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Prenatal phenotypes and outcomes of left-sided and duplicated inferior vena cava according to hepatic IVC continuity: a retrospective cohort study

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Abstract

Background

Fetal left-sided inferior vena cava (LIVC) and duplicated inferior vena cava (DIVC) are uncommon. Their importance may depend on hepatic IVC continuity and venous drainage, but classifications often combine anatomy and drainage. We characterised prenatal phenotypes, anomalies, and outcomes.

Methods

In this retrospective cohort, singleton fetuses with prenatally diagnosed LIVC or DIVC (1 January 2020-30 September 2025) were classified as type A (hepatic IVC continuity; single LIVC or DIVC) or type B (interrupted hepatic IVC with azygos/hemiazygos continuation; single LIVC). Ultrasound and fetal echocardiography were reviewed; STIC was descriptive. The primary outcome was IUFD after excluding TOP; the secondary outcome was a management composite of TOP or IUFD. Fisher exact tests and Firth penalised regression were used.

Results

Of 20349 screened pregnancies, 167 fetuses were included (151 type A, 16 type B). Isolated variants occurred in 83/151 versus 0/16 fetuses. Type B had more cardiac findings (14/16 [87.5%] versus 29/151 [19.2%]), structural heart disease (11/16 [68.8%] versus 19/151 [12.6%]), and complex or severe cardiac disease (10/16 [62.5%] versus 7/151 [4.6%]); $P < 0.001$ for all. Left isomerism features occurred in 9/16 type B fetuses. Among 161 fetuses with complete outcomes, 122 were liveborn, 32 had TOP, and 7 had IUFD. In the primary analysis excluding TOP (n = 129), IUFD occurred in 0/4 type B and 7/125 type A pregnancies; no adjusted model was stable. Firth analysis suggested associations with structural heart disease (OR 12.47, 95% CI 2.71–62.50) and extracardiac anomalies (OR 15.78, 95% CI 3.13-156.29). The secondary composite comprised 39/161 events and was associated with type B (OR 13.11, 95% CI 3.92–43.81), but this was driven by TOP and no stable adjusted estimate was possible.

Conclusions

The phenotypes differed in cardiac and laterality findings, but an independent effect of drainage pattern on natural fetal death was not established. Type B warrants comprehensive assessment; composites including TOP require cautious interpretation, and STIC remains a visualisation adjunct.

Background

Congenital anomalies of the inferior vena cava (IVC) are a heterogeneous group of developmental variants rather than a single clinical entity. The IVC develops through sequential anastomosis,

regression, and persistence of the posterior cardinal, subcardinal, supracardinal, and hepatocardinal venous systems. Disruption of this process can produce a left-sided IVC (LIVC), duplicated IVC (DIVC), interruption of the hepatic IVC, or combinations of these patterns [1, 2]. These variants are increasingly detected during standardised abdominal and fetal echocardiographic examinations .

LIVC usually results from persistence of the left supracardinal vein with regression of the right infrarenal segment [1]. In the most common form, the left infrarenal IVC joins the left renal vein, which crosses anterior to the abdominal aorta and drains into the right IVC; the hepatic IVC remains patent, and systemic venous return follows the normal pathway to the right atrium. DIVC results from persistence of both supracardinal veins [3]. When the right IVC remains patent and hepatic drainage is normal, DIVC is often an incidental finding. Consequently, neither LIVC nor DIVC should automatically be regarded as a cardiac or haemodynamic disorder. Representative venous patterns are shown in Fig. 1.

Clinical significance changes substantially when the hepatic segment of the IVC is interrupted. Failure of the right subcardinal-hepatocardinal connection prevents direct drainage of infrarenal systemic venous blood into the right atrium, and blood is redirected through the azygos or hemiazygos system [4]. This pattern is closely linked to disorders of left-right patterning [5]. Prenatal and pathological studies have confirmed that interrupted IVC is a consistent component of left atrial isomerism and may occur with complex cardiac or visceral malformations [6, 7]. In larger prenatal cohorts, interruption of the IVC is common among fetuses with left isomerism and is associated with a broad spectrum of cardiac and extracardiac findings [7].

The existing literature remains difficult to translate directly into prenatal counselling because study populations and terminology are heterogeneous [2]. Some studies of isolated interrupted IVC report predominantly favourable postnatal outcomes [8]. In contrast, tertiary fetal cardiology cohorts include a higher burden of complex heart disease, heterotaxy, arrhythmia, and extracardiac anomalies [7, 9]. The terms LIVC, interrupted IVC, azygos continuation, and hemiazygos continuation are sometimes used interchangeably [1, 3], which can obscure which anatomical or physiological feature is most relevant to prognosis.

Prenatal assessment must distinguish an isolated systemic venous variant from a laterality disorder. A structured evaluation should include systemic and pulmonary venous connections, atrial appendage morphology, cardiac rhythm, abdominal situs, and hepatic, biliary, and splenic findings [6]. Extracardiac anomalies may substantially influence postnatal morbidity and therefore require dedicated assessment [9]. A normal cardiac structural examination alone does not exclude milder forms of isomerism [8]. Conversely, interrupted IVC does not necessarily indicate clinically significant heterotaxy in every fetus [4].

Three- and four-dimensional techniques, including STIC, have been proposed to improve visualisation of abnormal systemic venous connections [10]. A recent case report further illustrates the use of STIC for a rare left-sided IVC without a hepatic segment [11]. However, most evidence remains limited to small

series or selected image reviews [2]. Fetal echocardiography is also less reliable for systemic and pulmonary venous anatomy than for intracardiac anatomy [12].

Outcome assessment requires careful definition of the denominator and the competing nature of pregnancy termination [9]. Intrauterine death, neonatal death, infant death, TOP, and postnatal surgical morbidity are distinct outcomes influenced by different factors. TOP is strongly affected by prenatal counselling, gestational age, local policy, and parental preference [9]. It should not be combined uncritically with spontaneous fetal or infant death in a single prognostic endpoint [9]. Postnatal phenotype may also differ from prenatal classification [13]. Reported live-birth and survival estimates can also vary according to cohort design and how TOP is handled [9, 14]. Failure to separate these outcomes may exaggerate risk and produce misleading associations [9].

Given these gaps, we conducted a single-centre retrospective cohort study of fetuses diagnosed prenatally with LIVC or DIVC. Our objectives were to: (1) describe prenatal phenotypes according to anatomical type, hepatic IVC continuity, and drainage pathway; (2) characterise associated cardiac, extracardiac, and laterality-related findings; (3) report pregnancy and infant outcomes using clearly defined denominators and separate TOP from natural death; and (4) describe the feasibility and visualisation findings of STIC in fetuses with suspected complex venous drainage. Comparisons between type A and type B were descriptive and were not interpreted as estimates of the isolated effect of drainage pathway.

Methods

Study design and setting

This was a single-centre, retrospective observational cohort study conducted in the fetal medicine and prenatal ultrasound unit of Lanzhou University Second Hospital, Lanzhou, Gansu, China. We reviewed singleton pregnancies with a prenatal diagnosis of LIVC or DIVC between 1 January 2020 and 30 September 2025. The report was prepared according to the Strengthening the Reporting of Observational Studies in Epidemiology (STROBE) recommendations for cohort studies. The analytical data lock was 30 September 2025. Liveborn infants were followed to 12 months of age or until the data-lock date, whichever occurred first.

