HSPI The Open Access Publisher

JCCM ISSN 2575-0143 JOURNAL OF CARDIOLOGY AND CARDIOVASCULAR MEDICINE

Research Article

Prevalence and pattern of congenital heart disease among children with Down syndrome seen in a Federal Medical Centre in the Niger Delta Region, Nigeria

Ujuanbi Amenawon Susan* and Onyeka Adaeze Chiemerie

Department of Paediatrics, Cardiology Unit, Federal Medical Centre, Yenagoa, Bayelsa, Nigeria

Abstract

Background: Down syndrome (DS), or Trisomy 21, is the most common genetic disorder in the world and congenital heart disease (CHD) contributes significantly to morbidity and mortality in this population. Early diagnosis and prompt cardiac intervention improve their quality of life. This study was done to determine the prevalence and pattern of congenital heart disease among children with Down syndrome seen at the Paediatric Cardiology Unit of Federal Medical Centre (FMC), Bayelsa State.

Method: A prospective study of children with Down syndrome referred for cardiac evaluation and echocardiography at the Paediatric Cardiology Unit of FMC, Bayelsa State over four years from 1st January 2016 to 30th December 2019. Data on socio-demographic information, echocardiographic diagnosis, and outcome were retrieved from the study proforma and analyzed.

Results: A total of 24 children with Down syndrome were seen over the study period. Their age ranged from 0 to 16 years. The majority, 20 (83.3%) of the children with Down syndrome were aged 5 years and below. There were 13 males and 11 females with a male to female ratio of 1.2:1. A total of 23 (95.8%) of the children with Down syndrome had CHD. The most common CHD was AVSD (including complete, partial, isolated, or in association with other defects) in 66.6% followed by TOF in 8.3%. Multiple CHDs were seen in 43.5% of the children. Only one child (4.2%) had a structurally normal heart on echocardiography. All the children with Down syndrome had pericardial effusion of varying severity while 33% had pulmonary artery hypertension (PAH). The fatality rate among the children seen with Down syndrome over the study period was 34.8% and only one child (4.2%) had open-heart surgery with the total repair of cardiac defect during the study period.

Conclusion: Morbidity and mortality are high among children with Down syndrome due to the high prevalence of CHD. Early referral, diagnosis, and prompt intervention are encouraged.

More Information

***Address for Correspondence:**
Ujuanbi Amenawon Susan, Cardiology Unit, Department of Paediatrics, Federal Medical Centre, Yenagoa, Bayelsa, Nigeria,
Email: asokoedion@yahoo.com

Submitted: January 28, 2022
Approved: April 08, 2022
Published: April 11, 2022

How to cite this article: Susan UA, Chiemerie OA. Prevalence and pattern of congenital heart disease among children with Down syndrome seen in a Federal Medical Centre in the Niger Delta Region, Nigeria. J Cardiol Cardiovasc Med. 2022; 7: 030-035.

DOI: 10.29328/journal.jccm.1001129

Keywords: Down syndrome; Prevalence; Pattern; Congenital heart disease; Niger delta; Nigeria

Introduction

Down syndrome also known as trisomy 21, is a genetic disorder and the most common chromosomal disorder in humans and clinical practice [1]. It is caused by the presence of all or part of the third copy of chromosome 21 and its incidence is estimated to be 1:800 live births [2,3]. It is usually associated with physical growth delays, hypotonia, intellectual disability, characteristics facial features, and other major organ malformations [2]. The distinct facial features and other clinical phenotype makes clinical diagnosis easy and hence cytogenetic analysis is done primarily to identify the few cases that are due to translocation or mosaicism [3]. Among the other major congenital malformations associated with DS, congenital heart defects (CHD) are of utmost interest because they are the leading cause of mortality and morbidity during the first two years of life in the DS population [1,2]. Studies have shown that 40% to 60% of DS patients have CHD [3,4]. Children with Down syndrome have been found to have varying patterns and severity of CHD and usually left to right shunt lesions predominate [3,4]. The most common CHD types reported worldwide are atrioventricular canal

