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Analysis of the process leading to termination of pregnancy in the third trimester

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Abstract

Objective: To evaluate fetal anomalies and processes leading to termination of pregnancy in the third trimester.

Methods: The study includes all cases who underwent termination of pregnancy after 28 weeks of gestation due to fetal anomalies between 2017 and 2022.

Results: Forty four of third trimester terminations were carried out in our clinic due to fetal anomalies incompatible with life or associated with severe sequelae. Structural anomalies including 35 (79.5%) cases were the most common reason of terminations followed by chromosomal or genetic abnormalities in 8 (18.2%) cases and intrauterine cytomegalovirus infection in 1 (2.3%) case. The processes leading to the third trimester termination were evaluated by dividing 44 patients into 5 groups. *(1)* Delayed diagnosis due to inadequate prenatal care (25 patients, 56.8%); *(2)* patients diagnosed with late-onset findings (5 patients, 11.4%); *(3)* patients with abnormal findings in prenatal care or history but delayed diagnosis (5 patients, 11.4%); *(4)* patients with abnormal findings requiring further evaluation (4 patients, 9.0%); *(5)* patients with a definitive diagnosis but latency in the decision of family for termination of pregnancy (5 patients, 11.4%).

Conclusion: Termination of pregnancy in the third trimester has an important role in countries where unfollowed pregnancies are common and access to health services is poor due to low socio-economic status.

Keywords: Third-trimester termination of pregnancy, fetal indications, fetal anomaly, late abortion.

Introduction

In Türkiye, termination of pregnancy after the 10 weeks of gestation can be performed for maternal indication in case of a condition that threatens the mother's life, or for fetal indication in major malformations that cause death or severe fetal sequelae. After the 10 weeks of gestation, termination of pregnancy can only be approved by two specialists who declare that there is a maternal or fetal indication requiring termination of pregnancy (until the 10 weeks of gestation, the couple's request is sufficient for the termination. Population Planning Law No. 2827, May 27, 1983).

As in many European countries such as England, France, Austria, Belgium, and Netherlands, there is no upper limit for the week of gestation for termination of pregnancy in Türkiye. But in 43 states of USA, Germany, Czechia, Sweden, Spain and Portugal, the upper limit was restricted to viability or maximum 24 weeks.[1,2] Considering that there is a frequent need for second- and third-trimester terminations, it is clear that the laws on this issue in Türkiye strengthen our hands.

Diagnosis of fetal anomalies incompatible with life or associated with severe fetal sequelae constitutes the cornerstone of the process leading to pregnancy termination. As the gestational age advances, termination of pregnancy becomes more complicated, both ethically and medically.[3]

Termination of pregnancy in the third trimester may be due to a late diagnosis of a severe fetal anomaly in the

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third trimester as a result of failure in the first- or second-trimester screenings or late-onset of the disease itself. In some fetal anomalies, in order to avoid hasty decisions and unnecessary terminations, the procedure may also be postponed to late weeks of gestation in the setting of an uncertain prognosis or clinical findings that are not fully established despite earlier diagnosis.[4]

We carried out this study to analyze fetal indications of termination of pregnancy in the third trimester (≥28 weeks) and to reveal the processes leading to late termination of pregnancy.

Methods

This study is carried out in a tertiary referral center for pregnant women suspected of having serious fetal abnormalities. In case of detection of a fetal anomaly incompatible with life or associated with serious sequelae after a comprehensive evaluation including detailed fetal anatomy scan, fetal echocardiography, genetic studies and alternative imaging techniques like fetal magnetic resonance imaging (MRI) in suitable cases, the families are offered the option of pregnancy termination by counseling about the related anomalies or genetic syndromes. Each application for termination of pregnancy is evaluated and decided by a multidisciplinary committee in accordance with its own merits and national law.

