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Prenatal echocardiography in Trisomy 18 — the key to diagnosis and further management in the second half of pregnancy

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ABSTRACT

Objectives: Trisomy 18 is an autosomal chromosomal disorder, which is associated with numerous ranges of congenital anomalies. Purpose of this largest study in Poland was to analyze diagnosis and follow-up of fetuses with the prenatal diagnosis of Trisomy 18 in our tertiary center.

Material and methods: The study was conducted in a tertiary center for fetal cardiology. The inclusion criteria comprised fetuses with karyotype of Trisomy 18. Data on number of delivery, number of pregnancy, cardiac and extracardiac diseases, type and date of childbirth, sex, birth date, Apgar score, survival time and autopsy were analyzed.

Results: There were 41 fetuses with diagnosis confirmed by amniocentesis: 34 were females, 7 males. CHD was detected prenatally in 73% cases at mean gestational age of 26 weeks. The most common CHD was AV-canal (13 cases, 43%) and VSD (13 cases, 43%). In 1999–2010 the average time to detect a heart defect was 29 weeks, in 2011–2021 it was 23 weeks ($p < 0.01$, U-Mann-Whitney). IUGR was diagnosed in the 3rd trimester in 29 cases (70%), polyhydramnion in 21 cases (51%).

Conclusions: Congenital heart defects in female fetuses with intrauterine growth restriction in 3rd trimester with polyhydramnios and in subsequent pregnancy, regardless of maternal age, were typical prenatal findings for Trisomy 18. Heart defects with incomplete septum such as AVC or VSD (which nowadays can be detected in the 1st half of the pregnancy) were the most common anomaly in Edwards Syndrome. These heart defects did not require intervention in the early neonatal period.

Key words: Trisomy 18; Edwards Syndrome; congenital heart defects; chromosomal disorder

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INTRODUCTION

Trisomy 18 also known as Edwards syndrome, is a chromosomal disorder due to the presence of an extra chromosome 18. It was first described in 1960 by Edwards et al. and Smith et al. [1, 2]. Worldwide study estimates the total prevalence of Trisomy 18 as 4.08 per 10,000 births [3]. The reported live birth prevalence is 0.96–1.12 per 10,000 births [3–5]. Mortality among infants with Trisomy 18 is high, secondary to malformations associated with this syndrome. Approximately 50% of babies with Trisomy 18 live no longer than 1 week and about 5-10% of children reach the first year [6].

Edwards syndrome is associated with a wide range of congenital anomalies, which could be detected by prenatal ultrasound, which sensitivity in this syndrome is reported by 80–90% [7]. One of the most frequent are cardiac malformations, however most of its data come from autopsy examinations [8, 9].

Due to development of prenatal care, some highly referenced hospitals started to offer surgical treatment of

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congenital anomalies (mainly cardiac), which contributes to extended time of survival [10]. Our analyzed group of Trisomy 18 is actually the largest studied group in Poland and unique because it shows the natural lifespan of this condition (there was only one case of termination of pregnancy).

MATERIAL AND METHODS

A retrospective cohort study was conducted that compiled fetal diagnosed with Trisomy 18 who were followed in a tertiary fetal cardiology center from 1999 to 2021 in which specialists focus on the diagnosis of cardiac and non-cardiac defects, diagnosis, prognosis and management. Examinations were performed by specialists in fetal medicine with the ISUOG recommendation, using GE Voluson E8, GE, Voluson 10 (GE Healthcare, Chicago, IL, USA), and Philips iU22 (Philips, Amsterdam, Netherlands) ultrasound equipment. Gestational age (GA) was calculated based on the last menstrual period (LMP) and fetal biometry. All patients gave their permission for their data to be used for scientific analysis. As the present study focused on the interpretation of previously collected data, rather than performing ultrasound — echocardiographic examinations, no additional approval was required from the local Ethical Committee.