Participants

Potentially eligible pregnancies were identified from the fetal ultrasound database and medical records. Eligible pregnancies were singleton gestations with a prenatal ultrasound diagnosis of LIVC or DIVC and sufficient imaging to define renal and hepatic venous anatomy. A total of 20349 pregnancies were screened; 20282 were excluded, leaving 167 pregnancies for analysis. Six included pregnancies with unknown outcome information were retained in the cohort description but excluded from outcome-specific denominators and the primary analysis.

Phenotype definitions

Prenatal phenotypes were defined using three dimensions recorded separately: anatomical type, hepatic IVC continuity, and route of systemic venous return. Type A comprised fetuses with hepatic IVC continuity and included single LIVC and DIVC. Type B comprised fetuses with interrupted hepatic IVC and azygos or hemiazygos continuation; all type B fetuses had a single LIVC with hemiazygos-azygos continuation in the current dataset. Because type A contained two anatomical patterns whereas type B contained only single LIVC, comparisons between types were descriptive and were not interpreted as estimates of the isolated effect of drainage pathway.

Ultrasound examination and STIC

All pregnancies underwent a standardised obstetric ultrasound examination and fetal echocardiography according to local protocols and relevant International Society of Ultrasound in Obstetrics and Gynecology (ISUOG) recommendations [15, 16]. The abdominal and thoracic venous systems were assessed using transverse, coronal, and sagittal views with grey-scale and colour Doppler imaging. The examination included the upper abdominal transverse, renal-level transverse, infrarenal transverse, thoracoabdominal coronal, and descending aorta-azygos/hemiazygos views. Cardiac assessment included the four-chamber view, outflow tracts, systemic and pulmonary venous connections, atrial appendage morphology when visible, and cardiac rhythm. STIC was acquired when an interrupted hepatic IVC or complex drainage pathway was suspected. Volume datasets were stored in Digital Imaging and Communications in Medicine (DICOM) format and reviewed offline using multiplanar reconstruction. STIC findings were used only to describe venous visualisation and were not treated as an independent diagnostic reference standard. Representative prenatal ultrasound and STIC examples are shown in Figs. 2–5.

Assessment of associated anomalies

Cardiac findings were classified hierarchically as no cardiac finding, soft marker or normal variant only, simple structural heart disease, or complex or severe structural heart disease. Ventricular echogenic foci and trivial or mild valve regurgitation were classified as soft markers and were not included in the definition of structural heart disease. Structural heart disease included atrial or ventricular septal defects, atrioventricular septal defects, outflow tract abnormalities, pulmonary atresia, ventricular outflow obstruction, anomalous pulmonary venous drainage, and other major congenital cardiac defects. Extracardiac anomalies were recorded by organ system, including the central nervous system, urinary tract, gastrointestinal tract, skeleton or face, umbilical cord, and other systems. Visceral heterotaxy, abnormal spleen number or function, and features compatible with left isomerism were recorded separately. Prenatal left isomerism was reported as definite, probable, possible, absent, or indeterminate; because autopsy or surgical confirmation was not available for all cases, the term "confirmed" was avoided unless supported by an independent reference standard.

Outcomes

The primary clinical outcome was IUFD among pregnancies that did not end in TOP. A secondary management composite outcome was defined as TOP or IUFD. Live birth, neonatal death within 28 days, infant death within 12 months, neonatal intensive care unit (NICU) admission, and surgery were secondary outcomes. TOP was reported separately by indication. Liveborn infants were followed to 12 months of age or until 30 September 2025, whichever occurred first; TOP and IUFD were not classified as completed follow-up.

Data collection and quality control

Data were abstracted using a standardised electronic case-report form. Variables included maternal age, gestational age at diagnosis, anatomical type, hepatic IVC continuity, drainage pathway, cardiac and extracardiac findings, laterality-related findings, STIC performance and image quality, independent postnatal reference findings, pregnancy outcome, TOP indication, neonatal outcomes, surgery, and duration of follow-up. Two fetal medicine specialists independently reviewed the ultrasound images. Disagreements were resolved by consensus, with a third reviewer consulted when necessary. Investigators performing outcome analyses were not involved in image interpretation. Follow-up duration was calculated from birth to the last available assessment, death, or the data-lock date.

Statistical analysis

Continuous variables are summarised as mean ± standard deviation, and categorical variables as frequencies and percentages. Fisher exact and chi-square tests were used for descriptive comparisons. Wilson confidence intervals were calculated for key proportions. The primary analysis was restricted to pregnancies that did not end in TOP and used IUFD as the outcome. Because only seven IUFD events occurred, Firth penalised logistic regression was used for crude associations, and no adjusted natural-outcome model was considered stable. The secondary management composite was analysed using conventional logistic regression. A prespecified model included structural heart disease and extracardiac anomalies; a second exploratory model additionally included type B phenotype. No stepwise selection was performed, and the exploratory model was not interpreted as a mediation analysis. Repeated five-fold cross-validation was used to describe internal discrimination in the study dataset. STIC was analysed descriptively; no specificity, predictive values, or overall accuracy estimates were calculated because no adequately sized reference-negative group was available. No a priori sample-size calculation was performed because all eligible cases during the study period were included. Missing outcome data were not imputed. Two-sided P values < 0.05 were considered statistically significant, and all analyses were exploratory without adjustment for multiple comparisons.

Ethical considerations

The study was approved by the Ethics Committee of Lanzhou University Second Hospital (approval number 2026A-1086). The requirement for informed consent to participate was obtained in accordance with local regulations for retrospective research using de-identified clinical data. The study was conducted in accordance with the Declaration of Helsinki. Further details are provided in the Declarations.

Results

Study population

A total of 20349 pregnancies were screened, and 20282 were excluded after eligibility review, leaving 167 pregnancies for analysis. The mean maternal age was 31.1 ± 3.9 years, and the mean gestational age at diagnosis was 24.4 ± 2.9 weeks. Type A was present in 151 fetuses, including 84 with single LIVC and 67 with DIVC. Type B was present in 16 fetuses; all had single LIVC with interrupted hepatic IVC and hemiazygos-azygos continuation. Complete pregnancy outcome information was available for 161 fetuses. Six fetuses, all in the DIVC group, had unknown pregnancy outcome (Table 1)..

