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RESEARCH ARTICLE

# Frequency of Congenital Malformations in The Fourth Level Neonatal Intensive Care Unit: 4 Year-Experience

## Dördüncü Seviye Yenidoğan Yoğun Bakım Ünitesinde Doğumsal Malformasyonların Sıklığı: 4 Yıllık Deneyim

Mustafa Oz<sup>1</sup>, Nuriye Emiroglu<sup>2</sup><sup>1</sup>Çağlayancerit State Hospital, Kahramanmaraş, Türkiye<sup>2</sup>Necmettin Erbakan University, Faculty of Medicine, Department of Child Health and Diseases, Konya, Türkiye**ABSTRACT**

**Objective:** Congenital malformations (CM) constitute one of the most important causes of neonatal and childhood deaths, chronic diseases and morbidity. This study aimed to identify CM, determine their frequency and investigate the factors that may be effective in etiology in patients treated in the Neonatal Intensive Care Unit (NICU) of Necmettin Erbakan University Medicine Hospital.

**Materials and Methods:** The files of 4860 patients hospitalized in the NICU between October 1, 2017 and October 15, 2021 were retrospectively reviewed.

**Results:** A total of 4860 patients were investigated within the scope of the study, and CM were detected in 423 cases. When the distribution of malformations according to gestational age was examined, 55% of all malformations were seen in term babies. When the distribution according to maternal age was examined, it was seen that the majority were born to mothers under 35 years of age (80%). The frequency of CM was found to be 8.7%. When the distribution of malformations according to organ systems was examined, the most frequently affected system was the cardiovascular system (24.3%). This was followed by anomalies of the central nervous system (23.4%), genitourinary (18.2%), gastrointestinal (13.2%), head-neck-face (9.9%), respiratory (6.6%) and musculoskeletal (4.3%). The most common isolated anomaly was hydronephrosis (13.2%). The presence of genitourinary system malformations in babies of pregnant women who had urinary tract infections, the occurrence of cardiovascular and gastrointestinal anomalies in preterm babies, and the high mortality rate due to respiratory malformations were among the prominent findings of the study. Death occurred for various reasons during NICU hospitalization in 13% of the cases. The most common anomalies among the babies who died were cardiovascular system anomalies (31%).

**Conclusion:** Determining the frequency of CM and determining the factors that may be effective in etiology in general and taking precautions accordingly will play an important role in both reducing morbidity and mortality and increasing the socioeconomic welfare of societies.

**Keywords:** Newborn, congenital malformation, frequency

**ÖZET**

**Amaç:** Konjenital malformasyonlar yenidoğan ve çocukluk çağı ölümlerinin, kronik hastalıkların ve morbiditenin en önemli nedenlerinden birini oluşturmaktadır. Bu çalışmada Necmettin Erbakan Üniversitesi Tıp Fakültesi Hastanesi Yenidoğan Yoğun Bakım Ünitesi'nde yatarak tedavi gören olgularda konjenital malformasyonların tanımlanması, sıklığının belirlenmesi ve etiyolojide etkili olabilecek faktörlerin araştırılması amaçlanmıştır.

**Gereç ve Yöntemler:** 1 Ekim 2017 ile 15 Ekim 2021 tarihleri arasında yenidoğan yoğun bakım ünitesinde yatan 4860 hastanın dosyaları retrospektif olarak incelendi.

**Bulgular:** Çalışma kapsamında toplam 4860 hasta araştırıldı, 423 olguda konjenital malformasyon saptandı. Malformasyonların gebelik haftasına göre dağılımına bakıldığında, tüm malformasyonların % 55'i term bebeklerde görüldü. Anne yaşına göre dağılımına bakıldığında büyük çoğunluğunun 35 yaş altı anneden doğduğu görülmektedir (% 80). Konjenital malformasyonların sıklığı % 8,7 olarak bulundu. Malformasyonların organ sistemlerine göre dağılımı incelendiğinde en sık etkilenen sistem kardiyovasküler sistemdi (%24,3). Bunu sırasıyla merkezi sinir sistemi (% 23,4), genitouriner sistem (% 18,2), gastrointestinal sistem (% 13,2), baş-boyun-yüz (% 9,9), solunum (% 6,6) ve kas-iskelet sistemi (% 4,3) anomalileri izledi. En sık izole anomali hidronefroz (% 13,2) idi. İdrar yolu enfeksiyonu geçiren gebelerin bebeklerinde genitouriner sistem malformasyonlarının varlığı, preterm bebeklerde kardiyovasküler ve gastrointestinal sistem anomalilerinin ortaya çıkması ve solunum sistemi malformasyonlarına bağlı yüksek mortalite oranı çalışmada öne çıkan bulgular arasındaydı. Olguların %13'ünde yenidoğan yoğun bakım yatışı esnasında çeşitli nedenlerle ölüm gerçekleşti. Ölen bebekler arasında en sık rastlanan anomaliler kardiyovasküler sistem anomalileriydi (%31).

