Original Research Article

Title: Congenital heart disease in patients with Down Syndrome and its association with maternal age.

Abstract

Background: Congenital heart disease **(**CHD) is an important feature of patients with Down syndrome (DS) and plays an important role on morbidity and mortality. Maternal age is a well-known risk factor associated with DS.

Objectives: The aim of the present study is to analyze the types of CHD and the association of CHDs and maternal age in DS.

Materials and Methods: Six hundred and thirty-one patients with DS who were admitted to pediatric cardiology department, between December 2014 and December 2018, were retrospectively analyzed. The detected CHDs were evaluated in association with maternal age.

Results: Four hundred forty-five (70.5%) had one or more congenital heart defect. Two hundred and seven patients (32.8%) had isolated simple defect while the remaining had complex or associated multiple CHDs (n:238, 37.7%). Considering all patients, secundum ASD (42.1%) was the most frequent CHD followed by PDA (33.9%), VSD (28.6%) and AVSD (9.6%). Regarding the maternal age, the lowest prevalence of CHD was seen in babies of whom maternal age was between 25-35 years. AVSD, was most frequent in patients born to mothers aging ≤20 years. Incidence of ASD did not markedly differ between maternal age groups while nearly half of the patients born to mothers aging between 21-25 years had PDA and incidence of VSD was markedly increased with the maternal age of >45 years.

Conclusion: Distribution of CHD also varies in accordance with maternal age. Babies born to mothers aged <25 or >35 years are more likely to have CHD. Incidence of AVSD, which had been reported to be the most common CHD in patients with DS, has been decreased in time and tends to be mostly associated with maternal age of ≤20 years.

Keywords: *Down syndrome, Congenital heart disease, maternal age.*

Introduction:

Down Syndrome (DS) is the most common autosomal chromosome anomaly and closely associated with congenital heart disease (CHD) [1]. CHD is an important feature of these patients which plays an important role on morbidity and mortality [2]. There are studies reporting differences in type of CHD in various geographical areas [3-5]. Maternal age is a well-known risk factor associated with DS [5, 6]. To our knowledge there is not any study in the literature that focuses on the relation between the type of the CHD and the maternal age. The aim of the present study is to analyze the types of CHD and the association of CHDs and maternal age in this special group of patient.

Patients and methods

Six hundred and thirty-one patients with DS who were admitted to pediatric cardiology department due to any reason of cardiac evaluation between December 2014 and December 2018, were retrospectively analyzed. Diagnosis of DS were made by either clinical criteria or genetic analysis. Patient demographics, maternal age at delivery and results of echocardiographic or angiographic records were noted. Patients were divided into 7 groups according to maternal age. Group 1 was consisting of patients with maternal age of equal or less than 20 years while

maternal age was 21-25 years, 26-30 years, 31-35 years, 36-40 years, 41-45 years and equal or more than 46 years in group 2, 3, 4, 5, 6 and 7, respectively. The detected CHDs were evaluated in association with maternal age. The congenital heart defects were classified as isolated or associated simple defects (Atrial septal defect (ASD), ventricular septal defect (VSD), patent ductus arteriosus (PDA)), complex defects (Atrioventrciular septal defect (AVSD), Tetralogy of Fallot (TOF), double outlet right ventricle (DORV), transposition of great arteries (TGA)) and other defects.

Statistical analysis:

The statistical analysis was performed using Statistical Package for Social Sciences Software (SPSS), version 21. Demographic and clinical variables were summarized with descriptive statistics. Categorical variables were summarized as absolute frequency and percentage, whereas continuous variables were summarized as median, mean and standard deviation.

Results

The mean and median age of patients at diagnosis was 3.32±4.25 years and 1.09 years, respectively (range: 0 days-17.41 years). The male-to-female ratio was 1.5/1. Three hundred and sixty patients (57.1%) were under 2 years-old while 147 patients (23.3%) were between 2-7 years and the remaining (n:124, 19.7%) above 7 years. The mean maternal age at delivery was 34.92±7.40 years (range: 17-50 years). Almost half of the mothers were between 31 and 40 years of age. The distribution of maternal age is shown on figure 1.

