INTRODUCTION

Congenital heart disease (CHD) is the most common congenital disorder in newborns. Congenital heart diseases accounts for about thirty percent of all major birth defects. [1] CHD is one of the leading causes of perinatal and infant death from congenital malformations. [2] In a report from the United Kingdom Northern Congenital Abnormality Survey, ten percent of deaths in this pediatric cohort with at least one congenital anomaly were associated with CHD. [1] There are approximately 1.5 million new cases of CHD per year worldwide. [3] The reported incidence of congenital heart disease at birth ranges from six to thirteen per thousand live births. [4] Variation is primarily due to the use of different methods to detect CHD, such as referral to a cardiac center or fetal echocardiographic data. [5]

A global perspective on the incidence of neonatal CHD is provided by the following studies:

- In England, incidence of cardiovascular malformations is 6.5 per 1000 live births. [2, 6]
- In a population-based study from Atlanta, the incidence of CHD is 8.1 per 1000 live births. The most common diagnosis was muscular and perimembranous ventricular septal defect (VSD), followed by secundum atrial septal defect (ASD) with incidence of 2.7, 1.1, and 1 per 1000 live births, respectively. Tetralogy of Fallot was the most common cyanotic congenital heart disease (CCHD) with incidence of 0.5 per thousand live births. [7]
- In a population-based study, the incidence of CHD in Denmark is 10.3 per 1000 live births. Chromosomal defects were detected in 7 percent of those patients, and extracardiac anomalies (ECA) in 22 percent. [8]
- In a population-based study. The incidence of CHD in Greater Paris is 9 per 1000 live births. [4]
- The highest incidence for CHD is observed in a population-based study from Taiwan with an incidence of 13.1 per 1000 live births. The most common defect was VSD, followed by secundum ASD and patent ductus arteriosus with incidence of 4, 3.2 and 2 per 1000 live births, respectively. [9]

The following chart shows time course of total congenital heart disease birth prevalence from 1930 until 2010. The blue line shows the time trend and the squares represent the calculated birth prevalence values for each time period. [10]

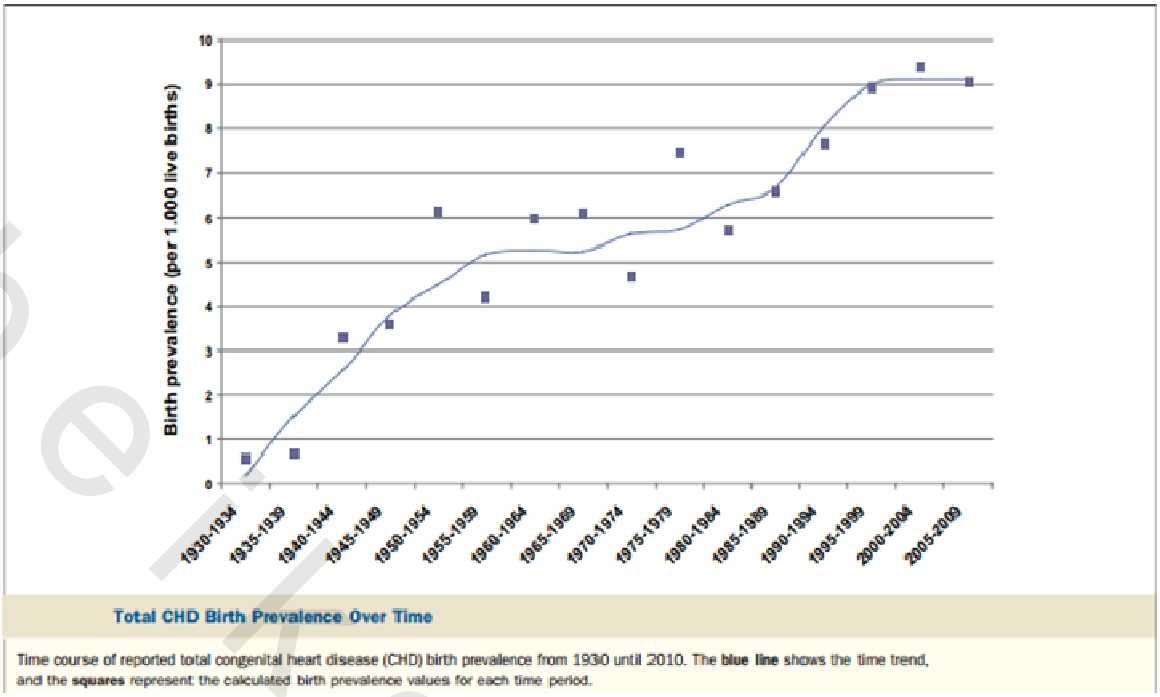

Figure (1): Time course of total congenital heart disease birth prevalence from 1930 until 2010

