Tetralogy of Fallot in the fetus — from diagnosis to delivery. 18-year experience of a tertiary Fetal Cardiology Center

Agnieszka Grzyb[1, 2], Adam Koleśnik[3, 4], Renata Bokiniec[5], Joanna Szymkiewicz-Dangel[1]

[1]Department of Perinatal Cardiology and Congenital Anomalies, Center of Postgraduate Medical Education, Warszawa, Poland
[2]Department of Cardiology, The Children's Memorial Health Institute, Warszawa, Poland
[3]Cardiovascular Interventions Laboratory, The Children's Memorial Health Institute, Warszawa, Poland
[4]Department of Descriptive and Clinical Anatomy, Medical University of Warsaw, Warszawa, Poland
[5]Department of Neonatology and Intensive Care, Medical University of Warsaw, Warszawa, Poland

Correspondence to:
Prof. Joanna Szymkiewicz-Dangel, MD, PhD,
Department of Perinatal Cardiology and Congenital Anomalies,
Center of Postgraduate Medical Education,
Agatowa 10, 03–680 Warszawa, Poland,
phone: +48 601 269 636,
e-mail: jdangel@cmkp.edu.pl

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ABSTRACT

Background: Tetralogy of Fallot (TOF) is a common congenital heart disease but very heterogeneous in terms of detailed cardiac anatomy, associated malformations, and genetic anomalies, especially when assessed prenatally.

Aims: We aimed to analyze the clinical spectrum of TOF in the prenatal period, including detailed cardiac morphology, coexisting anomalies, and their impact on short-term neonatal outcome. We also assessed changing trends in the prenatal diagnostic workup of TOF.

Methods: A retrospective cohort study including fetuses diagnosed with TOF between 2002 and 2019 was conducted in a tertiary Fetal Cardiology Center. Medical records and echocardiographic examinations were reviewed to collect demographic, sonographic, and genetic data.

Results: Among 326 TOF fetuses, 237 (73%) had pulmonary stenosis (TOF-PS), 72 (22%) pulmonary atresia (TOF-PA), and 17 (5%) absent pulmonary valve (TOF-APV). The yearly number of diagnoses increased during the study period, with decreasing fetal age at the time of diagnosis. Extracardiac malformations were found in 172 (53%) fetuses, cardiovascular malformations in 159 (49%), and genetic anomalies in 99 (39% of the tested group). Hypoplastic thymus, right aortic arch, and polyhydramnios were sonographic markers of microdeletion 22q11. Left-to-right ductal flow was predictive of postnatal ductal dependency. The perinatal outcome was dependent on the presence of associated anomalies and disease subtype, with TOF-APV having the worst prognosis.

Conclusions: Extracardiac and genetic anomalies are common in fetuses with TOF, and, together with disease subtype and ductal flow assessment, they impact the perinatal management and outcomes. Genetic testing with array comparative genomic hybridization should be offered in all cases.

Key words: congenital heart disease, fetal echocardiography, microdeletion 22q11, prenatal diagnosis, tetralogy of Fallot

INTRODUCTION

Tetralogy of Fallot (TOF) is the most common cyanotic congenital heart disease (CHD) occurring in 1 out of 2800 live births [1]. Morphologically, it is a conotruncal defect with an antero-cephalad deviation of the outlet septum combined with hypertrophy of the septoparietal trabeculation, which results in a large malalignment ventricular septal defect (VSD) with the overriding aorta and various degree of right ventricular outflow tract (RVOT) obstruction. Three groups of TOF are usually recognized: TOF with pulmonary stenosis (TOF-PS), TOF with pulmonary atresia (TOF-PA), and TOF with absent pulmonary valve (TOF-APV) [2] (Supplementary material, *Figures S1–S3*).

TOF may coexist with a multitude of genetic, extracardiac, and cardiovascular anomalies, which can all impact the outcome [3–6]. Prenatal diagnosis of TOF, feasible already in the first trimester of pregnancy [5, 7],

WHAT'S NEW?

