STUDY OF CONGENITAL HEART DEFECTS AMONG DOWN SYNDROME CASES ATTENDING A TERTIARY CARE CENTRE

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CERTIFICATE

Certified that this dissertation entitled **" STUDY OF CONGENITAL HEART DEFECTS AMONG DOWN SYNDROME CASES ATTENDING A TERTIARY CARE CENTRE"** is a bonafide work done by **Dr.A.SOMASUNDARAM, M.D,** Post graduate student of Paediatric Medicine, Institute of Child Health and Hospital for Children, Egmore, Chennai-8 attached to Madras Medical College, during the academic year 2003-- 2006

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DECLARATION

I declare that this dissertation entitled **" STUDY OF CONGENITAL HEART DEFECTS AMONG DOWN SYNDROME CASES ATTENDING A TERTIARY CARE CENTRE "** has been conducted by me at the Institute of Child Health and Hospital for Children,Egmore,Chennai-8, under the guidance and supervision of my unit chief **Prof.V.T.RAMAKRISHNAN, M.D, D.C.H.** It is submitted in part of fulfillment of the award of M.D [Paediatrics] for the September 2006 examination to be held under The Tamilnadu Dr. M .G. R . Medical University,Chennai.This has not been submitted previously by me for the award of any degree or diploma from any other University.

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CONTENTS

I INTRODUCTION

Down syndrome, the most frequent form of mental retardation caused by a microscopically demonstrable chromosomal aberration, is characterized by well defined and distinctive phenotypic features and natural history. It is caused by the triplicate state of all or a critical portion of chromosome 21.

In 1866, John Langdon Down [1] wrote,

"The face is flat and broad and destitute of prominence. The cheeks are round and extended laterally. The eyes are obliquely placed, and the internal canthi more than normally distant from one another. The palpebral fissure is very narrow; the lips are large and thick with transverse fissures. The tongue is long, thick and is much roughened. The nose is small."

This description of the clinical characteristics of the syndrome, which bears his name is a common genetic disorder with an overall incidence of 1in 800 [2]. All individuals with Down syndrome have extra chromosome 21 material. Children with Down syndrome have multiple malformations and mental retardation due to the presence of extra genetic material from chromosome 21. Although the phenotype is variable, usually there is enough consistency to enable the experienced clinician to suspect the diagnosis. Down syndrome decreases prenatal viability and increases prenatal and

postnatal morbidity. Affected children have delayed physical growth, maturation, bone development, and dental eruption.

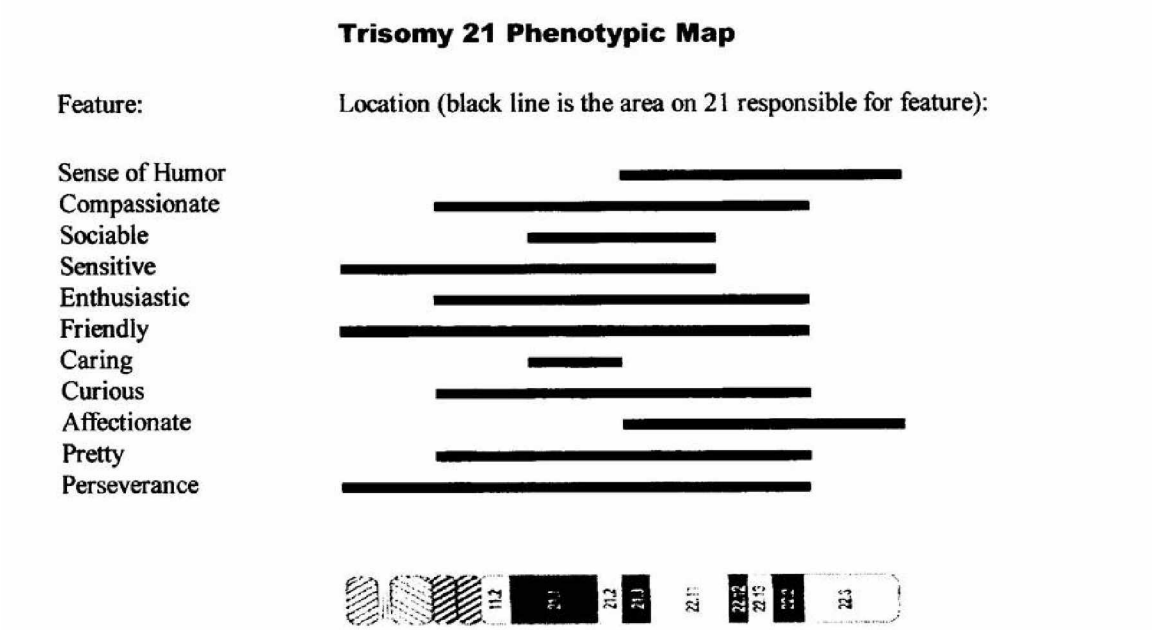
Genetics

It is the common genetic disorder occurring in 1/800 live newborns.

John Langdon Down 1866	:	First description
Lejeune 1959	:	Three copies of chromosome 21
Hattori et al 2000	:	DNA sequencing of chromosome 21

Information on Chromosome 21 [3]

- Smallest human autosome, “gene-poor”
- 33.8 mega bases (Mb)
- 225 genes: 127 known, 98 predicted
- DSCAM largest gene, 840 kb
- Contains locus for predisposition to AML
- Contains tumor suppressor gene



The extra copy of the proximal part of 21q22.3 appears to result in the typical physical phenotype. Molecular analysis reveals that the 21q22.1-q22.3 region, or Down syndrome critical region (DSCR), appears to contain the gene or genes responsible for the congenital heart disease observed in Down syndrome. A new gene, DSCR1, identified in region 21q22.1-q22.2, is highly expressed in the brain and the heart and is a candidate for involvement in the pathogenesis of Down syndrome, particularly in mental retardation and/or cardiac defects.

There are three main forms of Down syndrome, all of them a form of partial or complete aneuploidy.

Trisomy 21 due to non-disjunction

By far the most common form is the genetic condition Trisomy 21, in which there is an additional copy of chromosome 21; this accounts for 95% of all cases of Down syndrome. There are normally two copies of 23 chromosomes (46 in total), but individuals with Trisomy 21 have three copies of chromosome 21 (47 in total). Trisomy 21 is caused by a process called non-disjunction, a form of faulty cell division (generally occurring during meiosis) prior to or at conception that results in an embryo with three copies of chromosome 21 instead of two. As the embryo develops, the extra chromosome is replicated in every cell of the body.

Using DNA markers, it is possible to determine the parental origin of the extra chromosome in Trisomy 21. Studies of several hundred families with Down children have shown that nearly 95% of cases are of maternal origin, although a study of second trimester prenatally diagnosed cases of Trisomy 21 found a lower proportion of only 89% to be of maternal origin. The risk of errors in cell division leading to Trisomy 21 increases with maternal age.

Following the birth of a child with Trisomy 21 Down Syndrome, the risk of subsequent children also having Down Syndrome is about one in 100. The incidence of miscarriage in pregnancies where the fetus has Trisomy 21 is increased over that for fetuses without chromosomal abnormalities.

Mosaicism

A much rarer form of Down syndrome is a condition known as mosaicism, which accounts for only 1-2% of all cases of Down syndrome. Mosaicism occurs when nondisjunction of chromosome 21 takes place in one of the initial cell divisions after fertilization, resulting in a mixture of two types of cells in the body, some with 46 and some with 47 chromosomes. The physical features of Down syndrome may be milder in individuals with mosaicism Trisomy 21, especially if the proportion of normal cells is large. As with standard Trisomy 21, the risk that subsequent children born to the parents of a child with mosaicism Down Syndrome will also have Down Syndrome is around 1 in 100.

Translocation

Translocation is another form of chromosomal defect caused by faulty cell division prior to or at conception; in this instance chromosome 21 attaches to another chromosome (usually 14) forming a single chromosome, referred to as chromosome t(14;21) in the case of translocation between

chromosomes 21 and 14. All the cells in the body have two copies of chromosome 21, one of 14, and one t(14;21); this means that there are effectively three copies of chromosomes 21, which results in Down syndrome. Translocation accounts for 3-4% of all cases of Down Syndrome.

Up to one-third of cases of translocation Down Syndrome have a familial (inherited) basis; the rest are sporadic. Examination of the chromosomes can determine whether a parent carries the translocation. Unaffected carriers are said to be balanced, having one copy each of chromosomes 21, 14, and t(14;21); there is no extra chromosomal material and hence no features of Down syndrome present. The chance of subsequent children having Down child is around 15% if the mother is a balanced carrier of a t(14;21) translocation, but only around 2.5% if the father is the carrier.The frequency of translocation Down syndrome is not affected by maternal age. A 21,22 Robertsonian translocation may also give rise to Down syndrome in similar way.Very rarely a 21,21 translocation may arise. Carriers of this 21, 21 translocation can only produce zygotes that are either monosomic or trisomic for chromosome 21, their risk of producing a child with Trisomy 21 is virtually 100%.