Collected data

Clinical data were obtained through review of the hospital records. Collected data included numerous of pregnancy, numerous of delivery, congenital heart diseases, extracardiac malformations or extracardiac abnormalities, neonatal factors (gestational age at birth, birth weight, Apgar score). Date, circumstances of death, postnatal autopsy were included in the analysis.

Polyhydramnios has been estimated based on the AFI index (amniotic fluid index). Fetal growth restriction was defined as an estimated fetal weight inferior to the 10th percentile for the gestational age using the 2013 Fenton growth chart for preterm infants.

Statistical analysis

All statistical analyses were performed using Statistica 13.1 software. Descriptive analysis was performed. Categorical variables are presented as frequencies and percentages; continuous variables as means and standard deviations. To estimate the survival function from lifetime data, the Kaplan-Meier estimator was used.

RESULTS

41 fetuses with trisomy 18 (of 41 gravidae) were followed between 17th and 41st week of pregnancy, and by the time of conclusion of this study, none of them remained alive. Mean maternal age was 30 +/– 7 years. There were 25 plurigravidae (max. pregnant 6 times) and 16 primigravidae. Trisomy 18 were diagnosed in 41 fetuses within the study period by amniocentesis (Fig. 1). There were 1 up to 6 cases per year in our unit (with an average of 1200 pregnancies per year). There were 2 cases of mosaicism. 34 fetuses were females, and 7 fetuses were males, with female-to-male ratio of 4.86. Structural congenital heart defect (CHD) was detected prenatally in 30 cases (73%) at the mean gestational age of 26 weeks (Fig. 2). In the years 1999–2010, the average time to detect a heart defect was 29 weeks, in 2011–2021 it was 23 weeks, and the observation was statistically significant ($p < 0.01$, U-Mann-Whitney) (Fig. 3). The most common heart defect was atrioventricular canal (13 cases, 43%), which was

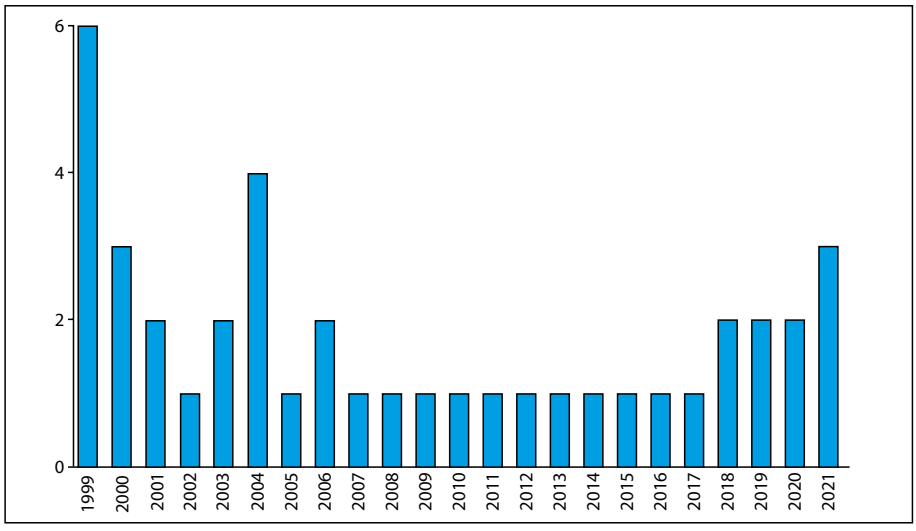

Figure 1. Number of fetuses with Trisomy 18, examined in the Department of Prenatal Cardiology in 1999–2021