Termination of pregnancy in the third trimester is performed in two stages. In the first step following the written consent of the couple in line with the termination request, KCl is injected into the fetal heart or umbilical vein under ultrasound guidance to permanently stop the fetal heartbeat. The second step involves induction of labor in accordance with the patient's obstetric history. Vaginal prostaglandin E1, prostaglandin E2 or mechanical extra-amniotic balloon dilators are frequently used as cervical ripening agents in our clinic. In need of augmentation, oxytocin infusion can be used afterwards. Also cesarean section is considered in patients with previous uterine surgery.

This study includes all cases greater than 28 weeks of gestation who underwent termination of pregnancy due to fetal anomalies between 2017 and 2022. In this retrospective study, patients' demographic features, medical histories, ultrasound findings and diagnosed fetal anomalies were obtained by searching patient files or electronic archives. The genetic test results, if available, were obtained from the archive of the medical genetics unit in our hospital. The study was approved by the local institution's ethics committee. In statistical analysis, descriptive statistics were utilized and descriptive parameters were given as mean±standard deviation, median [min–max] and frequencies as percentages.

Results

In the five-year study period between 2017 and 2022, a total of 764 pregnancy terminations were performed due to fetal anomalies. Forty-four of these terminations were greater than 28 weeks of gestation (**Fig. 1**).

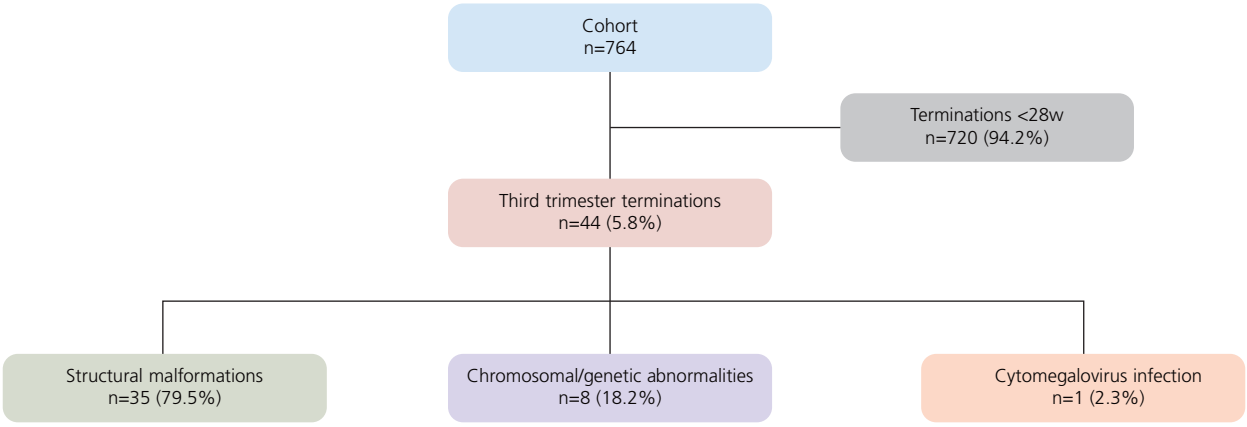

Fig. 1. Termination of pregnancy, cohort, and distribution of fetal indications in the third trimester.

In the study group, the mean age, median gravida and parity were 28.5±6.5, 2 (1–9) and 1 (0–5), respectively. The mean week of gestation for terminations was 29.6±2.7, and the mean family decision-making time between the diagnosis of fetal anomaly and termination procedure was 6.4±11.8 days. In 38 (86.3%) of 44 patients, pregnancy termination was performed vaginally and in 6 (13.7%) patients cesarean section was favored for the procedure. All 6 patients who underwent cesarean section and 5 (13.1%) of 38 pregnancies terminated by vaginal delivery had a history of previous uterine surgery. Uterine rupture was not observed in any case and there were no complications requiring hysterectomy.

