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Prenatal diagnosis of total and partial anomalous pulmonary venous connection: multicenter cohort study and meta-analysis

D. PALADINI[1], A. PISTORIO[2], L. H. WU[3], G. MECCARIELLO[1], T. LEI[3], G. TUO[4], G. DONARINI[1], M. MARASINI[4] and H.-N. XIE[3]

[1]*Fetal Medicine & Surgery Unit, Istituto Giannina Gaslini, Genoa, Italy;* [2]*Unit of Epidemiology and Biostatistics, Istituto Giannina Gaslini, Genoa, Italy;* [3]*Department of Ultrasonic Medicine, Fetal Medical Center, First Affiliated Hospital of Sun Yat-sen University, Guangzhou, China;* [4]*Department of Pediatric Cardiology and Cardiac Surgery, Istituto Giannina Gaslini, Genoa, Italy*

KEYWORDS: anomalous venous connection; echocardiography; fetus; meta-analysis of IPD; scimitar syndrome

ABSTRACT

Objectives *The aims of this study were to review systematically literature on and describe the sonographic features and associated anomalies of total (TAPVC) and partial (PAPVC) anomalous pulmonary venous connection and scimitar syndrome (SS).*

Methods *A retrospective cohort study was carried out of cases of TAPVC, PAPVC and SS that underwent comprehensive ultrasound examination, seen over a 20-year period at two tertiary referral centers. Assessed variables included TAPVC subtype, gestational age at diagnosis, area behind the left atrium, ventricular disproportion, vertical vein, pulmonary venous obstruction, mode of diagnosis, association with cardiac and extracardiac conditions, and pregnancy and fetoneonatal outcomes. The outcome was considered favorable if the individual was alive and well (no functional impairment from surgery or cardiac or extracardiac conditions). Cases associated with right isomerism were excluded from the analysis, as TAPVC in these cases was only one of several major cardiac anomalies affecting sonographic signs. A systematic review was performed in order to obtain a synthesis of characteristics associated with TAPVC, PAPVC and SS. The literature search of PubMed and EMBASE (1970–2016) included reviews, case series and case reports. A meta-analysis was conducted only for TAPVC. Random-effects models were used to obtain pooled estimates of the frequencies of clinical characteristics and sonographic features.*

Results *For TAPVC, a total of 15 studies involving 71 patients (including 13 from the current cohort study) were included in the systematic review and meta-analysis. The pooled estimate for the association of TAPVC with congenital heart disease was 28.3% (95% CI, 18.1–41.3%) and with extracardiac anomalies it was 18.5% (95% CI, 10.5–30.6%). Of TAPVC cases, obstructed venous return was observed in 34.1% (95% CI, 22.7–47.7%), a favorable outcome in 43.8% (95% CI, 24.0–65.8%), ventricular disproportion in 59.2% (95% CI, 45.1–72.0%), increased area behind the left atrium in 58.1% (95% CI, 41.1–73.5%) and a vertical vein in 59.3% (95% CI, 41.1–75.3%). Diagnosis was established by using color or power Doppler in 84.9% (95% CI, 67.3–93.9%) of cases. For SS, there were only three studies describing eight cases, to which the current study added another five. Ventricular disproportion was present in three out of nine SS cases for which data were available, but for two of these, there was a concurrent heart anomaly. Color Doppler was used for all SS diagnoses, and four-dimensional echocardiography was useful in two out of six cases in which it was used. Outcome for SS cases was generally good. For PAPVC, there were only five studies describing five cases, to which the current study added another two. Major cardiac anomalies were associated in four out of seven of these cases, and extracardiac anomalies in three out of six cases for which data were available.*

Conclusions *TAPVC can be associated with other cardiac and extracardiac anomalies in a significant percentage of cases. Leading sonographic signs are ventricular disproportion, increased area behind the left atrium and the finding of a vertical vein. Color/power Doppler is the key mode for diagnosis of TAPVC. Obstructed venous return can be expected in roughly one-third of cases of TAPVC and outcome is favorable in less than half of cases. Data for SS and PAPVC are too few to synthesize.*

Correspondence to: Prof. D. Paladini, Istituto Giannina Gaslini, Fetal Medicine & Surgery Unit, Via Gerolamo Gaslini, Genova 16147, Italy (e-mail: dpaladini49@gmail.com)

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INTRODUCTION

Total (TAPVC) and partial (PAPVC) anomalous pulmonary venous connections represent rare anomalies, accounting for 1–3% of all cardiac malformations detected after birth. They are characterized by an anomalous connection of some (PAPVC) or all (TAPVC) pulmonary veins that drain directly, or through one or more systemic veins, into the right atrium instead of the left atrium. TAPVC and PAPVC may occur as isolated lesions or associated with other cardiac defects, often right atrial isomerism[1]. In isolated TAPVC/PAPVC, the outcome depends on the type (total *vs* partial), subtype (supra-, intra- or infracardiac, or mixed) and possible presence of pulmonary venous obstruction[2]. Obstructed TAPVC represents a life-threatening neonatal emergency warranting immediate surgery. However, if TAPVC is detected early and corrected in due time, the prognosis is excellent[3]. The most common association is with cardiosplenic syndromes; in addition, an association with cat-eye syndrome has been reported in some cases, a condition characterized by congenital heart disease (most commonly TAPVC), preauricular tags or pits, anorectal atresia, mild neurodevelopmental delay and other malformations[4]. Scimitar syndrome (SS) represents a specific type of infradiaphragmatic PAPVC associated with right lung hypoplasia.

Prenatal diagnosis of TAPVC/PAPVC/SS has been reported[5–9], but the detection rate of these anomalies remains suboptimal despite the fact that the assessment of the left venoatrial junction is part of the four-chamber-view evaluation, according to national and international guidelines for fetal cardiac screening[10,11].

The aim of this study was to describe the sonographic features associated with TAPVC/PAPVC/SS and to review the relevant literature systematically in order to identify sonographic features for the effective prenatal detection of these rare conditions.