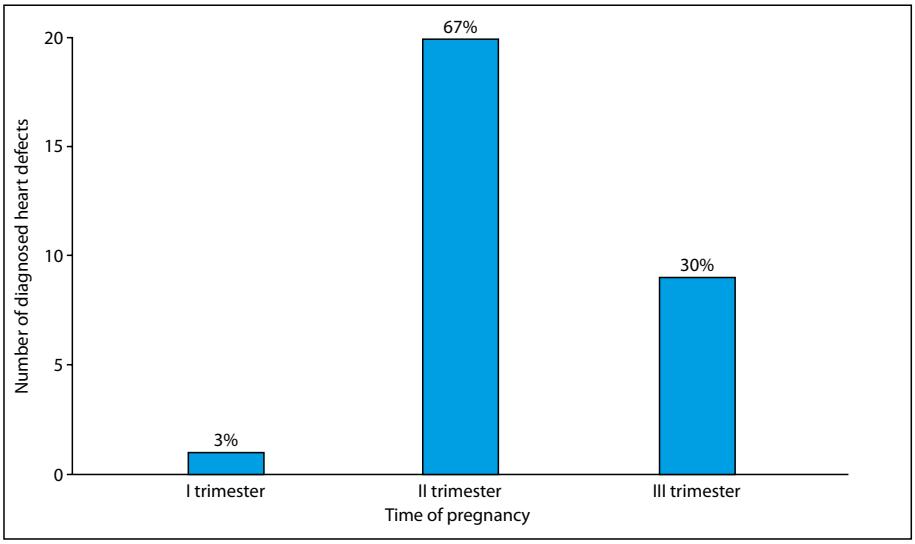

Figure 2. Number of diagnosed congenital heart defects with Trisomy 18 according to trimester of pregnancy

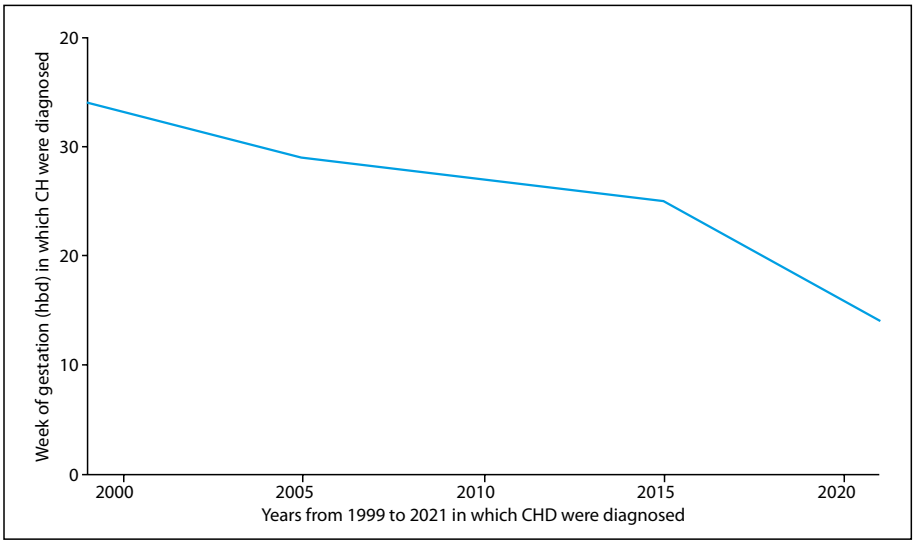

Figure 3. Graph presents the mean weeks of pregnancy in which congenital heart defect (CHD) were detected, depending on the year

simple in 11 cases and complex in 4 cases and ventricular septal defect (13 cases, 43%), which was simple in 8 cases and complex in 5 cases.

Intrauterine growth restriction was diagnosed in 29 cases (69%). Polyhydramnion was observed in 21 cases (51%). Detailed prenatal diagnosis of subsequent cases is presented in Table 1.

In terms of delivery: in 26 cases (66%) there was vaginal delivery (inclusively IUD) and in 14 cases (33%) there was a cesarean section. There were 6 cases of intrauterine demise (IUD) and 1 termination of pregnancy. The newborns were born on average in the 32th +/- 2 weeks with mean birth weight 1827 +/- 444 grams. None of the newborns reached 2500 grams at delivery. None of the newborns reached Apgar score 8 points. Figure 4 and 5 presents the postnatal lifespan of the study group.

