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Changing Trends over the Years in Pregnancy Termination due to Fetal Anomalies

Fetal Anomalilere Bağlı Gebelik Terminasyonunda Yıllar İçerisinde Değişen Eğilimler

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ABSTRACT

Introduction: To examine the indications for termination due to fetal anomalies performed in our clinic between January 2015 and October 2020 and to determine the differences between years.

Methods: This study is a retrospective, observational study involving 385 patients who underwent termination before the 24th week due to fetal anomalies at Karadeniz Technical University, Farabi Hospital, Clinic of Perinatology. Termination data were analyzed by dividing the sample into two groups: terminations performed between 11 and 14 weeks (first trimester) and those between 15 and 24 weeks (second trimester) of gestation.

Results: Structural malformations constituted 81.3% of termination of pregnancy (TOP) cases, chromosomal anomalies 14.5%, and genetic diseases 4.2%. Central nervous system (CNS) anomalies, at 43.4%, were the most common cause of termination. Aneuploidy was present in 56 (34.8%) of 161 cases for which karyotype analysis was available. The number of terminations that took place in both the first and the second trimesters was the highest in 2019. A continuous increase was observed in the number of terminations over the years evaluated. When the systems were evaluated individually, it was observed that the number of cases in the second trimester with CNS and face and neck anomalies was statistically significantly higher than that in the first trimester (p=0.002, p=0.037, respectively). In all, 28.3% of terminations were performed in the first trimester and 71.7% in the second trimester.

Conclusion: When the distribution of TOP indications over the years was examined, it was observed that the number of cases related to chromosomal anomalies, cardiovascular system anomalies, and genetic diseases had increased gradually.

Keywords: Aneuploidy, congenital anomalies, karyotype, prenatal diagnosis, termination of pregnancy

ÖZ

Amaç: Kliniğimizde Ocak 2015-Ekim 2020 yılları arasında yapılan fetal anomalilere bağlı gebelik terminasyonlarının endikasyonlarını incelemek ve yıllar arasındaki farklılıkları belirlemektir.

Yöntemler: Çalışmamız, Karadeniz Teknik Üniversitesi, Farabi Hastanesi, Perinatoloji Kliniği'nde, fetal anomaliler sebebiyle 24. gebelik haftasından önce terminasyon uygulanan 385 olguyu içeren retrospektif bir çalışmadır. Terminasyon verileri, 11-14 hafta (1. trimester) arası olgular ve 15-24 hafta (2. trimester) arası olgular olarak iki gruba ayrılarak analiz edilmiştir.

Bulgular: Terminasyon olgularının %81,3'ünü yapısal malformasyonlar, %14,5'ini kromozom anomalileri ve %4,2'sini genetik hastalıklar oluşturmaktaydı. %43,4 ile santral sinir sistemi (SSS) anomalileri, terminasyonların en sık nedeniydi. Karyotip analizi yapılan 161 olgunun 56'sında (%34,8) anöploidi mevcuttu. Hem 1. trimesterde hem de 2. trimesterde gerçekleşen terminasyon sayıları, 2019 yılında en yüksekti. Değerlendirilen yıllar içerisinde terminasyon sayılarında devamlı bir artış olduğu görüldü. Sistemler ayrı ayrı değerlendirildiğinde, SSS ve yüz ve boyun anomalileri açısından 2. trimesterdeki olguların 1. trimesterdeki olgulara göre istatistiksel olarak anlamlı derecede yüksek olduğu görüldü (sırasıyla; p=0,002, p=0,037). Olguların %28,3'ü 1. trimesterde, %71,7'si 2. trimesterde termine edilmişti.

Sonuç: Terminasyon olgularının yıllar içindeki dağılımı incelendiğinde; kromozom anomalileri, kardiyovasküler sistem anomalileri ve genetik hastalıklara bağlı olguların sayısının giderek arttığı görülmektedir.