defects (AVSD), ventricular septal defects (VSD), patent ductus arteriosus, atrial septal defects (ASD), and tetralogy of Fallot in decreasing order [5-8]. It has been suggested that the profile and types of these CHDs are variable according to the different geographical areas around the world with multifactorial causes implicated. Available studies in Nigeria show a varying pattern of CHD among children with Down syndrome. Reports by Ekure, et al. [9] suggest that AVSD and VSD as the leading defects among DS children in Lagos. Okeniyi, et al. [10] reported AVSD and a combination of VSD and ASD as the commonest cardiac malformations among children with CHD in Ile-Ife. Asani, et al. [4] and Sadoh, et al. [11] in Kano and Edo respectively reported AVSD as the most commonest cardiac defect among children with Down syndrome in their studies. In contrast, Otaigbe, et al. [12] showed that PDA and ASD are the commonest cardiac lesions in children with Down syndrome in Port Harcourt. Pericardial effusion was reported to be common in children with Down syndrome in some studies [13]. The Knowledge of the prevalence and pattern of CHD in DS children, as well as the associated complications are important for early intervention. Timely intracardiac repair of cardiac abnormalities in Down syndrome children is crucial for their optimal survival and improvement in their quality of life. Although studies on the pattern of CHD have been done in some parts of Nigeria, no study has been carried out in Bayelsa State which is located in the southern region of the country. This study was therefore done, to determine the prevalence and echocardiographic pattern of congenital heart disease among children with Down syndrome seen at the Paediatric Cardiology Unit of Federal Medical Centre (FMC), Bayelsa State.

Methodology

Study design and setting

This was a prospective hospital-based descriptive study of children 16 yrs and below with phenotypic features of Down syndrome referred for echocardiographic evaluation at the Paediatric Cardiology Unit, Federal Medical Centre, Bayelsa State. The recruitment period was over 4 years from 1st January 2016 to 30th December 2019. Federal Medical Centre, Bayelsa State receives referrals from other hospitals and clinics in Bayelsa as well as neighboring states like Rivers State, Delta State, Edo State, and other parts of Nigeria. The hospital is also a designated cardiac screening center for an Italian Non-Governmental Organization (Pobis Open Heart International) that visits Nigeria twice yearly to perform free cardiac operations on children suitable for open-heart surgery.

Data collection

All referred cases with phenotypic features suggestive of Down syndrome such as hypotonia, brachycephaly, small low-set ears, upslanting creases, and a gap between the first and second toes underwent full clinical assessment. Phenotypic features of these children were used for the clinical diagnosis of Down syndrome and no cytogenetic analysis was done due to lack of facilities. All Down syndrome children referred to our center during the study period were included and children who did not have Down syndrome were excluded. Also, children with other genetic disorders or features that did not fit into Down syndrome were excluded.

The diagnosis of CHD was done using chest radiography, electrocardiography, center, and echocardiography. Echo-cardiography was carried out using SIEMENS cardiac ultrasound system, manufactured in December 2008. The machine has the facility for M-Mode, 2D, Colour flow mapping, and Doppler studies. All measurements were done using a Paediatric probe with a 6.5 MHZ sector transducer. Data of the study participants such as age, gender, nutritional status, socioeconomic class, clinical presentation, age of parents, birth order, types of CHD based on echocardiographic findings, and outcome were entered into a study proforma.

The socioeconomic class was determined using the methods described by Oyedeji, et al. [14]. The patients' weights were measured using a bassinet weighing scale for infants and a calibrated weighing scale for older children, using standard methods. The heights of the children were taken using a stadiometer to the nearest 0.1 cm while those less than 2 years old had their lengths taken with a non-elastic tape rule. Wasting was assessed using weight for length/height.

Statistical analysis

Statistical analysis was performed using the Statistical Package for Social Sciences version 27 (IBM Corp., Armonk, NY, USA). Descriptive statistics for age, gender, and types of CHD were done and data was represented in frequency tables.

Ethical considerations

This study was approved by the Hospital's Ethical Review Committee. Informed consent was given by the guardians of all the participants and none declined.

Results

During the study period, a total of 24 children with clinical features suggestive of Down syndrome were seen in our hospital. Table 1 shows the Socio-demographic status of the 24 children with Down syndrome. Their age ranged from 0 to 16 years. A total of 20 (83.3%) of these children with Down syndrome were aged 5 years and below (Table 1). There were 13 males and 11 females with a male to female ratio of 1.2:1. All the children studied with Down syndrome were diagnosed based on clinical criteria.

