is primarily depended on other defects.[1] Recently, inclusion of the three-vessel tracheal view in routine fetal echocardiography[2] has led to the increased detection of a RAA in the absence of major congenital heart disease.[3] There is considerable uncertainty as to both the prenatal and postnatal management of fetuses/infants with apparently isolated RAA. In relation to prenatal management, there is contradictory evidence concerning the association with chromosomal and genetic abnormalities and therefore the option for invasive diagnostic testing. For example, in relation to the association with 22q11 microdeletion in some studies, the incidence was as high as 15% and in others as low as 0%.[1,3-10] In relation to postnatal management, there is no clear evidence-based pathway despite the fact that a RAA with a left arterial duct represents an anatomical vascular ring that encircles the trachea and esophagus.

The objective of this series of apparently isolated RAA from a single institution is to describe the associations of this condition with chromosomal or genetic abnormalities and tracheal compression.

2 | METHODS

This is a retrospective study of apparently isolated RAA diagnosed by specialists in fetal cardiology in a tertiary fetal medicine unit between January 2000 and December 2017. A RAA was defined as the transverse aortic arch passing to the right of the trachea (Figure 1). The arterial duct was similarly defined according to its relation to the trachea, and cases with a right or left arterial duct were included. This is a retrospective analysis of clinically acquired data, and therefore ethical approval for the study was not required.

In our unit, three groups of patients are examined in relation to fetal heart defects. First, local patients identified with an abnormality during routine ultrasound examination at 11 to 13 and 19 to 24 weeks' gestation; the ultrasound examination included the three-vessel tracheal view since 2000.[11-13] Second, patients undergoing specialist fetal echocardiography in the first- and/or second-trimester because during the 11- to 13-week scan, the fetal nuchal translucency (NT) thickness was greater than or equal to 99th or greater than or equal to 95th percentile for crown-rump length. Third, patients referred from other centres where a cardiac defect was suspected at routine ultrasound examination. All data from the fetal echocardiographic examination are recorded in a database, and a search of this database was carried out to identify all cases of RAA. The inclusion criteria for this study were RAA in the absence of major congenital heart disease or extracardiac defects. Cases with a prenatal diagnosis of a double aortic arch were excluded, but those with additional minor intracardiac findings, which had no expected hemodynamic effect, such as a small ventricular septal defect or persistent left superior vena cava, were included.

Prenatal counselling of the expectant parents, throughout the study period, included discussion regarding the possible association of an apparently isolated RAA with chromosomal/genetic abnormalities and the offer of invasive testing; such testing was initially confined to karyotyping and fluorescent in situ hybridization (FISH) for microdeletion of chromosome 22q11, and more recently, this was expanded to include array comparative genomic hybridization. In the first phase of the study, we advised the parents that if the child has airway symptoms, they should see a paediatrician. In 2014, we became aware of the association with asymptomatic tracheal compression, and we offered all patients with RAA and left arterial duct routine follow-up by a paediatric cardiologist.

Postnatal outcome was obtained from the hospital records, general practitioners, or the parents within the first year after birth. For all live-born patients, the paediatric cardiology database at Evelina London Children's Hospital, which is our postnatal paediatric cardiology referral centre, was reviewed. Some cases underwent a postnatal magnetic resonance imaging (MRI) or computerized tomography (CT) scan if the laterality/number of aortic arches was not clear after birth. Patients with airways or feeding symptoms suggestive of a vascular ring were investigated with bronchoscopy and MRI or CT scan. From 2014, all infants with RAA and left arterial duct, including those that were asymptomatic, were offered bronchoscopy and CT or MRI scan because of the poor correlation of symptoms with airway compression, and follow-up included a multidisciplinary approach including airway specialists.[14] The degree of airway compression was classified according to the Myer classification.[15] Postnatal cross-sectional imaging was used to correlate vascular anatomy relative to the airway.