Acyanotic congenital heart lesions can be classified according to the predominant physiologic load that they place on the heart. Although many congenital heart lesions induce more than one physiologic disturbance, it is helpful to focus on the primary load abnormality for purposes of classification. The most common lesions are those that produce a volume load, and the most common of these are left-to-right shunt lesions. Atrioventricular valve regurgitation and some of the cardiomyopathies are other causes of increased volume load. The second major class of lesions causes an increase in pressure load, most commonly secondary to ventricular outflow obstruction (pulmonic or aortic valve stenosis) or narrowing of one of the great vessels (coarctation of the aorta). [11]

Cyanotic congenital heart lesions can also be divided according to pathophysiology:

whether pulmonary blood flow is decreased as in tetralogy of Fallot, pulmonary atresia with an intact septum, tricuspid atresia and total anomalous pulmonary venous return with obstruction or increased as in transposition of the great vessels, single ventricle, truncus arteriosus, total anomalous pulmonary venous return without obstruction. [11]

There are eight common lesions, which account for about 80% of all CHD. They include ventricular septal defect (VSD), patent ductus arteriosus (PDA), atrial septal defect (ASD), tetralogy of Fallot (TOF), pulmonary stenosis (PS), coarctation of the aorta, aortic stenosis (AS) and transposition of great arteries (TGA). The remaining 20% is made up by a variety of more rare and complex lesions. [12]

Etiology of CHD is multifactorial and a large collection of environmental and genetic causes have a role in its pathogenesis. [13]

Over the past decade, there have been major breakthroughs in the understanding of inherited causes of congenital cardiovascular defects, including the identification of specific genetic abnormalities for some types of malformations. [14] There is ample evidence that nonsyndromic cardiovascular malformation is polygenic, and gene–gene and gene–environment interactions will play a significant role in pathogenesis. [15- 16]

While 60 to 75% children born with CHD do not have other birth defects, CHD occurs in association with other anomalies or as part of an identified syndrome in 25 to 40% cases. [17] In addition, approximately 30% of children with a chromosomal abnormality will have CHD. Aneuploidy, or abnormal chromosomal number, accounts for a significant proportion of CHD. Fifty percent of individuals born with Trisomy 21 (Down) have CHD, ranging from atrioventricular canal lesions to atrial and ventricular septal defects. In Trisomy 13 (Patau), the incidence increases to 80%, with heterotaxy and laterality defects becoming more common, and among individuals with Trisomy 18 (Edward), nearly all will have CHD, usually in the form of septal defects. Approximately one-third of individuals with Turner syndrome, or monosomy X, have CHD. The malformations are usually of the left-sided cardiac structures, and the most common diagnoses include bicuspid aortic valve, aortic stenosis, hypoplastic left heart syndrome, and coarctation of the aorta. In individuals with Klinefelter syndrome, or 47 XXY, there is a fifty percent incidence of CHD, with patent ductus arteriosus and atrial septal defects prevailing. [14]

Between 25% and 30% of children with CHD will have some form of additional congenital lesion, a comorbidity or structural extracardiac anomaly that may or may not be immediately appears. [18] However, comorbidity may have an important, even crucial, bearing on the course and outcome of the management of a child with a congenital heart lesion. In recent times the surgical options for complex congenital cardiac surgery have increased significantly and therefore the presence and severity of comorbidities have become increasingly important in the management of CHD. This includes both the complexity of the surgery in the first place and the decision to offer surgery at all. It is known that the surgical mortality of CHD surgery of children with ECA may be as high as 60%. [19] Patients with grown up congenital heart often need long-term expert medical care and healthcare-related costs are high. Therefore, the global health burden as a result of CHD increases quickly and their long-term functional morbidities have become the focus of increasing concern. [20]

Approximately 5% to 10% of children with CHD develop pulmonary arterial hypertension (PAH) of variable severity that affects quality of life, morbidity and mortality. [21]

