CHAPTER 1

Epidemiology of Congenital Heart Diseases

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Abstract: Congenital heart defects (CHD) are among the most common birth defects, occurring in 5 to 10 per 100 live births. This substantial variation in the reported epidemiology of CHD is due to differences in applied methodologies. An increasing total prevalence of CHD has been recently reported, mainly due to increase in prevalence of small defects easily diagnosed by echocardiography, as well as an increase in prevalence of conotruncal defects and atrioventricular septal defects.In order to provide a comprehensive epidemiological overview, future studies should use international classification system as well as consistent inclusion and exclusion criteria. Futher studies are also required to evaluate precisely the impact of fetal cardiac diagnosis on the prevalence and outcome of CHD. Epidemiology of CHD provides an overview of the distribution and characteristics of risk factors. Environmental potential risk factors are reviewed as they may provide an opportunity for prevention of some forms of CHD.

Key Words: Congenital Heart Disease, Epidemiology, Environmental Risk Factor.

INTRODUCTION

Congenital heart defects (CHD) defined as "gross structural anomalies of the heart or intrathoracic vessels that are actually or potentially of functional significance", are among the most common congenital anomalies affecting about 5 to 10 per 1000 live births and are considered as the leading cause of infant deaths resulting from congenital anomalies [1,2,3].

CAVEATS IN ASSESSMENT OF INCIDENCE OF CHD

Accurate determination of the incidence of CHD is difficult and subject to great variation across different populations and registries: some mild and asymptomatic cases may not be diagnosed and consequently they are underestimated; other severe cases may die in the neonatal period without a diagnosis or autopsy done. However development of echocardiography as an accurate diagnostic tool for CHD [2], resulted in increased estimated values for incidence of CHD, secondary to improved prenatal diagnosis [4,5], as well as improved diagnosis of overlooked and mild lesions (e.g., increased diagnosis of cases with small atrial septal defects (ASD), and isolated small ventricular septal defects (VSD), which tend to resolve spontaneously).

To avoid confusion, and in order to provide a comprehensive review, epidemiological studies reporting total prevalence of CHD, should cover a geographically well defined area, and should include CHD occurring in live births, termination of pregnancy, late miscarriages and stillbirths. Cases with functional or unspecified cardiac murmur, patent ductus arteriosus (PDA) associated to prematurity, peripheral pulmonary artery stenosis (PPS), should be excluded, according to the European Surveillance of congenital anomalies EUROCAT exclusion list [6]. Furthermore, it is better to relate the absolute incidence of each specific lesion, to live births, rather than describing its incidence as a proportion of all CHD. In a recent study from Denmark, the overall CHD birth prevalence, have been reported to have increased [7] from 73 to 113 per 10.000 live births from 1977 to 2005 with stabilization of the prevalence after 1996–1997. The increased prevalence was primarily due to an increase in VSD and ASD prevalence, related to improved diagnosis by echocardiography as reported by others [8,9,10,11]. The total prevalence of conotruncal defects, atrioventricular septal defects (AVSD), and right ventricular outflow obstruction (RVOTO) increased also significantly [7, 8], probably due to changes in the pregnancy risk factors particularly the increasing incidence of type 2 diabetes among women of childbearing age [7,12].

IMPACT OF FETAL DIAGNOSIS OF CHD

Fetal diagnosis of structural heart defects by ultrasound ranges from 8% in eastern Europe to 48% in France [4] due to an active policy in prenatal screening and involvement of obstetricians and sonographers in screening for cardiac

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malformations during routine obstetrical ultrasounds. This may have a potential impact on the incidence of CHD if termination of pregnancy is decided [4,13, 14]. In a study including 2454 cases with CHD, collected from 20 registries of congenital malformations in 12 European countries, termination of pregnancy was performed in 293 cases [12%) varying from 0% to 49% according to the registry [4]. In a recent analysis obtained from the Paris registry of congenital malformations, Koshnood et al. [5], reported increase rate of termination of pregnancy for cases with hypoplastic left heart syndrome (HLHS) detected by fetal echocardiography, that increased from 13.6%, between 1983-1988 to 72.4% between 1989-1994, before reaching a rate of 63% between 1995- 2000. Further studies are required to assess the impact of fetal medicine in the prevalence and outcome of CHD.

GEOGRAPHIC, RACIAL, ETHNIC & SOCIO-ECONOMIC DISTRIBUTION OF CHD

The reported incidence of various cardiac defects may vary according to different geographic regions [11, 15-17] probably related to genetic and racial factors. For example, studies of ethnic influence on the pattern of CHD in the United Kingdom revealed a higher incidence of left obstructive disease such as aortic stenosis (AS) and coarctation of aorta (Ao Coa) in non-Asian (9%) than Asian (3%) infants [15]. This was also reported from epidemiologic studies from Saudi Arabia [11] and Japan [16], where a low incidence of AS and Ao Coa was reported (4.8% and 3.7% respectively of all patients with CHD) contrasting with a higher incidence reported from Europe [17]. A low incidence of AVSD was also reported from Japan [16] contrasting with a higher incidence in United Kingdom [15].

