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Epidemiology, etiology and pathogenesis of congenital heart defects

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Summary. - Congenital heart defects (CHD) are a frequent cause of death and disability and cause a significant toll in terms of personal distress and social costs. The only satisfactory way of reducing this burden is through primary prevention, which in turn can be implemented only when the cause and mechanism of these defects is known. While current knowledge on the impact on the population and on the etiology and pathogenesis of CHD is still largely unsatifactory, some progress has been made in recent times and promising research is currently being performed; these topics are discussed in this paper, with special emphasis on quantitative risk assessment of putative cardiac teratogens.

Key words: congenital heart disease, malformations, epidemiology, teratogens, chromosomal defects.

Riassunto *(Epidemiologia, eziologia e patogenesi delle cardiopatie congenite)*. - Le cardiopatie congenite (CHD) sono causa relativamente comune di morte e di patologia, ed il loro impatto in termini di sofferenza personale e costo sociale è significativo. Il solo modo soddisfacente di ridurre questo carico è attraverso una prevenzione primaria, che a sua volta è possibile solo quando si conoscano la causa e possibilmente il meccanismo alla base di questi difetti. Se da un lato la conoscenza attuale sull'impatto nella popolazione e sull'eziologia e patogenesi delle CHD è ancora largamente insoddisfacente, dall'altro si è assistito recentemente a progressi significativi ed attualmente sono in corso ricerche promettenti. Questa rassegna si propone di discutere tali argomenti, con particolare attenzione alla qualificazione e quantificazione del rischio associato a teratogeni cardiaci possibili od accertati.

Parole chiave: cardiopatie congenite, malformazioni, difetti congeniti, epidemiologia, teratogeni, difetti cromosomici.

Introduction

Congenital heart defects (CHD) are among the most frequent of all major birth defects [1], accounting for approximately one-third of all significant anomalies [2]. The relative importance of CHD as a cause of early death is steadily increasing, as other causes of death have become less common. From an economic standpoint, the cost of surgery and rehabilitation on patients with CHD consume a considerable and growing proportion of the limited resources of the health services [3]. Most importantly, however, CHD cause considerable human suffering and strain upon the patients and their families.

Great advances have been made in the diagnosis and treatment of these defects. Much slower has been the progress in other aspects of CHD: the accurate assessement of the impact on the population and an understanding of the etiology and pathogenesis. These issues are basic to bring about a true reduction of CHD through primary prevention.

Birth prevalence

The birth prevalence of CHD has been estimated to be 8 per 1,000 live births. However, rather large differences between studies have been found, with most studies reporting rates somewhere between 3 and 10 per 1,000 live births [4]. Two of the most recent and quoted studies report rates of confirmed diagnoses at 1 year of age of 5.5 [5] and 3.7 per 1,000 livebirths (Table 1) [6].

It is likely that at least part of this variation between studies is due to differences in diagnostic criteria and other methodological factors [6]. These studies differ in many important aspects, such as population size, exclusion criteria, maximum age at diagnosis, diagnostic confirming criteria (clinical, echocardiographic, invasive), several of which may lead to the underestimation and distortion of prevalence rates; a few of these will be outlined.

Diagnostic criteria may differ. Most studies concentrate on gross structural defects; this approach may be acceptable, in that the inclusion of minor functional or

structural defects would not usually alter considerably these figures. However, there are at least three important exceptions: mitral valve prolapse, patent ductus arteriosus of prematurity and bicuspid aortic valve. Most studies exclude these defect categories from their case definition. The incidence of these three defects may be quite large, much larger than all CHD lumped together, and while it is debatable whether they should be considered congenital structural defects, their exclusion may lead to underestimate the impact of CHD in the population at large and the cost of medical care. Also, small ventricular septal defects of mild pulmonic stenosis may not have been included in all studies [4].

The examined population (livebirths *vs* all births) may differ. The rate of CHD in prenatal deaths is high; in stillbirths it is approximately ten times higher than in livebirths and possibly even higher in abortuses [7], as many early abortions are associated with chromosomal anomalies.