PAH is a dynamic and multifactorial process related to vasoconstriction and remodeling of the pulmonary vascular bed that may be aggravated by thrombosis. Several histopathological abnormalities associated with congenital heart disease and PAH, such as extension of smooth muscle cells into peripheral pulmonary arteries, medial hypertrophy, formation of plexiform lesions and rarification of the pulmonary arterial tree, have been observed. [22]

Restrictive lung function appears to be a prominent finding in many types of CHD both pre and post-surgical repair. In addition, both obstructive and diffusion defects can also be seen depending on the underlying pathophysiology. [23]

Respiratory tract infection in children with CHD is an important cause of morbidity and mortality including respiratory failure, prolonged mechanical ventilation, and hospitalization. [24] The incidence of nosocomial pneumonia in children after cardiac surgery varies from 9.6% to 21.5%. [25]

Neurological and developmental outcomes of congenital heart patients are influenced by many factors, both innate and acquired, with cumulative effects. Genetic syndromes such as trisomy 21 or 22q11 microdeletion may affect both the heart and the brain. Cerebral dysgenesis is reported to occur in 10% to 29% of children with congenital heart disease in autopsy series, with the incidence varying by lesion. Findings may range from microdysgenesis to gross abnormalities such as agenesis of the corpus callosum, incomplete operculization, and microcephaly. [26]

During fetal life, congenital heart lesions may be associated with changes in cerebrovascular blood flow distribution and resistance. [27] Postnatal neurodevelopmental risk factors may derive from the sequelae of congenital heart disease itself -eg, chronic severe hypoxemia, failure to thrive, arrhythmias with cardiac arrest or hypotension- or from the procedures used for cardiac correction or palliation. [28] Focal infarction has been ascribed to thromboembolic events, whereas a diffuse pattern of cerebral injury has been attributed to hypotension and hypoperfusion. [29]

Adults with CCHD often develop secondary erythrocytosis as a physiological response to tissue hypoxia with resultant increase in serum erythropoietin level, thereby stimulating the bone marrow erythropoiesis causing an elevated red cell mass, hematocrit, and whole blood viscosity. The increase in circulating red cells provides increased oxygen carrying capacity. [30] However, this effect is offset by the increase in serum viscosity that reduces blood flow and tissue perfusion and impairs tissue oxygen delivery with resultant hyperviscosity symptoms. The major consequence of hyperviscosity is thrombosis, which may manifest as a cerebrovascular accident (CVA), myocardial infarction, or other overt thrombotic event. [31]

Polycythemia not only increases the risk of CVA but can also mimic computed tomography (CT) sign of cerebral venous thrombosis. Magnetic resonance imaging (MRI) is necessary to confirm the diagnosis. [32]

Malnutrition in children with congenital heart defects has been linked to increased morbidity and mortality as indicated by frequent hospitalisation, poor surgical outcomes, persistent impairment of somatic growth and increased death. [33] Mechanism of malnutrition in children with CHD is multifactorial and appears when the need for, and losses of, energy and nutrients are greater than the intake. [34] Levels of malnutrition in children with congenital heart disease correlate with the type of heart defect and severity of hemodynamic disturbance. [35]

The renal functions of patients with acyanotic congenital heart disease has been less studied, and relatively few studies have focused on renal function in infants and young children with congenital heart diseases. [36] Those studies have documented proteinuria, decreased renal blood flow, and decreased glomerular filtration rate in patients with CHD; however, only a few reports have discussed renal tubular dysfunction in this group. [37]

Although in children with acyanotic pulmonary hypertension the existing proteinuria is not in the range of nephotic syndrome but significant proteinuria may be found up to 20% of them. In the acyanotic period, urine protein excretion in children is not related to age, pulmonary artery pressure, hematocrit and tricuspid regurgitation. The appearance of proteinuria may indicate that nephropathy begins at this period. [38]

It has been documented that chronic cyanosis affects renal glomerular structure and function. The structural hallmark of glomerular injury in patients with congenital cyanotic heart disease has been described as glomerulomegaly, capillary dilatation, thickening of the capillary walls, focal or diffuse proliferation of mesangial cells, and segmental or global glomerulosclerosis. [37] Although proteinuria is the major urinary abnormality in patients with cyanotic congenital heart disease, nephrotic syndrome is an uncommon complication and renal biopsy has been seldom perfomed. Adverse effects of chronic hypoxia on renal tubular function have been less frequently documented. Secondary renal tubular acidosis seems to be an acquired complication in patients with chronic cyanosis. [39]

