Outcome of prenatally diagnosed fetal heterotaxy: A systematic review and meta-analysis

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Abstract

Objectives: To assess the perinatal outcomes of fetuses affected by heterotaxy.

Methods: Medline, Embase and Cinhal were searched. Only studies reporting a prenatal diagnosis of isomerism were included. The outcomes observed were: associated cardiac and extra-cardiac anomalies, fetal arrhythmias, abnormal karyotype, type of surgical repair and perinatal mortality. The analysis was stratified according the type of heterotaxy syndrome (left, LAI, and right, RAI, atrial isomerism). Meta-analyses of proportions were used to combine data.

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Results: 16 studies (647 fetuses) were included. Atrioventricular septal defect (AVSD) was the most common associated major cardiac anomaly found in fetuses with LAI (Pooled Proportion [PP] 59.3%, 95% CI 44.0-73.7), while obstructive lesions of the right outflow tract occurred in 35.5% (95% CI 21.4-51.0). Fetal arrhythmias occurred in 36.7% (95% CI 26.9-47.2) of the cases and were mainly represented by complete atrio-ventricular block (26.5%, 95% CI 15.0-40.0). Abnormal stomach and liver position were found in 59.4% (95% CI 38.1-79.0) and 32.5% (95% 11.9-57.6) of cases, while intestinal malrotation was detected in 14.2% (95% CI 2.5-33.1). Hydrops developed in 11.8% (95% CI 2.9-25.6) of these fetuses. Biventricular repair was accomplished in 78.2% (95% CI 64.3-89.4) of the cases while univentricular repair or palliation was needed for 17.0% (95% CI 9.7-25.9). Death during or after surgery occurred in 26.8% (95% CI 4.6-58.7) of cases.

Almost all (99.0% 95% CI 97.5-99.9) cases with RAI had associated cardiac anomalies, with AVSD being the most common heart defect (PP 72.9%, 95% CI 60.4-83.7). Abnormal heart rhythm was not common with an incidence of 1.3% (95% CI 0.2-3.2). Abnormal stomach and liver position were found in 54.5% (95% CI 38.5-70.1) and 45.9% (95% CI 11.3-83.0) of cases, respectively, while intestinal malrotation was detected in 27.1% (95% CI 7.9-5.2). Most children with RAI had univentricular repair and 27.8% (95% CI 15.5-42.1) died during or after surgery.

Conclusion: Fetal heterotaxy is affected by a high prevalence of cardiac and extra-cardiac anomalies. Approximately one quarter of these fetuses died during or after surgery. Abnormal heart rhythm, especially heart block is common in fetuses with LAI while is uncommon in RAI. Univentricular repair is common in RAI.

Introduction

Heterotaxy encompasses a wide spectrum of conditions characterized by an abnormal arrangement of thoraco-abdominal organs across the left-right axis of the heart, differing from complete situs solitus and inversus.[1-4]

Although its precise nomenclature and classification is still under debate, heterotaxy is commonly referred with the term ‘‘isomerism’’ which describes a situation in which morphologically right or left structures are found on both sides of the body and it is the currently accepted term used to

describe hearts with isomeric atria and atrial appendages. Right atrial isomerism (RAI) is typically, but not invariably, associated with asplenia while left (LAI) with polysplenia (55%).[2,5]

Associated major cardiac anomalies are the main determinant in anticipating the outcome of children affected by heterotaxy; however, even those presenting with isolated defects can experience short and long-term morbidities such as intestinal malrotation, biliary atresia, respiratory and immune disorders.[6-9]

Assessment of thoraco-abdominal situs is an integral part of the sonographic screening examination of the fetal heart and has led to an increase in the prenatal diagnosis of heterotaxy.[10]

Despite this, assessment of atrial morphology and spleen anatomy on prenatal ultrasound is challenging and it has still to be validated on the general population, while lung lobulation cannot be reliably described in utero.[11,12]

In this scenario, prenatal diagnosis of fetal heterotaxy relies mainly on the identification of cardiac and extra-cardiac defects commonly reported to be associated with these anomalies post-natally. Interruption of inferior vena cava (IVC) with azygos continuation is usually considered a proxy of LAI, while juxtaposition of aorta and IVC in fetuses presenting with major congenital heart disease (CHD) is highly suggestive of RAI.

Paediatric literature reports high rates of associated cardiac and extra-cardiac anomalies in children affected by heterotaxy.[1,13,14] However, these series might be biased by the fact that only symptomatic children or those requiring surgery are included, and it is not entirely certain whether they can be used to counsel parents carrying a pregnancy affected by these defects.

The first aim of this systematic review was to evaluate the prevalence and the type of associated anomalies in fetuses with heterotaxy diagnosed on prenatal ultrasound; the secondary aim was to explore the perinatal outcome in these fetuses.

Methods

Protocol, eligibility criteria, information sources and search

This review was performed according to an a-priori designed protocol and recommended for systematic reviews and meta-analysis[15-18]. Medline, Embase and Cinhal were searched electronically on the 20th December 2016 utilizing combinations of the relevant medical subject heading (MeSH) terms, key words, and word variants for "isomerism", "heterotaxy," "cardiosplenic syndromes", and "outcome" (*Supplementary Material Table 1*). The search and selection criteria were limited to the last two decades (1996-2016) and restricted to English language. Reference lists of relevant articles and reviews were hand searched for additional reports. Prisma guidelines were followed.[19] The review was registered with the PROSPERO (registration number: CRD 42016053972, http://www.crd.york.ac.uk/PROSPERO).

Study selection, data collection and data items

The outcomes observed were:

- Associated cardiac anomalies
- Associated fetal arrhythmias
- Associated extra-cardiac anomalies
- Abnormal karyotype
- Termination of pregnancy (TOP)
- Intra-uterine death (IUD)
- Neonatal death (NND)
- Late death (LD)
- Need for uni- or bi-ventricular repair and associated intra and post-surgical mortality

All these outcomes were observed in fetuses with LAI and RAI separately. For the assessment of the associated cardiac anomalies, we explore the prevalence of the following defects: atrio-ventricular septal defect (AVSD), atrial septal defect (ASD) or common atrium, ventricular septal defect (VSD), single ventricle, left ventricular outflow tract obstruction (LVOTO), including either aortic stenosis or atresia, coarctation of aorta (CoA), right ventricular outflow tract obstruction (RVOTO), including either pulmonary stenosis or atresia, cono-truncal anomalies, including either Tetralogy of Fallot, double outlet right or left ventricle and common arterial trunk, transposition of the great arteries (TGA) including complete or congenitally corrected TGA and malposition, persistent left superior vena cava (PLSVC), interruption of IVC with azygos continuation, abnormal pulmonary venous return (APVR), including either the partial and total types of the anomaly, dextrocardia, defined as an abnormal cardiac axis pointing to the right, and arrhythmias.

For the assessment of the associated extra-cardiac anomalies we explored the prevalence of the following defects: polysplenia, asplenia, abnormal stomach and liver position, intestinal obstruction and malrotation, abnormalities of the hepatobiliary tract, hydrops, abdominal wall defects, central nervous system (CNS), thoracic, facial, renal, limb and spinal anomalies.

The prevalence of abnormal karyotype was observed only in the fetuses which had their full karyotype tested, either pre-or post-natally. Finally, the need for uni- or biventricular repair and the associated intra and post-surgical mortality were assessed only in liveborn infants.

IUD was defined as fetal loss from 20 weeks of gestation, while NND and LD as a demise occurring within and after 28 days of life, respectively.

