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Fetuses with right aortic arch: a multicenter cohort study and meta-analysis

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KEYWORDS: aortic arch syndromes; echocardiography; fetus; meta-analysis; prenatal diagnosis

ABSTRACT

Objectives *Use of recent antenatal screening guidelines for cardiac abnormalities has increased fetal diagnoses of right aortic arch (RAA). We aimed to establish the outcome of fetal RAA without intracardiac abnormalities (ICA) to guide postnatal management.*

Methods *In the retrospective cohort part of our study, outcome measures were rates of chromosomal abnormalities, 22q11.2 deletion, fetal extracardiac abnormalities (ECA), postnatal ICA and ECA, and symptoms of and surgery for vascular ring. A systematic review and meta-analysis was also performed; results are reported as proportions. Kaplan–Meier analysis of vascular ring cases with surgery as endpoint was performed.*

Results *Our cohort included 86 cases; 41 had a vascular ring. Rates of chromosomal abnormalities, 22q11.2 deletion and fetal ECA were 14.1%, 6.4% and 17.4%, respectively. Sixteen studies including our cohort (312 fetuses) were included in the systematic review. Overall rates of chromosomal abnormalities and 22q11.2 deletion were 9.0% (95% CI, 6.0–12.5%) and 6.1% (95% CI, 3.6–9.3%), whilst the respective rates for cases with no ECA were 4.6% (95% CI, 2.3–7.8%) and 5.1% (95% CI, 2.4–8.6%). ECA were seen in 14.6% (95% CI, 10.6–19.0%) prenatally and in 4.0% (95% CI, 1.5–7.6%) after birth. Postnatal ICA were identified in 5.0% (95% CI, 2.7–7.9%). Rate of symptoms of vascular rings (follow-up ≥ 24 months postpartum) was 25.2% (95% CI, 16.6–35.0%), and 17.1% (95% CI, 9.9–25.7%) had surgery. Two-year freedom from surgery was 83.0% (95% CI, 74.3–90.1%).*

Conclusions *Fetal RAA without ICA is more frequently associated with ECA than with chromosomal abnormalities. Most cases, however, are isolated. Vascular-ring symptoms occur in about 25% of cases. Postnatal surveillance is required mainly in the first 2 years after delivery.* *Copyright © 2015 ISUOG. Published by John Wiley & Sons Ltd.*

INTRODUCTION

Right aortic arch (RAA) is characterized by abnormal laterality of the aorta and brachiocephalic vessels. It courses to the right of the trachea, in contrast to the normal left aortic arch (LAA). Its incidence is estimated to be 0.1%[1,2]. Variations of aortic laterality and branching pattern result from abnormal regression of the primordial paired aortic arches during embryonic development. Normal regression leads to an LAA, left-sided arterial duct (AD) and the usual branching pattern: right innominate, left common carotid and left subclavian arteries (LSA). An RAA may have a mirror-image branching pattern, but aberrant origin of the LSA (ALSA) is common.

Prenatal diagnosis is important due to associated cardiac and extracardiac abnormalities (ECA) and chromosomal defects, in particular 22q11.2 deletion[3]. An RAA can form a vascular ring, which is a heterogeneous group of vascular abnormalities encircling the trachea and esophagus. The classical vascular ring formed by an RAA has a left-sided AD and an ALSA which arises from a remnant of the primordial aortic arch, known as Kommerell's diverticulum. Although such rings may be asymptomatic, symptoms of compression, e.g. dysphagia, stridor, wheeze and recurrent upper respiratory tract infections, are reported commonly. Other manifestations include cyanosis and obstruction of the ALSA[4,5].

Prenatal diagnosis of RAA and vascular rings has been reported for a number of years[2,6–12]. Recently published international guidelines for antenatal screening[13] recommend that the three-vessel view and the three-vessel and trachea view[14,15] be included in routine pregnancy

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screening. This is likely to increase further the prenatal detection of RAA and its variants. It is therefore important that perinatal management be optimized and that family counseling is not based only on postnatal series. These are likely to be biased as only symptomatic patients are reported, thus probably representing the most extreme end of the spectrum, which does not take into account asymptomatic individuals with isolated, probably undiagnosed, RAA.

The aims of this study were to ascertain the outcome of a large number of fetuses with RAA without associated major intracardiac abnormalities (ICA) and to review the relevant literature systematically in order to propose guidance for perinatal and postnatal management.

METHODS

Cohort study

This was a retrospective cohort study of cases of RAA without associated ICA seen in tertiary centers. Cases were identified from the fetal cardiology databases at St George's and Royal Brompton Hospitals (January 2001–December 2013) and King's College Hospital (January 2006–December 2013), London. The study was an audit of clinical practice and no ethical approval was needed. Ultrasound examinations were performed on an Aloka Alpha-10, Aloka ProSound 5500 PhD (Hitachi Aloka Medical, Ltd., Tokyo, Japan), Acuson Aspen Advanced (Acuson, Mountain View, CA, USA) or Voluson E8 (GE Medical Systems, Zipf, Austria). A comprehensive assessment of the fetal heart was carried out in all fetuses using conventional two-dimensional (2D) ultrasound, and color, power and pulsed-wave Doppler. An RAA was diagnosed when the transverse arch was imaged to the right of the trachea on axial views of the fetal chest, at the level of the three-vessel and trachea view. The laterality of the AD in relation to the trachea was also ascertained. More recently, attempts were made to determine the course of the LSA, using a similar approach to that described to identify an aberrant right subclavian artery associated with an LAA[16]. The diagnosis of a vascular ring was made in the presence of an RAA, left AD and ALSA. Isolated RAA was defined as having no associated major ICA or ECA detected prenatally.

The outcomes observed were rate of chromosomal abnormalities, 22q.11.2 deletion, associated fetal ECA at the time of anatomical survey, associated postnatal ICA and ECA, symptoms related to compression of airways/esophagus and surgery for vascular ring.

Statistical analysis

Descriptive statistics are reported as median (interquartile range). Main outcomes are reported as proportions. Statistical analysis was performed using Microsoft Excel for Mac 2011 (Version 14.4.9).

Table 1 Characteristics and outcomes of 86 fetuses with prenatal diagnosis of right aortic arch (RAA) with no associated intracardiac abnormalities

Characteristics	*Value*
Maternal age (years)	32.0 (27.3–36.0)
Gestational age at diagnosis (weeks)	21.0 (20.0–23.0)
NT > 2.5 mm	9/59 (15.3)*
NT > 99th centile	4/59 (6.8)*
Abnormal karyotype or phenotype	11/78 (14.1)
Abnormal karyotype (tested)	11/53 (20.8)†
22q11.2 deletion	5/78 (6.4)
22q11.2 deletion (tested)	5/53 (9.4)†
Left arterial duct	79/86 (91.9)
Right arterial duct	7/86 (8.1)
Vascular ring (RAA and ALSA)	41/86 (47.7)
ECA diagnosed prenatally	15/86 (17.4)
Neonates with cardiac abnormalities diagnosed postnatally only	4/64 (6.3)‡
Neonates with ECA diagnosed postnatally only	4/65 (6.2)‡
Termination of pregnancy	8/86 (9.3)
Intrauterine demise	3/72 (4.2)§
Postnatal symptoms	7/33 (21.2)¶
Surgery due to vascular-ring symptoms	5/33 (15.2)¶**

Data are given as median (interquartile range) or *n*/*N* (%). *Includes only those with measured/available nuchal translucency thickness (NT). †Includes only those tested. ‡Includes only live births with known outcome data. §Includes only those known to be at risk of demise. ¶Includes only live births with a vascular ring and known outcome data; excludes the child with double aortic arch. **Includes two children awaiting surgery at time of writing. ALSA, aberrant origin of left subclavian artery; ECA, extracardiac anomaly.

