Fetuses with right aortic arch

Multicentre cohort study and meta-analysis

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ABSTRACT

Objectives: Recent antenatal screening guidelines for cardiac abnormalities has increased fetal diagnosis of right aortic arch (RAA). We aimed to establish outcome of fetal RAA without intra-cardiac abnormalities (ICA) to guide postnatal management.

Methodology: Retrospective cohort study. Outcome measures were rates of chromosomal abnormalities, 22q11.2 deletion, fetal extra-cardiac abnormalities (ECA), postnatal ICA and ECA, symptoms and surgery for vascular ring. A systematic review and meta-analysis (reference: CRD42015016097) was 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 chromosomal abnormalities and 22q11.2 deletion rates were 9.0% (95% CI 6.0-12.5) and 6.1% (95% CI 3.6-9.3) whilst 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 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 (follow up ≥24 months) was 25.2% (95% CI 16.6-35.0) while 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 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 of life.

INTRODUCTION

Right aortic arch (RAA) is characterised 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 life. Normal regression leads to a LAA, left-sided arterial duct (AD) and the usual branching pattern: right innominate, left common carotid and left subclavian arteries (LSA). A 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 extra-cardiac abnormalities (ECA) and chromosomal defects, in particular 22q11.2 deletion.[3] A RAA can form a vascular ring which is a heterogeneous group of vascular abnormalities encircling the trachea and oesophagus. The classical vascular ring formed by a 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 commonly reported. 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 screening. This is likely to increase further the prenatal detection of RAA and its variants. It is therefore important that perinatal management be optimised and family counselling 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 intra-cardiac 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 centres. 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 is an audit of clinical practice and no ethical approval was needed. Ultrasound examinations were performed on 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 for all fetuses using conventional 2D ultrasound, colour, power and pulsed wave Doppler. A 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 a LAA.[16] The diagnosis of a vascular ring was made in the presence of a RAA, left AD and ALSA. An 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/ oesophagus and surgery for vascular ring.

Statistical Methods

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

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 on January 2015, utilising combinations of the relevant medical subject heading (MeSH) terms, key words, 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 (search strategy, Supplementary material 1). 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 peculiar imaging protocol, which included the assessment of three vessels and three vessels and trachea view, were considered suitable for the inclusion. Paediatrics series were excluded on the basis that mainly symptomatic patients are included, thus potentially overestimating the rate of

some of outcomes explored in the current review. Cohort and case series were included. Editorial, conference abstracts, case reports and cases series of fewer than three patients were excluded (Supplementary material 2). The outcomes analysed were: chromosomal abnormalities, 22q11.2 deletion, associated ECA detected prenatally, pressure symptoms and surgery for vascular ring, additional ICA and ECA diagnosed only postnatally. For chromosomal abnormalities and 22q11.2 deletion, the analysis was restricted to cases where karyotype or phenotype was known either pre or postnatally. The analysis of the pressure symptoms and surgery was restricted to those cases with a vascular ring (RAA, left AD and ALSA) and, if asymptomatic, had a minimum follow up time of 24 months.

Two authors (FD, AK) 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 the results

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

Statistical Methods

We used meta-analyses of proportions to combine data[19, 20]. Funnel plots displaying the outcome rate from individual studies versus their precision (1/standard error) were carried out 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 ten. In this case, the power of the tests is 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 0%

indicates no observed heterogeneity, whereas I^2 values of ≥ 50% indicate a substantial level of heterogeneity. A fixed effects model was used if substantial statistical heterogeneity was not present. On the contrary, if there was evidence of significant heterogeneity between studies included, a random effect 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 time 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, 9 Bonville Chase, Altrincham, Cheshire WA14 4QA, UK) and GraphPad Prism 6 (GraphPad Software, San Diego, California, 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 as Supplementary Material 3.

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 > 2.5mm in 3/10 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 cases (17.4%). 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 live births, 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.

Fourty one fetuses had a RAA, a left AD and an ALSA (Figure 1). Respiratory symptoms occurred in seven of the 33 known live births (21.2%). Five already had surgery or had planned operation to divide the ring. Another two had mild symptoms, which improved. Computed tomography angiogram and barium swallow, at 2 and 5 years of age showed no significant obstruction to airway or oesophagus. At the time of data collection they remained well, with no surgery. The child with postnatal diagnosis of double aortic (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 the previously published literature plus the current) were included in the systematic review. Table 2 shows their general characteristics. Supplementary material 2 shows the studies excluded from the analysis and reasons for exclusion.

The quality assessment performed using NOS is shown in Supplementary material 4. 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 and lack of ascertainment of all individual outcomes. Furthermore, most studies had a relatively short period of follow-up after birth.

Synthesis of the results

There were 312 fetuses in the 16 studies with sample size ranging between 3 and 86. The overall rates of chromosomal abnormalities, 22q11.2 deletion and associated ECA detected prenatally scan 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, Figure 3A-C. The rates of chromosomal abnormalities and 22q1.2 deletion were 4.6% (95% CI 2.3-7.8) and 5.1% (95% CI 2.4-8.6) (Table 3, Figure 3D-E). These rates were lower in fetuses with normal first and second trimester scans (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 postnatally were present in 5.0% (95% CI 2.7-7.9) and 4.0% (95% CI 1.5-7.6), respectively (Table 3, Figure 4A, B). The incidence of symptoms related to vascular rings within 24 months of life was 25.2% (95% CI 16.6-35.0), while the corresponding figure for surgery was 17.1% (95% CI 9.9-25.7) (Table 3, Figure 5A, B).

Data from 87 newborns with RAA forming a vascular ring were included in the time to event analysis. Figure 5C shows the Kaplan Meier curve illustrating freedom from symptoms requiring surgery. In most cases symptoms occurred within 24 months of life. The two-year freedom from surgery was 83.0% (95% CI 74.3-90.1).

DISCUSSION

Main Findings

Data from this study and meta-analysis suggest that most fetuses with RAA and normal intra-cardiac anatomy do not have associated chromosomal abnormalities, the risk being approximately 10% and about 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 own series, two fetuses had unilateral renal agenesis and three neonates presented with malformations of the gastro-intestinal system.

Strengths and weaknesses

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

The relatively small number of patients, the different periods of follow-up, with 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 carried out with an exploratory aim and did not show substantial heterogeneity for the large majority of the outcomes observed in this review (Supplementary material 5). Most of the studies included were small series reporting only 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 it was mainly due to the fact these studies were not adequately powered to detected any effect size, thus apparently lowering the degree of heterogeneity.[23]

In view of these limitations, large prospective studies are still needed in order to narrow further the confidence intervals reported here, especially regarding symptoms related to airway and oesophageal 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 6). 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 identify if a vascular ring is present. Attempts should be made to rule out the possibility of a double aortic arch. Razon et al[24] have recently highlighted 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 thoroughly assessed by a fetal medicine specialist. Current status of prenatal ultrasound allows investigation of extra-cardiac 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. 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 gastro-intestinal tract, such as oesophageal 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 oesophageal atresia in our cohort series, but three

neonates had gastro-intestinal 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 follow up fetal medicine assessment assess direct or indirect signs of gastro-intestinal 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 carefully assessed for possible additional abnormalities. We recommend that oesophageal atresia be ruled out prior to establishing oral feeds as this can be easily performed 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 oesophageal 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 of life. 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 tracheo-oesophageal compression that may require surgical intervention.