Anahtar Kelimeler: Anöploidi, gebelik terminasyonu, karyotip, konjenital anomaliler, prenatal tanı

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Introduction

In Turkey, termination of pregnancy (TOP) is permitted under three conditions. The first of these are unintended pregnancies, and these pregnancies can be terminated according to the couple's decision until the 10th pregnancy week, which is the legal limit (1). Maternal medical conditions, in which pregnancy threatens maternal life, are another reason, and there is no gestational week time limit for termination. Fetal anomalies that cause severe morbidity or mortality are another condition that permit termination (1,2).

The development of both advanced technology ultrasound devices and prenatal screening tests has now enabled clinicians to detect many structural malformations and chromosomal anomalies in the intrauterine period (3). The changing world and technological developments over the years have also affected people's view of medical practices. A pregnant woman bearing a fetus with an anomaly and her partner face a difficult decision: Will they continue with the pregnancy, or will they decide to terminate?

This article aims to examine the indications for termination due to fetal anomalies performed in our clinic between 2015 and 2020 and to determine the differences between years.

Methods

The study was conducted per the principles of the Declaration of Helsinki. This study approval was obtained from Karadeniz Technical University Local Ethics Board (approval number: 2019/29, date: 15.02.2019).

This study is a retrospective, observational study involving 385 cases who underwent TOP before the 24th week due to fetal anomalies between January 2015 and October 2020. Unintended pregnancies, multiple pregnancies, TOP cases due to maternal indications, and cases without a fetal heartbeat at the time of hospital admission were excluded. If an anomaly incompatible with life was detected after 24 weeks, the parents were given the necessary consultancy, and if these patients requested termination, they were transferred to centers where the termination process could be performed. Maternal age, gravida, parity, TOP gestational week, fetal weight, fetal gender, length of hospital stay, karyotype analysis (if present), and fetal diagnosis information of TOP cases were recorded from our hospital's data processing database. Termination data were analyzed by dividing the sample into two groups consisting of cases between 11 and 14 weeks (first trimester) and those between 15 and 24 weeks (second trimester) of gestation. Perinatology specialists performed fetal ultrasonographic examination via Voluson 730 (GE Medical Systems, Zipf, Austria) and Voluson E10 (General Electrics Healthcare, Zipf, Austria). Genetic counseling was given to each family who underwent karyotyping for prenatal diagnosis. Chorionic villus sampling, amniocentesis, or cordocentesis was applied to the cases per the weeks of gestation for genetic diagnosis. Cases in which the patient did not agree to karyotyping or karyotyping did not yield a clear result were not included in the chromosomal anomalies group. The decision to terminate the pregnancy was made by a multidisciplinary committee composed of experts in perinatology, medical genetics, pediatric surgery, pediatric cardiology, and pediatric neurology. Couples were informed about the termination methods and their possible risks, and informed consent was obtained from all patients who agreed to undergo the procedure. A fetal autopsy was recommended to all patients who underwent termination.

The preferred method of medical termination in our hospital is misoprostol (Cytotec, Ali Raif, İstanbul, Turkey). The route of administration of misoprostol (vaginal or oral), dosage, and intervals were determined according to the gestational week, personal obstetric history, and clinical features of the patient (4,5). If necessary, oxytocin induction or intracervical Foley catheter application was used to contribute to cervical dilation in addition to misoprostol. After the fetus and placenta were discarded, the remaining products of conception were removed by manual vacuum aspiration or dilatation and curettage. A hysterotomy was performed in patients with unsuccessful induction despite medical treatment and the use of an intracervical Foley catheter and also in patients with a history of three or more cesarean surgeries. Indications for termination were classified according to the International Classification of Diseases, Version-10.

Statistical Analysis

SPSS Statistics, Version 20 (IBM Corp. Armonk, NY) was used for statistical analysis. All continuous variables were defined as mean and standard deviation. Categorical variables were expressed as a percentage of the total. The Pearson's chi-square independence test and Fisher's exact test were used to examine the interdependence between categorical variables.