The article provides a detailed description of the largest reported to date single-center cohort of fetuses with tetralogy of Fallot. It contains data on diagnosis, coexisting anomalies, as well as natural history and early prognosis of this congenital heart defect. Multivariable logistic regression models to predict the presence of genetic anomalies, including microdeletion 22q11, were created. Pulmonary artery dimensions and ductus arteriosus morphology were analyzed in different subtypes of the disease. Altogether, the article may be helpful for prenatal counseling, and appropriate peripartum planning in prenatally diagnosed cases of tetralogy of Fallot.

allows cardiologists to fully appreciate these associations, including the most severe forms of the disease, unseen in the postnatal period [3, 5, 8].

This study aimed to analyze the group of fetuses diagnosed with TOF in a single tertiary Fetal Cardiology Center during 18 years. We assessed the associations between the subtypes of TOF, pulmonary arteries' size, genetic anomalies, and extracardiac malformations, as well as their impact on pregnancy outcomes and short-term postnatal management.

METHODS

This was a retrospective cohort study conducted in a single referral Fetal Cardiology Center (before 2017 — Perinatology Clinic at the 2nd Department of Obstetrics and Gynecology, Medical University of Warsaw, and since 2017 — Department of Perinatal Cardiology and Congenital Anomalies, Center of Postgraduate Medical Education). We browsed the databases for all cases of TOF diagnosed between 2002 and 2019; fetuses with ambiguous or postnatally revised diagnoses were excluded from the study.

Examinations were performed with three ultrasound machines: ACUSON Sequoia 512, GE Voluson 730 Expert, and Philips EPIQ 7G using transabdominal convex 5–9 MHz and sector 3.5–7 MHz transducers. The study protocol included biometric measurements, general fetal anatomy and peripheral flows assessment, and detailed echocardiographic examination. Fetuses were divided into three groups: TOF-PS, TOF-PA, and TOF-APV, as described earlier. Diameters of the pulmonary valve (PV), pulmonary trunk (MPA), and left and right pulmonary artery (LPA and RPA) were measured prospectively in the last available prenatal examination and converted to Z-scores according to published data [9]. Velocity across the pulmonary valve, the presence of the ductus arteriosus (DA), and the direction of ductal flow were noted. Associated demographic and medical data were collected from the records.

The available methods of genetic testing changed during the study period. Initially, it was classical karyotype followed by fluorescent in situ hybridization (FISH) for microdeletions, and since 2016 — usually array comparative genomic hybridization (aCGH).

Statistical analysis

Data were analyzed with STATISTICA 13 (TIBCO) software. Binary data were compared with the Fisher exact test. Student t-test and the Mann-Whitney u tests were used to compare quantitative variables, after assessing normality with the Shapiro-Wilk test. The Pearson correlation was used for continuous quantitative data. For multiple group comparisons, the Kruskal-Wallis ANOVA with *post-hoc* Dunn test was applied. Multivariable logistic regression models, including demographic and sonographic data (maternal age, presence, and the number of extracardiac malformations, selected associated cardiac anomalies, polyhydramnios, fetal growth restriction, and thymus hypoplasia), were created to define the risk factors of genetic anomalies. Backward stepwise regression was used, and receiver operating characteristic (ROC) curves were constructed to assess the fitness of the final model.

Patients' consent to use the data for research purposes was obtained before the studies. No additional ethics approval was necessary for the analysis of retrospective data.

RESULTS

Diagnosis

TOF was diagnosed in 326 fetuses within the study period, with a male-to-female ratio of 1.21. The most common subtype was TOF-PS (n = 237, 73%), followed by TOF-PA (n = 72, 22%) and TOF-APV (n = 17, 5%). In four fetuses with TOF-PS, we observed progression of RVOT obstruction resulting in no forward flow through the pulmonary valve at the end of pregnancy; they were included in the TOF-PS group.