DISCUSSION

Edwards syndrome is associated with a wide range of congenital anomalies such as congenital heart defect, choroid plexus cysts, gastrointestinal disease such as diaphragmatic hernia and imperforate anus, microcephaly, omphalocele, kidney abnormalities, early-onset of fetal growth restriction (FGR). Reported skeletal dysmorphology signs

Table 1. Detailed prenatal diagnosis of cases of Trisomy 18 examined in Prenatal Cardiology Department

No. of case	Structural Heart Defects	Functional Heart Defects	Cardio-megaly	IUGR	Polyhydra-mnion	Skeletal malforma-tions	Gastrointest-inal malforma-tions	Central nervous system malformations	Urinary malform-ations	Diaphra-gmatic hernia
1	+		+	+		+		+		
2	+			+	+					
3	+			+	+					
4	+		+	+	+	+	+			
5					+		+	+		+
6	+			+	+		+			
7	+			+	+		+			
8	+			+	+					
9	+			+				+		
10		+	+	+				+		+
11							+			
12	+			+		+		+		
13	+			+						
14	+			+						
15	+			+	+					+
16	+			+					+	
17	+			+	+					
18	+			+						
19	+			+						
20	+			+	+		+			
21	+			+	+	+		+		
22				+				+		
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24	+			+	+					
25	+			+	+		+			
26	+			+	+				+	
27	+			+				+		
28				+						
29	+			+	+				+	
30	+			+						
31					+	+				
32	+		+		+	+	+			
33	+		+		+	+				
34				+	+					
35		+	+	+		+			+	
36	+					+		+		
37	+		+			+		+		
38	+					+	+			
39					+	+	+	+		
40	+				+	+				
41		+				+	+	+		
Total	30	3	7	29	21	14	11	12	4	

3 IUGR — intrauterine growth restriction

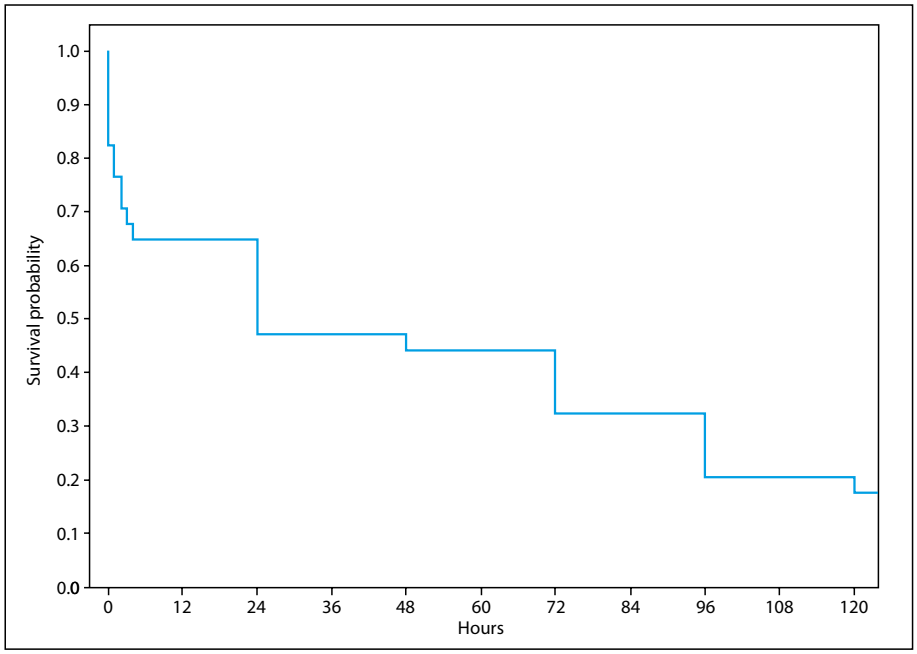

Figure 4. Kaplan-Meier graph presenting lifespan of prenatally detected trisomy 18 cases during the first 5 days of postnatal life

