Abstract

The burden of congenital heart anomalies is ancient but not inevitable, and can be decreased through primary prevention (removing causes) and improved survival. An epidemiologic, population-based evaluation of heart defects can help gauge and accelerate progress in that direction. Major heart defects are currently diagnosed in 1 in 110 newborns, and account for at least 1 in 3 infant deaths due to congenital anomalies. The reported rates of heart defects have increased over the last decades, in relation to improvements in ultrasound technology, though whether such technological advances accounts for all the reported increase in rates remains an open question. Mortality for children with heart defects has improved in the last decades (40% decline since 1979 in the US). However, population-based data suggest reveal a racial gap in mortality, which appears to be 20% higher among black compared of white infants. Such gap calls for further assessment and action to reduce preventable deaths. Among specific heart anomalies, hypoplastic left heart syndrome emerges because its associated mortality rate is higher and has declined more slowly compared to many other heart anomalies. Finding and removing the primary causes (primary prevention) of these conditions can dramatically improve the overall burden of disease. Effective primary prevention will benefit from aggressively pursuing parallel tracks of intervention and research. Intervention should maximize the potential for prevention by ensuring that known causes of heart defects (uncontrolled diabetes, teratogenic drugs and infections) are effectively removed from women of childbearing age. Research into the genetic and environment determinants of heart defects is also urgently needed because most of the cases of heart defects still remain without a known cause. One area of research that could potentially translate in key preventive opportunities is the role of periconceptional use of multivitamin supplements in reducing the risk for heart defects.

Keywords: Congenital heart defect; Causes; Etiology; Epidemiology; Prevalence; Survival

1. Introduction

The burden of congenital heart anomalies is ancient but not inevitable. This premise, whether articulated or not, is shared by the many professionals—surgeons, clinicians, epidemiologists, researchers, nurses—working to improve the outcomes and lessen the impact of heart defects in the population. From an epidemiologic and population-based perspective, which is the focus of this contribution, the burden of congenital heart defects can be decreased through two main approaches—primary prevention among those at risk, and improved survival among those affected.

Primary prevention removes the causes of heart defects, much like smallpox vaccination decreased and eventually eradicated the disease and has kept healthy untold millions who would have otherwise contracted the infection and died of it. Primary prevention is the ideal strategy because it directly lowers incidence and prevalence and, consequently, morbidity, mortality, personal pain and societal costs. Although an equivalent vaccine for heart defects is not yet available, certain primary prevention strategies (such as control of diabetes and infections) are currently available but are probably underused. In addition, to such strategies, we also discuss recent findings relative to the use of vitamin supplements that, if confirmed, could generate powerful prevention opportunities.

The second approach, improving outcomes among
those born with congenital heart defects, involves complex and integrated tasks, the clinical facets of which are discussed in detail by esteemed researchers in other contributions in this series. We complement that discussion with an assessment of survival that will underscore the recent improvements in the population at large, with emphasis on population-based data rather than surgical case-series. We also mention certain indicators, such as racial disparities in survival, which highlight areas in need of further consideration and action.

2. The impact of heart defects: what is it today?

We recently assessed the prevalence at birth of heart defects in a population-based setting to be 0.9%, or one in 110 newborns [1]. Because the change would have a major impact on the burden of heart defects in the population, it is important to know whether the occurrence of heart defects has changed in recent years. For example, in many countries and for reasons largely unknown, some defects (e.g. spina bifida) have been decreasing for many years [2], beyond the effect of selective pregnancy termination, and before the implementation of primary prevention strategies based on folic acid use. At the same time, other birth defects (e.g. gastrochisis) are increasing [3]. In the case of heart defects, the body of published literature shows no evidence of a decrease but rather an increase in reported occurrence. For example, we recently described a nearly two-fold increase in the reported rate of heart defects since the early 1970s [1] (Fig. 1), and similar findings have been reported by several other groups [4–7]. An important issue is, therefore, whether such an increase represents the change in occurrence or, rather, simply reflects improved ascertainment and reporting, driven by better ultrasound technology.

