The spectrum of congenital heart diseases in down syndrome

A retrospective study from Northwest Saudi Arabia

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ABSTRACT

الأهداف: تحديد وتيرة وأنواع أمراض القلب في الأطفال المصابين بمتلازمة داون و المولودين في شمال غرب المملكة العربية السعودية. ربطنا نتائج هذا البحث مع نتائج الأبحاث الأخرى المنشورة محلياً ودولياً لتحديد وتيرة وأنواع أمراض القلب في الأطفال المصابين بمتلازمة داون.

الطريقة: تشمل هذه الدراسة بأثر رجعي الأطفال المصابين بمتلازمة داون والمحولين إلى وحدة أمراض القلب للأطفال، مستشفى الأمومة والطفولة، المدينة المنورة، المملكة العربية السعودية خلال الفترة من يناير 2008م إلى ديسمبر 2013م.

النتائج: تم تشخيص 302 طفلا مصابين بمتلازمة داون, (50.3% ذكور). من هذا المجموع كان هناك 177 (58.6%) لديهم أمراض خلقية بالقلب. كان الخلل في منطقة الجدار الأذيني–بطيني (AVSD) الآفة الأكثر شيوعا التي تم تحديدها في 72/177 (40.7%), تليها عيوب تحويلات الدم المختلطة من اليسار إلى اليمين(14.7%) (mixed left to right shunts) والعيب في الحاجز الأذيني(11.8%) (secundum ASD). تم تحديد (10.7%) يعانون من عيب في الحاجز البطيني (VSD) و (8.5%) لديهم وصلة شريانية باقية إلى فترة ما بعد الولادة (PDA). لم يكن هناك فرق بين الجنسين في وتيرة حدوث الأمراض الخلقية بالقلب (p=0.9), ولم يكن هناك علاقة بين وجود الأمراض الخلقية بالقلب و النوع الجيني للأطفال المصابين بمتلازمة داون (p=0.9).

الخاتمة: تردد وأنماط من أمراض القلب الخلقية في الأطفال الذين يعانون من متلازمة داون في شمال غرب المملكة العربية السعودية قابلة للمقارنة مع الدراسات المنشورة لمناطق أخرى في المملكة العربية السعودية ومع معظم الدراسات المنشورة دولياً.

Objectives: To to define the frequency and patterns of congenital heart disease (CHD) among children with Down syndrome (DS) in Northwest Saudi Arabia.

Methods: We included children with confirmed DS referred to the regional pediatric cardiology unit in Madinah Maternity and Children Hospital between January 2008 and December 2013. Children were identified from the unit's data-base and the charts were reviewed retrospectively. We excluded term and preterm children with patent ducts arteriosus (PDA) and persistent foramen oval spontaneously resolved during the first 4 weeks of life.

Results: A total of 302 children with DS were identified (50.3% male). Of these, 177 (58.6%) had CHD. Atrioventricular septal defect (AVSD) was the most frequent lesion identified in 72/177 (40.7%) followed by mixed left to right shunt defects (14.7%) and secundum atrial septal defect (ASD) (11.8%). Ventricular septal defect was detected in 10.7% and 8.5% had PDA beyond the neonatal period. There was no gender difference in the frequency of CHD (p=0.9) and the presence of CHD was not related to the genetic cause of DS (p=0.9).

Conclusion: The frequency of CHD in our DS cohort is comparable with Europe, Asia ,and other KSA regions. However its pattern appears to be different from some areas in KSA.

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Down syndrome (DS) is the most common chromosomal abnormality associated with learning difficulties with reported incidence between 1/600 -1/1000 live births.[1] The condition results from the presence of an extra chromosome 21, either as trisomy or as part of Robertsonian translocation. The diagnosis of DS is based on the presence of characteristic dysmorphic features and confirmed by chromosomal karyotyping. Most children with DS have trisomy 21, due to chromosomal non-disjunction during meiosis; however, other abnormalities, such as Robertsonian translocation, mosaic, double or triple aneuploidies have been reported.[2] The association between DS and congenital heart disease (CHD) is well established. Congenital heart disease is the most common cause of death among patients with DS and affected children have an increased risk of mortality.[3-6] Therefore, it is essential that every patient with confirmed DS to undergo cardiac evaluation in early life. The frequency and pattern of CHD in DS varies between different populations. Data from kingdom of Saudi Arabia (KSA) are limited to 4 studies. These studies were conducted in different KSA regions and showed frequencies form 35-86% with different pattern of CHD.[7-10] However, no data are available from the Northwest KSA region. The aim of this study was to define the frequency and pattern of CHD among children with DS in Northwest KSA and compare it with other national and international data.