METHODS

Cohort study design and participants

A retrospective cohort study was performed of cases of TAPVC/PAPVC/SS seen over 20 years at two tertiary referral centers (Fetal Medicine and Surgery Unit/Pediatric Cardiology, Istituto G. Gaslini, Genoa and First Affiliated Hospital, Sun Yat-sen University, Guangzhou, China). Cases were identified from the databases of the two hospitals. Comprehensive ultrasound examinations were performed using ultrasound systems equipped fully with three-dimensional (3D) transducers (GE Voluson Expert 730, E8 and E10; GE Medical Systems, Zipf, Austria). Detailed fetal echocardiography was performed in all fetuses, using two-dimensional (2D) color and pulsed-wave Doppler. Whenever possible, in the last 10 years, four-dimensional (4D) echocardiography (spatiotemporal image correlation; STIC) was used in addition to conventional 2D ultrasound. Inclusion criteria were prenatal diagnosis of isolated TAPVC or PAPVC, known pregnancy and fetoneonatal outcomes, and videoclips or 4D volume datasets available for review. Cases of TAPVC with associated cardiosplenic syndrome were excluded as most major cardiac anomalies present in situs anomalies have an effect on sonographic signs, which would confound the study aim to assess the most common features of isolated TAPVC.

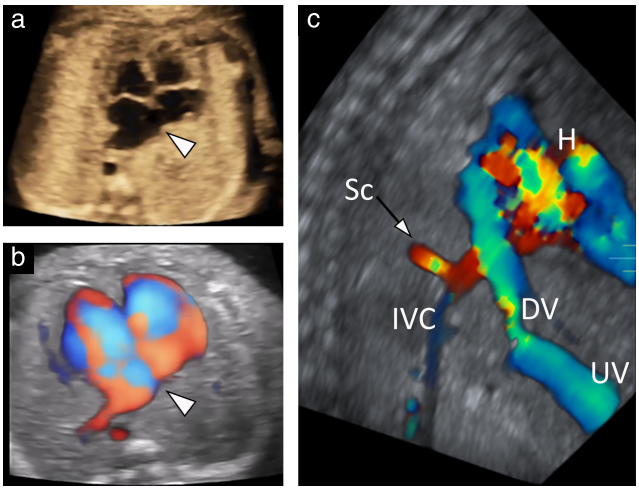


Figure 1 Imaging criteria used to diagnose scimitar syndrome in fetus (at 22 gestational weeks): (a) in four-chamber view, there is mesocardia due to moderately hypoplastic right lung and connection of right-sided pulmonary veins to left atrium is not visible (arrowhead); (b) on power Doppler, absence of right pulmonary venous drainage into left atrium is confirmed (arrowhead); and (c) on spatiotemporal image correlation, three-dimensional color Doppler reconstruction demonstrates scimitar vein (Sc) draining into inferior vena cava (IVC). DV, ductus venosus; H, heart; UV, umbilical vein.

TAPVC was diagnosed when all four pulmonary veins did not drain into the left atrium. PAPVC was diagnosed when three or fewer pulmonary veins did not drain into the left atrium. SS was diagnosed when the following three features were found: meso/dextrocardia due to a hypoplastic right lung; failure to demonstrate (on color/power Doppler) the connection between the right pulmonary veins and the left atrium; and detection (on color/power Doppler) of a vertical vein (the scimitar vein) collecting blood from the right pulmonary veins draining into the caval system (Figure 1).

Variables considered in the analysis were: type (TAPVC, PAPVC or SS) and subtype (supra-, intra- or infracardiac, or mixed) of anomaly, gestational age at diagnosis, sonographic signs, mode of diagnosis (grayscale, color/power Doppler or STIC), presence of pulmonary venous obstruction, association with cardiac, extracardiac or genetic conditions with specific reference to cat-eye syndrome, and pregnancy and fetoneonatal outcomes.

In terms of the assessed echocardiographic variables, area behind the left atrium was considered increased if the venous confluence/vertical vein was seen at that level, or if it exceeded the 1.27 cut-off limit, as described by Kawazu *et al.*[12]. Ventricular disproportion was defined as the ratio of right ventricular to left ventricular diameter

of ≥ 1.5[13]. Pulmonary obstruction was defined prenatally as flow velocity of > 0.5 m/s and/or loss of classic pulsatile flow.

Outcome was considered favorable if the individual was alive and well (no sequelae from surgery and no obvious functional impairment from cardiac or extracardiac conditions). Outcome was considered unfavorable in cases of termination of pregnancy, neonatal or infant death, or major functional impairment from cardiac or extracardiac conditions.

Systematic review and meta-analysis

The present meta-analysis was developed in line with the Preferred Reporting Items for Systematic reviews and Meta-Analyses (PRISMA) statement and follows prespecified rules for study selection, eligibility criteria, data extraction, quality assessment and statistical analysis[14].

Search strategy

A systematic literature search of PubMed and EMBASE was carried out for studies from 1970 up to and including December 2016. The final search was restricted to reports in English and all duplicates were removed. The following search strategies were used to retrieve all studies from databases: ((‘total’ OR ‘partial’) AND ‘anomalous pulmonary venous return’ AND (‘prenatal diagnosis’ OR ‘fetus’ OR ‘fetal’)); ((‘total’ OR ‘partial’) AND ‘anomalous pulmonary venous connection’ AND (‘prenatal diagnosis’ OR ‘fetus’ OR ‘fetal’)).

Study selection

All studies (reviews, case series and case reports) regarding the diagnosis of TAPVC, PAPVC or SS were included in the literature search. Articles not addressing TAPVC or PAPVC were excluded. Abstracts and reports from meetings were included if study results were published in the abstracts book.

Studies were selected initially on the basis of their title and abstract content. Two researchers (D.P. and G.M.) worked in a pair to review each abstract for inclusion, blinded to each other’s choices. The resultant list of 108 included articles was discussed by the two researchers to ensure accuracy of the final decision (Figure 2). Hard copies of selected studies were then collated and examined to ratify their study eligibility. Redundancy due to studies reporting on the same patient groups was checked, and duplications removed or considered for their more detailed information. The extraction of data from full-length articles was performed independently by two researchers (D.P. and G.M.) and key elements from each article were entered into predefined forms. The following information was collected from each study: study design, diagnosis and subtype, presence of associated congenital heart disease (CHD) or other extracardiac anomaly, presence of associated cat-eye syndrome, presence of and gestational age at ventricular disproportion, increased area behind the left atrium (including visualization of pulmonary vein connection behind the left atrium), detection of vertical veins, diagnosis suspected primarily on color or power Doppler diagnosis of obstructed abnormal return, diagnostic improvement with 3D/4D imaging, and pregnancy and neonatal outcomes.