**Sonuç:** Doğuştan malformasyonların sıklığının belirlenmesi ve genel olarak etiyolojide etkili olabilecek faktörlerin belirlenerek buna göre önlemler alınması hem morbidite ve mortalitenin azaltılmasında hem de toplumların sosyoekonomik refahının artırılmasında önemli rol oynayacaktır.

**Anahtar Kelimeler:** Yenidoğan, konjenital malformasyon, sıklık

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**Corresponding Author:** Nuriye Emiroglu, Necmettin Erbakan University, Faculty of Medicine, Department of Child Health and Diseases, Konya, Türkiye  
**e-mail:** nuriyetarakci@hotmail.com

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## INTRODUCTION

A congenital malformation (CM) or birth defect, is defined as any abnormality, either structural or functional, present at birth, which may have been inherited genetically, acquired during gestation, or inflicted with parturition (1). Congenital malformations constitute one of the most important causes of neonatal and childhood deaths, chronic diseases and morbidity (2). The incidence of congenital malformations varies between regions and countries depending on socio-economic status, nutritional habits, genetic and environmental factors (3). Congenital malformations pose a serious health problem in underdeveloped and developing countries and there isn't enough data regarding their etiology. Although it is known that some of them occur due to genetics, maternal diseases, exposure to teratogens and/or environmental reasons, the cause of approximately half of the cases is unknown (4).

Our study aims to determine the frequency of congenital malformations in Konya, a city with a large population density where our hospital is located. Additionally, it aims at determining the distribution of malformation cases according to the affected systems and the factors associated with these anomalies.

## MATERIALS AND METHOD

Our study included cases with congenital malformations followed up in the Neonatal Intensive Care Unit of Necmettin Erbakan University Faculty of Medicine Hospital between October 1, 2017 and October 15, 2021. The files of each of the 4860 patients hospitalized in the neonatal intensive care unit between the specified dates were reviewed. Babies with clinical, genetic or radiological congenital malformations were selected. Stillbirth, medical termination, live birth cases that did not require intensive care, and malformation cases diagnosed after neonatal intensive care hospitalization were not included in the study. Isolated hydrocephalus cases without underlying central nervous system malformation were excluded from the study. Approval was obtained from the Necmettin Erbakan University Faculty of Medicine Clinical Research Ethics Committee for the study. All analyzes were performed in the SPSS 21.0 program. Arithmetic mean $\pm$ standard deviation and median (min-max) values were used to summarize numerical data; frequency distributions (n) were used to summarize categorical data. The normal distribution of numerical data was tested using visual (Histogram) and analytical (Kolmogorov-Smirnov and Shapiro-Wilk tests) methods. In cases where the distribution was normal, the relationships between numerical data were evaluated using a single sample t test and an independent groups t test. In cases where the distribution was not normal, the Kruskal Wallis test was used in samples that were nonparametric equivalents of the same tests. The relationships between categorical data were investigated using the Chi-square test. Pearson correlation analysis was used to compare quantitative data with each other. The frequency of congenital anomalies, differences between genders, maternal infection and disease status, maternal age, gestational week and birth weight were calculated using the Chi-square and

Fisher exact tests with a Type-1 error level of 0.05. Statistically, cases where p was less than 0.05 were considered significant.

## RESULTS

Within the scope of the study, a total of 4860 patients receiving inpatient treatment in the neonatal intensive care unit of Necmettin Erbakan University Medical Faculty Hospital were studied, and a total of 423 cases with congenital anomalies were identified.

