

Epidemiology and Etiology of Congenital Heart Diseases

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1. Introduction

Congenital heart disease (CHD), the most common type of birth defect, is an abnormal cardio-circulatory structure or function present at birth, although the disease is often discovered later in life. During prenatal life, the incidence of cardiac defect is higher due to affected fetuses that are aborted. CHD stems from an alteration in the embryonic development from a normal structure, or a failure of a structure to properly develop beyond an early stage of embryonic and fetal development. The non-typical patterns of cardio-circulatory flow owing to an anatomical defect may significantly influence the structural and functional development of the remainder of the circulatory system. Additionally, postnatal events have a marked impact on the clinical presentation of a specific isolated malformation.

As CHD accounts for the most frequent cause of lethal malformation among infants, CHD is also considered a major problem affecting public health worldwide (Bernier et al., 2010). Despite the continuing progress in non-surgical and surgical treatments that allow for the survival of the majority of patients, some complex heart diseases are still associated with substantial morbidity and mortality. According to a report, 45% of infant deaths owing to congenital anomalies were caused by CHD in Western Europe. In Latin America, North America, Eastern Europe and the South Pacific region (including Japan) this proportion has been reported to be 35%, 37%, 42% and 48%, respectively (Botto, 2003). 20% of spontaneous abortions and 10% of stillbirths are attributed to CHD (Botto, 2001). CHD causes high morbidity and mortality among infants, and affects the quality of life during childhood and adulthood, depending on the progression of the disease (Majnener et al., 2008). It also affects social interactions and the quality of life for parents of children with CHD.

While newborns with the cardiac disorder are symptomatic and identified soon after birth, many others are not diagnosed until the disease progresses into a severe stage. Data from the Northern Region Pediatric Cardiology database suggest around 1 in 4 cases of congenital heart disease in the UK are diagnosed later in childhood (Petersen et al., 2003). The signs and symptoms of heart disease depend on the type and severity of the disease. Children with critical cardiac lesion generally exhibit high morbidity and mortality because the risk of morbidity and mortality increases as treatment and diagnosis is delayed.

The screening process is very important to detect congenital heart malformations. One of the major contributors to increased mortality and morbidity is clinical deterioration and heart

failure prior to diagnosis and treatment. Early detection of CHD in the fetus or in the asymptomatic period immediately after birth will reduce clinical deterioration by instigation of appropriate management of the disease. Technical improvements in sonographic systems during the past two decades have helped the obstetric sonographers detect congenital heart anomalies, especially in experienced hands. A fetal cardiac screening with fetal echocardiography allows for early detection of CHD allowing for the option of pregnancy termination in cases of complicated defects. In areas where termination of pregnancy is a realistic and supported option, a universal sonographic screening of all pregnancies with an average reported sensitivity of 35% and a termination rate of 43% following prenatal diagnosis, would result in a 15% overall reduction of the prevalence of most severe forms of CHD (Germanakis & Sifakis, 2006). The information from 20 registries of congenital malformation in 12 European countries demonstrated the overall prenatal detection rate of CHD was 25% (Garne et al, 2001). Echocardiography can be used for screening in live birth infants. Newborn echocardiographic screening enables pediatricians to detect abnormal cardiac characteristics early and accurately, especially heart diseases without murmur such as coarctation of the aorta (Coarc), atrial septal defect (ASD), atrioventricular septal defect (AVSD), hypertrophic cardiomyopathy and cardiac tumor. In addition, cardiopulmonary information obtained from the echocardiographic examination can be useful for neonatal care providers (Wang et al., 2007).

The echocardiographic screening in developing countries may be difficult due to lack of echocardiographic machines and sonographers. Fortunately, most of patients with CHDs can be detected by clinical presentations and physical examinations. Approximately 90% of patients with CHDs were referred for cardiovascular evaluation with cardiac murmur, arrhythmia, cyanosis, palpitation and chest pain. False positives occurred 22.3% of the time with innocent (functional) murmur, and non organic chest pain or other non cardiac diagnosis (Borzouee & Jannati, 2008). In a Toronto study, 0.28% of the school-age children were found to have innocent murmurs (Rose et al., 1964). Currently, infants are screened to detect CHD by clinical and physical examination after birth and another examination at 6-8 weeks. However, this screening program can detect only 50% of congenital defects (Knowles et al., 2005). Thailand has a lack of pediatric doctors and cardiologists, and, therefore, there has been training available for qualified nurses and health officers to screen patients for CHD using clinical and physical examinations. These screenings are not only for infants, but also for school-age children and adults too. Although we detected a lot of false positives from innocent murmurs and abnormal clinical presentations, we recognized many undiagnosed CHD patients and have found many CHD patients who choose to undergo proper treatment (Sayasathid et al., 2009, 2010). Another tool to recognize CHD is pulse oximetry. It can detect cyanotic CHD which are not detected by routine examination with high specificity (99.8%) and very low false positive rate (2%) although the sensitivity was only 63%. Either functional or fractional oxygen saturation was measured by pulse oximetry with oxygen saturation below 95% as the cut-off level in most studies (Thangaratinam et al., 2007). Children who are suspected of having CHD should be referred to a pediatric cardiologist for definitive diagnosis, suitable treatment and follow up.

Nonetheless, the cost-effectiveness remains a concern, especially in developing countries. Costs are very different between screening using echocardiography versus clinical examination. A cost-effectiveness analysis study for screening 100,000 newborns in the UK showed the total program cost £300,000 for clinical examination, £480,000 for pulse oximetry and £3.54 million for screening echocardiography. The addition cost per additional timely

diagnosis of life-threatening CHD ranges from £4,900 for pulse oximetry to £4.5 million for screening echocardiography (Knowles et al., 2005). Hence, the public health officers need to consider appropriate methods of CHD detections for their countries.

Although, there have been many studies to find the etiology of CHD, the cause of most CHDs continues to be unknown. Some reports suggested the cause to be a combination between genetic and environmental factors. Heart disease symptoms in a child are generally simple when compared with an adult, and have widely different pathology and physiology. Heart disease in an adult is a disease that often happens later in life (acquired heart disease) in the blood vessels (coronary artery disease) and heart valves. In this chapter, we will describe the possible causes and risk factors of CHD.

The first corrective surgery with cardiopulmonary bypass for intra-cardiac malformations began at the Mayo Clinic and the University of Minnesota Hospital in the 1950s (Lillehei, 1956). Through the past half century, the diagnosis and treatment of CHDs have markedly improved. The rapid evolution of diagnosis, medical and surgical therapies has reduced the morbidity and mortality rate. The surgical mortality has decreased from an average of 15% in 1990 to an average of 5% in 2000 (Kenny, 2008, as cited in Gibbs et al., 2004). The majority of infants with CHD are now expected to survive into adolescence and adulthood. Currently, the number of adults diagnosed with CHD exceeds the number of children diagnosed with CHD. Hence, the objectives of this chapter are to describe epidemiology and etiology of CHD, including preventative guidelines for pregnant mothers. The authors hope this will provide essential overview to not only physicians and public health officers but also pregnant women, interested readers and societal awareness for the possibility of CHD in newborns. We also hope to provide appropriate strategies for managing the problem. This would lead to an appropriate health care budget and plan for diseased children in the future.