Four hundred forty-five (70.5%) had one or more congenital heart defect. Two hundred and seven patients (32.8%) had isolated simple defect while the remaining had complex or associated multiple CHDs (n:238, 37.7%). There was not a significant difference by means of CHD in

accordance with gender. Distribution of CHDs detected in study population is shown on table 1. Considering all patients, secundum ASD was the most frequent CHD, but the vast majority of the patients with secundum ASD were under 2 years and most of secundum ASDs were small defects which were expected to have spontaneous closure with somatic grow-up (Figure 2). ASDs were isolated single defects in 91 patients (14.4%) whereas, the remainders (n:175, 27.7%) were in association of various defects. Sinus venosus type ASD was not detected in any of patients, while primum type ASD was detected only as a component of AVSD. PDA was the second most common CHD (33.9%). PDAs in patients under 3-month old were not included. Hemodynamically important PDAs were consisting 74.3% of all PDAs so a transcatheter closure was planned or performed while the remaining had silent or small ducts without hemodynamic importance. Isolated PDA as a single defect was accounting 9.8% of all subjects. VSD was the third most common defect (28.6%). Isolated single defect was found in 8.7% of all study population and perimembranous VSD was the most common type. AVSDs were detected in 61 cases (9.6%). The most common form was Rastelli type C. and the majority had balanced ventricles. The majority of the AVSDs were in association with other CHDs, whereas only 2.2% of all cases had isolated AVSD. More than half of the patients with CHD had two or more associated defect (53.4%). Association of ASD and PDA was the most frequent association of CHD followed by VSD with PDA and ASD (table 2). Tetralogy of Fallot was detected in 12 patients (1.9%) and was the most common cyanotic CHD.

Regarding the maternal age, the lowest prevalence of CHD was seen in babies of whom maternal age was between 25-35 years. Mothers who were below 25 years or above 35 years had similar prevalence of having a child with CHD to each other (Figure 3). There were differences in types of CHDs between groups (Figure 4). ASD was the most common CHD in all groups except in

group 2, in which PDA was the most common CHD. VSD was the most common CHD in group 7 with almost the same percentage with ASD in this group. AVSD, which has been reported to be the most common defect in various studies in patients with DS, was most frequent in group 1 (33.3%). Its incidence markedly decreased in patients whom mothers aged between 21-to-30 year-old and reached an account of %11.4-11.9 in in babies of mothers older than 40 years (Figure 5).

Discussion

CHD is a common cause of mortality and morbidity in patients with DS and it is reported in various studies that 44 to 79.2% of these patients have CHD [7-10]. The overall incidence of CHD within our study population was 70.5%. This rate was similar to that studies reported from different regions of our country [10, 11] but higher than some recently reported studies in the literature [12, 13]. The reason for the high incidence seen in our study could be that minor lesions such as small secundum ASDs in infants and young children as well as small PDAs without audible murmur which do not have hemodynamic importance were included. The incidence would be lower if these lesions were excluded.

Although varying studies have reported that the distribution of CHDs in DS may vary according to ethnicity, in the majority of the studies AVSD, VSD, and ASD are reported to be still the most common three types of CHD in this group of patients [6, 9, 14]. In western European countries and the USA AVSD (43%) is reported to be the most common CHD associated with DS followed by, VSD (32%); secundum atrial septal defect (10%); tetralogy of Fallot (6%); and isolated PDA (4%) and about 30% of patients have several cardiac defects [7, 15]. However, in Asia, isolated VSDs have been reported to be the most common defect, observed in about 40% of patients [16], whereas in most reports from Latin America, the secundum type of ASD is suggested to be the