The incidence of malformations in patients treated in the neonatal intensive care unit was calculated as 8.7%. Looking at the distribution of malformations by organ systems, the most common anomalies were cardiovascular system anomalies (24.3%). The second most common were central nervous system anomalies (23.4%). These were followed by genitourinary, gastrointestinal, head-neck-facial, respiratory and musculoskeletal system anomalies, respectively (Table 1). The most common isolated anomaly in our study was hydronephrosis (13.2%). This was followed by meningomyelocele (11.8%) and cleft lip (7%), respectively.

Of the cases with congenital anomalies included in our study, 59% were of male and 41% were of female gender. The most common anomalies detected in total were cardiovascular system anomalies, while when evaluated according to gender, the most common malformations in males were genitourinary system anomalies and in females were central nervous system anomalies. Genitourinary and gastrointestinal system anomalies were 11% and 8% in females and 23% and 17% in males, respectively, and the probability of genitourinary and gastrointestinal system anomalies was statistically significantly higher in males ( $p=0.001$  and  $p=0.018$ ).

In our study cohort, 84 mothers (19.8%) were found to have at least one maternal disease. The most common disease was gestational and/or pre-gestational diabetes, which was observed in 9.2% of all pregnant women and constituted 46.4% of all maternal diseases. Central nervous system (CNS) malformations were detected in 26% of children of diabetic mothers, while this rate was measured as 17% in children of non-diabetic mothers. This difference was statistically significant ( $p = 0.001$ ).

A history of maternal infection was present in 8.5% of the cases included in our study. The majority of these infections (69.4%) were urinary tract infections. The most commonly

**Table 1.** Distribution of malformations by affected organ systems

Systems	n (%)
Cardiovascular system	103 (24.3)
Central nervous system	99 (23.4)
Genitourinary system	77 (18.2)
Gastrointestinal system	56 (13.2)
Head-neck -face	42 (9.9)
Respiratory system	28 (6.6)
Musculo-skeletal system	18 (4.3)
Total	423 (100)

**Table 2.** Distribution of cardiovascular anomalies in early and late preterm neonates

Malformations	Gestational week			p
	<34 weeks n (%)	34-36(6/7) weeks n (%)	Total n (%)	
Cardiovascular anomalies	27 (14)	24 (12)	51 (26)	0.008
Other system anomalies	39 (21)	97 (53)	136 (74)	
Total	66 (35)	121 (65)	187 (100)	

**Table 3.** Distribution of gastrointestinal anomalies in preterm and term neonates

Malformations	Gestational week			p
	<37 weeks n (%)	37≤ weeks n (%)	Total n (%)	
Gastrointestinal anomalies	34 (8)	22 (5)	56 (13)	0.025
Other system anomalies	153 (36)	214 (51)	367 (87)	
Total	187 (44)	236 (56)	423 (100)	

**Table 4.** Distribution of central nervous system anomalies in preterm and term neonates

Malformations	Gestational week			p
	<37 weeks n (%)	37≤ weeks n (%)	Total n (%)	
Central nervous system anomalies	29 (7)	70 (16)	99 (23)	0.004
Other system anomalies	158 (37)	166 (40)	324 (77)	
Total	187 (44)	236 (56)	423 (100)	

observed anomalies in the infants of mothers with urinary tract infections were genitourinary system malformations. Genitourinary malformations were present in 54% of infants born to mothers with urinary tract infections during pregnancy, compared to 18% in those without such infections. The incidence of genitourinary malformations was found to be significantly higher in the children of mothers who experienced urinary tract infections during pregnancy ( $p=0.007$ ).

Among the malformed infants included in our study, 2.6% had mothers who did not receive folic acid supplementation during or prior to pregnancy. Neural tube defects were observed in 100% of infants whose mothers did not receive folic acid supplementation during pregnancy, compared to 16% of those whose mothers did. The occurrence of neural tube defects in infants born to mothers who did not receive folic acid supplementation during pregnancy was found to be statistically significant ( $p=0.001$ ).

Upon evaluating the distribution of congenital malformations by gestational age, it was determined that 55.8% of all malformations occurred in term infants. Among

neonates born before 34 weeks, 44% exhibited cardiovascular anomalies, whereas this figure was 20% among late preterm infants (between 34 and 36+6 weeks gestation). The increased frequency of cardiovascular system anomalies in infants born prior to 34 weeks, compared to those born in the late preterm period, was statistically significant. ( $p=0.008$ ) (Table 2).