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Table 1. Characteristics and outcomes of fetuses with prenatal diagnosis of RAA with no associated intra-cardiac abnormalities

Characteristics (n = 86 cases)	RAA
Maternal age in years, median (IQR)	32.0 (27.3 - 36.0)
Gestational age at diagnosis in weeks, median (IQR)	21.0 (20 - 23)
NT thickness > 2.5mm, n (%)	9/59 (15.3) *
NT thickness > 99th centile, n (%)	4/59 (6.8) *
Abnormal karyotype, n (%)	11/53 (20.8) †
Abnormal karyotype or phenotype, n (%)	11/78 (14.1)
22q11.2 deletion, n (%)	5/78 (6.4)
22q11.2 deletion (tested), n (%)	5/53 (9.4)
Left Arterial Duct, n (%)	79/86 (91.9)
Right Arterial Duct, n (%)	7/86 (8.1)
Vascular ring (RAA, ALSA), n (%)	41/ 86 (47.7)
Fetuses with ECA diagnosed prenatally, n (%)	15/86 (17.4)
Neonates with cardiac abnormalities diagnosed postnatally only, n (%)	4/64 (6.3)
Neonates with ECA diagnosed postnatally only, n (%)	4/65 (6.2) ‡
Termination of pregnancy, n (%)	8/86 (9.3)
Intrauterine demise, n (%)	3/72(4.2) §
Postnatal symptoms, n (%)	7/33 (21.2) ||
Surgery due to vascular ring symptoms, n (%)	5/33 (15.2) || ¶

* = includes only those with measured/available NT (nuchal translucency) thickness; † = 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

Table 2: General characteristics of the studies included in the systematic review

Author	Year	Country	Study design	Cases (n)	ALSA (n)	Outcome(s) observed	Follow up (months)
Current study	2015	UK	Retrospective	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	Retrospective	50	23	Chromosomal abnormalities, 22q11.2 deletion, symptoms and surgery related to vascular ring, associated ICA detected postnatally	Not stated
Miranda [28]	2014	UK	Retrospective	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	Not stated
Gul[29]	2012	Turkey	Retrospective	7	Not stated	Chromosomal abnormalities, 22q11.2 deletion, ECA detected prenatally, associated ICA and ECA detected postnatally	Not stated
Bronshtein[30]	2011	Israel	Retrospective	3	0	Chromosomal abnormalities, 22q11.2 deletion, Associated ECA detected prenatally, associated ICA and ECA detected postnatally	Not stated
Li[31]	2011	China/USA	Retrospective	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	Retrospective	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	Retrospective	15	14	Chromosomal abnormalities, 22q11.2 deletion, associated ECA detected prenatally, pressure symptoms and surgery related to vascular ring, associated ICA and EA detected postnatally.	12-55
Tuo[9]	2009	Italy	Retrospective	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	Retrospective	3	3	Chromosomal abnormalities, 22q11.2 deletion, associated ICA detected postnatally, associated ECA detected prenatally, pressure symptoms and surgery related to vascular ring, associated ICA and ECA detected postnatally	Not stated
Zidere[7]	2006	UK	Retrospective	25	Not stated	Chromosomal abnormalities, 22q11.2 deletion, ECA detected prenatally, associated ICA and ECA detected postnatally	Not stated
Berg[8]	2006	Germany	Retrospective	23	20	Chromosomal abnormalities, 22q11.2 deletion, associated ECA detected prenatally, associated ICA detected postnatally	Not stated
Patel[10]	2006	USA	Retrospective	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	Retrospective	18	1	Chromosomal abnormalities, 22q11.2 deletion, associated ECA detected prenatally, associated ICA detected postnatally	12-80
Chaoui[25]	2002	Germany	Retrospective	3	Not stated	22q11.2 deletion	Not stated
Bronshtein[6]	1998	Israel	Retrospective	5	5	Associated ECA detected prenatally, pressure symptoms and surgery related to vascular ring, associated ICA and ECA detected postnatally	Not stated

ICA = intra-cardiac abnormality; ECA = extra-cardiac abnormality

Table 3: Pooled proportions for the outcomes observed in this systematic review

Outcome	Studies (n)	Fetuses (n/N)	I^2 (%)	Raw proportions (95% CI)	Pooled proportions (95% CI)
		RAA with normal intra-cardiac 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 (prenatally)	14	37/259	12.3	14.23 (10.3-19.1)	14.56 (10.6-19.0)
Symptoms for 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 extra-cardiac 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 = extra-cardiac abnormalities, ICA = intra-cardiac abnormalities, RAA = right aortic arch

FIGURE LEGENDS

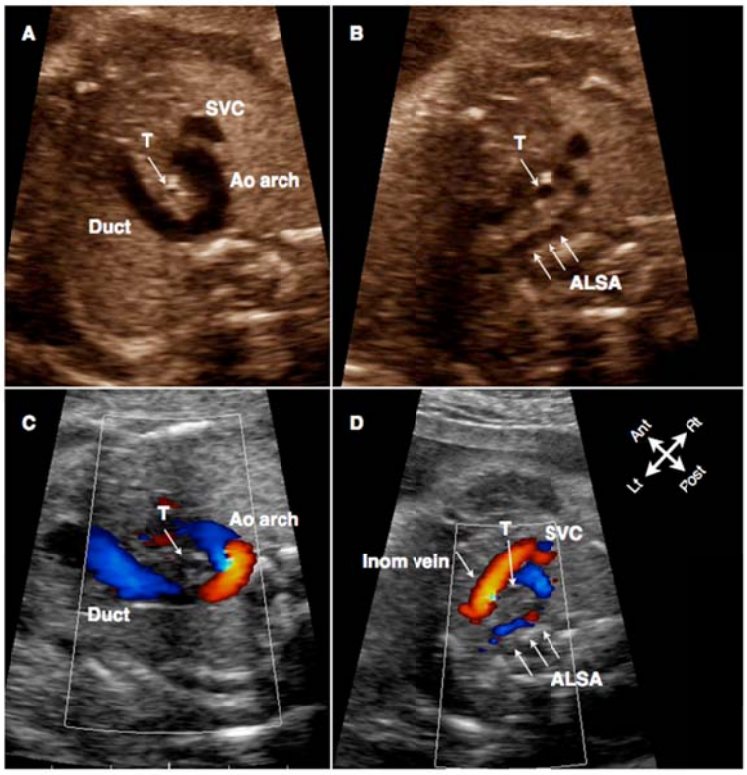


Figure 1: Images of the upper mediastinum obtained from case 22 at 28 weeks of gestation, on B-mode (A, B) and colour flow mapping (C, D). Note the right-sided aortic arch, the left-sided arterial duct and the ALSA, which courses behind the trachea. ALSA = aberrant origin of the left subclavian artery, Ao arch = aortic arch, SVC = superior vena cava, T = trachea