Because heart defects are so heterogeneous in anatomy, etiology, detection rates and (as will be seen) trends of occurrence, it is helpful to consider not only overall rates but also rates of specific anatomic subgroups. Table 1 compares such specific rates from two population-based studies (from Atlanta and the Baltimore–Washington areas [1,8]) that used similar classification schemes but were conducted several years apart. Such comparison shows that rates of several heart anomalies, particularly those that tend to be more severe or detected earlier in life, are remarkably similar in the two studies, whereas rates of milder defects such as ventricular and atrial septal defects differ to a much greater extent, with higher rates reported in the later Atlanta Study. Evidence of time trends for the milder defects can also be found internally in the two studies. In Atlanta, for example, we noted a significant increasing trend for ventricular and atrial septal defects or pulmonic stenosis, which drove the increase of heart defects overall [1]. Rates of severe anomalies (e.g. transposition of the great arteries, hypoplastic left heart) appeared to be stable [1].

These findings are consistent with the notion that an increase in apparent prevalence at birth is due to improvements in diagnostic (mainly ultrasound) technology that has taken place during the same period. However, although technology has certainly improved and has contributed to such trends, it is difficult to be certain that such improvements account entirely for the reported increase. In our view, better studies are needed to assess, for example, that the rate of ventricular septal defects are not increasing. Racial variations in the occurrence of heart defects also remain unexplained [1,9].

Certain change likely to occur in the years to come will impact the occurrence of heart defects. For example, the trend of increasing maternal age in the population is likely to increase the incidence of certain chromosomal anomalies (e.g. Down syndrome) and their associated heart defects. Contrariwise, increased prenatal detection

Fig. 1. Time trend in infant mortality due to congenital heart defects, United States, 1979 through 1997 (discussed in Circulation 2001;103(19):2376–81).

Mortality per 100,000 population

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<tr>
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</tr>
</thead>
<tbody>
<tr>
<td>Rate</td>
<td>3.0</td>
<td>2.5</td>
<td>2.0</td>
<td>2.0</td>
<td>2.5</td>
<td>3.0</td>
<td>2.5</td>
<td>2.0</td>
<td>1.5</td>
<td>1.0</td>
</tr>
</tbody>
</table>
Table 1
Prevalence (per 10,000 births) of major heart anomalies in population-based studies from Atlanta and Baltimore–Washington (BWIS), and estimated number of new cases yearly in the United States (4 million births)

<table>
<thead>
<tr>
<th></th>
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<tbody>
<tr>
<td>Heterotaxias and L-transposition (L-TGA)</td>
<td>1.6</td>
<td>1.4</td>
<td>647</td>
</tr>
<tr>
<td>Outflow tract defects, total</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Tetalogy of Fallot</td>
<td>4.7</td>
<td>3.3</td>
<td>1871</td>
</tr>
<tr>
<td>D-transposition of the great arteries</td>
<td>2.4</td>
<td>2.3</td>
<td>968</td>
</tr>
<tr>
<td>Double outlet right ventricle</td>
<td>2.2</td>
<td>0.7</td>
<td>871</td>
</tr>
<tr>
<td>Truncus arteriosus</td>
<td>0.6</td>
<td>0.5</td>
<td>258</td>
</tr>
<tr>
<td>Atroventricular septal defect (AV canal) with Down syndrome</td>
<td>2.4</td>
<td>2.3</td>
<td>968</td>
</tr>
<tr>
<td>without Down syndrome</td>
<td>1.0</td>
<td>1.0</td>
<td>419</td>
</tr>
<tr>
<td>Total anomalous pulmonary venous return</td>
<td>0.6</td>
<td>0.7</td>
<td>258</td>
</tr>
<tr>
<td>Ebstein anomaly</td>
<td>0.6</td>
<td>0.6</td>
<td>258</td>
</tr>
<tr>
<td>Right obstructive defects</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Tricuspid atresia</td>
<td>0.3</td>
<td>0.4</td>
<td>120</td>
</tr>
<tr>
<td>Pulmonary atresia, intact septum</td>
<td>0.6</td>
<td>0.6</td>
<td>258</td>
</tr>
<tr>
<td>Pulmonic stenosis, atresia</td>
<td>5.9</td>
<td>5.4</td>
<td>2355</td>
</tr>
<tr>
<td>Peripheral pulmonary stenosis</td>
<td>7.0</td>
<td></td>
<td>2807</td>
</tr>
<tr>
<td>Left obstructive defects</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Hypoplastic left heart</td>
<td>2.1</td>
<td>1.8</td>
<td>839</td>
</tr>
<tr>
<td>Coarctation of the aorta</td>
<td>3.5</td>
<td>1.4</td>
<td>1387</td>
</tr>
<tr>
<td>Aortic arch atresia or hypoplasia</td>
<td>0.6</td>
<td></td>
<td>226</td>
</tr>
<tr>
<td>Aortic valve stenosis</td>
<td>0.8</td>
<td>0.8</td>
<td>322</td>
</tr>
<tr>
<td>Septal defects</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Ventricular septal defect</td>
<td>24.9</td>
<td>11.2</td>
<td>9968</td>
</tr>
<tr>
<td>Atrial septal defect</td>
<td>10.0</td>
<td>3.2</td>
<td>4000</td>
</tr>
<tr>
<td>Patent ductus arteriosus</td>
<td>8.1</td>
<td>0.9</td>
<td>3240</td>
</tr>
<tr>
<td>Other major heart defects</td>
<td>9.7</td>
<td></td>
<td>3880</td>
</tr>
<tr>
<td>Total</td>
<td>90.2</td>
<td>48.4</td>
<td>36,080</td>
</tr>
</tbody>
</table>