most common lesion [4, 17, 18]. Kim et al.[12] reported ASD as the most common CHD, occurring in 30.5% of all DS, followed by VSD (19.3%), PDA (17.5%), and AVSD (9.4%) in Korean patients. In two studies from different regions of Turkey, Gul et al. [10] have reported ASD as the the most common CHD in patients with DS whereas, Nisli et al. [11] found AVSD as the leading CHD in this group. Vida et al reported a high frequency of PDAs [18]. In that study, PDA was the most common single defect and was also the most frequent concomitant malformation. Pfitzer et al. [14] have examined the dynamics in the prevalence of patients with CHD and DS over an extended period and reported that the prevalence of AVSD and complex CHD have decreased while simple defects such as ASD and VSD are increasing over the time. Similar to that, Bergström et al [5] have reported temporal changes with regard to specific defects during a 20-year period. They found that AVSD and VSD were accounting for 46% and 14% of CHD, respectively in the first periods of the study while this amount was shifted to 31% and 30%, respectively in the last periods of the study. They suggested that the overall incidence of congenital heart defects among newborns with DS remained stable over the time while the risk of complex malformations declined and simple defects like VSD and ASD increased. In our study, ASD was the most common CHD, while AVSD was lesser when compared with the majority of previously reported studies, but closely similar to the Korean study [12].

High maternal age is a well-known risk factor for meiotic non-disjunction and still the only established risk factor in the etiology of DS [19, 20]. Regarding the prevalence of CHD in infants with DS in accordance with maternal age, Kim et al. [12] and Scott et al. [9] have reported that mothers ≥35 years are more likely to give birth to a DS child with a CHD. However, there are studies which reports the increased incidence of DS in young mothers [21, 22]. Chaohab *et al* reported maternal age of under 32 years has a higher risk for CHD in DS [23]. Bergström et al. [5]. reported that the incidence of any CHD in DS is most common in patients with maternal age

of under 25 years with a percentage of 62.5% if maternal age is below or equal to 19 and 58.0% if maternal age is between 20-25 years. In the same study the incidence of any CHD was found to be between 53.9-56.4 in babies born to mothers aging 25-35 years, and 50-51% in babies born to mothers aging above 35 years. In our study, maternal age of between 25 and 35 years was found to be less associated with having CHD while maternal ages of <25 years or >35 years had a higher incidence of having CHD in patients with DS. Incidence of ASD did not markedly differ between maternal age groups while nearly half of the patients born to mothers aging between 21-25 years had PDA and incidence of VSD was markedly increased with the maternal age of >45 years. Interestingly, AVSD was mostly found in babies of young mothers aging 20 years or below with an incidence of more than three times to other maternal age groups.

Conclusion

This retrospective study confirms that the type of CHDs in DS varies with geographical areas and ethnicity. Distribution of CHD also varies in accordance with maternal age. Babies born to mothers aged <25 or >35 years are more likely to have CHD. Incidence of AVSD, which had been reported to be the most common CHD in patients with DS, has been decreased in time and tends to be mostly associated with maternal age of ≤20 years.

Ethical approval: All procedures performed were in accordance with the ethical standards and with the 1964 Helsinki Declaration and its later amendments. Institutional ethical committee approved the study.

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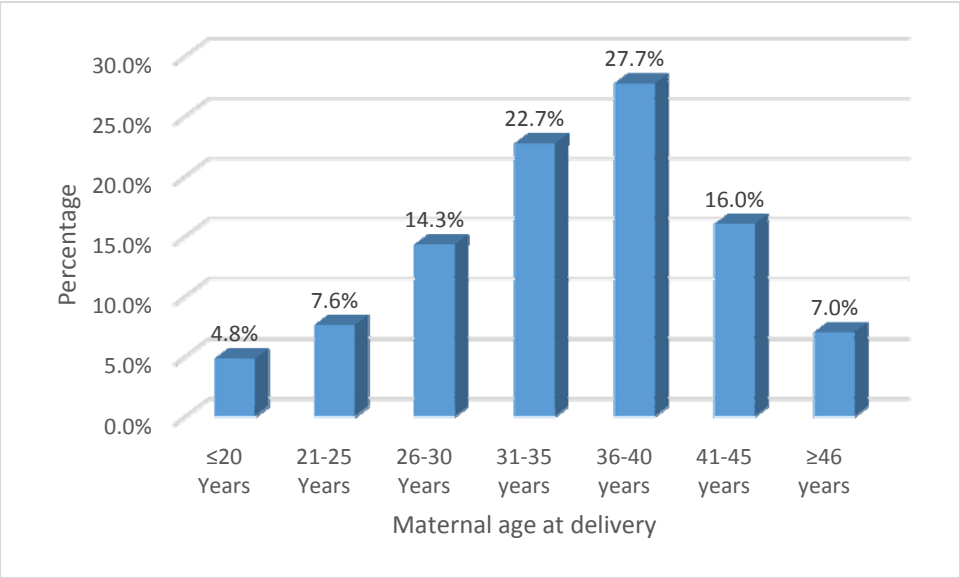