The number and distribution of third trimester termination indications were as follows: 35 (79.5%) structural anomalies, 8 (18.2%) chromosomal/genetic diseases and 1 (2.3%) intrauterine cytomegalovirus infection. Fetal indications in third trimester terminations are shown in detail in **Table 1**.

As a termination indication, when structural causes are subdivided according to the affected organ systems, the most common reason is central nervous system anomalies with 22 cases (50.0%) followed by multiple anomalies with 6 cases (13.6%) and anomalies affecting the musculoskeletal system with 5 cases (11.3%). In addition, 1 (2.3%) cardiovascular anomaly and 1 (2.3%) genitourinary anomaly were included in structural anomalies. No pregnancy termination was performed in any patient due to isolated face, neck, lung or gastrointestinal anomalies.

Table 1. Indications for third-trimester pregnancy terminations.

Central nervous system anomaly (n=22)	Hydrocephalus (n=2) Neural tube defects (n=13) Agenesis of corpus callosum (n=1) Holoprosencephaly (n=1) Lissencephaly (n=1) Vermian hypoplasia (n=1) Rhombencephalosynapsis (n=1) Intracranial tumor (n=1) Intracranial hemorrhage (n=1)
Multiple malformations with a normal/unknown karyotype (n=6)	Complex cerebral anomaly + cardiac anomaly (n=2) Unexplained hydrops (n=2) Complex cerebral anomaly + omphalocele (n=1) Limb-body wall complex (n=1)
Musculoskeletal anomaly (n=5)	Acrofacial dysostosis (n=1) Congenital myasthenic syndrome 10 (n=1) Lethal skeletal dysplasia (n=3)
Congenital heart disease (n=1)	Hypoplastic right heart (n=1)
Genitourinary anomaly (n=1)	Bilateral multicystic dysplastic kidney (n=1)
Chromosomal/genetic anomaly (n=8)	Trisomy 21 (n=2) Mosaic trisomy 16 (n=1) Di George syndrome (del 22q11.2) (n=1) Deletion 22q13 (n=1) Deletion 16p11 (n=1) Spinal muscular atrophy (n=1) Noonan syndrome (n=1)
Other (n=1)	Intrauterine infection (CMV) (n=1)

FGR: fetal growth restriction; **CMV:** cytomegalovirus.

The number of third trimester terminations due to chromosomal or genetic abnormalities was 8 (18.2%). These were trisomy in 3 (6.8%) patients (trisomy 21 in 2, mosaic trisomy 16 in 1), microdeletion in 3 (6.8%) patients (22q11 in 1, 22q13 in 1 and 16p11in 1) and genetic abnormality in 2 (4.5%) patients (spinal muscular atrophy in 1, Noonan syndrome in 1).

The processes leading to the third trimester termination were evaluated by dividing 44 patients into 5 groups (**Table 2**): *(1)* Delayed diagnosis due to inadequate prenatal care (25 patients, 56.8%); *(2)* patients diagnosed with late-onset findings (5 patients, 11.4%); *(3)* patients with abnormal findings in prenatal care or history but delayed diagnosis - anomalies that could be detected earlier (5 patients, 11.4%); *(4)* patients with abnormal findings requiring further evaluation (4 patients, 9.0%); *(5)* patients with a definitive diagnosis but latency in the decision of family for termination of pregnancy (5 patients, 11.4%). In the group 5, the mean decision time from the diagnosis to the termination of pregnancy was 34.5±25.5 days.

Table 2. Process leading to third-trimester pregnancy termination.