Abbreviations

AR	=	aortic regurgitation
AS	=	aortic stenosis
ASD	=	atrial septal defect
AVSD	=	atrioventricular septal defect
BAV	=	bicuspid aortic valve
CHD	=	congenital heart disease
Coarc	=	coarctation of the aorta
DORV	=	double outlet right ventricle
HLH	=	hypoplastic left heart
HRH	=	hypoplastic right heart
IAA	=	interrupted aortic arch
MR	=	mitral regurgitation, (MVP = mitral valve prolapse)
PA	=	pulmonary atresia
PDA	=	patent ductus arteriosus
PS	=	pulmonary stenosis
SV	=	single ventricle
TA	=	tricuspid atresia
T/PAPVR	=	total/partial anomalous pulmonary venous return
TGA	=	transposition of great arteries
TOF	=	tetralogy of Fallot
VSD	=	ventricular septal defect

2. Epidemiology of congenital heart diseases

2.1 Incidence rate

The incidence of CHD refers to the number of newly identified cases, children or adult, depending on the degree of defective development of the individuals' heart, per unit of time or population. Incidence demonstrates the rate of disease. The incidence of congenital heart defect is difficult to precisely determine, partly because of difficulties in definition. However, not all cases of congenital heart disease are diagnosed in infancy. Incidence rates based on diagnoses in pregnant women and the first 12 months of the baby's life will, therefore, be an underestimate of true incidence. Accurate assessment of incidence of CHD is important in determining the etiology of CHD, and in comparisons between populations over time, which might reflect population genetics or environment factors to a region or country. The incidence of CHD ranges from 4 to 85.9 per 1,000 pregnancies. Many congenital heart defects have been detected in stillbirths, particularly by an early loss in gestation due to chromosome anomalies. According to Hoffman (1978), the incidence of CHD among stillbirths is 79 per 1,000, whereas Mitchell (1972) reported an incidence of CHD in stillbirths and neonatal death (death after birth and before 28 days of age) to be 27.5 per 1,000 and 73.2 per 1,000, respectively. Yet, this number is likely an underestimate to the actual incidence of CHD because of difficulties in definition and unrecognized live births. The increasing incidence of CHD is primarily because of better methods of detection and data collection, as well as more advanced instruments, i.e. echocardiography, and highly skilled health officers. The increasing incidence of CHD could be due to more teratogenic environments affecting pregnant women and their offspring. Although an increased use of fetal echocardiography in pregnant women can help detect more CHD cases, many pregnancies are aborted prior to the mothers' awareness of the pregnancy and the effective assessment of a structural heart defect is still impossible for the early gestation phase. Moreover, the detection of heart malformation via fetal autopsy and heart examination remains rarely performed among the stillborns especially in developing country due to the lack of pathologists and the additional process for health professionals to request an autopsy.

2.2 Birth prevalence

Unlike incidence, the prevalence for CHD is the number of existing cases in the population of interest at one point in time. Prevalence represents the probability that a person in a given population will have the disease at a given time. Prevalence is a function of the incidence of the disease in a population and the duration of that disease. The sooner the recognition of birth prevalence of CHD, the better the planning will be by hospitals, health officers, pediatricians, pediatric cardiologists and pediatric cardiac surgeons. Social and economic support can also be found early for the patients' families. The global prevalence of CHD among newborns ranges from approximately 3.7 to 17.5 per 1,000, which account for 30-45% of all congenital defects. In Northern England, birth prevalence of CHD was as high as 79.7 per 1,000 live births (Dadvand et al., 2008). The extreme variation of the birth prevalence might be owed to a single or a combination of the following factors: inclusion criteria, for example that reports include bicuspid aortic valve and tiny muscular VSD or not, specificity and sensitivity of the diagnostic methodologies, properly trained and technique specialty of examiners, and ethnic and regional backgrounds of the examinees. Additional factors might be associated with the unavoidable limits of the retrospective studies that the data depend on previous medical records, possibly incorrect registration, missing or insufficient co-

ordination of cardiac pediatricians between outpatient and private clinics, and absence of autopsy to determine the cause of certain fetal death in stillbirths. Nonetheless, the estimation for birth prevalence of CHD remains simpler and more precise compared with the estimation for incidence of CHD from the baby population. Hence, most epidemiological studies report the birth prevalence rather than the baby incidence of CHD. Table 1 compares the birth prevalence of all CHD subtypes from 4 recent studies by Hoffman & Kaplan, 2002 (review literatures); Reller et al., 2008 (Metropolitan Atlanta Congenital Defects Program, MACDP); Dolk & Loane, 2009 (European Surveillance of Congenital Anomalies, Eurocat) and Wu et al., 2010 (Asian population, Taiwan). Table 2 shows different percent distribution of CHD lesions in live births from various countries

Cardiac Lesion	Hoffman & Kaplan, 2002* Mean/Median	Reller, 2008* (MACDP)	Dolk & Loane, 2009** (Eurocat)	Wu, 2010* (Asian population)
VSD	3.57 / 2.83	4.18	3.06	4.01
PDA	0.80 / 0.57	0.29	---	2.01
ASD	0.94 / 0.56	1.31	2.05	3.23
AVSD	0.35 / 0.34	0.41	0.19	0.20
PA	0.13 / 0.08	0.04	0.09	---
PS	0.73 / 0.53	0.55	0.40	1.22
AS	0.40 / 0.26	0.11	0.14	0.16
Coarc	0.41 / 0.36	0.44	0.34	0.25
TOF	0.42 / 0.36	0.47	0.28	0.63
TGA	0.32 / 0.30	0.23	0.35	0.21
HRH	0.22 / 0.16	---	0.04	---
HLH	0.27 / 0.27	0.23	0.26	0.06
TA	0.08 / 0.09	0.05	0.08	0.05
Ebstein's	0.11 / 0.04	0.06	0.05	0.05
Truncus	0.11 / 0.09	0.06	0.09	0.08
DORV	0.16 / 0.13	---	---	0.15
SV	0.11 / 0.09	0.10	0.07	---
TAPVR	0.09 / 0.09	0.08	0.05	0.11
All CHD	9.60 / 7.67***	8.14	7.05	13.08
BAV	13.56/9.24	---	---	---

*Live births

**Non-chromosomal CHD prevalence (Includes: Live birth, Fetal death and Termination of pregnancy for fetal anomaly)

***Excluding bicuspid non-stenosis aortic valves, isolated partial anomalous pulmonary venous connection and silent ductus arteriosus

Table 1. Prevalence of CHD based on CHD subtypes and per 1,000 births compared among the four recent studies.

More importantly, the trend for birth prevalence of CHD was found to be increasing, highlighting three chief concerns. First, the increased number of CHD prevalence among the newborns could represent the greater number of adults with CHD and the likely increased number of CHD in their offspring in the future. This poses the concern about the overall

increasing prevalence of CHD. A study in Hungary, estimates the prevalence of CHD to be 4.9% in offspring of individuals with CHD. More than half of these had the same malformation as the parent (Ceizel et al., 1981). Another study in 2001 showed the prevalence of CHD was 3.1% in offspring of individuals with CHDs and 1.3% in offspring of individuals without CHDs. The adjusted risk for offspring of parents with CHDs was 1.73 (95% CI, $p=0.02$) (Romano-Zelekha et al., 2001). On the other hand, if the high prevalence is due to the more common use of postnatal echocardiography for abnormal heart diagnosis, the greater birth prevalence of CHD signifies an underestimation of CHD among live births in the past and the importance for public health officers to have an accurate number of cases. For instance, fetal echocardiography screening could be performed to decide pregnancy termination of fetuses with severe cardiac malformation, and thereby reduce the birth prevalence of CHD. Finally, the rapid development of the world may increase many risk factors to develop CHD such as pollutants and teratogens. The number of births with CHD in Dallas county suggests an apparent increase in prevalence from approximately 5% in 1971 to 8% in 1984 (Fixler et al., 1990). Within the Baltimore-Washington Infant Study Group, the prevalence of CHD increased from 2.8 per 1,000 live births in 1981 to 4.3 per 1,000 live births in 1988 (Ferencz et al., 1989) and a recent report from North England demonstrated the total prevalence of CHD increased from 5.4 per 1,000 births and terminations of pregnancy in 1985 to 11.6 per 1,000 births and terminations of pregnancy in 2003 (Dadvand et al., 2008).

