



## Occurrence of Congenital Heart Disease among Children with Down syndrome: What is the Influence of Maternal Age?

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### Abstract

**Background:** The occurrence of Down syndrome is strongly dependent on maternal age and incidence varies at various maternal ages. This incidence may differ from one country to another according to the social and environmental factors predominant in such countries. The study aims to document the prevalence of congenital heart defects in patients with Down syndrome, identify the association between maternal age and occurrence of congenital heart disease among these subjects

**Methods:** The study was prospective, cross-sectional and consecutive, involving subjects from two centers which were; a tertiary hospital, a private hospital which is a major cardiology center. Children with clinical features of Down syndrome had transthoracic echocardiography done by a cardiologist.

**Results:** A total of 195 patients with Down syndrome were studied ages between 1 day to 12 years. The mean age + SD were 241.03 + 529.71 days and male to female ratio of 1.04:1. The mother's age range was from 19 to 44 years with a mean age + SD of 32.36 + 5.43 years. Up to 16.9% had structurally normal heart. The most common heart defect was atrioventricular septal defect 24.1%. There was no significant association between maternal age and occurrence of congenital heart defects in the subjects.

**Conclusion:** The incidence of congenital heart disease is high among subjects with Down syndrome. Atrioventricular defects were the commonest cardiac defect among the subjects. The incidence of congenital heart defect in the subjects was decreasing from maternal age 36 years and above. Routine cardiac evaluation including echocardiography is recommended for all patients with Down syndrome.

**Keywords:** Down syndrome; Children; Echocardiography; Congenital; Heart; Disease; Maternal; Age

### Introduction

Down syndrome, also known as trisomy 21 is the best known chromosomal aneuploidy disorder occurring in humans. It has multiple systemic manifestations. It results from three cytogenic variants: three full copies of chromosome 21 account for 95% due to

meiotic nondisjunction, unbalanced translocation three to four percent mosaicism one to two percent [1].

Down syndrome occurs in 1 in 800 live births [2]. Occurrence of Down syndrome is strongly dependent on maternal age and incidence varies at various maternal ages. This incidence may differ from one country to another according to the social and environmental factors predominant in such countries. According to the World Health Organization (WHO), the estimated incidence is between 1/1,000 to 1/1,100 live births worldwide [3].

Although there is variability in the clinical features, the constellation of phenotypic features is fairly consistent and permits clinical recognition of Down syndrome. Congenital heart defect is the main cause of mortality in children with Down syndrome [4]. The incidence of congenital heart defects in patients with Down syndrome have varied, but it is most commonly accepted to be 50% [5,6]. Prevalence of 40 to 60% have been reported [7] and several studies are consistent

With this prevalence, Asani et al. [8-10] in the northern part of Nigeria documented a prevalence of 77.1% while Otaigbe et al. [11,12] reported a prevalence of 100% among children from the Southern part of Nigeria.

Out of the congenital heart defects found in patients with Down syndrome, atrioventricular septal defect was reported to be the commonest followed by ventricular septal defects with prevalence of 45% and 35% respectively [13]. Conversely, some studies have identified other heart defects to be most common: A study done in Korea identified atrial septal defect to be the most common 30.5 [14]. Also, De Rubens et al reported atrial septal defect to be the commonest 24% [15]. In Guatemala, the most frequently identified heart defect was patent ductus arteriosus [16].

The effect of maternal age as a risk factor for Down syndrome was described as early as 1933 [17]. Ferguson-Smith and Yates determined maternal age specific rate for various chromosomal aberrations, the most common being rate of trisomy 21 increasing dramatically from maternal age of 35 years [18]. However, Adeyokunnu et al. [19] documented increased frequency of Down syndrome among mothers in young age groups. Otaigbe and her co-authors also identified Down syndrome to occur mostly in mothers of younger age groups [12]. The study by Adeyokunnu involved adults' subjects with Down syndrome and was done more than three decades ago while the studies by Asani and his co-workers and that of Otaigbe and her co-authors had few subjects recruited and were from single centers. Asani and his co-workers studied 35 subjects while Otaigbe and her co-authors studied 31 subjects, both were from a single center hence the need for this study which aims to document the prevalence of congenital heart defects in patients with Down syndrome, identify the association between maternal age and occurrence of congenital heart disease among these subjects.