Notes: (1) Hypothetical cohort of 4 million births. If rates in Atlanta and BWIS differ, expected number computed on later of two studies (Atlanta).
(2) Rate in BWIS is the average during study or rate for latest years if the trend was increasing.

followed by pregnancy termination should decrease the apparent, though not the real incidence of heart defects. Such decrease, however, represents a failure of primary prevention.

2.1. Mortality associated with heart defects

Mortality associated with congenital heart defects have been assessed in several studies. According to data from the World Health Organization, in North America, heart defects account for more than one-third of infant deaths due to congenital anomalies (Fig. 1) and for approximately one-tenth of all infant deaths [10]. These estimates are similar for other areas of the world.

We recently evaluated the trends of mortality due to heart defects in the United States [11]. Using death certificate information for the entire United States, we described heart defect-associated mortality in the entire population, as a complement to the survival data from surgical series reported by specific centers. Three findings were especially noteworthy.

Firstly, mortality from heart defects declined overall and for most specific heart defects. From 1979 through 1997, the overall decline was nearly 40%, from 2.5 to 1.5 deaths per 100,000 population (Fig. 2). However, even in the more recent years, heart defects still cause considerable number of deaths—nearly 6000 per year in 1995–1997. The decline in mortality rates was accompanied by an increase in average age at death, suggesting an overall increase in survival. The increasing number of children with heart defects who now survive into adolescence and adulthood underscores the need for the health-care community to prepare for the challenging and often complex needs of adults with congenital heart defects.

Secondly, mortality has not declined substantially for hypoplastic left heart, which was also the heart defect contributing most to infant deaths due to heart anomalies (Fig. 3). The complexities of surgical treatment of this condition underscore the critical need to understand its root causes and find effective measures for primary prevention.
Finally, mortality was nearly 20% higher among blacks than among whites, and this gap did not appear to be closing over time. The underlying causes of such disparities are unknown but could be related to access to health care or rate of complications, among other factors, just as is the case for the gap between poor countries and wealthy countries. An evaluation of such factors may provide the understanding needed to reduce such preventable burden of disease.

2.2. Causes and risk factors for heart defects

Rather than reviewing the spectrum of putative causes of heart defects, we briefly note the genetic contribution to heart defects and then focus on certain exposures that have, in our view, considerable potential for prevention and for which new data are available. We refer the reader elsewhere for a more general and systematic discussion of the epidemiology of risk factors for heart defects [12–14].

The explosive growth of genetic studies is increasingly generating clues to the genetic basis of heart defects. However, there are still only a small fraction of cases, perhaps 15%, which can be traced to a known cause, even when including environmental teratogens with genetic and chromosomal conditions.