Delayed diagnosis due to inadequate prenatal care (n=25)
• Neural tube defects (n=10), hydrocephalus (n=2), complex cerebral anomalies (n=3)
• Lethal musculoskeletal anomalies (n=3)
• Multiple gross malformations (n=3)
• Bilateral multicystic dysplastic kidney (n=1)
• Limb-body wall complex (n=1)
• Trisomy 21 (n=1) (diagnosed after the detection of AVSD and nasal hypoplasia)
• Di George syndrome (n=1) (diagnosed with cordocentesis after the detection of tubular aortic hypoplasia)
Diagnosed with late-onset findings (n=5)
• Patients who showed abnormal signs in the second-trimester anatomy scan and followed up with ultrasound exams for complete manifestation of pathology
– Lissencephaly (n=1)
– Lethal skeletal dysplasia (n=2)
• Normal second-trimester anatomy scan and late-onset pathology
– Intracranial hemorrhage (n=1)
– Intracranial tumor (n=1)
Patients with abnormal findings in prenatal care or history but delayed diagnosis (n=5)
• Abnormal second-trimester screening test result, latency in genetic work-up period
– Mosaic trisomy 16 (n=1)
– Trisomy 21 (n=1) (Ventriculomegaly+hemivertebrae detected at 20 weeks of gestation)
• AFP MoM >2.5 in the second-trimester screening, latency in patient approval for sonographic examination
– Myelomeningocele (n=2)
• Parental genetic disease carrier and history of an anomalous child (SMA disease), latency in patient approval for diagnostic fetal genetic tests
– Spinal muscular atrophy (n=1)
Findings requiring further evaluation (n=4)
• Deletion of chromosome 22q13 (n=1) (delay for further genetic work-up after a normal karyotype result)
• Deletion of chromosome 16p11 (n=1) (genetic work-up initiated after the diagnosis of early-onset FGR)
• Vermian hypoplasia (n=1) (confirmed with fetal MRI)
• Intrauterine CMV infection (n=1) (confirmed with amniocentesis)
Latency in the decision of the family for termination of pregnancy (n=5)
• Myelomeningocele (n=1)
• Hypoplastic right heart syndrome (n=1)
• Noonan syndrome (n=1)
• Multiple gross malformations (n=2)

AFP: alpha fetoprotein; **AVSD:** atrioventricular septal defect; **CMV:** cytomegalovirus; **FGR:** fetal growth restriction; **MoM:** multiple of the median; **MRI:** magnetic resonance imaging; **SMA:** spinal muscular atrophy.

Genetic analyzes revealing genetic anomalies that generate an indication for termination of pregnancy were performed due to high risk detected in screening tests or a structural anomaly detected in ultrasonography. In total, 25 (56.8%) of 44 patients underwent chromosomal/genetic diagnostic test, and 11 (25%) had a chromosomal or genetic anomaly (44% of patients who underwent diagnostic test). As demonstrated in **Table 3**, chromosomal/genetic abnormalities were the primary indications for termination of pregnancies in 8 patients. In 3 patients, abnormal genetic results could be obtained after the termination procedures completed in the context of major malformations.

Discussion

As the week of gestation advances, a fetus with anomalies is likely to provoke different problems. Late pregnancy terminations are challenging procedures for the parents to decide, for the members of the committee to approve, and for the healthcare professionals to perform.[5] Especially in countries where the legal boundaries of these practices are not clearly drawn, it brings about important ethical problems for the committee members.[6]

Termination of pregnancy for severe fetal anomalies is ethically and morally challenging and maybe considered illegal in countries with restrictive termination laws. The psychological and emotional impact of an impaired fetus or neonate often lead to moral distress and posttraumatic stress reactions in parents. Late termination of pregnancies is an issue of grave concern with many practical medical aspects, ethical questions, and professional dilemmas. Therefore, termination of pregnancy in the third trimester needs an additional

Table 3. Initial findings and genetic results of fetal anomalies grouped according to the process leading to third-trimester pregnancy termination.

