Birth Defects: Prevention, Diagnosis and Treatment

Chapter 1

Congenital Heart Disease: Prevention

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Abstract

Congenital heart defects are the most common congenital anomalies and occur in 0.8–1.2% of all live births with a prevalence of about 5.8 per 1000 people. They represent about 1/3 of the total of congenital anomalies and are responsible for the greatest proportion of infant mortality attributed to birth defects. Congenital heart disease is also the leading noninfectious cause of death in the first year of life. There is not much information available on noninherited modifiable factors that may have an adverse effect on the fetal heart, however there is a growing body of epidemiological literature on this topic. The proportion of cases of congenital heart disease that are potentially preventable through changes in the fetal environment is currently unknown. It has been suggested that the fraction of cases attributable to identifiable and potentially modifiable factors may be as high as 30% for some types of defects. Identifying modifiable risk factors of infants with congenital heart disease remains important for public health and clinical medicine. Advances in understanding how embryonic heart development occurs now provides tools for understanding how extrinsic and intrinsic factors acting on the mother can perturb the formation of the human heart. This could potentially make it possible for the first time to significantly reduce the prevalence of congenital heart disease worldwide.

Abbreviations: Congenital Heart Disease (CHD)

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1. Introduction

Overall, approximately 3–5% of deliveries are affected by a birth defect [1-3]. Congenital heart defects are the most common congenital anomalies and occur in 0.8–1.2% of all live births with a prevalence of about 5.8 per 1000 people [4] Congenital heart disease (CHD) affects approximately 2 million families in the United States, which is approximately 40 000 babies each year in this country [5-7].

They represent about 1/3 of the total of congenital anomalies and are responsible for the greatest proportion of infant mortality attributed to birth defects [8]. CHD is also the leading noninfectious cause of death in the first year of life [9]. Among combined fetal and neonatal deaths due to congenital anomalies, the most frequent category was congenital heart defects (32.0%). The most frequent congenital heart defects reported among fetal and neonatal deaths was unspecified congenital heart disease (65%) followed by hypoplastic left heart syndrome (3.2%), ventricular septal defect (2.8%), and aortic coarctation (2.4%) [10].

The incidence of moderate and severe forms of CHD is about 6/1,000 live births (19/1,000 live births if the potentially serious bicuspid aortic valve is included) [7]. About 30% (7-50%) of the patients also have extracardiac anomalies or genetic syndromes which increase morbidity and mortality and the risk of cardiovascular operations. [11-13].

Over the past decade, there have been major breakthroughs in the understanding of inherited causes of CHD, including the identification of specific genetic abnormalities for some types of malformations [14]. Although relatively less information has been available on noninherited modifiable factors that may have an adverse effect on the fetal heart, there is a growing body of epidemiological literature on this topic. The proportion of cases of CHD that are potentially preventable through changes in the fetal environment is currently unknown [15]. It has been suggested that the fraction of cases attributable to identifiable and potentially modifiable factors may be as high as 30% for some types of defects [16]. Identifying modifiable risk factors of infants with CHDs remains important for public health and clinical medicine. Such factors can be either an excess of a toxic substance, or the lack of an essential nutrient. In both cases, the factor can act directly on the embryo itself or indirectly, for example, by perturbing placental development and altering the nutrient supply to the embryo [17].

Advances in understanding how embryonic heart development occurs now provides tools for understanding how extrinsic and intrinsic factors acting on the mother can perturb the formation of the heart. This could potentially make it possible for the first time to significantly reduce the prevalence of CHD worldwide.

Large epidemiologic studies of the environmental causes of CHD potentially could be translated to provide clinical impact. They will also guide the formulation of health policy

recommendations to aid women planning pregnancy to minimize their exposure to such environmental risks [18].

The embryonic development of the human heart is a complex process. Considering the heart's seemingly simple function of pumping oxygen- and nutrient-rich blood, its development requires multiple critical and time-sensitive steps, all of which need to occur in the correct order to avoid the structural abnormalities collectively described as congenital heart disease. Heart development, in its simplest terms, can be put into the context of nine major steps [19].