A review of current data leads to some practical considerations. First, the contribution of the newly discovered mutations to heart defects in the population remains largely unknown. For example, although mutations of Jagged1 have been associated with syndromic and perhaps some non-syndromic heart defects [15,16], their contribution to heart defects in a population-based or unselected sample has not been established. The same is true for many other mutations. Population-based studies are needed to fill this important void.
of the exposure in the population. It is a well known result that a frequent exposure even if only mildly teratogenic, may cause more cases of birth defects than a very potent but rare teratogen.

As examples of these situations, we briefly discuss four risk factors (diabetes mellitus, environmental exposures such as medications and solvents, maternal obesity, and febrile illness) and a potential protective factor (periconceptional multivitamin use).

2.3.1. Diabetes

Infants of women with type I, type II, and gestational diabetes are at increased risk of having a heart defect [8,25–30]. Specific heart defects subgroups that have been strongly associated with maternal diabetes include laterality and looping defects, transposition of the great vessels, outflow tract anomalies, atrioventricular septal defects and hypoplastic left heart syndrome. Both human and animal studies have demonstrated that diabetic embryopathy is associated with hyperglycemia during organogenesis [31–35]. The precise mechanisms by which hyperglycemia results in malformations remains to be determined but are likely multifactorial [36], involving complex interactions between genetic susceptibilities and nutritional status, physical activity, and level of glycemic control before and during pregnancy.

The increasing prevalence of type II diabetes among women of childbearing age in recent decades [37] makes implementing prevention strategies in a high priority. It is now known that good glycemic control before conception and early in pregnancy is associated with a lower risk for birth defects [38,39]. Therefore, there is a need to identify effective communication messages and approaches targeting diabetic women of childbearing age about the importance of nutritional status and glycemic control in preventing heart defects and other adverse outcomes of pregnancy.

Recent studies have shown that administration of antioxidants to diabetic pregnant rodents can reduce the risk for diabetes-associated embryopathy [40–42], suggesting oxidative stress as a possible mechanism. Epidemiologic studies of the role of antioxidants in preventing heart defects and other adverse pregnancy outcomes in women with diabetes are warranted because they may suggest practical interventions with public health implications.

2.3.2. Environmental factors

The list of definite and potential human cardiac teratogens amenable to intervention is short and includes certain prescription medications and exposures to solvents. Maternal use of certain medications during the first trimester of pregnancy has been linked to congenital heart defects. Thalidomide has been associated with anomalies of the ventricular outflow tract [43,44]. Isoniazid, a

<table>
<thead>
<tr>
<th>Exposure</th>
<th>Heart defect</th>
<th>Odds ratio</th>
</tr>
</thead>
<tbody>
<tr>
<td>Diabetes</td>
<td>Heterotaxia</td>
<td>8.3</td>
</tr>
<tr>
<td></td>
<td>Tetralogy of Fallot</td>
<td>3.1</td>
</tr>
<tr>
<td></td>
<td>Truncus arteriosus</td>
<td>13.2</td>
</tr>
<tr>
<td>Fever</td>
<td>Pulmonic stenosis</td>
<td>2.9</td>
</tr>
<tr>
<td>Flu</td>
<td>D-transposition of great arteries</td>
<td>2.2</td>
</tr>
<tr>
<td>Solvents</td>
<td>Hypoplastic left heart</td>
<td>3.4</td>
</tr>
<tr>
<td></td>
<td>Coarctation of aorta</td>
<td>3.2</td>
</tr>
</tbody>
</table>

Second, the strongest genetic contributors to heart defects are still chromosomal abnormalities. Although earlier estimates placed the contribution of chromosomal anomalies at approximately 5% for liveborn infants with heart defects [17], this figure has long been considered an underestimate [18]. More recent studies [19,20] have more than doubled such estimate. Recently, the 22q11 deletion has joined the three common autosomal trisomies (trisomy 21, 18, 13) in leading the list of the most common chromosomal causes of heart defects [20–24].