Down syndrome and maternal age [5]

Researchers have established that the likelihood that a reproductive cell will contain an extra copy of chromosome 21 increases dramatically as a woman ages. Therefore, an older mother is more likely than a younger mother to have a baby with Down syndrome. However, of the total population, older mothers have fewer babies; about 75% of babies with Down syndrome are born to younger women because more younger women than older women have babies. Only about nine percent of total pregnancies occur in women 35 years or older each year, but about 25% of babies with Down syndrome are born to women in this age group.

The incidence of Down syndrome rises with increasing maternal age. Most specialists recommend that women who become pregnant at age 35 or older undergo prenatal testing for Down syndrome. The likelihood that a woman under 30 who becomes pregnant will have a baby with Down syndrome is less than 1 in 1000, but the chance of having a baby with Down syndrome increases to 1 in 400 for women who become pregnant at age 35. The likelihood of Down syndrome continues to increase as a woman ages, so that by age 42, the chance is 1 in 60 that a pregnant woman will have a baby with Down syndrome, and by age 49, the chance is 1 in 12.

Down syndrome incidence to maternal age [5]

Maternal age	Incidence of Down syndrome
Under 30	Less than 1 in 1000
30	1 in 900
35	1 in 400
38	1 in 180
40	1 in 105
42	1 in 60
44	1 in 32
46	1 in 20
48	1 in 12

Physical features

Shortly after birth, Down syndrome is diagnosed by recognizing dysmorphic features and the distinctive phenotype.

David S. Newberger [6] from The State University of New York in his article “Down syndrome: Prenatal Risk Assessment and Diagnosis” has identified the dysmorphic signs of Down syndrome.

Frequency of Dysmorphic Signs in Neonates with Trisomy 21

Dysmorphic sign	Frequency (%)
Flat facial profile	90
Poor Moro reflex	85
Hypotonia	80
Hyper flexibility of large joints	80
Loose skin on back of neck	80
Slanted palpebral fissures	80
Dysmorphic pelvis on radiograph	70
Small round ears	60
Hypoplasia of small finger, Middle phalanx	60
Single palmar crease	45

Approximately 75% of conceptions with Trisomy 21 die in embryonic or fetal life. Approximately 85% of infants survive to 1 year and 50% can be expected to live longer than 50 years. Congenital heart disease is the most important factor that determines survival. In addition, esophageal atresia with or without tracheoesophageal fistula, Hirschprungs disease, duodenal atresia and leukemia contribute to mortality. The high mortality rate later in life may be the result of premature ageing.

Incidence of Some Associated Medical Complications in Persons with Down syndrome [6]

Disorder	Incidence (%)
Mental retardation	>95
Growth retardation	>95
Early Alzheimer's disease	Affects 75% by age 60
Congenital heart defects	40
Hearing loss	40-75
Ophthalmic disorders	60
Epilepsy	5-10
Gastrointestinal malformations	5
Hypothyroidism	5
Leukemia	1
Atlantoaxial subluxation with spinal cord compression	<1
Increased susceptibility to infection	Unknown
Infertility	>99% in men; anovulation in 30% of women

Congenital Heart Disease in Down syndrome

The association of Congenital Heart Disease in Down syndrome was recognized by Garrod in 1894 and Maude Abbot in 1924 [1].The incidence is about 50% compared with an incidence of 0.4% in infants with normal

chromosomes.CHD is a common cause for morbidity and mortality in early years of life in Down syndrome.Congenital heart disease is the most important factor that determines survival.

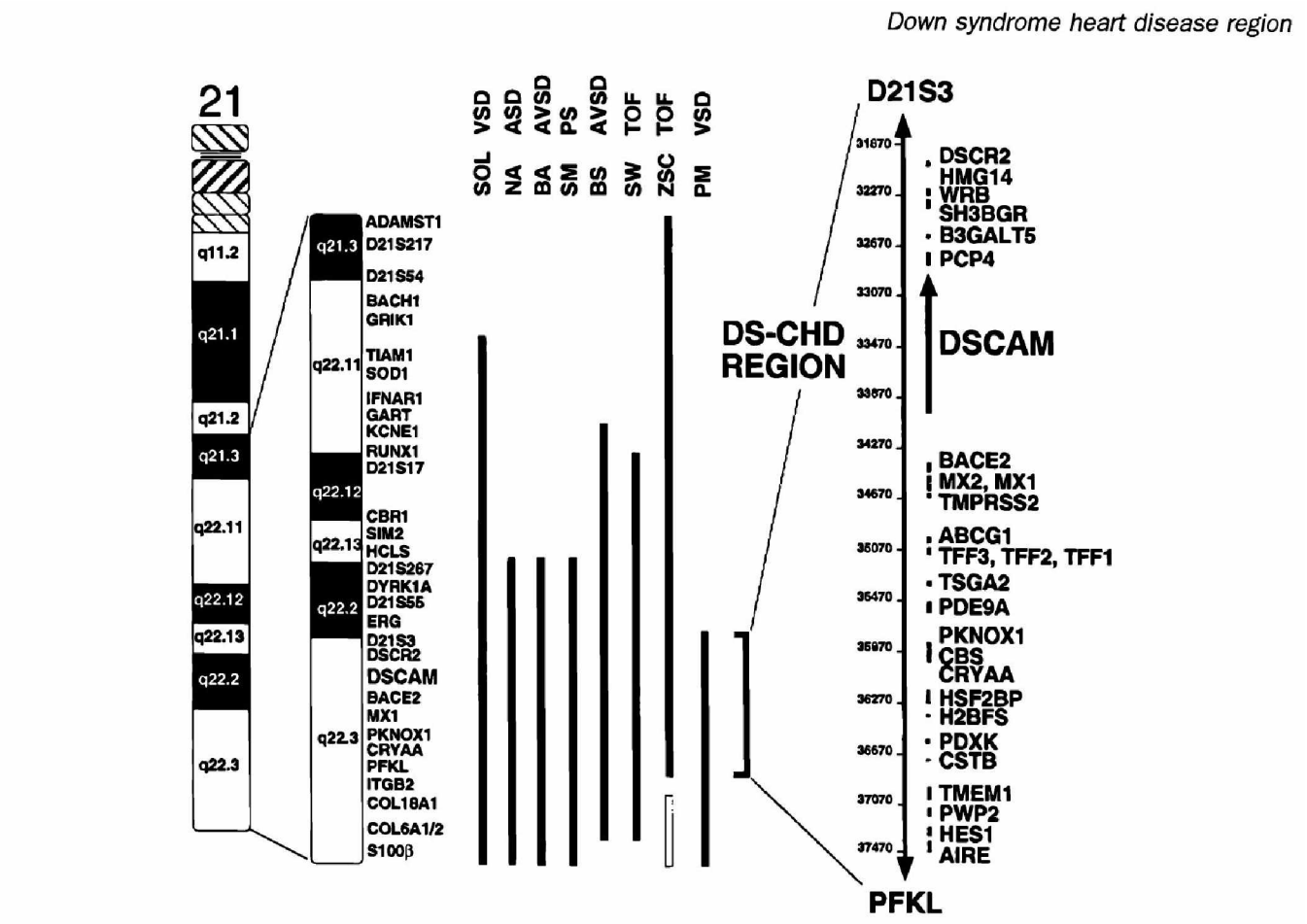
Down syndrome is an important variable in the proclivity for pulmonary vascular disease [1]. The proclivity does not depend on the size of the Ventricular Septal Defect or even on the presence of congenital heart disease. Moreover, pulmonary vascular disease occurs more rapidly in patients with Down syndrome who have left to right shunts. So physicians recommend routine echocardiography at the time of initial diagnosis, even in the absence of other clinical findings [2].

Genetic Basis of Congenital Heart Disease in Down Syndrome [7]

The genes for CHD are located in a small region of the long arm of chromosome 21 from q22.1 to q22.3, the Down syndrome critical region (DSCR). Duplication of one or more genes on chromosome 21 causes failure of the atrioventricular septum to form properly.

The Candidate gene in Down Syndrome-CHD is DSCAM (Down syndrome cell adhesion molecule). Increased “stickiness” of Down syndrome endocardial cushion fibroblasts results in failure to migrate normally.The pathogenesis of Tetralogy of Fallot may involve abnormal migration of neural crest cells.

Down syndrome heart disease region [3]



Between 40 and 50% of babies with Down syndrome have congenital heart defects.Of this 30-40% have complete Atrioventricular septal defects. There must be a high level of clinical suspicion of congenital heart disease for all newborns with the syndrome. It is essential to establish the cardiac status of every child by age 6 weeks. Clinical examination alone is not sufficient to detect all of even the most serious abnormalities. It must always

be remembered that despite a normal echo at birth, children with Down syndrome, like all other children, can develop corpulmonale at a later age secondary to airway problems.

In Down syndrome, Atrioventricular septal defects is the most common congenital heart disease [3] followed by Ventricular septal defect, Atrial Septal defect (ostium secundum type), Patent ductus arteriosus and Tetralogy of Fallot.

Down syndrome is not associated [3] with left heart obstructive lesions, muscular VSD, situs ambiguous, and transposition of the great arteries. It is also not associated with premature atherosclerotic heart disease.