Compared with black infants, white infants have been found to have an increased prevalence of Ebstein's anomaly, AS, Pulmonary atresia, AVSD, ASD, Ao Coa, Transposition of great arteries (TGA) and Tetralogy of Fallot (TOF), while less white infants were found among cases with Pulmonary stenosis (PS) and heterotaxia [18]. These results highlight racial variations in CHD and may suggest that socio-economic status (SES) account for some of this variation, as also evidenced by an increased risk for TGA reported with low SES that included mother's education, poverty, and unemployment [19].

SEX DISTRIBUTION

As regards sex distribution of CHD; some lesions such as Ao Coa, AS, TGA show strong male predominance [11, 20-21]. On the other hand, female predominance is observed in PDA, ASD, AVSD and PS [20, 21]. Gensburg et al [22], classifying isolated lesions according to the time of embryonic disturbed organogenesis, found male predominance in those lesions developing in later gestation.

ETIOLOGY OF CHD

Cardiovascular development involves a series of complex events precisely orchestrated and regulated by specific genes. CHD represent multiple underlying etiologies: genetic, environmental, teratogenic exposures, multifactorial and unkown mechanisms.

The precise links between genetic and environmental factors, are incompletely understood. Environmental factors may affect gene expression directly or may block the action of gene product. Some outflow tract (Truncus Arteriosus, Double outlet right ventricle) that may be associated with the DiGeorge (CATCH 22 syndrome) may result also from interfering with migration of neural crest cells by certain chemicals (bis-diamine, tran-retinoic acid), or by experimentally removal of cranial neural crest cells [23].

The current state of knowledge on genetic causes of CHD [24] is reviewed separately in another chapter. Environmental factors involved in the etiology of CHD are multiple and include maternal diseases, drug exposures, alcohol, and other environmental exposures [24,25,26]. The potential factors that might influence the risk for CHD including periconceptional folic acid intake which may reduce the risk [27-29] and those factors that increase the risk for CHD are discussed.

ROLE OF MULTIVITAMINS AND FOLIC ACID

Periconceptional intake of multivitamins supplements containing folic acid [27,28] was reported to possibly reduce the risk of CHD up to 60% [27]. In a recent work [29], fortification of grain products with folic acid in Canada, was followed by a significant decrease in the birth prevalence of severe CHD strongly supporting the protective effect of Folic acid. Specifically, the birth prevalence did not change in the eight years before fortification and decreased in the seven years after fortification with a significant change in time trend between the two periods for conotruncal defects and non-conotruncal defects [29].

MATERNAL DISEASES AND CONDITIONS

MATERNAL DIABETES

CHD is found in 3-5% of pregnant women with maternal pregestational diabetes [30-32]. Associations of CHD with gestational diabetes are probably due to inclusion of pregnant women with previously undetected type 2 diabetes among those classified as having gestational diabetes. Almost all cardiac lesions have been reported, mainly outflow tract lesions, conotruncal anomalies, AVSD, TGA, VSD, HLHS and Ao Coa [30-32]. Cardiac malformation occurs before the seventh week of gestation possibly by abnormal glucose level affecting the expression of a regulatory gene in the embryo, leading to apoptotic cellular changes [32]. Another possible mechanism is the generation of free radicals resulting from metabolic abnormalities as suggested by prevention of diabetic embryopathy in animal studies by antioxidants [33-34].

Phenylketonuria

Maternal phenylketonuria is associated with increased risk of heart defects through increased blood levels of phenylalanine and phenyl pyruvic acid [35,36]. The most frequent defects are TOF, Ao Coa, VSD, PDA, Single ventricle, and ASD. Diet control before conception and during pregnancy reduces the risk of CHD [36].

Rubella, Febrile Illnesses, and Influenza Maternal rubella infection during pregnancy can result in increased incidence of CHD about 35% [37-39]. Common reported defects are PS, PDA, VSD, PPS, and VSD [40,41]. Maternal febrile illnesses, influenza, during the first trimester of pregnancy, may also be associated with an increased risk for certain heart defects such as conotruncal lesions, right and left obstructive lesions , VSD and Ao Coa [42-44].

Maternal HIV

Children infected with HIV-1 has not been reported to be associated with an increased risk of CHD. [45]. Irrespective of their HIV-1 status, infants born to women infected with HIV-1 have significantly worse cardiac function than other infants [45-46].