	USA ¹	UK ²	UK ³	USA ⁴	India ⁵	Saudi ^{6*}	Jordan ⁷	Bangla ^{8*}	Germany ⁹
Cardiac Lesion									
VSD	29.1	28.1	32.5	26.3	34.8	33.9	43.4	16.9	48.9
VSD+PS	2.4	8.6	---	---	---	---	---	---	---
PDA	7.6	6.5	11.9	2.6	18.6	11.6	8.3	12.7	4.3
ASD	7.4	8.3	5.9	7.5	2.3	18.1	13.6	26.0	17.0
AVSD	4.3	7.4	2.4	---	2.3	3.5	3.6	3.5	2.7
PA	---	---	0.8	---	---	---	---	2.8	0.9
PS	8.1	2.7	7.5	7.0	---	12.4	6.2	7.8	6.1
AS	3.5	4.1	5.1	3.3	2.3	2.5	4.3	1.4	2.2
Coarc	4.3	5.6	6.3	6.8	---	2.3	3.4	2.1	3.6
TOF	3.5	---	5.9	9.2	4.6	3.5	9.5	9.9	2.5
d-TGA	2.4	5.6	5.0	5.0	---	2.1	5.5	4.2	2.2
HLH	---	3.3	2.8	5.7	---	---	---	---	1.4
TA	1.1	1.5	1.7	1.5	2.3	---	3.7	3.5	---
Ebstein's	---	---	---	---	---	---	---	---	0.4
Truncus	---	1.2	1.1	---	---	---	---	0.7	0.5
DORV	1.1	---	---	---	---	---	---	---	1.0
SV	0.9	1.5	1.7	---	2.3	---	---	1.4	---
TAPVR	---	2.1	1.3	1.7	---	---	---	1.4	0.6
MR	0.6	---	---	---	---	---	---	---	---

¹Mitchell et al., 1971, ²Bound & Logan, 1977, ³Dickinson et al., 1981, ⁴Ferencz et al., 1985, ⁵Khalil et al., 1994, ⁶Alabdulgader, 2006, ⁷Amro, 2009, ⁸Fatema et al., 2008, ⁹Lindinger et al., 2010

*Saudi = Saudi Arabia, and Bangla = Bangladesh

Table 2. Percent distribution of CHD lesions in live births in USA, UK, India, Saudi Arabia, Jordan, Bangladesh and Germany.

2.3 Adult prevalence

Similar to the knowledge of birth prevalence, the knowledge of adult prevalence can estimate the need for adult cardiology services. The accurate prevalence of CHD in the adult population is difficult to know. Although some patients with CHD have spontaneous recovery, for instance 35% of infants with VSD had their lesion close spontaneously (Mitchell et al., 1971), an overall number of adult diagnosed with CHD continues to rise and is now higher than that of the diagnosed pediatric cases. It was estimated that in 2000 there were fewer than 150,000 adults diagnosed with CHD in the UK. Of these, around 11,500 had the more complex forms of the disease, requiring life-long expert supervision and intervention (Report of the British Cardiac Society Working Party, 2002). It was also further estimated that by the year 2010 there would be over 185,000 adults in the UK living with CHD (over 17,000 with the complex form), a rise of around 25% in simple and 50% in complex conditions since 2000. Using a birth prevalence of CHD of 8.8 per 1,000 live births, it is estimated that more than 8,500 individuals with surgical repair of congenital heart defects reach adulthood each year in the USA (Morris, 2004). In year 2000, approximately 500,000 American adults were reported to have moderate to complex congenital heart defects. By 2020, nearly 760,000 adults will have CHD in the USA, with 200,000 having severe CHD, disregarding all those born before 1990 (Webb et al., 2002). Our review has only one study that reports exactly the adult prevalence of CHD. This study was done in a general population from 1985 to 2000 in Canada, it revealed the prevalence of CHD was 4.09 per 1,000 adults for all CHD and 0.38 per 1,000 for those with severe lesions (Table 3). 57% of the adult CHD population was female (Marelli et al., 2007). The authors extrapolated a prevalence of 4.09 per 1,000 to a Canadian and US population corresponds to 96,000 patients in Canada and 856,000 patients in the United States. A recent study in the Netherlands studied 8,595 adults with CHD, and found the most common defects in the distribution of CHD were ASD (17%), VSD (16%), AS/BAV (14%), TOF (10%) and Coarc (10%) but the highest mortality was found in patients with TA (14.7%) and patients with UV and double inlet left ventricle (11.4%) (Zomer et al., 2010).

Two main reasons can explain this situation. First, there is the process of natural selection in which children with previously undetected CHD or children with inoperable CHD survive into adulthood with uncorrected lesions. Up to 75% of children with CHD did not exhibit clinical signs of diseases until the diseases became severe. Moreover, around 10% of CHD are not diagnosed until adulthood (Mettler & Peeler, 2009), in particular secundum atrial septum defect, ventricular septal defect, pulmonary stenosis, anomalous coronary arteries, Ebstein's anomaly and congenitally corrected transposition of great arteries. One of the more recent CHD studies in Thailand reported 0.41 to 1.05 prevalent cases of unrecognized CHD for every 1,000 elementary-age students. This variation was due to the topography and the limitation of medical staff and facilities in the study areas. In this population, the most frequently identified heart defects were VSD 41.4%, PS 16.1%, PDA 12.6% and ASD 9.2% (Sayasathid, et al., 2010). The second reason is the improvement of surgical therapy and postoperative care of neonates and infants in the past few decades, this has led to increased survival of children with CHD. Currently, more than 90% of children born with CHD can survive into adulthood (Moons et al., 2009). From 1979 through 1997, mortality associated with CHD (all ages) declined 39% from 2.5 to 1.5 per 100,000 (Boneva et al., 2001). Although many children with CHD cannot be cured, the initial therapy, including corrective and palliative, allows the adult prevalence of CHD to continue to increase. At Mayo clinic, the number of adult patients with CHD who undergo operation has grown to approximately

300-400 patients per year (Brown et al., 2009). These patients have elevated risk of premature morbidity and mortality. CHD is often more severe and has more complicated treatment in adults than children. Moreover, a recent analysis of the United States administrative database found that mortality was greater for adults with CHD when the operations were performed by adult cardiac surgeons, compared with pediatric (congenital-trained) heart surgeons (4.8% versus 1.9%, $P < 0.001$) (Brown et al., 2009, as cited in Karamalou et al., 2008). For CHD adults, arrhythmias are more common, cardiac chambers often enlarge, and ventricles tend to develop systolic dysfunction. The main causes of death were progressive heart failure 26% and sudden cardiac arrest 22% (Zomer et al., 2010). Multidisciplinary care may also be required.

Lesion	prevalence per 1,000 adults
Severe lesion	
TOF or truncus	0.17
AVSD	0.14
TGA	0.04
SV	0.03
All severe lesions	0.38
Other lesion	
ASD	0.88
VSD	0.78
PDA	0.02
AS or AR	0.11
Coarc	0.07
Ebstein's	0.01
All other lesions	3.71
All CHD	4.09

Table 3. The prevalence of adult CHD based on subtypes in year 2000, Canada (Marelli et al., 2007).

Another problem that should be of concern is the transfer system from pediatric to adult health care. Many children with CHD did not follow-up when they were discharged from pediatric care and referred to adult care. In a Canadian study, only 47% of teenagers with CHD had transferred successfully to adult care (Reid et al., 2004). The results were similar in a German study, 76% of patients with CHD did not have follow-up care as an adult in a 5-year period (Wacker et al., 2005). The prevalence of adults with CHD is underestimated if it does not include this group of patients. These patients received medical care again when their diseases had progressed and their symptoms had become severe. This lack of care as an adult made it difficult to manage the disease and resulted in high morbidity & mortality in these patients. Patients with CHD must recognize the necessity of ongoing surveillance and the transfer system must be developed to prevent the loss of follow-up patients.

3. Etiology of congenital heart diseases

The heart development, which initiates at embryonic day 15 in vertebrates, comprises an organized series of molecular and morphologic events that involve five primary steps: (1)

migration of pre-cardiac cells from the primitive streak and assembly of the paired cardiac crescents at the myocardial plate, (2) coalescence of the cardiac crescents to form the primitive heart tube, establishment of the definitive heart, (3) cardiac looping, assurance of proper alignment of the future cardiac chambers, (4) septation and heart chamber formation, and (5) development of the cardiac conduction system and coronary vasculature (McFadden & Olson, 2002; Moorman & Christoffels, 2003; Gittenberger-de Groot et al., 2005). From a series of complex processes, each component occurs at the right time under the orchestration of a cascade of genes and gene products, resulting in the coordination of cell migration and the formation of the extracellular matrix. Thus, CHD is usually caused by altered development of embryonic structure, or a failure of the structure to develop beyond an early embryonic or fetal stage. The anatomical defect generally influences further structural and functional development. Although descriptions of abnormal heart development in fetuses and babies have remained unclearly defined, substantial knowledge about the etiology of CHD have been made during the last decade. Some malformations may be directly inherited through vertical gene transfer, underlying the individuals' genetic disorder, or be associated with the consequences of an environmental toxin or diet. Alternatively, random errors in cell migration leading to improper cardiac development are possible. Together, the findings emphasize the complex and multifactorial causes of the CHD where additional research remain needed.