The Congenital Heart diseases frequently reported in Down syndrome include Endocardial cushion defect, Ventricular septal defect, Atrial septal defect(Ostium secundum type) and Patent ductus arteriosus.

Endocardial Cushion defect [8]

It is also called AV canal defect. It may be complete or partial. Of all patients with complete ECD, 30% are children with Down syndrome. Of children with Down syndrome, 40 % have CHD and 40% of the defects are ECD.

- Complete AV Canal defect

Ostium Primum ASD, VSD in the inlet ventricular septum and clefts in the anterior mitral valve and the septal leaflet of the tricuspid valve (forming the common AV valve) are present in the complete form. A single orifice connects the Atrial and Ventricular orifices.

- Partial AV canal defect

When two AV orifices are present without an Interventricular shunt, the defect is called partial ECD or Ostium Primum defect.

Ventricular septal defect

The ventricular septum may be divided into a small membranous portion and a large muscular portion. Muscular septum has three components-the inlet septum, the trabecular septum and the outlet septum.

- 70% of VSD are Perimembranous [8].
- 5-7% of VSD are outlet defects.
- Inlet defects account for 5-8%.
- Trabecular defects are seen in 5-20% of all VSD.

The development of pulmonary vascular disease occurs early in Down syndrome irrespective of the size of the VSD.

Atrial Septal defect

Three types of ASD exist.

- Ostium Secundum defect.
- Ostium Primum defect. It is isolated in 15% of cases and part of ECD in the remainder.
- Sinus venosus type.

II REVIEW OF LITERATURE

Marie T. Mulcahy [9] et al studied 235 cases of Down syndrome in a 10-year study of Down syndrome in Western Australia. Cytogenetic studies performed on 222 subjects confirmed that 95% of cases were Trisomic due to nondisjunction, 4% were Trisomic due to translocation and 1% was mosaic.

Wells GL [10] et al in the University of Alabama reviewed the medical records of 118 newborn infants with Down syndrome. Of 102 infants having echocardiography, 49 (48%) had heart defects; 47 of these had Trisomy 21 and 2 had unbalanced translocation karyotypes. Of the 53 (52%) who did not have heart defects, all had Trisomy except 1 with a mosaic karyotype and 1 with a translocation karyotype. The most common heart malformation was an Atrioventricular canal defect, followed in frequency by Ventricular septal defect, Atrial septal defect, Patent ductus arteriosus and Tetralogy of Fallot.

In a similar study, **Bhatia S [11] et al** in the All India Institute of Medical Sciences, New Delhi, evaluated the utility of echocardiography in assessing the frequency and nature of cardiac malformations in children with Down syndrome. Fifty cases of chromosomally proven Down syndrome were studied. Twenty-two (44%) children had heart diseases. Endocardial cushion defect was the commonest anomaly, followed by Ventricular septal

defect. Three children with heart disease were asymptomatic and had normal X-ray films of chest and ECG.

Venugopalan P [12]et al conducted a prospective study on "Spectrum of congenital heart defects associated with Down Syndrome in high consanguinous Omani population." All children with Down Syndrome referred to the Clinic from 1995-1998 formed the subjects (Group I). Children without Down Syndrome or other known associations of CHD seen at the clinic during the same period served as controls (Group II). Two-dimensional echo-Doppler studies were performed on both groups and the results compared. CHD were detected in 54/90 (60%) children in Group I, compared to 698/2122 (32.9%) in Group II. The common CHD in Group I included secundum Atrial septal defect (ASD; 18/54), atrioventricular septal defect (AVSD; 15/54) and ventricular septal defect (VSD; 14/54), and in Group II included ASD (175/698), VSD (175/698), patent ductus arteriosus (123/698), pulmonary stenosis (PS; 76/698) and AVSD (35/698). AVSD was more common ($P < 0.001$) and PS less common ($P = 0.03$) in Group I. Aortic stenosis, Coarctation of aorta, transposition of great arteries and complex heart diseases were not detected. Compared to several studies from populations with low prevalence of consanguinous marriages, their study showed a higher frequency of CHD in Down syndrome. A high frequency of CHD was documented in Down Syndrome children from a population with widely prevalent consanguinity. AVSD was most frequent in Down

Syndrome. An interesting observation was the relative rarity of some CHD in the Down syndrome population studied.

Krishnadas Nandagopal [7] **et al** discussed the Molecular aspects of Down syndrome. The chromosome 21 contains 225 genes, some of which, located at the Down Syndrome Critical region (DSCR), are thought to contribute to the pathogenesis of Down Syndrome, although function of most of the encoded proteins still remains unknown.

DSCR contains genes coding for enzymes such as superoxide dismutase 1 (SOD1), cystathione beta synthase (CBS), glycinamide ribonucleotide synthase - aminoimidazole ribonucleotide synthase - glycinamide formyl transferase (GARS-AIRS-GART). The function of SOD1 is to remove harmful peroxide linkage. In fetal Down Syndrome brain, an increase in SOD1 activity has been observed, which may cause oxidative stress as well as gestational lipoperoxidation.Increased CBS activity may disrupt homocysteine metabolism, since in vitro studies have shown that increased CBS activity ultimately lead to folate trap.Over expression of Gars-Airs-Gart gene has been reported in fetal Down Syndrome brain. Additionally, elevated blood levels of uric acid, xanthine and hypoxanthine, catabolites of purine metabolism, have also been observed in Down Syndrome babies.

Down syndrome cell adhesion molecule gene (Dscam) at 21q22.2-22.3 is expressed in heart during cardiac development and is implicated in Down Syndrome related congenital heart disease.Altered expression of collagen VI alpha 1, located at 21q22.3, may lead to abnormal neuronal migration since collagen controls cell proliferation and neuronal differentiation.

Freeman SB [13] et al conducted, The Atlanta Down Syndrome Project, a population-based study of infants born with Trisomy 21. Of the 227 Down Syndrome infants, 44% had CHD including 45% Atrioventricular Septal defect (with or without other CHD), 35% Ventricular Septal defect (with or without other CHD), 8% isolated secundum Atrial septal defect, 7%, isolated patent ductus arteriosus, 4% isolated tetralogy of Fallot, and 1% others.

Hartyanszky I [14] et al analyzed 359 cases with Down syndrome and congenital heart defects registered between 1974-1997 in Hungary. The total death rate was 19.9% (70 cases). Mortality in the operated group (85 cases) was 10.5% (9 patients), in the non-operated group (274 cases) 22.2% (61 patients). The death rate was lower in the group with early primary reconstruction (2.3%) than in the group with palliation with reconstruction (15.3%), or in the group with only palliative procedure (20%). These results indicate that the life expectancy of infants and children with Down

syndrome and congenital heart disease after early primary reconstructive procedure is the same as in Down syndrome patients without cardiac defects.

Parvathy U [15] et al investigated the role of cardiac surgery in the management of CHD in Down syndrome. 21 patients with Down syndrome and congenital heart defects were operated. Four (19%) patients had palliative procedures while the rest (81%) underwent primary repair. All survived the operation. The early mortality was 0, while there were 2 (9.5%) late deaths. The number of hospitalizations was markedly reduced according to the parents. Follow-up showed near normal pulmonary artery pressure in 50 percent children with large shunts and a good developmental spurt was seen in 60 percent. From a purely surgical viewpoint, the prognosis for children with Down syndrome and congenital heart disease is good.

Calderon-Colmenero J [16] et al made a retrospective study of patients with Down syndrome that were surgically treated for correction or palliation for their congenital heart disease between January 1996 to December of the 2000 in the National Institute of Cardiology "Ignacio Chavez ".37 patients were surgically treated. The Ventricular septal defect was the most frequent one (35%) and six patients (16%) had Atrioventricular septal defect. Twelve patients (32%) had Patent ductus arteriosus. Three patients had Tetralogy of Fallot and two had Atrial septal defect. The surgical treatment was corrective in 89% patients and the average time of

stay in intensive care unit was 2.5 days. The most frequent complication was rhythm and conduction disorders in 8 patients (22%); three with complete AV block and the mortality was of 8%. In patients with Down syndrome, it is important to have a complete clinical evaluation with an eye toward establishing an opportune surgical treatment.

Mathew P [17] et al. did a long-term follow-up of children with Down syndrome with cardiac lesions. Two hundred and eighty four patients with Down syndrome were seen between 1951-1989. A definitive cardiac diagnosis was established in 47 (41%) patients, of which 38 had long term follow-up. There were 18 survivors (13 in the surgical group and five in the nonsurgical group) and 20 nonsurvivors (four in the surgical group and 16 in the nonsurgical group).They concluded that mortality remains high in such patients treated nonsurgically due to development of pulmonary vascular disease and congestive heart failure.

Shah PS [18] et al. identified seventeen infants with Down syndrome without structural congenital heart disease who presented with persistent pulmonary hypertension in the newborn period. Respiratory distress with or without hypoxia was the presenting feature in these infants. Pulmonary hypertension resolved in the majority of the survivors. Two infants with refractory pulmonary hypertension benefited from patent ductus arteriosus ligation. Autopsies in two infants demonstrated structural lung immaturity.