We examined the incidence of increased NT, chromosomal/genetic associations, position of the arterial duct, branching pattern of the head and neck vessels, and postnatal outcome.

3 | RESULTS

The fetal database search identified 282 cases of RAA during the study period, but 144 were excluded from further analysis because of the presence of major cardiac defects or extracardiac abnormalities

What is already known about the topic?

- Right aortic arch (RAA) has an association with extracardiac and chromosomal anomalies.
- RAA with left arterial duct can form a vascular ring.
- In children with RAA, there is poor correlation of symptoms and tracheal compression.

What does this study add?

- The majority of prenatal cases of an isolated RAA in our cohort are identified during routine screening.
- Microdeletion of chromosome 22q11 is the most common genetic association with an apparently isolated RAA, it is seen in a minimum of 4% of cases.
- A chromosomal or genetic anomaly is found in half of fetuses with RAA and increased nuchal translucency thickness (NT) and in one-fifth of those with normal NT.

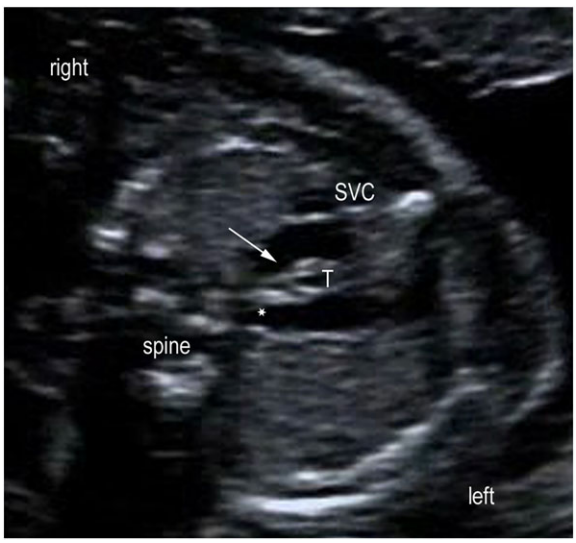

FIGURE 1 Three-vessel tracheal view demonstrating a right aortic arch (arrow) and a left arterial duct (*). These structures encircle the trachea (T) [Colour figure can be viewed at wileyonlinelibrary.com]

(Figure 2). In the study population of 138 cases of apparently isolated RAA, median gestational age at diagnosis was 21(range 11-36) weeks; in 22 fetuses, the diagnosis was made at less than 14 weeks. The indications for fetal echocardiography were suspected cardiac abnormality (n = 101), increased NT thickness (n = 12), suspected extracardiac anomaly (n = 8), heart difficult to image (n = 9), twin pregnancy (n = 4), family history of congenital heart disease (n = 2), maternal exposure to medications (n = 1), tricuspid regurgitation (n = 1), and maternal diabetes (n = 1). The distribution of indications changed over the years; for example, the indication of suspected cardiac defect at routine screening was responsible for 53% (19/36) of cases prior to