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233 *Figure 1: Incidence of any CHD in accordance with maternal age.*

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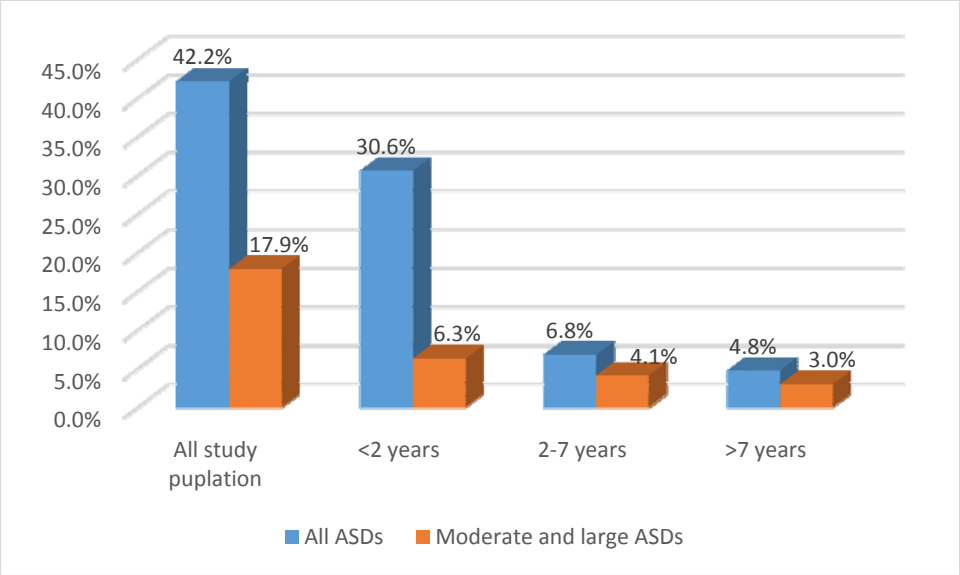

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236 *Figure 2: Distribution of ASD by means of defect size in patient age groups*

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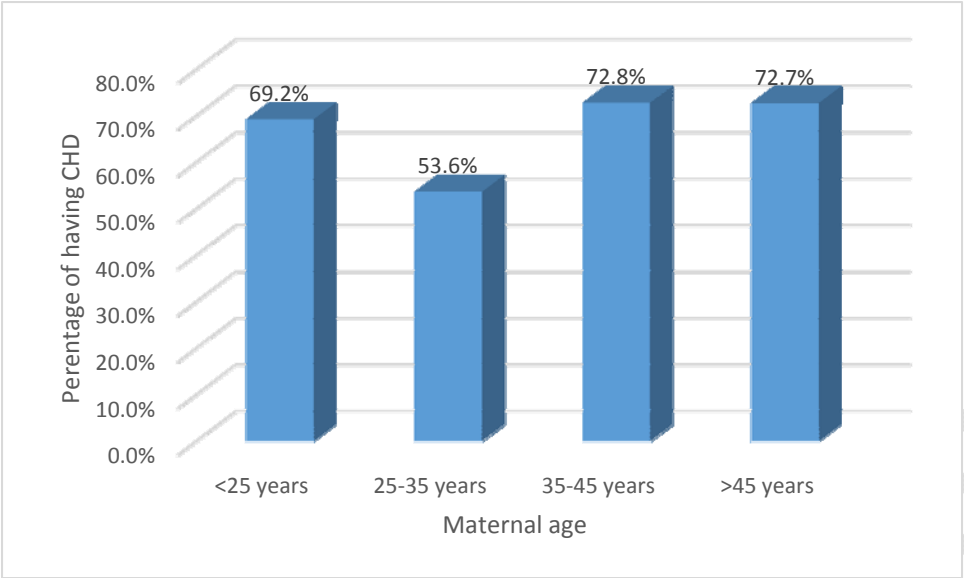