Only studies reporting a prenatal diagnosis of LAI or RAI were considered suitable for the inclusion in the current systematic review. Post-natal studies or studies from which cases diagnosed pre-natally could not be extracted were excluded. Studies reporting fetal isomerism in the setting of a specific cardiac or extra-cardiac anomalies were not considered suitable for inclusion. Autopsy based studies were excluded on the basis that fetuses undergoing TOP are more

likely to show associated major structural and chromosomal anomalies. Finally, studies not providing a clear classification of the anomaly and studies not differentiating between LAI and RAI were not considered suitable for inclusion in the current review. The wide heterogeneity in nomenclature among published studies resulted in heterogeneity in risk stratification of these fetuses, therefore we included only studies providing a definition of the anomaly in accordance with that reported above.

Only full text articles were considered eligible for the inclusion. Case reports, conference abstracts and case series with fewer than 3 cases of isomerism were also excluded in order to avoid publication bias.

Studies were assessed according to the following criteria: population, outcome, type of heterotaxy syndrome and time at a follow-up.

Two authors (DB, FD) reviewed all abstracts independently. Agreement regarding potential relevance was reached by consensus. Full text copies of those papers were obtained and the same two reviewers independently extracted relevant data regarding study characteristics and pregnancy outcome. Inconsistencies were discussed by the reviewers and consensus reached by discussion with a third author. If more than one study was published for the same cohort with identical endpoints, the report containing the most comprehensive information on the population was included to avoid overlapping populations. For those articles in which information was not reported but the methodology was such that this information would have been recorded initially, the authors were contacted.

Quality assessment of the included studies was performed using the Newcastle-Ottawa Scale (*NOS*) for cohort studies; according to NOS, each study is judged on three broad perspectives: the selection of the study groups; the comparability of the groups; and the ascertainment outcome of interest.[20] Assessment of the selection of a study includes the evaluation of the representativeness of the exposed cohort, selection of the non-exposed cohort, ascertainment of exposure and the demonstration that outcome of interest was not present at start of study. Assessment of the

comparability of the study includes the evaluation of the comparability of cohorts on the basis of the design or analysis. Finally, the ascertainment of the outcome of interest includes the evaluation of the type of assessment of the outcome of interest, length and adequacy of follow-up.[20] According to NOS a study can be awarded a maximum of one star for each numbered item within the Selection and Outcome categories. A maximum of two stars can be given for Comparability.

Risk of bias, summary measures and synthesis of the results

We used meta-analyses of proportions to combine data.[21] 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.[22-24]

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 $\geq$ 50% indicate a substantial level of heterogeneity. A random effect model was used for all the analyses.

All proportion meta-analyses were carried out using StatsDirect 2.7.9 (StatsDirect Ltd, Altrincham).

Results

A total of 2307 articles were identified, 134 were assessed with respect to their eligibility for inclusion (*Supplementary Material Table 2, excluded studies)* and a total of 16 studies included in the systematic review (Figure 1).[14,25-38] These 16 studies included 647 fetuses with a prenatal diagnosis of isomerism (61.7%, 95% CI 57.8-65.4 with LAI and 38.3%, 95% CI 34.6-42.2 with RAI) confirmed at birth.

All studies included a relatively small number of cases and had different periods of follow-up. Most of the included 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. Their main weaknesses were their retrospective design, small sample size and the inclusion of high-risk populations. Furthermore, the relatively short period of follow-up after birth did not allow a precise estimation of the long-term outcome of these children, especially those not undergoing surgery immediately after birth.

Synthesis of the results

Left isomerism

Associated cardiac anomalies

Associated major cardiac anomalies occurred in 83.4% (95% CI 74.4-90.7; I^2: 69.7%) of cases (Figure 2). AVSD was the most common associated cardiac defect with a prevalence of 59.3% (95% CI 44.0-73.7) in the overall population of fetuses with a prenatal diagnosis of LAI, while RVOTO and transposition or malposition of the great arteries occurred in 35.5% (95% CI 21.4-51.0) and 11.0% (95% CI 5.0-18.8) of the cases, respectively. Cono-truncal anomalies, especially double outlet right ventricle (DORV), were found in 21.2% (95% CI 16.0-27.0) of LAI while LVOTO were less common (8.2%, 95% CI 3.7-14.21 and 4.6%, 95% CI 1.4-9.4 respectively). Anomalies of systemic veins such as PLSVC (PP: 28.5%, 95% CI 17.0-41.6) and interruption of IVC (PP: 89.2%, 80.5-95.5) occurred in the large majority of cases, while those of pulmonary venous return, either partial or total, were less common (PP: 9.9%, 95% CI 5.4-15.5) (Table 3).

Fetal arrhythmias occurred in 36.7% (95% CI 26.9-47.2) of all cases and was mainly represented by CAVB (PP: 26.5%, 95% CI (15.0-40.0) (Table 4).

Associated extra-cardiac anomalies

Abnormalities of visceral arrangement occurred in 55.4% (95% CI 35.1-74.8) of fetuses with a prenatal diagnosis of LAI. When excluding anomalies of the abdominal situs and gastrointestinal tract, the rate of associated extra-cardiac anomalies was 16.0% (95% CI 7.5-26.9).

Abnormal stomach and liver position were found in 59.4% (95% CI 38.1-79.0) and 32.5% (95% 11.9-57.6) of cases with LAI, while malformations of the biliary tract such of the biliary tract such as biliary atresia were found in 8.0% (95% CI 3.5-14.3) (Table 5). Obstructive lesions of the bowel occurred in 4.9% (95% CI 2.7-7.7) of cases while malrotation was found in 14.2% (95% CI 2.5-33.1)

Hydrops developed in 11.8% (95% CI 2.9-25.6) of these fetuses mainly due to the presence of complete atrioventricular block (CAVB) (Table 5). Polysplenia was detected after birth in 56.6% (95% CI 48.1-65.0) of cases (PP: 51.1%, 95% CI 38.9-63.3), while only 5.8% (95% 1.9-11.8) had asplenia (Table 5).

Associated extra-cardiac anomalies involving other systems were less common (Table 5). Finally, the prevalence of chromosomal anomalies was 3.0% (95% CI 1.2-5.6).

Perinatal outcome

TOP was performed in 24.8% (14.9-36.2) of cases, while 6.7% (95% CI 3.9-10.2) of fetuses died in utero (Table 6). The majority of fetuses with a prenatal diagnosis of LAI (60.7%, 95% CI 44.3-76.0) were born alive, while NND or late death occurred in 11.1% (95% CI 6.1-17.3) and 6.2% (95% CI 4.0-8.9) of the cases, respectively (Table 6).

Surgical intervention for CHD took place in 73.4% (95% CI 44.4-94.3) of those cases who were born alive. Biventricular repair was accomplished in 78.2% (95% CI 64.3-89.4) of the cases, while

univentricular repair or palliation was needed for 17.0% (95% 9.7-25.9) of children. Overall, death during or after surgery occurred in 26.8% (95% 4.6-58.7) of cases (Table 7).

Right isomerism

Associated cardiac anomalies

The large majority of fetuses with a prenatal diagnosis of RAI had associated cardiac anomalies (PP: 97.8%, 95% CI 95.3-99.4; I^2: 11.9%) (Figure 2). AVSD was the commonest heart defect with a prevalence of 72.9% (95% CI 60.4-83.7) in the overall population of fetuses with a prenatal diagnosis of RAI, while RVOTO and cono-truncal anomalies (mainly DORV) occurred in 67.4% (95% CI 56.2-77.8) and 40.1% (95% CI 28.0-52.8) of cases, respectively (Table 3). Anomalies of IVC and pulmonary venous return were common, with a prevalence of 41.8% (95% CI 28.9-55.3) and 41.9% (95% CI 28.4-56.0) of cases, respectively (Table 3).