	Initial findings	Number of cases	Further evaluation (number of cases)	Diagnosed genetic/ chromosomal abnormalities
Delayed diagnosis due to inadequate prenatal care (n=25)	Multiple malformations	6	Karyotyping (4) CMA (1)	Tr 21
	CNS	15	Karyotyping (5) CMA (3) MGA (1)	-
	Skeletal malformations	2	Karyotyping (1) CMA (1) MGA (1)	CMS 10*
	Renal (bilateral MCDK)	1		-
	CVS (aortic hypoplasia)	1	Karyotyping (1) CMA (1)	Del 22q11.2
Diagnosed with late-onset findings (n=5)	CNS	3	Karyotyping (1) MRI (2)	-
	Skeletal malformations	2	Karyotyping (2) CMA (2) MGA (2)	Acrofacial dis.*
Abnormal findings but delayed diagnosis (n=5)	Multiple malformations (NTD+AVSD)	1	Karyotyping (1)	Tr 18*
	CNS	2	Karyotyping (2) CMA (1)	Tr 21
	Parental genetic disease (SMA) carrier (no finding)	1	Karyotyping (1) CMA (1) MGA (1)	SMA
	High risk of trisomy 21 in screening test	1	Karyotyping (1)	Mosaic Tr 16
Findings requiring further evaluation (n=4)	CNS	2	Karyotyping (2) MRI (1) Amniocentesis for CMV PCR (1)	-
	Renal (unilateral MCDK)	1	Karyotyping (1) CMA (1)	Del 22q13
	FGR	1	Karyotyping (1) CMA (1)	Del 16p11
Latency in the decision of termination (n=5)	Multiple malformations	2	Karyotyping (1) CMA (1) MGA (1)	-
	CNS (NTD)	1		-
	CVS (HRHS)	1		-
	Hydrops	1	Karyotyping (1) CMA (1) MGA (1)	Noonan syndrome

*Genetic material obtained at the time of fetocide, result acquired after the termination of pregnancy. **AVSD:** atrioventricular septal defect; **CMA:** chromosomal microarray; **CMS 10:** congenital myasthenic syndrome 10; **CMV:** cytomegalovirus; **CNS:** central nervous system; **CVS:** cardiovascular system; **FGR:** fetal growth restriction; **Del:** deletion; **HRHS:** hypoplastic right heart syndrome; **MCDK:** multicystic dysplastic kidney; **MGA:** molecular genetic analysis (whole exome sequencing and/or for single gene disorder); **MRI:** magnetic resonance imaging; **NTD:** neural tube defect; **PCR:** polymerase chain reaction; **SMA:** spinal muscular atrophy; **Tr:** trisomy.

invasive procedure, fetocide, bringing another burden on both mother's emotional and medical situations. This leads to further ethical concerns.[7] This is of particular concern due to the viability of the fetus and should only be carried out to prevent harm to the mother's physical and mental health or because of an anomaly or disability of the fetus.[3]

Detection of fetal malformations by sonographic evaluation is the first step of the process leading to third trimester terminations. Almost all of the late pregnancy termination cases have different fetal structural malformations detected by ultrasonography. This initial ultrasound finding sparks further investigation and generates the beginning of the process completed with termination of pregnancy. Likewise, in our study group, we saw that in the majority of the pregnancies that were terminated in the third trimester, there were major structural fetal anomalies detected on ultrasound and genetic diagnoses were made after the detection of abnormal ultrasound findings.

As the distribution of termination indications is evaluated in the literature, it is observed that the rate of chromosomal-genetic abnormalities decreases while structural anomalies increase in the pregnancies after 28 weeks of gestation compared to the pregnancies before 28 weeks. It can be interpreted that owing to screening tests performed in the first and second trimesters, there is less need for late pregnancy terminations due to chromosomal/genetic anomalies.[8–10] In addition, the parents' emotional attachment to pregnancy in the later stages of pregnancy may lead them to refuse the invasive diagnostic test and to continue the pregnancy, despite an ultrasound finding which may be an important sign of a genetic disease.

