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TITLE OF THE DOCTORAL THESIS

Natural History and Evolution of Conotruncal Anomalies Diagnosed Before 16 Weeks' Gestation: A Multicenter Retrospective Cohort Study

S.S.D. MED/40 GINECOLOGIA E OSTETRICIA

Coordinator: Prof. Andrea Ruzzenente

Signature

Tutor: Prof. Stefano Uccella

Signature

Co-Tutor: Dr. Paolo Volpe

Signature

AOUI VR - OSP. DI VENERE
U.O. MEDICINA FETALE
Dir. Dott. PAOLO VOLPE

Doctoral Student: Dr.ssa Mariachiara Bosco

Signature

Abstract

Objective: To assess the natural history and evolution of conotruncal anomalies (CTAs) diagnosed before 16 weeks' gestation, focusing on lesion progression, genetic associations, and pregnancy outcomes. A secondary aim was to establish nomograms for the fetal pulmonary artery and aorta between 12+0 and 15+6 weeks' gestation in normal fetuses.

Methods: This retrospective cohort study was conducted at two Italian tertiary fetal medicine centers between 2017 and 2023. Fetuses diagnosed with CTA on early fetal echocardiography (<16 weeks) were identified from institutional databases. Included anomalies were anterior malalignment ventricular septal defect (am-VSD), tetralogy of Fallot (TOF), TOF with pulmonary atresia (TOF-PA), truncus arteriosus (TA), double outlet right ventricle (DORV), transposition of the great arteries (TGA), congenitally corrected TGA (cTGA), and interrupted aortic arch type B (IAA-B). Only cases with postnatal or postmortem confirmation were included. Progression was defined as morphologic change requiring revision of diagnosis. Invasive genetic testing (CMA ± WES) was offered to all patients. Reference measurements of the great arteries were prospectively collected in normal fetuses between 12+0 and 15+6 weeks.

Results: A total of 131 fetuses were diagnosed with CTA before 16 weeks; 101 fulfilled inclusion criteria. Sixty-one pregnancies (46.6%) were terminated, most commonly for abnormal genetic findings (mostly 22q11.2 microdeletion). Among 70 ongoing pregnancies, intrauterine demise occurred in 5 cases (7.1%) and postnatal death in 2 (2.9%). Lesion progression occurred in 19/70 (27.1%), mainly between the second and third trimesters. The most frequent evolutions were am-VSD to TOF (n=8) and TOF to TOF-PA (n=4). Nomograms for early aortic and pulmonary valve dimensions were established. Progressive TOF cases had pulmonary artery diameters below the 5th centile, while stable cases were above this range.

Conclusions: CTAs diagnosed before 16 weeks are dynamic conditions, with one in four showing antenatal progression. Early diagnosis warrants detailed genetic assessment, serial echocardiography, and specialized prenatal counselling. Early vessel measurements may help identify fetuses at risk of evolution and guide tailored surveillance.

Keywords: cardiac embryology, fetal cardiology, prenatal screening, longitudinal assessment.

INTRODUCTION

Advances in ultrasound resolution and operator expertise now allow reliable fetal echocardiography as early as 12–14 weeks' gestation, with most authors defining "early fetal echocardiography" as an examination performed before 16 weeks.[1–3] Although the majority of structural heart defects are already established by the end of the 8th week of gestation, when fetal heart embryogenesis is largely complete, certain lesions including conotruncal anomalies (CTAs),[4–6] may evolve during gestation and their potential for progression complicates prenatal counselling. While mid-gestation echocardiography remains the cornerstone of prenatal CHD diagnosis,[7,8] the increasing use of early fetal echocardiography has raised questions regarding the diagnostic reliability of early findings, specifically for evolutive lesions such as CTAs. Indeed, available data are limited in the literature elucidating the natural history of these conditions particularly when diagnosed in the first trimester or early second trimester.[4,5] The primary aim of this study was therefore to evaluate the antenatal evolution of CTAs diagnosed before 16 weeks' gestation, with attention to lesion progression, genetic abnormalities, and pregnancy outcomes. A secondary aim was to establish early-gestation nomograms for aortic and pulmonary artery diameters (12+0–15+6 weeks), to assess whether great-artery size at first evaluation may help identify fetuses at risk of CTA progression.