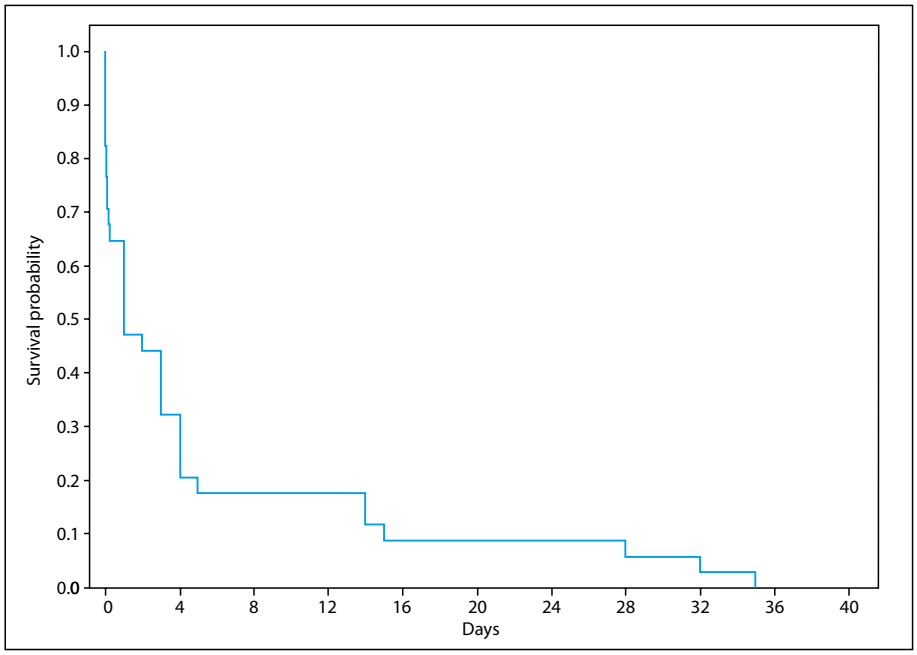

Figure 5. Kaplan-Meier graph presenting lifespan of prenatally detected trisomy 18 cases during the first 40 days of postnatal life

include limb abnormalities, overlapping fingers, polydactyly, radial aplasia, clenched hands, and rocker bottom feet which mostly are seen in partial types [10–15] (Tab. 1). These anomalies could be detected mostly by prenatal ultrasound, but at different gestational ages. In the past, Trisomy 18 was described as lethal. Currently is defined as a genetic defect that predicts a short survival time. Newborn with Trisomy 18 mostly were needed on hospital basis ventilatory support, oxygen, and feeding assistance [16, 17]. These needs and medical complexity sometimes lead to long hospital stays. Early referral and neonatal palliative care based on prenatal diagnosis and postnatal confirmation could be discussed in

advance to promote a holistic advanced care plan for both the patient and his family [14, 15, 18].

According to literature, for the detection of Trisomy 18, ultrasound findings seem to be more effective than biochemical screening. Sensitivity of ultrasound screening for Trisomy 18 was reported around 70%, while a multiple marker test [alpha fetoprotein, human chorionic gonadotropin (HCG), unconjugated estriol] was abnormal only in 43% of cases with Trisomy 18 [19]. In our series of Trisomy 18 the mean NT measure at I trimester was 1,6 mm. The combination with highest accuracy is sonography, triple test and amniocentesis [20–22]. To these days, sampling of fetal material obtained through invasive testing is essential for precise prenatal diagnosis of Edwards Syndrome.

Ultrasound anomalies could be observed in all organ systems, with the timing of detection dependent on the organ system involved. Becker et al. [23] in their article proved that nineteen of every twenty fetuses with Edwards Syndrome have at least one abnormal ultrasound finding. Also in our research, we noticed that all fetuses had more than one ultrasound abnormality. More than that, structural congenital heart defect (CHD) was detected prenatally in 30 cases (73%). In our group, the most common cardiovascular anomaly was common atrioventricular canal (AVC), which was presented by 13 fetuses (43%) (Fig. 6). AVC was isolated in 11 cases and complex in 4 cases. AVC results in a significant interatrial, interventricular and systemic-to-pulmonary shunt, thus inducing right ventricular pressure, volume overload and pulmonary hypertension. Due to newest studies, surgery may play a role in preventing pulmonary hypertension and prolonged survival [24]. The second common CHD was ventricular septal defect (13 cases, 43%), which was isolated in 8 cases and complex in 5 cases. What is more - sometimes specific for Trisomy 18 craniofacial abnormalities could be undetectable, that's why full echocardiographic examination is necessary (Fig. 7). Such evidence allow us to conclude that congenital heart defects affecting septum may be a diagnostic marker of Trisomy 18, which was confirmed by another Polish research [25].