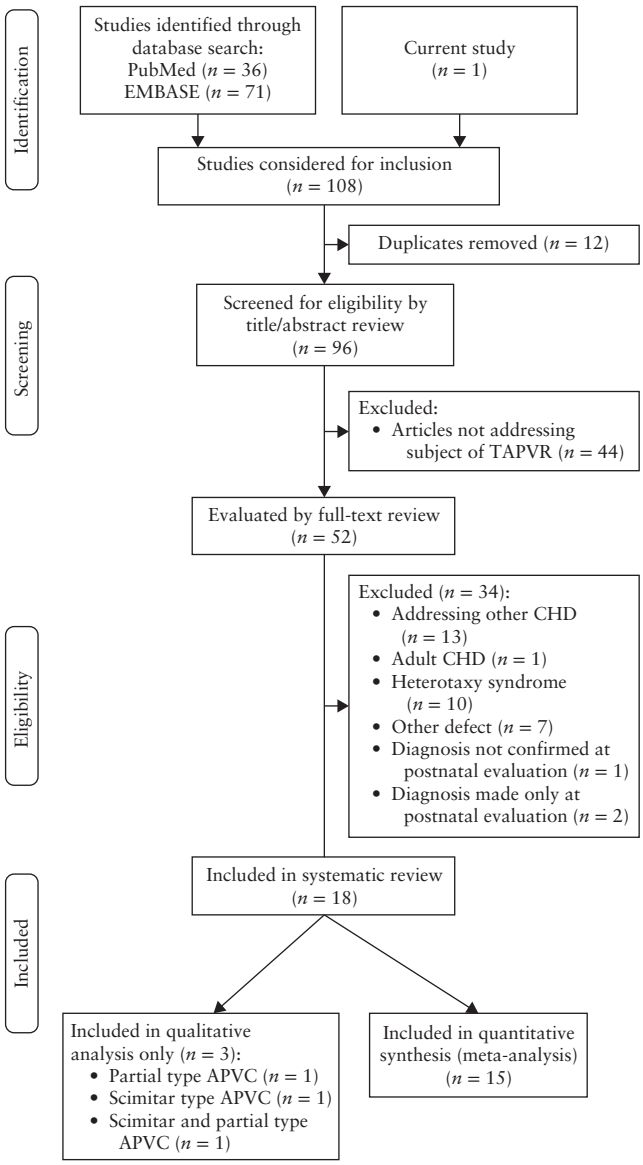


Figure 2 Flowchart for selection of studies on total/partial anomalous pulmonary venous connection (APVC) for inclusion in meta-analysis. CHD, congenital heart disease; TAPVR, total anomalous pulmonary venous return.

Quality evaluation

Newcastle–Ottawa Scale[15] analysis was undertaken by two researchers (D.P. and G.M.) to evaluate the quality of the studies included in the systematic review. For each study, a judgment of selection, comparability and outcome items was given and reported in Table S1. Disagreement on single items of the scale was resolved, when necessary, by gaining the consensus of the two authors.

Statistical analysis

Proportions were combined using meta-analytic methods. For each study, the outcome variable was expressed in terms of rate with 95% CI, weights were calculated and pooled estimates were calculated according to the random-effects model (REM) and displayed in forest plots.

To evaluate the heterogeneity of effects in individual studies, the following indices were calculated[16]: Q, degrees of freedom $(k-1)$, I^2 and T. Whenever the difference between Q and degrees of freedom was <0, it was considered plausible that the studies have a common effect size. I^2 was calculated as a measure of the percentage of dispersion that could not be explained by within-study error. In fact, I^2 reflects the proportion of the observed variance that could be explained by real differences in effect sizes. I^2 was considered very low when $\leq 25\%$, low when $>25\%$ and $\leq 50\%$, moderate when $>50\%$ and $\leq 75\%$, and high when $>75\%$, according to Higgins *et al.*[17]. The most important measure is τ, which is an indicator of the dispersion of the true effects. In the case of a common true effect, $Q-\text{df}$ is ≤ 0 and $T=0$, and the fixed-effects model can be applied. However, if the presence of different true effects is more plausible, $Q-\text{df}$ is >0 and T is >0, and, therefore, the REM should be applied. Due to the high level of heterogeneity, REMs were used to obtain all pooled estimates.

In the REMs (DerSimonian–Laird method), the following weight formula was used: $w_i^* = 1/(v_i+\tau^2)$, where v_i is the within-study variance and τ is the DerSimonian–Laird estimate of between-study variance of the population of studies[16]. Each weight is therefore calculated as the inverse of the variance which, in the REM, is the sum of v_i and τ^2. In the forest plots, 'relative weights' are reported: each weight is divided by the sum of all weights and multiplied by 100 to obtain a percentage of the total weight. Under the REM, small studies have more impact weight in comparison to the ones calculated under the fixed-effects model, in which the impact of small studies is trivial with respect to the impact of large studies.

Finally, correlation between quantitative variables was evaluated using Spearman's rank correlation coefficient (r_S) and classified as follows: $r_S<0.4$ is poor, ≥ 0.4–0.80 is moderate and ≥ 0.80 is good correlation.

Statistical analyses were performed using the software Comprehensive Meta Analysis (CMA), version 3.3.70 (Biostat Inc., Englewood, NJ, USA).

RESULTS

A total of 15 studies[5,8,9,12,18–27], including the present one, reporting on 71 patients were included in the systematic review and meta-analysis. Three additional studies[28–30] were included only in the systematic review and not in the meta-analysis. Characteristics of patients with a postnatally validated diagnosis of TAPVC are reported in Tables 1–3. SS and PAPVC cases were excluded from the meta-analysis, but included in the systematic review. The characteristics of the studies reporting on SS are reported

Table 1 Associated anomalies and outcome of 71 fetuses with postnatally confirmed diagnosis of total anomalous pulmonary venous connection (TAPVC), reported in 15 clinical studies