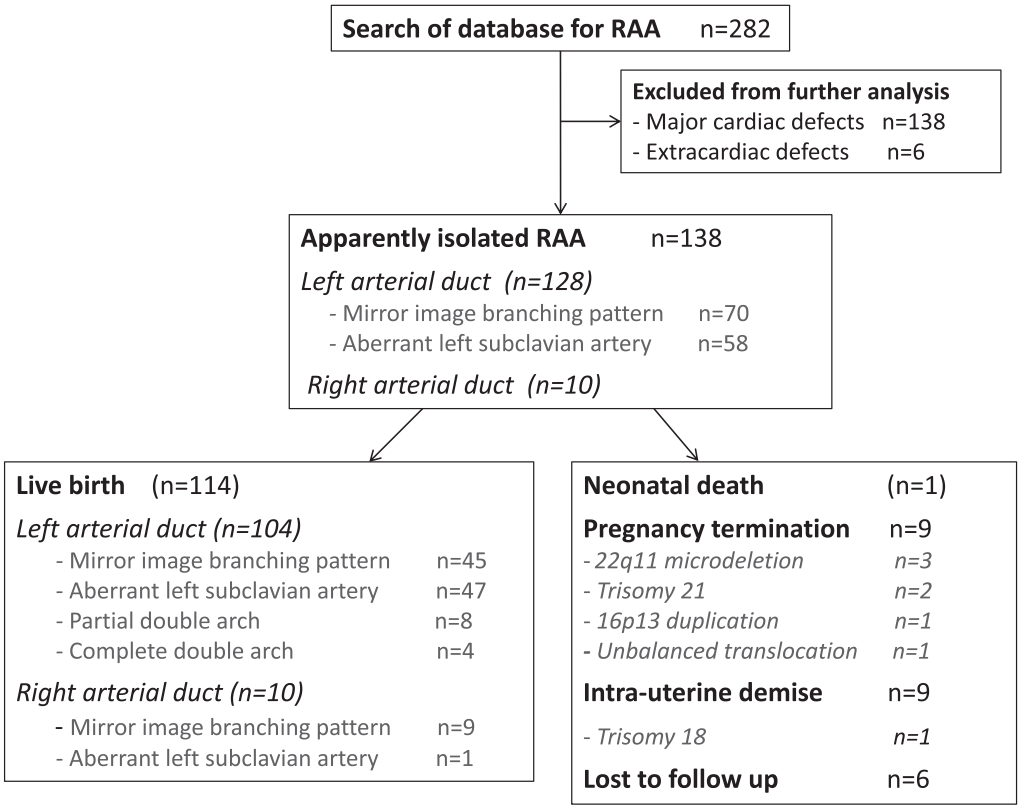

FIGURE 2 Prenatal findings with a right aortic arch

2006, 69% (25/36) at 2006 to 2011, and 86% (57/66) since 2012. Measurements of NT thickness at 11 to 13 weeks' gestation were available in 109 (81%) of the 138 cases, and the measurement was greater than 95th percentile in 12 (11%).

3.1 | Vascular morphology

The arterial duct was left-sided in 128 (93%) of cases (70 with mirror image branching and 58 with an aberrant left subclavian artery), and the arterial duct was right-sided in 10 (nine with mirror image branching and one with an aberrant left subclavian artery) (Figure 2). In the live-born cases with a left arterial duct and confirmed single RAA, 47/92 (51%) of cases had an aberrant left subclavian artery, and 49% of cases had mirror image branching pattern. In total, eight operated cases were identified to have an additional atretic left aortic arch with no luminal patency identified at the time of surgery, and in four children, a complete double aortic arch was identified with postnatal imaging.

3.2 | Chromosomal and genetic abnormalities

Prenatal or postnatal karyotyping and testing for 22q11 microdeletion was carried out in 75 cases; in the remaining 36 live-born cases examined in our paediatric cardiology unit after birth, the babies were phenotypically normal. Chromosomal abnormalities were diagnosed in six cases, including trisomy 21 (n = 3), trisomy 18 (n = 1), combined mosaicism of 45XO with 22q11 microdeletion (n = 1), and unbalanced translocation 46 XX,der(13)t(2:13)(p23:q33) (n = 1). Therefore, the incidence of chromosomal abnormalities was 8% in the 75 tested cases or 4% in the total cohort of 138 cases. In addition, there were nine cases of genetic abnormalities identified by microarray analysis or syndromic diagnoses, including 22q11 microdeletion (n = 5), Goldenhar syndrome (n = 2), Beckwith-Wiedemann syndrome (n = 1), and duplication of chromosome 16p13 with a recessive disorder of lymphogenesis (n = 1). One patient is under investigation for a mitochondrial disorder. Thus, the incidence of 22q11 microdeletion is 7% of the 73 tested cases and 4% of the total cohort. Overall, chromosomal, genetic, or syndromic abnormalities were confirmed in 21% of the 75 tested cases or 11% in the total cohort of 138 cases. A *de novo* balanced translocation with unknown clinical significance was present in one case, one infant was suspected to have fetal alcohol syndrome, and another was dysmorphic but karyotyping was declined.

