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Echocardiographic findings of children with Down syndrome

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Abstract

Aim: Down syndrome is the most common well-known chromosomal disorder. The incidence of congenital heart disease (CHD) in these patients is high and it is the most important cause of mortality. In this study, we reviewed the comorbid CHDs and their characteristics in patients with the diagnosis of Down syndrome. We compared our results with the results of studies conducted in different regions of our country in different years.

Materials and Methods: Between January 2020 and December 2022, data from a total of 385 patients (175 females, 210 males) with Down syndrome were evaluated. The age of the mothers at the time of delivery and the availability of prenatal diagnosis information in accessible patients were determined.

Results: Of 385 patients with Down syndrome, 38.2% (n=147) had CHD. Among patients with CHD, 57 patients had atrioventricular septal defect (AVSD)(38.7%), 35 patients had perimembranous ventricular septal defect (23.8%), 24 patients had secundum atrial septal defect(16.3%), 8 patients had patent ductus arteriosus(5.4%), and 10 patients without AVSD had CHD with multiple left-to-right shunts (6.8%). The most common cyanotic CHD was tetralogy of Fallot (n=7, 4.7%). Complete AVSD was present in 63.1% of AVSD patients. CHD was present in 36.2% of boys and 40.6% of girls. Among all female patients, 17.1% had AVSD, while this rate was 12.8% among all male patients ($p<0.05$). The mean maternal age at delivery was 32.59±6.9 (17-48) years. It was found that children with Down syndrome whose mothers had a maternal age of 33.5 years and above had a lower rate of CHD. Of the 170 mothers for whom prenatal diagnosis information was available, 58.2% (n=99) had a prenatal diagnosis.

Conclusion: Prenatal diagnosis opportunities have increased and become widespread over the years. However, no significant change was observed in the rates of CHD, which is most frequently responsible for mortality in children with Down syndrome. It is appropriate for every expectant mother with a prenatal diagnosis to be referred for fetal echocardiography or postnatal transthoracic echocardiography.

Introduction

Down syndrome is the most prevalent chromosomal abnormality and is well recognized by its phenotypic features. It is seen in 1-2 cases in every 1000 births [1]. Congenital heart disease (CHD) is present in 40% of individuals with Down syndrome, significantly affects the prognosis of the disease [2]. The most common cause of death in patients with Down syndrome is CHD [3]. For this reason, it is recommended that every newborn patient with Down syndrome be examined with transthoracic echocardiography soon after birth, regardless of physical examination findings [4]. The most common CHD in these patients is endocardial cushion defects, with some regional variations around the world [5].In our study, we examined the frequency of CHD in patients with Down syndrome and whether there was a change compared to previously reported studies from our country due to the widespread use of prenatal diagnosis methods.

Materials and Methods

Patients diagnosed with Down syndrome at the pediatric cardiology outpatient clinics of our hospital between January 2020 and December 2022 were retrospectively screened. Patients who did not have any cardiac examination as documented in the hospital records were excluded from the study. In our study, only patients with a cytogenetic diagnosis of Down syndrome were included. The presence of CHD in the patients was distinguished according to the findings of transthoracic echocardiography. Patent foramen ovale, a thin patent ductus arteriosus (PDA), a small secundum atrial septal defect (ASD), and

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mitral valve prolapse were evaluated as normal echocardiographic findings. Those with CHD were categorized into two groups: acyanotic CHD and cyanotic CHD. Patients with atrioventricular septal defect (AVSD) were classified as complete, partial, intermediate/transitional, and those with only mitral cleft. Patients with available prenatal diagnosis information were evaluated in two categories. Those who were suspected of having Down syndrome in any screening test (double marker or triple marker) and whose diagnosis was later confirmed by amniocentesis, or who did not want to undergo further diagnostic tests, were categorized as "prenatally diagnosed." Pregnant women without follow-up, those with normal prenatal screening tests, or those who had follow-up but declined testing were categorized as "without prenatal diagnosis". Previous studies on CHD in Down syndrome in our country were searched through Dergipark and Pubmed. A total of seven studies were cited in this manner [6, 7, 8, 9, 10, 11, 12]. The findings have been compiled in Table 1.

Ethics committee approval of the study was obtained from the Ankara Atatürk Sanatoryum Education and Research Hospital Clinical Research Committee from the number 15/26270 (date: 22.03.2023).