Matsuoka et al. [25] studied 15 autopsied cases of Trisomy 18 and focused on congenital heart defects. From their group, 73% infants had patent ductus arteriosus. Also, Bruns et al. [27] prepared a review from parent-reported information of 84 cases with full Trisomy 18. They focused on prenatal and postnatal assessment, and confirmation of cardiac defects. At birth, parent responses indicated the presence of 50 patient patent ductus arteriosus (PDA) (59.5%). From a prenatal cardiology point of view, the patent ductus arteriosus in a premature newborn is not a congenital heart defect but an acquired defect. Open ductus arteriosus during fetal life is necessary for fetal wellbeing and survival during gestational age.

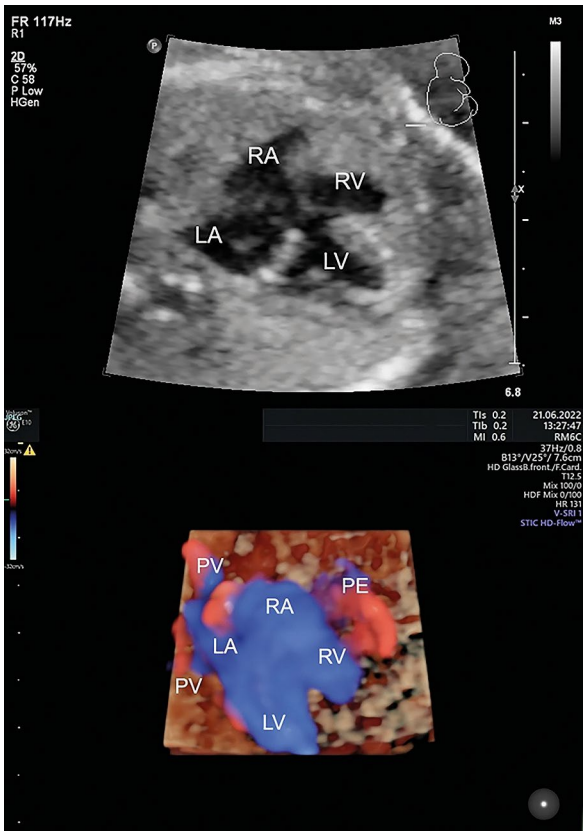

Figure 6. An example of common atrioventricular canal in Trisomy 18

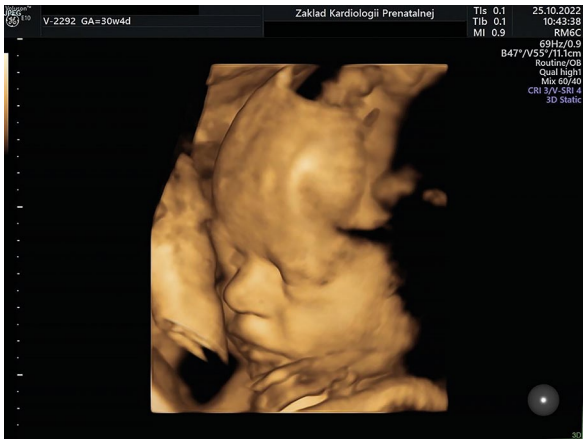

Figure 7. 3D scan of fetus with Trisomy 18

In another study other ultrasound parameters were examined. Czuba et al. focused on quantitative and qualitative Ductus Venosus (DV) blood flow evaluation in the screening for Trisomy 18 [28]. They concluded that assessment of blood flow in ductus venosus in the first trimester significantly influences the improvement of screening values focusing on Trisomy 18. Detection Rates of examined chromosomal

abnormalities using contingent screening were: 92.1% using DV abnormal a-wave and 94.84% using Ductus Venosus — Pulsatility Index for Vein (DV-PIV) [28].