Minor additional cardiac findings were observed in one of the cases of 22q11 microdeletion (bilateral superior vena cava), a small ventricular septal defect in one of the cases of trisomy 21, and a small ventricular septal defect was present prenatally, but spontaneously closed in one patient with Goldenhar syndrome.

Invasive prenatal testing was carried out in 59 of the fetuses with measurement of fetal NT thickness. A chromosomal or genetic abnormality was diagnosed in 55% (5/9) of those with NT thickness greater than or equal to 95th percentile (two cases of 22q11 microdeletion, one of trisomy 21, one case 16p13 duplication, and one of Beckwith Wiedeman) and in 18% (9/51) of those with NT thickness less than 95th percentile (three cases of 22q11 microdeletion, two of trisomy 21, one of trisomy 18, one of Goldenhar, one with the unbalanced translocation, and one with

combined mosaic 45XO with 22q11 microdeletion). The prevalence of genetic/chromosomal abnormalities was not impacted by the branching pattern of the aortic arch (Table 1).

3.3 | Pregnancy outcome

In the 138 cases of RAA, there were 114 live births, nine terminations of pregnancy, nine intrauterine deaths, and six cases were lost to follow up (Figure 2). The 114 livebirths included 104 cases with left arterial duct and 10 cases with right arterial duct; eight cases had a karyotypic or genetic anomaly. There was one neonatal death due to complications of Beckwith-Wiedeman syndrome. The nine terminations of pregnancy included two with trisomy 21, three with 22q11 microdeletion, one with 16p13 duplication, and one with the unbalanced translocation. Two of the nine intrauterine deaths were due to complications of monochorionic pregnancies and another with trisomy 18.

TABLE 1 Chromosomal/genetic findings according to different variables

	Chromosomal/Genetic Abnormalities
Nuchal Translucency	
- Greater than or equal to 95th centile	5/9 (55%)
- Less than 95th centile	9/51 (18%)
Branching pattern	
- Mirror image	7/37 (19%) tested; overall 7/68 (12%)
- Aberrant left subclavian artery	6/28 (21%) tested; overall 6/54 (11%)

3.4 | Postnatal airway findings

In 97 of the 104 live births with left arterial duct, there was longitudinal follow up in our paediatric cardiology unit (Figure 3). Symptoms, which could be considered to be due to a compressive vascular ring, were present in 24 (25%) of the 97 children at a median age of 7 months (range, 1 day-120 months); six of these children presented with airway symptoms beyond infancy.

Bronchoscopy was performed in 33 cases with a prenatal diagnosis of RAA and left arterial duct (these included 16 patients reported in a previous study[8]). There were 19 symptomatic and 14 asymptomatic infants investigated; there was significant tracheal compression in 18/19 symptomatic and 10/14 asymptomatic cases. Surgical division of the vascular ring was performed in 27 children at a median age of 15 months (range, 12 days-161 months). The sensitivity of symptoms before 2 years of age to identify tracheal compression was 59% with negative predictive value of 27%.

Two children with RAA and right arterial ductal ligament developed respiratory symptoms. One had additional findings of 22q11microdeletion, cleft palate, and left pulmonary artery stenosis. Following investigation significant right main bronchus compression due to interposition between the RAA and a dilated right pulmonary artery was identified. The second had an absent left pulmonary artery with left bronchus maldevelopment as the aetiology for respiratory symptoms.