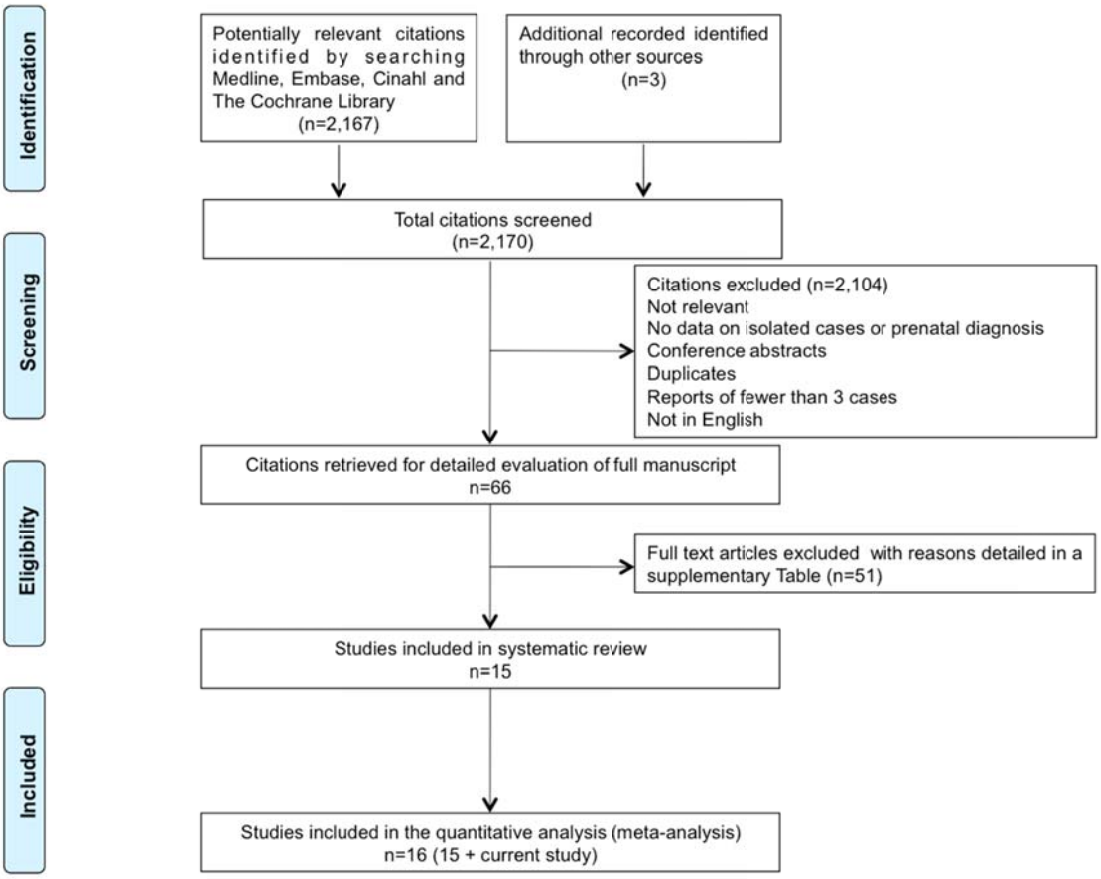
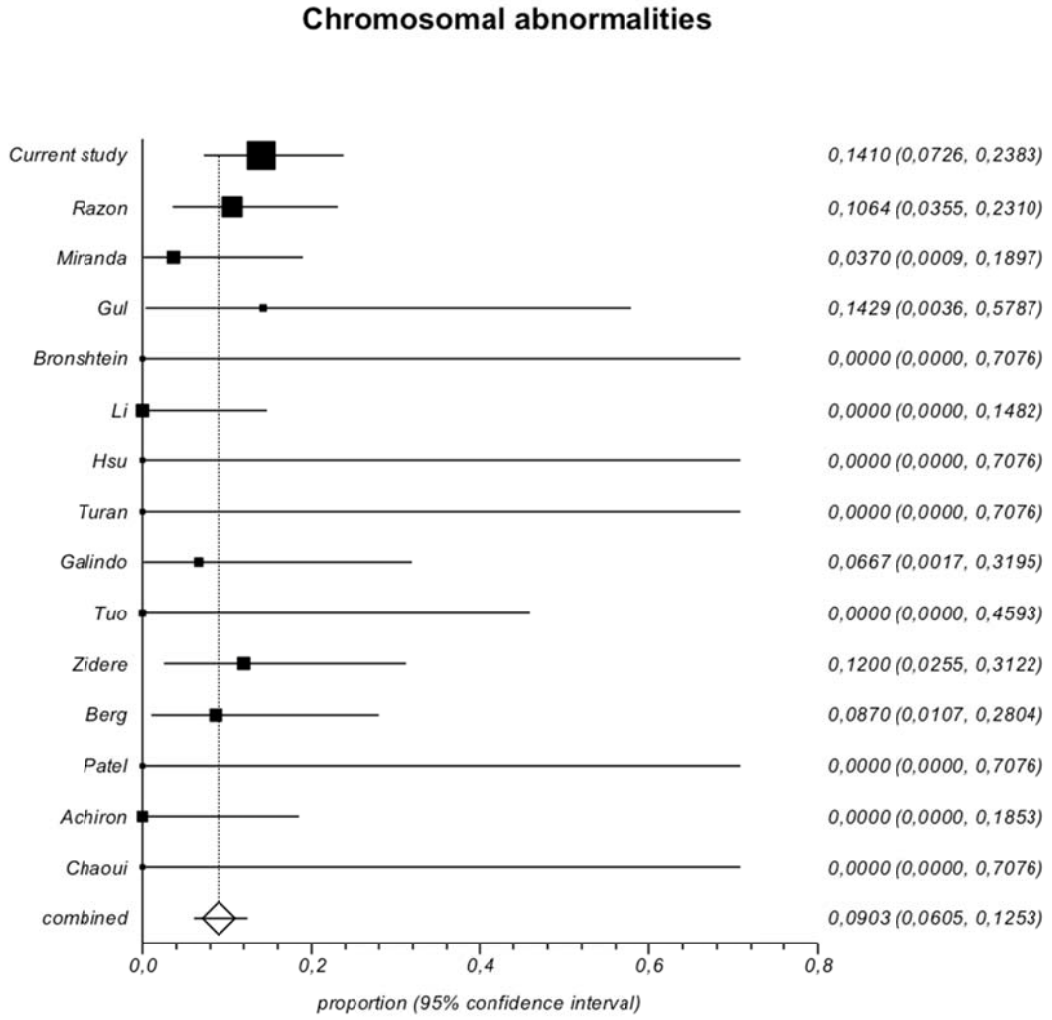
