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RESULTS OF THE TURKISH CONGENITAL MALFORMATION SURVEY*

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In order to acquire data about the incidence of congenital malformations in the Turkish population, we recorded all livebirths and stillbirths at 22 university hospitals between July 1993-July 1994. Congenital malformation incidence was 3.65 percent. Incidence of individual malformations were compatible with that reported from other populations, with the exception of neural tube defects and cleft palate which were found to be significantly frequent. Abnormal ultrasonographic findings and disorders such as hypertension, diabetes mellitus and vaginal bleeding during pregnancy were found to be valuable indicators for the presence of congenital malformations in the fetus. Incidence of congenital malformations was lower in the western Anatolian region. Variables such as maternal age, education and employment were found to be risk factors for congenital malformations. *Key words: congenital malformations, ultrasonography, prenatal diagnosis, neural tube defects, abnormal pregnancy.*

Congenital malformations are important causes of mortality and morbidity in infancy and childhood. Once detected no satisfactory treatment methods are available for some of these malformations. Both genetic and environmental factors are implicated in the etiology, leading to a variation in incidence of congenital malformations in different populations. A common congenital malformation in a given population is not necessarily frequent in another one.

Programs for prevention of congenital malformations have been launched in different countries in recent years. Naturally, priority is given to the most common malformation in each country. Congenital malformation surveillance studies that have been ongoing since the early 1980's in Europe have disclosed the most frequent malformations in each registry[1]. Results gave inspiration for the establishment of preventive programs.

No data is available on the incidence of congenital malformations in Turkey since the 1969 study by Say et al.[2] in a maternity hospital. Many factors contributing to the incidence of congenital malformations may have changed since then.

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We report the results of a congenital malformation survey conducted at 22 centers from different regions of Turkey between July 1993-June 1994.

Material and Methods

The study began on 1 July 1993. During the preceding two months a pilot study was done to assess the suitability and clarity of the questionnaire and ability of interviewers to collect accurate information from the mothers. This pilot study showed that the interviewers at Hacettepe University could successfully gather data using the questionnaire. Consequently, one interviewer from each center was invited to the registry center for a one-day course on how to collect data, including criteria for exclusion from the study group. The query form was prepared to obtain data about the following topics: a) social and cultural status of the mother, b) history and outcomes of previous pregnancies, c) history of the current pregnancy, d) family history and e) product of the current pregnancy. The interviewer was the pediatrician of each center who attended the training course. Records for each case were transmitted on a standard form to the registry center at Hacettepe University for processing.

All births in obstetrics and gynecology departments at all (22) university hospitals in Turkey between 1 July 1993-31 June 1994 were recorded. Each hospital was from one of five geographical regions (north, east, south, west and central) of Turkey. Distribution of cases by geographical region was made on the basis of the mother's residence, not according to the region in which the hospital of birth was located. Thus, this study was a hospital-based study analyzed according to mother's residence.

Stillbirths and abortions weighing less than 500 g or of less than 20 weeks of gestational age were excluded. Each newborn was examined by a pediatrician for identification of birth defects. A routine physical examination was performed, and weight, height and head circumference measurements were obtained for all newborns. All participating registries used the common coding system of the 10th revision of the International Classification of Diseases (ICD-10)[3] for definition of congenital anomalies. Malformations were classified by organ system according to the ICD-10.

Results

Of 21,907 babies included in the study 11,238 (51.3%) were male and 10,669 (48.7%) female. Stillbirths were recorded at 2.18 percent. Of these, 96.2 percent were singletons and 3.8 percent were multiple.

In the study population, 84 percent of mothers were between 20-35 years of age. Only seven percent were below 20 and nine percent above 35. Distribution

of newborns by maternal education and maternal employment showed that most were born to unemployed but well educated women. Only 5.7 percent of mothers were illiterate, and 72 percent were housewives (Table I).