Better understanding for the etiology and risk factors of CHD is important, and will help pave the way for proper preventative measures and treatment guidelines by physicians as well as public health officers. The followings represent all reported potential causes of CHD to date.

3.1 Genetic disorders

The human genome, which contains approximately 20,000 to 25,000 genes, is comprised of coding and non-coding regions that are essential for proper protein structure and expression. The coding DNA sequence determines the amino acid sequence and subsequently the protein structure, and structure determines function (Lander, 2011; Reid-Lombardo & Bartelings, 2010). The non-coding sequences may contain promoters and regulation of transcription. In general, the DNA sequences remain relatively unchanged during vertical genetic transfer to the offspring. Nonetheless, occasional changes in the nucleotide sequences, referred to as mutations, and horizontal gene transfer do occur. Mutations range from a single nucleotide substitution, also called single nucleotide polymorphism (SNP), to a deletion or insertion of a DNA fragment. Some mutations only appear visible at the level of the chromosome (chromosome abnormalities), while some mutations cause phenotypic changes and a heritable trait to the offspring.

Any change in the DNA sequence, including SNPs, insertion, deletion and shuffling of DNA fragment, that results in frameshift mutation of the gene-encoding sequence likely affects protein folding and protein function. Abnormal protein folding structure and function can cause an improper development of many organs, including the heart. Hence, genetics is responsible for one major role in cardiovascular malformation, and indeed the genetic disorders represent the most common cause of CHD. Certain chromosome abnormalities were linked to specific types of congenital heart lesions, and several types have been reported to be associated with specific gene defects. For instances, AVSD are often diagnosed in patients with trisomy 21.

Moreover, CHD that occur in multiple members of a family increases the incidence of CHD in familial lines, and support evidences of inherited genetic disorders towards the heart abnormalities. Molecular genetics in conjunction with cytogenetics provide an opportunity to decipher the genetic basis and pathogenesis of CHD. With the rapid era of DNA sequencing and genetic discoveries, it is expected that genetic diagnosis and screening will become incorporated into standard practice in the near future. Consequently, it is imperative that cardiologists understand the basis for genetic disorders, and the medical and ethical implications relevant to the genetic information. Today, genetics are predisposed to malformation of the hearts and blood vessels, and account for the highest number of human birth defects. Thus, hereditary and congenital diseases are classified into three broad categories

3.1.1 Chromosome defect

Defects in chromosomes associated with CHD are diverse; some examples are aneuploidy or polyploidy, improper rearrangement during mitosis and meiosis, translocation, inversion or deletions. Importantly, certain chromosomes were reported to have a greater degree of significance and of percentages to heart development, and thus the same defects in different chromosomes may not result in similar defects (Table 4). About 0.30-2.0% of all live births have chromosomal defects, usually the chromosomal defects were aneuploidy and trisomy 21, 18, 13 (Dolk et al., 2010). Among all CHDs detected during infant period, the chromosomal defects account for approximately 6 - 10% (Ferencz et al., 1989; Tennstedt et al., 1999; Zhang et al., 2010). In Table 4, defects in chromosomes X, 3, 4, 5, 7, 8, 9, 10, 11, 13, 17, 18, 21 and 22 showed association with CHD.

Nonetheless, the table summarizes the data reported by different studies, some conducted in different times and places. The incidence of CHD generally depends on multiple factors besides the type of genetic disorders and the chromosome where the disorders take place. The other factors include how many fetuses are conceived by the mothers, and how many of these fetuses reach term alive. Further, the affected number of fetuses also depends on the rate of the survival of the affected fetuses and the increased use of therapeutic abortion.

3.1.2 Single gene disorder

Heart development is controlled by multiple genes regulating a complicated network of transcription regulation, translation regulation, and signal transduction pathways, ranging from a control of muscle growth, patterning to contractility, to name a few. However, mutations in only one or a few components of the cardiac gene network can result in the improper development of the heart. One type of heart defect could also be caused by different types of single gene disorders. Since the 1990s, researchers have identified more than 10 different single gene mutations that can lead to heart defects. To date, many genes responsible for several congenital heart defects have been identified (table 5).

Transcription Factor Genes transcribe and translate proteins that serve to interact cooperatively with each other to control gene expression.

- **NKX2-5, the NK family, on chromosome 5q35;** Homeobox-containing genes play critical roles in regulating tissue-specific gene expression essential for specification of heart muscle progenitors (Komuro & Izumo, 1993; Toko et al., 2002). Mutations in NKX2-5 result in loss of heart formation in the embryo and have been found in sporadic

CCVM. Although the contributions of these variants to the disease phenotype remains uncertain, the linkage between this gene disorder and the atrioventricular conduction defect, ASD, VSD or TOF, have been found (Elliott et al., 2003; McElhinney et al., 2003; Stallmeyer et al., 2010).

- **TBX1, T-box 1 transcription factor, the T-box family;** The human TBX1 gene encodes another T-box transcription factor, expressed in neural crest and the developing cardiac outflow tract (conotruncus) (Calmont et al., 2009). Microdeletion TBX1 gene, located on chromosomal 22q11, causes DiGeorge syndrome, also known as Velocardiofacial syndrome. There are variable ranges of clinical phenotypes for DiGeorge syndrome, including IAA, truncus arteriosus, TOF, DORV and TGA (Jerome & Papaioannou, 2001; Xu et al., 2004; Yagi et al., 2003).
- **TBX5, T-box 5 transcription factor, the T-box family;** is a member of a phylogenetically conserved family of genes that share a common DNA-binding domain, the T-box. TBX5 was found expressed in embryonic human heart and limb. Mutations in this gene have been associated with Holt-Oram syndrome (Fan et al., 2003), which is characterized by skeletal malformations of the upper extremities and CHD, most commonly secundum ASD but also VSD and TOF (Basson et al., 1999; Faria et al., 2008; Li et al., 1997; Xin et al., 2009).
- **GATA4, GATA binding protein 4;** is related to zinc finger transcription factors. This protein is thought to regulate genes involved in embryogenesis and in myocardial differentiation and function. Furthermore, GATA4 interacts with Tbx5 and with Nkx2-5 to regulate cardiac gene expression. This provides evidence that a transcriptional complex including all three proteins may be necessary for proper septation of the human heart. Mutations in this gene have been associated with non-syndromic CHD cardiac septal defects (Gang et al., 2003; Tomita-Mitchell et al., 2007).
- **TFAP2B, transcription factor AP-2 beta;** This gene encodes a member of the AP-2 family of transcription factors. This protein functions in the differentiation of neural crest cell derivatives, and contributes to the embryogenesis of the ductus arteriosus (Hilger-Eversheim et al., 2000). Mutations in this gene result in autosomal dominant Char syndrome, a dominant disorder comprised of facial dysmorphism, hand anomalies, and patent ductus arteriosus (Mani et al., 2005; Satoda et al., 2000; Zhao et al., 2001).
- **ZFPM2/FOG2, zinc finger protein, multitype 2;** The zinc finger protein encoded by this gene is a widely expressed member of the FOG family of transcription factors. The FOG family members modulate the activity of co-factors with the GATA family of proteins, which are important regulators of hematopoiesis and cardiogenesis in mammals. In experimental gene targeting of ZFPM2/FOG2 in mice, the mutation resulted in cardiac malformation including TOF, endothelial specific disruption (DORV, a common AV valve), VSD and ASD as well as left ventricular wall hypoplasia, and the failure to form coronary arteries (Tevosian et al., 2000). Recent reports found mutations of the ZFPM2/FOG2 gene associated with TOF (De Luca et al., 2010; Pizzuti et al., 2003).
- **ZIC3, Zic family member 3 heterotaxy 1;** This gene encodes a member of the ZIC family of C2H2- type zinc finger proteins. Mutations in ZIC3 gene, located at chromosome Xq24-q27.1 (Casey et al., 1993), cause X-linked visceral heterotaxy and

complex CHD including ASD, AVSD, TGA, PS, and TAPVR (Zhu et al., 2007; Grinberg & Millen, 2005).