## 2.3. Environmental causes of heart defects

Research studies to identify cardiac teratogens face many challenges. Factors that might hinder the identification of true teratogens include the variability of the risk (e.g. depending on timing and dose of the exposure), exposure assessment, limitations of study design or conduction (e.g. too small a study, lacking statistical power), and etiologic heterogeneity of phenotypically similar outcomes. Conversely, chance, confounding and bias might lead to spurious positive associations, which can be confusing to clinicians and the public alike.

A review of published literature reveals a considerable number of putative teratogens proposed over the years. Table 2 shows selected risk factor associations noted in the Baltimore Washington Infant Study [14]. In evaluating the relevance of such associations, two considerations might be helpful. First, it is important to establish teratogenicity clearly, because in such case every effort should be made to prevent exposure, regardless of how common such factors are in the population. Every affected child whose heart defect is secondary to established, preventable teratogens (e.g. retinoic acid, diabetes mellitus) is a failure of the health care system. Second, for those factors whose teratogenicity is not clearly established but that recurrently surface as risk factors in epidemiologic studies, it might be useful to assess their potential relevance not only as a function of the magnitude of the estimated risk (e.g. magnitude of the relative risk or odds ratio), but also by the frequency
tretinoin (13-cis-retinoic acid), an analogue of vitamin A used to treat cystic acne, has been associated with a characteristic pattern of malformations including craniofacial anomalies, hydrocephalus, neural tube defects and congenital heart defects [45]. Although efforts have been made to restrict the use of these medications during pregnancy, some pregnant women continue to incur inadvertent exposures as a result of lack of awareness of pregnancy status when such medications are used or inadequate counseling about the risks of such medications [46]. These observations underscore the importance of weighing the potential risks and benefits when prescribing medications to women of childbearing age and the need to monitor the safety of such drug use during pregnancy. The Organization of Teratogen Information Services (OTIS, 866 626-OTIS, www.otispregnancy.org) is a valuable resource for health care providers interested in learning more about the potential risks associated with prenatal exposures to medications, chemicals and other agents.

Another environmental factor offering an opportunity for prevention is maternal exposure to organic solvents. Several studies have suggested an increased risk for selected cardiac defects with exposures to solvents and paints [8]. For instance, occupational exposure to organic solvents has been associated with ventricular septal defects [47]; dyes, lacquers and paints with conal malformations [48]; and mineral oil products with coarctation of the aorta [49]. Further studies are needed to elucidate the nature of these associations. Meanwhile, prudence would suggest recommending that pregnant women or women contemplating pregnancy avoid or minimize their exposure to solvents and paints.

Several recently published studies examine the relation between cardiac and other defects and maternal exposure to chlorination by-products in municipal water supplies [50–56]. The results from these investigations have been inconsistent and may reflect differences in study population and methods, including completeness of case ascertainment, specificity of exposure assessment, information on covariates and adequate consideration of potential underlying pathogenetic mechanisms. Further studies addressing such methodological challenges will help resolve this issue of chemical water quality.

2.3.3. Obesity

Studies of obesity and heart defects are difficult to assess and compare because of variations in methods and classification. We reported a modestly elevated risk (odds ratio, 1.4) among obese women for aggregate heart defects in their offspring [57]. A recent study found a 6.5-fold risk elevation for aggregate cardiac defects among black women [58]. Studies examining conotruncal defects show inconsistent findings. One study reported no risk elevation for conotruncal heart defects [59], whereas others reported risk elevations for truncus arteriosus and transposition of the great arteries [60] and for a grouped category of defects of the great vessels [61].

Many aspects of such potential association between obesity and heart defects remain unclear. Obesity is a complex condition and has to be studied carefully to minimize the possibility of associations due to chance, bias and confounding. For example, it will be important to distinguish the risk associated with obesity and that associated with diabetes. Without careful screening of the latter, the effect of diabetes and obesity might be confounded because some women who are obese might also have unrecognized diabetes. However, it is particularly important to confirm or exclude even small increases in risk because of the high and increasing prevalence of obesity in the population in many developed countries.

2.3.4. Febrile illnesses

That maternal infectious diseases can cause heart defects among offspring is a well-known fact since the studies of rubella during pregnancy. Maternal rubella infection carries an increased risk for stillbirth and birth defects. The risk is highest in the third to eighth week of pregnancy and decreased thereafter, and the associated heart defects frequently include septal defects (ventricular and atrial) and patent ductus arteriosus.