Table I: Distribution of Cases by Maternal Education and Employment

Education of Mother	%	n
Illiterate	5.7	1208
Primary incomplete	2.1	447
Primary graduate	39.7	8477
Secondary graduate	34.6	7393
High school graduate	17.9	3835
Employment		
Housewife	72.4	15339
Working without salary	1.2	256
Working with salary	26.4	5592

Estimation of infant, child and under-five mortality rates using the preceding birth history revealed that the mothers in the study group had higher risks than those in the general Turkish population (Table II). Estimated infant mortality rate was 89.6 percent. According to the results of the "Turkish Demographic and Health Survey (1993)", the infant mortality rate was 53 per 1,000 in Turkey[4].

Table II: Predicted Rates of Infant, Child and Under-five Mortality Using the Preceding Birth History (per thousand)

Sex	Infant Mortality Rate	Child Mortality Rate	Under-Five Mortality Rate
Male	101.8	29.7	128.5
Female	74.5	23.3	96.1
Total	89.6	27.5	114.6

All mothers were asked regarding complications during pregnancy, with special emphasis on hypertension, diabetes mellitus, vaginal bleeding, abortus imminens or incipiens, anemia, eclampsia or preeclampsia. Mothers with any one of these diseases were included in the group of "pregnancy with an abnormal finding". The frequency of congenital malformations in the "abnormal pregnancy" group was 3.8 percent versus only 1.5 percent in the group without abnormal findings (Table III).

Mothers were also asked if an obstetrical ultrasonography (USG) was performed in the course of this pregnancy. Of the 18,144 mothers who had an ultrasonographic examination, 885 (4.8%) were found to have an abnormal ultrasonographic finding; the remainder were normal. Among the babies born

to a mother with an abnormal obstetric USG, 10.5 percent had a congenital malformation. Only 1.4 percent of women with a normal obstetric USG had a baby with a congenital malformation (Table IV).

Table III: Frequency of Congenital Malformations in Babies of Women With and Without Abnormal Findings During Pregnancy (by Region)

	Congenital Malformation Frequency in Pregnancies with Findings			
	Abnormal		Normal	
Region	N	%	N	%
West	24	*4.0	47	1.0
South	10	**3.8	32	1.9
Central	45	*3.1	118	1.8
North	11	4.3	15	2.2
East	27	*5.3	52	1.4
Total	117	*3.8	264	1.5

The difference between congenital malformation frequency in pregnancies with and without abnormal findings was found to be statistically significant, (*) $p < 0.001$ and (**) $p < 0.05$, in all geographic regions with the exception of the northern region.

Table IV: Frequency of Congenital Malformations in Babies of Women With Abnormal and Normal Ultrasonographic (USG) Findings During Pregnancy

	Congenital Malformation Frequency in Pregnancies with			
	USG Abnormal		USG Normal	
Region	N	%	N	%
West	17	*8.6	49	1.0
South	6	*9.0	31	1.9
Central	45	*11.1	105	1.5
North	10	*16.4	15	1.9
East	15	*9.8	47	1.6
Total	93	*10.5	247	1.4

The difference between congenital malformation frequency in pregnancies with and without abnormal ultrasonographic findings was found to be statistically significant, (*) $p < 0.001$, in all geographic regions.

Incidence of congenital malformations was 3.65 percent in this study. A male preponderance was observed among malformed newborns, with 54 percent of malformations in boys. Distribution of congenital malformations according to organ system is listed in Table V. Comparison of the results with those of the previous Turkish study and with medical literature is also provided.