Study	n	*TAPVC subtype* (n)	*Associated CHD* (n (%))	*Associated extra-cardiac anomaly* (n (%))	*Outcome* (n)	*Favorable outcome** (n (%))
Allan (2001)[5]	4	Supra (1), Intra (2), Infra (1)	0 (0)	1 (25)	A-OP (1), NND (3)	1 (25)
Chen (2006)[18]	1	Mixed (1)	1 (100)	0 (0)	NND (1)	0 (0)
Chen (2013)[19]	1	—	0 (0)	1 (100)	TOP (1)	0 (0)
Ganesan (2014)[20]	5	Supra (4), Infra (1)	1 (20)	0 (0)	A-OP (5)	5 (100)
Kawazu (2014)[12]	1	Supra (1)	0 (0)	0 (0)	A-OP (1)	1 (100)
Laux (2013)[21]	10	Supra (5), Intra (1), Infra (3), Mixed (1)	1 (10)	0 (0)	A-OP (9), NND (1)	9 (90.0)
Lee (2010)[22]	1	Supra (1)	1 (100)	0 (0)	NND (1)	0 (0)
Patel (2005)[23]	5	Supra (4), Mixed (1)	3 (60)	1 (20)	NND (5)	0 (0.0)
Peng (2012)[24]	5	Supra (2), Intra (3)	1 (20)	0 (0)	A-OP (1), TOP (4)	1 (20.0)
Seale (2012)[25]	7	Supra (4), Intra (2), Infra (1)	2 (28.6)	1 (14.3)	A-OP (7)	7 (100)
Tongsong (2016)[26]	8	Supra (4), Intra (2), Infra (2)	4 (50.0)	—	A-OP (3), TOP (4), IUFD (1)	3 (37.5)
Valsangiacomo (2003)[8]	2	Supra (1), Infra (1)	1 (50.0)	0 (0)	NND (2)	0 (0)
Volpe (2007)[27]	7	Supra (3), Intra (2), Infra (2)	0 (0)	2 (28.6)	A-OP (4), TOP (2), NND (1)	4 (57.1)
Wessels (1996)[9]	1	Intra (1)	0 (0)	0 (0)	NND (1)	0 (0)
Current study	13	Supra (6), Intra (7)	2 (15.4)	3 (23.1)	A-OP (3), TOP (6), NND (4)	3 (23.1)

Only first author of each study is given. Cases of partial anomalous pulmonary venous connection and scimitar syndrome excluded. *Only alive-operated (A-OP) considered as favorable outcome. CHD, congenital heart disease; Infra, infracardiac; Intra, intracardiac; IUFD, intrauterine fetal death; NND, neonatal death; Supra, supracardiac; TOP, termination of pregnancy.

Table 2 Sonographic findings of 71 fetuses with postnatally confirmed diagnosis of total anomalous pulmonary venous connection, reported in 15 clinical studies

Study	n	*Associated cat-eye syndrome* (n *(%)*)	*VD* (n *(%)*)	*GA at diagnosis of VD (weeks, median (range))*	*Increased area behind LA* (n *(%)*)	*Detection of vertical vein* (n *(%)*)
Allan (2001)[5]	4	0 (0)	4 (100)	25 (19–32)	0 (0)	0 (0)
Chen (2006)[18]	1	0 (0)	0 (0)	—	0 (0)	0 (0)
Chen (2013)[19]	1	1 (100)	1 (100)	22	—	—
Ganesan (2014)[20]	5	0 (0)	2 (40.0)	23 (18–28)	5 (100)	5 (100)
Kawazu (2014)[12]	1	0 (0)	0 (0)	—	1 (100)	—
Laux (2013)[21]	10	—	6 (60.0)	28 (24–37)	0 (0.0)	9 (90.0)
Lee (2010)[22]	1	0 (0)	0 (0)	—	1 (100)	1 (100)
Patel (2005)[23]	5	0 (0)	—	—	4 (80.0)	5 (100)
Peng (2012)[24]	5	0 (0)	1 (20.0)	31	2 (40.0)	2 (40.0)
Seale (2012)[25]	7	0 (0)	4/5*(80.0)	27 (26–29)	5 (71.4)	5 (71.4)
Tongsong (2016)[26]	8	0 (0)	—	—	4/6*(66.7)	2 (25.0)
Valsangiacomo (2003)[8]	2	0 (0)	2 (100)	—	2 (100)	2 (100)
Volpe (2007)[27]	7	0 (0)	4 (57.1)	33.4 (32–35)	4 (57.1)	3 (42.9)
Wessels (1996)[9]	1	0 (0)	1 (100)	25	1 (100)	1 (100)
Current study	13	1 (7.7)	9 (69.2)	28 (23–34)	7 (53.8)	7 (53.8)

Only first author of each study is given. Cases of partial anomalous pulmonary venous connection and scimitar syndrome excluded. *Data missing for two cases. GA, gestational age; LA, left atrium; VD, ventricular disproportion.

Table 3 Additional characteristics and mode of diagnosis for 71 fetuses with postnatally confirmed diagnosis of total anomalous pulmonary venous connection (TAPVC), reported in 15 clinical studies

Study	n	*GA at diagnosis (weeks, median (range))*	*Diagnosis suspected on color/power Doppler** (n *(%)*)	*Diagnosis of obstr abn rtrn* (n *(%)*)	*Diagnosis improved with 4D imaging*† (n *(%)*)
Allan (2001)[5]	4	20 (19–32)	1 (25.0)	1 (25.0)	NA
Chen (2006)[18]	1	34	0 (0)	0 (0)	0 (0)
Chen (2013)[19]	1	22	NA	NA	NA
Ganesan (2014)[20]	5	21 (18–28)	5 (100)	2 (40.0)	NA
Kawazu (2014)[12]	1	31	NA	NA	NA
Laux (2013)[21]	10	27 (24–37)	10 (100)	4 (40.0)	NA
Lee (2010)[22]	1	21	NA	0 (0)	1 (100)
Patel (2005)[23]	5	32 (24–33)	5 (100)	3 (60.0)	NA
Peng (2012)[24]	5	28 (24–32)	NA	1 (20.0)	4 (80.0)
Seale (2012)[25]	7	26 (17–29)	7 (100)	0 (0)	NA
Tongsong (2016)[26]	8	21.5 (16–30)	8 (100)	NA	NA
Valsangiacomo (2003)[8]	2	30‡	2 (100)	1 (50.0)	NA
Volpe (2007)[27]	7	23 (21–32)	0 (0.0)§	3 (42.9)	4/4 (100)¶
Wessels (1996)[9]	1	25	1 (100)	1 (100)	0 (0)
Current study	13	28 (21–34)	12 (92.3)	3 (23.1)	8 (61.5)

Only first author of each study is given. Cases of partial anomalous pulmonary venous connection and scimitar syndrome excluded. *No diagnosis was suspected on pulsed wave Doppler. †Four-dimensional (4D) echocardiography/spatiotemporal image correlation. ‡Data missing for one case. §Data missing for six cases. ¶Data missing for three cases. GA, gestational age; NA, not available; obstr abn rtrn, obstructed abnormal return.

in Table S2[8,28,29] and of those on PAPVC in Tables S3 and S4[8,21,24,28,30].