Given these figures, if the incidence of stillbirths is about 2 per cent [8] and among spontaneous abortion about 22 to 43 per cent of pregnancies [9], the total incidence of CHD may be estimated to be five times higher than that reported in livebirths alone [3].

Therefore, if only livebirths are examined, the potential importance of genetic and chromosomal factors may be underestimated and the impact of teratogenic factors may be distorted or totally missed [10].

The incidence of CHD is similar in all major ethnic groups [11] and for males and females [12], though differences in sex ratio [13] and racial status [14] have been described for certain types of CHD.

The frequency of non-cardiac defects in patients with CHD varies considerably according to diagnostic criteria and ascertainment methods [15]; it is estimated that about 25-30% of livebirths with CHD present at least one additional non-cardiac defect [15]. Therefore major birth defects are about ten times more frequent in patients with CHD compared to the general population in whom the rate of major birth defects is about 3%; from a clinical perspective, the implication is that the presence of a CHD in a newborn should alert to the possibility of coexisting, clinically relevant defects.

About one half of patients with additional non-cardiac defects have a recognizable syndrome (Mendelian or non-Mendelian). The most frequent syndromes are chromosomal, mainly trisomy 21, 18 and 13, and account for about half of the syndromic cases [15].

In summary, CHD occurs in about 1 per cent of liveborn infants, but in a much higher proportion of those stillborn or spontaneously aborted. It is generally agreed that there has not been any major increase in the true incidence rates in these last few years [6]. Much of the difference in rates between studies may be accounted by differences in diagnostic and methodologic criteria. Most importantly, there are many potential pitfalls in the study of the incidence of CHD; very intensive studies, use of multiple sources of information and careful evaluation of data must be very high priorities in any investigation of this kind.

Etiology and pathogenesis of CHD

Known causes of CHD include chromosome abnormalities, single-gene disorders and teratogens. To date these causes combined account only for maybe 15% of cases. In the remaining 85% of cases it is generally, but not uniformily, accepted that the defect has a multifactorial etiology.

Table 1. - Comparison of proportion and rates of different types of congenital heart defects in three studies: Heritage Pediatric Cardiology Program (HPCP) [5], The New England Regional Infant Cardiac Program (NERICP) [69] and the Baltimore-Washington Infant Study (BWIS) [6]

Diagnostic category	HPCP		NERICP		BWIS	
	Rate per 10,000	%	Rate per 10,000	%	Rate per 10,000	%
Ventricular septal defect	6.0	17.9	3.8	17.3	3.5	14.5
Atrial septal defect	2.1	6.3	0.7	3.3	0.9	4.0
Transposition of great arteries	2.8	8.4	2.3	10.5	2.1	8.9
Tetralogy of Fallot	1.8	5.5	2.1	9.7	1.9	7.9
Double outlet right ventricle	1.4	4.3	0.3	1.5	0.6	2.3
Atrioventricular septal defect	2.0	6.1	1.2	5.4	2.5	10.5
Persistent ductus arteriosus	1.9	5.8	1.4	6.2	0.6	2.63
Total anomalous pulmonary venous return	0.9	2.6	0.6	2.6	0.8	3.5
Left-sided obstructive lesions	6.8	20.2	3.9	17.8	4.9	20.6
Right-sided obstructive lesions	4.0	11.8	2.0	9.1	1.9	7.9
Other lesions	3.8	11.2	3.6	16.5	4.1	17.3

(Modified from [5]).

Chromosomal abnormalities and CHD

Chromosomal abnormalities are an important cause of CHD. Until recently it was estimated that about 5% of liveborn cases with CHD had an associated chromosome abnormality [16, 17]. This figure has been recently challenged as unrealistic on the basis of simple arithmetic derivation [18] which shows that from the known prevalence rates of chromosomal abnormalites it can be estimated that the proportion of CHD due to chromosomal abnormalities should be over 10%. In fact, a recent survey [19] reported that about 13% of infants with CHD had a chromosomal abnormality. Most cases associated with abnormal chromosomes tend to have additional non-cardiac defects. This highlights the importance of performing a caryotype in patients with CHD, particularly in the setting of multiple malformations or abnormal central nervous system function.

