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Tetralogy of Fallot and Outlet Ventricular Septal Defect with Anterior Malalignment Detected at Early Fetal Echocardiography

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Keywords
Congenital heart defects · Evolution of heart defects · Fetal echocardiography · First trimester · Nuchal translucency

Abstract
Objectives: To examine the evolution of tetralogy of Fallot (TOF) and outlet ventricular septal defect (VSD) with anterior malalignment (am) from the initial diagnosis at early fetal echocardiography through the gestation and to evaluate the impact of the first-trimester scan on the outcome. ***Methods:*** We identified cases of TOF or outlet VSD with am diagnosed before 16 weeks' gestation. For all cases, prenatal data and pregnancy outcomes were evaluated. In continuing pregnancies, the evolution in severity of the disease was assessed. ***Results:*** Fifty-one fetuses with TOF or outlet VSD with am were diagnosed at early fetal echocardiography. Parents opted for termination of pregnancy in all 23 cases associated with additional anomalies. In 2 of 28 continuing pregnancies, there was an intrauterine death. In the remaining 26, there was progression in severity in 7 (by 20–22 weeks in 3 cases and during the third trimester in the remaining 4). ***Conclusions:*** TOF and outlet VSD with am diagnosed before 16 weeks' gestation can progress in severity throughout pregnancy in over one-quarter of cases. In addition, a high proportion of cases diagnosed in the first trimester may have associated extracardiac anomalies, with a significant impact on clinical management and on the rate of early termination of pregnancy.

Introduction

The majority of congenital heart defects (CHDs) develop during the first trimester of pregnancy, but some of these lesions continue to evolve throughout gestation [1]. Progression in severity of tetralogy of Fallot (TOF) and outlet ventricular septal defect (VSD) with anterior malalignment (am) [2], aortic override, and a normally sized pulmonary artery has been reported during the second half of pregnancy [1, 3, 4]. However, progression of these conditions during the first half of the pregnancy has not been systematically investigated. Commonly, detection of CHDs, which can progress throughout gestation, causes uncertainty for families and physicians; for this reason, knowledge of the history of TOF and outlet VSD with am throughout pregnancy is crucial for an appropriate counselling. Recently,

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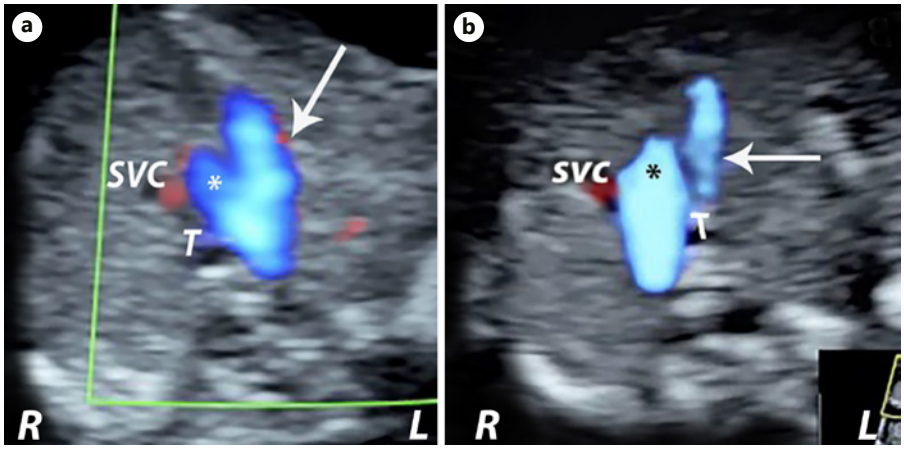

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Fig. 1. a Three-vessel trachea view in color Doppler in a 13-week gestational age normal fetus. The image shows the main pulmonary artery (arrow) and ductal arch in the most anterior position, the SVC in the most posterior position and the ascending aorta (*) and aortic arch in between. The main pulmonary artery lies on the left; the aortic arch is more central. On the right, the SVC is visualized in its cross section. Anterior to the spine, the trachea (T) is recognized as a black circular structure. Note the V shape of the great vessels pointing to the left of trachea. **b** Three-vessel trachea view in a fetus at 13 weeks' gestation with TOF and RAA (case 2, Table 2). Note the diminutive main pulmonary artery (arrow) and the course of aortic arch to the right side of the trachea (T). *Ascending aorta; SVC, superior vena cava; TOF, tetralogy of Fallot; RAA, right aortic arch; L, left; R, right.

with modern sonographic equipment, an accurate evaluation of the fetal heart can be made by experienced operators in the first and early second trimesters [5, 6]. These advances in the ultrasound technology [7–10] may allow investigation of the hemodynamic consequence and subsequent evolution of CHDs from the first trimester of pregnancy onwards. The objective of this study was to examine the evolution of TOF and outlet VSD with am with aortic override and a normally sized pulmonary artery from the initial diagnosis at early fetal echocardiography (<16 weeks) through the second and third trimesters of pregnancy and to assess the impact of an early diagnosis on subsequent pregnancy management and outcomes.