Statistical analysis

SPSS 16.0 package program was used in statistical evaluation. Descriptive statistics of categorical variables were reported as numbers and percentages (%). Descriptive statistics of continuous variables were reported as the mean, standard deviation, minimum, and maximum value. Categorical variables were evaluated with the chi-square test. Predictive values and cut-off values were used with ROC analysis in specificity and sensitivity calculations, $p \leq 0.05$ was considered statistically significant.

Results

There were a total of 385 Down syndrome patients evaluated by echocardiography. Of these, 210 (54.5%) were male and 175 (45.5%) were female. The patients' ages ranged from the neonatal period to 18 years old. When the echocardiographic findings of the patients were analyzed, 238 patients (61.8%) had normal echocardiographic findings. The remaining 147 patients (38.2%) had CHD requiring intervention or long-term follow-up. Among the patients with CHD, acyanotic CHD was predominantly present with 136 patients (92.5%), while the number of patients with cyanotic CHD was 11 (7.5%). Among patients with CHD, 57 had AVSD (38.7%), 35 had perimembranous ventricular septal defect (VSD) (23.8%), 24 had secundum atrial septal defect (ASD) (16.3%), and 8 had patent ductus arteriosus (PDA) (5.4%). There were 10 patients (6.8%) with two or more left-to-right shunts (ASD and VSD, ASD and PDA, VSD and PDA), excluding AVSD. Two patients had coarctation of the aorta (1.3%). The proportion of patients with AVSD was 14.8% among all Down syndrome patients. Among patients with CHD, tetralogy of Fallot was the most common cyanotic CHD, affecting 7 patients (4.7%). According to the type, 63.1% (n=36) of the 57 patients with AVSD had complete AVSD. Echocardiographic evaluations of the patients are summarized in Figure 1 and Figure 2.

When we evaluated the patients with CHD by gender, 51.7% were male (n=76) and 48.3% were female (n=71). In total, 36.2% of boys and 40.6% of girls with Down syndrome had CHD. Among all female patients, 17.1% had AVSD, while this rate was 12.8% among all male patients ($p<0.05$).

The mean maternal age at delivery for patients with Down syndrome was 32.59±6.9 years (17-48). While 36.9% of the mothers were 35 years or older at the time of delivery, 40.5% were between 18 and 34 years. When the relationship between maternal age and the presence of CHD was analyzed, it was found that CHD was less common in children with Down syndrome whose mothers were 33.5 years and older (area under the curve: 0.671, p=0,035, sensitivity %65 and specificity % 62).

Information regarding the prenatal Down syndrome diagnosis of a total of 170 patients was obtained. Prenatal diagnosis tests were normal in 28 of these mothers (16.4%),

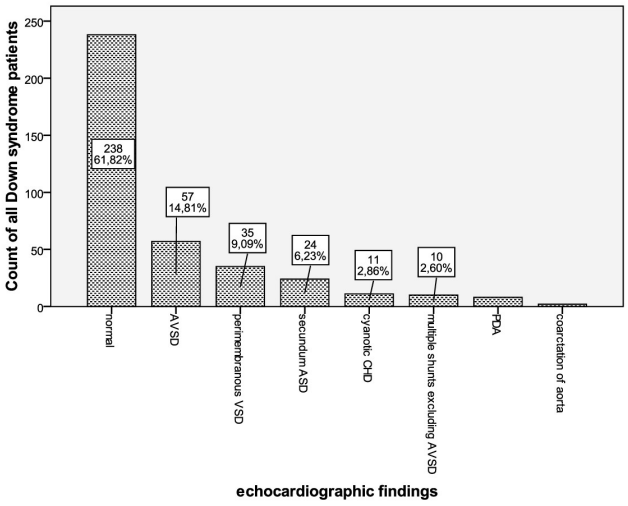

Figure 1. Distribution of all Down syndrome patients according to echocardiographic findings.

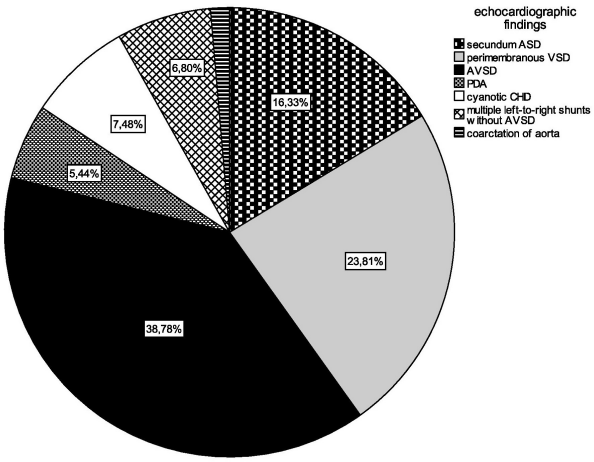

Figure 2. Distribution of Down syndrome patients with CHD according to echocardiographic findings.