They suggested that infants with Down syndrome are at risk of developing persistent pulmonary hypertension even in the absence of structural heart disease and these infants should be followed up until resolution of the pulmonary hypertension.

Amudha S [19] et al. analyzed the effect of consanguinity on chromosomal abnormality. Consanguinity was seen in 427 cases (29.14%), 305 cases were confirmed to have Chromosomal abnormality, among them 240 (78.7%) had numerical abnormality and 65 (21.3%) had structural abnormality. The presence of consanguinity in Chromosomal abnormality was seen in 53 cases (17%), including 43 (81.1%) with numerical and 10 (18.9%) with structural abnormality. The effect of consanguinity on Chromosomal abnormality was almost significant, whereas the effect was not significant for the type of Chromosomal abnormality.

Studies by **Khoury MJ [20] et al** showed an upward trend in the birth prevalence of several congenital cardiovascular malformations. He examined changes in the frequency of ascertained cardiovascular malformations among 532 cases of Down syndrome recorded in the Metropolitan Atlanta Congenital Defects Program from 1968 through 1989. Overall, 33% of the cases have reported cardiovascular malformations. However, the frequency of these defects in Down syndrome infants increased dramatically from about 20% in the early 1970s to more than 50%

in the late 1980s. These results show improvement in the ascertainment of cardiovascular malformations among Down syndrome infants in a surveillance population. They are also consistent with the hypothesis that the increasing rates of cardiac defects are related, at least in part, to improved ascertainment of these defects in the population.

Torfs CP [21] et al conducted a study on Anomalies in Down syndrome individuals in a large population based registry. The most common group of all anomalies were cardiac defects, at a rate of 108 times more common in Down Syndrome than non-Down Syndrome. The most common defect of all was the Ventricular septal defect, which is 1000 times more common in Down Syndrome than in non-Down Syndrome. The paper gives the incidence of all cardiac defects found in these children. Of the non-cardiac anomalies, the most common occurring in Down Syndrome were duodenal atresia at 265-fold, Hirschprungs disease at 101-fold, and annular pancreas at 430-fold. The paper lists 17 other anomalies more common with Down Syndrome than non-Down Syndrome.

Paladini D [22] et al assessed the relationship between congenital heart disease and Down syndrome in utero. In the group of 41 fetuses with known Down Syndrome, the incidence of CHD was 56% ([Atrioventricular septal defect (AVSD) 44%, Ventricular septal defect (VSD) 48%], the remainder having other heart defects). Conversely, considering the incidence of Down

Syndrome in fetuses with CHD, 43% of all AVSD(53% of AVSD with normal visceral situs) were associated with Down Syndrome, whereas none of the 39 cases of VSD was associated with Trisomy 21. They have confirmed that more than half of the fetuses with Down syndrome bear a CHD, which is an AVSD in 44% of cases. Conversely, 43% of fetuses with an AVSD have Trisomy 21. For VSD, the situation is controversial, due to the relatively low detection level of this heart defect at the routine mid-trimester obstetric scan.

Maria I [23] et al studied paternal age as a risk factor for Down syndrome. The results obtained in this study give no evidence that paternal age can be considered a risk factor for the conception of a child with Down syndrome.

M.M. Mokhtar and M. Abdel-Fattah [24] evaluated the hypothesis that the Trisomy 21 genome interacts with environmental factors during early pregnancy to increase the risk for birth anomalies in Down syndrome infants. A case–control study on 514 infants with confirmed Down syndrome was carried out from 1 July 1995 to 30 June 2000. Genetic, biological, environmental and reproductive factors were analyzed. Multiple logistic regression analysis showed the following factors to be independently associated with increased risk of congenital heart diseases among Down syndrome patients: parental consanguinity, maternal parents' consanguinity,

mother's antibiotics use in pregnancy, oral contraceptive use and diabetes in the mother. Fever in the mother during pregnancy was associated with increased risk of gastrointestinal anomalies.CHD was present in about 40%–45% of Down syndrome patients. They have been reported in two cases of partial duplications that include the distal region of q21q22, but have not been reported in any cases that do not include this region. CHD were the most common congenital anomalies in patients with Down syndrome in their study (38.5%).

Two recent Egyptian studies reported 38.7% and 36.8% CHD among individuals with Down syndrome. **Stoll et al**. found CHD in 46.2%, while **Kallen et al**. reported a frequency of 26%. Two other studies, one covering 11 years of ascertainment of Down Syndrome by the California Birth Defects Monitoring Program and another of 171 Down Syndrome infants in Texas , found cardiac defects in more than half of the patients.

The results of their study indicate that AVSD was the commonest type of CHD among patients with Down Syndrome, followed by Atrial septal defect and then Patent ductus arteriosus. On comparing their results with those of other studies, Atrioventricular canal lesions, Ventricular septal defect and Patent ductus arteriosus were the most frequent lesions in France. Another study performed in the United States of America reported that the most frequent lesions were Atrioventricular canal and Tetralogy of Fallot.

Evidence of wide variations in the frequency of CHD and their forms suggests that environmental factors can play an important role in the etiology of CHD among Down Syndrome individuals.

Harm Velvis, M.D [3] Pediatric Cardiologist, Albany Medical Center has shown that CHD is a risk factor for survival in Down syndrome.

- In Sweden 1973-1980 ,10 year mortality was 24%, 44% with CHD, 5% without CHD
- In Japan 1997,25 year survival in Down Syndrome without CHD 92%, Down Syndrome with CHD 75%, Down Syndrome with CHD and surgery 88% and without surgery 41%.
- In Sweden 1973-97,among 801 AVSD repairs in Down Syndrome, 5 yr survival was 65% from 1973-77, 90% from 1993-97 and so Down Syndrome is not a risk factor.
- Most recent studies indicate Down Syndrome is not a risk factor for operative mortality.
- Duke 1997 state that Down Syndrome is a risk factor for higher hospital costs.

Frid C[25] **et al**. investigated mortality in relation to congenital malformations. Medical records from all live born children with Down Syndrome delivered between 1973 and 1980 in northern Sweden were studied, and malformations and causes of death were recorded. Out of the 219 children included in the study, a congenital heart defect was reported in 47.5% of subjects, 42.1% of whom had complete Atrioventricular Septal defect. Gastrointestinal tract malformations were present in 7.3% of subjects, and were frequently associated with a cardiac malformation and a very high mortality rate. Other major and minor congenital anomalies were present in 5.5% and 5.5% of subjects, respectively. In the 14.5-year follow-up of 213 children, the rate of survival was 75.6%. Mortality rates within one and 10 years after birth were 14.6% and 23.5%, respectively. Mortality within 10 years differed significantly between children with (44.1%) and without (4.5%) a congenital heart defect. A very high mortality rate was observed among children with a congenital heart defect, especially when it was combined with a gastrointestinal malformation.

Amark K, Sunnegardh J.[26] described the evaluation, decision making, and care of children with a complete Atrioventricular Septal defect. Denial of surgery without obvious medical reasons was more common in the early years, as was parental refusal of offered surgery and institutional care of the children. Improved results in later years encouraged surgical treatment for all these patients, but more liberal attitudes towards use of

echocardiography as a screening method for all newborns with Down syndrome made it possible to plan for correction within the 1st months of life.

HB Laursen [27] , found eighty cases of Down syndrome with congenital heart disease among 1504 children under the age of 15 years. The most common cardiac anomaly, Ventricular septal defect was found in 49 per cent of the 80 cases studied, while the second most frequently encountered anomaly, common Atrioventricular canal was found in 15%.Pulmonary hypertension was found in all of 24 cases of Ventricular septal defect and in 7 of 9 cases of common Atrioventricular canal. The cumulative survival of upto 10 years was 64% for girls and 49% for boys. Death was most commonly the result of pulmonary complications, which occurred in 22 out of the 34 patients who died.

III STUDY JUSTIFICATION

The incidence of congenital heart defects among Down syndrome cases varies from 30 to 65 % in previous studies and the incidence in our setting can be calculated.

The pattern of congenital heart defects varies among geographic areas and the pattern of CHD in our tertiary care centre can be highlighted.

This study will throw light on the various factors like maternal age, order of birth, consanguinity of parents, maternal genetic compositions etc. which are likely to influence the expression of CHD in Down syndrome.

The overall outlook for individuals with Down syndrome has improved dramatically. Many adult patients are healthier, they are better integrated into society, and they have increased longevity than before. Patient education on career selection and prenatal testing in subsequent pregnancies will also form part of the study.

IV OBJECTIVE OF THE STUDY

To determine the incidence and pattern of congenital heart defects in children with karyotypically proved Down syndrome attending a tertiary care centre.

V MATERIALS AND METHODS

1.	Study design	:	Descriptive study
2.	Place of Study	:	Department of Cardiology, Pediatric wards and Genetic clinic of Institute of Child Health and Hospital for children,Egmore,Chennai-8
3.	Study Period	:	August 2004 – December 2005
4.	Study Population	:	
	Inclusion criteria	:	karyotypically proved Down syndrome
5.	Sample size	:	112

Manoeuvre :

All suspected cases of Down syndrome in the age group of 3 months - 12 years,fulfilling the clinical diagnostic criteria will be subjected to karyotyping.All karyotypically proved cases will be included in the study.