Systematic review and meta-analysis

Protocol, eligibility criteria, information sources and search

This review was performed according to a protocol designed *a priori* and recommended for systematic reviews and meta-analysis[17]. MEDLINE, EMBASE, CINAHL and The Cochrane Library were searched electronically in January 2015, utilizing combinations of the relevant medical subject heading (MeSH) terms, keywords and word variants for 'right aortic arch', 'prenatal diagnosis', 'ultrasound', 'Doppler', 'chromosomal abnormalities', 'aneuploidy', '22q11 deletion', 'Di George syndrome', 'associated abnormalities', 'structural abnormalities', 'cardiac defects', 'postnatal surgery', 'intrauterine death', 'outcome', 'postnatal surgery', 'postnatal symptoms', 'respiratory symptoms', 'compression symptoms', 'vascular ring', 'vascular steal', 'intrauterine death'. Reference lists of relevant articles and reviews were hand-searched for additional reports (for search strategy, see Appendix S1). Search was limited to the English language. This review was registered on PROSPERO international database for systematic reviews (reference: CRD42015016097).

Study selection, data collection and data items

Only studies reporting prenatal diagnosis of RAA using a particular imaging protocol, which included the assessment of three-vessels and three-vessels and trachea view,

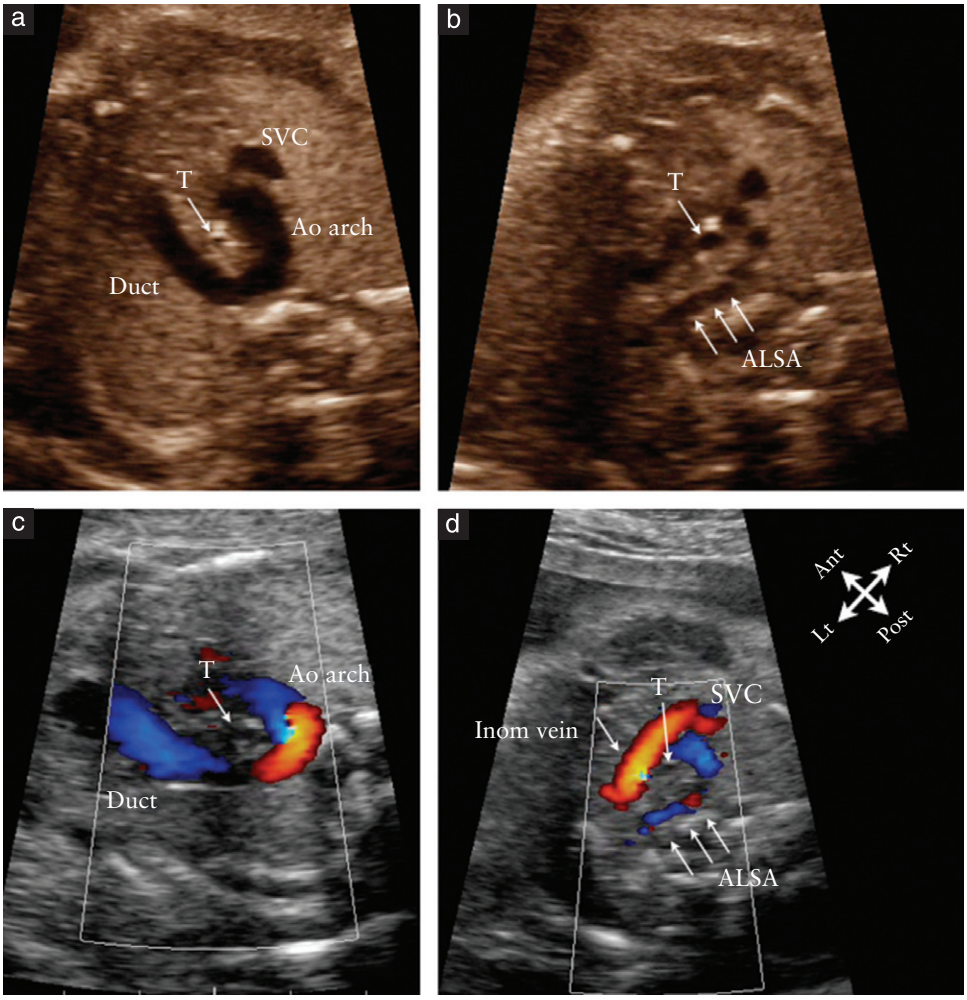

Figure 1 B-mode (a,b) and color Doppler (c,d) ultrasound images of upper mediastinum in Case 22 at 28 weeks of gestation. Note the right-sided aortic arch, left-sided arterial duct and aberrant origin of left subclavian artery (ALSA) coursing behind the trachea (T). Ao arch, aortic arch; Inom vein, innominate vein; SVC, superior vena cava.

were considered suitable for inclusion. Pediatrics series were excluded on the basis that mainly symptomatic patients are included, thus potentially overestimating the rate of some of the outcomes explored in this review. Cohort and case series were included. Editorials, conference abstracts, case reports and cases series of fewer than three patients were excluded (Appendix S2). The outcomes analyzed were chromosomal abnormalities, 22q11.2 deletion, associated ECA detected prenatally, pressure symptoms and surgery for vascular ring, additional ICA and ECA diagnosed postnatally only. For chromosomal abnormalities and 22q11.2 deletion, analysis was restricted to cases for which karyotype or phenotype was known, either pre- or postnatally. Analysis of pressure symptoms and surgery was restricted to cases with a vascular ring (RAA, left AD and ALSA) and that, if asymptomatic, had a minimum follow-up time of 24 months.

Two authors (F.D., A.K.) reviewed all abstracts independently. Agreement about potential relevance was reached by consensus, and full-text copies of those papers were obtained. The two reviewers independently extracted relevant data regarding study characteristics and pregnancy outcome. Inconsistencies were discussed by the reviewers and consensus reached.

Risk of bias, summary measures and synthesis of results

Quality assessment of the included studies was performed using the Newcastle–Ottawa Scale (NOS) for cohort studies[18].

Statistical analysis

We used meta-analyses of proportions to combine data[19,20]. Funnel plots displaying the outcome rate from individual studies *vs* their precision (1/standard error) were constructed with an exploratory aim. Tests for funnel-plot asymmetry were not used when the total number of publications included for each outcome was less than 10. In this case, the power of the tests was too low to distinguish chance from real asymmetry[21]. Between-study heterogeneity was explored using the I^2 statistic, which represents the percentage of between-study variation that is due to heterogeneity rather than chance. A value of I^2 of 0% indicates no