- Formation of the three germ layers (gastrulation)
- Establishment of the first and second heart fields
- Formation of the heart tube
- Cardiac looping, convergence, and wedging
- Formation of septa (common atrium, atrioventricular canal)
- Development of the outflow tracts
- Formation of cardiac valves
- Formation of vasculature (coronary arteries, aortic arches, sinus venosus)
- Formation of the conduction system

The primitive heart begins to beat at about day 21, and starts pumping blood by day 24-25 [19]. The period of human embryonic heart development that is vulnerable to teratogenic perturbation is gestational weeks 3–8 [18]. Therefore, in order to reduce the incidence of CHD by altering exposure to extrinsic and intrinsic modifiable risk factors has to take place in the preconceptional period and during the first trimester of pregnancy.

2. Rubella

Rubella is an eruptive, highly contagious, and generally mild viral disease without consequences in most cases. Primary infection usually occurs during childhood and provides long-term immunity. Rubella virus easily crosses the placenta of infected pregnant women; in the first trimester, rubella causes miscarriage or fetal death, or congenital rubella syndrome. Congenital rubella syndrome includes auditory, sensorineural, cardiac and ocular abnormalities. In cases in which the primary rubella infection occurs during the first 4 months of pregnancy, a prenatal diagnosis of fetal infection could be proposed [19].

This infection can be prevented effectively by vaccination. The antibody response rate

to a single dose is higher than 95%. After two doses, the response rate approaches 100%, and immunity is detectable at over 21 years of age, despite waning rubella virus-specific immunoglobulin G titers [20–23].

A review of the literature between 1991 and 2014 identified 427 cardiac abnormalities due to congenital rubella syndrome. Only 290 were clearly specified in the articles.

Those that may be accessible to prenatal diagnosis were: pulmonary artery stenosis 81/290 (28%), septal defects 69/290 (23%), tetralogy of Fallot 5/290 (2%), aortic stenosis 3/290 (1%), aortic coarctation two cases, one case of transposition of the great arteries and one case of Ebstein's anomaly. Patent ductus arteriosus was present in 115/290 (39%) which is not accessible to prenatal diagnosis [24].

Rubella virus infection is a leading vaccine-preventable cause of birth defects. In 2011, the World Health Organization updated guidance on the preferred strategy for introduction of rubella-containing vaccine into national routine immunization schedules, including an initial vaccination campaign for children aged 9 months–14 years. Global immunization partners have set targets to eliminate rubella and congenital rubella syndrome in at least five of the six World Health Organization regions by 2020. Elimination of rubella and congenital rubella syndrome was verified in the World Health Organization Region of the America in 2015, and 33 (62%) of 53 countries in the European Region have now eliminated endemic rubella and congenital rubella syndrome [25].

2.1. Tobacco Smoke

Currently, among the nutritional and environmental factors that are considered as teratogenic to fetal cardiovascular system is tobacco smoke. The Centers for Disease

Control and Prevention has reported that approximately 18 % of female adults between ages 25 and 45 in the United States choose to smoke [26] and this is the reproductive age for most women. Therefore, we can decrease the incidence of CHD through tobacco control if there is firm evidence to confirm the cardiovascular teratogenic effect of maternal smoking during pregnancy. To date, we know that tobacco smoke contains various types of toxic compounds, including cadmium, nicotine, benzo[a] pyrene, and other carbon monoxides.

There are some large observational studies investigating the teratogenic effect of maternal smoking during pregnancy [27-29]; however, they obtained different conclusions regarding the relation, and the inconsistency might be due to biological and methodological heterogeneity (e.g. subtypes of CHD, smoking consumption, study design, and sample size). This made the cardiovascular teratogenic effect of maternal smoking during pregnancy ambiguous to the public, which is adverse to tobacco control and CHD prevention.

One systematic review and meta-analysis including 33 observational epidemiologic studies was updated in 2013 [30]. The authors reported that there was an 11% relative increase in the risk of CHD among the offspring of mothers who had smoked during pregnancy. In another meta-analysis of 2011 by synthesizing odds-ratios from 19 observational studies, Hackshaw et al. found a 9% relative increase in the risk of CHD for smoking mothers [31].

The mechanism of CHD pathogenesis is not completely understood, but there are some existing hypotheses implying a possible relationship between tobacco smoke during pregnancy and the development of CHD. Previous studies suggested that hemodynamic changes could lead to morphological or functional alterations in the fetal cardiovascular system [32, 33] and it was reported that in utero exposure to nicotine could induce fetal hypoxia and elevate fetus blood pressure [34, 35]. Long-term change in blood pressure can influence the function of cardiac muscles and muscle cells in the aorta [36].