After a detailed history and physical examination, the cases will be subjected to Chest X-ray, ECG and Two dimensional Echocardiography with colour Doppler by experienced Paediatric Cardiologist using Hewlett Packard Sonos 2000 phased array imaging system with 5.0 and 3.7 MHz transducers.

Statistical analysis was done using chi square test and p value <0.05 is considered significant.

VI OBSERVATIONS

112 Down syndrome cases were recruited into the study. Among them 55 cases had congenital heart disease (CHD).

Table 1

FREQUENCY OF CHD IN DOWN SYNDROME

No. of Down syndrome cases studied	112
No. of cases with CHD	55
Frequency of CHD in Down syndrome	55/112 x100 = 49.1%

49.1% of cases had congenital heart defects.

Table 2

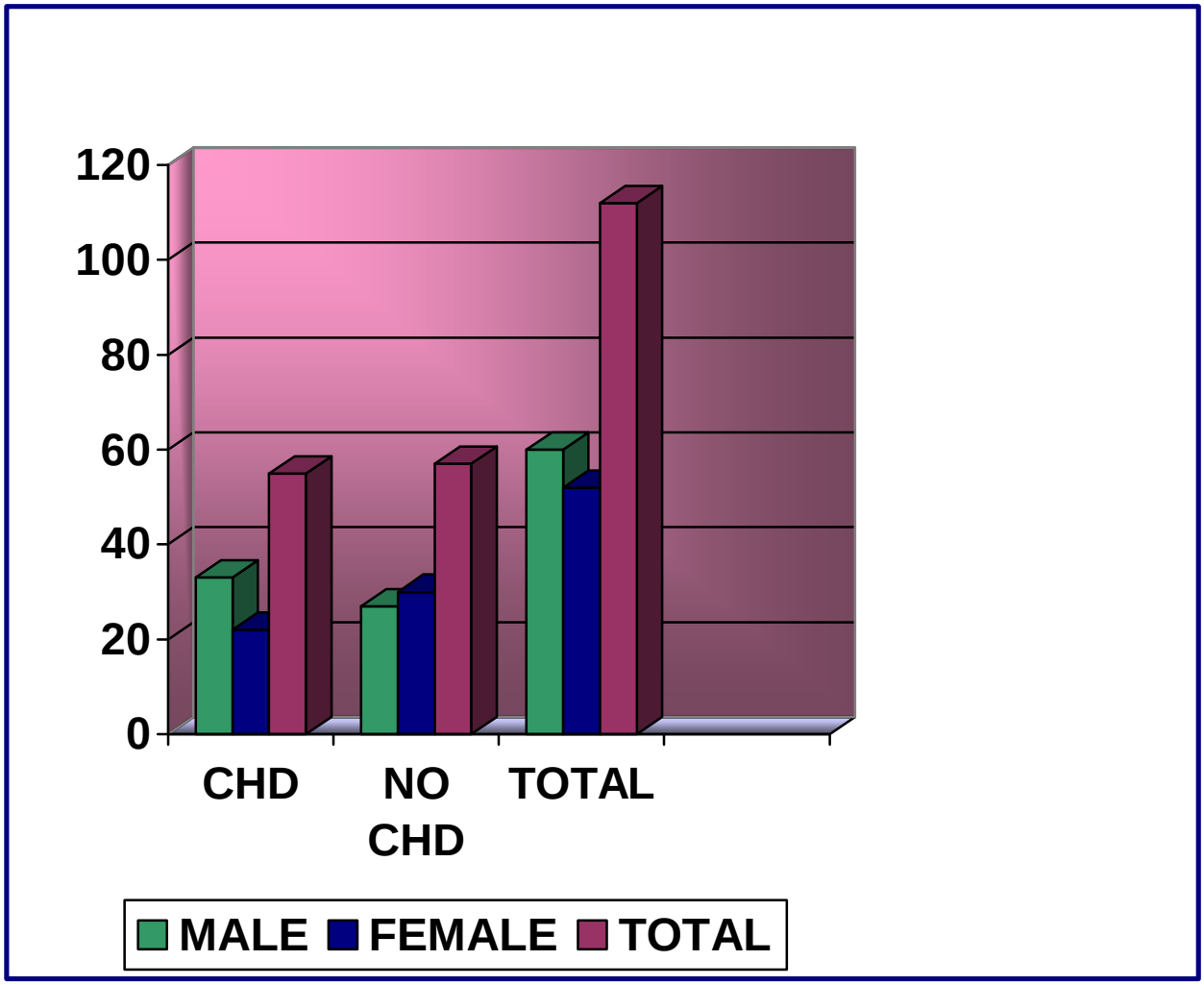
SEX DISTRIBUTION

Sex	CHD		No CHD		Total	
	n	%	n	%	n	%
Male	33	55.0	27	45.0	60	100
Female	22	42.3	30	57.7	52	100
Total	55	49.1	57	50.9	112	100

60 male cases and 52 female cases were recruited into the study with a male-female ratio of 1:0.87.

It was found that 55 % of male Down syndrome cases had CHD, where as only 42.3 % of female cases had CHD.The p value of 0.19 is not statistically significant.

SEX DISTRIBUTION AMONG CASES



Among 112 cases, the male-female ratio was 1:0.87.Among the 60 males, 33 had CHD and among the 52 females only 22(42.3%) had CHD.

Table 3

GENETIC COMPOSITION AMONG CASES

karyotyping	CHD		NO CHD		Total	
	n	%	n	%	n	%
Non-disjunction	51	49.5	52	50.5	103	100
Translocation (14,22)	2	40.0	3	60.0	5	100
Translocation (21,22)	2	66.7	1	33.3	3	100
Mosaicism	0	0	1	100	1	100

About 92% (103/112) of cases belonged to Non-disjunction, among which 49.5% had CHD.Translocation was noted in 8 cases (7%).About 67% of cases with Translocation (21,22) had CHD.Mosaicism is noted in one case which did not have any CHD.The p value of 0.68 is not statistically significant.

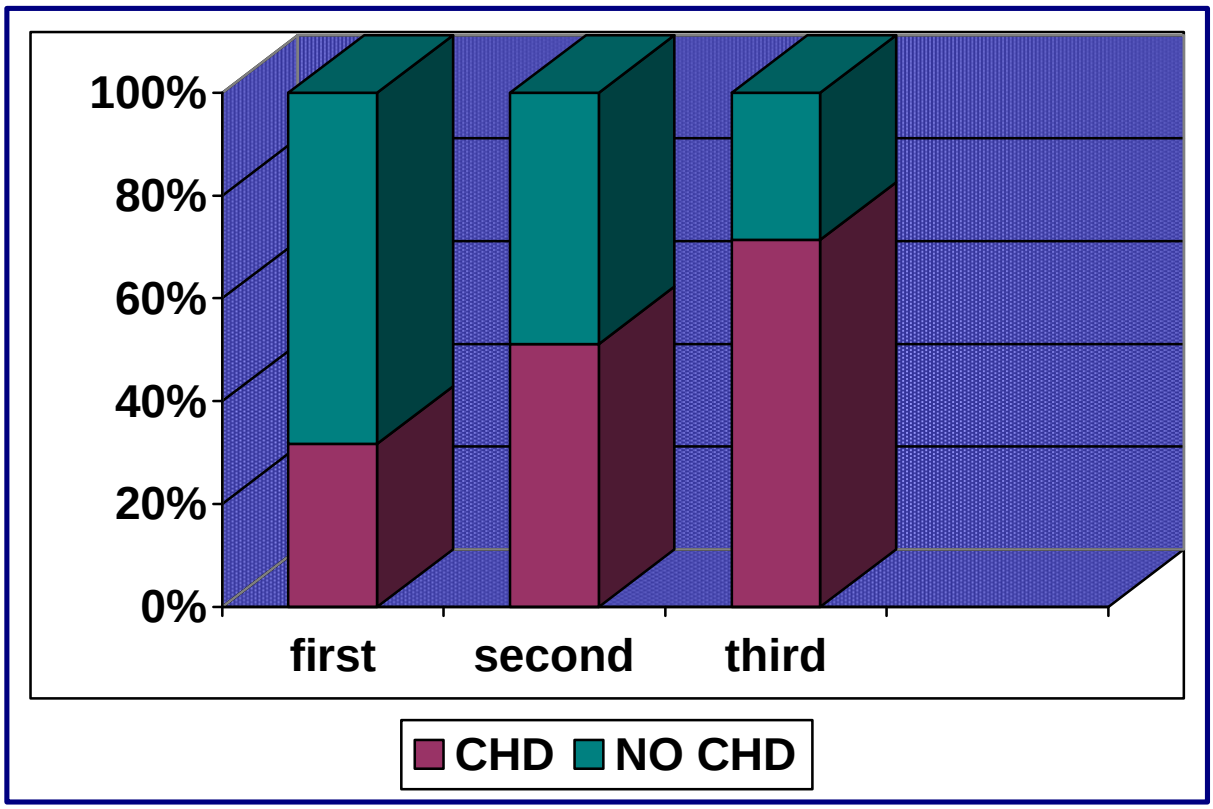
Table 4

ORDER OF BIRTH

Birth order	CHD		NO CHD		Total	
	n	%	n	%	n	%
First	13	31.7	28	68.3	41	100
Second	22	51.2	21	48.8	33	100
Third and above	20	71.4	8	28.6	28	100

31.7% of Down syndrome children born of the first order had CHD.In the second order birth about 51.2% cases had CHD whereas 20 cases (71.4%) born of the third order had CHD.The p value of 0.005 is statistically significant.