Methods. This retrospective study was conducted in the Maternity and Children Hospital (MCH), Al-Madinah, Northwest KSA, between January 2008 and December 2013. The MCH is the main referral hospital for Al-Madinah region, and hosts the only pediatric cardiology unit (PCU) in northwest KSA. The region has 7 cities and more than 300 small villages. The population is mostly Arab and 70% of them are living in Al-Madinah city. The diagnosis of DS was made by the local clinicians. Children diagnosed with DS in the region are routinely referred to the PCU at the MCH for cardiac assessment. The inclusion criteria comprised: all children with DS diagnosis based on typical clinical features and confirmed by cytogenetic studies. The exclusion criteria comprised: children with dysmorphic features and not confirmed to be DS by cytogenetic studies. All included children had electrocardiography and underwent 2-dimensional echocardiographic examination and Doppler studies. The diagnosis, severity and classification of cardiac malformation were determined according to the recommendations of the American Society of Echocardiography. Eleven Patients with CHD were referred for surgical intervention based on their hemodynamic status and the severity of the anatomical defect. Children with only one anatomical heart defect, such as ventricular septal defect (VSD), atrial septal defect (ASD), patent ductus arteriosus (PDA), or with a well-known combination, such as tetralogy of Fallot (TOF) were classified to have isolated CHD. The combination of VSD, ASD, and PDA was categorized as mixed left to right shunt. We considered the presence of PDA and persistent foramen oval, in preterm or term babies at birth, as normal unless these lesions persisted beyond 4 week of age. Clinical and demographic data of the referred children and the results of their cardiac evaluation were collected from the PCU data-base, which was established in 2008, and confirmed by chart review. The frequency of CHD was calculated from the total number of DS children refereed during the 6 years period. The pattern of CHD in our DS cohort was compared with other data from KSA and other populations. To define the frequency and pattern of CHD in DS in KSA we combined our DS cohort with other published Saudi DS cohorts who were screened for CHD. The study followed the Helsinki declaration and was approved by the ethics and research committee at the MCH.

Statistical analysis. Data were analyzed using the Statistical Package for the Social Sciences, version 16 (SPSS Inc., Chicago, ILL, USA). Categorical variables were presented as the number and percentage, and chi square or Fisher's exact test was used. The associations with *p*-values ≤0.05 were considered statistically significant.

Results. A total of 302 children with DS were referred to PCU between January 2008 and December 2013 from different hospitals in the region. Their mean age at referral was 4.3 ± 1.5 months and 85% of them were born in MCH. Of the 302 patients, 152 (50.3%) were males. Non-disjunction trisomy-21 was the most common genetic cause of DS identified in 283/302 (93.7%), followed by translocation (15/302, 4.9%), and the remaining 4/302 cases were mosaic type (1.3%). At least one form of CHD was identified in 177 of the 302 DS children, giving a frequency rate of 58.6%. There was no significant difference in the frequency of CHD between boys and girls in our cohort (p=0.9), neither the 3 genetic causes of DS (p=0.9). The frequency and patterns of CHD in our cohort are

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shown in **Tables 1 & 2**. The most frequent isolated congenital heart defect in our study was atrioventricular septal defect (AVSD, complete type) identified in 72/177 (40.7%), followed by mixed left to right shunt (26/177, 14.7%), Secundum ASDs (Sec. ASD) (21/177, 11.8%), VSD (19/177, 10.7%), Primum ASDs (Prim. ASD) (17/177, 9.6%), PDA (15/177, 8.5%), AVSD + TOF's (4/177, 2.3%), one case (0.6%) each of coarctation of the aorta (CoA), double outlet right ventricle, and dilated cardiomyopathy. All patients with AVSD underwent successfully surgical correction except one case who developed Eisenmenger syndrome due to late presentation. A comparison of the frequency and patterns of CHD between our cohort and other studies from different KSA areas is shown in **Tables 1 & 2,** and with other international studies is shown in **Table 3**. When we combined the rate of CHD in our DS cohort with patients studied in other KSA region, the cumulative frequency of CHD in DS in KSA was 65.1% and AVSD was the most common form of CHD (**Table 1 & 2**). Complete AVSD was the most common CHD pattern in our study and in Alhassa study; however, VSD was the most common in Riyadh and Aseer studies, and PDA was the most common pattern in Jeddah, KSA.