METHODS

This multicentre retrospective cohort study was conducted at two Italian tertiary fetal medicine units—IRCCS Ca' Granda Ospedale Policlinico in Milan and Ospedale di Venere in Bari—between January 2017 and December 2023. Institutional databases (Viewpoint™ and Astraia™, software GmbH, Germany) were queried to identify all fetuses who underwent early fetal echocardiography before 16 weeks' gestation and received a diagnosis of a conotruncal anomaly (CTA). Conotruncal anomalies included anterior malalignment ventricular septal defect (am-VSD), tetralogy of Fallot (TOF), TOF with pulmonary atresia (TOF-PA), TOF with absent pulmonary valve (TOF-APV), truncus arteriosus (TA), double outlet right ventricle (DORV), transposition of the great arteries (TGA), congenitally corrected TGA (cTGA), and interrupted aortic arch type B (IAA-B). Only cases with available prenatal follow-up and postnatal confirmation—via postnatal echocardiography, surgical findings, or postmortem examination—were eligible. First-trimester terminations of pregnancy (TOP) without postmortem confirmation were excluded. All examinations were performed using Voluson E8 or E10 ultrasound systems (GE Healthcare, Zipf, Austria) equipped with high-frequency probes (C4-8-D, RIC6-12-D, C2-9-D). Stored 2D/3D images and videoclips were reviewed

retrospectively by two experienced fetal cardiologists (PV, VDR). The primary objective was to identify antenatal progression of CTAs. Progression was evaluated at two timepoints: mid-gestation (19+0–20+6 weeks) and third trimester (28+0–34+0 weeks). Progression was defined as significant morphological changes across serial evaluations that required modification of the initial diagnosis. To interpret early biometric findings in CTA fetuses, we prospectively collected aortic and pulmonary valve measurements between 12+0 and 15+6 weeks' gestation in a separate cohort of structurally normal fetuses[9], given the absence of published reference nomograms for great artery dimensions in this gestational age window, and the limited data available before 16 weeks.[9–11] Pregnancies were eligible for the normative dataset if dating was confirmed by first-trimester crown-rump length (CRL) and the pregnancy resulted in a liveborn, appropriate-for-gestational-age infant without structural or genetic abnormalities. For each gestational week (12, 13, 14, and 15 weeks) we calculated centiles (1st, 3rd, 5th, 10th, 25th, 50th, 75th, 90th, 95th, 97th, 99th) for both the aortic and pulmonary valves. All patients with a prenatal diagnosis of CTA were offered invasive diagnostic testing (chorionic villus sampling or amniocentesis). Chromosomal microarray analysis (CMA) was performed in all tested cases. Whole-exome sequencing (WES) was offered when CMA returned normal results. Data extracted from institutional database included: gestational age at diagnosis, indication for early fetal echocardiography, serial echocardiographic finding, pregnancy outcomes and genetic test results. All patients provided informed in accordance with institutional protocols, including consent for image storage and the use of anonymized clinical data for research and quality-control purposes

RESULTS

During the study period, 131 fetuses were diagnosed with a conotruncal anomaly (CTA) before 16 weeks' gestation (**Figure 1**). Of these, 61 pregnancies (46.6%) underwent termination of pregnancy (TOP), including 30 in the first trimester and 31 in the second trimester. Because postmortem confirmation was unavailable for first-trimester TOP cases, they were excluded from the final analysis, leaving 101 fetuses in the study cohort. Among the 31 second-trimester TOPs, genetic abnormalities were identified in 14 fetuses, with 22q11.2 microdeletion representing the most common abnormality. Extracardiac anomalies were present in 15 cases, and in 12 cases the TOP was requested in isolated CTA. Of the 70 pregnancies that continued beyond the mid-trimester anomaly scan intrauterine demise (IUD) occurred in 5 cases (7.1%), and postnatal death occurred in 2 additional cases (2.9%). The most frequent prenatal diagnoses were anterior malalignment VSD (am-VSD) and tetralogy of Fallot (TOF) (**Figure 2**). Among the 70 ongoing pregnancies, 19 fetuses (27.1%) demonstrated antenatal progression of the cardiac lesion. Seven (7/19, 36.8%) showed progression before 22 weeks' gestation while 12 (12/19, 63.2%) exhibited progression during the