Juxtaposition of aorta and IVC, which constitutes one of the main feature of prenatal diagnosis of RAI in utero, was found in 81.5% (95% CI 59.2-96.2) while interruption of IVC was less common (PP: 4.9, 95% CI 2.6-7.8) (Table 3). Abnormal heart rhythm was not common, with a prevalence of 1.3% (95% CI 0.2-3.2) (Tables 3 and 4).

Associated extra-cardiac anomalies

Associated extra-cardiac anomalies occurred in 62.9% (95% CI 32.5-88.4; I^2: 93.6%) of cases of fetal RAI; among the other structural abnormalities, those involving gastro-intestinal tract were common. Abnormal stomach and liver position were found in 54.5% (95% CI 38.5-70.1) and 45.9% (95% CI 11.3-83.0) of fetuses with a prenatal diagnosis of RAI, respectively, while malformations of the biliary tract such as atresia were less common (Table 5). Intestinal malrotation occurred in 27.1% (95% CI 7.9-5.2) (Table 5). Asplenia was present in the large

majority of cases (PP: 87.6%, 95% CI 75.5-96.0) while polysplenia, a common feature of LAI, was rare (PP: 2.0%, 95% CI 0.4-4.8) (Table 5).

Only a small proportion (PP: 3.7%, 95% CI 1.4-6.8) of fetuses with RAI presented with hydrops, likely as the result of the low incidence of CAVB (Table 5). Finally, 4.0% (95% CI 0.8-9.6) of cases had abnormal karyotype.

Perinatal outcome

About one third of pregnancies affected by RAI were terminated, while 4.3% (95% CI 2.1-7.3) experienced IUD (Table 6). Of those cases born alive, 17.6% (95% CI 8.7-28.7) and 14.7% (95% CI 7.9-23.1) of cases died during or after the neonatal period, respectively (Table 6).

Surgical intervention for CHD was performed in 70.0% (95% CI 20.7-99.6) of children (Table 6). The large majority of those children required univentricular repair, while only in a small proportion of cases (PP: 7.4%, 95% CI 0.5-33.7) biventricular repair was accomplished (Table 7). Overall, 27.8% (95% CI 15.5-42.1) died during or after surgery.

Discussion

Main findings

The findings from this systematic review show that fetuses with heterotaxy are affected by a high rate of associated cardiac and extra-cardiac anomalies. Abnormalities of atrio-ventricular valves are among the most common anomalies in fetal heterotaxy. Abnormal heart rhythm, especially

CAVB can occur in up to 25% of LAI and is responsible for the high rate of cases presenting with hydrops at an early gestational age during the pregnancy, while are rare in RAI. In cases undergoing surgery after birth, biventricular repair was common in LAI while the large majority of children affected by RAI required univentricular repair. Finally, intra- or post-surgical mortality was high in both LAI and RAI and occurred in about a quarter of these cases.

Strengths and Limitations

The small number of cases per each study, their retrospective design, different periods of follow-up and inclusion criteria, with most of the series being from high risk population represent the major limitations of this systematic review. Unfortunately, the scarce number of studies did not permit meaningful stratified meta-analyses to explore the test performance in subgroups of studies 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.

Most of the studies included in the current review were from high risk populations. This might have led in turn to an over-estimation of the associated cardiac and extra-cardiac anomalies. Finally, the different times of follow-up and post-natal imaging protocols among the different studies might have biased the real occurrence of associated cardiac and extra-cardiac anomalies since some anomalies may manifest only later in childhood, while others can be easily overlooked at a standard clinical examination.

Despite these limitations, however, the present review represents the best published estimate of a number of outcomes in fetuses diagnosed with isomerism.

Interpretation of the findings, their Clinical and research implications

Routine assessment of the fetal situs is an integral part of the second trimester routine anomaly scan[10] and has led to an increase in the detection rate of heterotaxy syndromes. Despite this, a precise characterization of the type of heterotaxy syndrome is not always feasible in utero.

Autopsy studies have reported that morphology of the atrial appendages can reliably differentiate between LAI and RAI.[39]. Characterization of the morphology of the atrial appendage in utero has been reported to be feasible and can improve the detection of these anomalies especially when new ultrasound techniques such as four dimensional ultrasound are employed, but it may be challenging.[11,31]

Prenatal diagnosis of heterotaxy on ultrasound mainly relies on the presence of associated cardiac and extra-cardiac anomalies which are typically reported to co-exist with isomerism. RAI is almost invariably associated with CHD, especially, con-truncal anomalies, RVOTO, transposition and hypoplastic left heart syndrome and it is affected by a generally worse perinatal outcome compared to RAI in view of the higher incidence of associated CHD. Furthermore, abnormal TPVR occurs in the large majority of fetuses with RAI and represents one the major determinants of post-natal outcome in these children, especially when obstructed. Conversely, interruption of IVC can be the only sign of LAI thus making prenatal diagnosis of this anomaly challenging, although it has also been also reported in fetuses not affected by isomerism[40].

Hydrops developed in approximately 10% of fetuses affected by LAI, mainly because of the presence of a CAVB, which can occur in up to 25% of cases. Fetal hydrops is one of the major determinants of poor perinatal outcome in fetuses with LAI and can be evident since the first trimester of pregnancy.[41] CAVB was the most common fetal arrhythmias in fetuses with LAI and was associated with an high burden of perinatal mortality and morbidity; furthermore, CAVB in the setting of LAI can be associated with myocardial non compaction which is characterized by regional ventricular wall thickening and deep trabecular recesses and is almost invariably associated with a poor prognosis.4[2]

Chromosomal anomalies are not common in heterotaxy; in the present review, abnormal karyotype was present in 3.0% (95% CI 1.2-5.6) of cases in LAI and 4.0% (95% CI 0.8-9.6) of cases with RAI. These figures might influence the parental decision whether to proceed with invasive prenatal diagnosis or not.

Abnormalities of the biliary tract such as biliary atresia are typically associated with heterotaxy. Newborns with biliary atresia develop progressive cholestasis which may evolve towards irreversible cirrhosis and liver failure if untreated. Prompt recognition and treatment are fundamental to improve the outcome of these children.[43,44]

Prenatal diagnosis of biliary atresia is challenging. Non-visualization of the fetal gallbladder, combined with the assessment of the amniotic fluid digestive enzymes, has been reported to have an overall good detection rate for biliary atresia. However, it requires validation in larger studies[45-48]. In this scenario, fetuses suspected to be affected by heterotaxy should be referred for a detailed assessment of the hepatobiliary tract in order to rule out biliary atresia. Nevertheless, urgent post-natal assessment should be performed in order to rule out this anomaly.[43,44]

Intestinal malrotation has been variably associated with heterotaxy with a reported incidence ranging from 30% to 90% in the pediatric literature.[49-51] Intestinal malrotation increases the risk of midgut volvulus, which can potentially result in significant bowel loss, intestinal insufficiency, and death.[52,53]

A recent systematic review exploring the association between intestinal malrotation and heterotaxy reported a prevalence of 58% (95% CI 36%-78%) in children with heterotaxy undergoing screening for bowel anomalies, although there was a wide heterogeneity in screening regimens among the included studies.