Table 1
Population characteristics and venous phenotypes

Characteristic	Overall (n = 167)	Type A (n = 151)	A: single LIVC (n = 84)	A: duplicated IVC (n = 67)	Type B (n = 16)
Number of fetuses	167	151	84	67	16
Maternal age, years, mean ± SD	31.1 ± 3.9	31.0 ± 4.1	31.1 ± 3.9	30.9 ± 4.4	31.5 ± 1.6
Gestational age at diagnosis, weeks, mean ± SD	24.4 ± 2.9	24.6 ± 2.9	24.4 ± 2.8	24.8 ± 3.1	23.3 ± 1.8
Single left-sided IVC	100/167 (59.9%)	84/151 (55.6%)	84/84 (100%)	0/67 (0%)	16/16 (100%)
Duplicated IVC	67/167 (40.1%)	67/151 (44.4%)	0/84 (0%)	67/67 (100%)	0/16 (0%)
Interrupted hepatic IVC	16/167 (9.6%)	0/151 (0%)	0/84 (0%)	0/67 (0%)	16/16 (100%)
Hemiazygos-azygos continuation	16/167 (9.6%)	0/151 (0%)	0/84 (0%)	0/67 (0%)	16/16 (100%)
Complete pregnancy outcome information	161/167 (96.4%)	145/151 (96.0%)	84/84 (100%)	61/67 (91.0%)	16/16 (100%)
Unknown pregnancy outcome	6/167 (3.6%)	6/151 (4.0%)	0/84 (0%)	6/67 (9.0%)	0/16 (0%)

Prenatal phenotypes and associated anomalies

Type A subgroups and the type B group were similar in maternal age and gestational age at diagnosis. Isolated venous variants were present in 83/151 type A fetuses (55.0%) compared with 0/16 type B fetuses ($P < 0.001$). Any cardiac finding was present in 29/151 type A fetuses (19.2%) versus 14/16 type B fetuses (87.5%); structural heart disease in 19/151 (12.6%) versus 11/16 (68.8%); and complex or severe structural heart disease in 7/151 (4.6%) versus 10/16 (62.5%) ($P < 0.001$ for all comparisons). A soft marker or isolated normal variant was the only cardiac finding in 13 fetuses overall (7.8%). Detailed cardiac diagnoses are provided in Additional file 1 (Table S1). Representative images are shown in Figs. 2–5.

Extracardiac and laterality-related findings

Any extracardiac anomaly was present in 53/151 type A fetuses (35.1%) and 9/16 type B fetuses (56.3%) ($P = 0.109$)(Table 2). Coexisting cardiac and extracardiac anomalies were present in 14/151 type A fetuses (9.3%) and 7/16 type B fetuses (43.8%) ($P = 0.001$). Features compatible with left isomerism were present in 9/16 type B fetuses (56.3%), and splenic abnormalities were present in 9/16. No laterality-related abnormality was identified in type A fetuses. Anatomical details are provided in Additional file 1 (Table S2).

Table 2
Cardiac, extracardiac, and laterality findings

Finding	Overall (n = 167)	Type A (n = 151)	A: single LIVC (n = 84)	A: duplicated IVC (n = 67)	Type B (n = 16)	*P* value (A vs B)
Any cardiac finding	43/167 (25.7%)	29/151 (19.2%)	14/84 (16.7%)	15/67 (22.4%)	14/16 (87.5%)	< 0.001
Soft marker only	13/167 (7.8%)	10/151 (6.6%)	6/84 (7.1%)	4/67 (6.0%)	3/16 (18.8%)	0.114
Structural heart disease	30/167 (18.0%)	19/151 (12.6%)	8/84 (9.5%)	11/67 (16.4%)	11/16 (68.8%)	< 0.001
Complex or severe heart disease	17/167 (10.2%)	7/151 (4.6%)	2/84 (2.4%)	5/67 (7.5%)	10/16 (62.5%)	< 0.001
Any extracardiac anomaly	62/167 (37.1%)	53/151 (35.1%)	31/84 (36.9%)	22/67 (32.8%)	9/16 (56.3%)	0.109
Coexisting cardiac and extracardiac anomalies	21/167 (12.6%)	14/151 (9.3%)	7/84 (8.3%)	7/67 (10.4%)	7/16 (43.8%)	0.001
Left isomerism features	9/167 (5.4%)	0/151 (0%)	0/84 (0%)	0/67 (0%)	9/16 (56.3%)	< 0.001
Splenic abnormality	9/167 (5.4%)	0/151 (0%)	0/84 (0%)	0/67 (0%)	9/16 (56.3%)	< 0.001
Isolated venous variant	83/167 (49.7%)	83/151 (55.0%)	46/84 (54.8%)	37/67 (55.2%)	0/16 (0%)	< 0.001

Pregnancy outcomes

Among the 161 fetuses with complete pregnancy outcome data, 122 were liveborn (75.8%), 32 pregnancies ended in TOP (19.9%), and seven ended in IUFD (4.3%). In type A, 118/145 fetuses with available outcome data were liveborn (81.4%), 20/145 underwent TOP (13.8%), and seven had IUFD (4.8%). In type B, 4/16 were liveborn (25.0%), 12/16 underwent TOP (75.0%), and none had IUFD (0/16). All 83 isolated venous variants were liveborn(Table 3).

Table 3
Pregnancy and postnatal outcomes by phenotype

Outcome	Overall	Type A	A: single LIVC	A: duplicated IVC	Type B	*P* value (A vs B)
Complete pregnancy outcome information	161/167 (96.4%)	145/151 (96.0%)	84/84 (100%)	61/67 (91.0%)	16/16 (100%)	> 0.999
Live birth	122/161 (75.8%)	118/145 (81.4%)	65/84 (77.4%)	53/61 (86.9%)	4/16 (25.0%)	< 0.001
Termination of pregnancy	32/161 (19.9%)	20/145 (13.8%)	16/84 (19.0%)	4/61 (6.6%)	12/16 (75.0%)	< 0.001
Intrauterine fetal death	7/161 (4.3%)	7/145 (4.8%)	3/84 (3.6%)	4/61 (6.6%)	0/16 (0%)	> 0.999
Unknown pregnancy outcome	6/167 (3.6%)	6/151 (4.0%)	0/84 (0%)	6/67 (9.0%)	0/16 (0%)	> 0.999
NICU admission among live births	3/122 (2.5%)	0/118 (0%)	0/65 (0%)	0/53 (0%)	3/4 (75.0%)	< 0.001
At least one operation among live births	3/122 (2.5%)	0/118 (0%)	0/65 (0%)	0/53 (0%)	3/4 (75.0%)	< 0.001

Postnatal outcomes

No neonatal or infant deaths occurred among liveborn infants. Three of 122 liveborn infants required NICU admission and at least one surgical procedure; all three belonged to the type B group. Outcomes by phenotype and associated-anomaly subgroup are shown in Additional file 1 (Table S3).

Primary clinical outcome excluding termination of pregnancy

After excluding 32 TOPs, 129 pregnancies remained for the primary clinical analysis, and seven IUFDs occurred. No IUFD occurred among the four continuing type B pregnancies, whereas IUFD occurred in 7/125 type A pregnancies (5.6%); the type B OR was not estimable. Because only seven events were available, no adjusted primary-outcome model was fitted. Firth penalised univariable analyses produced estimates of 12.47 (95% CI 2.71–62.50) for structural heart disease, 9.71 (95% CI 1.49–53.07) for complex or severe heart disease, 15.78 (95% CI 3.13-156.29) for extracardiac anomalies, and 11.98 (95% CI 2.32–59.69) for coexisting cardiac and extracardiac anomalies. These estimates were imprecise and exploratory (Table 4, Panel A).