third trimester. The most common patterns of evolution were am-VSD to TOF (n=8), and TOF to TOF with pulmonary atresia (TOF-PA) (n=4). Additional phenotypic changes were documented in fetuses initially diagnosed with DORV (n=2) and fetuses with TGA (n=4). One fetus with congenitally corrected TGA (cTGA) developed complete atrioventricular block with hydrops in the third trimester, resulting in intrauterine death (**Figures 3–4**). Among the 66 ongoing cases with available first-trimester combined screening data, 48.5% (32/66) showed at least one abnormal indirect marker suggestive of congenital heart disease (CHD) such as increased nuchal translucency (NT), tricuspid regurgitation, or abnormal ductus venosus flow. Normative biometric data for the aortic and pulmonary valves between 12+0 and 15+6 weeks' gestation were used to generate centile charts (**Tables 1–3**). The distribution of aortic and pulmonary valve measurements throughout gestational age window is shown in **Figures 5** and **Figure 6**. Distinct biometric patterns were observed between progressing and non-progressing CTA cases. In TOF cases that progressed to TOF-PA, the pulmonary artery diameter was consistently below the 5th centile for gestational age, whereas in non-progressing TOF the hypoplastic pulmonary artery was above the 5th centile at diagnosis. Among am-VSD cases, all but one case (31st centile) that progressed had pulmonary artery diameters between the 10th and 25th centiles, whereas all non-progressing case showed values above the 25th centile.

DISCUSSION

Understanding the natural history of conotruncal anomalies (CTAs) diagnosed in the first trimester is essential to refine prenatal counselling, optimize surveillance, and anticipate perinatal needs. In this multicentre study, we evaluated 70 ongoing pregnancies with CTA diagnosed before 16 weeks' gestation and observed that approximately one in four fetuses (27.1%) exhibited antenatal progression of the cardiac lesion. This confirms that CTAs represent dynamic and evolving conditions rather than fixed anatomical defects, particularly when detected early in gestation. Most prior studies have examined CTA evolution from the mid-gestation diagnosis onward, with limited attention to earlier gestational ages[5,12] Only a small number of reports have followed fetuses longitudinally from the early gestational ages.[13] Our findings therefore provide a unique perspective on the earliest stages of CTA development and their subsequent morphological evolution. Notably, 63.2% of all progression events occurred between the mid-trimester and the third trimester, highlighting the importance of continued surveillance through late gestation. The most frequent progression was from anterior malalignment VSD (am-VSD) to tetralogy of Fallot (TOF) (in 8 out of the 17 total number of ongoing am-VSD), reflecting the embryological contribution of outlet septum deviation to progressive subpulmonary obstruction. Anterocephalad malalignment of the outlet/conal septum can occur even