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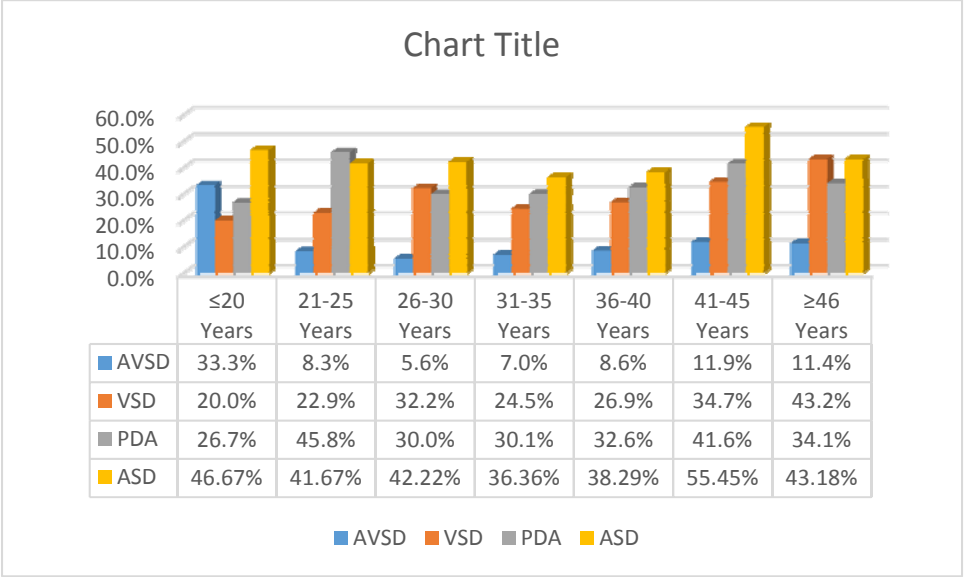
239 *Figure 3: Incidence of CHDs according to maternal age.*



	≤20 Years	21-25 Years	26-30 Years	31-35 Years	36-40 Years	41-45 Years	≥46 Years
AVSD	33.3%	8.3%	5.6%	7.0%	8.6%	11.9%	11.4%
VSD	20.0%	22.9%	32.2%	24.5%	26.9%	34.7%	43.2%
PDA	26.7%	45.8%	30.0%	30.1%	32.6%	41.6%	34.1%
ASD	46.67%	41.67%	42.22%	36.36%	38.29%	55.45%	43.18%

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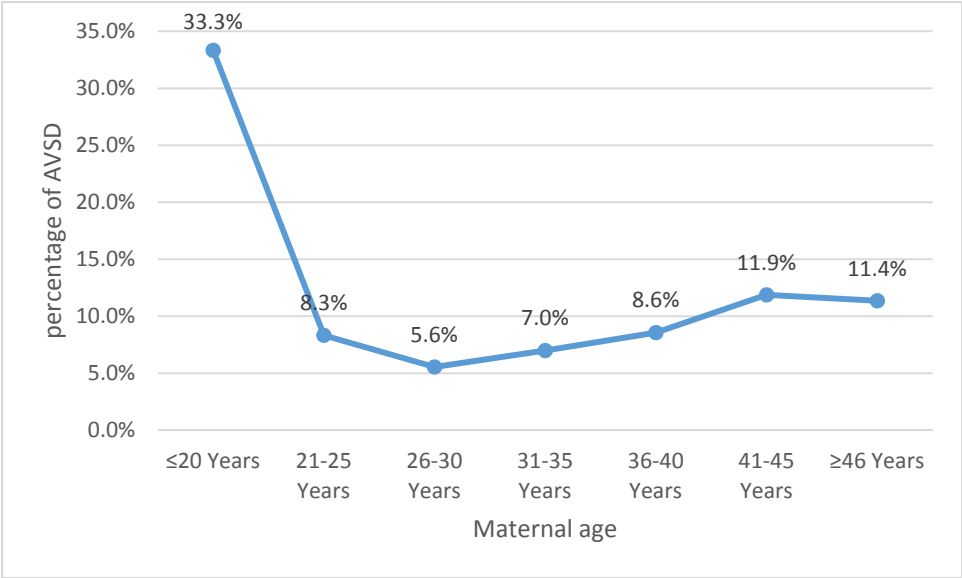
241 *Figure 4: Distribution of mostly seen CHDs in maternal age groups.*