As shown in Table 1 and Figure 3a, there was a significant association between TAPVC and CHD, with a pooled estimate of 28.3% (95% CI, 18.1–41.3%) and a range of 6–40% in the primary studies, with the exception of three studies[8,23,26] in which there was greater association with CHD (50%, 60% and 50%, respectively). Unexpectedly, there was clear statistical homogeneity of these results ($Q - \mathrm{df} = -0.368$ and $T = 0$; $I^2 = 0.0$) despite the large range in publication year (from 1996 to the current study) and clinical and methodological differences. The association between TAPVC and other extracardiac anomalies (Figure 3b) was lower, with a pooled estimate of 18.5% (95% CI, 10.5–30.6%), and even more evident homogeneity of the results ($Q - \mathrm{df} = -6.216$ and $T = 0$; $I^2 = 0.0$). On the contrary, as shown in Figure 4, there was evident statistical heterogeneity with regard to patient outcome ($Q - \mathrm{df} = 10.833$ and $T = 1.065$; $I^2 = 51.999$). According

to the REMs, the pooled estimate for the proportion of cases with a favorable outcome was 43.8% (95% CI, 24.0–65.8%) with wide variability in the results (percentages in the primary studies ranged from 8.3% in Patel *et al.*[23] to 93.8% in Seale *et al.*[25]). No relationship was observed between the rate of the outcome and the year of publication ($r_S = -0.14$; Figure S1). Cat-eye syndrome was very rarely associated with TAPVC. In fact, only two out of 71 (2.8%) cases showed this association (Table 2).

For sonographic findings, the pooled estimate of the proportion of cases with ventricular disproportion was 59.2% (95% CI, 45.1–72.0%; Figure 5a) and the results were statistically homogeneous ($Q - \mathrm{df} = -0.567$ and $T = 0$; $I^2 = 0.0$). No relationship was observed between the rate of ventricular disproportion and gestational age at diagnosis ($r_S = 0.01$; Figure S2). Increased area behind the left atrium was also observed quite frequently (pooled estimate, 58.1%; 95% CI, 41.1–73.5%; Figure 5b) and rate was quite heterogeneous ($Q - \mathrm{df} = 3.705$ and $T = 0.592$; $I^2 = 27.036$). In fact, in three studies fewer than 50% of cases showed this finding (10% in Allan *et al.*[5], 4.5% in Laux *et al.*[21] and 40% in Peng *et al.*[24]. A moderate inverse relationship was observed between the proportion of cases with increased area behind the left atrium and the ratio of intra to supra and infra types of TAPVC ($r_S = -0.74$; Figure S3). A vertical vein was detected frequently, with a pooled estimate of 59.3% (95% CI, 41.1–75.3%; Figure 5c); heterogeneity was evident ($Q - \mathrm{df} = 5.628$ and $T = 0.725$; $I^2 = 36.013$). No relationship was observed between the rate of a vertical vein and infra- as a proportion of supra- and infracardiac types of TAPVC ($r_S = -0.24$; Figure S4).

As for the mode of diagnosis, TAPVC was suspected most commonly on color/power Doppler (frequency in primary studies was almost always greater than 80%; Figure 6a); the pooled estimate was 84.9% (95% CI, 67.3–93.9%) and the degree of heterogeneity was quite low ($Q - \mathrm{df} = 2.283$ and $T = 0.726$; $I^2 = 22.203$). There were only two studies[5,18] in which the proportion of diagnoses suspected on color/power Doppler was particularly low, being 25.0% and 0%, respectively.

Obstructed pulmonary return was found in 34.1% (95% CI, 22.7–47.7%) of cases (Figure 6b); frequencies were quite homogeneous ($Q - \mathrm{df} = -3.733$ and $T = 0.0$; $I^2 = 0.0$). A moderate correlation was observed between the rate of obstructed abnormal return and infracardiac as a proportion of all other types of TAPVC ($r_S = 0.43$; Figure S5).

Only three published studies described SS, describing eight cases, while the present cohort study comprises five additional ones. Sonographic characteristics and outcome are described in Table S2. Ventricular disproportion was present in three out of nine cases, but in two of them another heart anomaly was present, one of which was possibly responsible for the finding (persistent left superior vena cava draining into the coronary sinus). Color Doppler was always employed to reach the final diagnosis, while 3D/4D ultrasound (STIC) was helpful in two out of the six cases in which it was used. Outcome was generally good (76.9%), with the exception of three cases including two terminations of pregnancy and one neonatal death, all described in the same report[8].

Only five studies described PAPVC[8,21,24,28,30], with SS dealt with separately. There were two cases of PAPVC in the current cohort study and five in the others. Sonographic characteristics and outcome are shown in Tables S3 and S4. As is evident from the very limited number of cases, major CHD were associated in most cases (four out of seven) and extracardiac anomalies in three out of six cases. Association with major CHD was responsible for less-than-optimal fetoneonatal outcome.

DISCUSSION

It should be underlined that all data reported and discussed in this study and meta-analysis regard fetuses with a prenatal diagnosis of TAPVC. It cannot be ascertained as to whether the described sonographic signs were present in undetected cases but missed at screening ultrasound, or were absent and, hence, contributed to the missed detection. This represents an important concept and, of course, limitation of the study because, from population-based studies[25], the detection rate for TAPVC is alarmingly low (< 2%).

Data from the present study indicate that, if cardiosplenic syndromes are excluded, TAPVC is still associated significantly with other CHD (pooled estimate, 28.3%; 95% CI, 18.1–41.3%; Table 1 and Figure 3a). This is in reasonable agreement with postnatal data. In fact, a retrospective multicenter study reported an association rate of 14.2%, excluding both cardiosplenic syndrome and univentricular circulation[31]. At the same time, the differences in the rate of association with extracardiac anomalies (18.5% in our study *vs* 5.5% in Seale *et al.*[31]) and cat-eye syndrome (2.8% in our study (Table 2) *vs* 1.4% in Seale *et al.*[31]) can be explained by the fact that the occurrence of associated cardiac or extracardiac anomalies may lead to a higher level of attention that, in turn, warrants higher accuracy in the diagnosis of TAPVC. Another explanation is that termination of pregnancy is often carried out if TAPVC is associated with other major cardiac or extracardiac anomalies, as was found in this meta-analysis.

Considering the sonographic features associated with TAPVC in the fetus, ventricular disproportion, a larger area behind the left atrium and the presence of a vertical vein are seen frequently in this disease (about 60% of cases in this study had each of these sonographic features; Figure 5). On the other hand, according to the meta-analysis, there is no apparent relationship between ventricular disproportion and advancing gestational age (Figure S2).