Methods

This was a retrospective multicentric study on a cohort of pregnancies undergoing early ultrasound assessment at three fetal medicine centers in Italy. The study population included both low-risk patients and cases referred because of an increased risk for chromosomal, cardiac, or extracardiac defects between 2012 and 2018. The databases of our fetal medicine units (Viewpoint and Astraia software GmbH, Germany) were searched for all fetuses who had a diagnosis of TOF (outlet VSD with am with aortic override and pulmonary outflow obstruction) or outlet VSD with am, at early echocardiography and confirmed by postnatal echocardiography, surgery, and/or postmortem examination. The obstruction of the right ventricular outflow tract (RVOT) was diagnosed when the main pulmonary artery appeared smaller than the ascending aorta [11]; in these cases, the outflow sweeps and three-vessel view (Fig. 1) demonstrated discrepancy in great artery size. Other TOF variants as TOF with absent pulmonary valve syndrome and pulmonary atresia (PA) with VSD were excluded from the study. Maternal biochemistry data (free β-human chorionic gonadotrophin and pregnancy-associated plasma protein A) and ultrasound parameters, including crown-rump length (CRL), nuchal translucency (NT) thickness, nasal bone, ductus venosus (DV) and tricuspid (TR) valve flow, associated cardiac and extracardiac anomalies, as well as fetal karyotype supplemented by microarray, were retrieved from the database, where available. In addition, gestational age at diagnosis and follow-up, indication for early echocardiography, and feto-neonatal outcomes were also collected. For each case, video clips and/or 4D heart volume datasets acquired using spatiotemporal image correlation, recorded at the time of the early scan, were reviewed offline retrospectively. All examinations were performed with a commercially available Voluson E8 and E10 ultrasound system (GE Healthcare Medical Systems, Zipf, Austria) equipped with high-resolution transabdominal and transvaginal transducers (RAB 4e8 MHz, C 2e9 MHz, RM6C matrix 1–7 MHz sector probes, and RIC 6e12 MHz). As a standard requirement of our institutions, all patients provided signed informed consent for fetal examination and agreed to storage of digital images and measurement data for identified quality control and offline data evaluation. Digital images were stored on the hard drive of the ultrasound equipment and transferred to the archiving and documentation system.

Results

A total of 51 fetuses with TOF or outlet VSD with am were diagnosed at early fetal echocardiography during the study period. In 23 cases, the parents opted for termination of pregnancy (TOP) because of associated cardiac, extracardiac, and/or chromosomal abnormalities, and 12 of these 23 cases were excluded from subsequent analysis

Table 1. Summary of termination of pregnancy cases with autopsy confirmation

Cases	Early echocardiography	Time of diagnosis	First trim markers	First trim associated findings	Autopsy findings	Fetal karyotype	Outcome, wk
1	TOF + RAA	13 + 4	TR, rDV	No	ND	22q11 microdel	TOP at 16
2	TOF + RAA	14 + 6	Not assessed	Bil. CLP	ND	Nl	TOP at 16
3	TOF + ARSA	14 + 6	Not assessed	Renal anomalies	ND	22q11 microdel	TOP at 17
4	TOF + AVSD	13 + 4	Increased NT, rDV	No	ND	Trisomy 21	TOP at 16
5	ml VSD + RAA	14 + 4	Not assessed	Renal anomalies	ND	22q11 microdel	TOP at 16
6	TOF	15 + 0	Not assessed	Abdominal cyst	ND	NO	TOP at 16
7	TOF + RAA	14 + 4	Not assessed	No	ND	22q11 microdel	TOP at 17
8	TOF + RAA	15 + 0	Not assessed	Abdominal wall defect	ND	NO	TOP at 16
9	TOF	13 + 4	Nl	Unil. absence of fibula	ND	Nl	TOP at 16
10	TOF + AVSD	12 + 6	Increased NT	No	ND	Trisomy 21	TOP at 16
11	TOF	14 + 1	Not assessed	SUA and DH	ND	Nl	TOP at 16