The leading reason for referral to the echocardiographic examination was an abnormal heart scan during the screening ultrasound (88%); 162 patients (50%) had more than one reason for referral (Supplementary material, *Table S1*). The yearly number of diagnoses was increasing, especially after the obligatory three-vessel view and outflow-tract views were added to the screening guidelines (in 2012). Fetal age at diagnosis ranged from 12 to 39 weeks (median [interquartile range, IQR], 23 [21–28] weeks) and decreased in subsequent years (Figure 1). Fetal and maternal age at diagnosis did not differ between disease subtypes.

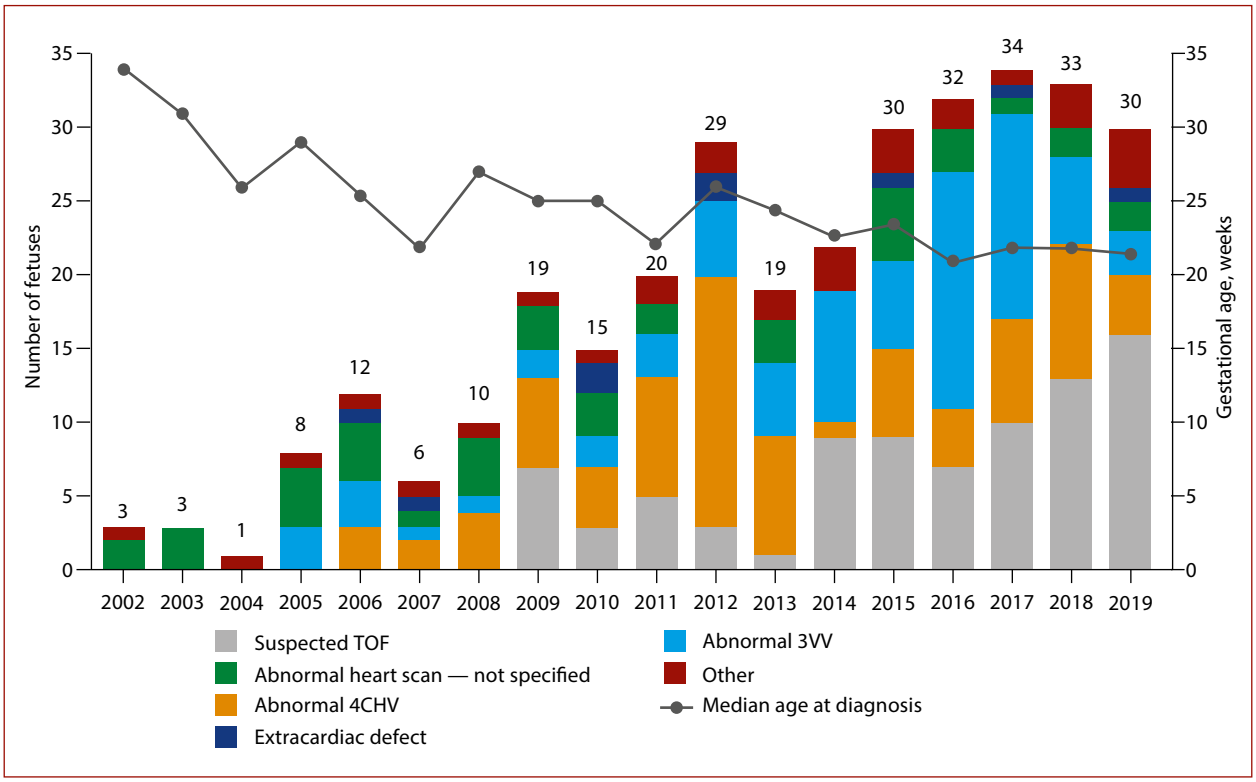

Figure 1. Number of fetuses diagnosed with tetralogy of Fallot (TOF), main reason for referral, and median gestational age at diagnosis by years

Abbreviations: 4CHV, four-chamber view; 3VV, three-vessel view

Genetic anomalies

Genetic tests were performed in 256 fetuses (78.5%); in the remaining cases patients refused to undergo invasive procedure. Overall, 188 (73%) fetuses had karyotype analysis, 128 (50%) together with FISH, and 68 (27%) — aCGH.