Table 1. Studies conducted on cardiac findings of children with Down syndrome in our country.

Study	The province where the study was conducted	Year	Number of patients (F/M)	Incidence of CHD	CHD (acyanotic/ cyanotic)	Most common CHD	AVSD rate in CHD	Rate of mothers >35 years old
Nişli et al. [6]	İstanbul	2007	1042 (477/565)	39.5 % (n=412)	94.2% / 5.8%	AVSD	49.2 % (n=203)	-
Kuzucu et al. [7]	Ankara	2008	170 (91/79)	52.9 % (n=90)	94.5% / 5.5%	VSD	24.4% (n= 22)	27.6%
Aldudak et al. [8]	Diyarbakır	2015	87 (34/53)	65.5 % (n=57)	94.8% / 5.2%	AVSD	29.8% (n=23)	-
Acar et al. [9]	Van	2015	198 (86/112)	54 % (n=106)	96.2% / 3.8%	AVSD	50% (n=53)	-
Gül et al. [10]	Isparta	2016	107 (51/56)	77.5 % (n=83)	99.1% / 0.9%	ASD	18.1% (n=15)	44%
Giray et al. [11]	Mersin	2019	184 (99/85)	82.1 % (n=151)	97.8% / 2.2%	AVSD	26.1% (n=48)	30.9%
Erol et al. [12]	İstanbul	2021	131 (59/72)	58.8 % (n=77)	96.2% /%3.8%	VSD	11.4% (n=15)	-
Sel et al.	Ankara	2023	385 (175/210)	38.2 % (n=147)	92.5% / 7.5%	AVSD	41.9% (n=57)	36.9%

(CHD: Congenital Heart Disease, AVSD: atrioventricular septal defect, VSD: ventricular septal defect, ASD: atrial septal defect).

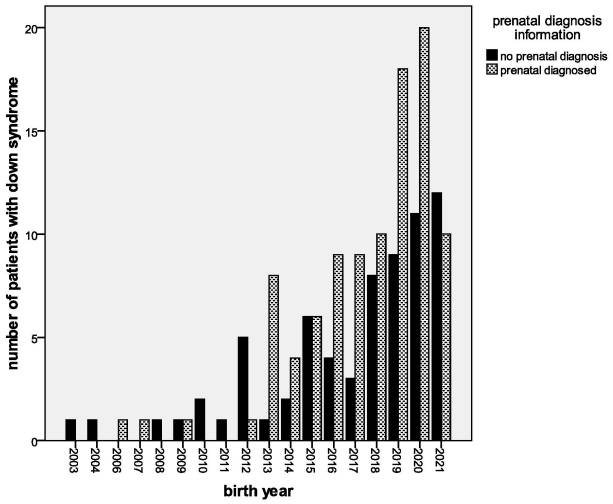

Figure 3. Increase in prenatal diagnosis rates over the years.

18 mothers were pregnant without follow-up (10.5%), and 99 had a prenatal diagnosis of Down syndrome (58.2%). CHD was present in 46.5% of patients who received a prenatal diagnosis (this rate is postnatal echocardiography information). The Figure 3 illustrates the growth in prenatal diagnosis knowledge over the years.