TOF, tetralogy of Fallot; ml VSD, outlet ventricular septal defect with anterior malalignment; RAA, right aortic arch; AVSD, atrioventricular septal defect; First trim markers, first trimester markers for aneuploidies and heart defects; TR, tricuspid regurgitation; rDV, abnormal ductus venosus; NT, nuchal translucency; No, absent; Bil. CLP, bilateral cleft lip and palate; Unil., unilateral; SUA, single umbilical artery; DH, diaphragmatic hernia; ND, not different from echo-based findings; 22q11 microdel: 22q11 microdeletion.

because postmortem findings were not available. The remaining 11 cases are listed in Table 1. The number of confirmed cases was 39 (the mean gestational age at diagnosis was 13 weeks, with a range of 12–15 weeks) (Tables 1, 2). In 2 of 28 continuing pregnancies, there was an intrauterine death (Table 2). The number of cases with pregnancy continuation resulting in live birth was 26. In 8 of these remaining 26 cases, the outlet VSD with am was in association with a normal right ventricular outflow tract; in 18 of 26 cases, a RVOT obstruction was documented and a diagnosis of TOF was made (Table 2). There was progression in severity of the heart defect in 7 (27%) (Figs. 2, 3) of 26 fetuses, and this was observed by 20–22 weeks in 3 cases and during the third trimester in the remaining 4 (Table 2). In 5 of these fetuses, the CHDs progressed from outlet VSD with am to TOF (in 3 cases within mid-trimester fetal echocardiography and in 2 in the third trimester – Table 2) because of development of RVOT obstruction. In the remaining 2 cases, the CHDs progressed in the second half of pregnancy from TOF to TOF with pulmonary atresia because a narrow pulmonary outflow progressed to atresia (Table 2). In these cases, there was no anterograde right ventricular outflow and retrograde flow from the ductus arteriosus could be demonstrated. Some other changes in diagnosis at the second trimester echocardiography were relatively minor, such as the recognition of a persistent left superior vena cava (PLSVC) and a right aortic arch (RAA), missed at early fetal echocardiography (Table 2). In 2 cases, an additional major CHD (complete atrioventricular septal defect) was associated (Table 1). In 11 of 39 cases (28%) (10 of TOF and 1 of outlet VSD with am) the aortic arch was right-sided (Tables 1, 2) and in 4 of 39 cases (10%), a 22q11 microdeletion was present (Table 1). Associated anomalies were detected already at the first trimester scan (Table 1) in all but 2 cases. Only 2 missed minor anomalies were identified at the second trimester scan and at birth, respectively (Table 2, cases 7 and 14). Among 25 cases in which first trimester markers of aneuploidies and CHDs were examined, NT was increased and/or an abnormal TR and/or DV flow were present in 13 cases (52%). Twenty two of 25 fetuses were chromosomally normal (Tables 1, 2). Among the 39 pregnancies for which the outcome was known, there were 3 deaths, 2 in utero demises in fetuses with early onset severe growth restriction and hydrops, respectively (Table 2, cases 27 and 28), and 1 during the postnatal period after surgery (Table 2, case 9). At present, all the remaining infants are alive and well (Table 2).

Discussion

TOF and outlet VSD with am are part of a spectrum of the same disease, sharing a common anatomical basis, but with different presentations after birth. The key anatomical features result from an outlet VSD with am with an anterior-cephalad deviation of conal septum and overriding of the aorta. Anterior deviation of the outlet septum

Table 2. Summary of data and clinical outcomes of pregnancies with continuation and confirmed anatomy