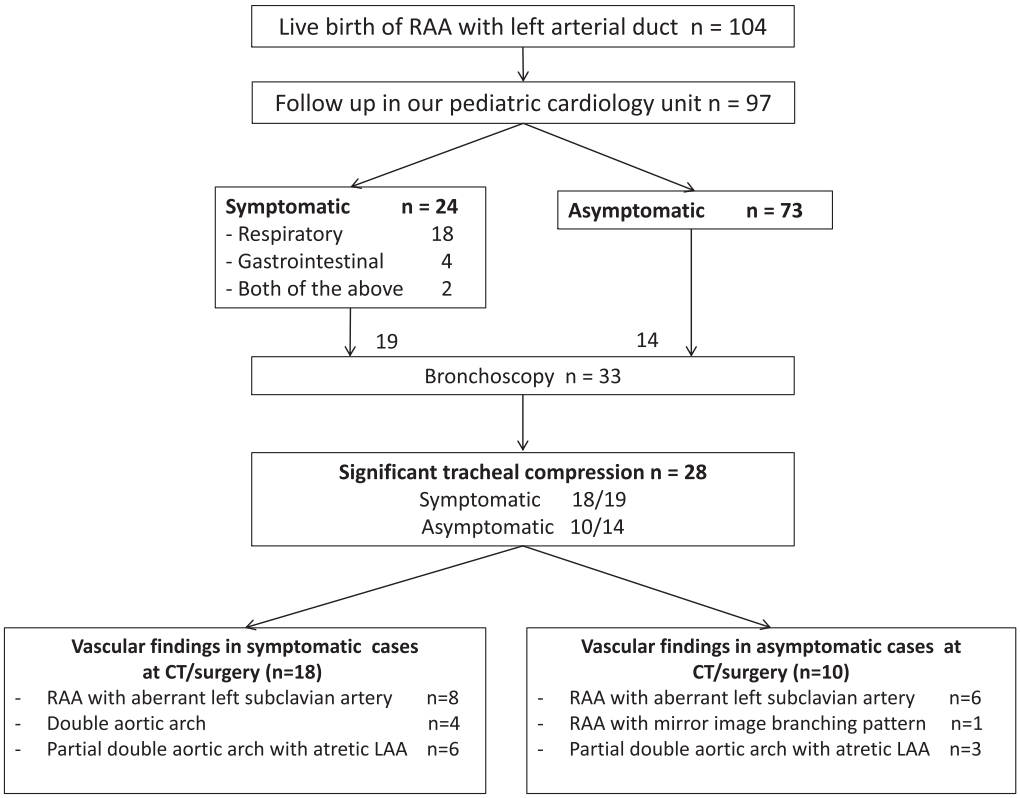

FIGURE 3 Postnatal vascular and airway findings in children with a prenatally diagnosed right aortic arch

4 | DISCUSSION

4.1 | Main findings of the study

This is the largest reported cohort from a single institution of prenatally diagnosed apparently isolated RAA. The condition was associated with a high incidence of chromosomal/genetic abnormalities, mainly microdeletion of chromosome 22q11. In early childhood symptoms of tracheal or oesophageal, compression were noted in one quarter of cases and in nearly all such cases bronchoscopy demonstrated significant tracheal compression. Significant tracheal compression was also demonstrated in two-thirds of asymptomatic infants. Anatomically, the majority of cases of RAA had a left arterial duct, an aberrant left subclavian artery was seen in over half and in a number of cases, partial patency of double aortic arch with an obliterated lumen of an atretic left arch was identified at the time of surgery.