The majority (58.3%) of the children with Down syndrome were born mainly to young mothers aged 35 years and below (Table 1). A total of 12 (50.0%) children with Down syndrome were fifth-born and above in the order of birth (Table 1).

Most 15 (62.5%) of the children with Down syndrome had underweight malnutrition while 48.5% of the children were of low socioeconomic status (Table 1).

The frequency distribution of the reasons for referral including clinical findings and co-morbidities in the 24 children with clinical features of Down syndrome are shown in Table 2. The commonest reasons for referral were dysmorphic features suggestive of Down syndrome and varying cardiac symptoms. The most common clinical findings were cardiac murmur in 22 children (91.7%) followed by recurrent chest infection in 16 (66.7%) children and by respiratory difficulty in 14 (58.3%) as shown in Table 2. Other clinical findings included cyanosis-hypoxia in 3 (12.5%) and heart failure in 13 (54.2%).

Table 3 depicts the Echocardiographic findings among the 24 children with Down syndrome. A total of 23 (95.8%) of the 24 children seen with Down syndrome had CHD. The most common CHD was AVSD (complete or partial; occurring solitarily or in combinations) in 66.6% as shown in Table 3. Multiple CHDs were seen in 43.5% of the children. The commonest cyanotic CHD was TOF (8.7%). Only one (4%) child had a structurally normal heart on echocardiography. The majority of the children 19 (79.1%) with CHD were aged less than one year.

Cardiac and non-cardiac complications as seen in the 24 children studied with Down syndrome are shown in Table 4. Complications directly related to the underlying Down syndrome or with the associated cardiac defects were common. All the children including the one with structurally normal heart had pericardial effusion of varying severity on echocardiography. As presented in Table 4, malnutrition was detected in 15 (62.5%) of the children with Down syndrome, especially in those with complex CHD such as complete AVSD. Pulmonary hypertension was observed in 8 (33.3%) of the children with CHD on echocardiography. The abnormalities most frequently associated with pulmonary hypertension were AVSD at an early age, seen in 6 children (25%).

Table 5 shows the outcome of the 24 children with Down

Table 1: Socio-demographic Characteristics and Parental Age Group of the 24 Children with Down syndrome.

Characteristics	Male (13)	Female (11)	Total (%)
Age (Years)			
< 5	12	8	20 (83.3)
≥ 5 - < 10	1	2	3 (12.5)
≥ 10 - 16	0	1	1 (4.2)
Socioeconomic Status			
High	3	2	5 (20.8)
Middle	4	4	8 (33.4)
Low	6	5	11 (45.8)
Nutritional Status			
Underweight	9	6	15 (62.5)
Normal weight	2	2	4 (16.7)
Overweight	2	3	5 (20.8)
Maternal Age (Years)			
< 35	9	5	14 (58.3)
≥ 35	4	6	10 (41.7)
Paternal Age			
< 50	8	3	11 (45.8)
≥ 50	5	8	13 (54.2)
Order of Birth			
1st	3	2	5 (20.8)
2nd	2	1	3 (12.5)
3rd	2	1	3 (12.5)
4th	1	0	1 (4.2)
5th and above	5	7	12 (50.0)

Table 2: Reasons for Referral of the 24 Children with Down syndrome.

Reasons For Referral	Number (N)	Percentage (%)
Dysmorphysm with other symptoms**	21	87.5
Dysmorphysm only	3	12.5
Cardiac murmur	22	91.7
Failure to thrive	13	54.2
Recurrent chest infection	16	66.7
Respiratory difficulty	14	58.3
Cyanosis-hypoxia	3	12.5
Heart failure	13	54.2

** Majority of the children had multiple reasons for referral.

Table 3: Echocardiographic Pattern of Congenital Heart Defects seen in the Down syndrome children.