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243 *Figure 5: The changing incidence of AVSD in accordance with maternal age.*

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Table 1: Distribution of CHDs in all patients with DS (n=631)

Congenital Heart Defect	***n***	***(%)***
Atrial septal defect	266	*(42.1)*
Ostium secundum	266/266	*(42.1)*
Sinus venosus	0	*0*
Patent Ductus Aretriosus	214	*(33.9)*
Ventricular septal defect	181	*(28.6)*
Perimembranous	131/181	*(72.3)*
Muscular	34/181	*(18.8)*
Inlet	16/181	*(8.9)*
Atrioventricular septal defect (AVSD)	61	*(9.6)*
Complete AVSD	57/61	*(93.4)*
Rastelli type A	15/57	*(26.3)*
Rastelli type B	2/57	*(3.5)*
Rastelli type A	40/57	*(70.2)*
Balanced	53/57	*(92.9)*
Unbalanced	4/57	*(7.1)*
Intermediate AVSD	4/61	*(6.6)*
Partial AVSD	0	*0*

Tatralogy of Fallot	12	*(1.9)*
Malpositon of the great arteries	1	*(0.16)*
Double outlet right ventricle	3	*(0.48)*
Other		
Left superior vena cava	4	*(0.64)*
Partial anomalous pulmonary venous connection	2	*(0.32)*
Coartaction of the aorta	1	*(0.16*
Pulmonary stenosis	5	*(0.8)*
Mitral valvular insufficiency	24	*(3.8)*
Aorticvalvular insufficiency	22	*(3.5)*
Mitral valve prolapsus	8	*(1.27)*
Bicuspid aortic valve	8	*(0.95)*
Subaortic discrete membrane	1	*(0.16)*
Small-sized asymptomatic coronary artery fistula	2	*(0.32)*
Hypertrophic cardiomyopathy	1	*(0.16)*
Right sided aortic arch	3	*(0.48)*

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Table 2: Types of associated CHDin DS

CHD associations	**n,238**	***(53.4%)***
ASD, PDA	62	*13,9%*
VSD,ASD,PDA	35	*7,9%*
VSD,ASD	33	*7,4%*
VSD,PDA	23	*5,2%*
AVSD	14	3,1%
AVSD,VSD,ASD,PDA	12	*2,7%*
AVSD,VSD,ASD	12	*2,7%*
Tatralogy of Fallot	10	2,2%
AVSD,PDA	9	*2,0%*
AVSD,ASD,PDA	8	*1,8%*
VSD,ASD,PS	3	*0,7%*
Tatralogy of Fallot, ASD	3	*0,7%*
AVSD, ASD	2	*0,4%*
ASD, PAPVC	2	*0,4%*
VSD,PS	2	*0,4%*
AVSD,VSD,ASD,PS	2	*0,4%*
AVSD,PS	1	*0,2%*

AVSD,ASD,PS	1	*0,2%*
COA, PDA	1	*0,2%*
AVSD,DORV,d-TGA, PDA,PS	1	*0,2%*
DORV,VSD,ASD,PS	1	*0,2%*
AVSD,DORV,PDA,PS	1	*0,2%*