4.2 | Comparison with findings from previous studies: Chromosomal/genetic anomalies

Our finding of a minimum 4% incidence of 22q11 microdeletion in cases of apparently isolated RAA is lower to that of three previous comparable studies with a combined total of 130 cases of apparently isolated RAA; 102/130 (78%) had invasive prenatal testing, and 10% had 22q11 microdeletion.[6,8,16] In contrast, six studies with a combined total of 145 cases of apparently isolated RAA reported a low uptake of invasive testing, and the overall incidence of chromosomal/genetic anomalies was only 6/145 (4%).[1,4,5,7,9,17] It is likely that the low rate of prenatal invasive testing in these studies may have underestimated the incidence of chromosomal/genetic anomalies. For example, in the case of 22q11 microdeletion, many of the associated facial features are not evident in the neonatal period, and many of the other features, such as learning difficulty, autistic spectrum disorder, and schizophrenia will not become apparent until school-age or early adulthood and thus, the incidence of 22q11microdeletion may be underestimated in our report given that not all underwent karyotyping and paediatric follow-up into school years did not occur.[18] Aside from the cardiac lesion itself, there are other reported prenatal ultrasonographic markers associated with 22q11 microdeletion. Assessment of the fetal cardiac angle may provide further evidence of 22q11 microdeletion, but no threshold angle has been identified.[19] The thymus is truly absent in only 1% of cases of 22q11 microdeletion[20] and thus, the presence of the thymus on prenatal ultrasonography does not exclude 22q11 microdeletion. Furthermore, the thymic:thoracic ratio does not differentiate fetuses with and without 22q11microdeletion.[19] The palate, brain, and kidneys should be assessed in fetuses at risk of 22q11 microdeletion, but may be normal. With the advent of non-invasive chromosomal testing and the ability to detect clinically relevant microdeletions, the true incidence of 22q11 microdeletion in cases of RAA may become apparent.[21]

A potential criticism of studies reporting a high association between apparently isolated RAA and chromosomal anomalies is that they have been from high-risk, tertiary fetal medicine units. However, most of our cases were identified by routine ultrasound examination, which includes assessment of the three-vessel tracheal view. Furthermore, we have excluded cases with major cardiac and extracardiac malformations.

4.3 | Comparison with findings from previous studies: Vascular morphology

The high incidence of an aberrant left subclavian artery and right arterial duct with RAA in this study, compared with previous reports,[3] is likely to be the consequence of improved ultrasound capabilities and better appreciation of the vascular structures in the upper mediastinum by experienced personnel. A complete double aortic arch with luminal patency of both limbs was identified after birth in four cases, and this possibility is raised during prenatal counselling especially where imaging has been suboptimal because of maternal factors. A RAA with an additional partial left aortic arch without luminal patency was identified during surgery in eight cases, which is unexpectedly high and although not reported in other series of prenatally detected RAA, it is a recognized entity.[22] In this variant, the left subclavian and left carotid arise separately from a diminutive left arch (which may be mistaken for an innominate artery) and a portion, usually the distal, of the left aortic arch is a thread-like vestigial structure without luminal patency. This partial left aortic arch cannot be diagnosed on postnatal echocardiography but can only be visualized on direct inspection during surgery or suspected with fetal echocardiography or with 3D sequences from fetal cardiac MRI, which is utilized in our institution.[23]

4.4 | Comparison with findings from previous studies: Tracheal compression

Within the literature, there is a misnomer about the term vascular ring, and it is used interchangeably to describe various entities. In the setting of an RAA with a left arterial duct, there is obligatory encircling of the trachea and esophagus by these vascular structures, even in the absence of an aberrant left subclavian artery. Once the lumen of the arterial duct obliterates, it remains as the arterial ligament and thus the left limb persists of the "ring" and continues to maintain the encirclement of the trachea and esophagus such that an anatomical ring is present as the right pulmonary artery passes anterior to the trachea. Classical teaching reports that an aberrant left subclavian artery is required to create a vascular ring;[24] however, our studies of the RAA population have provided further insights such as tracheal compression in the absence of an aberrant left subclavian artery.[14] Thus, patients with an RAA and left arterial duct/ligament should be considered to have an anatomical vascular ring. Three other factors may increase the propensity for tracheal or esophageal compression: first, if the descending aorta traverses from right to left in the upper mediastinum behind the trachea, second, presence of an atretic additional left aortic arch, and third, presence of a Kommerell's diverticulum.[22,24,25] A RAA with a right arterial duct does not create an anatomical vascular ring around the trachea and therefore is not deemed to be a high-risk variant for tracheal compression.

