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ORIGINAL ARTICLE

Ultrasonographic findings and natural history of pregnancies diagnosed as fetal trisomy 18, trisomy 13, and triploidy

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ABSTRACT

Objective: The aim of this study was to investigate fetal ultrasonographic findings and perinatal outcomes in pregnancies with fetal trisomy 18, trisomy 13, and triploidy.

Material and Methods: Pregnancies diagnosed as fetal trisomy 18, trisomy 13, and triploidy at a tertiary center between January 2013 and January 2020 were included in the study. Maternal ages, gestational ages at the time of diagnosis, antenatal follow-ups, prenatal fetal ultrasonography reports, perinatal outcomes, whether the pregnancies resulted in live births, and the outcomes of the newborns were obtained.

Results: A total of 104 cases (trisomy 18 [n=74, 71.2%], trisomy 13 [n=21, 20.2%], and triploidy [n=9, 8.6%]) were included in the study, and pregnancy was terminated in 79 (76.0%) of the cases. The most common anomaly was cardiac malformations in fetuses with trisomy 18 and triploidy, and central nervous system anomalies in fetuses with trisomy 13. Of 25 patients who preferred to continue the pregnancy, nine (36.0%) resulted in miscarriage and 13 (52.0%) resulted in fetal death. In all three pregnancies that resulted in live births, newborns died in the early neonatal period.

Conclusion: Most fetuses with trisomy 18, trisomy 13, and triploidy have severe fetal malformations. In cases where the pregnancy is not terminated, the risk of fetal loss is high. Patients with the expectation of self-termination should be informed that this loss may not occur until the third trimester and that pregnancy may result in a live birth.

Keywords: Aneuploidy, fetal screening, prenatal diagnosis, triploidy, trisomy.

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INTRODUCTION

Trisomy 18 and trisomy 13 are the most common autosomal aneuploidies in newborns after trisomy 21, with an incidence of 1/3000 and 1/15000, respectively.[1] Triploidy is a rarer condition, in which there is an extra haploid set of chromosomes, and its incidence in human conceptions is between 1and 2%.[2] However, because the vast majority of triploidy results in spontaneous abortion in the early weeks of gestation, it is rare for it to progress to the second half of pregnancy and result in a live birth.[2,3] These fetuses have high rates of spontaneous abortion in the early gestational weeks, intrauterine fetal death, and early neonatal death because fetuses with these three chromosomal abnormalities have major structural malformations with multiple system involvement.[4,5] As a result of the widespread use of fetal ultrasonography in antenatal care, there has been an increase in the detection rates of fetal structural malformations and aneuploidies in the prenatal period. Therefore, possible structural fetal malformations that can be detected in fetuses with aneuploidies such as triploidy, trisomy 18, and trisomy 13 have been identified and strategies have been developed to detect these aneuploidies in the antenatal period.

The previous studies have reported that in countries where medical termination of pregnancy is legally permitted, up to 78% of pregnant women with detected fetal aneuploidy prefer termination of pregnancy.[6,7] On the other hand, for parents who do not prefer medical termination of pregnancy, possible natural consequences of pregnancy at advanced gestational ages, intrauterine fetal death, or live birth rates are important questions. Data on the natural outcomes of these pregnancies are limited, because few pregnant women prefer to continue the pregnancy, cases resulting in live birth are very rare, and the approaches to the management of these pregnancies during the antenatal period differ between centers.[8–10] In addition, most studies evaluate the outcomes of cases diagnosed in the postnatal period, because most pregnancies with aneuploidy detected in the intrauterine period are terminated.[10,11] Therefore, data on the outcomes of pregnancies diagnosed as trisomy 18, trisomy 13, and triploidy in the prenatal period and choosing to continue the pregnancy are limited.

Data on the natural outcomes of these pregnancies are important to provide the appropriate counseling to patients who prefer to continue the pregnancy, guide the expectations of the patients, and ensure that they receive appropriate prenatal care. This study aimed to evaluate the pregnancy outcomes of pregnant women with fetal trisomy 18, trisomy 13, and triploidy detected in the antenatal period and who did not prefer to terminate their pregnancies.