Genetic test results were normal in 157 fetuses (61% of tested cases, 48% of the whole group). The most common chromosomal aberrations were trisomies 21, 18, and 13, and triploidy (Table 1). Trisomy 21 was the most common aberration in the TOF-PS group (n = 33, 17.9%). Microdeletion 22q11 was found in 38 fetuses (14.8%), with a significantly high prevalence in the TOF-APV group (n = 6, 46.2%). In eight newborns with either normal karyotype (n = 5) or not tested prenatally (n = 3), specific phenotypic features led to a postnatal diagnosis of genetic syndromes (Table 1).

For further analyses, genetic anomalies were classified as gross chromosomal aberrations (detectable in classical karyotype, excluding microdeletion 22q11), lethal chromosomal aberrations (e.g. trisomy 18), and non-lethal chromosomal aberrations (e.g. trisomy 21).

In the group with no genetic testing performed prenatally (n = 70, 21.5%), among 56 live-born children, 47 neonates were normal (based on the accessible medical documentation), five died before genetic testing, and four showed dysmorphic features.

Cardiovascular findings and associated extracardiac malformations

An increased cardiac angle was observed in all TOF subgroups, with the highest values in TOF-APV (mean, 80°; standard deviation [SD], 12°), followed by TOF-PA (73° [10°]), and TOF-PS (68° [13°]) (P <0.001 for TOF-APV vs. TOF-PS and P = 0.003 for TOF-PA vs. TOF-PS). The cardiac angle was bigger in fetuses with microdeletion 22q11 (mean 77° vs. 68°; P <0.001) and was unaffected by the presence of major aortopulmonary collateral arteries (MAPCAs) or sidedness of the aortic arch. Cardiac size was normal in the majority of fetuses, except for the TOF-APV group, where moderate cardiomegaly was usually observed. It is important to notice that some extracardiac anomalies observed in fetuses with TOF (e.g. congenital diaphragmatic hernia) may affect both cardiac size and angle, and hinder detailed heart examination.

Associated cardiovascular anomalies (excluding MAPCAs and anomalies of the DA) were present in 159 fetuses (49%) (Supplementary material, *Table S2*). The most common were right aortic arch (RAA, n = 80, 25%), left superior vena cava (LSVC, n = 35, 11%), and atrioventricular septal defect (AVSD, n = 26, 8%). Fetal arrhythmias and symptoms of fetal heart failure were infrequent; however, the latter were found almost exclusively in fetuses with TOF-APV (29% vs. 2%, P <0.001).

Table 1. Genetic anomalies found in fetuses with tetralogy of Fallot

	All	TOF-PS	TOF-PA	TOF-APV
Genetically tested	256 (78.5%)	184 (77.6%)	59 (81.9%)	13 (76.5%)
Normal	157 (61.3%)	118 (64.1%)	36 (61.0%)	3 (23.1%)
Karyotype only	21 (8.2%)	20 (10.9%)[b, e]	1 (1.7%)	
Karyotype and FISH	98 (38.3%)	67 (36.4%)[a, d]	28 (47.5%)[a]	3 (23.1%)
aCGH	38 (14.8%)	31 (16.8%)	7 (11.9%)	
Abnormal	99 (38.7%)	66 (35.9%)	23 (39.0%)	10 (76.9%)
Trisomy 21	35 (13.7%)	33 (17.9%)[f]	2 (3.4%)[f]	
Trisomy 18	7 (2.7%)	4 (2.2%)	1 (1.7%)	2 (15.4%)
Trisomy 13	8 (3.1%)	5 (2.7%)	2 (3.4%)	1 (7.7%)
Trisomy 9	1 (0.4%)			1 (7.7%)
47,XXY	1 (0.4%)		1 (1.7%)	
69,XXX	4 (1.6%)	1 (0.5%)	3 (5.1%)	
Microdeletion 22q11	38 (14.8%)	18 (9.8%)[g, h]	14 (23.7%)[g]	6 (46.2%)[h]
Other	5 (2.0%)	5 (2.7%)		
No genetic test done	70 (21.5%)	53 (22.4%)[a, b]	13 (18.1%)[c]	4 (23.5%)