Gastrointestinal system anomalies were detected in 18% of the preterm infants included in our study, whereas this rate was 9% among term infants. The prevalence of gastrointestinal system anomalies was significantly higher in preterm infants compared to term infants. ( $p=0.025$ ) (Table 3). A total of 70% of central nervous system anomalies were identified in term neonates, with this distribution showing statistical significance. ( $p=0.004$ ) (Table 4).

A majority (62.9%) of the congenital anomalies in our study were identified in infants with a birth weight of 2500 grams or above. Seventy-six percent of central nervous system anomalies were observed in infants with a birth weight of 2500 grams or more. This proportion was also statistically significant. ( $p=0.012$ ) (Table 5).

**Table 5.** Distribution of central nervous system anomalies according to birth weight

Malformations	Birth weight		Total n (%)	p
	<2500 g n (%)	2500 g≤ n (%)		
Central nervous system anomalies	23 (5)	76 (18)	99 (23)	0.012
Other system anomalies	34 (32)	190 (45)	324 (77)	
Total	157 (37)	266 (63)	423 (100)	

**Table 6.** Distribution of cardiovascular anomalies in very low and normal birth weight infants

Malformations	Birth weight		Total n (%)	p
	<1500 g n (%)	2500 g ≤ n (%)		
Cardiovascular anomalies	21 (6)	41(13)	62 (19)	0.001
Other system anomalies	23 (8)	225 (73)	248 (81)	
Total	44 (14)	266 (86)	310 (100)	

In our study group, 41% of the infants diagnosed with cardiovascular anomalies had a birth weight of  $\geq 2500$  grams, 38% had a birth weight between 1500 and 2500 grams, and 21% had a birth weight below 1500 grams. Cardiovascular anomalies were found to be significantly more frequent in newborns with normal birth weight compared to those with very low birth weight. ( $p=0.001$ ) (Table 6).

When the distribution of malformations according to maternal age was examined, the majority of cases (80%) were born to mothers under 35 years of age. Among cases with maternal age  $\geq 35$  years, the most common anomalies were cardiovascular system anomalies (36%). The rate of cardiovascular anomalies among infants born to mothers under 35 years of age was found to be 20%. The higher incidence of cardiovascular system anomalies in infants born to older mothers was also found to be statistically significant ( $p=0.001$ ).

In our study group, 13% of the cases died during their admission to the neonatal intensive care unit for various reasons. Among the deceased infants, cardiovascular system anomalies were the most common anomalies observed (31%), whereas musculoskeletal system anomalies were the least common (4%). The most frequently detected isolated anomaly was congenital diaphragmatic hernia (22%). Among 28 cases with respiratory system malformations, 42% died during their stay in the neonatal intensive care unit. When compared to non-respiratory anomalies, the higher mortality rate in patients with respiratory system anomalies was found to be statistically significant ( $p=0.01$ ).

## DISCUSSION

The incidence of malformation in the cases treated in the neonatal intensive care unit, which we included in the study, was calculated as 8.7%. In studies conducted in different countries, the prevalence of congenital anomalies in live births varies between 2-3%; It was noted as 0.8% in England, 1.8% in Iran, 3.3% in Nigeria, 2% in Mexico, 3% in America, and 2% in Japan (5, 6, 7, 8, 9). In Turkiye, Tunçbilek et al. (10) reported the frequency of congenital anomalies as 3.7% in a comprehensive study that included data from 22 university hospitals. In our study, the frequency of congenital anomalies was generally found to be higher than other studies. The factors in obtaining this result include the fact that our study group consists of babies treated in the neonatal intensive care unit, cases with an antenatal diagnosis are referred to our hospital before or after birth because our hospital is the referral hospital in the region, the relatively lower tendency for pregnancy termination in antenatally diagnosed cases due to the socio-demographic

characteristics of our region, and the relatively higher rate of consanguineous marriages in our region.