Discussion

Down syndrome is the most common genetic syndrome. It is also frequently seen in our country and has become well-known for its phenotypic characteristics over the years. Approximately 40 to 60 percent of children born with Down syndrome have a heart defect, and approximately 5 to 8 percent of all patients with CHD have a chromosomal disorder, usually Down syndrome [2, 13]. Although the region between bands 22.2 and 22.3 on the long arm of chromosome 21 is held responsible for CHD in these patients, the relationship between Down syndrome and CHD has not been fully explained [5]. The most important determinant of mortality and morbidity in these patients is CHD [14]. In addition, early diagnosis of CHD is important because it carries a high risk of pulmonary hypertension [15]. Transthoracic echocardiography plays an important role in the early detection of structural and functional heart diseases. The echocardiographic examination provides comprehensive real-time, non-invasive anatomical and functional information at a relatively low cost. During the neonatal period, echocardiographic windows are easier and clearer than at any other age because there are less obstacle in the lung tissue that ultrasound cannot pass through, and the heart and great vessels are closer to the probe. It is recommended that all newborn babies with Down syndrome undergo routine cardiac screening until at least their sixth week [4]. In our study, 38.2% of the patients had CHD requiring follow-up and treatment. Although this rate is similar to that reported by Nişli et al. in 2007, it is lower compared to rates reported in publications from various regions of our country over the years [6] (see Table 1). One reason for this may be due to the fact that in larger centers, there are patients who are being followed up for various diseases other than CHD. Another possibility is that families have a better chance of making an early decision about therapeutic abortion in centers where fetal echocardiography is available.

Although AVSD is the most common CHD in individuals with Down syndromes, VSD may be more common in different geographical regions. The prevalence of AVSD among patients diagnosed with Down syndrome is approximately 20% [16, 17]. Among patients with AVSD, approximately 65% have Down syndrome [18]. In our study, among Down syndrome patients with CHD 38.7% had AVSD and the second most common was VSD with a ratio of 23.8%. The frequency of VSD was higher in studies conducted in our country by Kuzucu et al. and Erol et al., while Aldudak et al. found the frequency of VSD close to AVSD [7, 8, 12]. There are countries in the world where VSD is more common in various regions. Gül et al. from our country found the frequency of ASD to be higher [10]. This may be because they included all ASD patients in the study, regardless of their size. In our study, we assessed small secundum ASDs as normal echocardiographic findings. Such variations may occur due to different classifications used in studies.

Cyanotic CHDs constitute 25% of all CHDs [19]. In studies compiling data from patients with Down syndrome in our country and around the world, the prevalence of cyanotic CHD is relatively low. Acyanotic CHD is predominantly observed in patients with Down syndrome. In studies from

our country, the prevalence of cyanotic CHD varies between 0.9% and 5.8% among all Down syndrome cases with CHD (see Table 1). As a tertiary hospital, the rate was thought to be higher (7.5%) in our study due to the referred cyanotic CHD patients.

In studies that compiled data on patients with Down syndrome, the proportion of boys was generally found to be slightly higher. In some geographic regions, studies in which girls were at the forefront were also reported. In studies conducted at various times and in different regions of our country, the number of male patients is generally higher, as in our study (Table 1). On the other hand, the prevalence of congenital heart disease is higher in girls with Down syndrome than in boys [20, 21]. In our study, 40.6% of the female patients had CHD, while 36.2% of the male patients had CHD. Erol et al. found that the frequency of CHD in girls was statistically significantly higher than in boys [12]. In our study, 17.1% of female patients had AVSD, while 12.8% of male patients had AVSD, and this difference was found to be statistically significant. Freeman et al. found AVSD to be significantly more common in girls with Down syndrome [17]. Giray et al. also found that AVSD was more common in girls, but they stated that it was not statistically significant [11].

It is known that advanced maternal age is a risk factor for Down syndrome [22]. This risk is especially high in pregnancies aged 35 and over. In our study, only 36.9% of the mothers were 35 years old or older. The rate was similar in other studies conducted in our country that reported maternal ages (Table 1). In our study, we found that the average maternal age of children with both CHD and Down syndrome was significantly lower compared to those without CHD, indicating a lower rate of CHD in older mothers. Although the significance level was not very high, a cut-off age of 33.5 years was determined for this situation. Giray et al. found that the frequency of CHD to be 44.6% in individuals with a maternal age of 35 and over, and 55.4% in those under 35 years of age. However, they stated that this difference was not statistically significant [11]. Studies have been conducted in different countries to identify this situation; Animasahun et al. reported a lower rate of CHD in mothers over 36 years of age, and Chehab et al. found a lower rate of CHD in children with Down syndrome born to mothers over 32 years of age [23, 24]. Giving more importance to prenatal diagnosis in older pregnancies may have expanded families' options and increased the rates of therapeutic abortion for patients with both Down syndrome and CHD.