in the presence of a formed subpulmonary infundibulum (am-VSD). However, the anterior deviation of the outlet septum might contribute to progressive outflow obstruction with evolution in TOF both during fetal life and after birth.[14–16] Similarly, 4 out of the 15 TOF cases progressed to TOF with pulmonary atresia (TOF-PA), reflecting advancing obstruction of the right ventricular outflow tract, which has been associated with poorer postnatal prognosis.[17–19] Evolution was also documented in fetuses with an initial diagnosis of DORV or TGA, emphasizing that even lesions traditionally considered structurally stable may undergo functional or anatomical changes as gestation advances. These changes included the emergence of pulmonary outflow obstruction and evolving coarctation—findings consistent with the concept that morphofunctional remodeling of the great arteries continues beyond early cardiac looping stages.[4,20] The case of cTGA complicated by late-onset complete atrioventricular block is also consistent with reported risks of rhythm disturbances emerging in the late second or early third trimester.[21,22] A major contribution of this study is the establishment of normative data for aortic and pulmonary artery diameters between 12 and 15+6 weeks' gestation. Existing reference charts for these structures before 16 weeks are scarce,[9–11] which has limited the interpretation of great-artery findings in first-trimester CTA assessments. Our data offer new insight into early great vessel development and support early risk stratification. Importantly, we observed that TOF cases progressing to TOF-PA consistently demonstrated pulmonary artery diameters below the 5th centile, while non-progressing TOF cases presented above this threshold. Likewise, evolving am-VSDs predominantly clustered between the 10th and 25th centiles, whereas non-progressing cases were above the 25th centile. These findings suggest that early great-artery biometry may have predictive value for identifying fetuses at risk of progression, warranting further validation in prospective studies. Our findings also underscore the strong genetic burden associated with CTAs. Consistent with previous literature, 22q11.2 microdeletion emerged as the most frequent cytogenetic abnormality.[13,23–26] Lastly, nearly half of the fetuses exhibited abnormal first-trimester cardiac markers—including increased nuchal translucency, tricuspid regurgitation, or abnormal ductus venosus flow—supporting the integration of cardiac evaluation into first-trimester risk assessment. Overall, this study highlights the need for structured management pathways for CTAs diagnosed early in gestation. This includes high-resolution ultrasound, serial fetal echocardiography, comprehensive genetic testing, and planned delivery in specialized centres. Early recognition and monitoring of these lesions can facilitate timely intervention and minimize unexpected perinatal complications.

Strengths and limitations

This study has several notable strengths. First, it represents one of the largest cohorts of CTAs diagnosed before 16 weeks' gestation with longitudinal follow-up through pregnancy. Second, all

included cases had definitive confirmation of the diagnosis through postnatal evaluation or postmortem examination, ensuring diagnostic accuracy. Third, the prospective collection of aortic and pulmonary artery biometry in the normal population provides valuable reference data for early gestational assessment of great-artery size—an area where validated nomograms have been lacking. However, some limitations must be acknowledged. The retrospective design introduces potential selection and information bias, despite the comprehensive image review by experienced fetal cardiologists. First-trimester TOP cases without postmortem confirmation could not be included, potentially underestimating the true prevalence of severe CTA phenotypes. Additionally, although the study identifies promising early predictors of lesion evolution, prospective studies with larger sample sizes are needed to validate their clinical utility, refine surveillance intervals, and optimize prenatal counselling strategies.

Conclusions

Conotruncal anomalies diagnosed before 16 weeks' gestation exhibit considerable antenatal variability, with approximately 27% demonstrating progression—most commonly during the third trimester. Early diagnosis should prompt comprehensive prenatal counselling and structured follow-up, particularly in settings where choices regarding pregnancy continuation are constrained by gestational age limits. Serial fetal echocardiography remains essential for monitoring anatomical and functional changes, and comprehensive genetic testing, including microarray and potentially WES, should be offered given the high prevalence of associated abnormalities. Early great-artery dimensions, particularly pulmonary artery calibre, may help differentiate stable from potentially progressive lesions within each CTA subgroup and thus support individualized risk stratification. By providing the largest dataset to date with longitudinal assessment of first-trimester CTA evolution and newly established early gestational nomograms, this study contributes substantially to the understanding of early cardiac development, improving prenatal management and perinatal planning for affected families.

Conflicts of interest: none.

Funding: none.

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Tables Legend

Table 1. Nomograms of pulmonary artery diameter (mm) in the normal population between 12+0- and 15+6-weeks gestations (median and 1st, 3rd, 5th, 10th, 25th, 75th, 90th, 95th, 97th, 99th centiles per gestational age).

Table 2. Nomograms of aorta diameter (mm) in the normal population between 12+0- and 15+6-weeks gestations (median and 1st, 3rd, 5th, 10th, 25th, 75th, 90th, 95th, 97th, 90th centiles per gestational age).

Table 3. Median for AO/AP ratio and AP/AO ratio according to gestational age.