Table 4
Factors associated with primary and secondary outcomes

Predictor	Unadjusted OR (95% CI)	*P* value	Adjusted OR (95% CI)	*P* value	Interpretation
Panel A: primary clinical outcome, IUFD after excluding TOP; n = 129, events = 7					
Type B versus type A	Not estimable	—	Not estimated	—	No IUFD among 4 continuing type B pregnancies
Structural heart disease	12.47 (2.71–62.50)	0.001	Not estimated	—	Firth univariable; no adjusted model due to 7 events
Complex or severe heart disease	9.71 (1.49–53.07)	0.014	Not estimated	—	Firth univariable; exploratory
Extracardiac anomaly	15.78 (3.13-156.29)	0.003	Not estimated	—	Firth univariable; exploratory
Coexisting cardiac and extracardiac anomalies	11.98 (2.32–59.69)	0.003	Not estimated	—	Firth univariable; exploratory
Panel B: secondary management composite, TOP or IUFD; n = 161, events = 39					
Type B versus type A	13.11 (3.92–43.81)	< 0.001	Not stable	—	Exploratory; driven by TOP and collinearity
Structural heart disease	7.80 (3.22–18.91)	< 0.001	8.37 (2.85–24.63)	< 0.001	Prespecified model
Extracardiac anomaly	12.31 (5.20-29.14)	< 0.001	12.88 (4.98–33.27)	< 0.001	Prespecified model
Complex or severe heart disease	8.07 (2.56–25.43)	< 0.001	Not included	—	Collinear with structural heart disease
Prespecified model performance	AUC 0.849	—	AUC 0.849	—	Structural heart disease plus extracardiac anomaly

Secondary management composite outcome

When TOP and IUFD were combined as a secondary management outcome, 39/161 fetuses had an adverse event. The unadjusted association with type B was strong (OR 13.11, 95% CI 3.92–43.81; P <

0.001), but this analysis was dominated by TOP, which occurred in 12/16 type B pregnancies. Structural heart disease and extracardiac anomalies remained associated in the prespecified model (OR 8.37, 95% CI 2.85–24.63 and OR 12.88, 95% CI 4.98–33.27, respectively; area under the receiver operating characteristic curve [AUC] 0.849). No stable adjusted estimate for type B was obtained because of collinearity with structural and extracardiac findings. These results describe the secondary management composite and do not establish a causal or independent effect of drainage pathway (Table 4, Panel B).

STIC findings

All 16 type B fetuses underwent STIC acquisition. An independent postnatal reference standard was available in a subset of cases and was concentrated among the earliest-detected fetuses. Two-dimensional ultrasound and STIC findings were therefore reported descriptively; no specificity, predictive values, or overall accuracy estimates were calculated.

Discussion

Principal findings

This single-centre retrospective cohort characterised prenatal phenotypes and outcomes in 167 fetuses with LIVC or DIVC. Type A, characterised by hepatic IVC continuity, included single LIVC and DIVC and was frequently an isolated variant. Type B was associated with complex cardiac disease, laterality findings, and a higher burden of adverse pregnancy outcomes. Importantly, the primary clinical analysis excluded TOP and identified only seven IUFDs, with no type B IUFD and no stable adjusted model. The strong association observed when TOP and IUFD were combined was therefore driven largely by pregnancy termination. The study supports phenotype-based prenatal assessment and risk stratification, but it does not establish that the drainage pathway itself independently determines natural fetal death.

Comparison with previous studies

The existing literature supports a broad clinical spectrum for fetal venous anomalies rather than a single prognostic entity. In a large integrated fetal echocardiography cohort, Tseng et al. identified congenital venous malformations in 98/7255 fetuses (1.35%); among fetal cardinal venous disorders, 43.1% had associated cardiac defects, and prognosis depended substantially on the associated anomalies [1]. Babaoğlu et al. studied 14 fetuses with hepatic interruption of the IVC and normal intracardiac anatomy, of whom six were considered isolated and all were delivered at term with good outcomes [8]. Conversely, Chen et al. reported 34 patients with congenital IVC interruption, most of whom had left isomerism; normal cardiac anatomy was present in only 11.8%, and severe congenital heart disease was the only significant risk factor for long-term survival [4]. Our results are consistent with this spectrum: type A was predominantly isolated, whereas type B was almost always accompanied by cardiac or laterality findings.

Associated anomalies and laterality

Interrupted IVC with azygos or hemiazygos continuation is an important marker of defective left-right patterning. The systematic review by Buca et al., including 647 fetuses with prenatally diagnosed heterotaxy, reported complete atrioventricular septal defect in 59.3%, right ventricular outflow tract obstruction in 35.5%, and fetal arrhythmia in 36.7% of fetuses with left atrial isomerism [5]. Detailed prenatal-pathological correlation studies have shown that left isomerism is characterised by interrupted IVC, azygos continuation, abnormal abdominal situs, and splenic abnormalities, and that a structured multi-view approach improves recognition of these findings [6, 17]. In our cohort, 9/16 type B fetuses had features compatible with left isomerism, all had hemiazygos-azygos continuation, and 10 had complex or severe structural heart disease. These findings reinforce the need for comprehensive assessment of cardiac anatomy, systemic and pulmonary venous return, atrial appendage morphology, rhythm, visceral situs, and splenic status when type B drainage is identified.

Prognostic significance of cardiac and extracardiac anomalies

Previous observational studies consistently indicate that cardiac severity and extracardiac involvement drive prognosis in fetal heterotaxy. Akalın et al. reported that univentricular physiology, hydrops, and conotruncal anomalies were associated with poor outcomes, and that extracardiac anomalies increased morbidity and mortality [6]. Gottschalk et al. found non-splenic extracardiac anomalies in 26/165 fetuses (15.8%); these anomalies influenced the postnatal course, and 49/165 pregnancies (29.7%) ended in TOP [9]. More recent cohorts have reported similarly high risks. Shu et al. found live birth in only 12/25 fetuses with left atrial isomerism (48.0%) and survival beyond infancy in 4/12 liveborn infants (33.3%) [18]. MacDonald et al. reported 5-year survival of 87% for left atrial isomerism versus 56% for right atrial isomerism [14]. These findings are broadly consistent with the major cardiac and extracardiac burden observed in our type B subgroup. In the present analysis, structural heart disease and extracardiac anomalies were associated with the secondary management composite after adjustment, whereas the primary natural-outcome analysis had too few events for adjusted modelling. However, we did not include important dynamic predictors such as complete heart block, ventricular dysfunction, hydrops, or pulmonary venous obstruction because these variables were not systematically collected. These variables predict fetal or postnatal mortality in contemporary cohorts and should be included in future prospective analyses [19].

Termination of pregnancy and outcome interpretation

A key methodological issue in prenatal studies is the competing nature of TOP. In our cohort, 32/161 pregnancies with complete outcome data ended in TOP, and the proportion was much higher in type B than in type A. The secondary composite outcome was therefore strongly influenced by parental decisions after prenatal counselling rather than by spontaneous fetal or neonatal death alone. Similar patterns have been reported in heterotaxy cohorts, in which TOP substantially affects estimates of live birth and survival [9]. Selection of liveborn cohorts can also affect survival estimates [14]. In the primary analysis excluding TOP, only seven IUFDs remained, and no IUFD occurred among the four continuing

type B fetuses; this absence of events cannot be interpreted as evidence of protection. Future studies should treat TOP as a competing event or report it separately.