At the genetic level, some previous studies have found that the pathogenesis of CHD was related to gene–environment interaction. It has been reported that periconceptional maternal smoking might be associated with an increased risk of CHD if the mothers had certain variant alleles [37]. Hobbs et al. demonstrated that the CHD pathogenesis was complex, and it might be related to the joint effects of elevations in maternal serum homocysteine, periconceptional smoking, and specific genetic alleles [38].

A recent meta-analysis concluded that, offspring of mothers who smoked during pregnancy are at a higher risk of CHD, particularly for septal defects. On average, for women who smoke during pregnancy, there is approximately a 10% relative increase in the risk of having a CHD-affected child, and the risk can be enlarged as the consumption of tobacco smoke increases. The result of these studies have some public health implications. Although the increase in the risk is modest, smoking is commonly observed for women at reproductive ages, and this may result in a substantial number of CDH cases each year.

3. Maternal Obesity

Obesity has become a major public health problem that challenges both developed and developing countries [39-41]. The most recent data from National health and nutrition survey indicated that the prevalence of obesity among American adults is 39.8%. Also 36.5 % of reproductive age women are obese [42].The association between maternal obesity and CHD in infants has been widely reported, but the results are not consistent.

In a very recent meta-analysis the authors discovered an increase of 8% risk of infants with CHD in maternal overweight group and an increase of 23% risk in maternal obesity group compared with the mothers with normal weight [43]. Subgroup analysis by study design showed that the significant association between maternal overweight and increased

risk of infants with CHD existed only in case-control studies, while the significant association between maternal obesity and increased risk of infants with CHD existed in both cohort studies and case control studies. Dose-response meta-analysis showed that each 5 kg/m^2 increase of maternal body mass index is accompanied by a 7% increment of risk of infants with CHD, and a significantly nonlinear relationship between maternal body mass index and infants with CHD risk was observed. When stratified by study design, the pooled relative risk of infants with CHD increased by 7% per 5 kg/m^2 increase of maternal body mass index, for both cohort and case-control studies.

Maternal obesity might be associated with increased risk of infants with CHD through several mechanisms. Data from epidemiology research suggest that folate, glutathione, and homocysteine metabolism related genetic variants in mother and fetus may have great impact on the heart development [44]. Another possible mechanism is that maternal metabolic environment plays an important role in fetal development [45]. ecreased intake of folate and glutathione and increased intake of homocysteine caused by maternal obesity may lead to abnormal in utero environment, which contribute to the onset and development of impaired fetal development [46-49].

Secondly, it was reported that maternal obesity may impair fetal cardiomyocyte contractility and affect cardiac development by altering intracellular Ca2+, overloading fetal Ca2+, and producing abnormal myofibrillar proteins [50]. Thirdly, maternal obesity significantly enhances TLR4 (Toll like receptor 4), IL-1a, IL-1b, and IL-6 expression, promotes phosphorylation of I-κB, decreases cytoplasmic NF-κB (nuclear factor kappa-light-chain-enhancer of activated B cells) levels, and increases neutrophil and monocyte infiltration, eventually leading to inflammation in the fetal heart and altering fetal cardiac morphometry [51]. Furthermore, a mini-review by Dong et al. reported that lipotoxicity resulting from maternal obesity is capable of activating a number of stress signaling cascades including proinflammatory cytokines and oxidative stress to exacerbate cardiovascular complications [52, 53]. In addition, overweight and obese women are more likely to have pregestational diabetes mellitus and it is well accepted that maternal diabetes significantly increases the risk of infant CHD. Another recent meta-analysis shows that there is an established relationship between maternal body mass index and congenital heart anomaly [43]. In most of the articles, the body mass index categories were in line with the World Health Organization guidelines (underweight,<18.5 kg/m^2; normal weight, 18.5–24.9 kg/m^2; overweight, 25.0–29.9 kg/m^2; obesity>30 kg/m^2) [44]. There was little significant evidence of an association between maternal underweight status (body mass index <18.5 kg/m^2) and offspring with CHD, and a positive effect of maternal overweight status (body mass index 25.0–29.9 kg/m^2) on the risk for CHD in infants. Moreover, the authors observed a significant association between maternal obesity (body mass index >30 kg/m^2) and CHD in their offspring. These findings suggest that obese

and overweight women should be aware of the risks and keep a healthy weight before they plan to conceive. Thus, reducing maternal prepregnancy obesity may reduce the occurrence of infant CHD.