MATERIAL AND METHODS

The medical records of patients who underwent prenatal invasive genetic diagnostic tests (chorionic villus sampling, amniocentesis, or cordocentesis) in the perinatology department of our hospital between January 2013 and January 2020 were retrospectively analyzed. The study was conducted in accordance with the Declaration of Helsinki and was approved by the ethics committee of our institution with approval number 136/2021 and written informed consent was obtained from all participants. Patients whose karyotype analysis results were reported as trisomy 18, trisomy 13, or triploidy were included in the study. In our hospital, advanced molecular analyses are not routinely performed to detect whether the triploidy is diandric or digynic. Fetuses with small placenta, absence of placental cystic enlargement, and early-onset fetal growth restriction with relative macrocephaly were considered digynic triploidy. Maternal ages, gestational ages at the time of diagnosis, antenatal follow-ups, prenatal fetal ultrasonography reports, perinatal outcomes, whether the pregnancies resulted in live births, and the outcomes of the newborns were obtained. Pregnant women whose prenatal follow-up could not be obtained were excluded from the study. GE Voluson E6 (GE Medical Systems, Milwaukee, USA) ultrasonography device with 4–8 Mhz transabdominal probe was used for fetal ultrasonographic scanning.

The option of termination of pregnancy was offered after appropriate genetic counseling was given to all patients, because the laws in our country allow termination of pregnancy in patients diagnosed as having trisomy 18, trisomy 13, and triploidy in the prenatal period. After obtaining the informed consent of the pregnant women who preferred termination of pregnancy, in fetuses who were before 22nd weeks of gestation or with an estimated fetal weight below 500 g, medical termination of pregnancy was performed by induction of labor. After the 22nd gestational week or in those with an estimated fetal weight above 500 g, feticide was performed after obtaining informed consent, and then, the pregnancy was terminated. Pregnancy loss before the 22nd gestational week was considered spontaneous abortion, and pregnancy loss after the 22nd gestational week was considered fetal death.

Statistical Analysis

Data analysis was performed using the SPSS version 21 (SPSS Inc., Chicago, IL, USA) package program. The assumption of conformity to normal distribution for continuous variables was tested using the Kolmogorov–Smirnov test. Descriptive statistics are given as mean±standard deviation for continuous variables, and as numbers (n) and percentage (%) for categorical variables. Student's t-test was used in independent groups for comparison between two groups, because the assumption of normality of continuous variables was provided. In the comparison of categorical variables between the two groups, the Chi-square test was used when the Chi-square assumption was met, and Fisher's exact test was used when it was not. Statistical significance was determined as $p \leq 0.05$.

RESULTS

A total of 4525 prenatal invasive diagnostic tests were performed in our hospital and trisomy 18, trisomy 13, or triploidy were detected in 108 fetuses. The flow chart of the patients included in the study is shown in Figure 1. Four (3.7%) cases for which prenatal follow-up could not be obtained were excluded from the study. Of the 104 fetuses included in the study, 74 (71.2%) had trisomy 18, 21 (20.2%) had trisomy 13, and nine (8.6%) had triploidy. The distribution of the ultrasonographic findings of the fetuses included in the study according to the karyotype analysis results is shown in Table 1. The most common fetal anomalies in fetuses with trisomy 18, trisomy 13, and triploidy were cardiac malformations (57.1%), central nervous system anomalies (71.4%), and cardiac malformations (77.8%), respectively.

Table 1: Distribution of the ultrasonographic findings of the fetuses included in the study according to the karyotype analysis results

Ultrasonographic findings	Total (n=104)		Karyotype analysis results					
			Trisomy 18 (n=74)		Trisomy 13 (n=21)		Triploidy (n=9)	
	n	%	n	%	n	%	n	%
Congenital heart diseases	59	56.7	40	54.1	12	57.1	7	77.8
Skeletal system anomalies	46	44.2	35	47.3	7	33.3	4	44.4
Central nervous system anomalies	35	33.7	15	20.3	15	71.4	5	55.6
Abdominal anterior wall defects	28	26.9	26	35.1	2	9.5	0	0.0
Head and face anomalies	25	24.0	10	13.5	12	57.1	3	33.3
Urinary system anomalies	25	24.0	12	16.2	10	47.6	3	33.3
Umbilical cord anomalies*	24	23.1	21	28.4	2	9.5	1	11.1
Cystic hygroma	14	13.5	11	14.9	2	9.5	1	11.1
Hydrops fetalis	13	12.5	12	16.2	1	4.8	0	0.0
Congenital diaphragmatic hernia	10	9.6	0	0.0	10	13.5	0	0.0
Gastrointestinal system anomalies	4	3.8	0	0.0	4	5.4	0	0.0

*: Umbilical cord anomalies include single umbilical artery, persistent right umbilical vein, and umbilical cord cyst.