In the present review, intestinal anomalies occurred in 14.2% and 27.1% in LAI and RAI, respectively. However, there was a significant heterogeneity in the reported incidence due to the different screening policies for intestinal anomalies among the included studies.

Fetal magnetic resonance imaging is an important adjunct imaging modality to ultrasound and has been shown to provide an optimal anatomical characterization of the bronchial, hepatic, intestinal and splenic anatomy. In view of these findings, it might seem reasonable to refer cases of suspected heterotaxy on ultrasound to undergo fetal MRI, in order to determine the spleen status and rule out associated abnormalities, such as biliary atresia and intestinal malrotation, which might influence the prognosis of children with heterotaxy.[54,29,55]

References

1. Degenhardt K, Rychik J. Fetal Situs, Isomerism, Heterotaxy Syndrome: Diagnostic Evaluation and Implication for Postnatal Management. *Curr Treat Options Cardiovasc Med* 2016; **18**: 77.
2. Jacobs JP, Anderson RH, Weinberg PM, Walters HL 3rd, Tchervenkov CI, Del Duca D, Franklin RC, Aiello VD, Béland MJ, Colan SD, Gaynor JW, Krogmann ON, Kurosawa H, Maruszewski B, Stellin G, Elliott MJ. The nomenclature, definition and classification of cardiac structures in the setting of heterotaxy. *Cardiol Young* 2007;**17**Suppl 2: 1-28.
3. Loomba RS, Hlavacek AM, Spicer DE, Anderson RH. Isomerism or heterotaxy: which term leads to better understanding?. *Cardiol Young* 2015; **25**: 1037-1043.
4. Icardo JM, Sanchez de Vega MJ. Spectrum of heart malformations in mice with situs solitus, situs inversus, and associated visceral heterotaxy. *Circulation.* 1991; **84**: 2547–2558.
5. Peoples WM, Moller JH, Edwards JE. Polysplenia: a review of 146 cases. *Pediatr Cardiol*1983; **4**: 129-137.
6. Kothari SS. Non-cardiac issues in patients with heterotaxy syndrome. *Ann Pediatr Cardiol* 2014; **7**: 187-192.
7. Tan YW, Khalil A, Kakade M, Carvalho JS, Bradley S, Cleeve S, Giuliani S. Screening and Treatment of Intestinal Rotational Abnormalities in Heterotaxy: A Systematic Review and Meta-Analysis. *J Pediatr* 2016; **171**: 153-62.e1-3.
8. Brueckner M. Heterotaxia, congenital heart disease, and primary ciliary dyskinesia. *Circulation* 2007; **115**: 2793-2795.
9. Kennedy MP, Omran H, Leigh MW, Dell S, Morgan L, Molina PL, Robinson BV, Minnix SL, Olbrich H, Severin T, Ahrens P, Lange L, Morillas HN, Noone PG, Zariwala MA, Knowles MR. Congenital heart disease and other heterotaxic defects in a large cohort of patients with primary ciliary dyskinesia. *Circulation* 2007; **115**: 2814–2821.
10. International Society of Ultrasound in Obstetrics and Gynecology, 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.

11. Berg C, Geipel A, Kohl T, Smrcek J, Germer U, Baschat AA, Hansmann M, Gembruch U. Fetal echocardiographic evaluation of atrial morphology and the prediction of laterality in cases of heterotaxy syndromes. *Ultrasound Obstet Gynecol* 2005; **26**: 538-545.

12. Abuhamad AZ, Robinson JN, Bogdan D, Tannous RJ. Color Doppler of the splenic artery in the prenatal diagnosis of heterotaxic syndromes. *Am J Perinatol* 1999; **16**: 469-473.

13. Lim JS, McCrindle BW, Smallhorn, Golding F, Caldarone CA, Taketazu M, Jaeggi ET. Clinical features, management, and outcome of children with fetal and postnatal diagnoses of isomerism syndromes. *Circulation* 2005; **112**: 2454-2461.

14. Lin AE, Ticho BS, Houde K, Westgate MN, Holmes LB. Heterotaxy: associated conditions and hospital-based prevalence in newborns. *Genet Med* 2000; **2**: 157–172.

15. Henderson LK, Craig JC, Willis NS, Tovey D, Webster AC. How to write a Cochrane systematic review. *Nephrology* 2010; **15**: 617–624.

16. NHS Centre for Reviews and Dissemination. Systematic reviews: CRD's guidance for undertaking reviews in health care. York (UK): University of York 2009.

17. Leeflang MM, Deeks JJ, Gatsonis C, Bossuyt PM; Cochrane Diagnostic Test Accuracy Working Group. Systematic reviews of diagnostic test accuracy. *Ann Intern Med* 2008; **149**: 889-897.

18. Cochrane Handobook for Systematic Reviews of Diagnostic Test Accuracy. http://srdta.cochrane.org/handbook-dta-reviews.

19. Prisma statement. http://www.prisma-statement.org/ [accessed 10 July 2016]

20. Wells GA, Shea B, O'Connell D, Peterson J, Welch V, Losos M, Tugwell P. Newcastle-Ottawa Scale for assessing the quality of nonrandomised studies in meta-analyses. http://www.ohri.ca/programs/clinical_epidemiology/oxford.asp [accessed 20 November 2015]

21. 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.

22. Egger M, Davey Smith G, Schneider M, Minder C. Bias in meta-analysis detected by a simple, graphical test. *BMJ* 1997; **315**: 629-634.

23. 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.

24. Higgins JPT, Green S. Cochrane Handbook for Systematic Reviews of Interventions Version 5.0.2 [updated September 2009]. The Cochrane Collaboration 2009.www.cochrane-handbook.org. [accessed 10 December 2016].

25. Gottschalk I, Stressig R, Ritgen J, Herberg U, Breuer J, Vorndamme A, Strizek B, Willruth A, Geipel A, Gembruch U, Berg C. Extracardiac anomalies in prenatally diagnosed heterotaxy syndrome. *Ultrasound Obstet Gynecol* 2016; **47**: 443-449.

26. Gaur L, Telemal L, Bulas D, D'Onofrio MT. Utility of fetal magnetic resonance imaging in assessing the fetus with cardiac malposition. *Prenat Diagn* 2016; **36**: 752-579.

27. Escobar-Diaz MC, Friedman K, Salem Y, Marx GR, Kalish BT, Lafranchi T, Rathod RH, Emani S, Geva T, Tworetzky W. Perinatal and infant outcomes of prenatal diagnosis of heterotaxy syndrome (asplenia and polysplenia). *Am J Cardiol* 2014; **114**: 612-617.

28. Lee MY, Won HS, Shim JY, Lee PR, Lee BS, Kim EA, Kim YH, Park JJ, Yun TJ, Kim A. Prenatal diagnosis of atrial isomerism in the Korean population. *Obstet Gynecol Sci* 2014; **57**: 193-200.

29. Nemec SF, Brugger PC, Nemec U, Bettelheim D, Kasprian G, Amann G, Rimoin DL, Graham JM Jr, Prayer D. Situs anomalies on pre- natal MRI. *Eur J Radiol* 2012; **81**: e495–501.

30. Ozkutlu S, Bostan OM, Deren O, Onderoğlu L, Kale G, Güçer S, Orhan D. Prenatal echocardiographic diagnosis of cardiac right/left axis and malpositions according to standardized Cordes technique. *Anadolu Kardiyol Derg* 2011; **11**: 131-136.