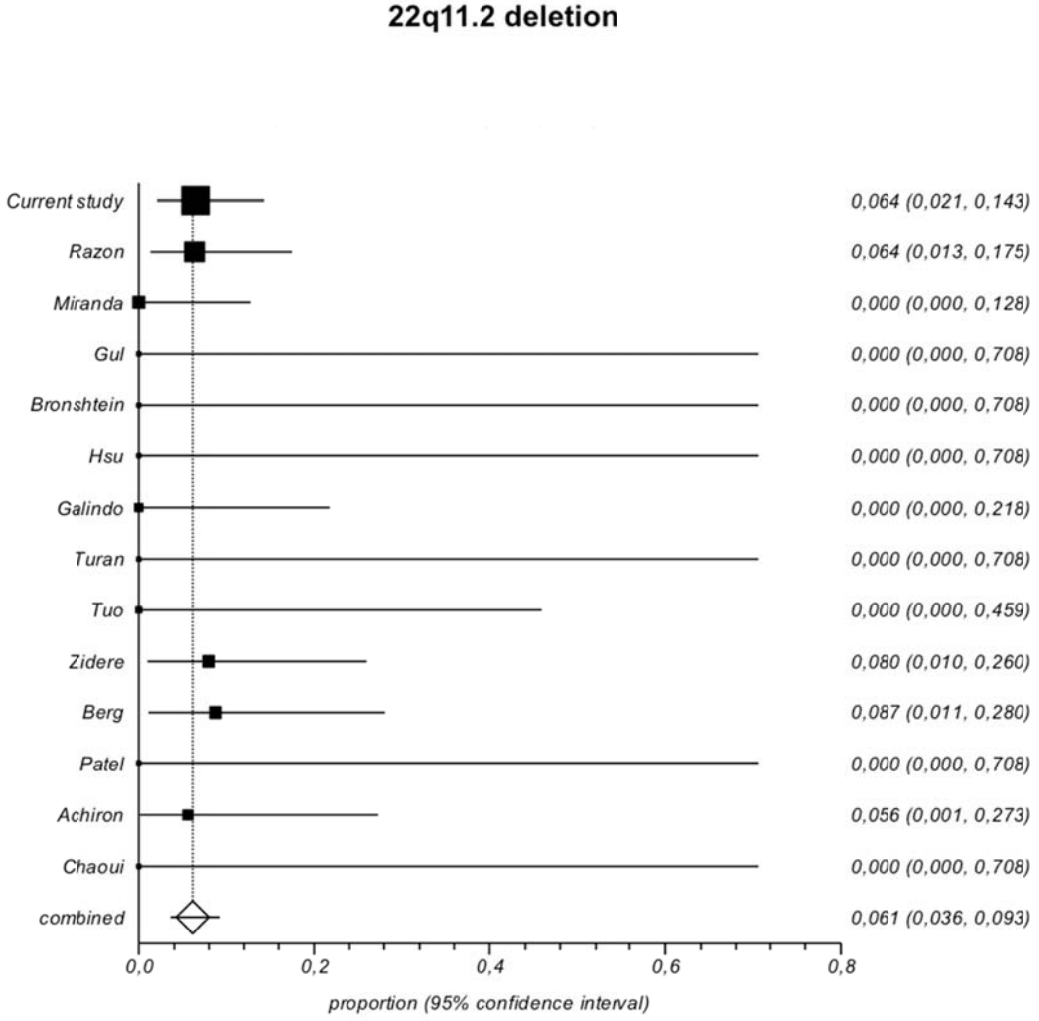