A series of intriguing reports suggests that febrile illnesses (mainly flu-like illnesses) might be associated with an increased risk for certain heart defects. Although methodological differences among studies make direct comparisons difficult, several points deserve comment. One is that first-trimester febrile illness appears to be quite common, and was reported by approximately 1 in 15–20 women in these studies [62–64]. We and others reported a 40–80% increase in risk for heart defects associated with first-trimester febrile illness [62–64].

Second, the data from these three studies also suggest a degree of specificity in the outcomes. The association with febrile illness appeared to be more marked for tricuspid atresia [8,64], some left obstructive defects [8,62,64], transposition of the great arteries [8,62,64], and perhaps ventricular septal defects [64]. Finally, in a smaller cohort study, one of 64 liveborn infants exposed prenatally to high fever had transposition of the great arteries [65]. These epidemiologic studies also have limitations, however, and the relatively consistent findings might simply indicate similar recall bias.

Animal studies provide further intriguing evidence. Hyperthermia in chick embryos causes malformations of the cardiac bulb (the outflow tract of the heart) and stenosis of the ventral aorta and aortic arches [66,67],
Table 3
Studies of maternal multivitamin use and risk for congenital heart defects in the offspring

<table>
<thead>
<tr>
<th>Type of study</th>
<th>Authors</th>
<th>Population-based?</th>
<th>Study participants (1)</th>
<th>Exposure (2)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Randomized clinical trial</td>
<td>Czeizel et al., 1998</td>
<td>–</td>
<td>2471 women on MV supplements; 2391 on trace elements</td>
<td>MV pill with 0.8 mg folic acid</td>
</tr>
<tr>
<td>Case–control</td>
<td>Shaw et al., 1995</td>
<td>Yes</td>
<td>126 with OTD, 679 controls</td>
<td>MV supplements</td>
</tr>
<tr>
<td>Case–control</td>
<td>Scanlon et al., 1997</td>
<td>Yes</td>
<td>481 controls</td>
<td>MV supplements</td>
</tr>
<tr>
<td>Case–control</td>
<td>Botto et al., 1996 and 2000</td>
<td>Yes</td>
<td>958 with heart defects, 3029 controls</td>
<td>MV supplements</td>
</tr>
<tr>
<td>Case–control</td>
<td>Werler et al., 1999</td>
<td>No</td>
<td>157 with OTD, 186 with VSD, 521 controls</td>
<td>MV supplements</td>
</tr>
</tbody>
</table>

Defects that are similar to those reported in epidemiologic studies of fever and heart defects. In humans, however, the exposure is febrile illness rather than hyperthermia, and distinguishing the effect of temperature elevation from that of underlying infection and medications is difficult. Common infections, such as flu-like illnesses, have been associated with an increased risk for congenital anomalies even in the absence of fever [68]. Although effect estimates are often higher, for example, for flu with fever compared with flu alone [63,68], such apparent increase might be due to greater severity of the underlying illness, of which fever may be but a hallmark.

Both fever and infection, however, have documented biological effects on specific developmental pathways. Apoptosis, for example, is affected by both hyperthermia [69,70] and viruses [71], including influenza viruses [72]. It has been suggested that altered apoptosis may cause birth defects [70], and apoptosis is known to be involved in cardiac morphogenesis, for example in the development of the cardiac outflow tract [73].

2.3.5. Folic acid and multivitamin supplements

Reports from the Hungarian randomized trial on birth defects suggested that periconceptional use of multivitamin supplements containing folic acid might decrease the risk for congenital heart defects [74,75]. Findings from subsequent case–control studies were mixed but encouraging [76–79]. Table 3 describes the studies, and Fig. 4 graphically summarizes some of the main results.

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Fig. 4. Risk of congenital heart defects and possible reduction associated with maternal use of multivitamin/folic acid supplements in the periconceptional period and early pregnancy: summary of published findings.
Two studies examined a broad range of heart defects [75,76]. Multivitamin use was associated with an approximately 50% overall reduction in risk for congenital heart defects in the randomized trial (relative risk, 0.48) [74,75], and approximately 25% reduction in risk in the Atlanta population-based case–control study (odds ratio 0.76) [76]. If these results are confirmed, it might be possible to prevent one-quarter to one-half of all heart defects by maternal periconceptional use of multivitamin supplements.