Pregnancies were terminated in 79 (76.0%) patients. Of the 79 patients whose pregnancy was terminated, 55 (69.6%) had trisomy 18, 19 (24.1%) had trisomy 13, and five (6.3%) had triploidy. The mean age of the pregnant women whose pregnancy was terminated was 35.9±7.8 years and the mean age of the pregnant women who decided to continue the pregnancy was 38.3±6.8 years; there was no significant difference between the groups (p=0.164). There was no significant difference between the mean diagnosis week of the patients whose pregnancy was terminated and the mean diagnosis week of the patients who decided to continue the pregnancy (18.0±4.1 and 18.3±3.9, respectively, p=0.661).

Of the 25 (24.0%) patients who decided to continue their pregnancies, 19 (76.0%) had trisomy 18, four (16.0%) had triploidy, and two (8.0%) had trisomy 13. Fetal ultrasonography findings and perinatal results of the pregnant women who preferred to continue their pregnancies are shown in Table 2. Of the 25 patients who preferred to continue the pregnancies, nine (36.0%) resulted in spontaneous abortion and 13 (52.0%) resulted in fetal death. Live birth occurred in only three (12.0%) pregnancies. Fetuses had trisomy 18 in all three pregnancies that resulted in live births. In the first of these fetuses (case #17), who was diagnosed as having mosaic trisomy 18, spontaneous vaginal delivery occurred after preterm premature rupture of membranes at the 24th gestational week and the neonate died on the postpartum 1st day. The second fetus (case #18) was born with a previous cesarean section indication at the 36th gestational week and died on the same day after delivery. The third fetus (case #19) was born by cesarean section and died after 7 months of hospitalization in the neonatal intensive care unit. All fetuses with trisomy 13 or triploidy died in the antenatal period. One trisomy 18 case (case #10) with fetal death at the 31st gestational week was a dichorionic diamniotic twin pregnancy and the other fetus was born at the 33rd gestational week after preterm premature rupture of membranes.

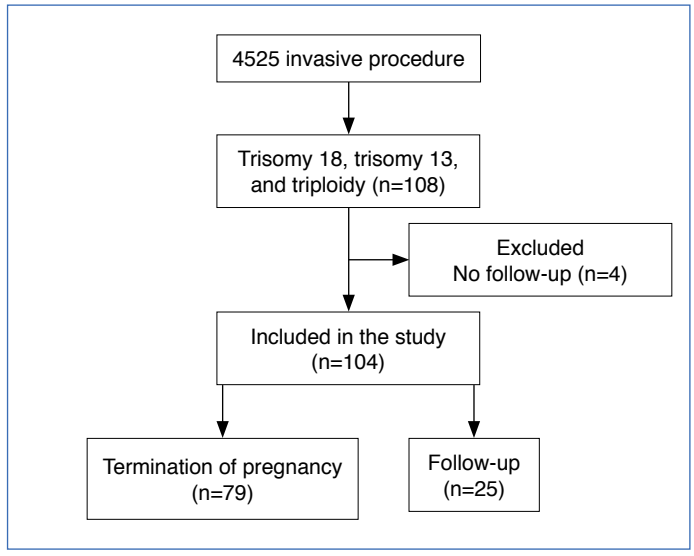

Figure 1: Flow chart of the patients included in the study.

There was no serious maternal complication in any patients who preferred to continue the pregnancy. Membrane rupture occurred in one patient at the 17th gestational week after amniocentesis and there was no sign of chorioamnionitis in this patient who was hospitalized. One patient received thyroid replacement therapy for hypothyroidism and one patient received antihypertensive therapy for chronic hypertension. Two women delivered by cesarean section and both cesareans were due to previous cesarean sections.