Discussion. This is the largest study addressing the spectrum of cardiac defects in DS in KSA and the first in northwest KSA. The study was conducted in the only pediatric cardiac unit in northwest KSA and studied patients referred from different hospitals in the region thus providing data on the frequency and pattern of CHD in DS in the whole region. The frequency of CHD in our DS cohort study was 58.6%.

Table 1 - The frequency of CHD among children with DS in Northwest KSA compared with other KSA regions.

Study (year)	Total number of DS patients	DS with CHD n (%)	Most common CHD n (%)
Present study (December 2013)	302	177 (58.6)	AVSD, complete type 72/177 (40.7)
Riyadh[10] (2009)	110	54 (49.0)	VSD 23/54 (43.0)
Jeddah[7] (2012)	106	124 (86.8)	PDA 44/124 (35.5)
Aseer[9] (2006)	98	57 (61.3)	VSD 19/57 (33.3)
Alhassa[8] (1999)	37	13 (35.2)	AVSD, complete type 5/13 (38.4)
Total	**653**	**425 (65.1)**	

CHD - congenital heart disease, DS - Down syndrome, KSA - Kingdom of Saudi Arabia, AVSD - atrioventricular septal defect, VSD - ventricular septal defect, PDA - patent ductus arteriosus

Table 2 - The patterns of CHD among children with DS in Northwest KSA compared with other KSA regions.

Study	VSD n (%)	Sec. ASD n (%)	Prim. ASD n (%)	PDA n (%)	Complete AVSD n (%)	Mixed L to R n (%)	CoA n (%)	AVSD +TOF n (%)	DORV n (%)	DCM n (%)	MVP n (%)
Present study	19 (10.7)	21 (11.8)	17 (9.6)	15 (8.47)	72* (40.6)	26 (14.6)	1 (0.56)	4 (2.26)	1 (0.56)	1 (0.56)	0
Riyadh[10]	23* (43.0)	14 (26.0)	0	4 (7.0)	8 (15.0)	2 (4.0)	0	2 (4.0)	1 (2.0)	0	0
Jeddah[7]	27 (21.7)	38 (30.6)	0	44* (35.4)	11 (8.87)	0	0	2 (1.6)	1 (0.8)	1 (0.8)	0
Aseer[9]	19* (35.3)	12 (21.1)	0	8 (14.0)	13 (22.8)	1 (1.75)	1 (1.75)	3 (5.3)	0	0	0
Alhassa[8]	1 (7.6)	4 (30.7)	0	0	5* (38.4)	0	0	2 (15.4)	0	0	1 (7.6)
Total (n=425)	89 (20.9)	89 (20.9)	17 (4.0)	71 (16.7)	109* (25.6)	29 (6.82)	2 (0.47)	13 (3.1)	3 (0.71)	2 (0.47)	1 (0.24)

CHD - congenital heart disease, DS - Down syndrome, KSA - Kingdom of Saudi Arabia, ASD - atrial septal defect, PDA - patent ductus arteriosus, AVSD - atrioventricular septal defect, CoA - coarctation of the aorta, TOF - tetralogy of Fallot, DORV - double outlet right ventricle.* Most common pattern of CHD in DS cases ventricle

This rate is comparable with other national published studies (Alhassa[8] 35.2%, Asser[9] 61.3% and Riyadh[10] 49% regions), and some large population-based studies, such as the California Birth Defects Monitoring Program registry[6] (43.9%), Muscat[18] (60%), Kurdistan[22] (53%), Guatemala[23] (54%), Kashmir[25] (50%), Malaysia[26] (49.3%), Japan[27] (50.5%), Goteborg[15] (52.5%), and Philadelphia[17] (65.7%). However our rate is lower than a recent frequency of 86.8% reported from Jeddah.[7] The most likely explanation for the difference between

Table 3 - Comparison of the frequency and patterns of CHD among DS patients between the present study and other international studies.