Maternal Stress

Intense maternal stress (e.g. divorce, death of a relative,..) 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 [47, 48].

MATERNAL DRUG INTAKE

Table **1** summarizes main maternal drug exposure -during the first trimester of pregnancy and periconceptional period - associated with CHD [24-26, 48-55].

Table 1: MATERNAL DRUG INTAKE AND CHD . Data from references [24, 25, 26, 48-55]

DRUG	CHD
Lithium	ASEEbstein's anomaly, Mitral & tricuspid regurge
Retinoic Acid	Conotroncal malformations
Trimethadione	TOF, HLHS, TGA,
Phenytoin	Coarctation, PDA,AS, PS
Coumadin	PPS, PDA
Thalidomide	PS, TGA, *TAPVR,VSD, ASD, TA, TOF
Ibuprofen	TGA, AVSD, VSD, Bicuspide valve
Trimethoprim-Sulfonamide,	
Sulfalazine	Any defects
Angiotensin-converting	
enzyme inhibitors	ASD, VSD, PS, PDA
Metronidazole	
Valproic acid	Outflow tract, VSD TOF, others

*TAPVR: Total Anomalous pulmonary Venous Return

Some of the drugs were reported with associated risks of CHD, but only limited information is available e.g. Angiotensin –converting enzymes [49], Trimethoprim-Sulfonamide [50-51], metronidazole [24] , fluconazole [52,53].

OTHER MATERNAL NON THERAPEUTIC & ENVIRONMENTAL EXPOSURE

Alcohol

Several studies have reported teratogenic effects of alcohol consumption during pregnancy, including cardiac defects [56]. A more recent case-control study that examined the risk of congenital anomalies with different sporadic and daily doses of alcohol consumption in spain, reported an increased risk of CHD only with the highest level of maternal consumption of alcohol per day [57].

Cocaine and Marijuana

Maternal cocaine ingestion was reported to induce coronary thrombosis in the developing fetal heart leading to single ventricle [58]. Association of maternal intake of cocaine with other defects was also reported : Ebstein's anomaly , VSD, heterotaxy [24,59, 60].

Cigarette Smoking

The relationship between gestational smoking and congenital defects has been studied, however the information is inconclusive. Some studies have reported associations of maternal smoking with ASD, AVSD, TOF [61], however, no associations were found in other reports [24,62]. Further research on large population-based studies is required to clarify this relationship.

Organic Solvents

Some studies reported increased risk of TGA, HLHS, Ao Coa, TOF, PS with maternal exposure to solvents and paints [24]. However the precise links are difficult to clarify, because the composition varies between different commercial preparations.

Pesticides & Other Toxic Substances

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 [24]. A more recent case-control study of various end-product uses reported an increased risk of conotruncal defects with maternal reports of exposure to insecticides [63].

Air Pollution

Gilboa et al [64], observed positive associations between carbon monoxide and isolated ASD, TOF, particulate matter <10 μm in aerodynamic diameter and isolated ASD as well as between ozone and VSD. Further studies are also required to clarify if air pollution exposure influences the risk for CHD.

Maternal Home Tape Water Consumption

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 [65].

Waste Sites and Ionizing Radiation

Much of the recent evidence about possible increase risk of CHD in communities situated near hazardous waste sites are inconsistent [66] and may not ultimately prove to be causal. Few reports on possible associations of CHD with maternal exposure to ionizing radiation in occupational settings or as part of medical or dental evaluations, found no clear evidence of any associations [24], and further studies are also required to clarify the precise relationship between these factors and CHD.

CONCLUSION

CHD is associated with a considerable disease burden at both country and individual levels. Although there is a substantial variation in the reported prevalence of CHD in the literature, due to differences in epidemiological

studies, however recent studies suggest an increased prevalence of CHD, mainly by increased incidence of small lesions easily detectable by echocardiography, as well as increased prevalence of conontruncal and atrioventricular septal defects.

Fetal diagnosis of CHD may affect the prevalence and the outcome of CHD. The impact of fetal diagnosis on prevalence, and outcome of CHD requires further investigations as there is no available uniform parental counselling and ethical guidelines.

Prevention of CHD is actually limited to our actual knowledge of the proportion of CHD attributable to non inherited potentially modifiable environmental fetal exposure, that although difficult to estimate, may account for 13.6% to 30.2% of cases [26].

Further epidemiological studies, based on large population-based studies, using more standardized case ascertainment and classification methods are required, to unmask some of the mysteries of abnormal cardiogenesis and clarify the precise links between inherited and non inherited risk factors and CHD, in order to be able to develop adequate prevention strategies.

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