Autosomal abnormalities and CHD. Down syndrome

In trisomy 21 (Down syndrome), the largest specific subgroup, about 40-60% of cases have a CHD [20]. In these patients, the distribution of specific heart defects is peculiar. There is a predominance of endocardial cushion defects (ECD); this defect is present in about 2.8 per cent of all children with a CHD, but if DS is also present, the proportion rises to about 60 per cent [19, 21]. Situs abnormalities and transposition of the great vessels (TGV) are strongly underrepresented in DS. In fact, though a few case reports have appeared in the literature, apparently no confirmed case has been produced yet [19].

These findings have interesting pathogenetic implications. The predominance of ECD in DS has been linked to the increased cellular adhesiveness found in this disease [22]; indeed a stochastic model with this variable has been reported to generate structures similar to ECD [23]. As for the striking absence of looping abnormalities and TGV in DS, it has been suggested [24] that the triple chromosome 21 gives a surplus genetic "dose" of situs solitus.

Other autosomal abnormalities and CHD

Less frequent autosomal abnormalities include trisomy 18 (1 in 3,500 births), trisomy 13 (1 in 7,000 births) and a host of others, reviewed elsewhere [25]. In the first two forms, the frequency of CHD is very high, exceeding 90%, and the most common defects are ventricular septal defects and atrial septal defects.

Sex chromosome abnormalities and CHD

While the risk associated with autosomal abnormalities is high, this is not always true with sex chromosome abnormalities. Turner syndrome (45,X0) is at high risk [26], in that 25% of patients have a CHD; among these a predominance of left sided obstructive defects has been reported (coarctation of the aorta, aortic stenosis, hypoplastic left heart syndrome). This finding has lead to speculate about a genetic factor which may predispose to these lesions. It was proposed [27] that these obstructive defects are secondary to decreased blood flow in the left atrioventricular canal of the developing heart due to compression of the ascending aorta by the distended thoracic duct; the latter leads also to the formation of cystic hygroma, a common finding in Turner syndrome. As mentioned above, not all sex chromosome abnormalities carry an increased risk for CHD: Klinefelter syndrome and 47,XXX, for instance, apparently are not high risk conditions.

In summary, chromosomal abnormalities are an important cause for CHD; in fact, they constitute the largest specific etiologic subgroup. Most often, the CHD is part of multiple organ involvement; the clinical implication is that the presence of multiple defects should alert to the possibility of a chromosomal syndrome and in this setting caryotyping must be routinely performed.

Single gene conditions

It has been estimated that about 3% of CHD are due to single-gene or Mendelian conditions [28, 29]. As with chromosomal abnormalities, Mendelian disorders usually cause a pattern of multiple defects rather than isolated defects. Prominent exceptions to this general rule are the dominant form of idiopathic hypertrophic subaortic stenosis (MIM, 19260) and a dominant (MIM, 10880) and recessive (MIM, 20940) form of atrial septal defect (ASD).

To date, hundreds of Mendelian disorders have been listed and are reviewed elsewhere [30]. A necessarely limited list of selected conditions is given in Table 2.

Single gene conditions, though individually rare, should not be dismissed as mere nosologic curiosities, since, if a specific diagnosis can be made, the accumulated knowledge on the natural history and therapy of that specific form may be exploited for a better management of the patient and, most importantly, for an accurate risk assessment for genetic counseling can be made. The risk of recurrence for parents who have had a child with a Mendelian condition depends upon the mode of inheritance of that specific condition. In recessive conditions, the risk for recurrence is 25%. In dominant conditions the risk is 50%, unless a new dominant mutation is present, in which case the recurrence rate equals the mutation rate, ie, nearly zero.

The clinical implication is that Mendelian conditions should be carefully sought, particularly in the setting of additional non-cardiac defects. In these cases, apart from an accurate examination of the child, a careful family history must be taken and sometimes other family members should be examined. Consultation with a clinical geneticist or dysmorphologist may be of help.