Pattern of Congenital Heart Defects	Number of Cases Males	Females	Total	Percentage (%)
Complete AVCD	4	5	9	37.5
Complete AVCD, OS ASD	1	2	3	12.5
Complete AVCD, Common Atrium, Common AV Valve, PDA, PAH	1	1	2	8.3
Complete AVCD,PDA, PAH	0	2	2	8.3
TOF	2	1	2	8.3
Subaortic VSD, OS ASD	1	0	1	4.2
OS ASD, PDA, Subaortic Stenosis	1	0	1	4.2
Isolated OS ASD	0	1	1	4.2
Isolated PDA	0	1	1	4.2
OS ASD, PM VSD, PDA	1	0	1	4.2
SNH	1	0	1	4.2

VSD: Ventricular Septal Defect; ASD: Atrial Septal Defect; AVSD: Complete Atrioventricular Septal Defect; PDA: Patent Ductus Arteriosus; OS: Ostium Secundum; PM: Perimembranous; PAH: Pulmonary Artery Hypertension; TOF: Tetralogy Of Fallot; SNH: Structurally Normal Heart

Table 4: Complications observed among the 24 Children with Down syndrome.

Complications	Frequency	Percentage (%)
Pulmonary hypertension	8	33.3
Pericardial effusion	24	100
Heart failure	13	54.2
Infective endocarditis	1	4.2
Malnutrition	15	62.5
Multiple complications	5	20.8

Table 5: Outcome of the Children with Down syndrome and CHD.

Outcome	Number of Patients (%)	Percentage (%)
Death	8	34.8
Lost to Follow Up	6	26.0
Follow Up/Awaiting Surgery	4	17.4
Follow Up /Inoperable	2	8.7
DAMA	2	8.7
Surgery	1	4.3

DAMA: Discharge Against Medical Advice

syndrome. The fatality rate among the children seen with Down syndrome over the study period was 33.3% and only one child had open-heart surgery with the total intracardiac repair of cardiac defect during the study period (Table 5). Of the children that died, 6 (75%) were children with complex complete AVSD. Two (8.7%) of the children with Down syndrome were discharged against medical advice by their parents to seek alternative care (spiritual and traditional care). Additionally, another 2 (8.7%) of the children with Down syndrome had inoperable cardiac defects due to severe pulmonary hypertension and are on follow-up with medical therapy.

Discussion

The prevalence of congenital heart disease among children seen with Down syndrome in our center is very high (95.8%), and much higher than the 40% to 60% described in incidence studies globally [7-9,15,16]. The prevalence reported in this study is also higher than the prevalence of 79.7% and 77.1% reported in the studies by sadoh, et al. [11] in Benin and Asani, et al. [4] in Kano both in Nigeria but lower than the prevalence of 100% reported by Otaigbe, et al. [12] in Port Harcourt, Nigeria. The very high prevalence in our study can be attributed to the fact that the study was performed in a referral and cardiac screening center in the southern region of Nigeria. Additionally, in our study, referral for echocardiography was based on the suspicion of a possible cardiac defect in the affected children.

Down syndrome is associated with maternal ages at the extremes of their childbearing period [17]. In our study, Down syndrome was most frequent among mothers younger than 35 years. This is consistent with previous studies that have shown a higher prevalence of Down syndrome in children born to younger mothers [12,18]. The occurrence of a growing number of children with Down syndrome born to younger mothers presents a strong reason for advocating Down syndrome screening for pregnant mothers as is done in some other countries [19,20]. There are factors that may militate against a successful screening program in our country. The fact that it is expensive and may be beyond the reach of the majority of Nigerians; however the cumulative cost of caring for a Down syndrome child certainly outweighs the cost of screening [21]. Another major factor in managing the outcome of a positive screening result. Nigerian couples may be unlikely and unwilling to accept the termination of pregnancies because of their religious and traditional beliefs.

The majority of the children with Down syndrome in this study were underweight. This may be due to the fact that the prevalence of CHD was high in this study and the majority of the CHD were shunt lesions that could lead to recurrent pneumonia and heart failure. The high prevalence of underweight children with Down syndrome demonstrated in our study is similar to the findings from the studies done in Brazil [22] and other parts of Nigeria where underweight malnutrition was a common occurrence [10-12].

The majority of our patients were diagnosed with congenital heart disease during the first year of life (79.1%). This is probably because of the phenotypic features of these children with Down syndrome and our hospital is a cardiac screening center with well-established obstetric and delivery facilities. Diagnosis of Down syndrome in our study was based on clinical criteria and cytogenetic analysis was not performed due to the non-availability of such services in our center and the high cost of sending samples to other centers and abroad for analysis. This was a limitation in our study.