Cell signaling genes produce proteins involved in cell signal transduction, which allow cells to respond to their environment and are therefore involved in regulation of many important biological functions.

- **JAG1, Jagged 1;** The jagged 1 protein encoded by JAG1 is the human homolog of the *Drosophila* jagged protein. Human jagged 1 is the ligand for the receptor NOTCH, which is essential in many organ developmental programs. Analysis of JAG1 expression during mammalian embryogenesis showed its high level of gene expression during the heart and vessel developing periods, and the finding was consistent with the crucial role of its patterning of the right heart and pulmonary vasculature (Loomes et al., 1999). Mutations in the jagged 1 protein cause Alagille syndrome, a complex disease characterized by liver problem, PS, and with or without TOF (Heritage et al., 2002; McElhinney et al., 2002; Colliton et al., 2001).
- **NOTCH1, NOTCH2, The NOTCH family receptors;** The NOTCH gene encodes a single-pass transmembrane protein receptor that interacts with the ligands named Delta and Serrate/Jagged, and perform many cellular regulatory function. Mutations in NOTCH1 have been shown to cause autosomal-dominant aortic valve defects, and bicuspid (two-leaflet) aortic valve (Grag et al., 2005; McKellar et al., 2007; Mohamed et al., 2006). Because BAV is a risk factor for valve calcification, it has previously been hypothesized that calcification was due to increased blood flow turbulence across the valve leaflets (Robicsek et al., 2004), leading to progressive aortic stenosis and regurgitation in later life. Furthermore, mutation in NOTCH2 receptor was recently found to be able to cause Alagille syndrome even in the patients with no Jagged1 mutations (El-Rassy et al., 2008; McDaniell et al., 2006).
- **PTPN11;** The protein encoded by this gene is a member of the protein tyrosine phosphatase (PTP) family. PTPs are known to be signaling molecules that regulate a variety of cellular processes including cell growth, differentiation, mitotic cycle, and oncogenic transformation. Mutations in this gene are a cause of Noonan syndrome, located on chromosome 12q24 (Jamieson et al., 1994), it is an autosomal dominant disorder characterized by dysmorphic facial features, skeletal malformations, short stature, and cardiac abnormalities, most characteristic are PS, ASD, AVSD and hypertrophic cardiomyopathy (Jongmans et al., 2005; Sarkozy et al., 2003).
- **CFC1, cryptic family 1;** This gene encodes a member of the EGF-Cripto, Frl-1, and Cryptic (CFC) family. These proteins play key roles in intercellular signaling pathways during vertebrate embryogenesis. This protein is involved in left-right asymmetric morphogenesis during organ development. Mutations in this gene can cause autosomal visceral heterotaxy with complex CHD including TGA, septal defects and systemic vein anomalies (Goldmuntz et al., 2002; Ozcelik et al., 2006; Yan et al., 1999).
- **SOS1, son of sevenless homolog 1;** This gene encodes a protein that is a guanine nucleotide exchange factor for RAS proteins, membrane proteins that bind guanine nucleotides and participate in signal transduction pathways. Mutations in this gene are associated with gingival fibromatosis 1 and Noonan syndrome (Serrano-Martin et al., 2008).

- **PROSIT240, also known as THRAP2;** An evolutionarily conserved THRAP genes encode a family of proteins that regulate embryonic development. Missense mutation PROSIT240 gene has been identified as a cause of transposition of the great arteries (Muncke et al., 2003).
- **CRELD1, cysteine-rich with EGF-like domains 1;** CRELD1 is the member of a family of matrix cellular proteins. Matrix cellular proteins contain epidermal growth factor-like repeats, and are grouped in a class of cysteine-rich domains that mediate interactions between proteins of diverse functions. Mutation in CRELD1 genes, locating on chromosome 3p25 locus, represents a vital gene position for AVSD (Guo et al., 2010; Zatyka et al., 2005; Robinson et al., 2003).
- **EVC, EVC2;** This gene encodes a protein containing a leucine zipper and a transmembrane domain. The functions of EVC and EVC2, which share a promoter, are aligned in control limb, skeleton and teeth development. Mutation of this gene has been implicated in both Ellis-van Creveld syndrome and Weyers acrodistal dysostosis, the disease locus mapped to chromosome 4p16 (Polymeropoulos et al., 1996). Ellis-van Creveld syndrome is an autosomal recessive disorder characterized by chondrodysplasia and CHD, typically a common atrium of the atrioventricular septal defect type or secundum type atrial septal defects (Ali et al., 2010; Hills et al., 2011; Tompson et al., 2007). Some heterozygous carriers of these mutations manifested Weyers acrodistal dysostosis suggesting it is allelic with Ellis-van Creveld syndrome (Riiz-Perez et al., 2000).
- **TGFBR1 and TGFBR2, transforming growth factor receptor 1 and 2;** This gene encodes a member of the Ser/Thr protein kinase family and the TGFBR receptor subfamily. Mutations in this gene have been associated with Marfan syndrome, Loeys-Deitz Aortic Aneurysm syndrome (Loeys et al., 2006; Singh et al., 2006).

Extracellular Matrix Protein Genes encode extracellular matrix proteins which cause congenital syndromes involving arteriopathies of different forms.

- **ELN, elastin;** This gene encodes a protein is one of the two components of elastic fibers. It resides in the Williams critical region on 7q11.23. Deletions and mutations in this gene are associated with Williams or Williams-Beuren syndrome in which the phenotype is comprised of characteristic endocrine, cognitive, and facial features in association with areas of arterial narrowing, most typically non-syndromic supravalvular AS (Micale et al., 2010; Rodriguez-Revenga et al., 2005; Arrington et al., 2006).
- **FBN1, fibrillin 1;** This gene encodes a member of the fibrillin family. This fibrillin has long been assumed to be critical in the aortic wall and other connective tissues as a structural protein. Mutations in this gene are associated with Marfan syndrome (Brautbar et al., 2010; De Backer, 2009; Li et al., 2008). Marfan syndrome is an autosomal dominant disease of connective tissue principally involving the skeletal, ocular systems and cardiovascular malformation whose manifestations include mitral valve prolapse and regurgitation, presenting in infancy in the most severe cases, and progressive aneurysmal dilation of the aortic root with the potential for catastrophic aortic dissection and rupture. Marfan syndrome was first mapped to chromosome 15 using traditional genetic linkage analysis (Dietz et al., 1991). Other studies have revealed that fibrillin has a regulatory role in TGF- signaling, and dysregulation of the pathway may instead underlie Marfan pathogenesis (Neptune et al., 2003).

Type of abnormality	Predominant of CHD	Percentage of CHD	Reference
Numeric aberrations;			
Autosomes:			
• Monosomy			
X (Turner syndrome)	Left-sided obstruction, PAPVR, MVP, aortic route dilatation	35	1 - 5
• Trisomy			
13 (Patau syndrome)	VSD, PDA, ASD, dextroposition	80-90	6 - 8
18 (Edward syndrome)	VSD, PDA, ASD, TOF, DORV, CPVD	80-100	9 - 11
21 (Down syndrome)	VSD, AVSD, ASD	40-50	12, 13
• Tetrasomy			
22pter-q11 (Cat-Eye syndrome)	TAPVR, HLH	40	14 - 16
Structural aberrations:			
• Duplication			
3q26-27 (Cornelia de Lange)	PS, VSD, ASD, DORV	40	17 - 19
8q	VSD, TA	45	20, 21
9p	ASD	40	22
11q	ASD	35	22
• Deletion			
3p (3p-syndrome)	AVSD	25	23, 24
4p (Wolf-Hirschhorn)	ASD, VSD, PDA, PS	30-50	25
4q	ASD, VSD, PS	50	26 - 28
5p (Cri du chat syndrome)	VSD, PDA, TOF	30	29
8p (8p-syndrome)	AVSD	65-80	30, 31
10p	VSD, ASD, PS	50	32, 33
11q (Jacobsen syndrome)	VSD, left heart obstructive malformations, HLH	60	34, 35
18p	VSD, PDA, PS, heterotaxy phenotype	10	36, 37
18q	ASD, VSD, PS	30	38, 39
• Microdeletion			
7q11 (Williams syndrome)	SVAS, PS	60	40, 41
17p11.2 (Smith-Magenis syndrome)	VSD, ASD, PS, AV malformation	30	42, 43
22q11.2 (DiGeorge syndrome)	TOF, TAPVR Aortic arch anomalies, IAA type B, TOF, TA, ASCA	75-85	44, 45