Table 2: Ultrasonographic findings and perinatal outcomes of cases diagnosed with trisomy 18, trisomy 13, and triploidy, but whose pregnancy was not terminated

Cases	Karyotypes	Ultrasonographic findings	Gestational week at delivery	Perinatal outcomes
Case-1	Trisomy 18	Cystic hygroma	13	Spontaneous abortion
Case-2	Trisomy 18	Cystic hygroma, AVSD, absence of nasal bone	14	Spontaneous abortion
Case-3	Trisomy 18	NT thickness	15	Spontaneous abortion
Case-4	Trisomy 18	NT thickness, megacystis	16	Spontaneous abortion
Case-5	Trisomy 18	Hydrops fetalis	16	Spontaneous abortion
Case-6	Trisomy 18	Cystic hygroma	18	Spontaneous abortion
Case-7	Trisomy 18	Omphalocele, megacystis, pes equinovarus	16	Spontaneous abortion
Case-8	Trisomy 18	Spina bifida, omphalocele, clenched hand	24	Fetal death
Case-9	Trisomy 18	Holoprosencephaly, pleural effusion	29	Fetal death
Case-10	Trisomy 18	Holoprosencephaly, muscular VSD, early-onset FGR, clenched hand	31	Fetal death
Case-11	Trisomy 18	Spina bifida, hypoplastic left heart syndrome, pes equinovarus, clenched hand	32	Fetal death
Case-12	Trisomy 18	Congenital diaphragmatic hernia, tetralogy of fallot, pes equinovarus, early onset FGR	34	Fetal death
Case-13	Trisomy 18	Omphalocele, early-onset FGR, umbilical cord cyst, single umbilical artery	35	Fetal death
Case-14	Trisomy 18	Omphalocele, malalignment VSD, Pes equinovarus, early-onset FGR	37	Fetal death
Case-15	Trisomy 18	Triventricular hydrocephalus, malalignment VSD, umbilical cord cyst, pes equinovarus, clenched hand, cystic hygroma	39	Fetal death
Case-16	Trisomy 18	Early-onset FGR, severe polyhydroamnios	40	Fetal death
Case-17	Mosaic trisomy 18	Early-onset FGR	24	Live birth
Case-18	Trisomy 18	Holoprosencephaly, hypoplastic left heart syndrome, median cleft lip, clenched hand	36	Live birth
Case-19	Trisomy 18	Omphalocele	36	Live birth
Case-20	Triploidy	Early-onset FGR	18	Spontaneous abortion
Case-21	Triploidy	AVSD, vermian agenesis, early-onset FGR	28	Fetal death
Case-22	Triploidy	Ventriculomegaly, subaortic VSD, Horseshoe kidney, early-onset FGR	31	Fetal death
Case-23	Triploidy	Ventriculomegaly, inlet VSD, unilateral renal agenesis, pelvic kidney, early-onset FGR	34	Fetal death
Case-24	Trisomy 13	Holoprosencephaly, NT thickness	13	Spontaneous abortion
Case-25	Trisomy 13	Median cleft lip and palate, micrognathia, AVSD, NT thickness, early-onset FGR	30	Fetal death

AVSD: Atrioventricular septal defect; FGR: Fetal growth restriction; NT: Nuchal translucency; VSD: Ventricular septal defect.

DISCUSSION

Trisomy 18, trisomy 13, and triploidy are chromosomal diseases that rarely result in live births and are mostly lethal in the intrauterine or neonatal period.[4] In our country and in other countries where laws allow termination of pregnancy, parents choose between continuation or termination of pregnancy in pregnancies diagnosed as fetal trisomy 18, trisomy 13, and triploidy. Lakovschek et al.[6] reported that 22% of the parents in their population decided to continue the pregnancy. According to the results of our study, the rate of continuation of pregnancy was similar in our patient population. Parents who decide to continue the pregnancy should be informed about the natural course and perinatal consequences of these chromosomal anomalies. The present study provides a comprehensive evaluation of fetal ultrasonography findings and natural histories of pregnancies diagnosed as fetal trisomy 18, trisomy 13, and triploidy in the prenatal period.

In the previous studies, fetal death rates in fetuses diagnosed as trisomy 18 were variable due to different study designs. Won et al.[12] reported the intrauterine loss rate as 32%, Morris et al.[13] at 56%, and Yamanaka et al.[14] at 45% in fetuses with trisomy 18. In the present study, our rates of intrauterine fetal death were much higher than in the previous studies. The reason for these high intrauterine fetal death rates may be that patients in our population mostly rejected invasive diagnostic tests when there were no fetal ultrasonographic findings, but accepted invasive procedures when an anomaly was detected in fetal ultrasonography. Fetuses with multiple system anomalies have an increased risk of intrauterine fetal death. It can be predicted that mortality will be higher if different system anomalies are detected in fetuses with trisomy 18 as a result of invasive procedures performed due to high risk in screening tests. Detection of multiple system anomalies in most of the followed fetuses whose pregnancy termination was rejected in our study may explain our high fetal death rates.