Polyhydramnios combined with an intrauterine growth restriction is associated with high incidence of malformations [29]. As a result of that, this combination may indicate Trisomy 18 and had particularly poor prognosis [30], but intrauterine growth restriction (IUGR) is obvious relatively late. In our group of 41 fetuses, intrauterine growth restriction was diagnosed in 29 cases (69%), polyhydramnion was observed in 21 cases (51%). In another retrospective study, which included 255 pregnancies complicated by periviable FGR, a confirmed genetic abnormality (Trisomy 18) accounted for 33% cases of FGR [31]. Also, Silva et al. [32] in their study based on 6 cases of Trisomy 18 provided that all patients had a diagnosis of fetal growth restriction. Saller et al. [33] reinforce the importance of a karyotypic evaluation of selected pregnancies complicated by intrauterine growth retardation, even in the third trimester. They presented results in which undiagnosed Trisomy 18 pregnancies are associated with an increased cesarean section rate. In our group, cesarean sections were in 33% of cases, much lower compared to Schneider's et al. [34] in which the primary cesarean section rate for Trisomy 18 was 55.6%. So it seems that correct diagnosis allowed to avoid unnecessary surgical deliveries.

Trisomy 18 pregnancies have a high risk of fetal loss and stillbirth [35–37]. The probability of survival to term increases with the increase of gestational age, it was 41% at 20 weeks [35]. In our group of 41 fetuses in 6 cases (14.63%) there were intrauterine demise (IUD). Goel et al. in their multipopulational group proved that almost half of the mortality occurred within the first week and 87–88% by the first year [3]. In our group, we did not register any case that lived a year. The longest survival time was 35 days (Fig. 4, 5).

In our group no one case was qualified for surgery, however in the last decade publications showed that surgical intervention contributes to greater than 1-year survival ranging 43% and 5-year survival varying between 7.7 and 12.3% [38]. Moreover, Nakai et al. [39] reviewed a group of patients with VSD and Trisomy 18 who underwent two-stage ICR at the Japanese Red Cross Medical Center between 2005–2019. They proved that surgical intervention like two-stage intracardiac repair improves the long-term survival of patients with VSD and Trisomy 18. The median duration of survival was 46.3 months since birth [39].

Nevertheless, among and different abnormalities seen by ultrasonography in fetuses with Trisomy 18, cardiac heart defects could be seen since 1st trimester. Polyhydramnion, IUGR were seen much later. Fetal face evaluation, despite 3D technique, could be misleading (Fig. 7). Detection of heart defects may be a key in proper diagnosis of Trisomy 18 in early pregnancy. In most cases, we observed CHD in Trisomy 18 which are quite uncomplicated and do not require absolute intervention in the early neonatal period. Abnormalities which appear later, such as IUGR and which can affect the neonate's prognosis, even despite the initial good haemodynamic performance.

CONCLUSIONS

Congenital heart defects, in female fetuses with intrauterine growth restriction in the 3rd trimester with polyhydramnios and in subsequent pregnancy, regardless of maternal age, were typical prenatal findings for Edwards Syndrome. Heart defects with incomplete septum such as AVC or VSD (which nowadays can be detected in the 1st half of the pregnancy) were the most common anomaly in Edwards Syndrome. These heart defects did not require intervention in the early neonatal period.

Limitations

The limitation of our study is an incomplete medical history of the first trimester of pregnancy, so we did not analyze the results of biochemistry exams in the 1st trimester, but we took for analysis medical records about NT measurements. The majority of pregnant women came to our department for detailed diagnoses in the second trimester of pregnancy.

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Conflict of interest

All authors declare no conflict of interest.

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