When factors influencing malformations in terms of gender were examined, it was observed that males had a higher incidence of malformations compared to female cases. Of the 423 malformation patients included in our study, 252 were male (59%) and 171 (41%) were female. This rate also coincides with the current study conducted by Özdil (13) in Turkiye with 12,053 cases. In our study, we detected genitourinary system and central nervous system anomalies as the most frequent anomalies in males and females, respectively. We identified genitourinary and gastrointestinal system malformations significantly higher in males compared to females ( $p=0.001$  and  $p=0.018$ ). In a study conducted in Europe by Garne et al. (14), renal anomalies were found to be higher in men. This result is compatible with our study. In two different studies, central nervous system anomalies were observed more frequently in the male gender (15, 16). Different information is given in the literature for digestive system anomalies; In a study conducted in Iran, gastrointestinal malformations were found to be higher in girls, while in America, the rates were found to be higher in boys (17, 18). Different results obtained from different studies may be due to the difference in the number of patients and other factors affecting malformations. Different results obtained from different studies may be due to the difference in the number of patients and other factors affecting malformations.

The most common maternal disease in our study was gestational and/or pregestational diabetes; Its frequency among all pregnant women was 9.2%, and its rate among mothers with maternal diseases was 46.4%. In a study conducted with a large patient population in Turkiye, the most common disease in mothers giving birth to babies with anomalies was reported as diabetes mellitus, which is also consistent with our study (15). In the study conducted by Akarsu et al. in the children of diabetic mothers (19), the most common anomalies were reported as cardiovascular anomalies. In another study as well, cardiovascular system anomalies were found to be the most frequent in infants of diabetic mothers, followed by gastrointestinal and genitourinary system anomalies in decreasing frequency (20). In our study, Genito-urinary system anomalies were the most common anomalies in the children of diabetic mothers; the central nervous system was in second place, and the cardiovascular system was in third place. The reason for this may be attributed to the difference in other environmental and genetic factors that may influence the formation of anomalies. Central nervous system malformations were found to be statistically significantly higher in children of

mothers with diabetes compared to those without ( $p=0.001$ ). This result was also consistent with the literature (21, 22).

Infections during pregnancy are one of the causes of morbidity and mortality for both the mother and the fetus and may cause abortion, intrauterine death, congenital anomalies, and infection in the neonatal period (23, 24). Urinary tract infections are the most common health problem during pregnancy after anemia and are seen in approximately 17-20% of all pregnancies (25). In our study, 36 (8.5%) of 423 malformation cases had a history of maternal infection. Urinary tract infection accounted for 69.4% of pregnant women with maternal infections. There is no reported evidence in the literature suggesting that urinary tract infections during pregnancy directly result in congenital anomalies in the fetus (26, 27). In our study, however, we found a statistically significant higher incidence of genitourinary malformations in children of mothers who had urinary tract infections during pregnancy ( $p=0.007$ ). Studies on this subject with larger patient groups may contribute to the literature.

It is known that folic acid replacement during pregnancy is effective in preventing the development of central nervous system anomalies, especially neural tube defects (28, 43). The mothers of 2.6% of the babies with malformations included in our study had not used folic acid during or before pregnancy. Neural tube defect was present in all of these patients, and the occurrence of neural tube defects in the babies of mothers who had not taken folic acid replacement during pregnancy was found to be statistically significant ( $p = 0.001$ ).

Approximately 12.5% of babies with congenital malformations are born prematurely (29, 30). Premature babies have a two-fold higher risk of having congenital anomalies compared to full-term babies (31). In our study, 44.2% of all malformations were found in premature babies. This result is consistent with the large patient-based study conducted by Özdil in 2012 (13). When organ systems are examined, the occurrence of cardiovascular system anomalies in premature cases was found to be statistically significant ( $p=0.008$ ). Similarly, in a study conducted in the USA in 2007 and examining approximately 7000 cases, the probability of cardiovascular anomalies in premature babies was found to be high (42). Central nervous system anomalies were mostly seen in full-term babies. In an analysis of data from 13 states in the USA, cardiovascular and central nervous system anomalies were reported to be more common in full-term infants, while gastrointestinal system anomalies were more common in premature infants (31). Similarly, in our study, gastrointestinal anomalies were found to be significantly higher in preterm infants, and CNS anomalies were found to be significantly higher in term infants ( $p=0.025$  and  $p=0.004$ ).