Teratogens and CHD

It is estimated that 1-2 per cent of CHD are caused by fetal exposure to teratogens. Cardiac teratogens are a broad category and include maternal diseases, drugs, environmental exposures and infectious diseases. Though they account only for a minority of cases of CHD, numerically it amounts to about 300-600 cases every year in the United States and 60-120 in Italy. More importantly, teratogens are in fact the only risk factors we know of and for which primary prevention is at least theoretically possible. Strictly speaking, even chromosomal abnormalities are not an etiologic category, as the causes of the aneuploidy are still unclear and therefore primary prevention is not yet possible. Every case of preventable CHD must be considered a failure of the medical and public health system and an unacceptable burden of human suffering and social costs.

The identification of teratogens is fraught with difficulties. The effect of an agent may depend on the timing and dose of the exposure and on the genetic suceptibility of the developing embryo. Moreover in epidemiologic studies the association between an exposure and an outcome may not reach statistical significance for methodologic limitations, for instance, if the number of exposed pregnant women is small or if the induced defect is not highly specific. However, a number of putative teratogens have been proposed in the years. Their relative importance depends on the rate of exposure in the population of pregnant women and the

Table 2. - Selected Mendelian conditions and syndromes with cardiovascular involvement

Abnormality	Types of cardiovascular disease
Autosomal dominant cardiovascular abnormalities	
Apert syndrome	Ventricular septal defect (VSD), tetralogy, coarctation of the aorta (CA)
Crouzon disease	CA, patent ductus arteriosus (PDA)
Ehlers-Danlos syndrome	AV valve regurgitation, rupture of large blood vessels
Holt-Oram syndrome	Atrial septal defect (ASD), VSD
Idiopathic hypertrophic subaortic stenosis (IHSS)	Obstructive myocardial disease
Marfan syndrome	Mitral and aortic disease
Noonan syndrome	PA, ASD, left ventricular disease
Osteogenesis imperfecta	AI
Romano-Ward syndrome	Prolonged Q-T, syncope, sudden death
Williams syndrome	Supravalvar aortic and pulmonary stenosis, peripheral pulmonary stenosis
Treacher Collins syndrome	VSD, PDA, ASD
Tuberous sclerosis	Myocardial rhabdomyoma and angioma
Waardenburg syndrome	VSD
Autosomal recessive cardiovascular abnormalities	
Carpenter syndrome	Patent ductus arteriosus (PDA), ventricular septal defect (VSD), pulmonary stenosis PS), transposition of the great arteries (TGA)
Chondrodysplasia punctata	VSD, PDA
Ellis-van Creveld syndrome	Atrial septal defect (ASD); most commonly single atrium, other congenital heart lesions
Fanconi pancytopenia	ASD, PDA
Glycogenosis IIa (Pompe)	Myocardiopathy
Ivemark syndrome	Asplenia with cardiovascular anomalies
Jervell and Lange-Nielsen syndrome	Prolonged QT, sudden death
Laurence-Moon (Bardet-Biedl) syndrome	VSD and other structural defects
Meckel-Gruber syndrome	Both complex and simple structural defects
Muscular dystrophy I,II	Miocardiopathy
Seckel syndrome	VSD, PDA
Smith-Lemli-Opitz syndrome	VSD, PDA, and other congenital heart diseases
Thrombocytopenia absent radius (TAR)	ASD, tetralogy, dextrocardia
X-linked recessive and dominant (R and D) syndromes with associated cardiovascular abnormalities	
Muscular dystrophy (Duchenne and Dreifuss types) X-R	Myocardiopathy

teratogenic potency of the exposure, i.e., the proportion of exposed fetuses with the defect. This implies that a frequent exposure though only mildly teratogenic may cause more cases of birth defects than a very potent but rare teratogen.