Table V: Distribution of Malformations by Organ System

ICD10 Code	Malformation	No. Case	Incidence %0.	Literature %0.	Prev. Study %0.
81.0	Epidermolysis bullosa	6	0.27		
18.0	Hemangioma	13	0.59	62	
	Others	5			
	Total Skin	24	1.09		
00.0	Anencephaly	24			
0.1	Encephalocele	6			
			3.0	1.0	1.2
01.1	Nasal encephalocele	7			
05.0	Spina bifida (meningocele, myelocele, meningomyelocele)	29			
03.0	Congenital hydrocephaly	22	1.0	0.4	0.87
	Others	11			
	Total Central Nervous System	99	4.51		
02.0	Microcephaly	21			
75.3	Macrocephaly	26			
	Others	50			
	Total Head-Neck	97	4.42		
11.2	Microphthalmia	5			
12.0	Congenital cataract	1			
13.3	Congenital corneal opacity	3			
	Others	49			
	Total Eye	58	2.64		
16.1	Congenital absence/atresia of the external auditory canal	1			
17.1	Macrotia	1			
17.2	Microtia	5			
30.0	Choanal atresia	1			
35.0	Cleft palate	17	0.77	0.4	0.3
36.0	Cleft lip	17	0.77	1	0.4
37.0	Cleft lip and palate	21	0.95	1	0.4
	Others	70			
	Total Otorhinolaryngeal	133	6.07		
39.1	Tracheoesophageal fistula and esophagus atresia	3	0.13	0.3	0.1
42.3	Imperforate anus	8	0.3	0.2	1.1
79.2	Omphalocele	5	0.22	0.2	
79.3	Gastroschisis	2	0.09	0.1	
	Others	17			
	Total Gastrointestinal System	35	1.59		
21.0	Ventricular septal defect	14			
21.1	Atrial septal defect	12			
	Others	15			
	Total Cardiovascular System	41	1.87	8	1.7
67.6	Pectus excavatum	6			
67.7	Pectus carinatum	8			
83.3	Accessory nipple	1			
	Others	3			
	Total Respiratory System	18	0.82		
52.5	Labial fusion	2			
53.1	Cryptorchidism (unilateral)	9			
			1.9	30	4.2
53.2	Cryptorchidism (bilateral)	33			

Table V: Distribution of Malformation by Organ System (Continued)

ICD10 Code	Malformation	No. Case	Incidence %0.	Literature %0.	Prev. Study %0.
54.0	Hypospadias	37	1.6	0.8-8	2.6
64.0	Epispadias	3			
56.4	Genital ambiguity	13	0.5		0.2
	Others	25			
	Total Genitourinary	122	5.56		
65.0	Congenital hip dislocation (unilateral)	6			
			0.5	1	1.4
65.1	Congenital hip dislocation (bilateral)	6			
66.7	Pes cavus	5			
66.8	Pes equinovarus	43	1.9		2
67.5	Congenital scoliosis	2			
69.0	Polydactyly	17	0.77	0.3-1.5	2.6
70.0	Syndactyly	10	0.45	0.3	1.3
70.4	Polysyndactyly	6	0.27		
	Others	29			
	Total Skeleton-Musde	124	5.66		
	Total Unclassified	20	0.91		
90.0	Down syndrome	27	1.2	1.2-1.6	0.7
91.0	Trisomy 18	1			
96.4	Turner syndrome	1			
	Total Chromosomal Abnormality	29	1.32		
	Total	800	36.5	20-32	

Incidence of congenital malformations was significantly lower in the western Anatolian region, the most developed part of the country. There was no statistically significant difference between the other geographic regions. Regional distribution of malformations is shown in Table VI.

Table VI: Distribution of Malformations by Regions

	Malformation				
	+		-		
Region	n	%	n	%	Total
West	154	2.7	5507	97.3	5661
South	70	3.6	1855	96.4	1925
Central	313	3.7	8069	96.3	8382
North	38	4.0	909	96.0	947
East	176	3.8	4503	96.2	4679
Subtotal	751	3.5	20843	96.5	21594
Not recorded*	49	15.7	264	84.3	313
Total	800	3.7	21107	96.3	21907

* Not included in the statistical analysis.
The difference of incidence in the west is significant, ($p < 0.001$); that between the other regions is not significant.

Malformation incidence was significantly higher in the babies of mothers older than 35 years of age ($p < 0.001$). The group of those less than 18 years had the lowest congenital malformation incidence ($p < 0.05$). Table VII shows the distribution of malformations by maternal age.