ASCA: aberrant subclavian artery, CPVD: congenital polyvalvular disease, CVM: cardiovascular malformations, DCM: dilated cardiomyopathy, RAA: right aortic arch, SVAS: supra-aortic stenosis (Ref: ¹Douchin et al., 2000; ²Lichiardopol & Morta, 2004; ³Mazzanti & Cacciari, 1998; ⁴Poprawski et al., 2009; ⁵Tan & Yeo, 2009; ⁶Lin et al., 2007; ⁷Lizarraga et al., 1991; ⁸Musewe et al., 1990; ⁹Van Praagh et al., 1989; ¹⁰Matsuka et al., 1981; ¹¹Musewe et al., 1990; ¹²Paladini et al., 2000; ¹³Weijerman et al., 2010; ¹⁴Berends et al., 2001; ¹⁵Rosias et al., 2001; ¹⁶Wilson et al., 1984; ¹⁷Akdeniz et al., 2009; ¹⁸Barisic et al., 2008; ¹⁹Selicorni et al., 2009; ²⁰Digilio et al., 2003; ²¹Giltay et al., 1998; ²²Roskers et al., 1990; ²³Green et al., 2000; ²⁴Shuib et al., 2009; ²⁵Battaglia et al., 1999; ²⁶Tsai et al., 1999; ²⁷Strehle & Bantock, 2003; ²⁸Huang et al., 2002; ²⁹Hills et al., 2006; ³⁰Devriendt et al., 1999; ³¹Wat et al., 2009; ³²Lindstrand et al., 2010; ³³Van Esch et al., 1999; ³⁴Grossfeld et al., 2004; ³⁵Mattina et al., 2009; ³⁶Digilio et al., 2000; ³⁷Movahhedian et al., 1991; ³⁸Cody et al., 1999; ³⁹Linnandivi et al., 2006; ⁴⁰Eronen et al., 2002; ⁴¹Ferrero et al., 2007; ⁴²Edelman et al., 2007; ⁴³Potocki et al., 2003; ⁴⁴Ballesta et al., 2008; ⁴⁵Shprintzen, 2008)

Table 4. Chromosome abnormality associated with congenital heart anomalies and their percentages.

Gene	Syndrome	Chromosome location	Inheritance	Congenital heart malformation
<u>Transcription Factor Gene</u>				
NKX2-5	Non-syndromic	5q34	AD	ASD, AVB, VSD, TOF, HCM, TV abnormality
TBX1	DiGeorge Syndrome	22q11.21	Sporadic	VSD, PTA, IAA, TOF
TBX5	Holt-Oram Syndrome	12q24.1	AD	HOS, ASD, AVSD, AVB, TOF, TAPVR, TA, PS
GATA4	Non-syndromic	8p23.1p22	AD	ASD
TFAP2B	Char syndrome	6p12	AD	PDA
ZFPM2/FOG2	Non-syndromic	8q23	Sporadic	TOF
ZIC3	Heterotaxy Syndrome	Xq26	X-linked	Heterotaxy, ASD, AVSD, TGA, PS, DORV, TAPVR
<u>Cell signaling Genes</u>				
Jagged 1	Alagille Syndrome	20p12	AD	PS, TOF
NOTCH1	Non-syndromic	9q34-35	Sporadic	BAV
NOTCH2	Alagille Syndrome	1p12	AD	PS, TOF
PTPN11	Noonan syndrome	12q24	AD	PS, PV dysplasia, ASD, AVSD, HCM
CFC1	Heterotaxy syndrome	2q21	Unknown	Heterotaxy, TGA, DORV
SOS1	Noonan syndrome	2p21	AD	PS, septal defect, HCM
PROSIT240	Non-syndromic	12q24	Unknown	TGA
CRELD1	Non-syndromic	3p21	Sporadic	AVSD
EVC/EVC2	Ellis- van Creveld syndrome	4p16	AR	Common atrium, ASD
TGFBR2	Marfan syndrome	3p22	AD	Aortic aneurysm
<u>Extracellular Matrix Protein Genes</u>				
FBN1	Marfan Syndrome	15q21.1	AD	MVP, aortic root dilatation
ELN	Williams Syndrome	7q11.23	AD	SVAS

AD: autosomal dominant, AR: autosomal recessive, AVB: atrioventricular block; HCM: hypertrophic cardiomyopathy, HOS: Holt-Oram syndrome, SVAS: supravalvular aortic stenosis

Table 5. Gene abnormality and contiguous gene syndromes associated with congenital heart anomalies.

3.1.3 Polygenic / Multifactorial inheritance

Multifactor inheritance, also known as polygeny, relies on the concept of threshold limit, when the threshold limit of the combined genetic and environmental factors is reached, malformation results. Below the threshold level, the malformation is absent. One common

key risk is that the babies are genetically oriented towards some level of atypical cardiovascular formation and/or development, together with the exposure to other causative factors. Different stages of cardiac development possess various degrees of vulnerability to environmental factors. Some clues to multifactorial inheritances are a reason for CHD, including a lack of consistent CHD people in the pedigree of the family, and an occasional abnormality with no recognizable pattern in the pedigree of the family.

3.2 Maternal factors

Various teratogenic agents have been implicated as the etiologic agents of CHD. For example, women who have insulin-dependent diabetes mellitus, and those who take certain medications, such as acne and epilepsy medication, have a higher risk for having babies with CHD. Women with drug or alcohol abuse also have predisposing risks. The basic biological principle mechanism of teratogens action that cause CHD include susceptible stage of organogenesis development, genetic differences in susceptibility, dose response relationships, and specific actions of the teratogenic agent. The highest degree of embryonic and fetal sensitivity or susceptibility to adverse effects of exposure to teratogens occurs during the first trimester, especially during the 2nd to 8th week of embryonic life. Dose response relationship implies that for each teratogen there is a dose threshold, theoretic dose below which no adverse effects can be observed.

3.2.1 Maternal health and medical disease

Certain chronic illnesses in the mother (table 6), such as diabetes, and other viral infections, such as the flu, may contribute to heart defects.

- **Maternal diabetes mellitus;** The study by Correa et al. found odds ratios for pre-gestational diabetes mellitus (PGDM) and all cardiac defects was 4.64 (2.87-7.51), while gestational diabetes mellitus (GDM) was associated with cardiac defects found 1.59 (1.27-1.99) (Correa et al., 2008). This excess risk is related to the level of maternal hyperglycemia during the embryonic period. The overall risk of one or more major anomalies is 6 to 7 percent, which is double the risk in the general obstetric population (Wyatt et al., 2005). Congenital heart defects increased in diabetic pregnancy include heterotaxy, TOF, TGA, septal defects, anomalous pulmonary venous return, and various defects causing left or right outflow obstruction (Lisowski et al., 2010; Corrigan et al., 2003; Wren et al., 2003). The possible mechanism is that embryonic hyperglycemia may cause disturbances in metabolism of arachidonic acid, inositol and promote excessive formation of oxygen free radicals which causes mitochondrial damage, and activation of apoptotic pathways.
- **Maternal phenylketonuria;** One of the most common teratogen of pregnancy complications, when these pregnancies are untreated, 90% of the offspring suffer microcephaly, mental retardation and increased risk of heart defects through increased blood levels of phenylalanine and phenyl pyruvic acid (Rouse & Azen, 2004). Frequencies of congenital abnormalities increased with increasing maternal phenylalanine levels. The MPKUCS has demonstrated an increased rate of CHD (7.5%), the most frequent cardiac defects are TOF, Coarc, PDA, HLH and VSD (Levy et al., 2001). Diet control before conception and during pregnancy reduces the risk of CHD (Matalon et al., 2003; Michals-Matalon et al., 2002).