Percentages calculated out of genetically tested groups

Other chromosomal aberrations included 45 XX t(13;14)(q10;q10), 46,XY,inv.(9)(p11q13)+mar, 47,XY,inv(9)(p12q13)+der(22),t(11:22)(q23.3q11.2), mosaicism 45,X0/46,XX, and trisomy 22 mosaicism. In 8 newborns, genetic anomalies were diagnosed postnatally — Alagille syndrome in 3 cases[a], microdeletion 22q11 in 2 cases[b], trisomy 21[c], CHARGE association[d], and Robinow syndrome[e] in 1 case each. [f]$P = 0.005$. [g]$P = 0.01$. [h]$P < 0.001$, remaining comparisons are not significant

Abbreviations: aCGH, array comparative genomic hybridization; APV, absent pulmonary valve; FISH, fluorescent in-situ hybridization; PA, pulmonary atresia; PS, pulmonary stenosis; TOF, tetralogy of Fallot

Table 2. Predictive factors for gross chromosomal aberration and microdeletion 22q11 in fetuses with tetralogy of Fallot

Variable	Parameter	OR (95% CI)	*P*-value
Gross chromosomal aberration	Maternal age	1.08 (1.01–1.15)	0.02
	Number of ExCM	1.42 (1.09–1.86)	0.01
	AVSD	12.69 (4.55–35.35)	<0.001
	Right aortic arch	0.36 (0.15–0.87)	0.02
	Fetal growth restriction	2.42 (1.18–4.99)	0.02
Microdeletion 22q11	Hypoplastic thymus	130.3 (30.44–557.92)	<0.001
	Right aortic arch	6.22 (1.75–22.16)	0.005
	Polyhydramnios	18.51 (3.43–99.77)	0.01

Abbreviations: AVSD, atrioventricular septal defect; ExCM, extracardiac malformation; OR, odds ratio

Extracardiac malformations (ExCM), excluding fetal growth restriction (FGR) were found in 172 patients (53%). Most often they affected genitourinary and skeletal systems (Supplementary material, *Table S2*). Seventy-five (23%) fetuses had more than one ExCM, and 58 (18%) had critical malformation, defined as either lethal (e.g. bilateral renal agenesis), or seriously debilitating and requiring early intervention (e.g. myelomeningocele). Fourteen newborns presented with defects that were not evident prenatally (e.g. esophageal or anal atresia, included in the statistics). The frequency of ExCM was the highest (n = 13, 76%) in the TOF-APV group, but due to genetic correlations of ExCM, the sole impact of the TOF subtype is difficult to determine.

Multivariable logistic regression models were developed to account for the combined influence of demographic data, cardiovascular and extracardiac malformations on the risk of gross chromosomal aberrations and microdeletion 22q11 (Table 2). ROC curves showed good fitness of final models (area under the curve [AUC], 0.77; 95% confidence interval [CI], 0.70–0.84 and AUC, 0.92; 95% CI, 0.86–0.98, respectively). The presence and increasing number of ExCM in the fetuses were indicative of gross chromosomal aberration, together with AVSD (specific for trisomy 21), FGR, and increasing maternal age.

Thymus assessment was feasible in 315 (97%) fetuses, and in 60 (18%), it was qualitatively described as hypoplastic (Supplementary material, *Figure S2*). Hypoplastic thymus was found in 34/40 (85%) fetuses with microdeletion 22q11, serving as a specific marker of this genetic anomaly, together with right aortic arch and polyhydramnios (Table 2). Polyhydramnios, however, usually appeared in the late second or third trimester of pregnancy.