The most commonly used imaging mode for diagnosis was power/color Doppler (84.9%; 95% CI, 67.3–93.9%), with a minority of reports showing benefit for spectral Doppler or STIC. In particular, STIC proved

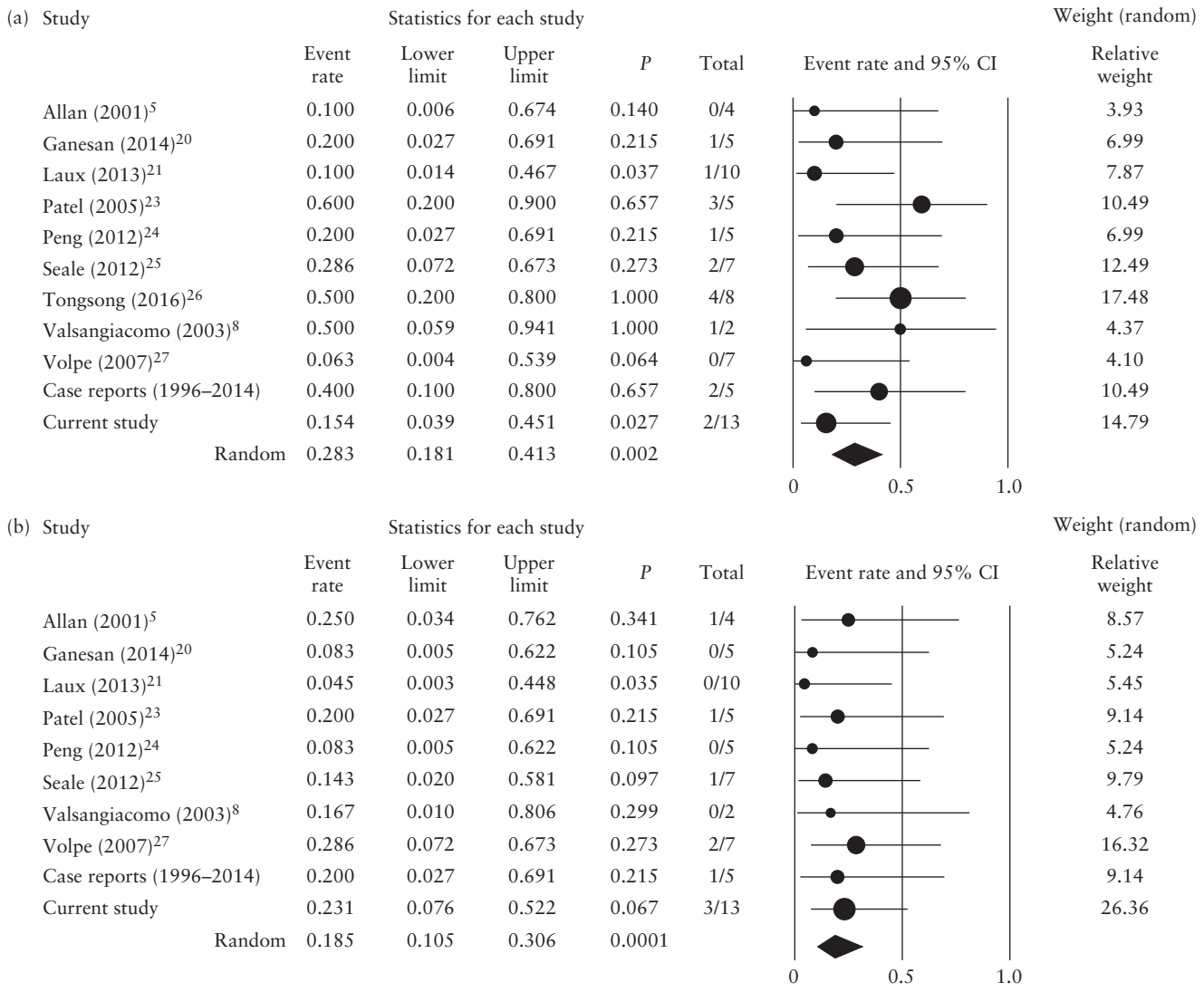


Figure 3 Forest plots for studies on cases of total anomalous pulmonary venous connection, of rate of prenatally detected congenital heart disease reported in 10 primary studies and five case reports[9,12,18,19,22] (a) and extracardiac anomalies reported in nine primary studies and five case reports[9,12,18,19,22] (b). Only first author of each study is given.

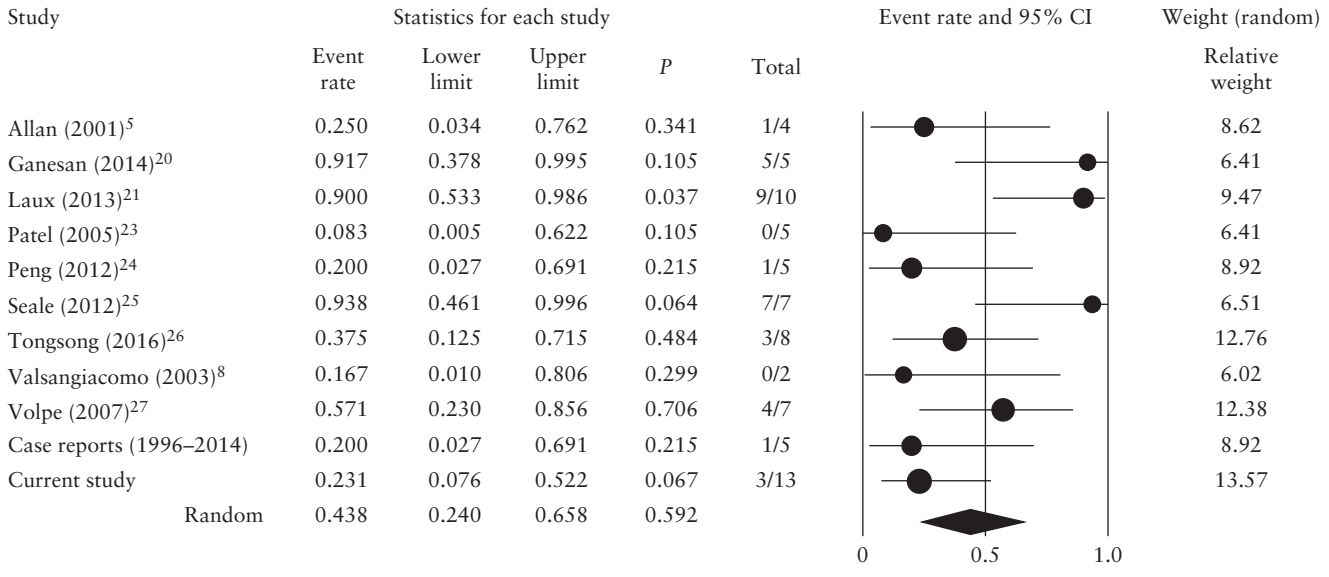
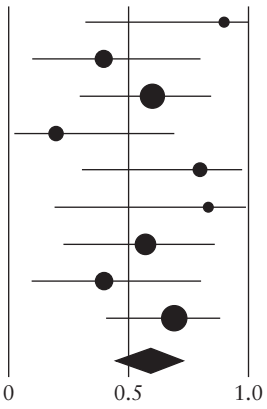


Figure 4 Forest plot of rate of favorable outcome (alive operated) for fetuses with total anomalous pulmonary venous connection, reported in 10 primary studies and five case reports[9,12,18,19,22]. Only first author of each study is given.