Table VII: Distribution of Malformations by Maternal Age

	Malformation				
	+		−		
Maternal Age	n	%	n	%	Total
< 19	14	1.9	735	98.1	749
19-34	625	3.3	18357	96.7	18982
35+	132	7.0	1777	93.0	1909
Total	**771**	**3.6**	**20869**	**96.4**	**21640**
Not recorded*	29	10.9	238	89.1	267
Total	800	3.7	21107	96.3	21907

* Not included in the statistical analysis.
The difference of 35+ group is statistically significant, ($p < 0.001$). When this group is excluded, the difference between the other two groups is also significant, ($p < 0.05$).

Illiteracy of the mother was closely related with malformations (Table VIII): 9.3 percent of illiterate mothers had a malformed child ($p < 0.001$). Congenital malformation incidence was found to be highest in babies born by operational delivery (forceps, vacuum extraction, etc.) or cesarean section. We observed that fetuses with congenital malformation were more likely to have a presentation other than vertex. Babies with vertex presentation and breech presentation had significantly different incidences of congenital malformations, at 3.1 and 8 percent, respectively.

Table VIII: Distribution of Malformations by Maternal Education

	Malformation				
	+		−		
Education of Mother	n	%	n	%	Total
Illiterate	112	9.3	1096	90.7	1208
Primary incomplete	16	3.6	431	96.4	447
Primary graduate	321	3.8	8167	96.2	8488
Secondary graduate	215	2.9	7200	97.1	7415
High school graduate	89	2.3	3754	97.7	3843
Total	**753**	**3.5**	**20648**	**96.5**	**21401**
Not recorded*	47	9.3	459	90.7	506
Total	800	3.7	21107	96.3	21907

* Not included in the statistical analysis.
The difference between the groups is statistically significant ($p < 0.001$). The illiterate mothers' group is different. When this group is excluded, the primary in complete and graduate groups are also found to be different, ($p < 0.05$).

As expected, congenital malformations were significantly frequent in the stillbirth and perinatal death groups in comparison to livebirths (Table IX).

Table IX: Distribution of Malformations by the Outcome of the Pregnancy

	Malformation				
	+		−		
Outcome	n	%	n	%	Total
Livebirth	567	2.7	20477	97.3	21044
Stillbirth	123	25.9	355	74.1	478
Perinatal death	72	40.7	105	59.3	177
Total	762	3.5	20937	96.5	21699
Not recorded*	38	18.3	170	81.7	208
Total	800	3.7	21107	96.3	21907

* Not included in the statistical analysis.
The difference between the groups is statistically significant, ($p < 0.001$). The perinatal death group is different. When this group is excluded, the stillbirth group is also found to be different, ($p < 0.001$).

Discussion

The present study was based on a study population defined by the residence of the mother who delivered a child in one of the 22 university hospitals between July 1993-July 1994. Thus, this is a hospital-based study analyzed according to mother's residence. While results of this study may not be comparable with the previous Turkish studies because of different ascertainment methods, we believe they give a better idea about the prevalence of congenital malformations in the different geographical regions of Turkey. In contrast to the previous surveys[2,5] which were based on the registration of congenital malformations at a single hospital, our study included all malformed babies from 22 centers dispersed throughout the country.

Evaluation of the mothers in the study population showed that they had a higher social and cultural level than those in the general Turkish population. This might lead to a bias and an incorrect estimation of a low prevalence of congenital malformations, since it is known that environmental factors related to poor social and cultural status impact the occurrence of birth defects. However, these women also had higher infant, child and under-five mortality rates than Turkish women in the general population, which might have led them to choose university hospitals for prenatal care and delivery of their baby. Higher mortality rates estimated with the preceding birth history make the mothers in the study a high risk population for congenital anomalies, again leading to another bias. Induced abortions after prenatal diagnosis were impossible to ascertain for lack of data and were not registered in this study.