CNS malformations were the most common subgroup (50.0%) of the structural anomalies in our study which is consistent with the literature.[11–13] This can be explained with late-onset sonographic findings of many CNS anomalies (vermian hypoplasia, lissencephaly, bleeding, tumor, etc.). However, as the subgroups are analyzed, more than half of our cases had the anomalies that could have been diagnosed even in the first trimester such as neural tube defects (NTD) and holoprosencephaly. This raises the suspicion of insufficient antenatal monitoring. When the literature is investigated, it is seen that there is a noteworthy decline in both terminations due to NTD in the third trimester and the proportion of the patients who did not undergo first- and second-trimester screenings from 1999 to 2017.[4,11,12]

In our cohort, only one pregnancy was terminated due to isolated cardiac malformation without a chromosomal anomaly (hypoplastic right heart) which is the lowest rate in the literature.[11,14,15] The first reason of this low rate is the fact that the patients followed-up in our fetal echocardiography outpatient clinic are mostly consisted of the ones who are willing to continue the pregnancy and are referred to benefit our coordination with a tertiary cardiovascular surgery center. The second reason is that the pediatric cardiology department of our center is not inclined to approve the termination of the cases as they consider most of the isolated cardiac anomalies are correctable by surgery.

Regarding the processes leading to the termination of pregnancy in the third trimester, the patients who had not received routine pregnancy follow-ups and antenatal screening tests were more than half of all cases. Almost all of these patients were diagnosed with an anomaly that could have been detected by early or late antenatal screenings. In İstanbul, where it is easy to access health services, not having regular antenatal follow-ups is considered as negligence. Another reason is that some patients tend to continue their pregnancy regardless of the anomaly type due to cultural and religious reasons and they do not undergo the screenings on purpose. However, the diagnosis of a severe anomaly on sonography performed for various reasons in this group of patients led to change in point of view and made them request the termination of pregnancy.

In the group of patients with late-onset findings, even if adequate follow-ups were performed by experts using the most up-to-date equipment and technology, the anomalies probably would not have been diagnosed earlier. CNS abnormalities such as acute hemorrhagic/ischemic lesions, intracranial tumors like teratomas or malformations of cortical development constitute the majority of this group of abnormalities.[10,16] This indicates that third-trimester sonography requires a high level of attention, even in patients with antenatal screenings and regular follow-ups.

In cases of third-trimester terminations due to delayed diagnosis, there was increased risk due to either abnormal screening findings or obstetric history

(history of a child with SMA) that shows the importance of antenatal counseling about the family history, the screening test results or pathological ultrasonographic findings. The delay in diagnosis in third-trimester terminations is also related with the genetic work-up which requires time. This fact underlines the priority of the first-trimester aneuploidy screenings along with the early fetal anatomic evaluation over the second-trimester screenings, which delay the onset of genetic study period and result in late diagnoses.

The decision period of the families about whether having an invasive test or not also contributes to delay in definitive genetic diagnosis. Making a decision about termination of pregnancy may also take time for the families, as five of our cases which had been diagnosed earlier and could have been terminated before the third trimester.

Conclusion

The developments in prenatal screening tests, fetal imaging and genetic diagnostic techniques enable the health professionals to diagnose the fetal anomalies in early weeks of gestation. One of the main goals of maternal and fetal medicine is to detect these fetuses as early as possible to save enough time to complete the prenatal investigations, to make a definitive diagnosis, and to provide the families optimal time for making decisions with the help of adequate counseling. Early and adequate screenings can significantly reduce the need for termination of pregnancy in the third trimester. Nonetheless, there is a group of fetal anomalies that may develop in the later stages of pregnancy. This group requires a high level of awareness and attention during the third-trimester examinations. The laws about the upper limits of weeks of gestation on which terminations can be performed in some countries are a big challenge in the management of these late-onset anomalies. Considering that the majority of these late-onset anomalies are central nervous system anomalies that may cause severe neurological sequelae and necessitate expensive palliative care, termination of pregnancy in the third trimester has an important role in those countries where unfollowed pregnancies are common and access to health services is poor due to low socio-economic status.

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