4. Pregestational and Gestational Diabetes

High-quality cohort studies [54-57] have shown that mothers with diabetes mellitus compared with non-diabetics have increased risk of CHD in their offspring.

Although pregestational diabetes was associated with an increased risk of CHD, the magnitude of the association varied between studies [58-61]. Moreover, it remains unclear the relationship between gestational diabetes and CHD, as well as the precise risks for specific subtypes of CHD associated with maternal diabetes.

A recent meta-analysis showed that overall, mothers who had diabetes compared with those without diabetes mellitus experienced a significantly increased risk of CHD in the offspring [62].

When maternal diabetes was further divided into pregestational and gestational, the authors found that both mothers with pregestational diabetes and mothers with gestational diabetes had a significantly higher risk of CHD in the offspring. Of note, the risk of pregestational diabetes on CHD was significantly higher than that of gestational diabetes.

Overall, maternal diabetes was significantly associated with increased risk of most subtypes of CHD such as heterotaxia, patent arterial duct, conotruncal defects, tricuspid atresia, transposition of the great arteries, tetralogy of Fallot, double outlet right ventricle, atrioventricular septal defect, eft ventricular outflow tract obstruction, aortic coarctation, hypoplastic left heart syndrome, right ventricular outflow tract obstruction, pulmonary valve stenosis, tricuspid valve stenosis, septal defects (ventricular septal defect, atrial septal defect, ventricular septal defect+ atrial septal defect), valve defects and single ventricle. Of these, double outlet right ventricle, atrioventricular septal defect, tricuspid atresia, heterotaxia and patent arterial duct were identified as the first five most common subtypes of CHD associated with maternal diabetes.

Prepregnancy diabetes may lead to hyperglycemia condition in the uterine environment at a critical stage of cardiovascular development, which may change the key molecular pathways, resulting in abnormal embryonic heart development [63-64].

The mechanisms underlying the association between maternal diabetes and CHD malformations may also differ between women with pregestational and women with gestational diabetes.

Women with pregestational diabetes would have a diabetic intrauterine environment during the critical period of heart development. Gestational diabetes, however, does not develop until the 24th–28th weeks of gestation [65], after the critical period of cardiogenesis.

Because the onset of gestational diabetes occurs after cardiac development, two mechanisms have been proposed to explain the observed associations with gestational diabetes. First, some women with pregestational diabetes, particularly those without a diagnosis before late pregnancy, may have been misclassified as having gestational diabetes [66-68]. Second, there could be factors related to a prediabetic state that influences CHD risk during early pregnancy, before gestational diabetes is clinically recognizable [69-71].

The American College of Obstetricians and Gynecologists recommends screening for undiagnosed type 2 diabetes among women with risk factors (e.g., previous gestational diabetes, obesity) in early pregnancy [72] and for gestational diabetes during the 24th–28th weeks of gestation [73], so that women who are diagnosed can attempt to regulate their glycemic levels through individually tailored diet, exercise, and a pharmacological regimen [73]. However, because many women have their first prenatal visit after the critical period of heart development, research is needed to assess the impact of pregestational screening for diabetes among reproductive-age women.

Poor glycemic control in early pregnancy is associated with an increased risk of CHD for infants of women with preexisting diabetes [74]. Among the patients with poor glycemic control, 8.3 % delivered an infant with CHD, whereas 3.9 % of those with an HbA1c level lower than 8.5 % delivered an infant with CHD. The incidence of CHD in patients with adequate glycemic control still is sufficiently high to justify routine fetal echocardiography for all gravidas with preexisting diabetes regardless of HbA1c level.

5. Alcohol

Maternal alcohol consumption is associated with a variety of harmful effects to the fetus, as demonstrated by a range of impairments defined as fetal alcohol syndrome [75]. Various clinical signs have been described, which led to the classification of different degrees of embryopathy, ranging from patients with minor symptoms, the so-called “alcohol effects”, to the most severely affected individuals [76]. Up to one-third of affected children have CHD [77]. However, the evidence has been mixed, with some studies showing positive associations and others providing null results. CHD includes distinct subtypes (e.g., conotruncal defects, left ventricular outflow track defects, septal defects), and there is potential for etiologic heterogeneity. A recent meta-analysis indicated that maternal alcohol consumption during pregnancy might have no association with increased risk of CHD [78]. Ethyl alcohol has been suggested to play a positive role in heart disease. The authors speculate that a small amount of alcohol may have little influence in increasing the risk of CHD. However, these statistics do

not intend to say that maternal drinking is safe.