Figures Legend

Figure 1. Flow chart displaying the 131 CTAs cases and outcomes. *Abbreviations: TOP, termination of pregnancy; CTA: conotruncal anomaly; amVSD, ventricular septal defect with anterior malalignment; TOF: tetralogy of Fallot; DORV: double outlet right ventricle; TGA: transposition of great arteries; cTGA: congenitally corrected TGA.*

Figure 2. Bar chart showing the distribution of the 70 ongoing CTA cases according to CTA subtype. *Abbreviation: am-VSD: anterior malalignment ventricular septal defect; TOF: tetralogy of Fallot; PA: pulmonary atresia; TA: truncus arteriosus; DORV: double outlet right ventricle; TGA: transposition of the great arteries; cTGA: congenitally corrected TGA; IAA-B: interrupted aortic arch type B.*

Figure 3. Fetus with an outlet VSD with anterior malalignment (am) and right-sided aortic and ductal arches detected at 14 weeks of gestation, which progressed to TOF in the second trimester. A. Early echocardiography showed an isolated outlet VSD with am. B-C. Second-trimester echocardiography documented progression from outlet VSD with am to TOF. B. An outlet VSD with am. C. The main pulmonary artery was diminutive (arrow), smaller than the ascending aorta (*), with aortic and ductal arches positioned to the right of the trachea (T). Antegrade pulmonary artery flow is present (arrow). *Abbreviations: VSD with am: ventricular septal defect with anterior malalignment; TOF, tetralogy of Fallot; L, left; R, right.*

Figure 4. Fetus with TOF diagnosed at 13 weeks of gestation, which progressed to TOF with pulmonary atresia (PA) by the third trimester. A. Early fetal echocardiography demonstrated an outlet

VSD with anterior malalignment (am) and a main pulmonary artery (arrow) smaller than the ascending aorta. B. Mid-trimester echocardiography showed the same findings: an outlet VSD with am and a hypoplastic pulmonary artery (arrow) relative to the ascending aorta. C. Third-trimester echocardiography documented progression to TOF with PA, characterized by absent antegrade right ventricular outflow and retrograde flow via the ductus arteriosus (arrow). *Abbreviations: TOF, tetralogy of Fallot; PA, pulmonary atresia; VSD with am: ventricular septal defect with anterior malalignment.*

Figure 5. Distribution of pulmonary artery diameters according to gestational age at measurement.

Figure 6. Distribution of aortic diameters according to gestational age at measurement.

Tables

Table 1. Nomograms of pulmonary artery diameter (mm) in the normal population between 12+0 and 15+6 weeks gestations (median and 1st, 3rd, 5th, 10th, 25th, 75th, 90th, 95th, 97th, 99th centiles per gestational age).

Gestational age (wks)	Mean GA	1st	3rd	5th	10th	25th	50th	75th	90th	95th	97th	99th	n
12	12,46	1,29	1,30	1,30	1,40	1,50	1,65	1,70	1,80	1,80	1,80	1,86	38
13	13,13	1,41	1,45	1,48	1,55	1,60	1,70	1,76	1,80	1,83	1,86	1,88	16
14	14,30	1,61	1,65	1,68	1,76	1,90	2,00	2,20	2,24	2,25	2,28	2,29	20
15	15,29	2,0	2,00	2,00	2,04	2,10	2,22	2,70	3,12	3,21	3,21	3,21	15

Table 2. Nomograms of aorta diameter (mm) in the normal population between 12+0 and 15+6 weeks gestations (median and 1st, 3rd, 5th, 10th, 25th, 75th, 90th, 95th, 97th, 90th centiles per gestational age).

Gestational age (wks)	Mean GA	1st	3rd	5th	10th	25th	50th	75th	90th	95th	97th	99th	n
12	12,46	1,06	1,10	1,10	1,17	1,20	1,30	1,48	1,53	1,60	1,60	1,64	38
13	13,13	1,21	1,25	1,28	1,30	1,34	1,40	1,50	1,55	1,60	1,60	1,61	16
14	14,30	1,50	1,53	1,55	1,60	1,64	1,75	1,80	1,91	2,01	2,04	2,08	20
15	15,29	1,89	1,90	1,90	1,94	2,00	2,10	2,40	2,53	2,57	2,58	2,59	15

Table 3. Median for AO/AP ratio and AP/AO ratio according to gestational age.