Actually, if therapeutic abortions had been recorded, the prevalence of congenital malformations in this study would have been higher. Despite all the mentioned methodological issues, we believe that this is the best possible study that can be done in Turkey, if one keeps in mind that only 60 percent of all births take place in a health department and still a great majority of them are not registered[4]. We compared the incidence of certain malformations with the results of the previous Turkish study[2] and those provided in the medical literature. While many of them had similar incidences, some showed significant differences. One obvious difference is in the frequency of neural tube defects (NTDs) in Turkey and in Europe. When compared with the EUROCAT registries, Turkey has a very high prevalence rate of NTD (30/10,000). Within Europe, diversity in the epidemiology of NTDs was observed. The prevalence was much higher in the British Isles than in continental Europe in the early 1980's[6]. Periconceptional use of folic acid by women of childbearing age lowered the prevalence of NTDs significantly in England and Ireland. The decreasing trend in the prevalence rate of NTDs confirms the impact of environmental factors, especially folic acid, on the etiology of neural tube defects. In Turkey, prevalence of NTDs is very high when compared to Europe. Maternal illiteracy, maternal advanced age and residence in either the northern or eastern regions of Turkey are shown to be risk factors for having a baby with a NTD. Women who live in western Anatolia, have graduated from a high school or university, and are below 35 years of age are less likely to have an offspring with a NTD. Lower social and economic status may correlate with the lesser consumption of folic acid and other environmental factors. We believe that this is the more likely explanation for the high frequency of NTDs in Turkey.

Cleft palate incidence was two times higher in our study than in the previous Turkish study and medical literature, but cleft lip with/without cleft palate was not significantly different. We know that cleft palate is related to maternal smoking habits and folate intake[7]. Folate intake is also closely related with the prevalence of neural tube defects as mentioned previously.

Incidence of gastrointestinal malformations such as imperforate anus, omphalocele and gastroschisis in our study was very close to that reported in the literature[8]. Tracheoesophageal fistula was three times lower in both the current and previous Turkish studies, probably due to the difficulty of identifying the malformation in the early neonatal period.

Cardiovascular system (CVS) malformations, congenital hip dislocation and cryptorchidism were found to be less frequent in our study than in medical literature[1,9]. Hemangiomas were also very rare[8].

We think that the malformations found to be infrequent in this study were not easy to identify on the physical examination just after birth (e.g. CVS malformations). We believe that some other malformations are undiagnosed by the physician, incorrectly appearing to be infrequent in our study.

In this study, incidence for all malformations was 36.5 per 1,000. Previously, congenital malformation incidence has been reported as 20-32 per 1,000 in various studies[1,9]. Since we did not know which malformations were included in the literature available, we decided to take all detected malformations into consideration in this study. However, comparison of the incidence of every single malformation with, that reported in literature showed no significant differences except concerning incidence of neural tube defects and cleft palate. Thus, the difference of the included malformations might account for the difference between the incidences observed in the current study and those found in the literature. Analysis of the data showed that congenital malformations were more frequent in the babies of mothers who were illiterate and older than 35 years of age. In a Utah study[10], congenital malformations were also found to be more frequent in babies born to illiterate mothers.

Babies who presented other than vertex and were born by operational delivery or cesarean section had a higher incidence of congenital malformations. High incidence in operational delivery may be explained by the fact that obstetricians preferred interfering with the normal process of labor when they observed that the fetus was malformed.

In this study, congenital malformation incidence was significantly higher among those pregnancies in which an ultrasonographic abnormality was observed. This indicates that ultrasonography is a very valuable tool for the prenatal diagnosis of malformations. However, many babies with ultrasonographically recognizable malformations were born even though an ultrasonography had been performed early in those pregnancies. While ultrasonography is a valuable diagnostic tool for prenatal detection of congenital malformations, it may fail unless done by an expert. It can be concluded that a considerable amount of ultrasonographic examinations in this study were done by inexperienced medical staff.

High frequency of congenital malformations in babies of mothers with diabetes mellitus, eclampsia, preeclampsia or vaginal bleeding showed that these abnormalities might be indicators of birth defects during pregnancy.

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