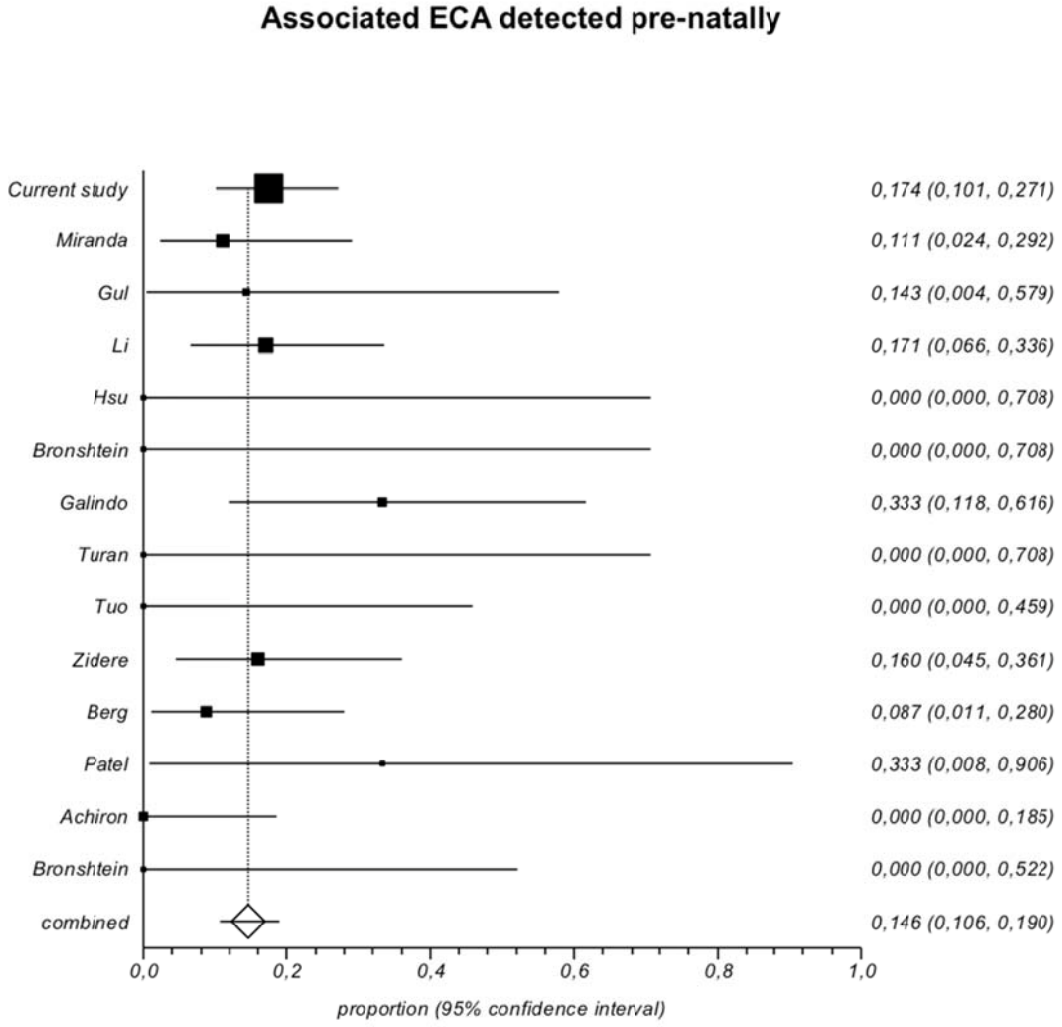
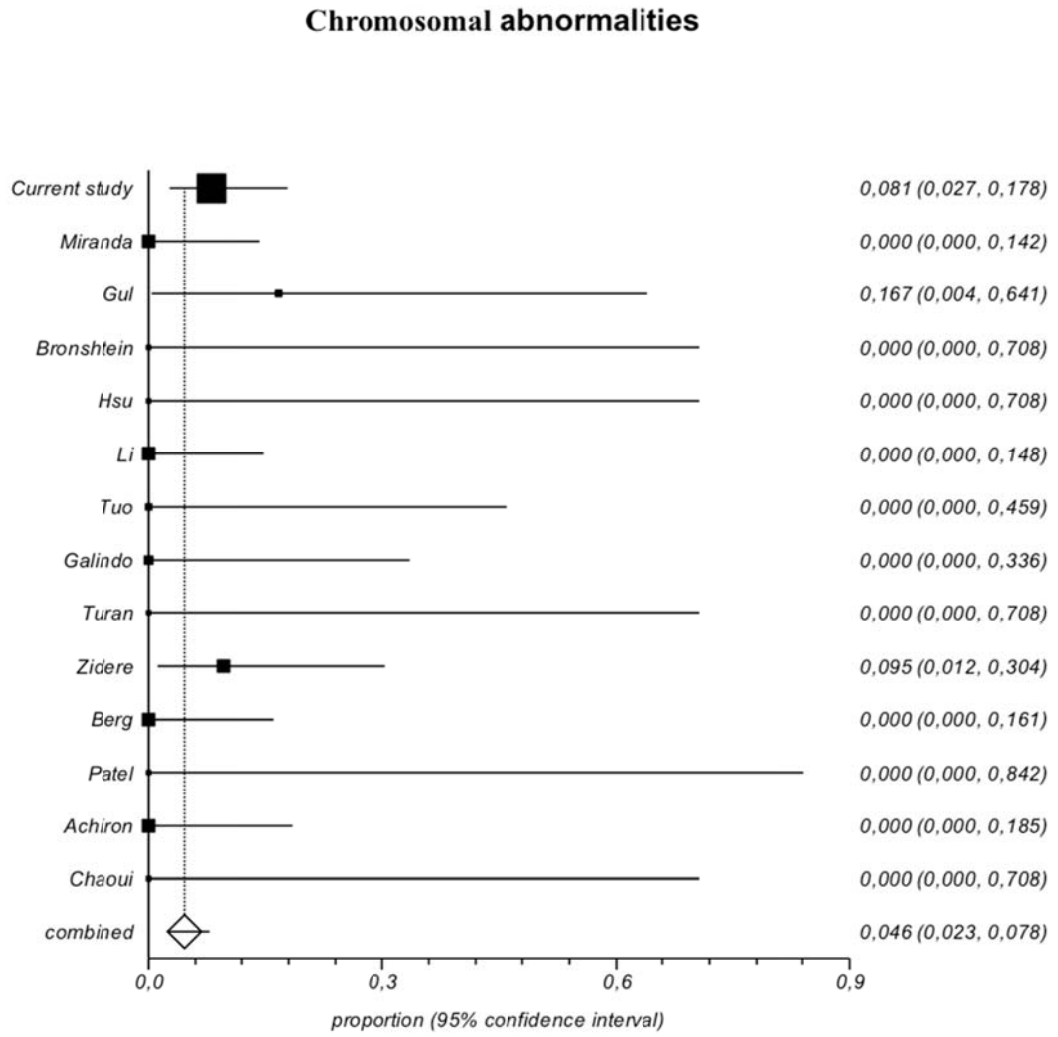