ORDER OF BIRTH



It is observed that about 71.4% of cases belonging to the third order and above had CHD, whereas it is only 31.7% in the first order and 51.2% in the second order births.

Table 5

CONSANGUINITY OF PARENTS

Consanguinity	CHD		NO CHD		TOTAL	
	n	%	n	%	n	%
2nd degree	3	100	0	0	3	100
3rd degree	18	58.1	13	41.9	31	100
Non - consanguinous	34	43.6	44	56.4	78	100

All the 3 cases (100%) of Down syndrome born of 2nd degree consanguinous parents had CHD and 58.1% of cases born to 3rd degree consanguinous parents had CHD.It dropped to 43.6% when both parents were non-consanguinous.The p value is 0.08.

Table 6

MATERNAL AGE

Maternal age	CHD		NO CHD		Total	
	n	%	n	%	n	%
< = 20years	4	66.7	2	33.3	6	100
21 - 25	11	30.6	25	69.4	36	100
26 – 30	25	51.0	24	49.0	49	100
31 and above	15	71.4	6	28.6	21	100

66.7% of Down syndrome cases born to mothers in the age <20years had CHD .In the maternal age group of 21-25 years, 30.6 % of cases and in the age group of 26-30 years, 51% of cases had CHD.When the maternal age is above 31 years the chances of CHD in Down syndrome increases to 71.4%.The calculated p value of 0.02 is statistically significant.

Table 7

PATERNAL AGE

Paternal age in years	CHD		NO CHD		Total	
	n	%	n	%	n	%
21- 30	20	39.2	31	60.8	51	100
31 –40	33	55.9	26	44.1	59	100
41& above	2	100	0	0	2	100

Tabulation of Paternal age shows that, in the age group of 21-30 years the risk of being born with a CHD is 39.2%.But in the age group of 31-40 years the risk rises to 55.9% and when the age is 40 and above there is 100% chances of CHD.The p value was calculated to be 0.08.

Table 8

MATERNAL GENETIC COMPOSITION

	CHD		NO CHD		Total	
	n	%	n	%	n	%
Normal	54	48.6	57	100	111	100
Abnormal	1	100	0	0	1	100

The chromosomal pattern of mothers of children with Down syndrome was abnormal in only one case. It was a balanced translocation and she was a carrier with chromosomal pattern of 45XX,-14,-21(i.e.) one 14 chromosome, one 21 chromosome, and one fused 14, 21 chromosome giving rise to a total of 45 chromosomes and was phenotypically normal. The Down child born to that carrier mother had CHD- Endocardial cushion defect. The Chromosomal pattern in the remaining mothers was normal. The p value of 0.49 is not statistically significant.

Table 9

H/o PREVIOUS ABORTION

H/o previous abortion	CHD		NO CHD		TOTAL	
	n	%	n	%	n	%
Yes	11	68.8	5	31.2	16	100
No	44	45.8	52	54.2	96	100

Among them 112 cases,16 mothers gave history of previous abortions, among which 11 cases (68.8%) had CHD.In the remaining 96 cases, CHD was present in 44 cases(45.8%).The p value was calculated to be 0.11.

Table 10

CHD IN DOWN CHILDREN BORN

AFTER PREVIOUS ABORTION IN MOTHER

CHD	**No. of cases**
Atrial septal defect (ostium secundum type)	5
Ventricular septal defect	2
Patent ductus arteriosus	2
Tetralogy of Fallot	2
Total	11

Among the 11 cases born after previous abortions in the mother, 5 (45.5%) had Atrial septal defect. Ventricular septal defect,Patent ductus arteriosus and Tetralogy of Fallot were detected in 2 cases each.

Table 11

FAMILY H/O DOWN SYNDROME

Family H/o Down syndrome	CHD		NO CHD		TOTAL	
	n	%	n	%	n	%
Yes	1	33.3	2	66.7	3	100
No	54	49.5	55	50.5	109	100

In 3 cases family history was positive, i.e. there was a previous Down syndrome child in the family. Among them 1 case had CHD and the p value of 1.00 is not statistically significant.

Table 12

ASSOCIATED FINDINGS

Non cardiac anomaly	**n**	**%**
None	104	92.9
Cryptorchidism	3	2.7
Hypothyroidism	3	2.7
Hirschprungs disease	1	0.9
Neonatal cholestasis	1	0.9

In 92.9 % of cases included in the study, no major associated finding was detected. Remaining 7.1% had some form of noncardiac anomaly. Three each had Hypothyroidism and Cryptorchidism and one case of Hirschprungs disease and another case of Neonatal cholestasis was detected.

Table 13

PATTERN OF CHD ASSOCIATED WITH NONCARDIAC ANOMALIES

CHD	No of cases
No CHD	2
Ventricular septal defect	2
Endocardial cushion defect	2
Patent ductus arteriosus	2

8 cases among the 112 cases had non cardiac anomalies.Among them two did not have any CHD. Ventricular septal defect, Endocardial cushion defect and Patent ductus arteriosus were detected in 2 cases each.

The case with Hirschprungs disease had a Ventricular septal defect. Two cases of Hypothyroidism had Endocardial cushion defect and another had a Ventricular Septal Defect.Patent ductus arteriosus was noted in 2 cases of Cryptorchidism.

Table 14

PATTERN OF CHD IN DOWN SYNDROME

S.No	**CHD**	**N**	**%**
1	Ventricular Septal defect	19	34.5
2	Endocardial cushion defect (Complete & Partial)	12	21.8
3	Atrial Septal defect (OS type)	11	20.0
4	Patent ductus arteriosus	8	14.5
5	Tetralogy of Fallot	3	5.4
6	Others	2	3.6
	Total	55	

Ventricular Septal defect is the most common defect identified in 34.5 % of cases with CHD followed by Endocardial cushion defect in 21.8% and Atrial Septal defect in 20% of cases. Patent ductus arteriosus was detected in 14.5% of cases.Tetralogy of Fallot was found in 2 cases and one case had Coarctation of Aorta and another had Dextrocardia with situs inversus totalis.

Table 15

UNIVARIATE ANALYSIS

Variable	OR	95% C.I	p-value
Order of birth			
1st	1.0	Reference	
2nd	2.3	0.9,5.5	0.01
3rd & greater	5.4	1.9 , 15.4	
Maternal age			
<= 20 years	4.5	0.7 , 28.6	
21-25 years	1.0	Reference	0.03
26-30 years	2.4	1.0 , 5.8	
31-35 years	5.7	1.7 , 18.5	

Order of birth and maternal age are statistically significant risk factors for the expression of CHD in Down Syndrome.