The authors assume that by including studies that assessed exposure beyond the critical period of cardiogenesis may have biased their result towards the null. That is, the summary results may be a misestimate of the relative risk of CHD associated with alcohol consumption.

Another recent quantitative meta-analysis evaluating the association between maternal alcohol consumption before and during pregnancy and the risk of CHD also suggested that maternal alcohol has no significant association with CHD risk when adjusted for smoking [79]. Heterogeneity exists among the studies; this heterogeneity may affect the interpretation of the overall results. However, the findings from these studies, especially with regard to the different subtypes of CHDs, need to be confirmed in future research.

6. Phenylketonuria and Hyperphenylalaninemia

Phenylketonuria is an inborn error of metabolism. Phenylketonuria is due to a defect in the hepatic enzyme phenylalanine hydroxylase, which converts amino acid phenylalanine into tyrosine. If undiscovered and, therefore, untreated, phenylketonuria may lead to intellectual disability and neurologic disorders [80].

Hyperphenylalaninemia is classified by the serum phenylalanine concentration: >1200 μmol/L (classical phenylketonuria), between 600 and 1200 μmol/L (mild phenylketonuria), or <600 μmol/L (hyperphenylalaninemia) [81].

Metabolic control of phenylketonuria can be achieved by a strict diet with minimal phenylalanine intake to decrease the serum phenylalanine concentration in combination with tyrosine enriched supplements [82, 83]. Untreated maternal phenylketonuria or hyperphenylalaninemia during pregnancy may lead to maternal phenylketonuria syndrome in the neonate. Previous literature, including the international Maternal Phenylketonuria Collaborative Study, reported that elevated maternal phenylalanine concentrations resulted in maternal phenylketonuria syndrome with the following neonatal sequelae: low birth weight, microcephaly, CHD and fetal death [84].

In a study by Prick et al in the untreated group, 19.2% of neonates were small for gestational age, 46.2% of neonates had microcephaly and 6.6% of neonates had CHD [80]. In conclusion, this study underlines the importance of treatment of hyperphenylalaninemia to prevent pregnancy complications and maternal phenylketonuria syndrome in neonates. The study also implies that women with a desire to become pregnant are advised to use a strict diet that starts before conception to prevent teratogenic effects in the fetus.

7. Isotretinoin and Vitamin A Supplementation

Isotretinoin is a retinoid which is derived from Vitamin A. It is indicated for severe cystic acne treatment, but it has been classified as teratogenic. A wide spectrum of birth defects including craniofacial, heart, and nervous system malformations have been described with prenatal exposure to this drug [85]. Lammer *et al*. [86] set forth the spectrum of structural defects of 21 affected infants. Seventeen individuals had defects of craniofacial area, 12 had cardiac defects, 18 had altered morphogenesis of central nervous system, and 7 had anomalies of thymic development [87]. 35% risk for the isotretinoin embryopathy exists in the offspring of women who continue to take isotretinoin beyond the 15th day following conception [88]. The mechanism responsible for producing many of the malformations in infants exposed to retinoic acid is an abnormality of cephalic neural crest cell activity. Human embryos are more sensitive to isotretinoin than embryos of other species due to the slow elimination of the drug and continuous isomerization of retinoic acid. wo simultaneous contraception methods should be used 1 month before the administration of isotretinoin until 1 month after stopping its use. According to the programme IPLEDGE and teratology society, the patients should be advised to have a negative pregnancy test before using isotretinoin and repeat every month during treatment to confirm and 1 month after stopping [89]. An excess of retinoic acid can have dramatic effects on human embryonic development. This can occur in either the offspring of women undergoing therapeutic treatment with the synthetic retinoid isotretinoin (13-cis-retinoic acid), or in the offspring of women with excess dietary vitamin A supplementation [90].

7.1. Folate supplementation

There is general acceptance that folate aids the prevention of neural tube defects [91]. There is evidence that folate supplementation may prevent or reduce the risk and severity of CHD induced by an abnormal uterine microenvironment [92]. In human epidemiological studies, folate doses of 10 mg/kg have proven effective in preventing cardiovascular defects [93]. However, the results of clinical studies have been inconsistent.