Among the more frequent exposures are some maternal illnesses. Maternal insulin dependent diabetes mellitus is associated with an incidence of birth defects estimated around 6-9% [31], 25% of which are CHD [32]. The most frequent CHD are transposition of great vessels (TGV) and ventricular septal defects (VSD) [33]; a recent study reported an increased risk for two specific conotruncal defects, double outlet right ventricle and truncus arteriosus [34]. Of great importance is that strict glycemic control, during pregnancy and the pre-conceptual period, reduces the risk to the offspring to that of the general population [35]. Also untreated maternal phenilketonuria is associated with an increased incidence of birth defects, including mental retardation and microcephaly. Heart defects were present in about 25% of 524 untreated phenilketonuria offspring [36]; the most frequent defect is tetralogy of Fallot, followed by VSD, patent ductus arteriosus (PDA) and single ventricle. There are encouraging reports that strict preconceptual diet may decrease the risk to the offspring [37, 38].

The teratogenic risk in maternal epilepsy is a complex and controversial issue. Maternal epilepsy carries an increased risk of birth defects; moreover, some anticonvulsant drugs have been indicated as teratogenic. It is difficult to indicate exactly in what proportion the increased risk is due to the disease, to the drug or combination of drugs used to control the disease or to the interaction of the disease with the drugs. Moreover, it is important to keep the disease under control during pregnancy, as seizures pose a definite risk to the offspring. These risks must be weighed against those associated with anticonvulsant drugs. This whole issue is illustrated in detail in the paper on epilepsy reported in this issue [39].

Coumarin derivatives, used as anticoagulants, are associated with birth defects in 10-29% of exposed pregnancies but infrequently with CHD; however, when coumarin was substituted with heparin in weeks 6-12 of pregnancy, the risk is minimized [40].

Exposure to lithium, an effective drug for the treatment of major affective disorders, has been associated with increased risk for CHD, especially for the rare Ebstein anomaly on the basis of retrospective, sometimes voluntary, studies, particularly the Danish Register for Lithium Babies (1968). These studies have strong methodologic shortcomings, particularly for selection and recall bias. More recent retrospective [41] and prospective [42] case-control studies have reported a much lower frequency of CHD. In the prospective study [42] no significant difference between exposed and non-exposed infants was observed (1 Ebstein anomaly in the exposed group and 1 VSD in the controls). The exposed babies were heavier. The conclusion is that lithium is not a major cardiac teratogen. If necessary, lithium therapy can be continued in pregnancy, but as there may be a slightly increased risk for CHD in the offspring, prenatal echocardiography is reccomended. When planning a pregnancy, lithium should be substituted before conception for all the period of organogenesis.

Some vitamine A derivatives, especially isotretinoin, used as anti-acne preparations, are potent teratogens and the malformation pattern they cause frequently includes CHD, mainly conotruncal defects [43]. These substances are thought to interfere with the organogenesis of the heart through their action on cells of the neural crest, a structure present in the early embryo. The neural crest, in particular its cranial portion, is thought to contribute a key population of cells which migrate into specific areas of the developing embryo, including the face, pharingeal region and developing heart, particularly the outflow region [44]. Interference with the normal fuction of neural crest cells would determine a pattern of defects of these regions. This cell population is only one of the many which are thought to contribute to the developing heart and future research in this field is expected to contribute greatly to the understanding of the pathogenesis of a number of defects and defect patterns which include CHD.

While oral contraceptives have been regarded as teratogenic on the basis of two case-control reports [45, 46], the review and meta-analysis of 12 prospective studies, including other more recent and better designed case-control studies, fail to disclose any association between oral contraceptives and CHD [47].

Even the use of acetyl-salicilic acid (ASA) in the first trimester of pregnancy has been proposed as cardiac teratogen, particularly left-sided obstructive defects and transposition of great vessels [48, 49]. However, these studies were based on few exposed cases and are therefore unstable. To verify this hypothesis, a large case-control study was conducted [50] and found no increase in CHD among the exposed offspring compared to controls; in particular no increase was seen in left- sided obstructive defects and transposition of great vessels.