In our country, prenatal screening for Down syndrome has been routinely performed for a long time, and prenatal diagnosis can be made with further tests in case of suspicious screening results. When Down syndrome is diagnosed prenatally or postnatally, it is important to inform families about congenital heart diseases, which are still the leading cause of mortality associated with the condition. In our study, the proportion of patients in whom Down syndrome was suspected by screening tests performed during pregnancy or confirmed by further diagnostic methods was close to 60%. Of the patients with a prenatal diagnosis, 46.5% also had CHD. In studies conducted using questionnaires from various regions in our country, it was reported that 35% to 57% of families expressed a desire to proceed with the birth if a defect was detected in the baby prenatally [25, 26]. In a study conducted by Adıyaman et al. on families with a prenatal diagnosis of Down syndrome in our country, 21% decided to continue the pregnancy [27]. In the study conducted by Mürsel et al., data from 2300 mothers were collected. In this study, a total of 9 patients were prenatally diagnosed with Down syndrome, one patient diagnosed with Down syndrome by chorionic villus sampling gave birth, and one mother who did not request further examination gave birth to a child with Down syndrome (22%)[28]. In another study by Balkan et al., the rate of pregnancy continuation was reported to be 25% for Down syndrome [29]. This perhaps suggests that families' decisions may differ in real-life situations compared to hypothetical scenarios. In addition to all these, the survival rates of individuals with Down syndrome have increased over the years with innovations in technology and medicine [30].

Limitations

Our article is a cross-sectional study focused solely on echocardiographic diagnosis. Our study has limitations due to its retrospective nature, but it is difficult to reach such a large number of patients in prospective studies. There is no clinical follow-up of the patients. Additionally, prenatal diagnosis information for Down syndrome was not available for all patients.

Conclusion

In our study, we collected CHD data from Down syndrome patients at our hospital, which is a tertiary reference center, and compared it with findings from other studies conducted in our country. Despite the advancements in prenatal diagnosis over the years and its widespread use throughout the country, there has been no significant change in the rates of CHD in children with Down syndrome. It should be kept in mind that even today, the most common accompanying anomaly in patients with Down syndrome is CHD, and it is the most important cause of mortality in this syndrome. Since there has been no significant change or decrease in the rates of CHD in children with Down syndrome despite the developing prenatal diagnosis methods over the years, it is advisable for every expectant mother with a prenatal diagnosis to be referred for fetal echocardiography or postnatal transthoracic echocardiography.

Ethical approval

Ethics committee approval of the study was obtained from the Ankara Atatürk Sanatoryum Education and Research Hospital Clinical Research Committee from the numbers 15/26270.

References

1. Vis JC, Duffels MGJ, Winter MM,et al. Down syndrome: a cardiovascular perspective. J Intellect Disabil Res. 2009;53[5):419–25.
2. Charleton PM, Dennis J, Marder E. Medical management of children with Down syndrome. Paediatrics and Child Health. 2010; 20: 331-337.