Hypoxia has been shown to induce proliferation of renal tubular and glomerular cells, changes that are part of the pathogenesis of renal injury. Research has shown that renal injury is correlated with duration of CHD. The incidence of moderate-to-severe GFR reduction has been reported to be 35-fold higher in adults with CCHD than in the general population, with an associated fivefold higher mortality. [40]

Accurate estimation of kidney function in children is important from a clinical, research, and public health perspective. From a clinical standpoint, the most commonly used marker of kidney function, serum creatinine, varies by body size, sex, and race, and given the wide range of maturation of skeletal muscle and growth observed in the pediatric population, recognition of abnormal creatinine values is more challenging. [41]

Estimation of glomerular filtration rate (GFR) may aid in the identification and management of acute and chronic kidney injury, including facilitation of appropriate fluid and medication dosing. The international epidemic of chronic kidney disease (CKD) in adults mandates research and public health interventions to identify CKD and slow its development and progression. [42]

Because of the great reserve capacity of the kidney, tests used for assessing the functional integrity of the kidney (such as serum creatinine or urea and GFR) are not sufficiently sensitive because these measurements can be in the normal range despite considerable impairment of renal function, and they become significantly altered only after considerable damage to the kidney has occurred with major functional impairment. [43]

Serum and urinary biomarkers, both glomerular and tubular, play an important role in the early detection of renal damage. Urine as a diagnostic medium allows for noninvasive detection of biomarkers. Detection of renal tubular proteins and enzymes in the urine demonstrates a tubular involvement that leads to renal complications. [43]

The methods to evaluate renal tubular function include the measurement of levels of low molecular weight proteins like ß2-microglobulin(ß2M), retinol binding protein, 1-microglobulin and urine protein 1 in urine, urinary excretion of Na and N-acetyl-ß-D-glucosaminidase (NAG). [44] ß2M is excreted from the blood through the glomeruli into the urine, and most is reabsorbed from renal tubular cells. In the case of renal tubular dysfunction,

urinary ß2M excretion increases. In contrast to ß2M, NAG is a lysosomal enzyme present in most of the organs, including the brain, liver, kidney, etc. With its large molecular weight, NAG is not excreted from the blood into the urine. Therefore, urinary NAG is considered to derive from membrane surface components of the most vulnerable and damaged proximal tubule epithelia. Thus, increased urinary ß2M and NAG levels are useful markers to detect tubular dysfunction. [45]

Plasma ß2M levels depend on their production rate and the patient's GFR. [46] The rate of production of ß2M can increase significantly in active neoplasms, infections, or autoimmune diseases. Serum ß2M levels are also elevated in patients with increased arterial stiffness and in patients with peripheral arterial disease due to several factors, such as declining renal function and repeated bouts of ischemia and reperfusion. [47]

Due to the limitations of serum creatinine for screening of acute kidney injury (AKI), Researchers have discovered numerous novel biomarkers that have proven value in the differential diagnosis, early detection, and prognosis of AKI. One such marker is neutrophil-gelatinase-associated lipocalin (NGAL), a polypeptide whose production is upregulated in animal models of AKI and whose elevation can be detected in urine and serum. Elevated levels of NGAL have enabled detection of AKI within a few hours after cardiac catheterization. Plasma NGAL has also been used to predict morbidity and mortality in pediatric patients who undergo cardiac surgery. A recent study demonstrated that a single measurement of urinary NGAL in the emergency room could better predict clinical outcomes such as the need for nephrology consultations, intensive care unit admission, dialysis initiation, or mortality than could an elevated serum creatinine. [48] The appearance of NGAL in the urine was related to the dose and duration of renal ischemia and preceded the appearance of other urinary markers such as NAG and ß2M. There is now strong evidence that increased urinary and serum NGAL reflect damage across a spectrum of kidney diseases as well as AKI and may predict progression of CKD. [49]

Another biomarker is interleukin -18, (IL-18), a cytokine that may play a role in the pathogenesis of ischemic acute tubular necrosis through the recruiting of neutrophils in response to ischemic injury. Kidney Injury Molecule-1 (KIM-1) can also serve as a marker. This molecule is upregulated in postischemic injury in the proximal tubule. [50]