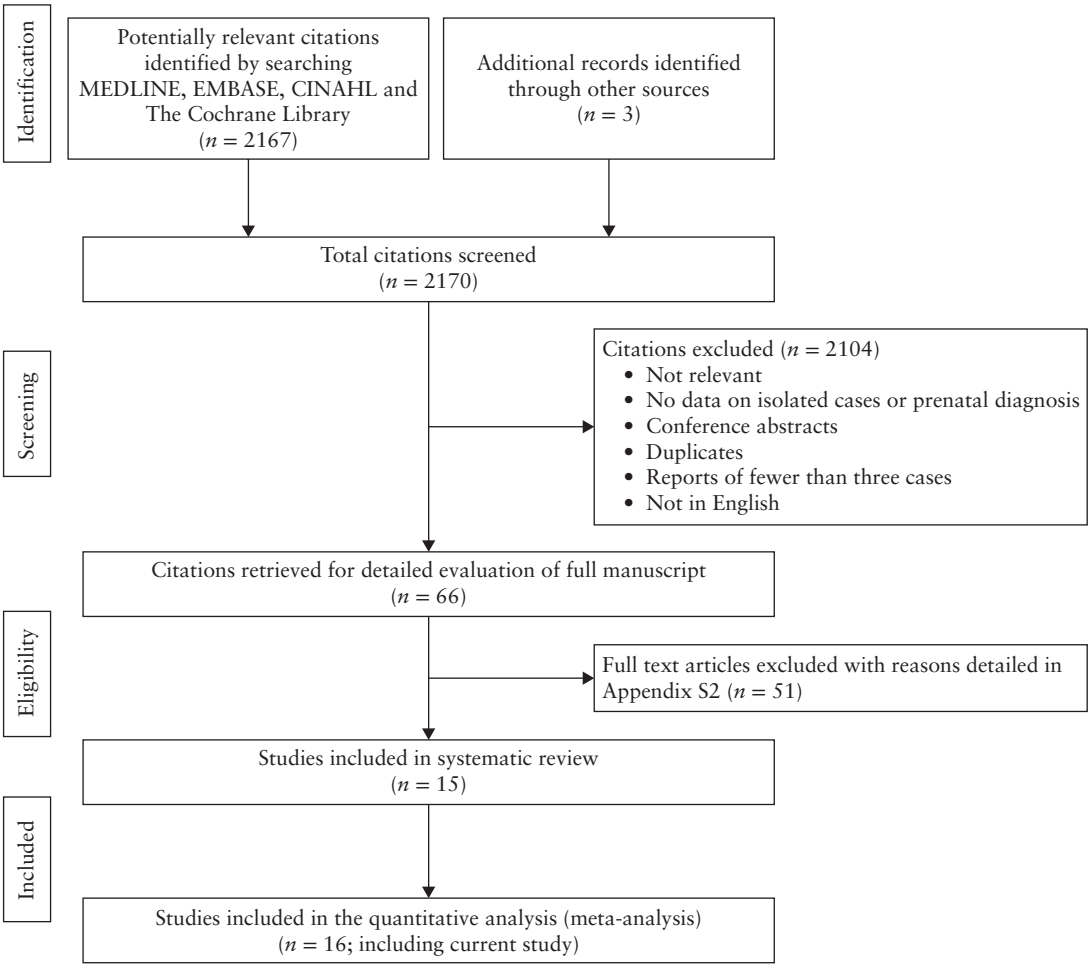

Figure 2 Flowchart of studies included in systematic review of fetuses with right aortic arch.

observed heterogeneity, whereas values of ≥ 50% indicate a substantial level of heterogeneity. A fixed-effects model was used if substantial statistical heterogeneity was not present; if there was evidence of significant heterogeneity between included studies, a random-effects model was used.

A time-to-event (Kaplan–Meier) analysis was carried out in order to evaluate the time of occurrence of symptoms requiring surgery related to the presence of vascular rings. For this analysis, only cases forming a vascular ring and with known individual follow-up times were included. Studies reporting only median or mean follow-up time were not included.

Statistical analysis was performed using Stats Direct version 2.7.8, (Stats Direct Ltd, Altrincham, UK) and GraphPad Prism 6 (GraphPad Software, San Diego, CA, USA) statistical software.

RESULTS

Cohort study

There were 86 cases in the cohort study. Maternal and fetal characteristics are reported in Table 1. Individual pre- and postnatal data for all cases are shown in Table S1.

The overall rate of chromosomal abnormalities was 14.1% (11/78 cases with known karyotype or phenotype). Of these 11 cases, the nuchal translucency thickness was measured in 10 and found to be > 2.5 mm in three cases. The rate of 22q11.2 deletion was 6.4% (5/78). Associated ECA were identified at the time of prenatal diagnosis in 15/86 (17.4%) cases. Six of the 11 fetuses with chromosomal abnormalities had normal anatomical surveys. There were three intrauterine deaths, two due to complications of twin pregnancies. Eight pregnancies were terminated (seven with chromosomal abnormalities, one with spina bifida). Six cases were lost to follow-up. Of the 69 livebirths, there was one case each of anal atresia, anorectal malformation and hypertrophic pyloric stenosis diagnosed postnatally. Three children had small ventricular septal defects on postnatal assessment and another was found to have a double aortic arch.

Forty-one fetuses had an RAA, a left AD and an ALSA (Figure 1). Respiratory symptoms occurred in seven (21.2%) of the 33 known live births. Five had surgery or had a planned operation to divide the vascular ring. Another two had mild symptoms, which improved. Computed tomographic angiography and barium swallow at 2 and 5 years of age showed no significant obstruction

Table 2 General characteristics of 16 studies included in systematic review of fetuses with right aortic arch

Study	*Country*	*Cases* (n)	*ALSA* (n)	*Outcome(s) observed*	*Follow-up (months)*
Current study (2016)	UK	86	42	Chromosomal abnormalities, 22q11.2 deletion, associated ECA detected prenatally, symptoms and surgery related to vascular ring, associated ICA and ECA detected postnatally	0–165
Razon[24] (2014)	Israel	50	23	Chromosomal abnormalities, 22q11.2 deletion, symptoms and surgery related to vascular ring, associated ICA detected postnatally	NS
Miranda[28] (2014)	UK	27	12	Chromosomal abnormalities, 22q11.2 deletion, associated ECA detected prenatally, pressure symptoms and surgery related to vascular ring, associated ICA and ECA detected postnatally	NS
Gul[29] (2012)	Turkey	7	NS	Chromosomal abnormalities, 22q11.2 deletion, ECA detected prenatally, associated ICA and ECA detected postnatally	NS
Bronshtein[30] (2011)	Israel	3	0	Chromosomal abnormalities, 22q11.2 deletion, associated ECA detected prenatally, associated ICA and ECA detected postnatally	NS
Li[31] (2011)	China/USA	35	29	Chromosomal abnormalities, associated ECA detected prenatally, pressure symptoms and surgery related to vascular ring, associated ICA and ECA detected postnatally	1–42
Hsu[32] (2011)	Taiwan	3	3	Chromosomal abnormalities, 22q11.2 deletion, associated ECA detected prenatally, pressure symptoms and surgery related to vascular ring, associated ICA and ECA detected postnatally	9–42
Galindo[11] (2009)	Spain	15	14	Chromosomal abnormalities, 22q11.2 deletion, associated ECA detected prenatally, pressure symptoms and surgery related to vascular ring, associated ICA and ECA detected postnatally	12–55
Tuo[9] (2009)	Italy	6	6	Chromosomal abnormalities, 22q11.2 deletion, associated ECA detected prenatally, pressure symptoms and surgery related to vascular ring, associated ICA and ECA detected postnatally	14–33
Turan[12] (2009)	USA	3	3	Chromosomal abnormalities, 22q11.2 deletion, associated ECA detected prenatally, pressure symptoms and surgery related to vascular ring, associated ICA and ECA detected postnatally	NS
Zidere[7] (2006)	UK	25	NS	Chromosomal abnormalities, 22q11.2 deletion, ECA detected prenatally, associated ICA and ECA detected postnatally	NS
Berg[8] (2006)	Germany	23	20	Chromosomal abnormalities, 22q11.2 deletion, associated ECA detected prenatally, associated ICA detected postnatally	NS
Patel[10] (2006)	USA	3	2	Chromosomal abnormalities, 22q11.2 deletion, associated ECA detected prenatally, pressure symptoms and surgery related to vascular ring, associated ICA and ECA detected postnatally	24–72
Achiron[2] (2002)	Israel	18	1	Chromosomal abnormalities, 22q11.2 deletion, associated ECA detected prenatally, associated ICA detected postnatally	12–80
Chaoui[25] (2002)	Germany	3	NS	22q11.2 deletion	NS
Bronshtein[6] (1998)	Israel	5	5	Associated ECA detected prenatally, pressure symptoms and surgery related to vascular ring, associated ICA and ECA detected postnatally	NS

Only the first author of each study is given. All studies were retrospective in design. ALSA, aberrant origin of left subclavian artery; ECA, extracardiac abnormality; ICA, intracardiac abnormality; NS, not stated.