31. Paladini D, Sglavo G, Masucci A, Pastore G, Nappi C. Role of four-dimensional ultrasound (spatiotemporal image correlation and sonography-based automated volume count) in prenatal assessment of atrial morphology in cardiosplenic syndromes. *Ultrasound Obstet Gynecol* 2011; **38**: 337-343.

32. Pepes S, Zidere V, Allan LD. Prenatal diagnosis of left atrial isomerism. *Heart* 2009; **95**: 1974-1977.

33. Yan YL, Tan KB, Yeo GS. Right atrial isomerism: preponderance in Asian fetuses. Using the stomach-distance ratio as a possible diagnostic tool for prediction of right atrial isomerism. *Ann Acad Med Singapore* 2008; **37**: 906-912.

34. Taketazu M, Lougheed J, Yoo SJ, Lim JS, Hornberger LK. Spectrum of cardiovascular disease, accuracy of diagnosis, and outcome in fetal heterotaxy syndrome. *Am J Cardiol* 2006; **97**: 720-724.

35. Pasquini L, Tan T, Yen Ho S, Gardiner H. The implications for fetal outcome of an abnormal arrangement of the abdominal vessels. *Cardiol Young* 2005; **15**: 35-42.

36. Hoefstaetter C,Plath H, Hansmann M. Prenatal diagnosis of abnormalities of the fetal venous system. *Ultrasound Obstet Gynecol* 2000; **15**: 231-241.

37. Atkinson DE, Drant S. Diagnosis of heterotaxy syndrome by fetal echocardiography. *Am J Cardiol* 1998; **82**: 1147-1149.

38. Phoon CK, Villegas MD, Ursell PC, Silverman NH. Left atrial isomerism detected in fetal life. *Am J Cardiol* 1996; **77**: 1083-1088.

39. Ho SY, Cook A, Anderson RH, Allan LD, Fagg N. Isomerism of the atrial appendages in the fetus. *Pediatr Pathol* 199; **11**: 589–608.

40. Bronshtein M, Khatib N, Blumenfeld Z. Prenatal diagnosis and outcome of isolated interrupted inferior vena cava. *Am J Obstet Gynecol* 2010; **202**: 398.e1-4.

41. Baschat AA, Gembruch U, Knöpfle G, Hansmann M. First-trimester fetal heart block: a marker for cardiac anomaly. *Ultrasound Obstet Gynecol* 1999**; 14**: 311-314.

42. Friedberg M, Ursell P, Silverman N. Isomerism of the left atrial appendage associated with ventricular noncompaction. *Amer J Cardiol* 2006: **96**; 985-990.McKiernan PJ, Baker AJ, Kelly DA. The frequency and outcome of biliary atresia in the UK and Ireland. *Lancet* 2000; **355**: 25–29.

43. Varela-Fascinetto G, Castaldo P, Fox IJ, Sudan D, Heffron TG, Shaw BW, Langnas AN. Biliary atresia-polysplenia syndrome: surgical and clinical relevance in liver transplantation. *Ann Surg* 1998; **227**: 583–589.

44. Shen O, Rabinowitz R, Yagel S, Gal M. Absent gallbladder on fetal ultrasound: prenatal findings and postnatal outcome. *Ultrasound Obstet Gynecol* 2011; **37**: 673–677.

45. Dreux S, Boughanim M, Lepinard C, Guichet A, Rival JM, de Becdelievre A, Dugueperoux I, Muller F. Relationship of non-visualization of the fetal gallbladder and amniotic fluid digestive enzymes analysis to outcome. *Prenat Diagn* 2012; **32**: 423–426.

46. Bardin R, Ashwal E, Davidov B, Danon D, Shohat M, Meizner I. Nonvisualization of the Fetal Gallbladder: Can Levels of Gamma-Glutamyl Transpeptidase in Amniotic Fluid Predict Fetal Prognosis?. *Fetal Diagn Ther* 2016; **39**: 50-55.

47. Shen O, Rabinowitz R, Yagel S, Gal M. Comment on ‘‘Relationship of nonvisualization of the fetal gallbladder and amniotic fluid digestive enzymes analysis to outcome’’. *Prenat Diagn* 2012; **32**: 1119–1120.

48. Nakada K, Kawaguchi F, Wakisaka M, Nakada M, Enami T, Yamate N. Digestive tract disorders associated with asplenia/polysplenia syndrome. *J Pediatr Surg* 1997; **32**: 91-94.

49. Ditchfield MR. Intestinal rotational abnormalities in polysplenia and as- plenia syndromes. *Pediatr Radiol* 1998; **28**: 303-306.

50. Collins DC. 71 000 human appendix specimens. A final report, summarizing forty years’ study. *Am J Proctol* 1963; **14**: 265-281.

51. Ladd WE. Congenital obstruction of the duodenum in children. *N Engl J Med* 1932; **206**: 277-280.

52. Pockett CR, Dicken BJ, Rebeyka IM, Ross DB, Ryerson LM. Heterotaxy syndrome and intestinal rotation abnormalities: a survey of institutional practice. *J Pediatr Surg* 2013; **48**: 2078-2083.

53. Loomba R, Shah PH, Anderson RH. Fetal magnetic resonance imaging of malformations associated with heterotaxy. *Cureus* 2015; **7**: e269.

54. Kheiri, M, Lesieur, E, Dabadie, Colombani M, Capelle M, Sigaudy S, Guidicelli B, Heckenroth H, Delagausie P, Pico H, Philip N, Bretelle F, Gorincour G. Prenatal diagnosis of bowel malposition using T2-weighted fetal MRI sequences. *Diagn Interv Imaging* 2016; **9**: 857-861.

Table 1. General characteristics of the included studies.

Author	Year	Country	Study design	Period analysed (year)	GA at diagnosis (week)	Heterotaxy	Fetuses (n)	Time at follow-up
Gottschalk[25]	2016	Germany	Retrospective	1999-2013	24.0±6.7	LAI, RAI	165	29 months
Gaur[26]	2016	United States	Retrospective	2008-2013	23.0±4.2	LAI, RAI	15	NS
Escobar-Diaz[27]	2014	United States	Retrospective	1995-2011	22 (19-30)	LAI, RAI	154	5 years
Lee[28]	2014	Korea	Retrospective	1999-2011	26.9 (16.5-38.6)	LAI, RAI	71	26.5 months (1-138)
Nemec[29]	2012	Austria	Retrospective	2002-2009	NS	LAI, RAI	5	NS
Özkutlu[30]	2011	Turkey	Retrospective	1999-2006	29.2 (21-37)	LAI, RAI	6	NS
Paladini[31]	2011	Italy	Retrospective	2004-2009	22 (13-34)	LAI, RAI	22	NS
Pepes[32]	2009	United Kingdom	Retrospective	1998-2008	18 (12-29)	LAI	41	NS
Yan[33]	2008	Singapore	Retrospective	1998-2005	21.3 (18-33)	LAI, RAI	22	NS
Taketazu[34]	2006	Canada	Retrospective	1992-2002	24.3±6.4	LAI, RAI	71	NS
Pasquini[35]	2005	United Kingdom	Prospective	1997-2003	25 (18-39)	LAI, RAI	8	NS
Lin[14]	2002	Taiwan	Retrospective	1994-1998	NS	LAI, RAI	29	0-2 years
Hoefstaetter[36]	2000	Germany	Retrospective	1995-2000	22.2 (21-25)	LAI, RAI	7	NS
Abuhamad[12]	1999	United States	Prospective	1995-1998	20.1 (17.4-24.4)	LAI, RAI	8	NS
Atkinson[37]	1998	United States	Retrospective	1991-1997	26 (18-36)	LAI, RAI	13	NS
Phoon[38]	1996	United States	Retrospective	1990-1994	NS	LAI	10	1-24 months

GA: gestational age; NS: not specified; LAI: left atrial isomerism; RAI: right atrial isomerism

Table 2. Quality assessment of the included studies according to Newcastle-Ottawa Scale (NOS) a study can be awarded a maximum of one star for each numbered item within the Selection and Outcome categories. A maximum of two stars can be given for Comparability.