Cases	Early echocardiography	Time of diagnosis	First trimester markers	Second trimester echocardiography	Third trimester echocardiography	Fetal karyotype	Outcome
1	TOF	13 + 2	Increased NT, DVr, TR	NC	NC	Nl	Alive
2	TOF + RAA	13 + 4	Nl	NC	NC	Nl	Alive
3	TOF + ARSA	12 + 5	Increased NT, rDV	NC	NC	Nl	Alive
4	TOF	12 + 6	Increased NT	TOF + RAA	NC	Nl	Alive
5	TOF	13 + 4	Nl	TOF + PLSVC	NC	Nl	Alive
6	TOF	13 + 4	Increased NT, rDV	NC	TOF + PA	Nl	Alive
7	TOF	14 + 6	Not assessed	NC	NC	Nl	Alive[b]
8	TOF	12 + 3	Nl	NC	NC	No	Alive
9	TOF	12 + 3	Increased NT	NC	TOF + PA	Nl	Died after surgery
10	TOF	12 + 4	Nl	NC	NC	Nl	Alive
11	TOF + RAA	14 + 6	Not assessed	NC	NC	Nl	Alive
12	TOF	13 + 2	Increased NT, rDV, TR	TOF + PLSVC	NC	Nl	Alive
13	TOF	15 + 0	Not assessed	NC	NC	Nl	Alive
14	TOF	13 + 6	Nl	NC[a]	NC	Nl	Alive
15	TOF	13 + 2	Nl	NC	NC	No	Alive
16	TOF	14 + 6	Not assessed	NC	NC	No	Alive
17	TOF	13 + 4	Nl	NC	NC	Nl	Alive
18	TOF	13 + 2	Nl	NC	NC	Nl	Alive
19	ml VSD	12, 4	Increased NT, rDV	NC	TOF	Nl	Alive
20	ml VSD + RAA	14 + 6	Not assessed	TOF + RAA	NC	Nl	Alive
21	ml VSD	13 + 4	rDV, TR	NC	NC	Nl	Alive
22	ml VSD	12 + 5	Increased NT	TOF	NC	Nl	Alive
23	ml VSD	15 + 0	Not assessed	NC	TOF	Nl	Alive
24	ml VSD	14 + 6	Not assessed	TOF	NC	Nl	Alive
25	ml VSD	13 + 4	Increased NT	NC	NC	Nl	Alive
26	ml VSD	13 + 6	Nl	NC	NC	Nl	Alive
27	TOF + RAA	12 + 4	Nl	Not available	Not available	No	IUD at 19 wk
28	TOF + RAA	13 + 4	Nl	Not available	Not available	No	IUD at 16 wk

TOF, tetralogy of Fallot; ml VSD, outlet ventricular septal defect with anterior malalignment; RAA, right aortic arch; ARSA, aberrant right subclavian artery; NT, nuchal translucency; TR, tricuspid regurgitation; rDV, abnormal ductus venosus; Nl, normal; NC, no change in diagnosis; PLSVC, persistent left superior vena cava; PA, pulmonary atresia; No, not performed; IUD, intrauterine death. [a] Mild ventriculomegaly detected at the second-trimester scan. [b] Mild hydronephrosis detected at birth.

contributes to progressive outflow obstruction that may be subtle at early gestations. This latter feature may be variable in severity and timing of evolution [12]. Recently, the recognition of increased NT at 11–14 weeks' gestation as a marker for aneuploidies and its association with an increased risk of CHDs [13–15], especially when associated with TR and DV anomalies, have led to sonographic evaluation of the fetal heart at this early stage. In fact, in our series, a significant number of cases (52%) underwent fetal echocardiography because of presence of these indirect markers of CHDs (Tables 1, 2). A further 25% of cases were at high risk for CHDs on the basis of familiar, maternal, or fetal factors. The remaining 23% of cases occurred in a low-risk group, and early echocardiography was performed because of suspected cardiac abnormalities at the first trimester evaluation of the fetal heart approached in our clinical setting [16]. With modern sonographic equipment, a detailed evaluation of the heart can be made by experienced operators in the first trimester [5–10]. Our study confirmed that despite the small size of anatomical structures at this early stage, the diagnosis of outlet VSD with am and TOF was feasible. However, the objective of this study was not to evaluate the accuracy of the early fetal echocardiography for the detection of these CHDs. Progression of an outlet VSD with am in TOF and of TOF in TOF with PA in the second half of pregnancy or after birth has been reported [1, 3–5, 12, 17, 18] (Table 3), and the progression in severity of the disease was described in association with a worse outcome. Previous studies reported a poor outcome of TOF