Fetal growth is affected in most fetuses with congenital malformations (32, 44). It has been observed that the digestive system, genital organs and musculoskeletal system are particularly affected in malformed fetuses with intrauterine growth retardation (8). It has been reported that newborns with congenital heart disease (such as transposition of the great arteries, tetralogy of Fallot, hypoplastic left heart and

coarctation of the aorta) show abnormal fetal development, especially in terms of weight (33, 45). When the malformation cases in our study were classified according to birth weight, 266 (62.9%) of the cases were 2500 grams and above, 113 (26.7%) were between 1500-2500 grams and 44 (10.4%) were below 1500 grams. These results are similar to a study conducted in a university hospital in Türkiye and examining 11,434 live births (13). In our study, central nervous system and cardiovascular anomalies were significantly more common in babies with a birth weight of 2500 grams and above ( $p=0.012$  and  $p=0.001$ , respectively). In a study examining 329 cases with central nervous system anomalies in Turkey, the mean birth weight was reported as 3045 grams, which is consistent with our study (16). Similarly, in a retrospective study conducted in 2012 and evaluating congenital heart diseases, it was stated that congenital heart diseases were more common in babies with normal birth weight, which is consistent with our study (34).

Looking at the distribution of the cases included in our study by maternal age, it is notable that the majority of them were born to mothers under 35 years of age (80%). When the relationship between maternal age and congenital anomaly is examined in studies conducted in different regions in Turkey, it is seen that cases with anomaly are most frequently in the 21-30 age group (35, 36). The results of our study seem to be compatible with existing studies. Although advanced maternal age is one of the factors involved in the etiology of fetal anomalies, the fact that anomalies are seen more in babies of young mothers indicates the necessity of detailed prenatal diagnosis and follow-up for all patients. Advanced maternal age has also been found to be associated with congenital heart diseases (37, 46). In our study as well, cardiovascular system anomalies were found to be the most common anomaly in the babies of mothers aged 35 and over, and the presence of cardiovascular system anomalies in the babies of these mothers was found to be statistically significant ( $p = 0.001$ ).

In the literature, it has been stated that central nervous system malformations are identified as the primary cause of stillbirths, and during the neonatal period, cardiovascular and pulmonary malformations are the most common causes of death (38). In Europe as well, the most common group of congenital anomalies leading to perinatal mortality has been reported to be congenital heart diseases and central nervous system malformations (39). Isolated congenital diaphragmatic hernias still have high mortality today (40). In a study conducted by Celayir and colleagues (41), the mortality rate in congenital diaphragmatic hernia was determined to be 73%. Death occurred in 54 cases (13%) for various reasons during neonatal intensive care unit admission within our study group. The most common anomalies found in the deceased infants were primarily cardiovascular system anomalies (31%), which is consistent with the literature. The most common isolated anomaly found in deceased infants was congenital diaphragmatic hernia (22%). Death occurred during neonatal intensive care admission in 12 of 28 cases with respiratory malformation (42%). All of these cases were as well cases of congenital diaphragmatic hernia. The high incidence of

mortality associated with respiratory system anomalies was found to be statistically significant ( $p = 0.01$ ). When all this data was evaluated together, it was concluded that it was consistent with the literature.

## CONCLUSION

Congenital malformations constitute one of the most important causes of neonatal and childhood deaths, chronic diseases and morbidity. Early and accurate diagnosis is important both for the medical termination decision and for treatment and prognosis in live-born cases, as well as for prenatal diagnosis and preventive medicine in subsequent pregnancies. As a result of this study, the rate of malformations in babies requiring neonatal intensive care was found to be 8.7%. The most frequently detected anomalies were cardiovascular system anomalies. The most frequently detected isolated anomaly was hydronephrosis. In our study, the presence of genitourinary system malformations in the children of pregnant women who had urinary tract infections was notable. In addition, the emergence of cardiovascular and gastrointestinal system anomalies in preterm babies and the high death rate from respiratory system malformations were among the other prominent findings. We expect our study to make a significant contribution to the literature by emphasizing that the incidence of congenital anomalies in live births may be directly affected by the high patient load of our quaternary center and the conservative socioeconomic profile of the region. In general, identifying the frequency of congenital malformations and determining the factors that may be effective in etiology and taking precautions accordingly will play an important role in reducing morbidity and mortality and increasing the socioeconomic welfare of societies.

## DECLARATIONS

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**Address correspondence to:** Nuriye Emiroglu, Necmettin Erbakan University, Faculty of Medicine, Department of Child Health and Diseases, Konya, Türkiye

**e-mail:** nuriyetarakci@hotmail.com

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