Prenatal diagnosis and the role of STIC

Standardised two-dimensional ultrasound and fetal echocardiography remain the foundation of prenatal diagnosis, as recommended by current ISUOG guidelines [15, 16]. An integrated venous assessment can identify most systemic venous abnormalities, whereas three- and four-dimensional techniques are generally supplementary [2]. Romanowicz et al. found that fetal echocardiography was less reliable for systemic and pulmonary venous anatomy than for intracardiac anatomy, highlighting the difficulty of predicting complex postnatal venous and surgical phenotypes [12]. STIC and HDlive Flow may improve spatial visualisation of an interrupted IVC and its azygos or hemiazygos continuation [10, 11]. In the present study, STIC was available in all type B cases, and a selected subset had independent postnatal confirmation; because this subset was small, the findings are descriptive. This finding is hypothesis-generating and should not be interpreted as diagnostic accuracy: no reference-negative cases were available, the number of confirmed cases was very small, and STIC was used during phenotype ascertainment. Blinded comparative studies with an independent reference standard are required before STIC can be recommended as a diagnostic test rather than a visualisation adjunct.

Clinical implications

For fetuses with normal hepatic drainage and no additional anomalies, our findings support generally favourable short-term outcomes and are consistent with previous reports of isolated IVC variants [8]. Nevertheless, a detailed mid-trimester anomaly scan and fetal echocardiography remain necessary because associated cardiac or extracardiac anomalies may be present [15]. When hepatic IVC interruption with azygos or hemiazygos continuation is identified, the fetus should be referred to a fetal medicine or fetal cardiology service. Assessment should include cardiac rhythm, ventricular function, systemic and pulmonary venous connections, abdominal and thoracic situs, and splenic number or function [6]. Extracardiac anomalies, including intestinal malrotation and biliary abnormalities, should also be considered [9]. Genetic counselling and testing should be discussed. Yi et al. reported diagnostic or likely pathogenic variants in 11/72 fetuses with heterotaxy (15.3%) using copy number variation sequencing and whole-exome sequencing, with primary ciliary dyskinesia genes accounting for most identified variants [20]. Postnatal planning should involve neonatology, paediatric cardiology, genetics, and surgery when indicated.

Long-term vascular and procedural considerations

Although most fetal systemic venous variants are not haemodynamically significant during intrauterine life, some may have long-term implications. Kim et al. found that IVC hypoplasia or aplasia was strongly associated with deep vein thrombosis, with ORs of 17.0 for any deep vein thrombosis and 34.2 for iliofemoral deep vein thrombosis [21]. In a multicentre registry of 210 patients with IVC agenesis, 53% had venous thrombosis, the estimated annual risk was 1.15%, and extrahepatic IVC agenesis carried a higher thrombotic risk than hepatic interruption [22]. These findings cannot be directly extrapolated to

isolated LIVC or DIVC with normal hepatic drainage, but they emphasise the importance of documenting the precise IVC phenotype and considering long-term follow-up. Complex systemic venous anatomy may also complicate cardiac catheterisation, electrophysiology procedures, extracorporeal circulation, and thoracic surgery [23]. The need for long-term surveillance should therefore be individualised rather than applied uniformly to all isolated fetal venous variants.

Strengths and limitations

The strengths of this study include a phenotype-centred classification, standardised ultrasound and fetal echocardiography based on contemporary guidelines [15], separate reporting of cardiac and extracardiac findings, explicit distinction between TOP and natural death, and a primary Firth analysis that avoided incorporating TOP into the natural-outcome endpoint. However, several limitations should be acknowledged. First, this was a retrospective single-centre study, and referral patterns may have enriched the cohort for complex anomalies. Second, type B included 16 fetuses, and the natural-outcome analysis had only seven IUFD events; adjusted primary-outcome modelling was therefore not feasible. Third, type A and type B differed in both anatomical composition and drainage pathway, so associations with phenotype cannot be attributed to drainage alone. Fourth, six cases had unknown pregnancy outcomes, and although they were excluded from outcome denominators, this may have introduced bias. Fifth, genetic testing was not systematically performed; previous data indicate a clinically relevant diagnostic yield in heterotaxy [20], and the absence of uniform testing limits inference about the genetic architecture of our cohort. Sixth, the diagnosis of left isomerism was based on prenatal findings in most cases, and autopsy or surgical confirmation was not universally available; postnatally discordant phenotypes are well documented [13]. Seventh, STIC was not evaluated in a blinded diagnostic-accuracy design, and no reference-negative cases were available, so specificity and predictive values could not be estimated [10, 11]. Eighth, the secondary management models were internally validated only and may have been overfitted because of the modest number of events. Finally, follow-up was limited to 12 months; longer follow-up is needed to evaluate arrhythmia, biliary disease, intestinal complications, thromboembolism, and late surgical outcomes [9].

Future research

Future studies should use a multicentre prospective design and a consensus classification that records anatomical type, hepatic IVC continuity, drainage pathway, cardiac severity, laterality findings, splenic status, and genetic results separately. Core outcome sets should distinguish TOP, IUFD, neonatal death, infant death, major surgery, and long-term morbidity, with natural mortality analysed separately from TOP. Blinded comparisons of two-dimensional ultrasound, STIC, and other advanced imaging should use an independent postnatal, surgical, or autopsy reference standard. Genetic testing, including chromosomal microarray and exome sequencing where appropriate, should be integrated into prospective phenotyping [20]. Long-term follow-up should evaluate venous thrombosis and procedural outcomes among individuals with specific IVC phenotypes; however, evidence from IVC agenesis should

not be extrapolated directly to isolated LIVC or DIVC [22]. Finally, collaboration across fetal medicine, cardiology, genetics, neonatology, and surgery will be required to generate sufficiently large cohorts for reliable risk stratification [5].

Conclusions

The type A and type B phenotypes differed in associated cardiac and laterality findings and in the burden of adverse pregnancy outcomes. However, after TOP was excluded, only seven IUFDs remained, no IUFD occurred among the four continuing type B pregnancies, and no adjusted natural-outcome model was feasible. These data therefore do not establish that drainage pattern independently determines natural fetal death. Type B should prompt comprehensive cardiac, visceral, splenic, and rhythm assessment and referral to fetal medicine services. Management composites that include TOP should be interpreted cautiously, and STIC should be regarded as a descriptive visualisation adjunct until validated with an appropriate reference standard.

Abbreviations

AUC
area under the receiver operating characteristic curve
AZ
azygos vein
CI
confidence interval
DA
ductus arteriosus
DAO
descending aorta
DICOM
Digital Imaging and Communications in Medicine
DIVC
duplicated inferior vena cava
HAZ
hemiazygos-azygos connection
HV
hepatic vein
ISUOG
International Society of Ultrasound in Obstetrics and Gynecology
IUFD
intrauterine fetal death
IVC
inferior vena cava

LK
left kidney
LKV
left renal vein
LIVC
left-sided inferior vena cava
NICU
neonatal intensive care unit
OR
odds ratio
RA
right atrium
RK
right kidney
RIVC
right inferior vena cava
SD
standard deviation
STIC
spatiotemporal image correlation
SVC
superior vena cava
TOP
termination of pregnancy.

Declarations

Ethics approval and consent to participate

This study was approved by the Ethics Committee of Lanzhou University Second Hospital (approval number 2026A-1186). The requirement for informed consent to participate was obtained in accordance with local regulations for retrospective research using de-identified clinical data.

Consent for publication

Written informed consent for publication of the de-identified ultrasound images was obtained from the parents or legal guardians of the fetuses shown in Figures 2-5.

Availability of data and materials

The de-identified dataset generated and analysed during the current study is available from the corresponding author on reasonable request, subject to approval by the institutional ethics committee of Lanzhou University Second Hospital and applicable data-sharing regulations.