These and other studies also examined, specific types of heart defects and in particular, some conotruncal defects, including tetralogy of Fallot and D-transposition of the great arteries. Multivitamin use was associated with a reduced risk for conotruncal defects in two population-based case–control studies (54% reduction in one, 30% in the another) [76,77]. The Hungarian trial provides suggestive data (no case of conotruncal defects in the supplemented group, two cases in the non-supplemented) but the size of the trial was too small to provide definitive results. A third study showed mixed results [78] (possible risk reduction for one but not all types of conotruncal heart defects). Fourth, a hospital-based case–control study [79], showed no evidence of reduction.

For ventricular septal defects, two studies, a population-based case–control study and the Hungarian randomized trial, were consistent with a reduction in risk (40% and 85% reduction, respectively) [75,76]. The hospital-based case–control study from Boston found no risk reduction [79].

In addition to these studies, directly testing the association between multivitamin use and risk for heart defects, other studies present ancillary evidence supporting a protective effect of folic acid-containing supplements on heart defects. In one study [80], women who used medications that are folic acid antagonists had a two-fold increased risk of having babies with heart defects. Such a risk was reduced among those who also took multivitamin supplements containing folic acid.

Another line of evidence includes studies that examine the effect of multivitamins in high-risk groups. In one such study [64], the increased risk for heart defects associated with febrile illness appeared to be reduced among women using multivitamin supplements around the time of conception and during early pregnancy. Similar findings have been reported for other birth defects as well [81].

In summary, the evidence of a protective effect of multivitamins is encouraging, and is supported by evidence from a randomized clinical trial and two respected population-based case–control studies. Because of the potential impact of these findings, this hypothesis deserves careful and immediate study. Ideally, such studies would assess the heart defects which can be prevented with multivitamin use, and the strength of such effects; the specific role of folic acid and other micronutrients; the most effective dosages; the role of genetic susceptibility and gene-environment interaction; and the mechanisms of action.

Furthermore, key evidence can come from well-designed clinical trials, from monitoring rates of heart defects following flour fortification with folic acid, and from well-designed observational (e.g. case–control) studies. Each of these options has its advantages and limitations. Clinical trials are costly and complex and, because all arms must include at least 400 μg of folic acid for ethical reasons, can best provide information on the relative effect of high vs. low dosages of micronutrients. Monitoring rates of heart defects before and after fortification with folic acid is technically challenging because of such rates are already changing due to the combination of increased reporting, changing maternal age structure and elective pregnancy termination, among other factors. Discriminating changes due to fortification amongst such shifting background can be difficult. For these reasons, well-designed case–control studies that include examination of genetic and environmental influences of micronutrients intake and metabolism might still provide some key contribution to the balance of evidence.

3. Concluding remarks

The coupled strategies of primary prevention and outcome improvement (secondary prevention) promise to reduce the burden of heart defects in families and populations. The challenges are considerable, however, particularly for primary prevention, as it involves finding and removing causes. As researchers continue the quest to unravel the web of genetic and environmental determinants of heart defects, certain evidence-based prevention strategies are already available, including control of diabetes, rubella vaccination and avoidance of teratogenic drugs. A key question is whether we are maximizing this potential, and if not, what needs to be done if such potential is maximized.

If confirmed, newer evidence can lead to exciting opportunities for primary prevention, including the increasing evidence of a possible protective effect of periconceptional use of multivitamin supplements containing folic acid. From a population perspective, research priorities include careful monitoring of the incidence of heart defects to detect increases signaling a shift or introduction of risk factors in the population. Also, population-wide monitoring of outcomes, including disability, morbidity and mortality, will provide the information necessary to gauge how improvements in medical and surgical care translate into tangible benefits.
for the entire population, regardless of social status and racial group. The effective and ongoing collaboration of medical and public health professionals will be a key factor in the success of such activities.

References