Author	Year	Selection	Comparability	Outcome
Gottschalk[25]	2016	★★★	★★	★★★
Gaur[26]	2016	★★	★	★★
Escobar-Diaz[27]	2014	★★★	★★	★★★
Lee[28]	2014	★★	★	★★
Nemec[29]	2012	★★	★	★★
Özkutlu[30]	2011	★★	★★	★★
Paladini[31]	2011	★★	★	★
Pepes[32]	2009	★★★	★★	★★★
Yan[33]	2008	★★★	★	★★
Taketazu[34]	2006	★★★	★★	★★★
Pasquini[35]	2005	★★	★	★
Lin[14]	2002	★★	★	★★
Hoefstaetter[36]	2000	★★	★★	★★
Abuhamad[12]	1999	★★	★	★★
Atkinson[37]	1998	★★	★	★★
Phoon[38]	1996	★★	★★	★★

Table 3. Pooled proportions (PP) for the prevalence of associated intra-cardiac anomalies (ICA) anomaly in fetuses with left atrial isomerism (LAI) and right atrial isomerism RAI.

ICA	Studies	Fetuses (n/N)	PP (95% CI)	I^2 (%)		Studies	Fetuses (n/N)	PP (95% CI)	I^2 (%)
	Left isomerism					***Right isomerism***			
AVSD	15	205/386	59.28 (44.0-73.7)	85.5		13	180/246	72.86 (60.4-83.7	70.3
VSD	13	27/233	10.99 (3.1-22.9)	77.2		12	4/193	2.65 (0.9-5.3)	0
ASD	13	22/233	19.61 (6.8-37.0)	85.2		12	36/193	21.49 (2.8-50.9)	94.0
Single ventricle	13	56/347	13.76 (6.5-23.3)	71.8		12	104/238	37.84 (18.1-60.0)	89.9
LVOTO	15	35/386	8.17 (3.7-14.21)	59.4		13	18/246	6.91 (3.5-11.3)	21.8
CoA	15	18/386	4.57 (1.4-9.4)	58.8		13	5/246	3.01 (1.3-5.54)	0
RVOTO	15	108/386	35.49 (21.4-51.0)	86.3		13	173/246	67.43 (56.2-77.8)	61.3
Cono-truncal anomalies	15	75/386	21.23 (16.0-27.0)	26		13	109/246	40.06 (28.0-52.8)	68.2
TGA	15	36/386	10.98 (5.0-18.8)	70.1		13	42/246	21.33 (10.9-34.1)	74.8
PLSVC	13	109/341	28.49 (17.0-41.6)	77.8		12	100/221	41.80 (28.9-55.3)	67.2
Interrupted IVC	15	336/386	89.15 (80.5-95.5)	75.4		13	11/246	4.86 (2.6-7.8)	0
Juxtaposition Ao/IVC	15	2/386	1.19 (0.3-2.5)	0		9	127/173	81.50 (59.2-96.2)	89.1
TAPVR	15	30/381	9.85 (5.4-15.5)	48.4		13	102/234	41.87 (28.4-56.0)	72.9
Dextrocardia	11	65/262	25.87 (13.3-40.9)	77.6		12	57/239	24.25 (10.4-41.6)	85.1
Arrhythmias	13	123/378	36.73 (26.9-47.2)	66.9		10	2/218	1.30 (0.2-3.2)	0

AVSD: atrio-ventricular septal defect; VSD: ventricular septal defect; ASD: atrial septal defect; LVOTO: left ventricular outflow tract obstruction; CoA: coarctation of aorta; RVOTO: right ventricular outflow tract obstruction; TGA: transposition of the great arteries; PLSVC: persistent left superior vena cava; IVC: inferior vena cava; Ao: aorta; TAPVR: Total anomalous pulmonary venous return

Table 4. Pooled proportions (PP) for the prevalence of associated cardiac arrhythmias in fetuses with left atrial isomerism (LAI) and right atrial isomerism RAI.

	Studies	Fetuses (n/N)	PP (95% CI)	I^2 (%)		Studies	Fetuses (n/N)	PP (95% CI)	I^2 (%)
	Left isomerism					***Right isomerism***			
Arrhythmias (overall)	13	123/378	36.73 (26.9-47.2)	66.9		10	2/218	1.30 (0.2-3.2)	0
AVB (overall)	11	96/367	28.82 (16.9-42.5)	82.3		9	1/216	1.14 (0.1-3.0)	0
I degree AVB	11	0/367	0 (0-1.5)	0		9	0/216	0 (0-2.4)	0
II degree AVB	11	2/367	0.72 (0.1-1.9)	0		9	0/216	0 (0-2.4)	0
III Degree AVB (CAVB)	11	93/367	26.51 (15.0-40.0)	82.5		9	1/216	1.14 (0.1-3.0)	0
Tachycardia	11	5/367	1.64 (0.3-4.2)	41		9	0/216	0 (0-2.4)	0

AVB: atrioventricular block; CAVB: complete AVB

Table 5. Pooled proportions (PP) for the prevalence of associated extra-cardiac anomalies (ECA) anomaly in fetuses with left atrial isomerism (LAI) and right atrial isomerism RAI.

ECA	Studies	Fetuses (n/N)	PP (95% CI)	I^2 (%)		Studies	Fetuses (n/N)	PP (95% CI)	I^2 (%)
	Left isomerism					***Right isomerism***			
Polysplenia	10	134/236	56.63 (48.1-65.0)	65.3		9	2/159	2.03 (0.4-4.8)	0
Asplenia	9	14/226	7.14 (2.1-14.9)	60		9	138/159	87.59 (75.5-96.0)	69.4
Abnormal stomach position	8	37/65	59.39 (38.1-79.0)	58.7		7	44/76	54.53 (38.5-70.1)	36.8
Abnormal liver position	6	24/53	32.54 (11.9-57.6)	68.5		7	50/76	45.89 (11.3-83.0)	90.1
Abnormal hepatobiliary tract	9	17/278	8.02 (3.5-14.3)	46.7		9	5/179	3.75 (0.5-9.8)	54.6
Intestinal malrotation	9	46/278	14.21 (2.5-33.1)	90.2		9	47/179	27.12 (7.9-52.0)	90.5
Gastrointestinal obstruction	9	12/278	4.91 (2.7-7.7)	0		9	6/179	3.97 (1.6-7.3)	0
Hydrops	11	45/258	11.76 (2.9-25.6)	83.4		10	6/180	3.67 (1.4-6.8)	0
Central nervous system anomalies	9	4/249	2.43(0.9-4.7)	0		9	3/143	2.77 (0.7-6.0)	0
Facial anomalies	9	3/249	1.57 (0.3-3.9)	10		8	1/120	1.45 (0.1-4.3)	0
Thoracic anomalies	9	2/249	1.10 (0.2-2.7)	0		8	1/120	1.92 (0.3-5.1)	0
Abdominal wall defects	9	1/249	0.97 (0.1-2.5)	0		8	2/120	2.38 (0.4-5.8)	0
Limb anomalies	9	0/249	0 (0-1.8)	0		8	2/120	2.44 (0.2-7.2)	0
Kidney anomalies	9	7/249	3.24 (0.6-7.8)	37.8		8	3/120	3.43 (1.0-7.3)	0
Spine anomalies	9	2/249	1.10 (0.2-2.7)	0		8	0/120	0 (0-3.7)	0

Table 6. Pooled proportions (PP) for the prevalence of abnormal perinatal outcome in fetuses affected with left atrial isomerism (LAI) and right atrial isomerism RAI.