Figure 2: Flow chart of the studies included in the systematic review.









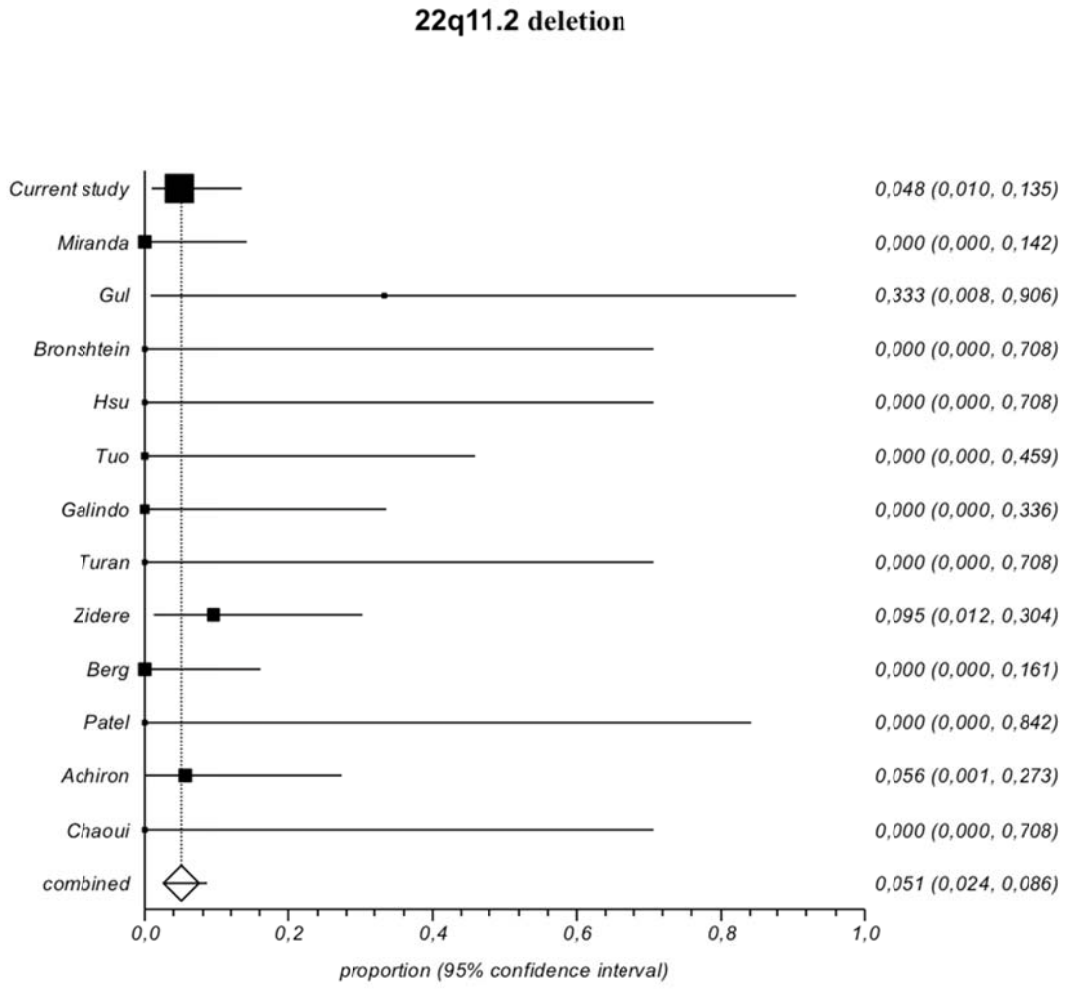
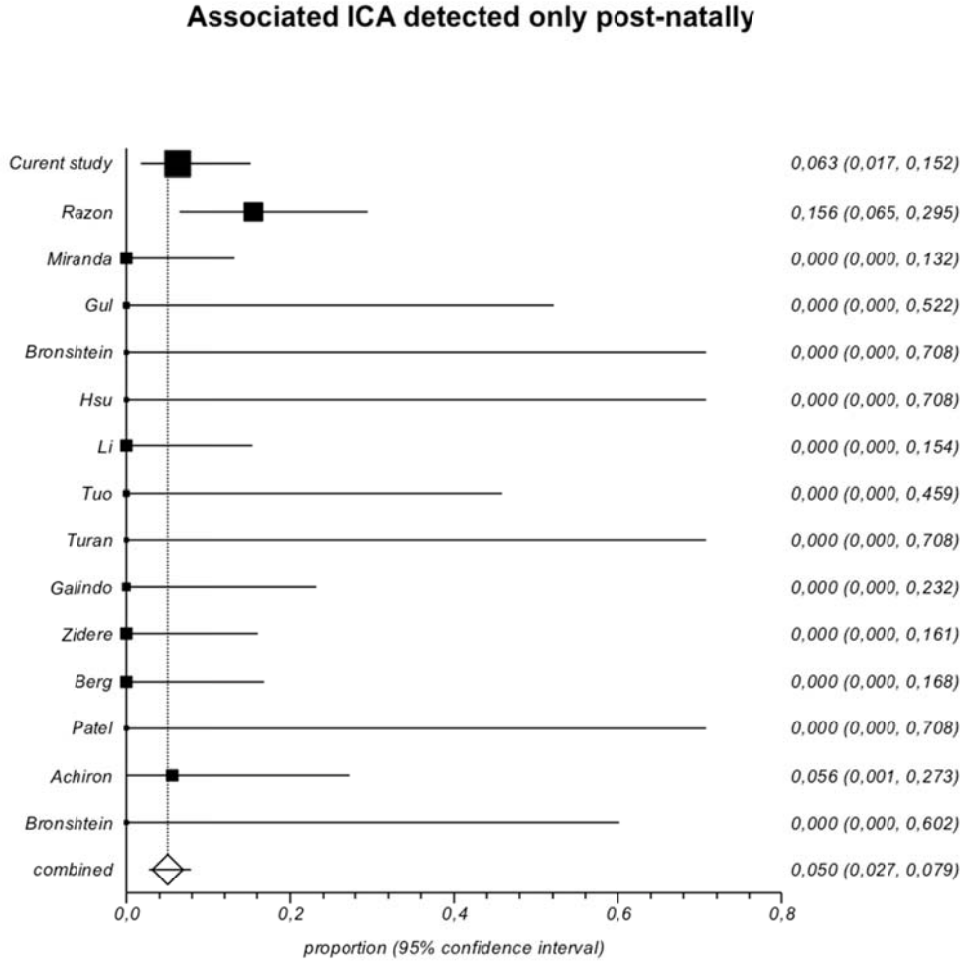