FGR, defined as estimated fetal weight below the third percentile, was observed in 63 (19%) fetuses and was usually associated with either chromosomal aberrations (but not microdeletion 22q11) or ExCM (n = 47, 75%). Estimated fetal weight in cases with no coexisting anomalies was within normal limits for gestational age.

Pulmonary arteries and ductus arteriosus

Measurements of pulmonary arteries were feasible in 310 (95%) cases and showed marked differences between groups (Table 3). They were usually within normal limits in TOF-PS and TOF-PA cases with DA; hypoplastic in TOF-

Table 3. Mean diameters (Z-scores) of pulmonary valve and arteries in different subtypes of tetralogy of Fallot

Structure	TOF-PS	TOF-APV	TOF-PA (DA only)	TOF-PA (MAPCAs, no DA)	*P*-value
PV	–3.05 (1.70)	–1.69 (2.31)			0.005
MPA	–2.40 (1.45)	0.82 (3.25)			<0.001
RPA	–0.62 (1.17)[a]	5.98 (2.57)	–0.72 (1.19)[a]	–3.24 (1.58)	[a]*P* = 1.0, other comparisons *P* <0.001
LPA	–0.22 (1.09)[a]	4.60 (2.85)	–0.53 (1.38)[a]	–2.67 (1.32)	

Abbreviations: DA, ductus arteriosus; MAPCAs, major aortopulmonary collateral arteries; MPA, main pulmonary artery; LPA/RPA, left/right pulmonary artery; PV, pulmonary valve; other — see Table 1

Table 4. Pregnancy outcome and follow-up of live-born patients

	TOF-PS	TOF-PA	TOF-APV
Live-born (one-month follow-up)	195 (82.3%)	54 (75.0%)	11 (64.7%)
Alive after intervention	38	25	3
Alive, no intervention	136	20	2
Died after intervention	2	2	2
Died before intervention	4	5	3
Palliative care	8	2	1
Unknown	7		
Intrauterine death	17 (7.2%)[a]	7 (9.7%)	4 (23.5%)[a]
Lethal chromosomal aberration	3	3	3
Not lethal chromosomal aberration	4		
Microdeletion 22q11	1	1	
Extracardiac malformation	14	6	4
Critical extracardiac malformation	5	5	1
Fetal growth restriction	6	5	
Isolated heart defect	1	1	
Termination of pregnancy	20 (8.4%)	7 (9.7%)	1 (5.9%)
Lethal chromosomal aberration	3	1	
Not lethal chromosomal aberration	6	1	
Microdeletion 22q11	2	1	
Extracardiac malformation	16	5	1
Critical extracardiac malformation	10	2	1
Fetal growth restriction	3		
Isolated heart defect	2	2	
Unknown follow-up	5 (2.1%)	4 (5.6%)	1 (5.9%)

Intervention refers to surgical or interventional augmentation of pulmonary blood flow. [a]*P* = 0.02, remaining comparisons are not significant

Abbreviations: see Table 1

PA with MAPCAs and no DA, and markedly distended in TOF-APV (Supplementary material, *Figures S1–S3*). Peak velocity across the pulmonary valve in TOF-PS fetuses was above 100 cm/s in most cases; however, it was highly variable (mean 116 cm/s, SD 41 cm/s). It showed significant, yet weak inverse correlation with PV diameter Z-score (r = –0.16; *P* = 0.03).

DA was absent in all fetuses with TOF-APV, which is considered typical for this subtype [10]. In the TOF-PA group, DA was the sole source of pulmonary blood flow in 32 (44%) cases, together with MAPCAs in 15 (21%), and was considered absent in 25 (35%) fetuses. Microdeletion 22q11 occurred more frequently in TOF-PA fetuses with multiple MAPCAs vs. DA only (40% vs. 9% of genetically tested fetuses; *P* = 0.01). Out of 13 newborns having both DA and MAPCAs, 5 (38%) were prostaglandin-dependent. In the TOF-PS group, DA was absent in 16 (7%) fetuses.