Country	Total no. DS	DS with CHD %	VSD %	Secondum ASD %	PDA %	Complete AVSD %	Mixed L to R shunt%	CoA. of aorta %	AVSD +TOF %	TOF %	PS %
Present Study	302	177/302 (58.6)	19 (10.7)	21 (11.86)	15 (8.47)	72* (40.7)	26 (14.69)	1 (0.56)	4 (2.26)	0	0
Muscat, Oman[18]	90	54/90 (60.0)	14 (25.9)	18* (33.3)	5 (9.3)	15 (27.7)	-	-	0	0	1 (1.9)
Tripoli, Libya[19]	1193	537/1193 (45.0)	76 (14.0)	125* (23.0)	-	103 (19.0)	0	0	0	5 (6.0)	0
Khartoum, Sudan[12]	80	80/80 (100)	19 (23.0)	-	-	38* (48.0)	0	0	0	5 (0.7)	0
Mansoura, Egypt[20]	712	135/712 (19.0)	56* (7.9)	40 (5.6)	20 (2.8)	19(2.7)	-	-	-	6 (1.5)	3 (0.4)
Alexandria, Egypt[21]	514	198/514 (38.5)	56 (11.0)	-	13 (3.0)	91* (18.0)	0	0	0	6 (3.0)	0
Kurdistan, Iraq[22]	445	236/445 (53.0)	68* (29.0)	14 (5.0)	32 (14.0)	48 (20.0)	-	-	-	0	0
Guatemala[23]	349	189/349 (54.0)	52 (27.5)	23 (12.5)	55* (28.5)	18 (9.5)	0	0	0	0	0
Istanbul, Turkey[13]	1042	421/1042 (40.0)	68 (16.5)	69 (16.7)	0	141* (34.2)	0	0	0	8 (8.57)	0
Kerala, India[24]	404	256/404 (63.4)	72* (28.1)	32 (12.5)	43 (16.8)	70 (27.3)	25 (9.76)	0	1 (0.4)	10 (3.9)	1 (0.4)
Kashmir, India[25]	50	25/50 (50.0)	12* (24.0)	4 (8.0)	2 (4.0)	7 (14.0)	0	0	0	3 (8.5)	0
Malaysia[26]	71	35/71 (49.3)	7* (20.0)	6 (17.1)	4 (11.4)	7* (20.0)	0	0	0	5 (5.0)	0
Japan27	196	99/196 (50.5)	33* (33.3)	9 (9.0)	12 (12.0)	7 (7.0)	8 (8)	0	0	0	0
Amsterdam, Netherlands[28]	482	207/482 (43.0)	69 (33.3)	36 (17.3)	12 (5.8)	112* (54.0)	29 (14.0)	1 (0.5)	0	16 (5.0)	13 (6.2)
Newcastle, UK[14]	821	342/821 (41.6)	106 (31.0)	52 (15.0)	14 (4.0)	125* (36.5)	0	7 (2.0)	22 (6.0)	0	7 (2.0)
Göteborg, Sweden[15]	219	115/219 (52.5)	12 (9.0)	17 (12.5)	43 (32.0)	69* (51.0)	0	0	0	6 (8.0)	0
Copenhagen, Denmark[29]	278	80/278 (28.7)	15 (19.0)	3 (4.0)	5 (6.0)	39* (49.0)	0	1 (1.0)	0	13 (11.0)	3 (4.0)
Philadelphia, USA[17]	114	75/114 (65.7)	17 (14.0)	0	7 (6.0)	33* (30.0)	0	0	2 (2.0)	38 (6.0)	0
Atlanta, USA[16]	1469	647/1469 (44.0)	278* (43.0)	272 (42.0)	0	252 (39.0)	0	0	0	1 (1.9)	0

* Most common pattern of CHD in DS cases, ASD- atrial septal defect. DS - Down syndrome, CHD - congenital heart disease, PDA - patent ductus arteriosus, CoA - coarctation of the aorta, AVSD - Atrio ventricular septal defect, TOF - tetralogy of Fallot