Gestational age (wks)	Median AO_AP	Median AP_AO
12	0,82	1,22
13	0,87	1,15
14	0,89	1,13
15	0,95	1,05

Figures

Figure 1. Flow chart displaying the 131 CTAs cases and outcomes. *Abbreviations: TOP, termination of pregnancy; CTA: conotruncal anomaly; amVSD, ventricular septal defect with anterior malalignment; TOF: tetralogy of Fallot; DORV: double outlet right ventricle; TGA: transposition of great arteries; cTGA: congenitally corrected TGA.*

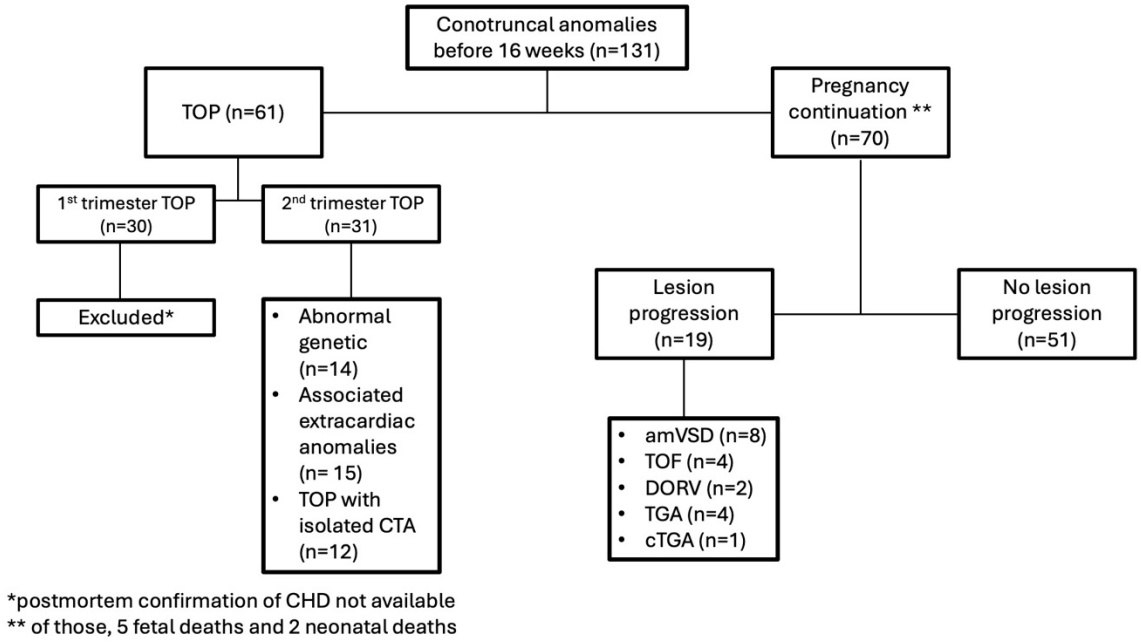

Figure 2. Bar chart showing the distribution of the 70 ongoing CTA cases according to CTA subtype. *Abbreviation: am-VSD: anterior malalignment ventricular septal defect; TOF: tetralogy of Fallot; PA: pulmonary atresia; TA: truncus arteriosus; DORV: double outlet right ventricle; TGA: transposition of the great arteries; cTGA: congenitally corrected TGA; IAA-B: interrupted aortic arch type B.*