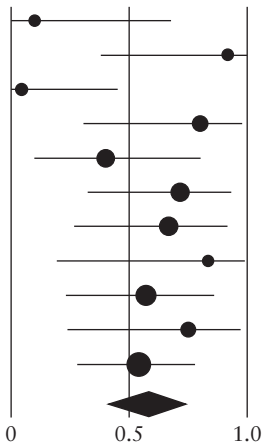
(a)

Study	Event rate	Lower limit	Upper limit	*P*	Total	Weight (random) Relative weight
Allan (2001)[5]	0.900	0.326	0.994	0.140	4/4	3.83
Ganesan (2014)[20]	0.400	0.100	0.800	0.657	2/5	10.21
Laux (2013)[21]	0.600	0.297	0.842	0.530	6/10	20.43
Peng (2012)[24]	0.200	0.027	0.691	0.215	1/5	6.81
Seale (2012)[25]	0.800	0.309	0.973	0.215	4/5	6.81
Valsangiacomo (2003)[8]	0.833	0.194	0.990	0.299	2/2	3.55
Volpe (2007)[27]	0.571	0.230	0.856	0.706	4/7	14.59
Case reports (1996–2014)	0.400	0.100	0.800	0.657	2/5	10.21
Current study	0.692	0.409	0.880	0.177	9/13	23.57
Random	0.592	0.451	0.720	0.199		



(b)

Study	Event rate	Lower limit	Upper limit	*P*	Total	Weight (random) Relative weight
Allan (2001)[5]	0.100	0.006	0.674	0.140	0/4	4.82
Ganesan (2014)[20]	0.917	0.378	0.995	0.105	5/5	4.90
Laux (2013)[21]	0.045	0.003	0.448	0.035	0/10	5.07
Patel (2005)[23]	0.800	0.309	0.973	0.215	4/5	7.75
Peng (2012)[24]	0.400	0.100	0.800	0.657	2/5	10.47
Seale (2012)[25]	0.714	0.327	0.928	0.273	5/7	11.80
Tongsong (2016)[26]	0.667	0.268	0.916	0.423	4/6	11.27
Valsangiacomo (2003)[8]	0.833	0.194	0.990	0.299	2/2	4.51
Volpe (2007)[27]	0.571	0.230	0.856	0.706	4/7	13.28
Case reports (1996–2014)	0.750	0.238	0.966	0.341	3/4	7.36
Current study	0.538	0.282	0.776	0.782	7/13	18.78
Random	0.581	0.411	0.735	0.350		



(c)

Study	Event rate	Lower limit	Upper limit	*P*	Total	Weight (random) Relative weight
Allan (2001)[5]	0.100	0.006	0.674	0.140	0/4	5.17
Ganesan (2014)[20]	0.917	0.378	0.995	0.105	5/5	5.25
Laux (2013)[21]	0.900	0.533	0.986	0.037	9/10	8.68
Patel (2005)[23]	0.917	0.378	0.995	0.105	5/5	5.25
Peng (2012)[24]	0.400	0.100	0.800	0.657	2/5	10.45
Seale (2012)[25]	0.714	0.327	0.928	0.273	5/7	11.59
Tongsong (2016)[26]	0.250	0.063	0.923	0.178	2/8	11.92
Valsangiacomo (2003)[8]	0.833	0.194	0.990	0.299	2/2	4.85
Volpe (2007)[27]	0.429	0.144	0.770	0.706	3/7	12.81
Case reports (1996–2010)	0.667	0.154	0.957	0.571	2/3	7.01
Current study	0.538	0.282	0.776	0.782	7/13	17.02
Random	0.593	0.411	0.753	0.316		

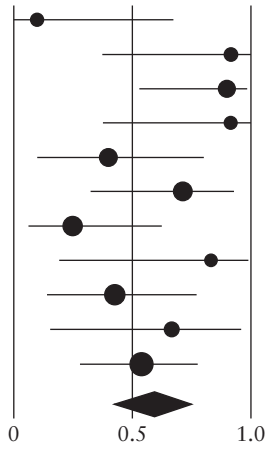


Figure 5 Forest plots for studies on cases of total anomalous pulmonary venous connection, of rate of prenatally detected ventricular disproportion reported in eight primary studies and five case reports[9,12,18,19,22] (a), increased area behind left atrium reported in 10 primary studies and four case reports[9,12,18,22] (b) and vertical vein reported in 10 primary studies and three case reports[9,18,22] (c). Only first author of each study is given.

