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Research Article/Araştırma Makalesi

Evaluations of pregnancy admitted to perinatology clinics that pregnants have fetal anomalies

Perinatoloji kliniğine başvuran fetal anomalileri bulunan gebeliklerin değerlendirilmesi

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ABSTRACT

Objective: Our objective was to investigate the most common anomalies in our region with a retrospective evaluation of the congenital anomaly cases, who applied to the outpatient department of perinatology

Material and Method: We was reviewed file of congenital anomaly cases, who applied to the outpatient department of perinatology in the Medical Faculty at Ondokuz Mayıs University between May 2014 and May 2019,and to determine the risk factors related to these anomalies. Seven hundred twenty-five pregnant women, whose infants were diagnosed with congenital anomalies in our center, were included in the present study. Parameters like the mother's age, consanguineous parents, history of previous habitual abortions, history of siblings with anomalies, number of parity and abortus history, gestational week at diagnosis, smoking, alcohol and drug consumption in the first trimester, periconceptional folic acid use, co-morbidities, ultrasonographic findings, presence of the karyotype analysis, double and triple screening tests, termination decisions were compared with the anomaly types.

Results: In our study, we determined the incidence of anomalies in our region with some limitations. Except for the central nervous system anomalies (most common anomaly group), the incidence ranking of the anomalies in our region was different from the rankings reported in other national studies The CVS anomalies were the second most common anomaly group.

Conclusion: An education program prepared for the pregnant women in our region about the goal of the diagnostic and screening tests and routine pregnancy controls will increase the chance of early diagnosis. We believe that the conduction of region-based prenatal and postnatal studies instead of hospital-based studies will contribute more to a clear understanding of the anomaly incidences in our region.

Keywords: Fetal anomalies, central nervous system anomalies, neural tube defect

ÖZ

Amaç: Konjenital anomaliler; doğuşta var olan, yapısal, fonksiyonel ve biyokimyasal bozukluklardır. Özelliklede az gelişmiş ve gelişmekte olan ülkeler için ciddi bir maddi ve manevi sorundur.

Gereç ve Yöntem: Çalışmamızda Ondokuz Mayıs Üniversitesi Tıp Fakültesi perinatoloji polikliniğine Mayıs/2014-Mayıs/2019 yılları arasında başvuran konjenital anomalili olguları retrospektif değerlendirilerek bölgemizde en sık tespit edilen anomaliler ve anomalilerle bağlantılı olabilecek risk faktörlerinin araştırılması amaçlandı. Merkezimizde değerlendirilen konjenital anomli tanısı almış 725 gebe çalışmamıza dahil edilmiştir. Anne yaşı, anne-baba arasında akrabalık olup olmadığı, habitüel abortus öyküsü, anomalili kardeş öyküsü, annenin gebelik sayısı ve düşük öyküsü, tanı konulduğu andaki gebelik haftası, hamileliğin ilk trimesterinde sigara, alkol, ilaç kullanımı, prekonsepsiyonel folik asit kullanımı olup olmadığı, ek hastalık varlığı, ultrasonografi bulguları, karyotip analizi yapılıp yapılmadığı, ikili ve üçlü tarama testinin varlığı, terminasyon kararları anomali tipleri ile karşılaştırılmıştır.

Bulgular: Çalışmamızda bölgemizdeki anomalilerin görülme sıklığını tespit ettik, en sık görülen santral sinir sistemi anomalilerinin dışında bölgemizdeki anomali sıklık sıralaması ülkemizde yapılan diğer çalışmalara göre farklı izlenmiştir. KVS anomalileri ikinci en sık izlnen anomali grubu olmuştur.

Sonuç: Bölgemizde tanı ve tarama testlerinin amacı ve rutin gebelik kontrollerinin önemi hakkında gebelerin bilgilendirilmesi erken tanı başarımızı daha da arttıracaktır. Hastane bazlı çalışmalar yerine bölgesel bazlı prenatal ve postnatal çalışmaların yapılması, bölgemizdeki anomali insidansına net ulaşılmasını sağlayacağını düşünmekteyiz.