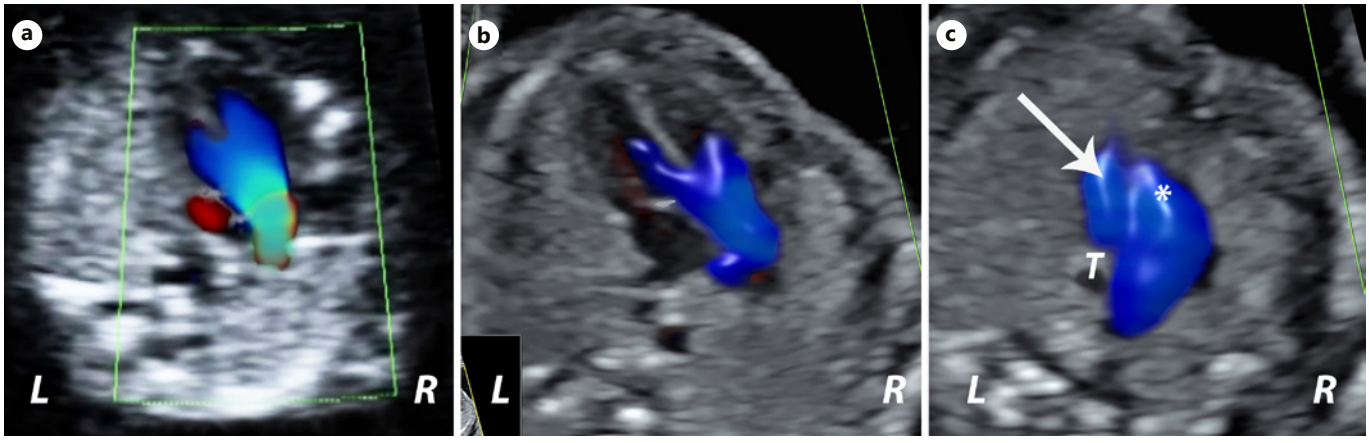

Fig. 2. Fetus with outlet VSD with am and right aortic and ductal arches detected at 14 weeks of gestation progressed to TOF in the second trimester (case 20, Table 2). **a** At early echocardiography an isolated outlet VSD with am was detected. **b**–**c** At second trimester echocardiography, evolution from outlet VSD with am to TOF was documented. **b** An outlet VSD with am was associated with (**c**) a diminutive main pulmonary artery (arrow), smaller than the ascending aorta (*). Aortic and ductal arches are to the right of the trachea (T). Note the presence of antegrade pulmonary artery flow (arrow). VSD, ventricular septal defect; am, anterior malalignment; TOF, tetralogy of Fallot; L, left; R, right.

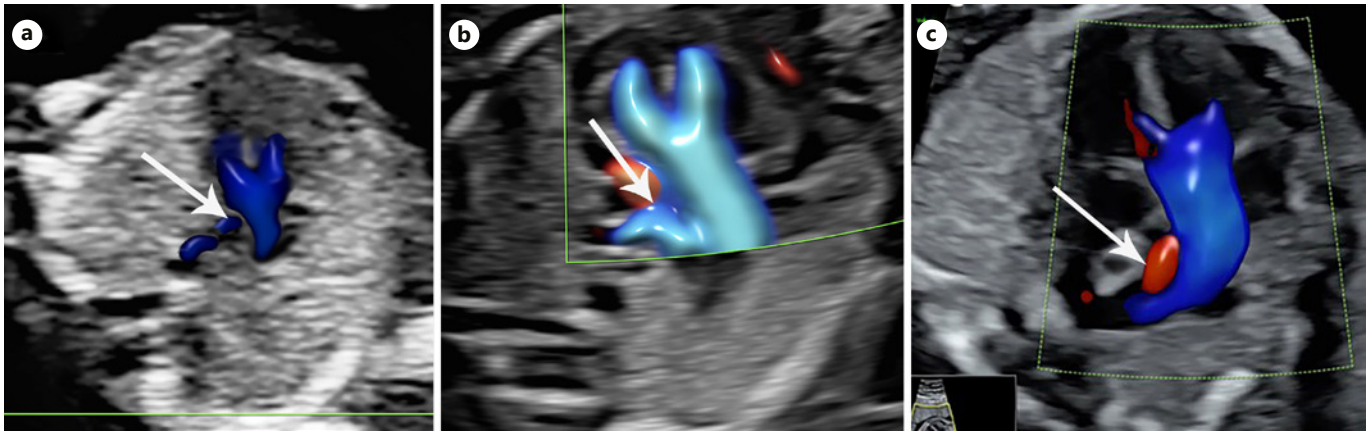

Fig. 3. Fetus with TOF diagnosed at 13 weeks of gestation progressed to TOF with PA in the third trimester (case 6, Table 2). **a** At early fetal echocardiography an outlet VSD with am associated with the main pulmonary artery (arrow) smaller than the ascending aorta was detected. **b** At mid-trimester echocardiography the diagnosis was unchanged: an outlet VSD with am associated with the pulmonary artery (arrow) smaller than the ascending aorta was evident. **c** At third trimester echocardiography, evolution from TOF to TOF with PA was documented: detectable antegrade right ventricular outflow was absent and retrograde flow from the ductus arteriosus was present (arrow). TOF, tetralogy of Fallot; PA, pulmonary atresia; VSD, ventricular septal defect; am, anterior malalignment.