Table 3 Pooled proportions for outcomes observed in this systematic review of fetuses with right aortic arch (RAA)

Outcome	*Studies* (n)	*Fetuses* (n/N)	I^2 (%)	*Raw proportion (% (95% CI))*	*Pooled proportion (% (95% CI))*
RAA with normal intracardiac anatomy					
Chromosomal abnormalities	15	24/284	0	8.5 (5.5–12.3)	9.0 (6.0–12.5)
22q11.2 deletion	14	13/257	0	5.1 (2.7–8.5)	6.1 (3.6–9.3)
Associated ECA diagnosed prenatally	14	37/259	12.3	14.2 (10.3–19.1)	14.6 (10.6–19.0)
Symptoms of vascular rings	11	18/74	20.1	24.3 (15.1–35.7)	25.2 (16.6–35.0)
Surgery for vascular ring	11	12/74	28.3	16.2 (8.7–26.6)	17.1 (9.9–25.7)
RAA with normal intra- and extracardiac anatomy					
Chromosomal abnormalities	14	8/204	0	3.9 (1.7–7.6)	4.6 (2.3–7.8)
22q11.2 deletion	13	7/178	0	3.9 (1.6–7.9)	5.1 (2.4–8.6)
Additional ICA diagnosed postnatally	15	12/257	0	4.7 (2.4–8.0)	5.0 (2.7–7.9)
Additional ECA diagnosed postnatally	11	4/148	0	2.7 (0.7–6.8)	4.0 (1.5–7.6)

ECA, extracardiac abnormalities; ICA, intracardiac abnormalities.

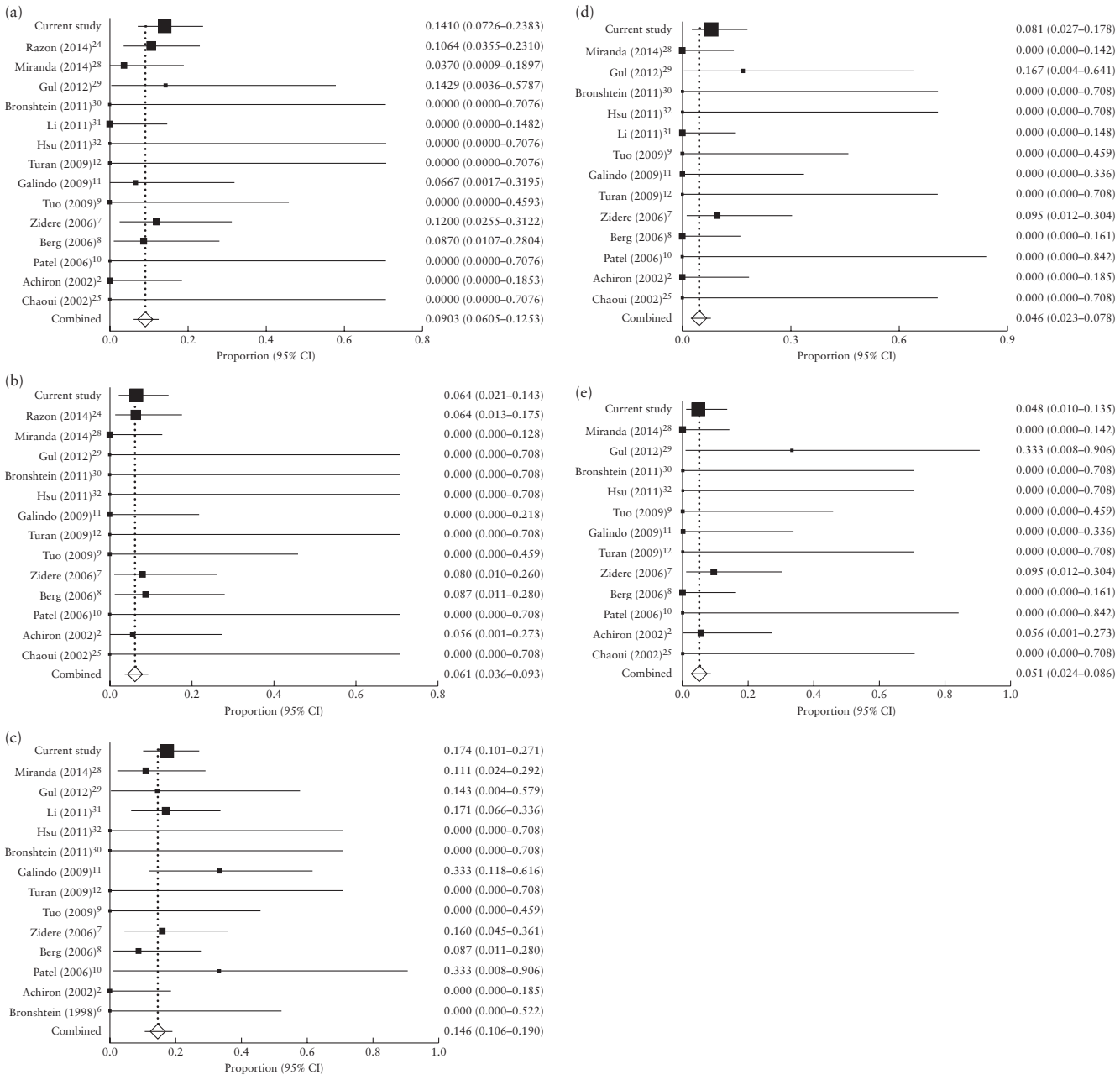

Figure 3 Pooled proportions (forest plot) of prevalence of chromosomal abnormalities (a), 22q11.2 deletion (b) and associated extracardiac anomalies detected prenatally (c), in fetuses with right aortic arch (RAA) without intracardiac anomalies, and pooled proportions of the prevalence of chromosomal abnormalities (d) and 22q11.2 deletion (e), in fetuses with isolated RAA. Only the first author of each study is given.

to airway or esophagus. At the time of data collection they remained well, with no surgery. The child with a postnatal diagnosis of double aortic arch (Case 19) was thought prenatally to have normal origin of the LSA. Surgery was undertaken at 6 months of age.

Systematic review and meta-analysis of published studies

Study selection and characteristics

A total of 2170 articles were identified, of which 66 were assessed with respect to their eligibility for inclusion (Figure 2). Sixteen studies (15 from previously published literature plus the current cohort study) were included in the systematic review. Table 2 shows the general characteristics of the included studies. Appendix S2 shows the studies excluded from the analysis and reasons for exclusion.