Perinatal outcome

Pregnancy outcome was known in 316 (97%) cases and is detailed in Table 4. There were 260 live births (80%), at median 38 weeks of gestation (range 26–42 weeks; IQR, 37–39 weeks); 116 (46%) children were born via cesarean section, mostly for obstetrical reasons. Most newborns were in good condition (median first and fifth minute Apgar score 9; IQR, 8–10), with a mean (SD) body weight of 2980 (670) g.

Twenty-eight (8.5%) fetuses died in utero, and there were 28 terminations of pregnancy (8.5% of all cases, 18.3% of cases diagnosed before the 23rd week of gestation). Most of these fetuses presented with a coexisting genetic or extracardiac anomaly. Among factors analyzed as predictors of intrauterine death, only lethal chromosomal aberration occurred statistically significantly (odds ratio [OR], 18.2; 95% CI, 5.9–55.6; *P* <0.001).

Neonatal follow-up was available in 253 cases (97% live births). Early neonatal deaths were rare (n = 12, 4.6%), usually due to cardiorespiratory failure in TOF-APV, refractory desaturation with pulmonary anatomy unsuitable for surgery in TOF-PA, and coexisting anomalies and prematurity in TOF-PS. Eleven (4%) children received palliative care due to lethal genetic aberration or critical ExCM. Overall, the worst prognosis was observed in the TOF-APV group, with only 5 (45%) children alive at one month of age.

Prostaglandin infusion in the newborn with TOF-PS was indicated if there was left-to-right DA flow in the last prenatal examination, proximal narrowing or isolation of the branch pulmonary artery, and, in a few cases with coexisting critical ExCM (e.g. diaphragmatic hernia) to provide stable pulmonary blood flow in the perioperative period. Overall, 40 (20.5%) neonates with TOF-PS required interventional or surgical treatment to augment pulmonary blood flow within the first month of life, prostaglandin infusion was started at birth in 37 (92.5%) of them.

DISCUSSION

Despite its precise morphological definition, TOF constitutes a heterogeneous group, with various degree of RVOT obstruction, associated defects, and genetic anomalies significantly influencing clinical presentation and outcomes [3–6].

Diagnosis

The predominant indication for referral to the fetal echocardiographic examination and time of diagnosis in our study were similar to other reports [5–7, 11, 12]. Even though TOF may be diagnosed already in the first trimester of pregnancy, a detailed examination is difficult at that time, which may result in an incorrect diagnosis or underestimation of the disease severity [7, 13]. Therefore, in our opinion, early echocardiographic findings should be always reassessed to provide full and reliable counseling to the parents.

Increased cardiac angle is considered a characteristic feature of fetal conotruncal defects, often prompting the diagnosis [14, 15]. Single reports suggest its impact on the prognosis [16]; however, considering the multitude of factors affecting the heart position in the chest, we think it is not fully justified.

Genetic anomalies

Our study confirms a high prevalence of chromosomal anomalies and microdeletion 22q11 among fetuses with TOF (higher than reported in postnatal series), with microdeletion 22q11 especially common in TOF-APV (46%) [5, 6, 12, 17–21]. The frequency of reported genetic anomalies depends on the rate and method of genetic testing, and therefore, the true prevalence may be even higher.

Microdeletion 22q11 in the fetus may be associated with other sonographic findings. Hypoplasia of the thymus [22] seems to be the best marker, highly specific, and relatively easy to assess in the mediastinal section. Other previously reported indicators included polyhydramnios, FGR, extracardiac malformations, anomalies of aortic branching and pulmonary arteries, and MAPCAs [6, 17, 21, 23–25]. In our study, we could confirm the predictive value of RAA and polyhydramnios only.