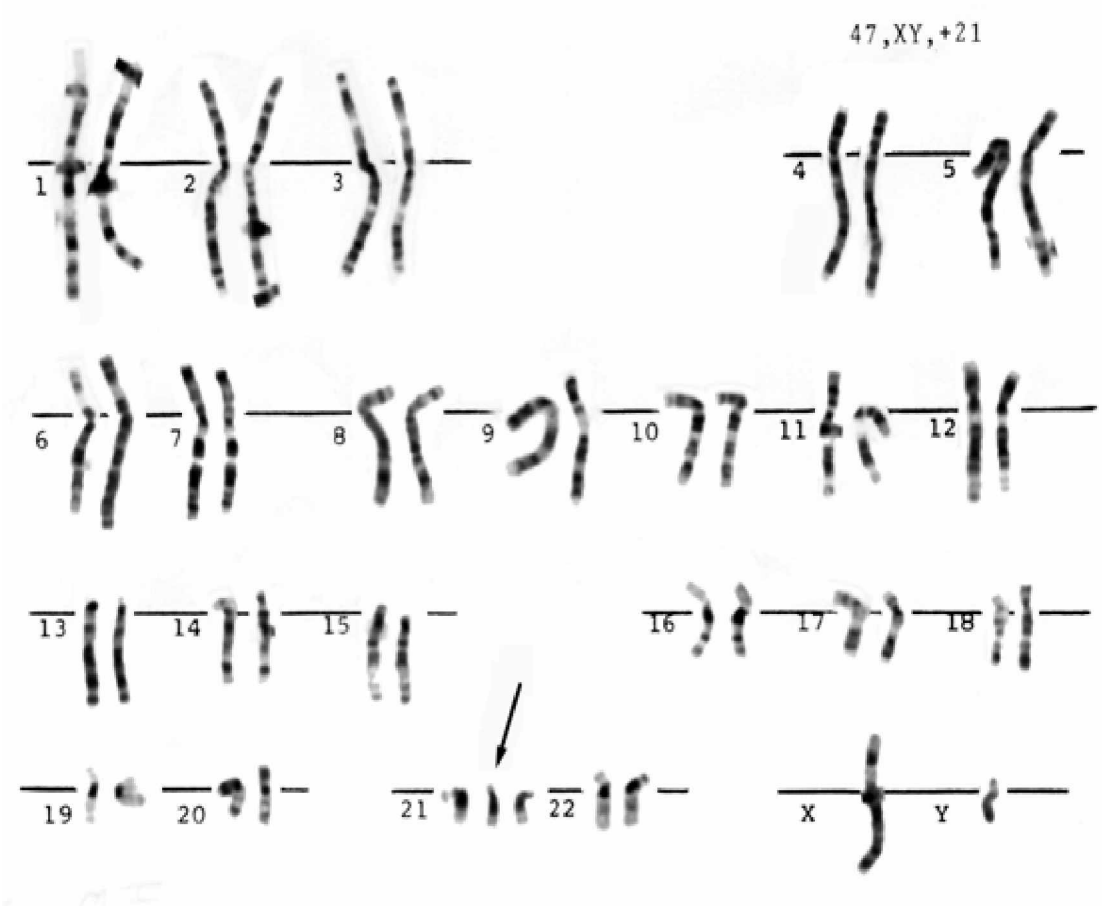
Table 16

MULTIPLE LOGISTIC REGRESSION

Variable	OR	95% C.I	p-value
Order of birth			
1st	1.0	Reference	
2nd	2.0	0.8 , 5.1	0.04
3rd & greater	4.2	1.4 , 12.9	
Maternal age			
<= 20 years	5.1	0.8 , 33.5	
21-25 years	1.0	Reference	
26-30 years	1.9	0.8 , 4.9	0.13
31-35 years	3.5	1.0 , 12.4	

When evaluated using multivariate analysis, Order of birth is the only significant risk factor for the expression of CHD in Down syndrome.

Karyotyping image of Trisomy 21



There is an extra chromosome 21 accounting for the Trisomy.

VII DISCUSSION

Congenital heart disease is the common cause for long term morbidity and mortality in Down syndrome. Between 40-50% of babies with Down syndrome have congenital heart defects [28]. Of these 30-40% have complete Atrioventricular septal defects. Most AVSD can be successfully treated if the diagnosis is made and the baby referred for full corrective surgery before irreversible pulmonary vascular disease is established.

The incidence of Congenital heart defects in our present study is 49.1% .Various published studies have reported frequencies ranging from 30-65% [17].Studies by **Wells GL [10] et al** in the University of Alabama showed an incidence of 48% close to our statistics. In a similar study by **Bhatia S [11] et al** in the All India Institute of Medical Sciences, New Delhi, the incidence was 44%.

The incidence of CHD in Down syndrome varies among geographical areas. The incidence of CHD in our present study is comparable to that conducted in Alabama, Atlanta, France and Saudi Arabia.

Table 17

Comparison of the incidence of CHD in Down Syndrome[17]

in various places

S.No	**Place of study**	**%**
1	Present study	49.1
2	Alabama	48
3	Atlanta	44
4	Australia	33
5	California	56
6	France	46
7	Oman	60
8	Saudi Arabia	48
9	Turkey	65

The male-female ratio in the present study is 1: 0.85 which corresponds to the study done by **Venugopalan [12] et al** in Oman.55% of male children with Down syndrome had CHD in our present study whereas only 42.3% of female children had CHD.So the possibility is more for a male child with a Down syndrome to be born with a CHD but it is not statistically significant.

In 92% of cases, the cause for Down syndrome is a Non- disjunction. Half of them had CHD.A translocation (14,21) was found in 5 cases and 40 % of them had CHD.Translocation(21,22) was detected in 3 cases and 2 of them had CHD.One child was found to be mosaic and no CHD was detected. In a study by **Wells GL [10] et al** in the University of Alabama, 49 (48%) had heart defects; 47 of these had Trisomy 21 and 2 had unbalanced translocation karyotypes.Of the 53 (52%) who did not have heart defects, all had Trisomy except 1 with a mosaic karyotype and 1 with a translocation karyotype.So a translocation carries more risk of being born with a CHD.

As the birth order of the child increases, the chances of being born with a CHD also increases. In our present study about 71% of Down syndrome born of the third order had CHD against 31.7% and 51.2% in the first order and second order respectively.This may be compounded by the maternal age which increases as the order of birth increases. The p value is 0.005 which is statistically significant.

A case–control study on 514 infants with confirmed Down syndrome by **M.M. Mokhtar and M. Abdel-Fattah** [24] evaluated the hypothesis that the Trisomy 21 genome interacts with environmental factors during early pregnancy to increase the risk for birth anomalies in Down syndrome. Multiple logistic regression analysis showed the following factors to be

independently associated with increased risk of congenital heart diseases among Down syndrome patients: parental consanguinity, maternal parents consanguinity, mother's antibiotics use in pregnancy, oral contraceptive use and diabetes in the mother.

Consanguinity increases the risk of CHD in the general population. Likewise when the Down syndrome child is born of consanguinous marriage it has more chances of being born with a CHD.In our study all the 3 cases of 2^{nd} degree consanguinity had CHD.58 % of cases born of 3^{rd} degree consanguinity had CHD.Among non-consanguinous parentage only 43% had CHD. Consanguinous marriage is common in Arab countries, exceeding 50% in some communities. In a study by **Venugopalan [12] et al** in Oman,it was found that in high consanguinous areas the incidence of CHD in Down is more like in Turkey where it is 65% and in Oman it is 60%.

As maternal age advances, the risk of giving birth to a Down syndrome child also increases.35 years is taken as the cut off, above which prenatal testing is mandatory. In our present study, in the mother age group of < =20 years,66% of Down syndrome babies born had CHD.This may because of the small proportion (6) of mothers in that age group. In the age group 21-25 it is 30% and in 26-30 it is 51%.The risk is higher in the age group more than 31 years, where 71 % of babies born had CHD.It is statistically significant.

Studies by **Maria I [23] et al** give no evidence that paternal age can be considered a risk factor for the conception of a child with Down Syndrome**.**In our study when the paternal age was between 21-30 years, the incidence of CHD was 39% and in the 31-40 age group it was 55%.In 2 cases, the father age was above 40 years and both of them had CHD.It is not statistically significant.

Genetic pattern was abnormal in the mother of one child. It was a balanced translocation. She was asymptomatic.The Down child born to that mother had CHD and is statistically insignificant. **Paul J. Benke [29]** showed in about one-fourth of translocation Down Syndrome individuals, the translocation is inherited. When it runs in families, the carriers are usually unaware that they have a translocation because there are no problems for the balanced translocation carrier. Only with the birth of a Down syndrome child or Down Syndrome fetus by miscarriage, does the couple find out one parent is a translocation carrier.

Sixteen mothers gave history of previous abortions before the birth of the Down child.Among them 11 cases (68%) had CHD.Atrial Septal defect was detected in 5 among the 11 cases and Ventricular septal defect, Endocardial cushion defect and Patent ductus arteriosus in 2 each.

In 3 occasions, there was a previous Down syndrome child in the family.CHD was found in one out of the three cases.

Hypothyroidism(2.7%) and Cryptorchidism(2.7%) was detected in 3 cases each.One child had Hirschprungs disease(0.9%).93% of cases were free of associated non-cardiac abnormalities. The reported incidence of gastrointestinal anomalies by **Frid C[25] et al is 7.5%.**The low incidence reported in our study may be due to the early operative mortality associated with these lesions.

In our present study Ventricular septal defect(VSD) is the most common abnormality accounting for 34.5% of CHD followed by Endocardial cushion defect(22%).Even though most studies point to Atrioventricular septal defect(AVSD) as the most common abnormality, there are studies depicting VSD as the most common defect.

HB Laursen [27] , found eighty cases of Down syndrome with congenital heart disease among 1504 children under the age of 15 years. The most common cardiac anomaly, Ventricular septal defect was found in 49 per cent of the 80 cases studied, while the second most frequently encountered anomaly, common Atrioventricular canal was found in 15%.

Paladini D [22] et al assessed the relationship between congenital heart disease (CHD) and Down syndrome in utero. In the group of 41 fetuses with known Down syndrome, the incidence of CHD was 56% [Ventricular septal defect in 48%, Atrioventricular septal defect (AVSD) in 44% and the remainder having other heart defects].These results are comparable with our

study. In Hong Kong, studies report [12] Ventricular septal defect as the most common anomaly and in Turkey the most common anomaly is Atrial septal defect.

A study by **Bhatia S [3] et al** in the All India Institute of Medical Sciences, New Delhi, on fifty cases of chromosomally proven Down syndrome showed twenty-two (44%) children had heart diseases. Endocardial cushion defect was the commonest anomaly, followed by Ventricular septal defect.