Complete atrioventricular septal defects either occurring in isolation or in combination with other cardiac defects such as ostium Secundum atrial septal defect, ventricular septal defect, and patent ductus arteriosus accounted for 58.3% of the cardiac abnormalities observed in Down syndrome in our study. Cyanotic CHD- Tetralogy of Fallot was the most common isolated cardiac defect (8.3% of the total). Ventricular septal defect of the perimembranous type in combination with PDA was seen in 4.1%. Isolated ostium secundum ASD, as well as isolated PDA, were seen in another 4.1% of the children in our series. It is noteworthy that a similar trend of a higher proportion of complete AVSD among Down syndrome children was reported in the studies by Asani, et al. [4] in Kano, Nigeria, Benhaourech, et al. [16] in Morocco, Boussouf, et al. [17] in Algeria, and Nisli, et al. [23] in Turkey. The pattern of CHD reported in our study however contrasts the findings from the study by de Reuben Figueroa, et al. [24] in Mexico in which Atrial septal defect, VSD, and PDA accounted for 90% of the cardiac abnormalities observed among children with Down syndrome. Also, in contrast to our study Otaigbe, et al. [12] in Port Harcourt, Nigeria found that Patent ductus arteriosus, occurring solitarily or in combination with other defects was the commonest cardiac defect followed by ventricular septal defects in their study. There is still no clear explanation for this variation in the patterns of CHD observed worldwide or even within the same region. Genetic factors, specific embryological mechanisms, and cell characteristics that determine the type of cardiac malformation [25], ethnic, geographic, and socio-demographic factors may also influence the formation of these cardiac abnormalities in children with Down syndrome.

The atrioventricular septal defect was associated with a poor prognosis in 75% of affected children in our study, This is because complete correction is required before the age of six months to avoid residual lesions (most frequently left atrioventricular valve regurgitation) and because the high incidence of associated pulmonary hypertension in these subsets of children with Down syndrome [26,27]. Children with Down syndrome with an associated heart defect(s) often have an increased risk of pulmonary vascular resistance and develop considerable pulmonary vascular injury at early ages; thus, AVSD has a good prognosis in patients who

receive early surgical treatment [28]. Also because of inherent lung parenchymal issues and sleep apnoea in children with Down syndrome progression to pulmonary vascular disease is common [29]. However, when the associated heart abnormalities are left-to-right shunts (as seen in some of our cases), the prognosis is more favorable than when there is associated AVSD, which is linked with pulmonary hypertension, a condition commonly associated with high mortality [29].

It is noteworthy that all the children with Down syndrome seen in our study had pericardial effusion of various magnitudes (mild to severe). This is similar to what was previously reported by Concolino, et al. [13]. The reason for this occurrence is generally unknown. However, it could be due to the effect of heart failure, viral infections, and the presence of hypothyroidism in Down syndrome children. Interestingly, none of the children with Down syndrome with pericardial effusion in our study presented with cardiac tamponade.

The clinical course of Down syndrome in children with cardiac defects and the outcome of medical or surgical treatment is more favorable when the condition is detected early and pulmonary hypertension averted. In our study, however, due to late presentation, only a few were amenable to surgery, while others either succumbed or were inoperable. The fatality rate among children with Down syndrome resulting from congenital heart defects was 33.3% in our study. This is in tandem with what was previously reported in other studies in Nigeria [4,9,10,12,30]. Additionally, although the rate of discharge against medical advice in our study was not too alarming, it is usually a source of concern because, most of the children in this category with severe cardiac defects are often left to die at home out of ignorance, traditional and spiritual beliefs even with early detection and chances of timely intervention. The children lost to follow-up in this study were those with inoperable cardiac defects with complications needing frequent hospitalization. The parents had born out and were probably unwilling to continue care. Follow-up calls to the parents were unanswered and unreturned.

It is important for medical practitioners, especially health care personnel who sometimes care for and manage children with Down syndrome to be aware of the factors related to a poor clinical course in those with cardiac defects. This will enable early referral to a cardiologist for prompt diagnosis and the initiation of medical or surgical treatment as soon as possible. This will go a long way in reducing the morbidity and mortality found in Down syndrome children with heart disease.