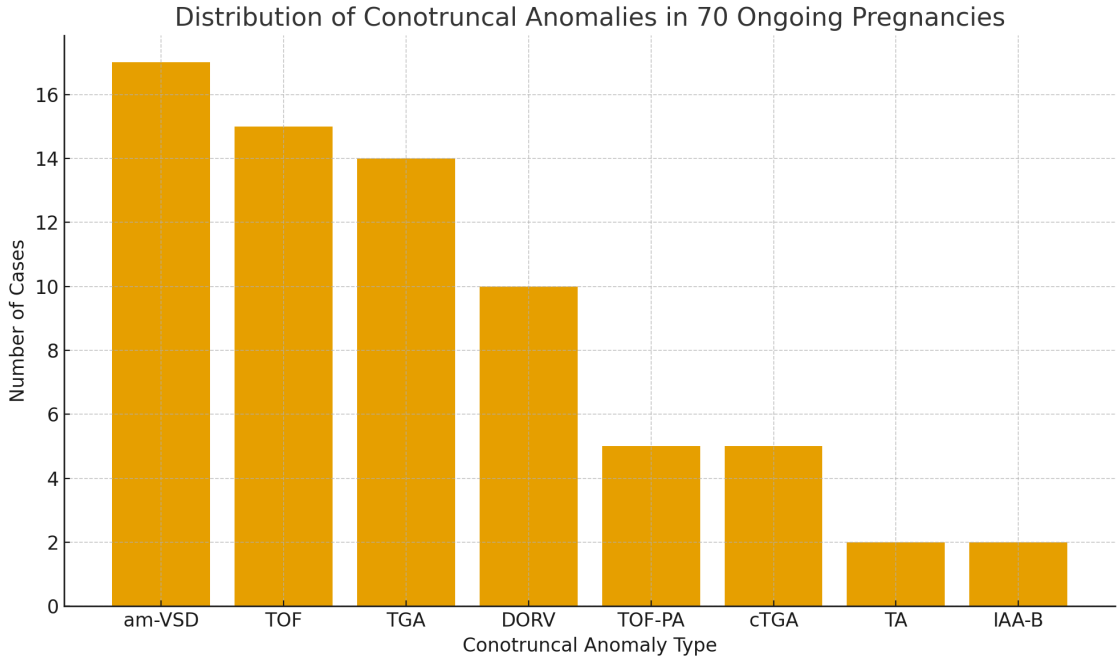

Figure 3. Fetus with an outlet VSD with anterior malalignment (am) and right-sided aortic and ductal arches detected at 14 weeks of gestation, which progressed to TOF in the second trimester. A. Early echocardiography showed an isolated outlet VSD with am. B-C. Second-trimester echocardiography documented progression from outlet VSD with am to TOF. B. An outlet VSD with am. C. The main pulmonary artery was diminutive (arrow), smaller than the ascending aorta (*), with aortic and ductal arches positioned to the right of the trachea (T). Antegrade pulmonary artery flow is present (arrow). *Abbreviations: VSD with am: ventricular septal defect with anterior malalignment; TOF, tetralogy of Fallot; L, left; R, right.*