Competing interests

The authors declare that they have no competing interests.

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Authors' contributions

Bin Ma contributed to study conception and design, data acquisition, and manuscript drafting. Yanfang Wang contributed to image review and data verification. Lan Bu contributed to clinical interpretation and statistical analysis. Fang Nie contributed to critical revision and supervision. All authors read and approved the final manuscript.

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Figures

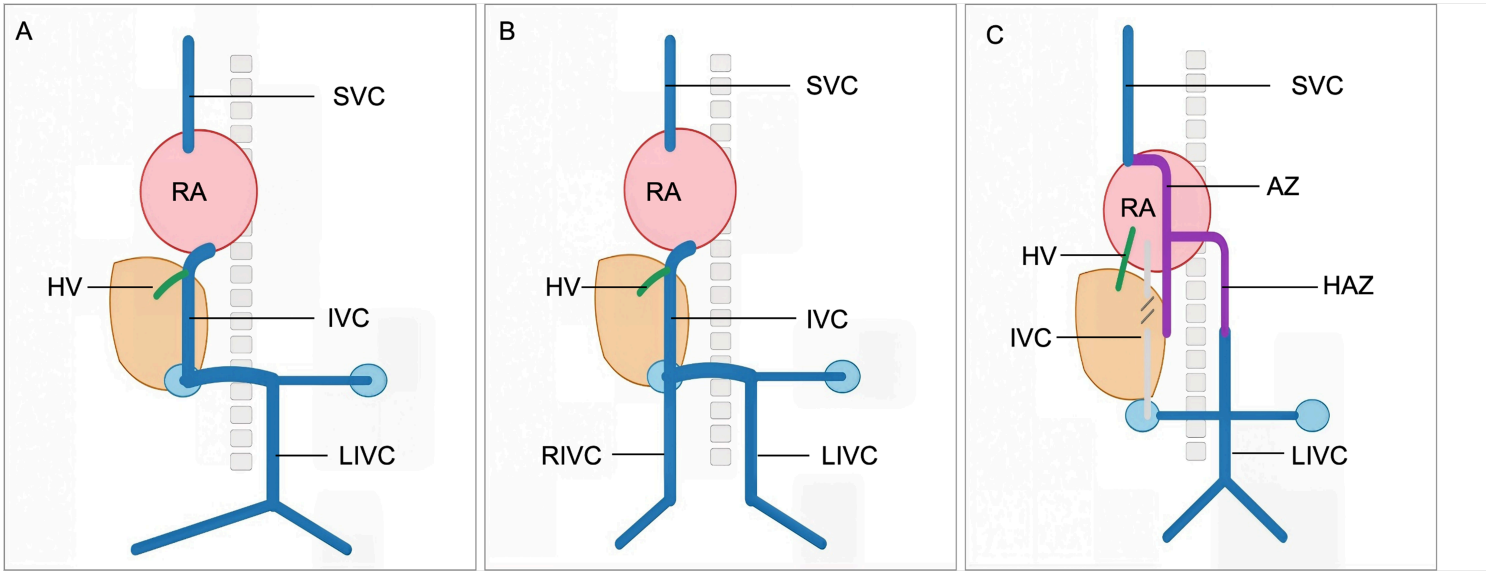


Figure 1

Schematic of representative systemic venous drainage patterns

A: left-sided IVC with normal hepatic drainage; B: duplicated IVC with bilateral infrarenal IVCs and a patent hepatic IVC; C: left-sided IVC with interrupted hepatic IVC and hemiazygos-azygos continuation. AZ, azygos vein; HAZ, hemiazygos-azygos connection; HV, hepatic vein; IVC, inferior vena cava; LIVC, left-sided inferior vena cava; RA, right atrium; RIVC, right inferior vena cava; SVC, superior vena cava.

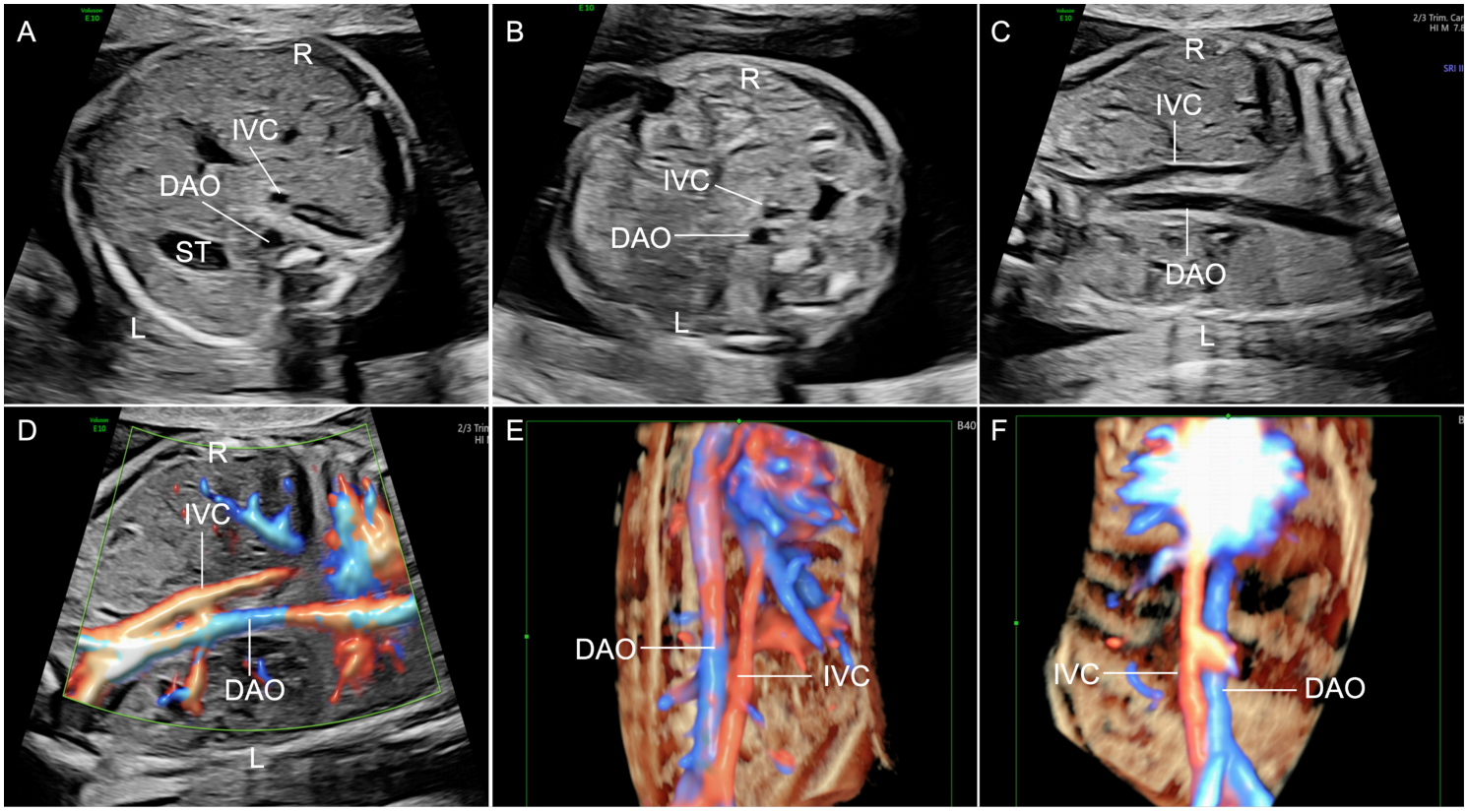


Figure 2

Normal inferior vena cava on prenatal ultrasound and STIC

A and B: transverse abdominal views showing a right-sided IVC adjacent to the DAO. C: longitudinal view showing the IVC and DAO. D: colour Doppler image confirming flow within the IVC. E and F: three-dimensional STIC/HDlive Flow reconstructions showing the spatial relationship between the IVC and DAO. DAO, descending aorta; IVC, inferior vena cava; ST, stomach.