The quality assessment performed using NOS is shown in Table S2. Almost all studies showed an overall good rate with regard to the selection and comparability of the study groups and for the ascertainment of the outcome of interest. The main weaknesses of these studies were their small sample size, being series from high-risk populations,

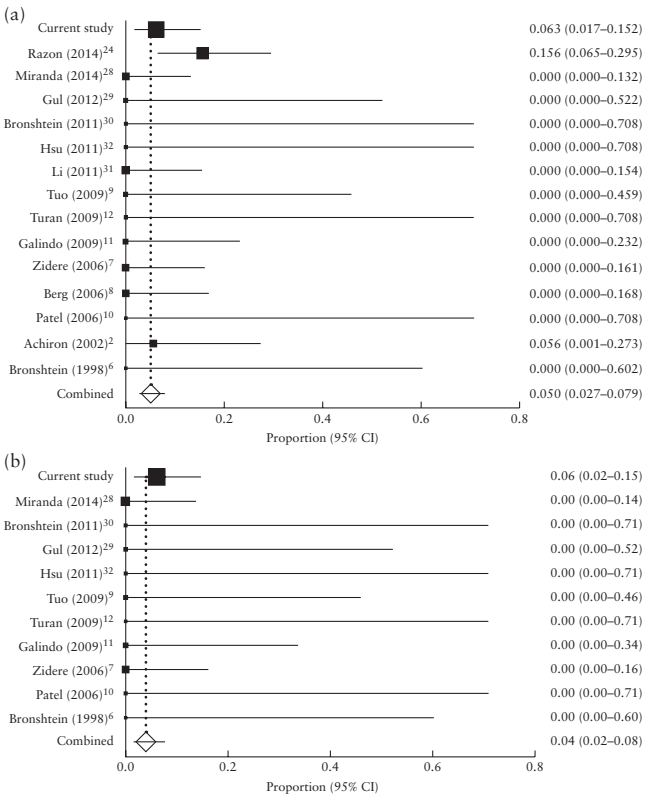

Figure 4 Pooled proportions (forest plot) of prevalence of intracardiac anomalies (a) and extracardiac anomalies (b) detected only postnatally in fetuses with right aortic arch. Only the first author of each study is given.

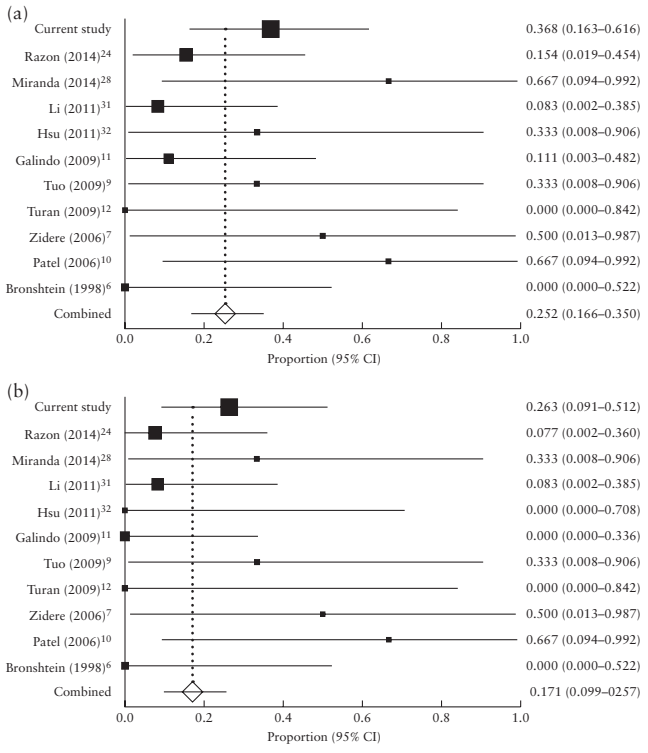

Figure 5 Pooled proportions (forest plot) of incidence of pressure symptoms (a) and surgery for vascular rings (b) in infants with right aortic arch and normal intracardiac anatomy. Only the first author of each study is given.

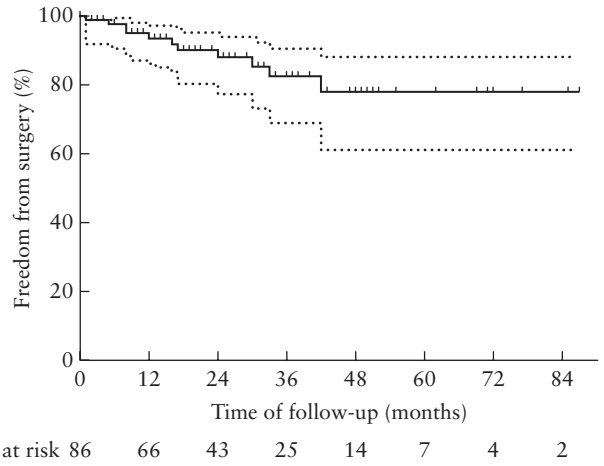

Figure 6 Kaplan–Meier analysis of postnatal pressure symptoms requiring surgery in cases with right-sided aortic arch forming a vascular ring. Survival curve (——) with 95% CI (·····) is shown.

and lack of ascertainment of all individual outcomes. Furthermore, most studies had a relatively short period of follow-up after birth.

Synthesis of results

There were 312 fetuses included in the 16 studies, with a sample size ranging between 3 and 86. The overall rates of chromosomal abnormalities, 22q11.2 deletion and associated ECA detected prenatally in fetuses with RAA without ICA were 9.0% (95% CI, 6.0–12.5%), 6.1% (95% CI, 3.6–9.3%) and 14.6% (95% CI, 10.6–19.0%), respectively (Table 3 and Figure 3a–c). The rates of chromosomal abnormalities and 22q11.2 deletion in fetuses with isolated RAA were 4.6% (95% CI, 2.3–7.8%) and 5.1% (95% CI, 2.4–8.6%) (Table 3 and Figure 3d and e). These rates were lower in fetuses with normal first- and second-trimester ultrasound examinations (pooled proportions, 2.8% (95% CI, 0.9–5.8%) and 2.9% (95% CI, 0.8–6.2%), respectively). Associated ICA and ECA detected only postnatally were present in 5.0% (95% CI, 2.7–7.9%) and 4.0% (95% CI, 1.5–7.6%), respectively (Table 3 and Figure 4a and b). The incidence of symptoms related to vascular rings occurring within 24 months after delivery was 25.2% (95% CI, 16.6–35.0%), while the corresponding value for surgery for vascular ring was 17.1% (95% CI, 9.9–25.7%) (Table 3 and Figure 5a and b).

Data from 87 newborns with RAA forming a vascular ring were included in the time-to-event analysis. Figure 6 shows the Kaplan–Meier curve illustrating the freedom from symptoms requiring surgery over time. In most cases, symptoms occurred within 24 months. The 2-year freedom from surgery was 83.0% (95% CI, 74.3–90.1%).