Conclusion

The prevalence of congenital heart disease in children with Down syndrome was high in our series (95.8%). The complex atrioventricular septal defect was found in 58.3% of our Down syndrome children with CHD. Pulmonary hypertension was a frequent complication that occurred most often in children with AVSD. Mortality was relatively high at 33.3%. The high prevalence of CHD among children with Down syndrome underscores the need for early referral, diagnosis, and prompt intervention to improve their quality of life. Routine cardiac evaluation for children with features suggestive of Down syndrome in the first few weeks of life is encouraged.

Acknowledgment

The authors gratefully acknowledge the House Officers who did a rotation in the Paediatric Cardiology unit during the study period and assisted in entering some of the data in the study proforma.

References

1. Spicer RL. Cardiovascular disease in Down syndrome. Pediatr Clin North Am. 1984; 31: 1331-1343.
PubMed: https://pubmed.ncbi.nlm.nih.gov/6239137/

2. Hoffman JIE, Kaplan S. The incidence of congenital heart disease. J Am College Cardiol. 2002; 39: 1890–900.
PubMed: https://pubmed.ncbi.nlm.nih.gov/12084585/

3. Lacro RV. Dysmorphology and genetics. In: Keane JF, Lock JE, Fyler DC, editors. Nadas' Pediatric Cardiology. UK: Elsevier; 2007: 49-72.

4. Asani M, Aliyu I, Also U. Pattern of congenital heart diseases among children with Down syndrome seen in Aminu Kano Teaching Hospital, Kano, Nigeria. Niger J Basic Clin Sci. 2013; 10: 57-59.

5. Ko JM. Genetic syndromes associated with congenital heart disease. Korean Circ J. 2015; 45: 357-361.
PubMed: https://pubmed.ncbi.nlm.nih.gov/26413101/

6. Freeman SB, Taft LF, Dookey KJ, Allran K, Sherman SL, et al. Population based study of congenital heart disease in Down syndrome. Am J Med Genet. 1998; 80: 213-217.
PubMed: https://pubmed.ncbi.nlm.nih.gov/9843040/

7. Wells GL, Baker SE, Finley SC, Colvin EV, Finley WH. Congenital heart disease in infants with Down syndrome. South Med J 1994; 87: 724-727.
PubMed: https://pubmed.ncbi.nlm.nih.gov/8023205/

8. Cleves MA, Hobbs CA, Cleves PA, Tilford JM, Bird TM, et al. Congenital defects among live born infants with Down syndrome. Birth Defects Res A Clin Mol Teratol. 2007; 79: 657-663.
PubMed: https://pubmed.ncbi.nlm.nih.gov/17696161/

9. Ekure EN, Animashaun A, Bastos M, Ezeaka VC. Congenital heart disease associated with identified syndromes and other extra cardiac congenital malformations in children in Lagos. West Afr J Med. 2009; 28: 33-37.
PubMed: https://pubmed.ncbi.nlm.nih.gov/19662743/

10. Okeniyi JA, Onakpoya UU, Samuel I, Adegoke OT, Okolugbo J. Spectrum of congenital heart disease in children with Down syndrome in Ile-Ife Nigeria. Curr Paediatr Res. 2017; 21: 410-415.

11. Sadoh WE, EKI-Udoko FE, Isah IA. Profile of clinical features, congenital heart disease and other comorbidities in children with Down syndrome in a tertiary care centre in Nigeria. Sri Lanka J Child Health. 2018; 47: 50-55.

12. Otaigbe BE, Tabansi PN, Agbedeyi GO. Pattern of congenital heart defects in children with down syndrome at the University of Port Harcourt Teaching Hospital, Port Harcourt. Niger J Paed. 2012; 39: 164-167.

13. Concolino D, Pascuzzi A, Pietragalla E, Lia R, Canepa S, et al. High prevalence of isolated pericardial effusion in down syndrome. Am J

Med Genet A. 2005; 132A: 331-332.
PubMed: https://pubmed.ncbi.nlm.nih.gov/15523613/

14. Oyedeji GA. Socio-economic and cultural background of hospitalized children in Ilesha. Nig J Pediatr 1985; 12: 111-117.