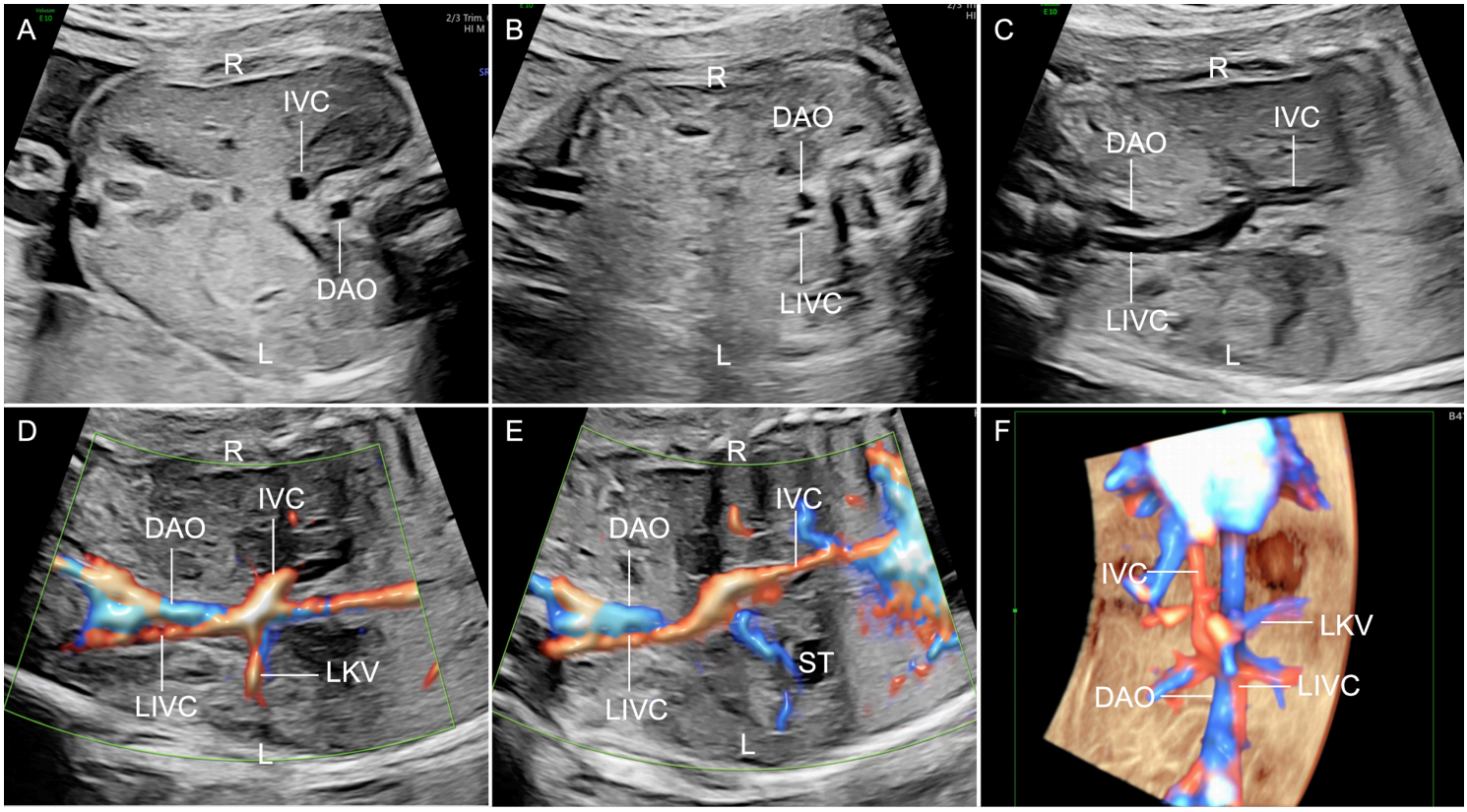


Figure 3

Left-sided inferior vena cava with normal hepatic drainage

A: transverse abdominal view above the renal level showing the IVC to the right of the DAO. B: transverse abdominal view below the renal level showing the LIVC to the left of the DAO. C: coronal view showing the LIVC to the left of the DAO. D and E: colour Doppler images showing the LIVC, LKV, and drainage pathway. F: three-dimensional STIC/HDlive Flow reconstruction showing the LIVC and the crossing left renal vein. DAO, descending aorta; IVC, inferior vena cava; LKV, left renal vein; LIVC, left-sided inferior vena cava.