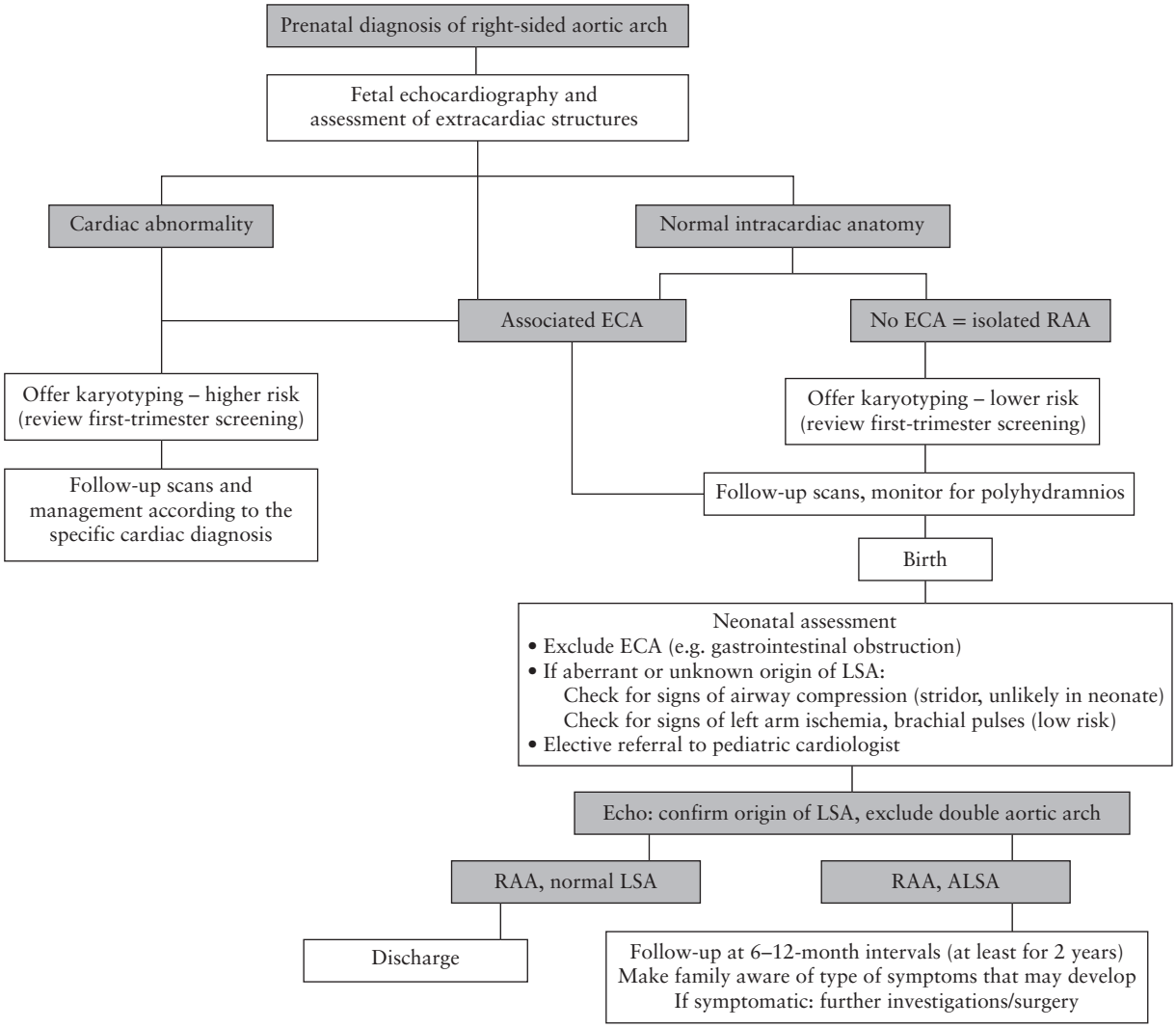

Figure 7 Proposed algorithm for management of right aortic arch (RAA) diagnosed prenatally. ALSA, aberrant origin of left subclavian artery; ECA, extracardiac anomaly; LSA, left subclavian artery.

DISCUSSION

Main findings

Data from this study and meta-analysis suggest that the majority of fetuses with RAA and normal intracardiac anatomy do not have associated chromosomal abnormalities, the risk being approximately 10%, and 5% in the absence of ECA. Similarly, most children with RAA and ALSA are asymptomatic. Pressure symptoms occur in approximately 25% of cases with the majority being free from surgery at the age of 2 years. The association of RAA with ECA was slightly higher. This was documented prenatally in about 15% of cases and, additionally, in about 5% after birth. In our series, two fetuses had unilateral renal agenesis and three neonates presented with malformations of the gastrointestinal system.

Strengths and weaknesses

This is the first systematic review and meta-analysis exploring the significance of fetal RAA with normal intracardiac anatomy. We have reported rates of different fetal outcomes.

The relatively small number of patients, different periods of follow-up, differences in prenatal and postnatal imaging protocols and reporting of symptoms related to vascular ring represent the main weaknesses of this review. Furthermore, the scarce number of studies did not permit meaningful stratified meta-analyses to explore the test performance in subgroups of patients that may be less or more susceptible to bias. The assessment of the potential publication bias was also problematic, both because of the outcome nature (rates with the left side limited to the value zero), which limits the reliability of funnel plots, and because of the scarce number of individual studies, which strongly limits the reliability of formal tests. Funnel plots displaying the outcome rate from individual studies *versus* their precision (1/standard error) were constructed with an exploratory aim and did not show substantial heterogeneity for the large majority of the outcomes observed in this review (Appendix S3). Most of the studies included were small series reporting only a few cases of

RAA; smaller series tend to report greater intervention effects than larger studies[22]. In the present meta-analysis, the degree of heterogeneity of the smaller series was lower than that of the large studies and this was mainly due to the fact these studies were not adequately powered to detect any size effect, thus apparently lowering the degree of heterogeneity[23].

In view of these limitations, large prospective studies are still needed in order to further narrow the confidence intervals reported here, especially regarding symptoms related to airway and esophageal compression (95% CI, 16.6–35.0%), and to confirm the relatively low incidence of associated chromosomal abnormalities including 22q11.2 deletion (95% CI, 6.0–12.5%). This study also highlights the association between RAA and ECA, some of which can only be diagnosed with certainty postnatally, such as anal atresia and pyloric stenosis.

Implications for clinical practice and future research

Based on data from our cohort and previous studies, we propose an algorithm for management of fetuses and infants with prenatal diagnosis of RAA (Figure 7). Upon prenatal identification of RAA, a detailed fetal cardiac assessment is indicated. The position of the AD and the course of the LSA should be noted to determine whether a vascular ring is present. Attempts should be made to rule out the possibility of a double aortic arch. Razon *et al.*[24] highlighted recently the fact that a double arch may be overlooked on prenatal scans due to the presence of a small, or even atretic, left arch. The remainder of the fetal anatomy should be assessed thoroughly by a fetal medicine specialist. Current status of prenatal ultrasound allows investigation of extracardiac defects, which may increase the suspicion of 22q11.2 deletion syndrome, such as thymus agenesis[25,26] and isolated defects in the palate. Further studies are needed to evaluate if assessment of chromosomal abnormalities could be improved by looking at these specific markers, thus reducing the number of invasive tests. First-trimester combined risk of chromosomal abnormalities should be reviewed to evaluate pre-existing individual risks. We observed three cases of trisomy 21 in our series of which maternal age was 36, 38 and 44 years. One fetus had an isolated RAA, the other two had abnormal first- and/or second-trimester scans. Nevertheless, in the presence of an isolated RAA with normal first-trimester scan, the risk of associated chromosomal abnormalities is low (< 5%). This information may help parents make an informed decision regarding the option of an invasive procedure to assess fetal karyotype. However, there still remains a relatively small risk (~ 5%) of an ECA being diagnosed postnatally. Abnormalities of the gastrointestinal tract, such as esophageal atresia, have been reported in neonates with RAA[27]. However, due to the small number of papers considering this outcome, it was not included in the meta-analysis. We did not observe any case of esophageal atresia in our cohort series, but three neonates had gastrointestinal malformations diagnosed postnatally. It is unlikely that these conditions will be diagnosed at the time of the routine mid-trimester pregnancy scan, which highlights the importance of a follow-up fetal medicine assessment to assess direct or indirect signs of gastrointestinal obstruction later in pregnancy. Similarly, abnormalities of arterial supply to the left arm have also been documented in neonates with RAA and an ALSA[5].