	Studies	**Fetuses (n/N)**	**PP (95% CI)**	**I^2**		**Studies**	**Fetuses (n/N)**	**PP (95% CI)**	**I^2**
	Left isomerism					***Right isomerism***			
Termination of the pregnancy	15	99/380	24.79 (14.9-36.2)	76.2		13	77/238	33.46 (22.6-45.3)	63.3
Intrauterine death	15	25/380	6.73 (3.9-10.2)	19.4		13	9/238	4.32 (2.1-7.3)	1.7
Neonatal death	14	34/668	11.12 (6.1-17.3)	50.1		11	36/232	17.55 (8.7-28.7)	69.4
Late death	13	21/365	6.24 (4.0-8.9)	0		11	37/232	14.69 (7.9-23.1)	54.3

Table 7. Pooled proportions (PP) for the prevalence of abnormal surgical outcome in fetuses affected with left atrial isomerism (LAI) and right atrial isomerism RAI.

	Studies	**Fetuses (n/N)**	**PP (95% CI)**	**I^2**		**Studies**	**Fetuses (n/N)**	**PP (95% CI)**	**I^2**
	Left isomerism					***Right isomerism***			
Need for surgery	3	82/109	73.43 (44.4-94.3)	82.9		3	41/62	70.06 (20.7-99.6)	93.1
Biventricular repair	2	64/80	78.16 (64.3-89.4)	34.6		2	3/39	7.42 (0.5-33.7)	79.3
Univentricular repair	2	13/80	17.03 (9.7-25.9)	0		2	36/39	92.60 (66.3-99.5)	79.3
Deaths during or after surgery	3	11/82	26.80 (4.6-58.7)	78.3		3	11/41	27.81 (15.5-42.1)	27.0

Figure Legends

Figure 1: FLOW CHART

Figure 2: Pooled Proportions for the occurence of Intracardiac Anomalies (ICA)

Figure 3: Pooled Proportions for the occurence of Arrhythmias

Figure 4: Pooled Proportions for the occurence of Extracardiac Anomalies (ECA)

Figure 5: Pooled Proportions for the occurence of Intrauterine Death (IUD)

Figure 6: Pooled Proportions for the occurence of Neonatal Death (NND)

Figure 1 FLOW CHART

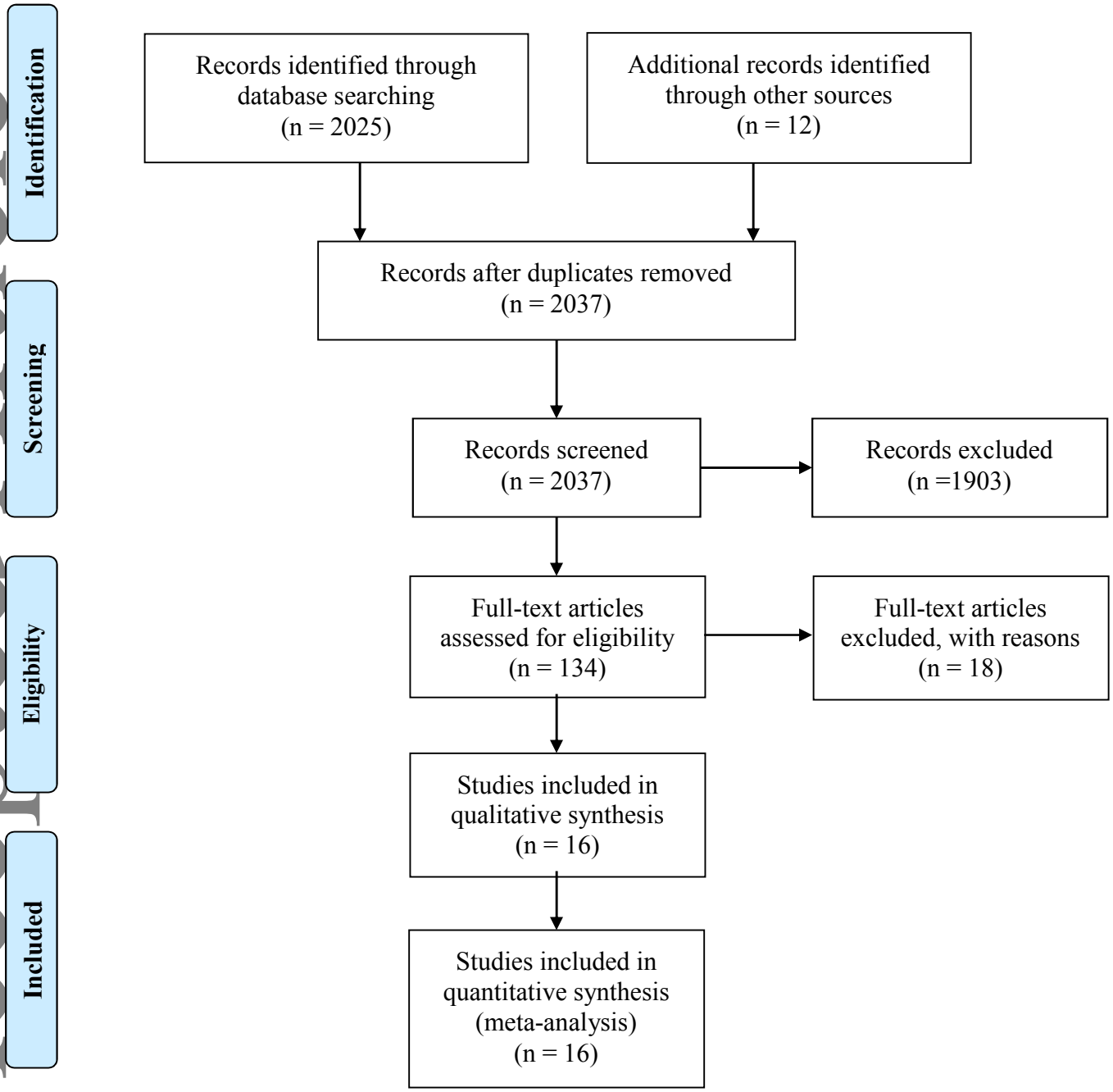

Figure 2 Pooled Proportions for the occurence of Intracardiac Anomalies (ICA)