### Subjects and Methods

A cross-sectional and descriptive study carried out in two centers, Lagos State University Teaching Hospital (LASUTH) and a private specialist hospital in Lagos, between February 2008 and December 2014 as part of a larger study. The subjects were recruited consecutively based on physical features suggestive of Down syndrome.

Echocardiography was done using a GE Vivid Q echocardiography machine with appropriate sized transducers. Information on the age, sex, maternal ages of the subjects were obtained.

Data was entered into a personal computer and analyzed using Microsoft excel software supplemented with Statistical Package for Social Sciences (SPSS) version 20. Tables are used to depict variables. Means of continuous variables were compared using the Student t test and proportions using Chi-square test. Level of significance set at  $p < 0.05$ .

## Results

The subjects were 195 patients with Down syndrome with their age's between 1 day to 12 years. The mean age + SD were 241.03 + 529.71 days and male to female ratio of 1.04:1. The mother's age range was from 19 to 44 years with a mean age + SD of 32.36 + 5.43 years.

Table 1 shows the age distribution of the mothers. Occurrence of Down syndrome was most frequent in the age group 31 to 35 years. Majority of the mothers (70.3%) were less than 35 years while 29.7% were greater than 35 years of age.

Age group	Frequency (n=64)	Percentage
≤20	1	1.6
21-25	7	10.9
26-30	15	23.4
31-35	22	34.4
36-40	16	25.0
≥41	3	4.7

**Table 1:** Age distribution of mothers.

Table 2 shows the spectrum of heart defects identified in the subjects. Up to 16.9% had structurally normal heart. Among those with congenital heart defects 56.5% had isolated heart defects while 26.6% had multiple heart defects. The most common heart defect was atrioventricular septal defect 24.1%.

Isolated atrioventricular septal defect was found in 17.9%, and 6.2% had coexisting heart defects like patent ductus arteriosus (PDA) and pulmonary stenosis. Ventricular septal defect was the second most common heart defect 11.3% followed by atrial septal defect, 10.8%, patent ductus arteriosus, 5.6%, tetralogy of Fallot 2.6%.

Table 3 shows the association between maternal age and occurrence of congenital heart defects in patients with Down syndrome. Mothers in the age group 36 to 40 years had mostly children with structurally normal heart. However, mothers between 26 to 35 years also had most of their children with congenital heart defects. All the mothers above 40 years had children with congenital heart defect. However the association was not statistically significant ( $p < 0.211$ ).

## Discussion

Cardiac evaluation is pertinent in patients with Down syndrome. The American Academy of Pediatrics recommends an echocardiogram performed on patients with Down syndrome and referral to a pediatric cardiologist regardless of whether a fetal echocardiogram was performed or if postnatal echocardiogram results are abnormal [1].

Heart defect	Frequency (n=195)	Percentage
Normal	33	16.9
VSD	22	11.3
ASD	21	10.8
AVSD	35	17.9
PDA	11	5.6
TOF	5	2.6
PS	2	1
DORV	4	2.1
PFO	4	2.1
Cor Pulmonale	1	0.5
Pericardial Effusion	4	2.1
Hyper dynamic Circulation	1	0.5
AVSD, PDA	9	4.6
AVSD, Pericardial Effusion	1	0.5
AVSD, PS	1	0.5
AVSD, PDA, PS	1	0.5
VSD, ASD	8	4.1
VSD, PDA	5	2.6
VSD, PS, AS	5	2.6
VSD, ASD, PDA	3	1.5
VSD, ASD, PS	2	1
VSD, PDA, PFO	2	1
VSD, PS, PDA	2	1
ASD, PS	5	2.6
ASD, PDA	1	0.5
ASD, PDA, PS	1	0.5
PDA, PFO	1	0.5
DORV, PS	1	0.5
Truncus, PDA	1	0.5
TA, VSD, PDA, ASD	1	0.5
TOF, Pericardial effusion	2	1