our frequency and that reported from Jeddah is the study methodology. In our study, we have only included patients with persistent PDA and PFO beyond 4 weeks of age, whereas such age limit was not considered in the Jeddah study, which led to a higher rate of CHD in their cohort. In the present study, AVSD pattern was the most common isolated CHD defect (72/177, 40.7%), the same ratio and common pattern of CHD in children with DS was reported nationally in Alhassa region (38.4%). Most international studies confirmed that AVSD is the most common CHD in DS patients (ranging from 18-63%),[12-15,17,21,26,29] which is similar to our study figure of 40.6%. The results of the present study showed that mixed left to right shunt (26/177, 14.7%), Sec. ASD (21/177, 11.8%), and VSD (19/177, 10.7%) represent the second most common patterns of CHD in children with DS followed by Prim. Atrial septal defect (17/177, 9.6%) and PDA (15/177, 8.5%) comes as the third common pattern of CHD in children with DS. This observation is contrary to other studies in KSA in which VSD represent the most common pattern of CHD in children with DS (Asser [35.3%] and Riyadh [43%] studies).[9,10] VSD pattern is also the most common CHD pattern in some international studies like Kurdistan[22] (29%), Kerala[24] (28.1), Kashmir[25] (24%), Japan[27] (33.3%), Atlanta[16] (43%), Malaysia[26] (20%), and Mansoura[20] (7.9%). Also, our study results disagrees with studies carried out in Muscat[18] (33.3%) and Tripoli[19] (23%), which showed that Sec. ASD is the the most common pattern of CHD in children with DS. The lack of a national study on the association between CHD and DS prompted us to combine our results with previously reported data from 4 KSA studies.[7-10] We found that 65% of 653 children with DS in KSA have CHD with AVSD being most common cardiac defect. Although this figure is comparable with rates in neighboring countries and could arguably represent KSA we have to take into account that these studies were conducted in different periods of time and used different inclusion and exclusion criteria. Clearly a national study using same method will provide more insight into the spectrum of CHD in children with DS in KSA.

Our study has 2 limitations: first, due to the retrospective nature of the study, it is possible that some patients with DS were missed either because they were not referred to our centre or died before cardiac assessment. Clearly establishing a regional register for DS will allow for better ascertainment and provide more accurate results. Second, the DS cohort is relatively small; however, this is the largest cohort of DS reported from KSA and all our patients had detailed cardiac assessment.

In conclusion, the frequency CHD in DS in the Northwest Region of KSA is high and comparable with the rates reported from other parts of the KSA and most international studies. With the exception of Al-Hassa region, the pattern of CHD in our cohort is different from other KSA regions. Further studies on larger population are needed to confirm these findings and explore the underlying cause of possible variation between different KSA regions. A national registry for DS and CHD would provide more accurate data to study contributing factors for CHD in DS.

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References

1. Smith G, Berg J. Down's anomaly. 2nd ed. Edinburgh and New York: Churchill Livingstone; 1976.
2. Morris JK, Alberman E, Mutton D, Jacobs P. Cytogenetic and epidemiological findings in Down syndrome: England and Wales 1989-2009. ***Am J Med Genet Part A*** 2012; 158A: 1151-1157.
3. Freeman SB, Taft LF, Dooley KJ, Allran K, Sherman SL, Hassold TJ, et al. Population-based study of congenital heart defects in Down syndrome. ***Am J Med Genet*** 1998; 80: 213-217.
4. Nahar R, Kotecha U, Puri RD, Pandey RM, Verma IC. Survival analysis of Down syndrome cohort in a tertiary health care center in India. ***Indian J Pediatr*** 2013; 80:118-123.
5. Shin M, Kucik JE, Correa A. Causes of death and case fatality rates among infants with down syndrome in metropolitan Atlanta. ***Birth Defects Res A Clin Mol Teratol*** 2007; 79: 775-780.
6. Torfs CP, Christianson RE. Anomalies in Down syndrome individuals in a large population-based registry. ***Am J Med Genet*** 1998; 77: 431-438.
7. Al-Aama JY, Bondagji NS, El-Harouni AA. Congenital heart defects in Down syndrome patients from western Saudi Arabia. ***Saudi Med J*** 2012; 33: 1211-1215.
8. Narchi H, Kulaylat N. High incidence of Down's syndrome in infants of diabetic mothers. ***Arch Dis Child*** 1997; 77: 242-244.
9. Abbag FI. Congenital heart diseases and other major anomalies in patients with Down syndrome. ***Saudi Med J*** 2006; 27: 219-222.
10. Al-Jarallah AS. Down's syndrome and the pattern of congenital heart disease in a community with high parental consanguinity. ***Med Sci Monit*** 2009; 15: 409-412.
11. Lai WW, Geva T, Shirali GS, Frommelt PC, Humes RA, Brook MM, et al. Guidelines and Standards for Performance of a Pediatric Echocardiogram: A Report from the Task Force of the Pediatric Council of the American Society of Echocardiography. ***J Am Soc Echocardiogr*** 2006; 19: 1413-1430.