Results

Within the scope of the study, a total of 385 TOP cases related to fetal anomalies were evaluated. The mean maternal age was 29 (range: 18-43), and the mean gestational age at termination was 19 (range: 12-24) weeks. The number of cases who underwent karyotyping was 161 (41.8%). The demographic data on the cases are shown in Table 1.

Considering all causes of TOP due to fetal anomalies, central nervous system (CNS) anomalies (43.4%), chromosomal anomalies (14.5%), and cardiovascular system (CVS) anomalies (13.5%) were the most common causes. When the distribution of all TOP cases was analyzed by year, an increase was observed in the number of cases in recent years: The lowest proportion (12.2%) was seen in 2015 and the highest (22.3%) in 2019. Also, the number of terminations in both the first and the second trimesters was the highest in 2019 (Figure 1).

Table 1. Demographic characteristics of TOP cases

	Median
Age, year	29 (18-43)
Gravida	2 (1-5)
Parity	1 (0-4)
Gestational week at TOP* (week)	18 (12-24)
Fetal weight, grams	251 (70-682)
Length of hospital stay (days)	2 (1-8)
Prenatal karyotype, n (%)	161 (41.8%)
Fetal sex, F/M/I*, n (%)	134/139/112 (34.8%, 36.1%, 29.1%)

F: Female, M: male, I: indefinite, TOP: termination of pregnancy

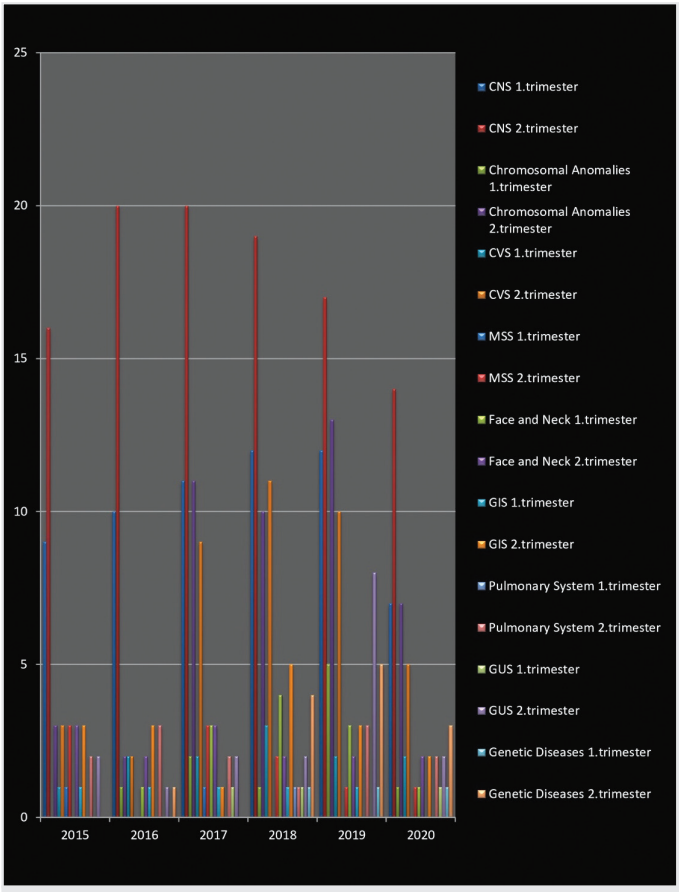

Figure 1. Distribution of TOP cases by years

TOP: Termination of pregnancy, CNS: central nervous system, MSS: musculoskeletal system, GIS: gastrointestinal system, GUS: genitourinary system

The cases were divided into two groups according to gestational age at termination. The first group consisted of cases terminated between 11 and 14 weeks, and the second consisted of cases terminated between 15 and 24 weeks. The mean gestational age at termination time of the patients in the first group was 13 weeks (range: 12-14), and the mean gestational age at termination of the patients in the second group was 21 weeks (range: 15-24). When the systems were evaluated individually, it was observed that the number of CNS and face and neck anomalies was statistically significantly higher among cases terminated in the second trimester than among those terminated in the first trimester (p=0.002, p=0.037, respectively). CNS anomalies are the most common TOP indication in both the first (56%) and second (38.4%) trimesters. When all 385 TOP cases were evaluated, the second group constituted 71.7% (276/385) of cases, and the first group constituted 28.3% (109/385) (Table 2).