Anahtar Kelimeler: Fetal Anomaliler, merkezi sinir sistemi anomalileri, nöral tüp defekti

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INTRODUCTION

Congenital anomalies are a serious problem in the underdeveloped and developing countries. As a result of the studies over the etiology of the congenital anomalies in the western countries, it was found that 60% of the anomalies were idiopathic, 20% of them were multifactorial, 7.5% of them were monogenetic, 6% were chromosomal, and 3% were caused by maternal diseases, 2% were due to congenital infections and 1.5% were due to drugs, x-rays, and alcohol (1). The absence of risk factors in 90% of fetuses with anomaly shows the importance of routine pregnancy screening and etiology-based studies (2). The Turkish Public Health Institute recommends the pregnant women to undergo ultrasonographic nuchal translucency examination and double screening test (DST) between the 11th and 14th gestational weeks; maternal serum alpha-fetoprotein (AFP) measurement between the 16th and 20th gestational weeks; triple screening test (TST) (if combined test is not done), and ultrasonographic fetal anomaly screening between the 18th and 22nd gestational weeks. The ultrasonographic detection of the congenital anomalies mostly depends on the experience of the specialist and the quality of the device (particularly the cardiac anomalies), which is one of the main problems in the obstetric practice. An experienced specialist can detect 70% of the anomalies with the ultrasonographic examination (3, 4). The rate of a successful diagnosis will decrease due to maternal obesity, unsuitable fetal position, oligo-/polyhydramnios, and giant myomas even if the specialist is highly experienced. The rate of diagnosis of congenital anomalies changes from country to country due to different health politics, conditions related to the accessibility of the diagnostic and screening tests, and fetal prenatal US tests. Therefore, we intended to determine the anomaly rates and their relationship to the risk factors in our region.

MATERIAL AND METHOD

In this study, we retrospectively investigated the files of patients who had applied to Ondokuz Mayıs University, Medical Faculty Hospital Perinatology Clinic between May 2014 and May 2019. A total of 725 patients between the gestational weeks 10 and 37 were included in the study. The patients were between 15 and 45 years of age. All study data were obtained from the archives of the Perinatology Council Decisions, and the Medical Genetics Department of Ondokuz Mayıs University Medical Faculty Hospital.

Ethical Consideration

Our study was approved by the Ethics Committee for Clinical Research (Date 27.06.2019; No: B.30.2.ODM.0.20.08/546)

The congenital anomalies have 10 sub-categories:

1-Central Nervous System (CNS)

2-Cardiovascular System (CVS)

3-Musculoskeletal System (MSS)

4-Genitourinary System (GUS)

5-Skin and Lymphatic System (SLS)

6-Thorax and Respiratory System (RS)

7-Defects of the anterior abdominal wall and Gastrointestinal System (GIS)

8-Craniofacial System

9-Multiple Fetal Anomalies (involvement of more than one system was considered as multiple fetal anomalies).)

10-Syndromes

The parameters were: The mothers' age, number of gravidity, parity, abortion and living children, maternal diseases, habits (smoking, alcohol and substance use, etc.), medication (drugs with the pregnancy category C, D, and X), history of siblings with anomalies, history of infants with anomalies in the family, presence of consanguinity, history of habitual abortion, gestational week at diagnosis, DST, TST and results of amniocentesis and folic acid use. The pregnant women were divided into six subgroups according to the following age intervals: 15-19 years; 20-24 years; 25-29 years; 30-34 years; 35-40 years and 41-44 years. By doing this, we aimed to separate the age group 15-19, which is considered as early pregnancy and the >40 years group, which is considered as late pregnancy. Patients with a habitual abortion history of two or more abortions before the gestational week 20 were recorded as having a "history of habitual abortion." Anomalies were grouped into three subgroups according to the gestational week at diagnosis (diagnosed before the gestational week 24, diagnosed between weeks 24 and 28; diagnosed after week 28). As we do not perform pregnancy termination after the gestational week 24 in our center, the 24th week was accepted as the lower limit and the 28th week as the upper limit for the groups diagnosed in the last trimester.

The results of the DST and TST has done in our center or other centers and verbal statements of the patients were included. The folic acid use in the pre-or postconceptional periods was recorded as "used." The verbal statements of patients were taken for other parameters. The results of US examinations carried out in our center were also included.

The SPSS v13.0 software package was used for the statistical analysis of the study data. Chi-square and ANOVA tests were used in the thesis. For statistical analyses, $p<0.05$ was accepted as significant.