Torfs CP [21] et al conducted a study on Anomalies in Down syndrome individuals in a large population based registry. The most common group of all anomalies were cardiac defects, at a rate of 108 times more common in Down Syndrome than non-Down Syndrome. The most common defect of all was the Ventricular septal defect, which is 1000 times more common in Down syndrome than in non-Down Syndrome.

Table 18

Comparison of CHD in Down Syndrome from various studies

	Study by	% of CHD	Most common Cardiac anomaly	%
1	Present study	49.2	Ventricular septal defect	34.5
2	Freeman SB [13] et al	44	Endocardial cushion defect	45
3	Calderon-Colmenero J[16] et al	%NR	Ventricular septal defect	35
4	Paladini D [22] et al	56	Ventricular septal defect	48
5	Frid C [25] et al.	47.5	Endocardial cushion defect	42.1
6	Venugopalan P [12] et al	60	Endocardial cushion defect	%NR
7	Bhatia S [11] et al	44	Endocardial cushion defect	%NR
8	Wells GL [10] et al	48	Endocardial cushion defect	%NR
9	HB Laursen [27] et al	%NR	Ventricular septal defect	61

% NR= percentage not reported in the study.

The frequency of Patent ductus arteriosus reported in our study is 14.5 % and that of Tetralogy of Fallot is 5.4% , which is similar to previous reports[12]. Another finding similar to other reports is the absence of certain CHD (left heart obstructive lesions, transposition of the great arteries and complex CHD).It is possible that Down syndrome does not have significant role in the pathogenesis of these lesions.

VIII SUMMARY AND CONCLUSION

- Incidence of Congenital Heart defects in Down syndrome is 49.2%.
- Ventricular Septal defect(34.5%) is the most common CHD followed by Endocardial cushion defect(21.8%).
- Incidence of CHD is more in a male with Down syndrome(55%) than in a female(42.8%).
- Down syndrome is due to non-disjunction in 92% of cases and translocation in 7% of cases.1% is due to mosaicism.Percentage of CHD was more in translocation (67%) than due to non-disjunction(49.5%).
- As the order of birth increases, the chances of being born with a CHD also increases.
- Advanced maternal age is not only a risk factor for increased incidence of Down syndrome, but also an independent risk factor for CHD.Percentage of CHD when maternal age is above 30 years is 71%.

- Risk of CHD in down syndrome is 100% when born to 2nd degree consanguinous parents and 58.1%, if it is 3rd degree and 43.6% if non-consanguinous.

- 68.8% of Down syndrome cases born after a previous history of abortion in the mother had some form of CHD.Atrial septal defect was detected in 5 cases among the 11.

- 7.1% of cases had some form of noncardiac anomaly.

- Hypothyroidism(2.7%) and Cryptorchidism(2.7%) was detected in 3 cases each. One child had Hirschprungs disease(0.9%) and another had Neonatal cholestasis syndrome(0.9%).

Congenital Heart Disease in Down syndrome

PROFORMA

1. Name : I.P.No :

2. Age : Genetic No :

3. Sex : CD No :

4. Place :

5. Pedigree Chart

6. Mothers age at conception: Fathers age:

7.Family History of Down syndrome:

8.History

breathing difficulty :

feeding problems :

facial puffiness/pedal edema :

cyanosis :

recurrent respiratory tract infection :

9.Physical exam

Respiratory distress :

Cyanosis :

Clubbing :

Auscultation :

10. Karyotyping:

Case :

Parents :

11. Echo finding:

12. Associated abnormalities:

BIBLIOGRAPHY

1. Joseph K .Perloff, The Clinical Recognition of congenital Heart disease, 5th edition, Elsevier science (USA) 2003, pages 233-350.

2. Richard E. Behrman, Robert M .Kleigman, Hal B.Jenson, Nelson Text Book of Pediatrics, 17 th edition, Elsevier science (USA).

3. Harm Velvis, M.D, Pediatric Cardiologist, Albany Medical Center, Congenital Heart Disease in Down Syndrome.

4. Neil McInthosh, Peter Helms, Rosalind Smyth, Forfar and Arneil's Text Book Of Pediatrics, 6th edition, Churchill Livingstone pages 415-417.

5. Andrew D Carothers, Christina A Hecht, Ernest B Hook, International variation in reported livebirth prevalence rates of Down syndrome, adjusted for maternal age, J Med Genet 1999;36:386-393.

6. David S. Newberger, M.D, Down Syndrome: Prenatal Risk Assessment and Diagnosis, Am Fam Physician 2000; 62:825-32,837-8.

7. Krishnadas Nandagopal, Samikshan Dutta, Prasanta Kumar Gangopadhyay, Molecular Aspects of Down Syndrome, Indian Pediatrics 2005; 42:339-344.

8. Myung K.Park ,Pediatric Cardiology for practitioners,4 th edition, Harcourt(India) private limited, pages 129-152.

9. Marie T. Mulcahy, Down syndrome in Western Australia: Cytogenetics and incidence, Hum Genet. 1979;48(1): 67-72.

10. Wells GL, Barker SE, Finley SC, Colvin EV, Finley WH, Congenital heart disease in infants with Down syndrome, South Med J. 1994 ;87(7):724-7.

11. Bhatia S, Verma IC, Shrivastava S, Congenital heart disease in Down syndrome: an echocardiographic study, Indian Pediatr 1992 ; 29(9):1113-6.

12. P. Venugopalan, A. K. Agarwal, Spectrum of Congenital Heart Defects Associated with Down syndrome in High Consanguinous Omani Population, Indian Pediatrics 2003; 40:398-403

13. Freeman SB, Taft LF, Dooley KJ, Allran K, Sherman SL, Hassold TJ, Khoury MJ, Saker DM, Population based study of congenital heart defects in Down syndrome, Am J Med Genet 1998 16;80(3):213-7.

14. Hartyanszky I, Dobos M, Szabolcs J, Mihalyi S, Lozsadi K, Fekete G,Life expectancy in Down syndrome infants and children with congenital heart defects, 1974-1997, Orv Hetil. 2000 ; 141(39):2119-22.

15. Parvathy U, Balakrishnan KR, Ranjith MS, Saldanha R, Sai S, Vakamudi M, Surgical experience with congenital heart disease in Down syndrome, : Indian Heart J. 2000 ;52(4):438-41.

16. Calderon-Colmenero J, Flores A, Ramirez S, Patino-Bahena E, Zabal C, Garcia-Montes JA, Rizo S, Buendia A, Attie F, Surgical treatment results of congenital heart defects in children with Down syndrome, Arch Cardiol Mex. 2004 ;74(1):39-44.

17. Mathew P, Moodie D, Sterba R, Murphy D, Rosenkranz E, Homa A, Long-term follow-up of children with Down syndrome with cardiac lesions, Clin Pediatr (Phila) 1991 ; 30(2):128.

18. Shah PS, Hellmann J, Adatia I, Clinical characteristics and follow up of Down syndrome infants without congenital heart disease who presented with persistent pulmonary hypertension of newborn, J Perinat Med. 2004;32(2):168-70.

19. Amudha S, Aruna N, Rajangam S, Consanguinity and chromosomal abnormality, Indian Journal of Human Genetics, 2005;11(2):108-110.

20. Khoury MJ, Erickson JD, Improved ascertainment of cardiovascular malformations in infants with Down syndrome, Atlanta, 1968 through 1989. Implications for the interpretation of increasing rates of cardiovascular malformations in surveillance systems, Am J Epidemiol. 1992 ; 136(12):1457-64.

21. Torfs CP, Christianson RE, Anomalies in Down syndrome individuals in a large population-based registry, Am J Med Genet 1998 ; 77(5):431-438.

22. Paladini D, Tartaglione A, Agangi A, Teodoro A, Forleo F, Borghese A, Martinelli P,The association between congenital heart disease and Down syndrome in prenatal life,Ultrasound Obstet Gynecol. 2000 ;15(2):104-8.

23. María I, de Michelena MI, Burstein E, Lama JR, Vasquez JC, Paternal age as a risk factor for Down syndrome, Am J Med Genet. 1993 ; 45(6):679-82.

24. M.M. Mokhtar and M. Abdel-Fattah, Major birth defects among infants with Down syndrome in Alexandria, Egypt (1995–2000): trends and risk factors , Eastern Mediterranean Health Journal, Volume 7, No. 3, 2001, 441- 451.

25. Frid C, Drott P, Lundell B, Rasmussen F, Anneren G. Mortality in Down syndrome in relation to congenital malformations; J Intellect Disabil Res. 1999 ;43 (Pt 3):234-41.

26. Kerstin Amark, Jan Sunnegardh , The effect of changing attitudes to Down syndrome in the management of complete atrioventricular septal defects; Arch Dis Child 1999;81:151-154.

27. Laursen HB, Congenital heart disease in Down syndrome; Br Heart J. 1976 ;38(1):32-8.

28 Tubman., TRJ., Shields, MD., Craig, BQ., Mulholland, HC., Nevin, NC., 991) Congenital heart disease in Down syndrome; Two year prospective early screening study. BMJ; 302 : 1425-1427.