Table 3 shows the distribution of termination indications by system. Structural malformations constituted 81.3% of TOP cases, chromosomal anomalies constituted 14.5%, and genetic diseases constituted 4.2%. CNS anomalies, especially the anencephaly-acrania-exencephaly sequence and spina bifida, were the most common reasons for termination in both the first trimester and the second trimester in the 6-year study period. Chromosomal anomalies were second with 14.5%, and trisomy 21 was the most common chromosomal anomaly (9.1%). Aneuploidy

Table 2. Comparison of groups by termination week

	Frequency (%)		
Groups	**11-14 w**	**15-24 w**	**p**
CNS	61 (56%)	106 (38.4%)	**0.002**[a]
Chromosomal anomalies	10 (9.2%)	46 (16.7%)	0.060[a]
CVS	12 (11%)	40 (14.4%)	0.368[a]
MSS	2 (1.8%)	10 (3.6%)	0.522[b]
Face and neck	12 (11%)	14 (5.1%)	**0.037**[a]
GIS	5 (4.5%)	17 (6.2%)	0.549[a]
Pulmonary system	1 (0.9%)	13 (4.7%)	0.126[b]
GUS	3 (2.8%)	17 (6.2%)	0.175[a]
Genetic diseases	3 (2.8%)	13 (4.7%)	0.572[b]
Total	**109 (100%)**	**276 (100%)**	**-**

CNS: Central nervous system, CVS: cardiovascular system, MSS: musculoskeletal system, GIS: gastrointestinal system, GUS: genitourinary system, [a]: chi-square independent test, [b]: Fisher's exact test

was present in 56 (34.8%) of 161 cases for which karyotype analysis was available. Head and neck anomalies and CVS anomalies in cases terminated in the first trimester were in second place together (11%), and CVS anomalies in the cases terminated in the second trimester were in third place (14.5%). Omphalocele in gastrointestinal system anomalies, congenital diaphragmatic hernia in pulmonary system anomalies, and bilateral renal agenesis in genitourinary system anomalies were the most common termination indications of the mentioned systems. The most common termination cause due to genetic diseases was spinal muscular atrophy (1.3%).

In this study, pregnancies were terminated vaginally in 98.7% (98.7) of cases. In 26 cases (6.8%) with insufficient cervical dilatation with misoprostol, cervical dilation was achieved with an intracervical Foley catheter, and termination was performed. In 1.3% (1.3) of cases, hysterotomy was applied. Previous uterine surgery was the most important risk factor in choosing hysterotomy for gestational termination.

Discussion

Both medico-legal attitudes and cultural and ethical values and perceptions in the countries in question make termination practices a critical medical procedure (6,7). According to the Population Planning Law in Turkey, termination of unintended pregnancies is legal until the 10th gestational week upon the couple's request (or with the permission of the unmarried woman). Termination application after the 10th gestational week is only possible in life-threatening maternal situations or situations that may cause severe fetal disability, with the reasoned report of an obstetrician and a specialist from a related branch (1,2). While in some countries there is no upper limit on gestational age at termination, in others, this upper limit may change even among institutions. The upper limits of the termination week vary among health institutions in our country. Pregnancy terminations due to fetal anomalies are not accepted for ethical reasons after the 24th week of pregnancy, according to the Maternal-Fetal and Perinatology Society of Turkey Ankara Declaration (8-10). The decision made by our university's