RESULTS

A total of 735 patients were discussed in Ondokuz Mayıs University, Medical Faculty Hospital Perinatology Council between May 2014 and May 2019. The mean age of the 725 pregnant women was 27.66 years. Two hundred fifteen of the pregnant women (29.6%) were primigravida, and 510 (70.4%) were multigravida. Of all the pregnancies, 719 of them were spontaneous, 4 of them had in vitro fer-

tilization (IVF), and 2 of them had intrauterine insemination (IUI). There was no statistically significant correlation between the age distribution and anomaly types ($p<0.05$). Thirty (4.1%) of the 725 pregnant women had a habitual abortion in their medical history, 32 (4.1%) of them had siblings with anomalies, and 117 of them (16.1%) had a consanguineous marriage. There was a significant correlation between habitual abortion and the presence of siblings with anomaly and consanguinity ($p \geq 0.01$). There was also a significant increase in the musculoskeletal system (MSS) anomalies in pregnant females with the history of consanguinity ($p<0.05$). Comparison of the demographic characteristics of the patients diagnosed with congenital anomalies have shown in **Table 1.**

Table 1. Comparison of the demographic characteristics of the patients diagnosed with congenital anomalies

	Minimum	Maximum	Mean
Maternal age	16	44	27.66
Gravida	1	9	2.60
Parity	0	7	1.13
Abortion	0	5	0.47
Alive	0	6	1.03

The congenital anomalies were grouped according to the gestational week at diagnosis:

576 (80%) were diagnosed before the gestational week 24,

83 (11.5%) were diagnosed between the weeks 24-28,

66 (8.5%) were diagnosed after week 28,

The most commonly diagnosed anomalies were CNS anomalies in all three groups. The second and third most common anomalies were multiple fetal anomalies (MFA) and CVS anomalies in week 24, cardiovascular system (CVS) and genitourinary system (GUS) anomalies between weeks 24 and 28 and GUS and CVS after week 28, respectively (**Table 2**).

Table 2. Distribution of the anomalies of patients with congenital anomalies according to the week of diagnosis

	<24 WEEK	24-28 WEEK	>28WEEK
CNS anomalies	310	22	19
CVS anomalies	45	19	10
GUS anomalies	37	14	16
MSS anomalies	39	7	5
. CFS anomalies	10	1	2
THORAX – RS anomalies	25	6	1
Defects of the anterior abdominal wall–GIS anomalies	20	2	2
SLS anomalies	29	3	4
Syndromes	15	-	-
MFA	46	9	7

No co-morbidities were observed in 614 of 725 patients (84.6%). Goiter (n=48; 6.6%), DM Type 2 (n=13; 1.79%) and asthma (n=10; 1.37%) were the most commonly observed co-morbidities. Fourteen of the participants were smokers. We did not determine substance abuse in any patient. One of the patients had been using a drug with the pregnancy category C, two with the pregnancy category D and three with the pregnancy category X. We evaluated the relationship between the date of the last menstruation and anomalies to determine any possible correlation between the anomaly rate and seasonal cycles and found no correlation ($p >0.05$**)**. Five hundred seventeen of 725 patients (71%) had not undergone a double screening test (DST) and 379 (52.2%) of them had not undergone a triple screening test (TST). A total of 119 patients were diagnosed before the time of TST and 80 of them had been diagnosed with neural tube defects (NTD). We detected NTD in 24 patients who had low risk according to the TST. Two hundred seven pregnant women had undergone DST and the most common anomaly was detected as CVS anomaly in 19 women (subgroup: AVSD), who had high trisomy 21 risk. Only two patients were diagnosed before the DST time (**Table 3**).

Table 3. Comparison of DST and TST results in congenital anomalies

	DST	TST
Not performed	517	379
Low-risk	185	154
Patients with high trisomy 21 risk	19	21
Patients with high NTD risk	-	49
Patients with high trisomy 18 risk	3	2
Patients with high trisomy 21 and 18 risks	-	1

In our study, the most common anomalies were CNS anomalies (48.4%),

CVS anomalies were at the second rank (10.2%),

GUS anomalies were at the third rank (9.2%),

MFA anomalies were at the fourth rank (8.5%),

MSS anomalies were at the fifth rank (7%),

SLS anomalies were at the sixth rank (4.9%),

Thorax and RS anomalies were at the seventh rank (4.4%),

Defects of the anterior abdominal wall and GIS were at the eighth rank (3.31%),

Syndromes at the ninth rank (2%),

CFS anomalies at the tenth rank (1.7%) (**Figure**).

The distribution of patients according to the amniocentesis results is summarized in **Table 4**. The distribution of anomalies according to the systems is listed in **Table 5**. Patient distribution according to age is presented in **Table 6**. And the distribution of the maternal age according to history is given in **Table 7**.