3. Hoffman JI, Kaplan S. The incidence of congenital heart disease. J Am Coll Cardiol.2002; 39: 1890-1900.
4. American Academy of Pediatrics Committee on Genetics. American Academy of Pediatrics: health supervision for children with Down syndrome. Pediatrics. 2001;107:442-9.
5. Barlow GM, Chen XN, Shi ZY, et al. Down syndrome congenital heart disease: A narrowed region and a candidate gene. Gen Med. 2001;3:91-101.
6. Nişli K, Öner N, Candan S, et al. Congenital heart disease in children with Down's syndrome: Turkish experience of 13 years. Acta Cardiol.2008; 63: 585-589.
7. Kuzucu A, Vidinlisan S, Kibar AE, et al. Down sendromunda konjenital kalp hastalığı sıklığının ve ekokardiyografik bulguların değerlendirilmesi. Genel Tıp Derg. 2008;18[3]:105-110.
8. Aldudak B, Çelik M, Akar M, et al. Türkiye'nin Güneydoğu Anadolu Bölgesi'ndeki Down sendromlu yenidoğanlarda konjenital kalp hastalığı prevalansı ve dağılımı. Ege Tıp Dergisi.2016;55[2]:78-81.
9. Acar OÇ, Üner A, Ece İ, Epçaçan S. Çocuk Kardiyoloji Polikliniğine Başvuran Down Sendromlu Hastalarda Ekokardiyografi Bulguları. Kocaeli Tıp Dergisi. 2015; 4;3:1-3.
10. Gül Ö, Gürses D, Doğan M. Down Sendromlu Çocukların Klinik ve Ekokardiyografik Değerlendirmesi. Türkiye Çocuk Hast Derg. 2017; 2: 116-119.
11. Giray D, Aydemir SS, Karpuz DD, Hallıoğlu O. Down sendromlu hastalarda doğuştan kalp hastalığı: Tek merkez, beş yıllık retrospektifanaliz.. Mersin Üniv Saglık Bilim Derg. 2019;12[3]:489-494.
12. Erol N, Yılmaz C, Alpınar A. Congenital Cardiac Anomalies: The Most Common Anomaly in Children with Down Syndrome. Haydarpasa Numune Med J. 2021;61[4]:440–444.
13. Hoffman JI. Congenital heart disease: incidence and inheritance.Pediatr Clin North Am. 1990 Feb;37[1]:25-43.
14. Hayes C, Johnson Z, Thornton L, et al. Ten-year survival of Down syndrome births. Int J Epidemiol. 1997;26[4]:822–9.
15. Banjar HH. Down's syndrome and pulmonary arterial hypertension. PVRI Review 2009;1: 213-216.
16. Flanders L, Tulloh R. Cardiac problems in Down syndrome. Paediatr Child Health. 2011;21[1]:25–31.
17. Freeman SB, Bean LH, Allen EG, et al. Ethnicity, sex, and the incidence of congenital heart defects: a report from the National Down Syndrome Project. Genet Med. 2008;10[3]:173–80.
18. Ferencz C, Neill CA, Boughman JA, et al. Congenital cardiovascular malformations associated with chromosome abnormalities: an epidemiologic study. J Pediatr. 1989;114[1]:79–86.
19. Ossa Galvis MM, Bhakta RT, Tarmahomed A, et al. Cyanotic Heart Disease. [Updated 2023 Jan 31]. In: StatPearls [Internet]. Treasure Island [FL]: StatPearls Publishing; 2023 Jan.
20. Diogenes TCP, Mourato FA, Lima Filho JL, Mattos SDS. Gender differences in the prevalence of congenital heart disease in Down's syndrome: a brief meta-analysis. BMC Med Genet. 2017 6;18[1]:111.
21. Loane M, Morris JK, Addor MC, et al.Twenty-year trends in the prevalence of Down syndrome and other trisomies in Europe: Impact of maternal age and prenatal screening. Eur J Hum Genet. 2013;21:27–33.
22. Freeman SB, Taft LF, Dooley KJ, et al. Population based study of congenital heart defects in Down syndrome. Am J Med Genet.1998;80:213-217.
23. Animasahun BA, Oladimeji OA, Gbelee HO, Njokanma OF. Occurrence of Congenital Heart Disease among Children with Down syndrome: What is the Influence of Maternal Age? Prensa Med Argent. 2016, 102:6.
24. Chéhab G, Chokor I, Fakhouri H, et al. [2007] Congenital heart disease, maternal age and parental consanguinity in children with Down's syndrome. J Med Liban. 2007 Jul-Sep;55[3]:133-7.
25. Yanikkerem E, Ay S, Ciftçi AY, et al. A survey of the awareness, use and attitudes of women towards Down syndrome screening. Journal of Clinical Nursing.2013 Jun;22[11-12]:1748-58.
26. Karakuş R. Gebelerin ikili ya da üçlü testler hakkındaki bilgi düzeyinin araştırılması. Jinekol Obstet Neonatol Tıp Derg. 2015;12[5]:174-8.
27. Adiyaman D, Atakul BK, Kuyucu M, et al. Termination of pregnancy following a Down Syndrome diagnosis: decision-making process and influential factors in a Muslim but secular country, Turkey. J Perinat Med. 2020 Sep 14;49[2]:170-177.
28. Mürsel K, Kadıoğlu N, Özel Ş, Üstün YE. Down Sendromu İçin Gebelere Yapılan Prenatal Tarama ve TanıTestlerinin Sonuçları; Maliyet Analizi. Ankara Med J. 2019;[1]:108-14.
29. Balkan M, KalkanlıS, Akbas H, et al. Parental Decisions Regarding a Prenatally Detected Fetal Chromosomal Abnormality and the Impact of Genetic Counseling: An Analysis of 38 Cases with Aneuploidy in Southeast Turkey. J Genet Counsel.[2010] 19:241–246.
30. Rankin J, Tennant PWG, Bythell M, et al. Predictors of Survival in Children Born with Down Syndrome: A Registry- based Study. Pediatrics. 2012, 129 [6]:e1373.