- **Maternal connective tissue diseases;** Connective tissue disease is a group of multi-system disorder, such as systemic lupus erythematosus (SLE), which have been associated with congenital complete atrioventricular heart block in offspring. With regard to maternal anti-Ro and anti-La autoantibodies can transmit from a mother to the fetus, which causes a fetal inflammatory response that damages the AV nodal and myocardial tissue in susceptible fetus' which may result in myocarditis, endocardial fibroelastosis and cardiac arrhythmias (Buyon et al., 2009; Clancy & Buyon, 2004).
- **Maternal rubella;** Women who contract rubella during pregnancy have a high risk of having a baby with congenital rubella syndrome (CRS) which will cause effects such as miscarriage, stillbirth, and a series of birth defects. The risk of fetal infection varies according to the time of onset of maternal infection. Infection rates are highest during the first trimester. The most common manifestations of CRS are congenital cataracts, sensorineural deafness, and congenital heart defects (especially PDA). When the heart is targeted, there is direct viral damage to the myocardium, affecting primarily the left atrium and the heart septa, leading to thrombosis, necrosis, and hemorrhage that cause of PDA, PS, and ASD (De Santis et al., 2006; Webster, 1998).
- **Maternal febrile illness;** Influenza during the first trimester of pregnancy is associated with febrile illness, which appears to cause more right-sided obstructive heart defects, especially TA and PA, some left obstructive defects and VSD (Oster et al., 2011; Tikkanen & Heinonen, 1991; Yu et al., 2008; Botto et al., 2001). In both hyperthermia and infection there have been documented biological effects on developmental apoptosis pathways. It has been suggested that altered apoptosis may cause birth defects, and apoptosis is known to be involved in cardiac morphogenesis, such as in the development of the cardiac outflow tract.
- **Maternal Stress;** Intense maternal stress during the periconceptional period was associated with increased risk of delivering infants with certain congenital anomalies particularly with conotruncal heart defects and neural tube defects (Carmichael & Shaw, 2000; Adams et al., 1989).
- **Maternal obesity;** Many studies have examined the association between maternal prepregnancy and during pregnant obesity (elevated BMI >25.0 Kg/m²) with CHD such as ASD, VSD, conotruncal defects and right ventricular outflow tract defects (Cedergren & Kallen, 2003; Mills et al., 2010; Oddy et al., 2009; Gilboa et al., 2010). Several aspects of such potential associations between obesity and heart defects remain unclear due to studies of obesity and heart defects which are difficult to assess and compare because of the possibility of bias in obesity that may associated with unrecognized diabetes. While some literature found no association between maternal weight and isolated CHDs (Khalil et al., 2008; Watkins & Botto, 2001).

3.2.2 Maternal drug and medical use

Consumption of many drugs, such as thalidomide and isotretinoin, during early gestation can interfere with the normal cardiogenesis of the fetus. This list of definite and potential human cardiac teratogens was showed in table 6.

3.2.3 Maternal drugs abuse

Some studies suggest that drinking alcohol or using cocaine, especially during the pregnancy, can increase the risk of congenital heart defects (table 6).

- **Caffeine;** Caffeine can cross the placenta, and the concern that caffeine may causes birth defects prompted the FDA to caution pregnant women to limit their caffeine intake. Today, there is no evidence associating caffeine ingestion during pregnancy and teratogenicity of congenital heart disease (Pejtsik et al., 1992; Linn et al., 1982).
- **Alcohol;** Maternal alcohol use during pregnancy is associated with fetal alcohol syndrome which comprise a spectrum of abnormal face, growth restriction, central nervous system abnormality and cardiac defects with VSDs occurring most commonly (Pejtsik et al., 1992; Carmichael et al, 2003; Burd et al., 2007; Loser et al., 1992). In Spain, a case-control study by Martinez-Frias et al. reported that a higher risk of developing CHDs was found in the group with the highest-level daily doses of alcohol consumption (the absolute alcohol ingestion was more than 92 gram per day. However, mechanism in teratogenic effect of alcohol on the developing heart malformation is as of now unclear.
- **Cocaine;** Maternal cocaine ingestion was reported to induce coronary thrombosis in the developing fetal heart leading to formation of a single ventricle, other defects were also reported, such as Ebstein’s anomaly, VSD, heterotaxy (Linn et al., 1982; Kueh & Loffredo, 2002; Lipshultz et al., 1991; Martin & Houry, 1992).
- **Cigarette Smoking;** Smoking during pregnancy enhances the risk of adverse pregnancy outcomes such as low birth weight. The relationship between gestational smoking and congenital heart defects has been studied, however the information is inconclusive. Some studies have reported associations between maternal smoking and ASD, AVSD, TOF (Alverson et al., 2011; Malik et al., 2008; Kallen, 1999). A recent study in Greece found that periconceptional tobacco smoking was associated with increased risk of CHD in the offspring (OR=2.7) and has been associated with a quantity of cigarette smoking (Karatzas et al., 2011). However, no associations were found (Kallen, 1999) so research on large population-based studies is required to evaluate.

3.3 Environment or lifestyle factors

Evidence of teratogenic contamination in certain environments and workplaces is sporadic, albeit environmental factors are a more common cause for multifactorial inheritance CHD. Definitive evidence for the causal relationship between certain exposure and CHD is still unavailable. Available evidence suggests the finding of the higher incidence of CHD babies from women who reside in area with drinking water contaminated by trichloroethylene, dichloroethylene and chromium. While maternal exposure to paint, lacquer, agricultural chemicals, organic solvents, dyes and lead have also been occasionally found statistically associated with CHD. Ingestion of heavy metals and lifetime accumulation of a considerable amount of heavy metals through diet also affects CHD development in babies (table 6).

- **Organic Solvents;** A few studies reported increased risk of HLH, Coarc, PS, TGA with intact ventricular septum, TOF, TAPVR, non-chromosomal AVSD and Ebstein’s anomaly. Other reports of occupational exposure to organic solvents have been associated with an increased risk of VSD (Tikkanen & Heinonen, 1991, 1992; Shaw et al., 2003). However the precise links are difficult to clarify, because solvent composition varies between different commercial preparations.
- **Pesticides & Other Toxic Substances;** A study by Adam et al suggests an association of maternal employment in the agricultural industry with an increased risk of conotruncal defects that suggests a possible association with chemicals used in agriculture (Adams

Risk factor	Common lesion of CHD	Estimated risk of CHD (OR)	Reference
Maternal health:			
• Diabetes mellitus in pregnancy	Heterotaxy, TOF, TGA, septal defects, left or right outflow obstruction	4.6-10.0	1 - 3
• Phenylketonuria	TOF, COA, PDA, VSD, HLH	>6	4
• Connective tissue disease	Complete atrioventricular heart block	Increased	5, 6
• Rubella infection	PDA, PS, ASD	Increased	7 - 9
• Febrile illness	Tricuspid or pulmonary atresia, VSD	1.8-2.8	10
• Stress	Conotruncal heart defects	Increased	11, 12
• Obesity	Conotruncal heart defects, TAPVR, HLH, septal defects	1-3	13 - 16
Maternal medical use:			
• Lithium	Ebstein's anomaly, MR, TR	7.7	17, 18
• Vitamin A >10,000 IU/d	Outflow tract defect	increased	19, 20
• Isotretinoin (RoAccutane)	Overriding aorta, interrupted, hypoplastic aortic arch, ASD, VSD	increased	21, 22
• Trimethadione	TOF, HLH, TGA,	increased	23
• Phenytoin	Coarc, PDA, AS, PS	increased	24
• Valproic acid	Outflow tract, VSD TOF	increased	25, 26
• Coumadin	PDA	increased	27
• Thalidomide	PS, TGA, TAPVR, VSD, ASD, TA, TOF	increased	28
• Ibuprofen	TGA, AVSD, VSD	1.8	29
• Naproxen	Any defects	1.7	29
• Trimethoprim-Sulfonamide	Any defects	2.1-4.8	30
• Sulfasalazine	Any defects	3.4	31
• Nitrofurantoin	HLH, ASD, VSD	1.6	32
• Angiotensin-converting Enzyme inhibitors	ASD, VSD, PS, PDA	3.7	33
• Tricyclic /tetracyclic Antidepressant	VSD	2.2	34
• Paroxetine	VSD, ASD	1.3-1.7	35, 36
Maternal illegal drug:			
• Alcohol	VSD	1.3-1.7	37 - 40
• Cigarette Smoking	ASD, AVSD, TOF	1.0-3.0	41 - 43
• Cocaine and Marijuana	Single ventricle, Ebstein's anomaly, VSD, heterotaxy	Increased	44 - 47
Environmental:			
• Organic Solvents	TGA, HLH, Coarc, TOF, PS	2.3-3.9	48 - 50
• Pesticides	TGA, TAPVR, VSD	Increased	12
• Air pollution:			
-CO	VSD, TOF, PS	1.2-2.6	51, 52
-NO	TOF	1.1	51, 52