Thus, the newborn with known diagnosis of RAA should be assessed carefully for possible additional abnormalities. We recommend that esophageal atresia be ruled out prior to establishing oral feeds as this can be performed easily by insertion of a nasogastric tube. Additionally, whilst compromise of vascular supply to the left arm may be uncommon if there is an ALSA, we recommend that normality of brachial as well as femoral pulses be checked prior to neonatal discharge from hospital. This provides family reassurance until the neonate has an elective cardiac assessment. Symptoms related to airway or esophageal compression are unlikely to occur in the neonatal period. Later manifestation and severity of such symptoms are linked to the tightness of the vascular ring itself and cannot be determined prenatally. Initial postnatal cardiac assessment should consist of transthoracic echocardiography. In the presence of subclinical or clinical symptoms, other imaging modalities such as barium swallow, cardiac magnetic resonance imaging, computed tomography and bronchoscopy should be considered to rule out airway compression and reduce potential morbidity. Our Kaplan–Meier analysis shows that if symptoms requiring surgery develop, they are more likely to occur within the first 24 months after delivery. Thus, parents should be aware of potential symptoms and be able to contact the cardiology team if symptoms such as feeding difficulty/dysphagia, stridor, wheeze and recurrent upper respiratory tract infections occur.

Conclusions

The data from this study and review of the literature show that the risk of aneuploidy in prenatally diagnosed cases of isolated RAA is low, but significant enough for families to consider the option of invasive prenatal testing. There remains a small risk of postnatal diagnosis of associated malformations, some of which can only be diagnosed with certainty after birth. Serial follow-up, both before and after birth, is required in order to look for associated abnormalities and for signs of tracheoesophageal compression that may require surgical intervention.

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REFERENCES

1. Hastreiter AR, D'Cruz IA, Cantez T, Namin EP, Licata R. Right-sided aorta. I. Occurrence of right aortic arch in various types of congenital heart disease. II. Right aortic arch, right descending aorta, and associated anomalies. *Br Heart J* 1966; **28**: 722–739.
2. Achiron R, Rotstein Z, Heggesh J, Bronshtein M, Zimand S, Lipitz S, Yagel S. Anomalies of the fetal aortic arch: a novel sonographic approach to in-utero diagnosis. *Ultrasound Obstet Gynecol* 2002; **20**: 553–557.
3. McElhinney DB, Clark BJ 3rd, Weinberg PM, Kenton ML, McDonald-McGinn D, Driscoll DA, Zackai EH, Goldmuntz E. Association of chromosome 22q11 deletion with isolated anomalies of aortic arch laterality and branching. *J Am Coll Cardiol* 2001; **37**: 2114–2119.
4. Bonnard A, Auber F, Fourcade L, Marchac V, Emond S, Revillon Y. Vascular ring abnormalities: a retrospective study of 62 cases. *J Pediatr Surg* 2003; **38**: 539–543.
5. Tschirch E, Chaoui R, Wauer RR, Schneider M, Rudiger M. Perinatal management of right aortic arch with aberrant left subclavian artery associated with critical stenosis of the subclavian artery in a newborn. *Ultrasound Obstet Gynecol* 2005; **25**: 296–298.
6. Bronshtein M, Lorber A, Berant M, Auslander R, Zimmer EZ. Sonographic diagnosis of fetal vascular rings in early pregnancy. *Am J Cardiol* 1998; **81**: 101–103.
7. Zidere V, Tsapakis EG, Huggon IC, Allan LD. Right aortic arch in the fetus. *Ultrasound Obstet Gynecol* 2006; **28**: 876–881.
8. Berg C, Bender F, Soukup M, Geipel A, Axt-Fliedner R, Breuer J, Herberg U, Gembruch U. Right aortic arch detected in fetal life. *Ultrasound Obstet Gynecol* 2006; **28**: 882–889.
9. Tuo G, Volpe P, Bava GL, Bondanza S, De Robertis V, Pongiglione G, Marasini M. Prenatal diagnosis and outcome of isolated vascular rings. *Am J Cardiol* 2009; **103**: 416–419.
10. Patel CR, Lane JR, Spector ML, Smith PC. Fetal echocardiographic diagnosis of vascular rings. *J Ultrasound Med* 2006; **25**: 251–257.
11. Galindo A, Nieto O, Nieto MT, Rodriguez-Martin MO, Herraiz I, Escribano D, Granados MA. Prenatal diagnosis of right aortic arch: associated findings, pregnancy outcome, and clinical significance of vascular rings. *Prenat Diagn* 2009; **29**: 975–981.
12. Turan S, Turan OM, Maisel P, Gaskin P, Harman CR, Baschat AA. Three-dimensional sonography in the prenatal diagnosis of aortic arch abnormalities. *J Clin Ultrasound* 2009; **37**: 253–257.
13. Carvalho JS, Allan LD, Chaoui R, Copel JA, DeVore GR, Hecher K, Lee W, Munoz H, Paladini D, Tutschek B, Yagel S. ISUOG Practice Guidelines (updated): sonographic screening examination of the fetal heart. *Ultrasound Obstet Gynecol* 2013; **41**: 348–359.
14. Yoo SJ, Lee YH, Kim ES, Ryu HM, Kim MY, Choi HK, Cho KS, Kim A. Three-vessel view of the fetal upper mediastinum: an easy means of detecting abnormalities of the ventricular outflow tracts and great arteries during obstetric screening. *Ultrasound Obstet Gynecol* 1997; **9**: 173–182.
15. Yagel S, Arbel R, Anteby EY, Raveh D, Achiron R. The three vessels and trachea view (3VT) in fetal cardiac scanning. *Ultrasound Obstet Gynecol* 2002; **20**: 340–345.
16. Chaoui R, Heling KS, Sarioglu N, Schwabe M, Dankof A, Bollmann R. Aberrant right subclavian artery as a new cardiac sign in second- and third-trimester fetuses with Down syndrome. *Am J Obstet Gynecol* 2005; **192**: 257–263.
17. Stroup DF, Berlin JA, Morton SC, Olkin I, Williamson GD, Rennie D, Moher D, Becker BJ, Sipe TA, Thacker SB. Meta-analysis of observational studies in epidemiology: a proposal for reporting. Meta-analysis Of Observational Studies in Epidemiology (MOOSE) group. *JAMA* 2000; **283**: 2008–2012.
18. Newcastle-Ottawa Scale for assessing the quality of nonrandomised studies in meta-analyses. http://www.ohri.ca/programs/clinical_epidemiology/oxford.asp. [Accessed 1 March 2015]
19. Manzoli L, De Vito C, Salanti G, D'Addario M, Villari P, Ioannidis JP. Meta-analysis of the immunogenicity and tolerability of pandemic influenza A 2009 (H1N1) vaccines. *PloS One* 2011; **6**: e24384.
20. Hunter JP, Saratzis A, Sutton AJ, Boucher RH, Sayers RD, Bown MJ. In meta-analyses of proportion studies, funnel plots were found to be an inaccurate method of assessing publication bias. *J Clin Epidemiol* 2014; **67**: 897–903.
21. Higgins JP, Thompson SG, Deeks JJ, Altman DG. Measuring inconsistency in meta-analyses. *BMJ* 2003; **327**: 557–560.
22. Sterne JA, Gavaghan D, Egger M. Publication and related bias in meta-analysis: power of statistical tests and prevalence in the literature. *J Clin Epidemiol* 2000; **53**: 1119–1129.
23. Turner RM, Bird SM, Higgins JP. The impact of study size on meta-analyses: examination of underpowered studies in Cochrane reviews. *PloS One* 2013; **8**: e59202.
24. Razon Y, Berant M, Fogelman R, Amir G, Birk E. Prenatal diagnosis and outcome of right aortic arch without significant intracardiac anomaly. *J Am Soc Echocardiogr* 2014; **27**: 1352–1358.
25. Chaoui R, Kalache KD, Heling KS, Tennstedt C, Bommer C, Korner H. Absent or hypoplastic thymus on ultrasound: a marker for deletion 22q11.2 in fetal cardiac defects. *Ultrasound Obstet Gynecol* 2002; **20**: 546–552.
26. Paladini D. How to identify the thymus in the fetus: the thy-box. *Ultrasound Obstet Gynecol* 2011; **37**: 488–492.
27. Wood JA, Carachi R. The right-sided aortic arch in children with oesophageal atresia and tracheo-oesophageal fistula. *Eur J Pediatr Surgery* 2012; **22**: 3–7.
28. Miranda JO, Callaghan N, Miller O, Simpson J, Sharland G. Right aortic arch diagnosed antenatally: associations and outcome in 98 fetuses. *Heart* 2014; **100**: 54–59.
29. Gul A, Gungorduk K, Yildirim G. Perinatal outcomes and anomalies associated with fetal right aortic arch. *J Turk Ger Gynecol Assoc* 2012; **13**: 184–186.
30. Bronshtein M, Zimmer EZ, Blazer S, Blumenfeld Z. Right ductus arteriosus: facts and theory. *Eur J Obstet Gynecol Reprod Biol* 2011; **159**: 282–288.
31. Li S, Luo G, Norwitz ER, Wang C, Ouyang S, Yao Y, Chen C, Wen H, Chen X, Bi J. Prenatal diagnosis of congenital vascular rings and slings: sonographic features and perinatal outcome in 81 consecutive cases. *Prenat Diagn* 2011; **31**: 334–346.
32. Hsu KC, Tsung-Che Hsieh C, Chen M, Tsai HD. Right aortic arch with aberrant left subclavian artery–prenatal diagnosis and evaluation of postnatal outcomes: report of three cases. *Taiwan J Obstet Gynecol* 2011; **50**: 353–358.