Table 3. Detailed examination of termination indications

	n	%
Central nervous system	**167**	**43.4**
Anencephaly-acrania-exencephaly sequence	56	14.5
Spina bifida	38	9.9
Dandy-walker malformation	24	6.2
Hydrocephaly	23	6
Encephalocele	7	1.8
Holoprosencephaly	7	1.8
Agenesis of corpus callosum	6	1.6
Other	6	1.6
Chromosomal anomalies	**56**	**14.5**
Trisomy 21	35	9.1
Trisomy 18	9	2.3
Trisomy 13	3	0.8
Trisomy 16	1	0.3
Triploidy	1	0.3
Other	7	1.8
Cardiovascular anomalies	**52**	**13.5**
HLHS	20	5.2
VSD/AVSD	11	2.9
TOF	6	1.6
DORV	5	1.3
Ebstein anomaly	4	1
Other	6	1.6
Face and neck	**26**	**6.8**
Cystic hygroma	22	5.7
Cleft palate-cleft lip	2	0.5
Epignathus	2	0.5
Gastrointestinal system	**22**	**5.7**
Omphalocele	12	3.1
Gastroschisis	3	0.8
Esophageal atresia	3	0.8
Other	4	1
Genitourinary system	**20**	**5.2**
Bilateral renal agenesia	7	1.8
MCDK	5	1.3
PCKD	3	0.8
PUV	3	0.8
Other	2	0.5
Genetic diseases	**16**	**4.2**
Spinal muscular atrophy	5	1.3
Thalassemia major	4	1
DiGeorge syndrome	3	0.8
Other	4	1
Pulmonary system	**14**	**3.6**
CDH	9	2.3
CPAM	2	0.5
Lymphangioma	2	0.5
Laringeal atresia	1	0.3
Musculoskeletal system	**12**	**3.1**
Lethal skeletal dysplasia	8	2.1
Kyphoscoliosis	2	0.5
Other	2	0.5
Total	**385**	**100**

TOF: Tetralogy of fallot, AVSD: atrioventricular septal defect, VSD: ventricular septal defect, HLHS: hypoplastic left heart syndrome, DORV: double outlet right ventricle, CDH: congenital diaphragmatic hernia, CPAM: congenital pulmonary airway malformation, PCKD: polycystic kidney disease, PUV: posterior urethral valve, MCDK: multicystic dysplastic kidney

ethics committee complies with this statement and has determined the 24th week of pregnancy to be the upper limit for pregnancy termination due to fetal anomalies.

Between 3% and 5% of pregnancies are complicated due to structural anomalies or genetic disorders (11). Congenital structural anomalies are the most common causes of pregnancy termination, and among these anomalies, those originating from the CNS have been reported as the most frequently observed group (12). When we examine the literature, the most common causes of pregnancy termination in the study of Corbacıoğlu et al. (13) are CNS anomalies (51.8%), multiple anomalies (10.2%), and chromosomal anomalies (9.4%). In a study by Hern (14) published in 2014, the main causes of termination were structural and chromosomal anomalies. The development of ultrasound technology and increase in the experience of clinicians showed that almost all CNS anomalies, such as acrania, alobar holoprosencephaly, and encephalocele, could be recognized as early as the first trimester (15). This condition allowed pregnancies with these anomalies to be terminated early. According to our study results, structural malformations were evaluated as the main cause of TOP, and CNS anomalies were found to be the most common causes of structural malformation. The results we found in our study are compatible with the literature. The striking point is that, while the number of terminations in our clinic has been increasing gradually over the years, the distribution of CNS anomalies in first trimester TOP cases between 2017 and 2020 did not increase at the same rate year over year. This situation is thought to be the result widespread use of folic acid in the pregestational and early gestational period.