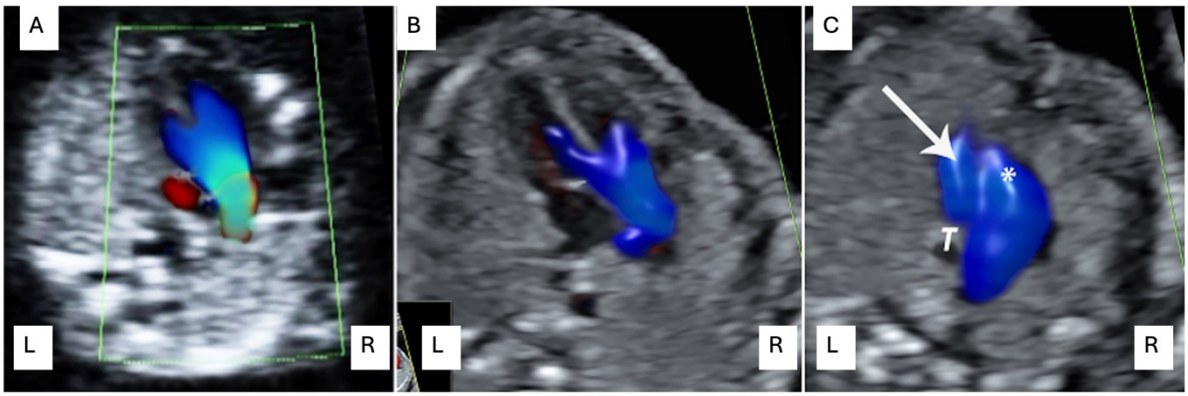

Figure 4. Fetus with TOF diagnosed at 13 weeks of gestation, which progressed to TOF with pulmonary atresia (PA) by the third trimester. A. Early fetal echocardiography demonstrated an outlet VSD with anterior malalignment (am) and a main pulmonary artery (arrow) smaller than the ascending aorta. B. Mid-trimester echocardiography showed the same findings: an outlet VSD with am and a hypoplastic pulmonary artery (arrow) relative to the ascending aorta. C. Third-trimester echocardiography documented progression to TOF with PA, characterized by absent antegrade right ventricular outflow and retrograde flow via the ductus arteriosus (arrow). *Abbreviations: TOF, tetralogy of Fallot; PA, pulmonary atresia; VSD with am: ventricular septal defect with anterior malalignment.*

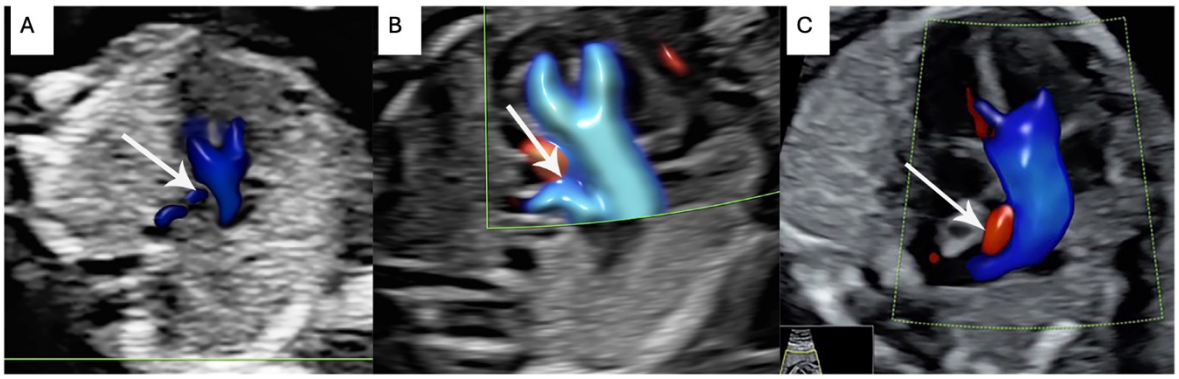

Figure 5. Distribution of pulmonary artery diameters according to gestational age at measurement.

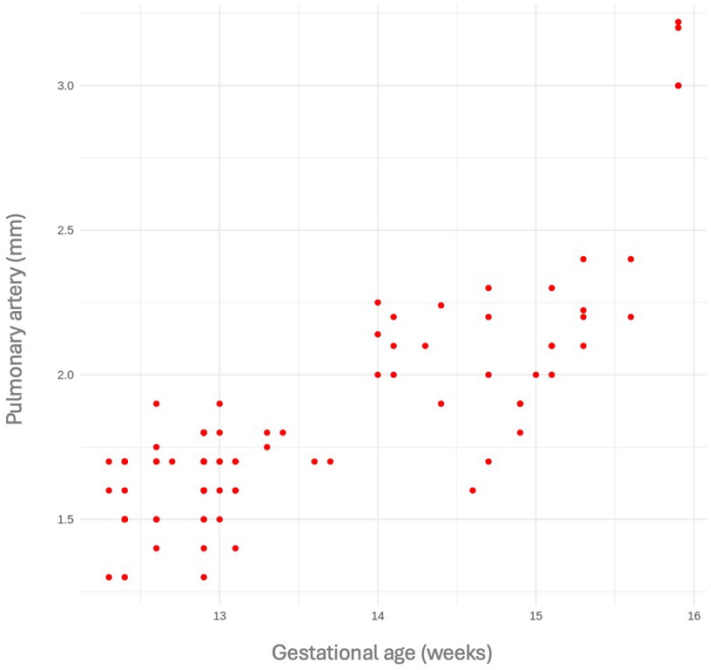

Figure 6. Distribution of aortic diameters according to gestational age at measurement.