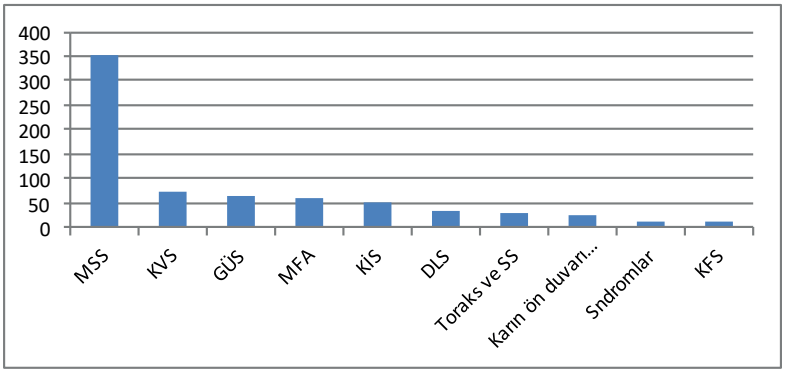

Figure. Distribution of the congenital anomalies according to the systems

Table 4. Results of amniocentesis

	A/C results
Trisomy 21	7
Trisomy 18	5
Trisomy 13	4
45 –X0	2
Others	7

Table 5. Distribution of anomalies according to the systems

SYSTEM	Number of cases (n)	Percentage of cases (%)
Central nervous system	351	48.4
Cardiovascular system	74	10.2
Genitourinary system	67	9.2
Musculoskeletal system	51	7
Craniofacial system	13	1.7
Thorax and respiratory system	32	4.4
Anterior abdominal wall and gastrointestinal system	24	3.3
Skin and lymphatic system	36	4.9
Syndromes	15	2
Multiple fetal anomalies	62	8.5

Table 6. Distribution of patients according to age

Maternal age	Percentage %	Number of Patients
15-19	7	51
20--24	27.3	198
25-29	29.5	214
30-34	20.8	151
35-40	13.2	96
41-45	2	15

Amniocentesis had not been recommended to 400 of 725 patients (55.1%) and 186 (25.6%) refused the amniocentesis. No proliferation was observed in the culture of the amniotic fluid in 6 patients (0.8%), and 133 (18.3%) had

Table 7. Distribution of the maternal age according to medical history

Maternal age	Number of patients with a history of habitual abortion	Number of patients with a history of siblings with anomaly	Number of patients with a history of consanguinity
15-19	-	2	16
20--24	9	10	32
25-29	6	7	31
30-34	8	8	27
35-40	7	4	16
41-45	-	1	1

a normal karyotype. Four of 7 patients, who had trisomy 21 according to the amniocentesis, were referred to our hospital due to the development of non-immune hydrops fetalis and the remaining 3 due to the diagnosis of a CVS anomaly.

In our hospital, 423 of 725 patients (58.3%) accepted pregnancy termination, and

133 (18.3%) of them refused the process.

We recommended monitorization instead of termination in 131 patients (18%).

Intrauterine fetal death occurred in 5 cases (0.6%) during the follow-up.

Twenty-one (2.8%) patients had quit the follow-up program of our hospital.

Thirteen (1.7%) patients had been referred to other centers.

A follow-up program was scheduled for 68% of patients diagnosed with GUS anomalies and 53% with RS anomalies, and thus they became the most common anomaly groups in our clinic. Four hundred twenty-three of 725 participants (58.3%) had been using folic acid.

DISCUSSION

The majority of the congenital anomalies are health problems that are difficult and expensive to treat and rehabilita-

te and pose a serious material and non-material burden for families and society. In spite of the several epidemiological and experimental studies, the etiology of the congenital anomalies was not fully elucidated yet. Their incidences vary according to socioeconomic status, nutritional habits, geographic regions, ethnic, and environmental factors. Regarding the relationship between the maternal age and rate of births with a congenital anomaly, we found that the congenital anomalies were most common in the 21-30 age group similar to other studies. In our study, CNS anomalies constituted 48.1% of all anomalies. This condition is normal according to the embryological development of CNS. In the study conducted at Gazi University between 1988 and 2005 on 17,259 births, CNS anomalies constituted 48.1% of all anomalies. The same study showed that 17% of all congenital anomalies were NTD. The same rate was 36.1% in our study (5). This rate shows the importance of NTD for mortality and morbidity in our region. Environmental and nutritional factors were blamed in the etiology of NTD. In a study conducted in the USA, periconceptional folic acid administration for 6 years was observed to decrease the NTD incidence from 1.89% to 0.95% (6). In our study, the total rate of folic acid use was 58% and it was 52%, and 51% in patients with CNS anomalies and patients with NTD, respectively. The rate of folic acid use was 64.2% in a study conducted by Yüce et al. (7). As we could not follow in our records for how long our patients had used folic acid, there is a need for more detailed studies, and implementation of certain precautions should be considered to increase the folic acid use.