Screening for congenital defects began with the use of ultrasound for obstetric care in the 1950s. Real-time gray-scale imaging became available in the 1970s and provided prenatal diagnostic opportunities in the early stages (16). Prenatal screening concepts, which started by screening for neural tube defects with a single maternal serum marker, made more than one serum marker and ultrasound marker available for Down syndrome screening over time. Today, a completely new approach is available for aneuploidy screening with maternal plasma cell-free DNA (17). In the face of this development, countries have developed various national policies and recommendations regarding prenatal screening and diagnostic tests. When we evaluated the last 6-year period, the rate of chromosomal anomalies increased from 6.4% to 20.9% among all termination cases, and the general rate was 14.5%. This finding may be a result of the widespread use of chromosomal screening tests in Turkey. Moreover, the results show that more couples prefer termination for chromosomal anomalies. Despite this, our termination cases due to aneuploidies are at a low level compared with those in other studies (25%-39%) (18,19). The reason for this is that from the point of view of couples in our country, regarding prenatal diagnosis tests and termination, especially compared with those of couples in Western countries, religious and cultural differences still seem to be an essential factor. Prenatal screening strategies aim to identify fetal karyotype anomalies as early as possible. In this regard, scans are carried out in the early stages of the first and second trimesters. This finding is due to the changing attitude and awareness of couples and the improvement in prenatal screening programs. In our study, when the systems are evaluated separately, the group with the earliest termination is the

group with cases with chromosomal anomalies. In studies involving TOP cases that occurred after the 24th week of pregnancy, it was reported that terminations were performed mostly for isolated major structural anomalies, and the frequency of cases with chromosomal anomalies decreased with increasing gestational age (14,20). These results seem to be compatible with the objectives of screening strategies.

Due to clinicians' increasing experience in fetal echocardiographic evaluation, the frequency of termination due to CVS anomalies has increased. Moreover, the assessment of tricuspid regurgitation and abnormal ductus venous Doppler flow in addition to nuchal translucency in the first trimester has contributed to the early recognition of these diseases (21). In the study of Corbacıoğlu et al. (13), in TOP cases below the 24th week, the termination rate due to cardiac anomalies is 1.7%, while this rate is 13.5% in our study. The development in terms of early recognition of fetal cardiovascular diseases in the 8 years between the two studies is promising.

The fact that most of the genetic diseases cannot be cured has led to the development of genetic tests in the prenatal period. The introduction of new technologies used for the prenatal diagnosis of chromosomal anomalies into medical genetic practice has enabled the recognition of single-gene diseases. In our study, 4.2% of termination cases were performed due to genetic diseases. This rate is 1.4% in the study of Ozyuncu et al. (22). The main feature of our TOP cases with regard to genetic diseases is the fact that most of them were referred to our clinic by a primary or secondary healthcare center, and a detailed family history was available for them, which helped us with early diagnosis. Moreover, it is extremely important that these diseases are followed up by a multidisciplinary team in our clinic.

Terminations of pregnancy were mostly realized through the vaginal route in our study. All patients who underwent hysterotomy were second trimester TOP cases and had a history of uterine surgery. In the study by Garofalo et al. (23), while uterine surgery history was considered as a critical risk factor for maternal complications in second trimester TOP cases, it did not increase maternal complications in first trimester TOP cases. This condition shows that performing terminations due to fetal anomaly in the early weeks of gestation reduces maternal complications as well as facilitating couples' acceptance of the situation ethically and psychologically.

Study Limitation

The study's main limitations are that it was performed in a single-center, did not include cases of late termination (>24 weeks), and its design was retrospective.

Since our clinic is the largest perinatology center in the region, it accepts patients from many cities, and a study such as this one is therefore essential to provide detailed information about TOP cases.

Conclusion

When the distribution of TOP indications over the years is examined, it is observed that the number of cases related to chromosomal anomalies, CVS anomalies, and genetic diseases is increasing gradually. Thus, we believe that clinicians should conduct pregnancy follow-ups much more carefully and know all the medico-legal regulations in detail.

Ethics Committee Approval: The study was conducted per the principles of the Declaration of Helsinki. This study approval was obtained from Karadeniz Technical University Local Ethics Board (approval number: 2019/29, date: 15.02.2019).

Informed Consent: Informed consent was obtained from all patients who agreed to undergo the procedure.

Peer-review: Externally and internally peer-reviewed.

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