SUPPORTING INFORMATION ON THE INTERNET

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

Appendix S1 Search strategy

Appendix S2 Excluded studies

Appendix S3 Funnel plots with the assessment of publication bias for the outcomes ascertained in the systematic review

Table S1 Individual pre- and postnatal data for all cases of the cohort study

Table S2 Quality assessment of the studies included in the systematic review

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RESUMEN

Objetivos *El uso reciente de protocolos de cribado prenatal de anomalías cardíacas ha aumentado los diagnósticos de fetos con arco aórtico derecho (AAD). El objetivo de este estudio fue tratar de establecer los resultados perinatales en fetos con AAD sin anomalías intracardíacas (ICA, por sus siglas en inglés) como guía para el cuidado postnatal.*

Métodos *En la parte de cohorte retrospectiva de nuestro estudio, los parámetros estudiados fueron las tasas de anomalías cromosómicas, la deleción 22q11.2, las anomalías fetales extracardíacas (ECA, por sus siglas en inglés), las ICA y ECA postnatales, y los síntomas de anillo vascular y la cirugía para corregirlo. También se realizó una revisión sistemática y un metaanálisis, cuyos resultados se presentan como porcentajes. Se realizó un análisis de Kaplan-Meier de los casos de anillo vascular con cirugía como resultado final.*

Resultados *La cohorte incluía 86 casos, de los cuales 41 tenían anillo vascular. Las tasas de anomalías cromosómicas, deleción 22q11.2 y ECA fetal fueron del 14,1%, 6,4% y 17,4%, respectivamente. En la revisión sistemática se incluyeron 16 estudios con una cohorte de 312 fetos. Las tasas totales de anomalías cromosómicas y deleción 22q11.2 fueron del 9,0% (IC 95%, 6,0-12,5%) y 6,1% (IC 95%, 3,6-9.3%), mientras que las tasas respectivas para casos sin ECA fueron del 4,6% (IC 95%, 2,3-7,8%) y 5,1% (IC 95%, 2,4-8,6%). Se observaron ECA prenatales en un 14,6% (IC 95%, 10,6-19,0%) y postnatales en un 4,0% (IC 95%, 1,5-7,6%). Se identificaron ICA postnatales en un 5,0% (IC 95%, 2,7-7,9%). La tasa de síntomas de anillo vascular (seguimiento ≥ 24 meses después del parto) fue del 25,2% (IC 95%, 16,6-35,0%), y se intervino quirúrgicamente al 17,1% (IC 95%, 9,9-25,7%). El porcentaje que no requirió cirugía al cabo de dos años fue del 83,0% (IC 95%, 74,3-90,1%).*

Conclusiones *El AAD en el feto sin ICA se asocia con mayor frecuencia a ECA que a anomalías cromosómicas. La mayoría, sin embargo, son casos aislados. Los síntomas de anillo vascular aparecen en el 25% de los casos aproximadamente. El seguimiento postnatal es necesario sobre todo en los dos primeros años después del parto.*

目的：最新心脏畸形产前筛查指南的应用，提高了胎儿右位主动脉弓（right aortic arch，RAA）的诊断。我们的目的是证实未合并心内畸形（intracardiac abnormalities，ICA）的胎儿 RAA 的结局，以指导产后治疗。

方法：在本研究的回顾性队列中，结局指标为染色体异常、22q11.2 缺失、胎儿心外畸形（extracardiac abnormalities，ECA）、产后 ICA 和 ECA、出现血管环症状并进行手术的发生率。还进行了系统综述和荟萃分析；结果以构成比表示。对终点为进行手术的血管环患者进行 Kaplan-Meier 分析。

结果：我们的队列包括 86 例患者，其中 41 例出现血管环。染色体异常、22q11.2 缺失和胎儿 ECA 的发生率分别为 14.1%、6.4%和 17.4%。将包括我们队列在内的 16 项研究（312 例胎儿）纳入系统综述。染色体异常和 22q11.2 缺失总的发生率为 9.0%（95%CI，6.0%~12.5%）和 6.1%（95%CI，3.6%~9.3%），而无 ECA 的患者相应的发生率为 4.6%（95% CI，2.3%~7.8%）和 5.1%（95% CI，2.4%~8.6%）。产前 14.6%（95% CI，10.6%~19.0%）的患者出现 ECA，产后 4.0%（95% CI，1.5%~7.6%）的患者出现 ECA。5.0%（95% CI，2.7%~7.9%）的患者产后出现 ICA。血管环症状的发生率（随访时间≥产后 24 个月）为 25.2%（95% CI，16.6%~35.0%），17.1%（95% CI，9.9%~25.7%）的患者进行了手术。2 年未行手术率为 83.0%（95% CI，74.3%~90.1%）。

结论：未合并 ICA 的胎儿 RAA 更常合并 ECA 而非染色体异常。然而，大多数病例为单发。约 25%的患者出现血管环症状。产后监测主要是在出生后头 2 年。