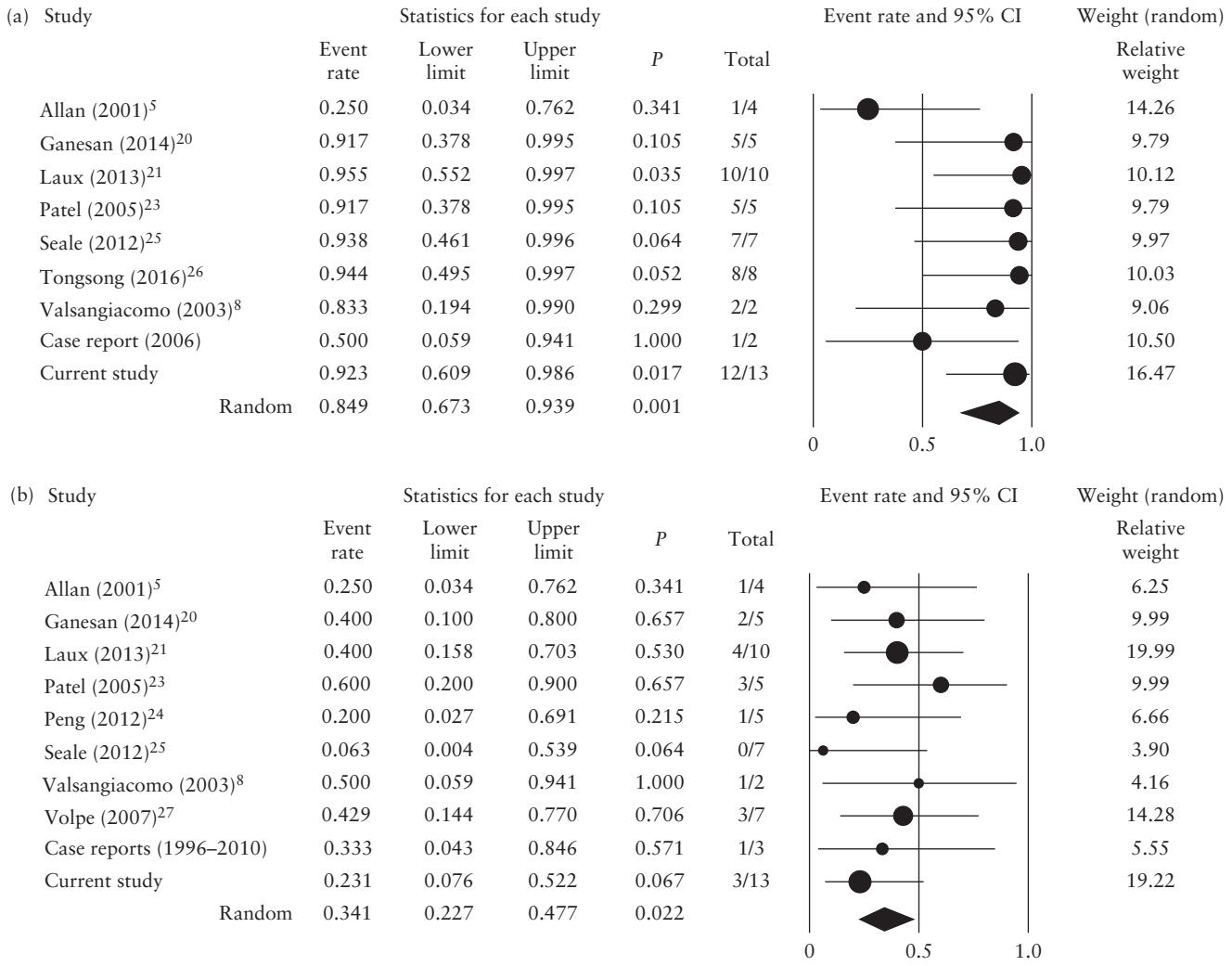


Figure 6 Forest plot of rate of total anomalous pulmonary venous connection (TAPVC) suspected primarily on color/power Doppler reported in eight primary studies and one case report[18] (a) and obstructed abnormal return reported for cases of TAPVC in nine primary studies and three case reports[9,18,22] (b). Only first author of each study is given.

useful for diagnosis in 17 of 24 (71%) cases in which it was employed (Table 3). In our cohort study, the use of multiplanar imaging coupled with volume contrast imaging was quite helpful in assessing challenging cases in which the pulmonary veins were separated from the left atrium by an extremely thin wall. On the contrary, STIC has so far not been demonstrated to be helpful in obstetric screening ultrasound. In such a setting, several national and international guidelines[10,11] recommend the use of grayscale ultrasound to visualize the entrance of at least two pulmonary veins into the left atrium. This evaluation is of the utmost importance for raising the suspicion of TAPVC, as was also underlined by Ganesan *et al.*[20].

A final comment regards the incidence of pulmonary venous obstruction that, in this cohort and meta-analysis, was 34.1% (Figure 6b). In postnatal surgical cases[25], its incidence is 25%, similar to that of the current study. Hence, we can expect one-third of cases to show prenatal evidence of obstruction, most likely including some false-positive cases; this finding is moderately more common in infradiaphragmatic TAPVC (Figures 6b and S5).

To the best of our knowledge, this is the first comprehensive systematic review and meta-analysis exploring the diagnostic signs, outcome and associated anomalies of fetal TAPVC. The relatively small number of patients, different periods of follow-up and differences in pre- and postnatal imaging protocols 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 who may be less or more susceptible to bias. The assessment of potential publication bias was also problematic because of the small number of individual studies. Most of the included studies were small series reporting on only a few cases of TAPVC.

This cohort study adds significantly to the limited number of published reports on SS, contributing five cases to the total of 13 reported in this systematic review of the literature. In this condition, color/power Doppler was

again the diagnostic mode of choice (Figure 1b,c), being able to confirm the absence of right pulmonary venous drainage to the left atrium; STIC was helpful in one of five cases (Figure 1c). In agreement with postnatal data[32,33], good outcome was reported in all but three cases from the same group[8]. Four of the 11 (36.4%) cases reaching term were operated on, a proportion not dissimilar to the 45% reported after birth[34].

The number of cases of PAPVC described prenatally is very small, totaling seven, including two of the current cohort study. The two main features for this defect, which is very rarely diagnosed prenatally, are the high association rates with cardiac and extracardiac major anomalies (four out of seven and three out of six, respectively). It is clear that the associated defects are responsible for the high rate of unfavorable outcome (five out of seven, Table S3).

In conclusion, we have reviewed all cases of prenatally diagnosed TAPVC, PAPVC and SS described in the relevant literature, as well as contributing a significant number of cases for each type of defect from our own series. We have described the major clinical and imaging characteristics that may help in the screening, diagnosis and management of these pathologies in the fetus. We believe that more data are needed to assess the diagnostic role of STIC, due to the rarity of the considered heart defects (TAPVC, PAPVC, SS) and the fact that STIC was used in only a minority of reported cases. Despite the low incidence, we believe that, should TAPVC be diagnosed in a fetus, invasive diagnosis for cat-eye syndrome should be offered, considering that the overall association rate in our series was 2.8% (2/71).

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SUPPORTING INFORMATION ON THE INTERNET

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

Table S1 Newcastle–Ottawa scale quality assessment of 14 studies reporting on fetuses with total anomalous pulmonary venous connection

Table S2 Characteristics of 13 patients with scimitar syndrome, reported on in four clinical studies

Table S3 Clinical characteristics of seven patients with partial anomalous pulmonary venous connection, reported on in six clinical studies

Table S4 Sonographic and Doppler characteristics of seven patients with partial anomalous pulmonary venous connection, reported on in six clinical studies

Figures S1–S5 Forest plots of outcome, sonographic features and associated anomalies reported for cases of prenatally detected total anomalous pulmonary venous connection.