Figure 3 (A-E): Pooled proportions (forest plot) of the prevalence of (A) chromosomal abnormalities, (B) 22q11.2 deletion and (C) associated ECA detected prenatally in fetuses with RAA without ICA. Pooled proportions of the prevalence of (D) chromosomal abnormalities and (E) 22q11.2 deletion in fetuses with isolated RAA. ECA = extra-cardiac abnormality, ICA = intra-cardiac abnormality, RAA = right aortic arch



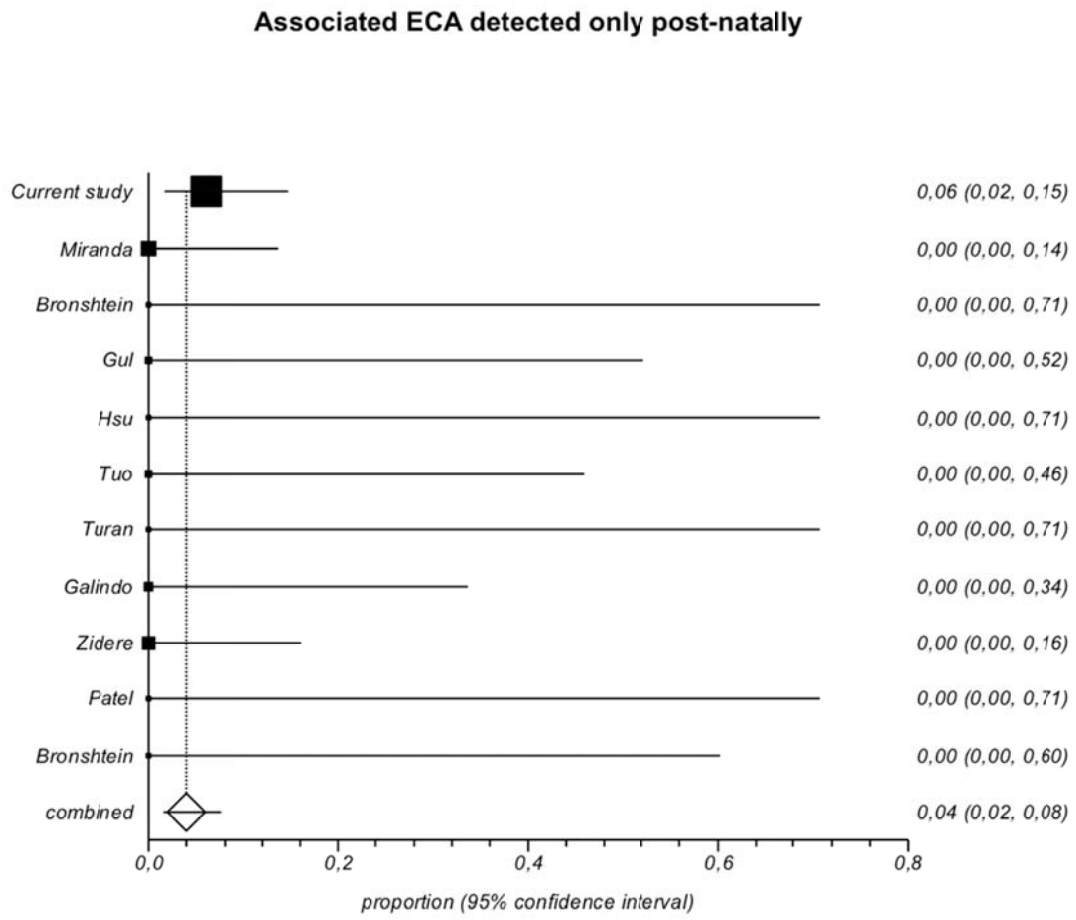
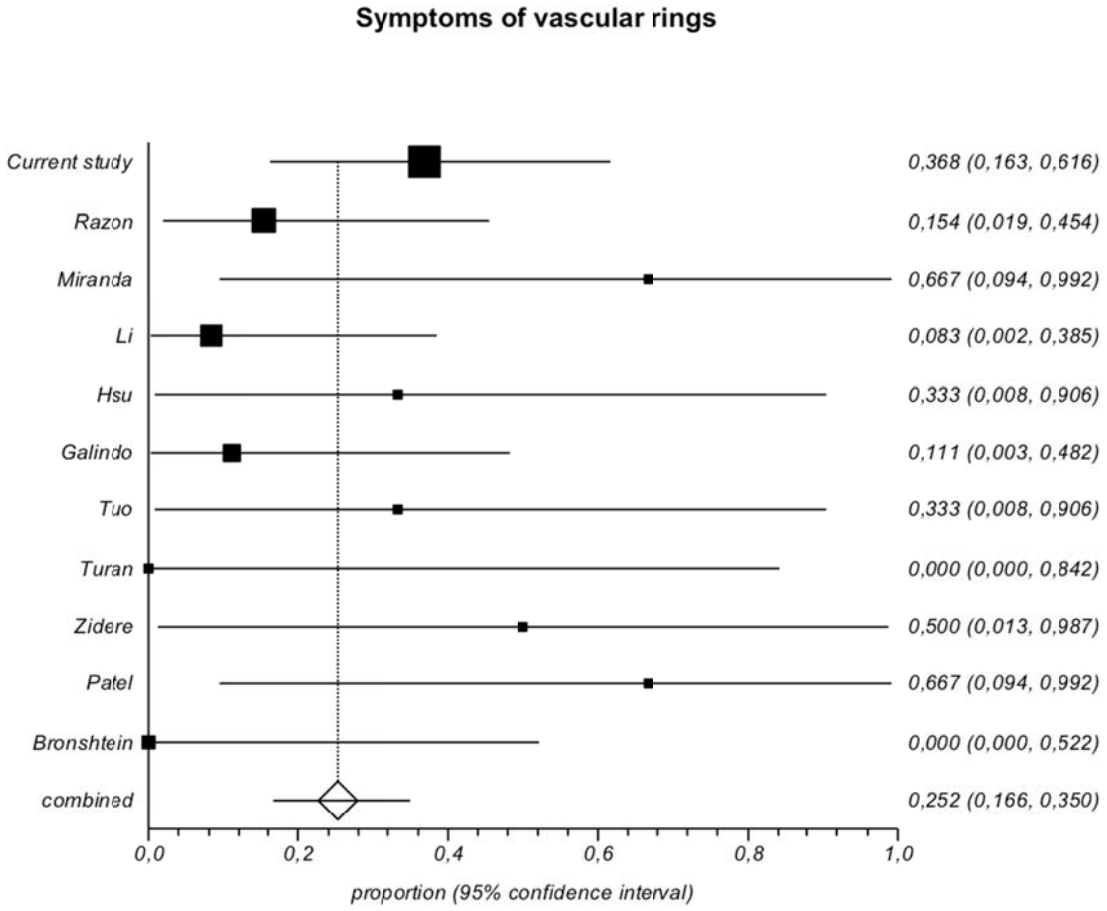
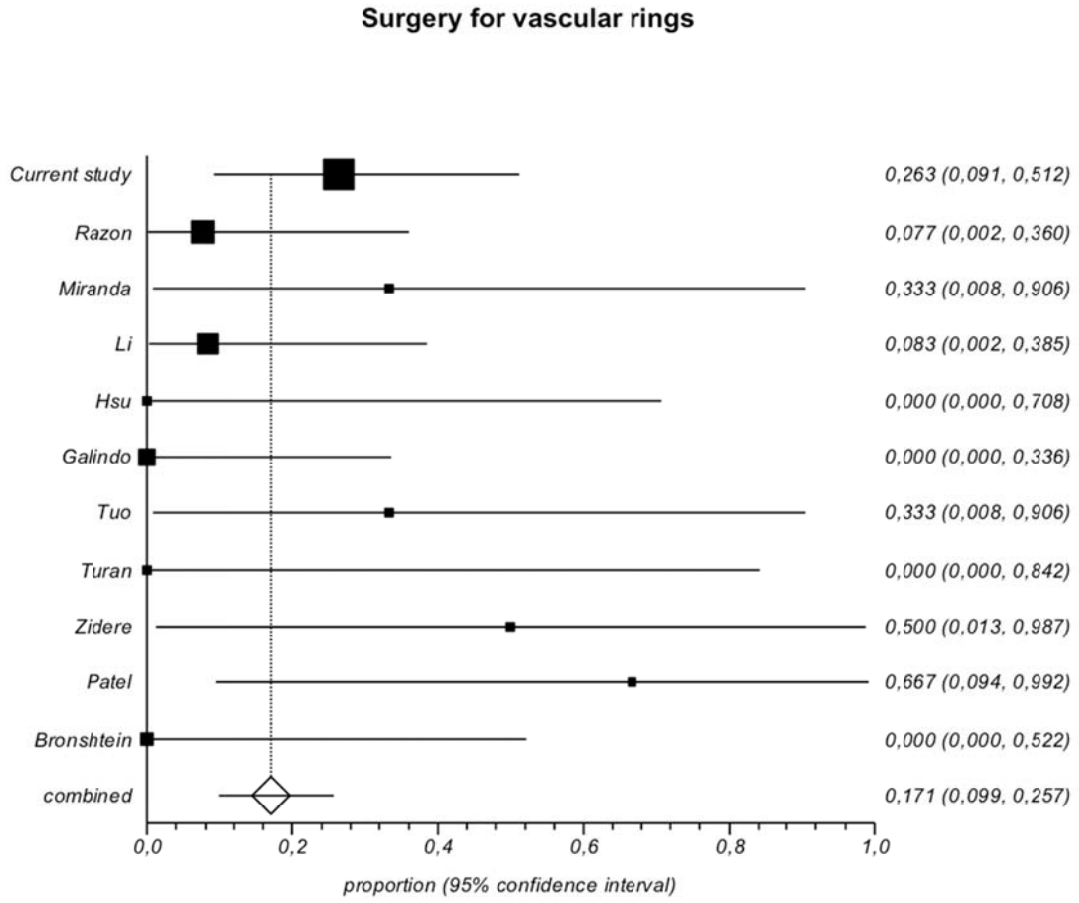