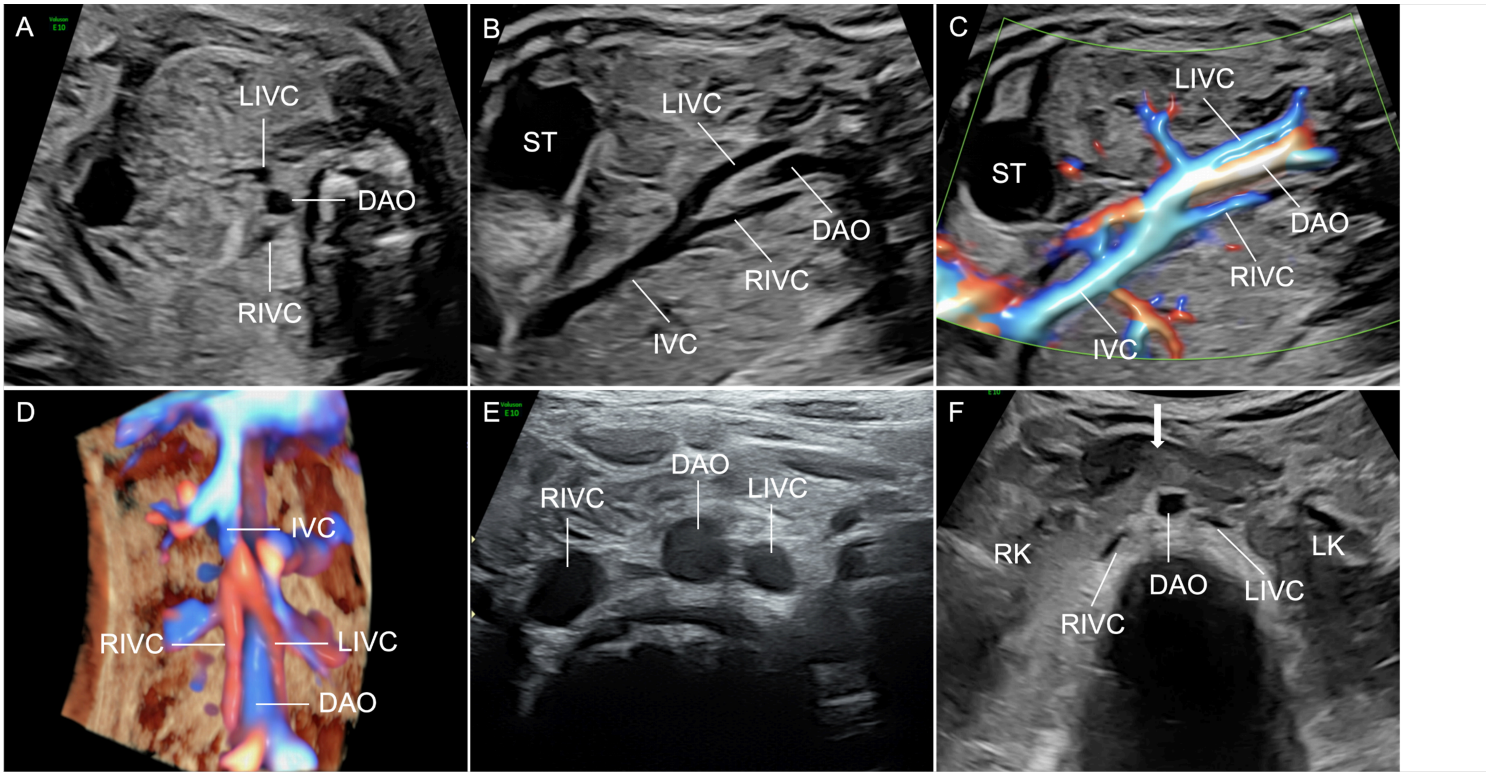


Figure 4

Prenatal and postnatal ultrasound images of duplicated inferior vena cava

A-D: prenatal images. A: transverse abdominal view at the infrarenal level showing a round-to-oval anechoic vessel on each side of the DAO. B: coronal view showing bilateral para-aortic venous channels, producing the “double-vein sign” or “para-aortic double-channel sign.” C: colour Doppler image showing the LIVC and left renal vein crossing anterior to the aorta and draining into the RIVC. D: three-dimensional STIC/HDlive Flow reconstruction showing the spatial relationship among the bilateral infrarenal veins, left renal vein, and RIVC. E and F: postnatal ultrasound images. E: transverse abdominal view showing a round-to-oval anechoic vessel on each side of the DAO. F: image showing a horseshoe kidney. DAO, descending aorta; IVC, inferior vena cava; LIVC, left-sided inferior vena cava; LK, left kidney; RK, right kidney; RIVC, right inferior vena cava.

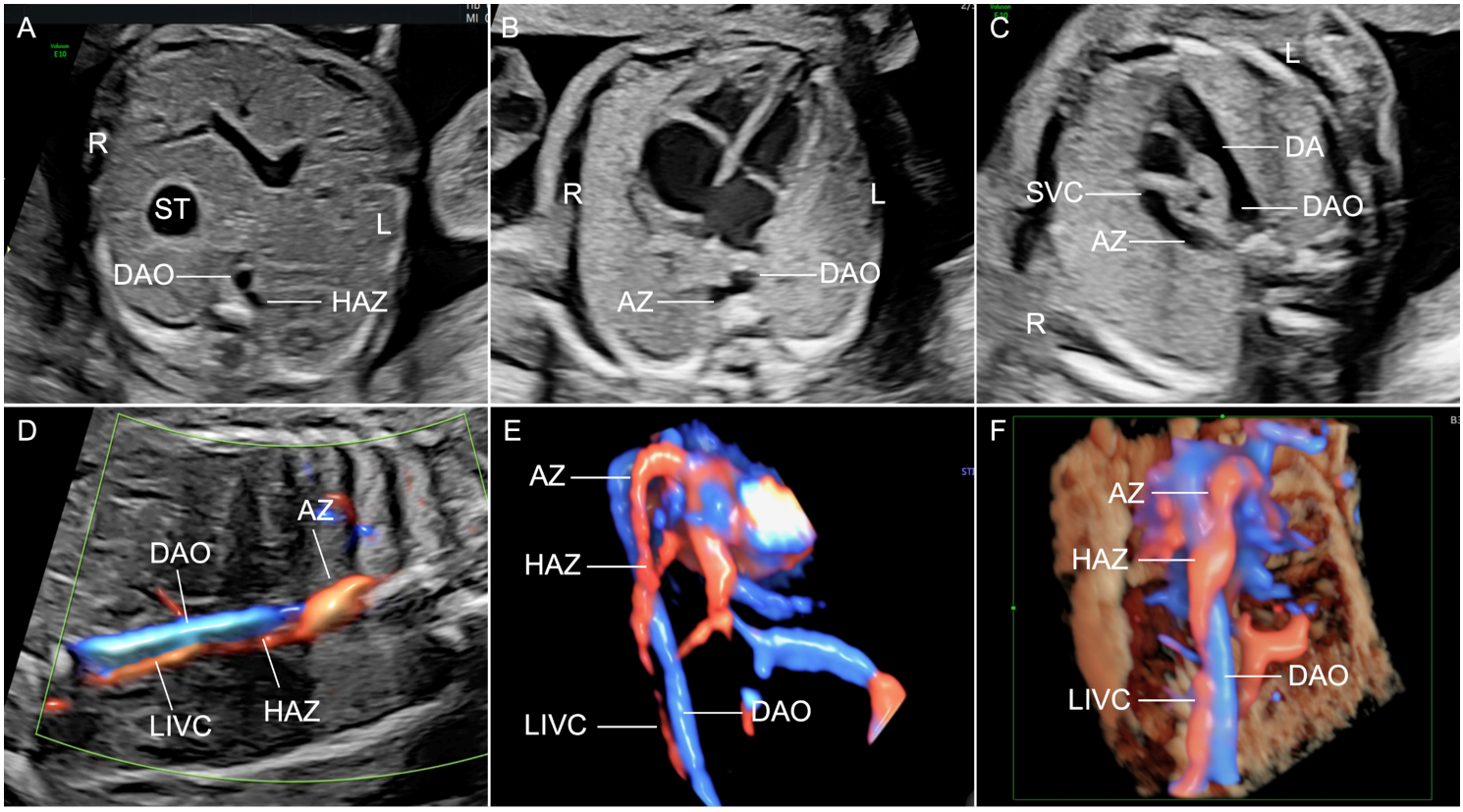


Figure 5

Left-sided inferior vena cava with hemiazygos-azygos continuation

A: transverse abdominal view at the level of the gastric bubble showing a dilated hemiazygos vein posterior and to the left of the DAO, with interruption of the hepatic IVC. B: four-chamber view showing a dilated azygos vein posterior and to the right of the DAO. C: three-vessel and trachea view showing the dilated azygos vein draining into the SVC. D: coronal view showing the LIVC to the left of the DAO and its continuation via the hemiazygos and azygos veins. E and F: three-dimensional STIC/HDlive Flow reconstructions showing the spatial relationships among the LIVC, hemiazygos-azygos continuation, DAO, and SVC from different angles. AZ, azygos vein; DA, ductus arteriosus; DAO, descending aorta; HAZ, hemiazygos-azygos connection; IVC, inferior vena cava; LIVC, left-sided inferior vena cava; ST, stomach; SVC, superior vena cava.

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