Alcohol use in pregnancy has been recognized to cause a pattern of multiple defects, including growth retardation, mental retardation, microcephaly, cranio-facial defects and other organ defects including heart defects [51]. Among heart defects atrial septal defects (ASD) seem to be to most common, together with VSD [52]; other defects are tetralogy of Fallot and left sided obstructive lesions. Much research has been done on this topic and has been reviewed elsewhere [53]. Alcohol may well be the most common teratogen to which the fetus is liable to be exposed and therefore it is of great importance that the teratogenic effects be recognized; furthermore, in this context, primary prevention is a realistic possibility.

Prominent among central nervous system stimulants and putative cardiac teratogens are dextroamphetamine and cocaine, which are widely used and abused recreationally.

Dextroamphetamine was not proved to be associated with an increased risk in two large cohorts (sample size of 1069 and 1694) of exposed pregnancies [54, 55]. A less recent case-control study [56] found instead an excess risk for CHD in exposed women. Experimentally dextroamphetamine induces fetal death, cardiac, skeletal, eye and other defects in mice embryos, but in doses which are toxic to the mother [57].

The relevance of these findings in human pregnancies is uncertain; the magnitude of teratogenic risk of dextroamphetamine should be considered minimal. Exposure to cocaine is considered a significant risk factor for placental abruption and some congenital anomalies, mainly dysruptive brain anomalies, segmental intestinal atresia, transverse limb reduction defects. It has not been firmly established whether or not cocaine induces CHD. An increased frequency of CHD was observed among 214 infants with neonatal toxicology screens which were positive for cocaine in one study [58] but meta-analysis of six other epidemiologic studies revealed no significant association between maternal cocaine use in pregnancy and fetal CHD [59].

Maternal diseases may cause CHD in the exposed offspring. Among the infectious diseases the best known example is rubella. Maternal rubella infection carries an increased risk for stillbirth and birth defects which is highest in the third to eighth week of pregnancy and decreased thereafter, the defects most frequently encountered being deafness and CHD, specifically PDA, ventricular and atrial septal defects [60].

Also other infectious agents have been implicated. There have been reports on the possible association between intrauterine infection with mumps and endocardial fibroelastosis which have been disproved in two large cohort studies [60].

Maternal infection with Coxsackie virus may be associated in a minority of cases with fetal myocarditis [60]. Maternal collagen disease such as systemic lupus erithematosus (SLE) can be associated with congenital heart block (CHB) in the offspring [61]. The risk seems to be linked to an antibody Ro(SS-A) present in the mother; babies with CHB were born of mothers without overt disease but with this serum antibody present. On the other hand this antibody is not specific, in that not all babies born of mothers with Ro(SS-A) antibody have CHB; other factors may well be important [62].

In summary, a fraction of all CHD can be attributed to specific teratogens. The challenge for the future is to identify all cardiac teratogens and through this knowledge to implement measures of primary prevention. However, a word of caution is necessary: identifying a teratogen is a complex and error-prone process which must be undertaken with appropriate methodologies; moreover, once the teratogen is identified, the associated risk must be qualified (what defects does it cause?) and quantified (what proportion of all exposed fetuses is affected ?) in order to give appropriate counselling.

Multifactorial models and CHD

In the majority of cases of CHD a specific etiologic factor cannot be identified: no known teratogenic exposure can be traced in the parental history, chromosomes are normal and no Mendelian syndrome or pattern of inheritance are recognized in the index patient. It has been suggested that the etiology in this large group of cases is multifactorial [28]. The details of the multifactorial model have been reviewed elsewhere [25]. In summary, the multifactorial model implies an interaction between polygenic predisposition and environmental factors to produce the occurrence of a CHD. The polygenic component of the model would account for the genetic predisposition to CHD which seems to exist in families where at least one case has occurred; the assumption is that a number of genes interact additively, each contributing a small effect; the total effect would be the sum of individual contributions. Environmental factor would add in their own effects or modify the contribution of the genes.