15. El-Gilany AH, Yahia S, Wahba Y. Prevalence of congenital heart diseases in children with Down syndrome in Mansoura, Egypt: a retrospective descriptive study. Ann Saudi Med. 2017; 37: 386-392. **PubMed:** https://pubmed.ncbi.nlm.nih.gov/28988253/

16. Benhaourech S, Drighil A, El Hammiri A. Congenital heart disease and Down syndrome: various aspects of a confirmed association. Cardiovasc J Afr. 2016; 27: 287–290. **PubMed:** https://pubmed.ncbi.nlm.nih.gov/27805241/

17. Boussouf K, Zoubida Z, Mounira A, Naima H, Malika M, et al. Study of congenital heart diseases in patients with Down syndrome in Algeria. East Mediterr Health J. 2017; 23: 632-636..

18. Torfs CP, Christianson RE. Anomalies in Down syndrome individuals in a large population-based registry. Am J Med Genet. 1998; 77: 431-438. **PubMed:** https://pubmed.ncbi.nlm.nih.gov/9632176/

19. Jou HJ, Kuo YS, Hsu JJ, Shyu MK, Hsieh TT et al. The evolving national birth prevalence of Down syndrome in Taiwan. A study on the impact of second trimester maternal serum screening. Prenat Diagn. 2005;: 665–670. **PubMed:** https://pubmed.ncbi.nlm.nih.gov/16049991/

20. Agathokleous M, Chaveeva P, Poon LC, Kosinski P, Nicolaides KH. Meta-analysis of second-trimester markers for trisomy 21. Ultrasound Obstet Gynecol. 2013; 41: 247-461. **PubMed:** https://pubmed.ncbi.nlm.nih.gov/23208748/

21. Geelhoed EA, Bebbington A, Bower C, Deshpande A, Leonard H. Direct health care costs of children and adolescents with Down syndrome. J Pediatr. 2011; 159: 541-545. **PubMed:** https://pubmed.ncbi.nlm.nih.gov/21784457/

22. Bertelli ECP, Biselli JM, Bonfim D, Goloni-Bertollo EM. Clinical profile of children with Down syndrome treated in a genetics outpatient service in the Southeast of Brazil. Rev Assoc Med Bras. 2009; 55: 547–552. **PubMed:** https://pubmed.ncbi.nlm.nih.gov/19918654/

23. Nisli K, Candan SKH, Tansel TTE, Karaman B, Omeroglu RE, et al. Congenital heart disease in children with Down's syndrome: Turkish experience of 13 years. Acta Cardiol. 2008; 63: 585-589. **PubMed:** https://pubmed.ncbi.nlm.nih.gov/19014001/

24. de Rubens Figueroa J, del Pozzo Magaña B, Pablos Hach JL, Calderón Jiménez C, Castrejón Urbina R. Heart malformations in children with Down syndrome. Rev Esp Cardiol. 2003; 56: 894-899. **PubMed:** https://pubmed.ncbi.nlm.nih.gov/14519277/

25. Ferencz CH, Neill C, Boughman J, Rubin J, Brenner J, et al. Congenital cardiovascular malformations associated with chromosome abnormalities: an epidemiologic study. J Pediatr. 1989; 114: 79-86. **PubMed:** https://pubmed.ncbi.nlm.nih.gov/2521249/

26. Hayes C, Johnson Z, Thornton L, Fogarty J, Lyons R, et al. Ten year survival of Down syndrome births. Int J Epidemiol. 1997; 4: 822-821. **PubMed:** https://pubmed.ncbi.nlm.nih.gov/9279615/

27. Maroto CM, Enríquez de Salamanca F, Herráiz IS, Zabala JA. Guías de práctica clínica de la Sociedad Española de Cardiología en las cardiopatías congénitas más frecuentes. Rev Esp Cardiol. 2001; 54: 67-82.

28. Ping T, Jerome K. The pulmonary vascular bed in children with Down syndrome. J Pediatr 1975 ; 86: 533-538. **PubMed:** https://pubmed.ncbi.nlm.nih.gov/123955/

29. Guía JM, Bosch V, Castro FJ, Téllez C, Mercader B, et al. Factores influyentes en la evolución de la mortalidad de las cardiopatías congénitas. Estudio sobre 1216 niños en la Comunidad Autónoma de Murcia (1978-1990). Rev Esp Cardiol. 2001; 54: 299-306.

30. Onalo R, Babaniyi IB. Congenital cardiac defectds in children with Down syndrome as seen in the University of Abuja Teaching Hospital, Gwagwalada, Abuja. New Niger J Clin Res. 2014; 4: 528–532.