(Ref: ¹Lisowski et al., 2010; ²Corrigan et al., 2009; ³Wren et al., 2003; ⁴Rouse & Azen, 2004; ⁵Buyon et al., 2009; ⁶Clancy & Buyon, 2004; ⁷Row, 1973; ⁸De Santis et al., 2006; ⁹Webster, 1998; ¹⁰Botto et al., 2001; ¹¹Carmichael & Shaw, 2000; ¹²Adam et al., 1989; ¹³Cedergren & Kallen, 2003; ¹⁴Mills et al., 2010; ¹⁵Oddy et al., 2009; ¹⁶Gilboa et al., 2010; ¹⁷Cohen et al., 1994; ¹⁸Jacobson et al., 1992; ¹⁹Rothman et al., 1995; ²⁰Botto et al., 2001; ²¹Lammer et al., 1985; ²²Willhite et al., 1986; ²³Rischbieth, 1979; ²⁴O'Brien & Gilmour-White, 1993; ²⁵Sonoda et al., 1993; ²⁶Winter et al., 1987; ²⁷Hou, 2004; ²⁸Smithells & Newman, 1992; ²⁹Ericson & Kallen, 2001; ³⁰Czeizel et al., 2001; ³¹Newman & Correy, 1983; ³²Crider et al., 2009; ³³Cooper et al., 2006; ³⁴Kallen & Otterblad Olausson, 2006; ³⁵Bar-Oz et al., 2007; ³⁶Berard et al., 2007; ³⁷Pejtsil et al., 1992; ³⁸Carmichael et al., 2003; ³⁹Burd et al., 2007; ⁴⁰Losser et al., 1992; ⁴¹Alverson et al., 2011; ⁴²Malik et al., 1999; ⁴³Kallen, 1999; ⁴⁴Linn et al., 1982; ⁴⁵Kuehl & Loffredo, 2002; ⁴⁶Lipshultz et al., 1991; ⁴⁷Martin & Khoury, 1992; ⁴⁸Tikkanen & Heinonen, 1991; ⁴⁹Shaw et al., 2003; ⁵⁰Tikkanen et al., 1992; ⁵¹Gilboa et al., 2005; ⁵²Dadvand et al., 2011)

Table 6. Risk factors that are known or believed to be associated with the congenital heart defects.

et al., 1989). In the Baltimore-Washington Infant Study (BWIS), potential exposure to herbicides and rodenticides was associated with an increased risk of TGA, while potential exposure to pesticides was associated with TAPVR and VSD. A case-control study of various end-product uses reported an increased risk of conotruncal defects with maternal reports of exposure to insecticides (Shaw et al., 1999).

- **Air Pollution;** Ambient air pollution such carbon monoxide (CO), nitric oxide (NO), ozone (O₃), and sulfur dioxide (SO₂) may cause CHD dependent on pollutant levels (Ritz et al., 2002; Rankin et al., 2009). A study by Gilboa et al, observed positive associations between carbon monoxide and isolated ASD, TOF, particulate matter < 10 µm in diameter and isolated ASD as well as between ozone and VSD (Gilboa et al., 2005). From a study by Dadvand et al, exposure to CO and NO has been associated with ventricular septal defect and cardiac septa malformations. CO was also associated with congenital pulmonary valve stenosis and NO was associated TOF (Dadvand et al., 2011). Further studies are also required to clarify if air pollution exposure influences the risk for CHD.
- **Maternal Home Tap Water Consumption;** It has a positive association between a mother's consumption of home tap water during the first trimester of pregnancy and cardiac anomalies. This was unrelated to water contamination, mother's race, or her educational level (Shaw et al., 1990).
- **Waste Sites;** Many of the recent studies about possible increased risk of CHD in communities situated near hazardous waste sites are inconsistent (Croen et al., 1997) and may not ultimately prove to be causal.
- **Ionizing Radiation;** there are few reports on possible associations of CHD with maternal exposure to ionizing radiation in occupational settings or as part of medical or dental evaluations. Studies found no clear evidence of any association. Further studies are also required to clarify the precise relationship between these factors and CHD.

4. Prevention

Excluding genetic counseling, the genetic disorder cannot be protected against; simple guidelines to pregnant mothers for prevention of CHD in their newborns are good diet, physical activity, lifestyle, environments and occupation that the parents should discuss with their primary care provider or obstetrician. Women of childbearing age also should obtain prenatal care, including testing for diabetes and past rubella immunization, they should also discuss any medication use with their obstetrician; and should avoid contact with ill people, especially those with rubella or influenza. Women of childbearing age should take 400 micrograms of folic acid on a daily basis starting before pregnancy, which can reduce congenital heart and neural tube defects, and should avoid certain types of behaviors such as exposure to organic solvents, smoking and heavy alcohol use. If a woman has no immunity to rubella, she should get vaccinated prior to pregnancy. Preconception care and appropriate dietary management for women with phenylketonuria should be an important strategy. Detection and appropriate management of diabetes before and during pregnancy should be an important step for reducing risk of CHD in offspring. Avoidance of medications that are suspected to cause congenital defects, including congenital heart disease, should be taken, and the medications should have warnings about that risk to allow mothers and physicians to make informed decisions about the risks and benefits of the use of the medication during pregnancy. Recommendations also are possible for screening for

possible cardiac defects using fetal echocardiography during pregnancy when warranted by reports of prenatal maternal illnesses or exposures. The need for screening any individual should be made on an individual basis from the type, likelihood, and level of potential exposure, as well as the time of gestation during which it occurred. This decision typically will be made as a result of the obstetrical history. Because congenital heart defects represent some of the more prevalent birth defects, that result in significant lifelong morbidity, and are an important cause of mortality attributed to birth defects, the development of effective prevention interventions is paramount from a public health perspective.

5. Conclusion

The number of patients, both children and adults, with CHD has continued to rise. The most common reasons for CHD are associated with multiple factors. Epidemiology studies reveal underestimated cases of CHD, and together with the etiology the studies help to define potential risk factors for CHD. The epidemiology and etiology of CHD also help prioritize the areas needed for intervention and additional regulations the public health officers may impose. Patients and parents of babies with CHD must understand the significance of routine medical checkups, which can be accomplished through an effective transition program and collaboration among healthcare providers.

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7. References

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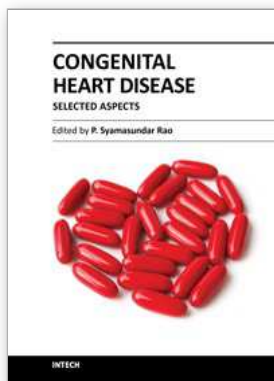
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There are significant advances in the understanding of the molecular mechanisms of cardiac development and the etiology of congenital heart disease (CHD). However, these have not yet evolved to such a degree so as to be useful in preventing CHD at this time. Developments such as early detection of the neonates with serious heart disease and their rapid transport to tertiary care centers, availability of highly sensitive noninvasive diagnostic tools, advances in neonatal care and anesthesia, progress in transcatheter interventional procedures and extension of complicated surgical procedures to the neonate and infant have advanced to such a degree that almost all congenital cardiac defects can be diagnosed and "corrected". Treatment of the majority of acyanotic and simpler cyanotic heart defects with currently available transcatheter and surgical techniques is feasible, effective and safe. The application of staged total cavo-pulmonary connection (Fontan) has markedly improved the long-term outlook of children who have one functioning ventricle. This book, I hope, will serve as a rich source of information to the physician caring for infants, children and adults with CHD which may help them provide optimal care for their patients.

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