In the study conducted by Biri et al. (5) the second, third, and fourth most common anomalies were urinary system (14.4%), musculoskeletal system (11.7%), and cardiovascular system (8.28%) anomalies, respectively while the second, third, fourth, and fifth most common anomalies in our study were CVS (9.5%), GUS (8.6%), MFA (7.9%) and MSS (6.5%), respectively. In the study conducted at Dicle University between 1990 and 1999, the most common anomaly was CNS anomalies (49.5%) followed by MSS (28.5%), CFS (21%) and GIS (10.5%) anomalies (8). These conflicting results may depend on that CVS anomalies are referred to us, as our center is a regional reference hospital of Middle Black Sea Region and other anomalies are followed up in the related centers and were not referred unless there is an indication for termination. In a similar study found in the literature, the incidence of multiple malformations was 30%, while the same incidence was 8.5% in our study (5). This incidence was 22.3% in a study conducted by Bayhan et al (8). These conflicting results may depend on differences in the records of the minor criteria or on the geographical factors. More reliable results about the anomaly incidences in the regions may be obtained with the determination of the rates of other postnatal anomalies, and rates of the missed prenatal diagnoses in terminated pregnancies. In a second study conducted at Dicle University between 2009 and 2012, the rates of the consanguinity and history of siblings with anomalies were 23.3% and 11.5%, respectively (9). In our study, the same rates were 16.1% and 4.1%, respectively. These results showed that the consanguinity rate was relatively lower in our region. Özler et al. (9) observed that 54.4% of the congenital anomalies were diagnosed before the gestational week 24; 12.8% between the weeks 24 and 28, and 32.8% after week 28. In our study, we observed that 80% of the cases were diagnosed before week 24, 11.5% between weeks 24-28 and 8.5% after week 28. We believed these conflicting findings depended on different socioeconomic factors between the regions and diagnosis of unfollowed pregnant females during their application for birth in the last trimester.

In the Eurofetus study (4), 44% of the congenital anomalies were diagnosed before the 24th gestational week. In our region, there is a need for clarification of the diagnosis rates with further studies focusing on the diagnosis rates of postnatal anomalies. The diagnosis week for the congenital anomalies in the prenatal period also changes the course of pregnancy management. In pregnancies with late diagnosis, parents may decide in favor of birth (10,11). If the diagnosis rate of fetuses with congenital anomalies exceeds 36% during the routine US examination performed in low-risk pregnancies and patients accept termination, neonatal mortality rates will drop significantly (12). On the other hand, maternal mortality related to the pregnancy termination in the first trimester is 1/100,100 while the same rate is 7-10/100,000 in the second trimester (13). Early diagnosis is critical for the decrease of both neonatal and maternal mortality and morbidity. The increased rate of musculoskeletal system (MSS) anomalies among the patients with consanguinity indicates that more advanced genetic analyses are necessary for these patients. According to the DST, TST, and folic acid use rates (29%, 48%, and 58.3%, respectively) of the participants in our study, we believe that improvements in the accessibility to the care services for pregnant women, and correction of the deficiencies in the care services will be appropriate. As most of the participating patients came from nearby cities and did not give birth in our hospital, we were not able to make a comprehensive assessment of the congenital anomaly incidences in our region. We believe that a region-based study instead of a hospital-based study will be more appropriate. Although goiter is endemic in our region, only 65 of the participating females were diagnosed with goiter, and the rate of the substance use was very low indicating that the patients did not share reliable information about their medical history. Approximately 2%-5% of the fetuses and neonates have congenital anomalies and these anomalies are responsible for 20%-30% of all neonatal mortalities (14). The intrauterine detection of the anomalies and the proposal of therapy or termination options will increase survival and decrease morbidity rates in the treated group; it will also cause a decrease in the neonatal mortality in the termination group (15). This difference can be explained by the experience of the US specialist. Therefore, referral of high-risk groups to a tertiary health center for the routine second-trimester screening should be prioritized.

CONCLUSION

According to the rate of prenatal screening tests in our region, we believe that increasing the prenatal care intensity and quality will increase the rate of early diagnosis. Thus, the neonatal and maternal mortality and morbidity rates will improve, and the material and non-material burden on the families and society will decline. Prenatal care services are also vital as the NTD rates were observed higher compared to other Turkish studies, and the rate of the folic acid use, which is a controllable risk factor, was observed to be low. The high rate of CVS anomalies in our region (the second most common anomaly group) indicated that there is a need for the studies focused on the etiology of the CVS anomalies and region-based incidences.

DECLARATION OF CONFLICTING INTERESTS

The author declared no conflicts of interest with respect to the authorship and/or publication of this article.

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