Monitoring and assessment of children with an RAA and left arterial duct/ligament is variable, and our current practice provides a more consistent approach to this cohort. The recent meta-analysis suggests monitoring until 2 years of age,[3] but subsequent evidence has shown that symptoms do not correlate with tracheal compression,[14] and further examples of this were seen in this current cohort. Stridor may not be apparent in infancy because of low air flow rates, and there may be insufficient muscle power to generate clear obstructive symptoms. Other symptoms, such as recurrent respiratory tract infections, may not reach a threshold for investigation and dysphagia may not present until weaning onto solid foods. In order to optimize growth of the tracheal cartilage, early surgery to relieve pulsatile compression of the tracheal may be warranted given the evidence for ongoing symptoms and tracheomalacia after longstanding pulsatile tracheal compression,[26-32] but this needs to be confirmed with longitudinal studies. Thus, involvement of a respiratory specialist even in asymptomatic patients is warranted.

4.5 | Implications for clinical practice

On the basis of findings from our study, the following recommendations should be considered following the prenatal diagnosis of RAA (Table 2). First, a detailed anomaly scan should be carried out for diagnosis/exclusion of other cardiac and extracardiac defects. Second, the parents should be offered the option of invasive testing for associated chromosomal/genetic abnormalities with a microarray. Third, the parents should be counselled regarding the implications of an anatomical vascular ring. Fourth, the parents should be made aware of symptoms such as stridor, recurrent respiratory infections, croup, premature diagnosis of asthma, and dysphagia, which may not be apparent until the child is fully weaned. Given the difficulty in diagnosing a double or partial double aortic arch before birth, we would also offer a fetal cardiac MRI. Fifth, a postnatal cardiac review should be offered given the possibility that hemodynamically significant ventricular septal defects were overlooked or valvar lesions have developed, but patients may not require long term follow-up by a cardiologist. Sixth, in children with an RAA and left arterial duct/ligament, review by an airway specialist should be undertaken even in the absence of symptoms, and a bronchoscopy may be carried out to look for significant tracheal compression. Further research is required to inform how these infants should be monitored, the length of monitoring, criteria for treatment, and risk stratification for tracheal compression.

TABLE 2 Suggested management following prenatal detection of a right aortic arch

Timing	Recommendation
Before birth	1) Detailed anomaly scan 2) Discuss genetic associations and option of invasive karyotype including microarray 3) Counselling regarding postnatal airway/feeding symptoms 4) Offer fetal cardiac MRI to exclude double aortic arch
After birth	1) Cardiac review 2) Airway review if RAA with left arterial duct/ligament

Abbreviations: MRI, magnetic resonance imaging; RAA, right aortic arch.

5 | LIMITATIONS

The study was conducted at a specialist fetal medicine unit and therefore ascertainment bias may exist. However, since the routine anomaly screen protocol has included transverse sweeps of the fetal heart, many cases have presented with a suspected cardiac abnormality during routine first- and second-trimester ultrasound examination of the fetus. In cases of RAA, the incidence of NT thickness greater than 95th percentile was 55%, suggesting that either RAA is more prevalent in fetuses with high NT thickness or that greater attention is paid to the fetal heart in the presence of high NT, and thus an RAA is more likely to be identified. Similarly, in 93% of cases of RAA, there was a left arterial duct, but this may reflect poor recognition of an RAA with right arterial duct. A number of patients moved out of the area and therefore postnatal outcome is not known for all, and the study may be under-representative of postnatal findings in an isolated RAA.

6 | CONCLUSION

An apparently isolated RAA is associated with a high incidence of genetic abnormalities. Significant tracheal compression is commonly found in both in infants with and those without symptoms and with both variants of aortic arch branching.

CONFLICT OF INTEREST

None declared.

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