Figure 4 (A, B): (A) Pooled proportions (forest plot) of the prevalence of ICA and (B) ECA detected postnatally only. ECA = extra-cardiac abnormality, ICA = intra-cardiac abnormality, RAA = right aortic arch





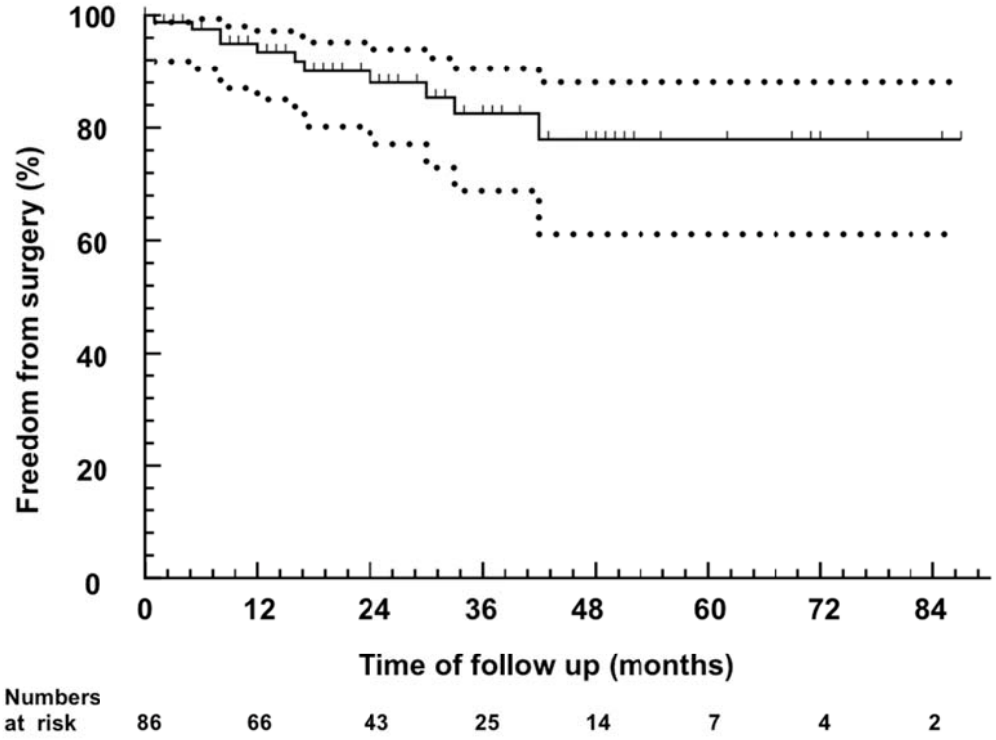


Figure 5 (A-C): Pooled proportions (forest plot) of the incidence of (A) pressure symptoms and (B) surgery for vascular rings in patients with RAA and normal intra-cardiac anatomy. RAA = right aortic arch. (C): Kaplan Meier analysis of postnatal pressure symptoms requiring surgery in cases with right-sided aortic arch forming a vascular ring.

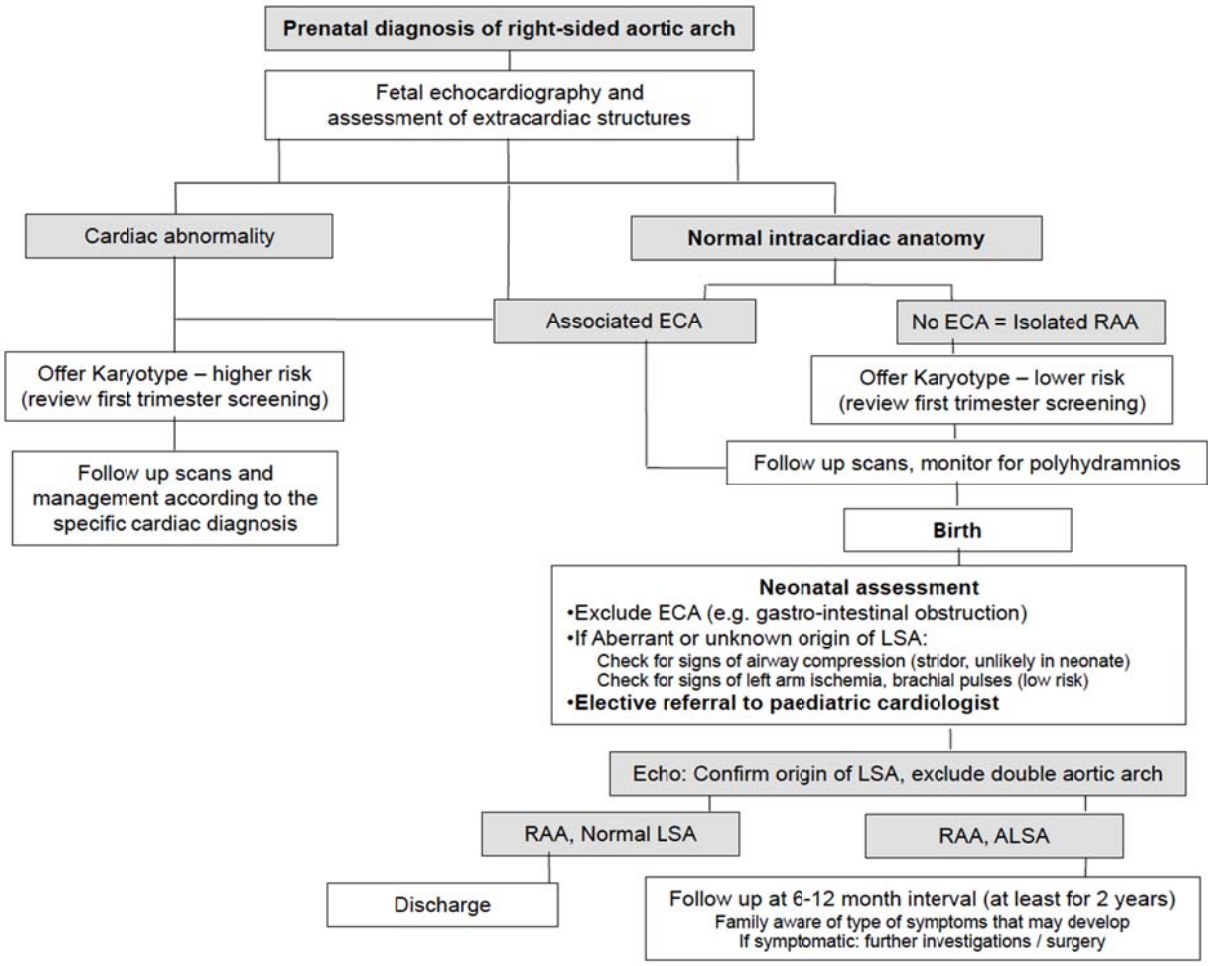


Figure 6: Proposed algorithm for management of right aortic arch (RAA) diagnosed in fetal life.

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