12. Ali SK. Cardiac abnormalities of Sudanese patients with Down's syndrome and their short-term outcome. ***Cardiovasc J Afr*** 2009; 20: 112-115.
13. NisliK, Oner N, Candan S, Kayserili H, Tansel T, Tireli E, et al. Congenital heart disease in children with Down's syndrome: Turkish experience of 13 years. ***Acta Cardiol*** 2008; 63: 585-589.
14. Irving CA, Chaudhari MP. Cardiovascular abnormalities in Down's syndrome: spectrum, management and survival over 22 years. ***Arch Dis Child*** 2012; 97: 326-330.
15. Amark K, Sunnegard J. The effect of changing attitudes to Down's syndrome in the management of complete atrioventricular septal defects. ***Arch Dis Child*** 1999; 8: 151-154.
16. Freeman SB, Bean LH, Allen EG, Tinker SW, Locke AE, Druschel C, et al. Ethnicity, sex, and the incidence of congenital heart defects: a report from the National Down Syndrome Project. ***Genet Med*** 2008; 10: 173-180.
17. McElhinney DB, Straka M, Goldmuntz E, Zackai EH. Correlation between abnormal cardiac physical examination and echocardiographic findings in neonates with Down syndrome. ***Am J Med Genet*** 2002; 113: 238-241.
18. Venugopalan P, Agarwal AK. Spectrum of congenital heart defects associated with Down Syndrome in high consanguineous Omani population. ***Indian Pediatr*** 2003; 40: 398-403.
19. Elmagrpy Z, Rayani A, Shah A, Habas E, Aburawi EH. Down syndrome and congenital heart disease: why the regional difference as observed in the Libyan experience? ***Cardiovasc J Afr*** 2011; 22: 306-309.
20. El-Gilany A, Yahia S, Shoker M, El-Dahtory F. Cytogenetic and comorbidity profile of Down syndrome in Mansoura University Children's Hospital, Egypt. ***Indian J Hum Genet*** 2011;17: 157-163.
21. Mokhtar MM, Abdel-Fattah M. Major birth defects among infants with Down syndrome in Alexandria, Egypt (1995-2000): trends and risk factors. ***East Mediterr Health J*** 2001;7: 441-451.
22. Salih AF. Congenital heart disease in Down Syndrome: Experience of Kurdistan of Iraq. ***Duhok Med J*** 2011; 5: 1-6.
23. Vida VL, Barnoya J, Larrazabal LA, Gaitan G, de Maria Garcia F, Castañeda AR. Congenital cardiac disease in children with Down's syndrome in Guatemala. ***Cardiol Young*** 2005; 15: 286-290.
24. Narayanan DL, Yesodharan D, Kappanayil M, Kuthiroly S, Thampi MV, Hamza Z, et al. Cardiac spectrum, cytogenetic analysis and thyroid profile of 418 children with Down syndrome from South India: a cross-sectional study. ***Indian J Pediatr*** 2014; 81: 547-551.
25. Ashraf M, Malla R ,Chowdhary J, Malla M, Akhter M, Rahman A, et al. Consanguinity and pattern of congenital heart defects in Down syndrome in Kashmir, India. ***Am J Sci Ind Res*** 2010; 1: 573-577.
26. Azman BZ, Ankathil R, Siti Mariam I, Suhaida MA, Norhashimah M, Tarmizi AB, et al. Cytogenetic and clinical profile of Down syndrome in Northeast Malaysia. ***Singapore Med J*** 2007; 48: 550-554.
27. Masaki M, Higurashi M, Iijima K, Ishikawa N, Tanaka F, Fujii T, et al. Mortality and survival for Down syndrome in Japan. ***Am J Hum Genet*** 1981; 33: 629-639.
28. Weijerman ME, van Furth AM, van der Mooren M, van Weissenbruch MM, Rammeloo L, Broers CJ et al. Prevalence of congenital heart defects and persistent pulmonary hypertension of the neonate with Down syndrome. ***Eur J Pediatr*** 2010; 169: 1195-1199.
29. Mikkelsen M, Poulsen H, Nielsen KG. Incidence, survival, and mortality in Down syndrome in Denmark. ***Am J Med Genet Suppl*** 1990; 7: 75-78.