The purposefulness of genetic testing for microdeletion 22q11 in all fetuses with TOF used to be a matter of debate [24]. However, considering both the high frequency and multisystemic impact of microdeletion 22q11 (CATCH 22 syndrome), testing all fetuses with TOF seems not only justified, but indicated, especially when additional risk factors are present [19]. The next step in prenatal genetic testing may be whole-exome sequencing (WES), whose usefulness has already been shown in the diagnostic setup of fetuses with CHDs. However, limited accessibility, difficult interpretation, and high cost preclude its routine use so far [26].

Associated cardiovascular findings and extracardiac malformations

According to the literature, ExCM occurs in 34%–60% of fetuses with TOF and most commonly affects the skeletal, urogenital, gastrointestinal, and central nervous systems, which finds confirmation in our material [3, 5, 6, 8, 12, 19]. Detection of ExCM before heart defect should prompt an early diagnostic assessment, including echocardiography and genetic testing. The latter is valid especially in cases with severe or multiple ExCM, or with FGR, which suggest underlying genetic anomaly. Contrary to some previous studies [27, 28], our data do not confirm retarded growth of all fetuses with isolated TOF.

Heterogeneity of TOF is also reflected in the possible spectrum and high frequency of associated cardiovascular anomalies. Some of them are of little hemodynamic importance but may indicate underlying genetic abnormality (e.g. RAA — microdeletion 22q11). AVSD strongly correlates with trisomy 21 (65% of fetuses with AVSD in our study) and impacts postnatal surgical management. Finally, rarely encountered associations (e.g. myocardial non-compaction) require an individualized approach with variable outcomes. [5, 6, 8, 17, 19–21, 23–25, 29].

Pulmonary arteries' growth in fetuses with TOF was reported as variable and often unpredictable, together with a possibility of progressive RVOT obstruction [30–33]. Our study shows that diameters of pulmonary arteries often fall within the normal range in fetuses with TOF-PS and TOF-PA supplied by DA, contrary to the TOF-PA group with multiple MAPCAs, where pulmonary arteries are markedly hypoplastic. Some fetuses with TOF-PA may have both small DA and MAPCAs, and it may be difficult to differentiate between them or to correctly identify central pulmonary arteries. Therefore, we tend to commence prostaglandin infusion in all neonates with TOF-PA until more detailed imaging.

DA assessment in TOF-PS patients is equally important, but not always easy [34]. In some cases, it may be absent or

close spontaneously during pregnancy. Left-to-right flow across the DA is considered the best predictor of ductal dependency after birth [30, 33, 35, 36], also from our perspective. Data about other factors (e.g. diameter of the PV and pulmonary arteries, velocity across the PV) are ambiguous, and a detailed analysis falls beyond the scope of this article and will be addressed in another study. Agenesis of the DA in TOF-APV fetuses is recognized as a characteristic feature; however, its pathophysiology remains unclear [10, 37, 38].

Outcomes

Compared to the previously published series, our study shows a slightly higher rate of in-utero deaths and a much lower rate of terminations of pregnancy. Both observations may be associated and reflect the natural history of the disease, as most fetuses who died prenatally had either genetic abnormality or ExCM, which are reported as the main reasons for pregnancy terminations [5, 6, 8, 39]. Among possible predictors of in-utero demise, only lethal chromosomal aberrations occurred significant in our study. The impact of heart failure, TOF-APV subtype, or extracardiac malformations, as suggested by other reports [40], could not be sufficiently proven.

The short-term prognosis of neonates with TOF is generally good but dependent on the coexistence of genetic aberrations, and extracardiac malformations (as discussed earlier), and except for the TOF-APV group, where heart failure and bronchial compression are often present [10, 20, 38]. Therefore, all anatomical and genetic factors should be taken into account to provide reliable counseling to the parents. Considering the potential progression of RVOT obstruction, the disease severity should be reassessed possibly close to term.

Limitations

The retrospective character of the study affects the availability and quality of data. Genetic coverage and follow-up of the study population were not complete.

Supplementary material

Supplementary material is available at https://journals.viamedica.pl/kardiologia_polska.

Article information

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