**Table 2:** Echocardiographic findings among subjects.

In this study, the prevalence of congenital heart defect in patients with Down syndrome was 83.1%. This is comparable to the study by Ekure et al. [20] who reported a prevalence of 87% and 80% by Shrestha et al. [21]. This high prevalence may be attributed to the

increased awareness in the occurrence of Down syndrome and availability of echocardiogram in these centers.

n=64	Congenital heart disease		Total
	Normal (n=15)	Heart defect (n=49)	
Age group			
≤20	1(6.7)	0(0.0)	1(1.6)
21-25	1(6.7)	6(12.2)	7(10.9)
26-30	2(13.3)	13(26.5)	15(23.4)
31-35	5(33.3)	17(34.7)	22(34.4)
36-40	6(40.0)	10(20.4)	16(25.0)
>41	0(0.0)	3(6.1)	3(4.7)

**Table 3:** Maternal age and cardiac findings among subjects

Also this may be evidence that the earlier report that approximately 50% of patients with Down syndrome having structurally normal heart may be lower, as it is in this study (16.9%) and other studies [21-24].

Atrioventricular septal defect was the most common heart defect in this study (24.1%). This is closely related to a previous study carried out in same center on children with Atrioventricular septal defect, for which of 33.3% were patients with Down syndrome [25]. Other studies have reported prevalence of 45% [26] and 48% [27]. The reason for the higher prevalence in the above may be due to the fact that the earlier was a population based study while the later involved older children up to the age of 18 years. The later study also had fewer subjects involved and was a single center based study. Atrioventricular defect which was found as the most common cardiac defect in this subject is contrary to the reports and also from Lagos who reported ventricular septal defect as the most common defect in patients with Down syndrome seven years earlier, it is also contrary to the report of Otaigbe and her co-authors who reported patent ductus arteriosus as the commonest defect among children from the southern part of Nigeria but similar to the report by Asani and his co-authors from the Northern part of the country. The current report has the advantage of involving more subjects and involved more than one center hence may be more representative of the true pattern among Nigerian Children.

Up to 26.6% of the subjects had multiple cardiac defects which is comparable to the Libyans study by Elmagrapy et al. [24]. Patent ductus arteriosus has been reported by some studies to be the most commonly co-existing heart defect with atrioventricular septal defect in these patients [13,28]. This was also found in this study. The most common cyanotic congenital heart defect in this study was Tetralogy of Fallot which was also detected in previous studies [9,26].

Women of younger age groups were found to have children with Down syndrome which is similar to study by Bertelli et al. [29]. This may probably be due to occurrence of unbalanced translocation in these mothers and possibly by other environmental risk factors such as cigarette smoking, exposure to chemicals, toxins, ionizing radiation, and folate deficiency. The effect of advanced maternal age as a risk factor for having a child with Down syndrome is limited to non-disjunction errors that occur in the ovum [30].

In assessing for the association of maternal age with the occurrence of congenital heart defects in these subjects. The incidence of congenital heart defect in the subjects was decreasing from maternal age 36 years and above, although this was not statistically significant. This finding is similar to the report by Chehab et al. [31] who documented lesser occurrence of congenital heart defect in Down syndrome patients with maternal age above 32 years. They also found consanguineous marriage not to be a risk factor for congenital heart defect in the subjects, although, consanguinity was not assessed as a risk factor in the current study because the practice is very rare in this part of the world.

In conclusion, incidence of congenital heart disease is high among subjects with Down syndrome. Atrioventricular defects were the commonest cardiac defect among the subjects. The incidence of congenital heart defect in the subjects was decreasing from maternal age 36 years and above. Routine cardiac evaluation including echocardiography is recommended for all patients with Down syndrome. There is a need for a larger, multi-centered and population based study to allow for a more representative report in these groups of subjects.

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### Ethical Disclosures

The authors declare that no patient data appeared in this write-up. No experiments were performed on the patients for this article.

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