This model has been applied to quantitative or interval data, like blood pressure or height; for apparently dychotomous effects, like presence or absence of CHD, a modification of the simple model has been suggested, i.e., the liability-threshold model. This model simply assumes that there genetic and environmental factors contribute to a variable, called liability, which has an approximately normal distribution in the population; only when the liability reaches a certain critical threshold the event, e.g., the heart defect, occurs. In its simplest form this model gives a number of predictions. Firstly, it predicts an excess risk for the defect among relatives of affected infants, the risk for first degree relatives being equal to the square root of the frequency of the defect in the population; if the population frequency of a certain CHD is 1 per thousand, the risk of CHD among first degree relatives would be 3 per cent. Second, the risk for offspring would tend to be equal to the risk for sibs. Third, the risk for recurrence would be higher the more severe the defect. Fourth, the risk would be higher for relatives of an affected infant of the more rarely affected sex (Carter effect).

These predictions are not uniformily consistent with empiric data [25], so that they should be used as an heuristic approach rather than for counselling purposes.

Table 3. - Recurrence risks for congenital heart defects for siblings and offspring

Lesion	Recurrence risk (%) *(a)*			
	One sibling	Two siblings	Mother affected	Father affected
Ventricular septal defect	3	10	6-10	2
Atrial septal defect	2.5	8	4-4.5	1.5
Tetralogy of Fallot	2.5	8	2.5	1
Pulmonary stenosis	2	6	4-6.5	2
Ebstein anomaly	1	3		
Coarctation of the aorta	2	6	4	2
Hypoplastic left heart	2	6		
Aortic stenosis	2	6	13-18	3
Endocardial cushion	3	10		

(a) Recurrence for any congenital defect.
(Modified from [63]).

Table 4. - Classification of congenital heart defects based on pathogenetic mechanism

Mechanistic group	Example of malformation
Mesenchymal tissue migration errors	Tetralogy of Fallot
Intracardiac blood flow defects	Coarctation of aorta
Extracellular matrix abnormalities	Endocardial cushion defect
Abnormal cell death	Ebstein anomaly
Looping and situs abnormalities	L-transposition of great vessels
Abnormal targeted growth	Total anomalous pulmonary venous return

(Modified from [67, 70]).

In fact, empiric risk estimates are used for reproductive counselling. These risk estimates, based on numerous population and family studies, have been summarized [63] and are presented in Table 3. In summary, it has been suggested that the empiric risk for recurrence is between 1 and 4 per cent, and it is higher for the offspring that for sibs of affected cases. For the osffspring the risk seems to be higher if the mother is affected.

Other models

Models other than the multifactorial have been proposed to explain these data. These include a stochastic model which emphasizes the chance factor [64], the possibility of maternal transmission via mithochondrial/ cytoplasmatic factors [65], maternal vertical viral transmission [66].

Recently it has been proposed that more accurate risk assessment can be given if defects are classified according to the their possible developmental mechanisms rather than by individual structural anomaly [67]. An example for such a classification includes disorders of mesenchymal tissue migration, cardiac hemodynamics, cellular death, or extracellular matrix abnormalities (Table 4). A recent study using this approach [68] reported a high precurrence risk for disorders due to altered hemodynamics of the left side of the heart (13.5% for hypoplastic left heart), much higher than that predicted with the multifactorial model.

Conclusions

Congenital heart defects do have a relevant impact on the population, both in terms of human suffering and economic costs. The challenge for the future is to reduce the incidence of CHD through primary prevention and to give accurate genetic counselling. To achieve this, the etiology and pathogenesis of CHD must be elucidated, but unfortunately progress in this field has not paralleled the progress in cardiac diagnostics and surgery; the majority of CHD remain today without a known cause and the recurrence risk in these cases is an overall 1 to 4 per cent. However, some advance has been made. More

genetic syndromes are recognized, though no specific gene for CHD has yet been mapped; teratogens are being investigated with more correct methodologies; developmental mechanisms are being suggested and validated. It is not unlikely that major breakthroughs will come from basic sciences, embryology and genetics, allowing more effective forms of primary prevention.

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