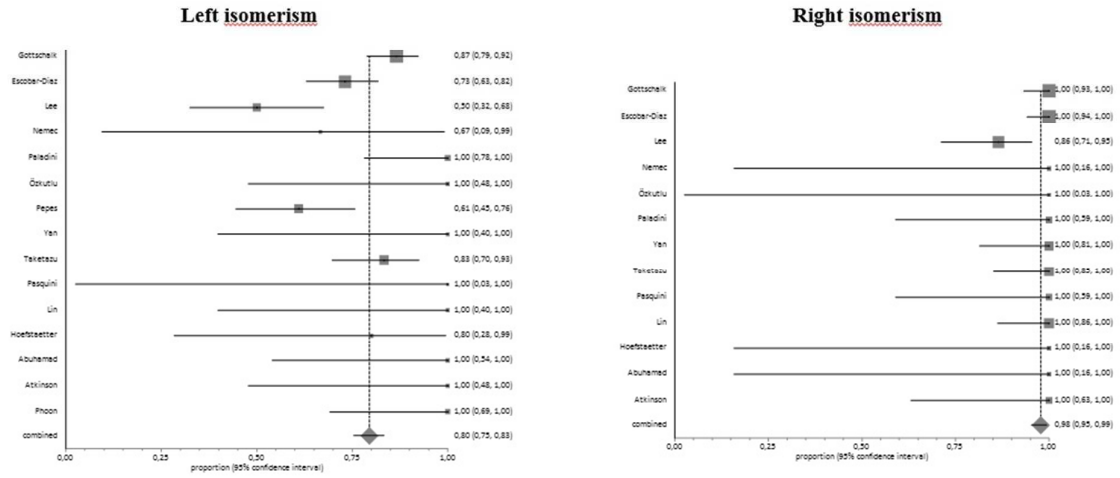

Figure 3 Pooled Proportions for the occurence of Arrhythmias

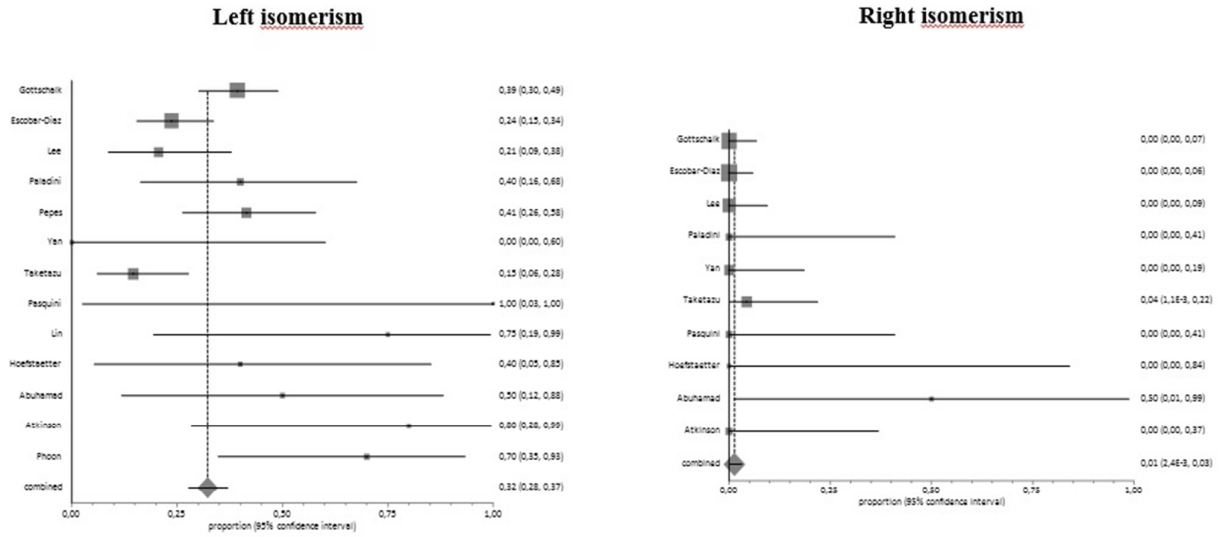

Figure 4 Pooled Proportions for the occurence of Extracardiac Anomalies (ECA)

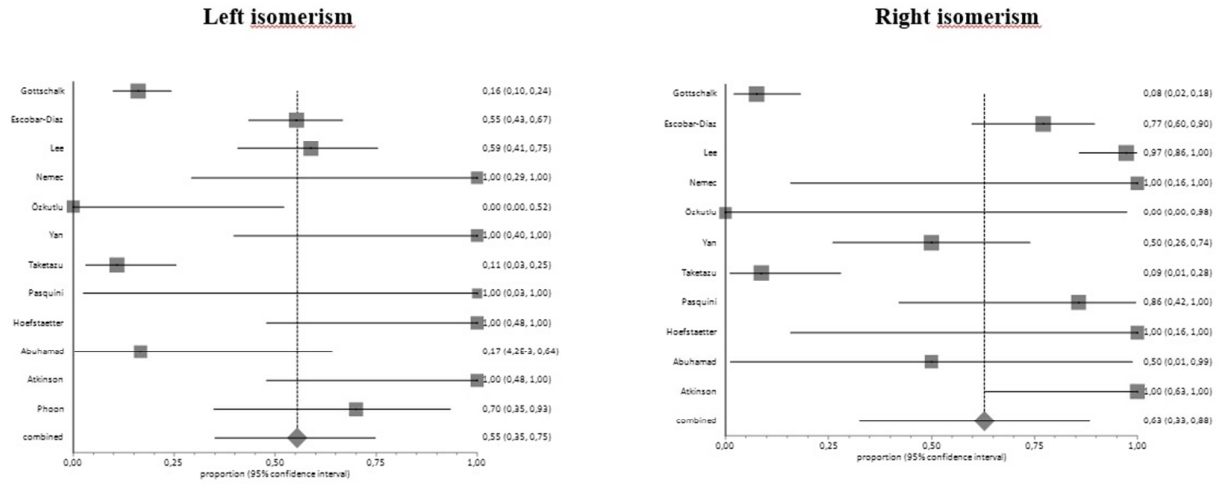

Figure 5 Pooled Proportions for the occurence of Intrauterine Death (IUD)

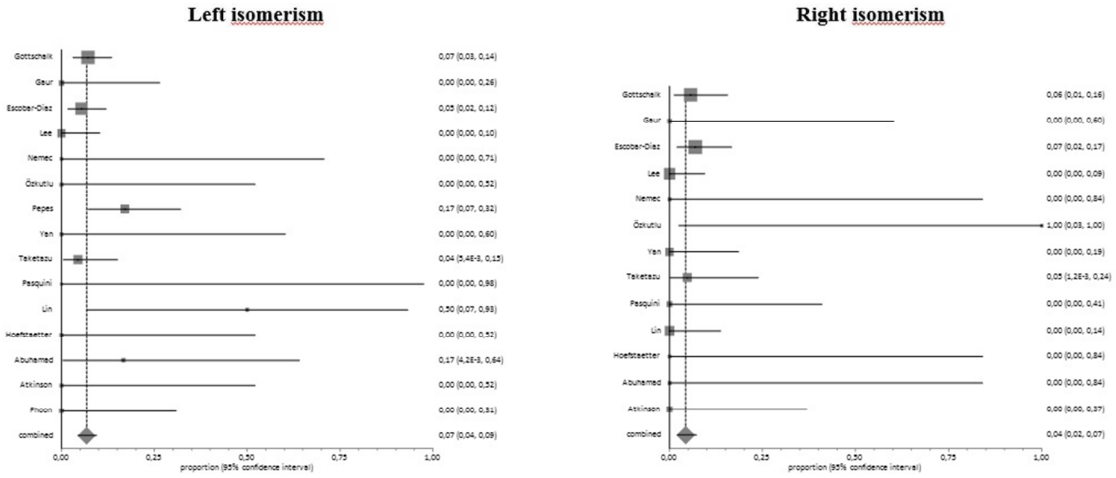

Figure 6 Pooled Proportions for the occurence of Neonatal Death (NND)