Severe central system anomalies, which are found at high rates in fetuses with trisomy 13, may be a reason for the high mortality rates in the fetal and neonatal period. When termination of pregnancy is not performed in fetuses with trisomy 13, intrauterine fetal loss rates have been reported to be approximately 50%. In a study that included 198 fetuses with trisomy 13, the rate of fetal death was reported as 48%.[13] Similarly, in another study in which the 23-year experience of a single center in Brazil was reported, the intrauterine death rate of fetuses with trisomy 13 was reported as 46%.[15] In our study, only two parents decided to continue the pregnancy and both fetuses died in the antenatal period.

Triploidy is caused by an extra set of haploid chromosomes from the father (diandric) or the mother (digynic). Digynic triploidy results from the fertilization of a diploid ovum with a normal haploid sperm. Diandric triploidy can occur when a normal haploid ovum is fertilized by one diploid sperm or two sperm (dyspermia/double fertilization). Samples from both parents can be matched to the triploid fetal sample and tested for parental origin using quantitative fluorescent polymerase chain reaction. Since there are severe structural malformations in fetuses with triploidy, spontaneous abortion, intrauterine fetal death, and early neonatal death rates are high.[4,5] Pregnancies diagnosed as having fetal triploidy in the antenatal period rarely result in a live birth.[16,17] In our study, all of the pregnancies diagnosed as fetal triploidy for which the parents did not prefer to terminate the pregnancy resulted in fetal death in the antenatal period. In the previous studies, 98–99% of pregnancies with fetal triploidy resulted in fetal death at the early gestational ages.[6,18,19] In the study of Lakovschek et al.,[6] fetal death occurred between 14 and 18 weeks of gestation in all six cases. However, contrary to other studies, fetal death occurred in three of our cases at more advanced gestational ages (28, 31, and 34 weeks of gestation). This is especially important when counseling patients on the continuation and prognosis of pregnancy. In our study, vaginal bleeding or preeclampsia did not occur in any cases of triploidy whose pregnancy continued and reached the third trimester. On the other hand, considering that maternal complications are more common at advanced gestational ages in diandric-type triploidies, cases of triploidy in which pregnancy is not terminated can reach advanced gestational ages and therefore should be followed closely.

Our study had some limitations. First, there are inherent limitations due to the relatively small number of cases and the retrospective design of the study. However, because triploidy, trisomy 13, and trisomy 18 are relatively rare chromosomal abnormalities and most parents prefer to terminate the pregnancy, it would be difficult to conduct a prospective study with a large number of cases. Second, because the majority of the cases included in the study had severe fetal malformations, the results of this study may not reflect the outcomes of all pregnancies with trisomy 13, trisomy 18, or triploidy, but no serious fetal malformation was detected in ultrasonography. Live birth rates may be higher in pregnancies without severe malformations in fetal ultrasonography. The strength of our study is that it is based on 7 years of experience in a single tertiary center and fetal ultrasonography is performed by experienced physicians.

CONCLUSION

In summary, fetuses with trisomy 18, trisomy 13, and triploidy have serious fetal malformations, especially cardiac malformations, skeletal system anomalies, and central nervous system anomalies. Most pregnancies diagnosed in the prenatal period that are not terminated result in fetal death. Parents who prefer the continuation of pregnancy should be informed about high intrauterine fetal death rates while counseling about the prognosis of pregnancy. Patients with the expectation of self-termination should be informed that this loss may not occur until the third trimester and that pregnancy may result in a live birth. However, the neonatal survival rate in pregnancies resulting in a live birth is quite low. Studies with a larger number of cases evaluating the perinatal outcomes of these lethal chromosomal abnormalities are needed.

Statement

Ethics Committee Approval: The Zeynep Kamil Maternity and Children's Training and Research Hospital Clinical Research Ethics Committee granted approval for this study (date: 23.06.2021, number: 136).

Informed Consent: Written informed consent was obtained from patients who participated in this study.

Peer-review: Externally peer-reviewed.

Author Contributions: Concept – OD; Design – GED, MEÖ; Supervision – ÖK, AK; Resource – OD, AK; Materials – OD, MEÖ, AÖ; Data Collection and/or Processing – AÖ, MEÖ, ÖK; Analysis and/or Interpretation – MA, GED; Literature Search – AÖ, ÖK; Writing – GED, MA; Critical Reviews – MA, AK.

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