diagnosed prenatally at mid-trimester echocardiography, essentially because of the high rate of associated extracardiac and chromosomal anomalies and the evolution in more severe forms such as TOF with PA [4]. A progressive narrowing of the pulmonary artery branches has been observed in several forms of TOF from mid-trimester to birth [4, 17, 18]. However, no studies investigated in utero progression of TOF and outlet VSD with am from 12 weeks onwards. In our report, only one case of associated anomalies (Table 2, case 14) was missed at the first trimester scan and detected at the mid-trimester scan. This occurred because in all the other cases, associ-

Table 3. Progression during pregnancy from TOF to TOF with PA

Authors	From TOF to TOF with PA, %
Allan et al. [18]	(3/16) 18
Hornberger et al. [23]	(2/16) 12
Pepas et al. [17]	(2/25) 8
De Robertis et al. [current study]	(2/18) 11

TOF, tetralogy of Fallot; PA, pulmonary atresia.

ated anomalies were detected early in pregnancy and parents opted for early TOP (Table 1). As previously reported, an early scan performed at 12–14 weeks' gestation by a competent sonographer can identify about half of the prenatally detectable structural anomalies and all of those expected to be detected at this stage, particularly severe anomalies [19]. Furthermore, several studies documented that the frequency of chromosomal and structural abnormalities in fetuses depends on the gestational age and that it is higher in the first trimester [7–20]. For these reasons, moving prenatal screening to early stages of pregnancy seems to significantly reduce the number of fetuses with CHDs and/or associated comorbidities usually detected later in pregnancy. In our study, at the present, except for 1 case all infants are alive and well (Table 2). In all but 2 cases, no extracardiac, cardiac, or chromosomal defects were associated at birth. Although this study has the drawback of including a relatively limited number of cases, it represents, to the best of our knowledge, the first attempt at outlining the course of specific types of CHDs, including the availability of follow-up information, when the diagnosis is made at early echocardiography. Even if it is not easy to assess the size of pulmonary vessels at the early stage of pregnancy in view of technical limitations and because the Doppler flow patterns are not of major utility in this setting, our data confirmed that TOF and outlet VSD with am progressed in severity during pregnancy and that this occurred in over one-quarter of cases when diagnosed at early echocardiography. If confirmed by other studies, this is important for providing couples with correct information about the progression of these CHDs and for planning the most appropriate clinical management. In addition, a high proportion of cases diagnosed in the first trimester may have associated anomalies, with a significant impact on clinical management and on the rate of early TOP, with a consequent reduction both in the overall prevalence of these defects and in the rate of non-isolated cases seen at the mid-trimester scan. In fact, it has been previously reported that the spectrum and frequency of the CHDs found prenatally differ from those found postnatally [21, 22]. In this study, we documented that TOF and outlet VSD with am cases at early echocardiography and mid-trimester echocardiography differed significantly as well with more comorbidities, pregnancy terminations, and intrauterine deaths in the first and early second trimesters. Further studies are necessary to confirm our results on larger populations of fetuses with TOF and outlet VSD with am diagnosed in the first trimester of pregnancy.

Statement of Ethics

The authors have no ethical conflicts to disclose. Subjects gave their written informed consent. No animal experiments were performed as part of this study. Our research complies with the guidelines for human studies and was conducted ethically in accordance with the World Medical Association Declaration of Helsinki. Ethics approval was not required for this study as it was a retrospective analysis of imaging performed for clinical reasons.

Conflict of Interest Statement

The authors have no conflicts of interest to declare.

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Author Contributions

All authors have made substantial contributions to the study and endorsed the data and conclusions. N.P., G.V., I. F., C.O., and A.G. performed data collection, imaging interpretation, and data analysis. V.D. conceived and designed the study. G.R. and P.V. were involved in the interpretation of results, data analysis, and critical appraisal of the report. All authors were involved in writing the paper.

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