Most recently, Liu and colleagues in a study published in Circulation [94] conducted an ecologic analysis of CHD prevalence before and after the initiation of a public policy in Canada mandating folic acid fortification of food. In this article, the authors describe trends in prevalence rates of CHD (overall), and CHD subtypes, among all live births and stillbirths/late-pregnancy terminations (>20 weeks gestation) before and after folic acid fortification of food was mandated in Canada in 1998.

Also evaluation of medically recorded use of folic acid (calculated daily average 5.6mg) during the critical period of development of eight types of CHD (verified through autopsy reports or after catheter examination and/or surgical correction) in the population-based

Hungarian Case-Control Surveillance of Congenital Abnormalities (HCCSCA), 1980-1996 showed that there was a significant decrease in the prevalence of cases with ventricular septal defect, tetralogy of Fallot, d-transposition of the great arteries and secundum atrial septal defect in infants born to mothers who had taken high doses of folic acid during the critical period of CHD development [95].

However, a study that was published in 2019 which recruited women in early pregnancy within the DNBC (Danish National Birth Cohort), 1996-2003, and MoBa (Norwegian Mother and Child Cohort Study), 2000-2009, who were followed until delivery and on which information was analysed on periconceptional intake of folic acid and other supplements, which was then linked with information on heart defects from national registers showed that folic acid was not associated with offspring risk of heart defects, including severe defects, conotruncal defects, or septal defects [96].

The folate pathway relates not only to purine and pyrimidine synthesis, which are important in DNA synthesis and cell proliferation, but also to the synthesis of the primary methyl donor S-adenosyl methionine, which is important in methylation reactions of cellular lipids, proteins, RNA and DNA. DNA methylation is critical to epigenetic regulation of gene expression [97-99]. Epigenetic factors that predispose to CHD and placental dysfunction are suspected to be the cause of an increase in the recurrence risk of CHD after one affected child. Therefore folic acid supplementation may be recommended in future mothers with a previously affected child with CHD [100].

8. Antidepressants and lithium

It is uncertain whether the use of selective serotonin-reuptake inhibitors and other antidepressants during pregnancy is associated with an increased risk of CHD in the newborn.

Several studies have reported that paroxetine exposure during the first trimester of pregnancy is associated with fetal cardiac abnormalities such as septal defects, right ventricular outflow tract obstruction defects, left ventricular outflow tract obstruction defects and conotruncal abnormalities [101-104]. In 2005, The United States Food and Drug Administration issued a public health advisory on its use in first trimester [101-103]. The Food and Drug Administration warned healthcare professionals that early prenatal exposure to paroxetine may increase the risk of congenital cardiac malformations and reclassified it to pregnancy category D [105].

A meta-analysis estimated a 50% increased prevalence of cardiac defects overall with first trimester paroxetine use [106]. It has remained unclear, however, whether these associations are causal, or due to systematic error or chance. Another meta-analysis conducted by Myles et

al. did not find any congenital malformation in mothers who were on citalopram during their pregnancy [101].

Until we have prospective long-term safety studies, careful risk-benefit analysis needs to be applied when considering the use of serotonin selective reuptake inhibitors or serotonin-norepinephrine reuptake inhibitors in pregnancy.

Decisions by clinicians and women about whether to continue or discontinue treatment with antidepressants during pregnancy must balance potential risks of treatment with the risks of not treating women with severe depression [107]. The results of a recent large population study suggest that first trimester use of antidepressants does not substantively increase the risk of specific cardiac defects. The accumulated evidence implies low absolute risks and argues against the existence of important cardiac teratogenic effects for the most commonly used antidepressant medications [108].

There has also been concern that exposure to lithium early in pregnancy may be associated with a marked increase in the risk of Ebstein's anomaly in infants and overall congenital cardiac defects, but data are conflicting and limited [109]. Despite the warnings, lithium remains a first line treatment for the 1% of women of reproductive age with bipolar disorder in the United States population. [110] This persistent use has been justified by the existence of more evidence on effectiveness than with other drugs, including data showing that lithium continuation is associated with a reduced risk of mood-episode recurrence during pregnancy and the postpartum period. [111] Furthermore, a large body of evidence has shown teratogenicity for some other mood stabilizers.

In a large population study cardiac malformations were present in 2.41% of the infants exposed to lithium, and in 1.15% nonexposed infants. The prevalence of right ventricular outflow tract obstruction defects was 0.60% among lithium-exposed infants versus 0.18% among unexposed ones [112].

Maternal use of lithium during the first trimester was associated with an increased risk of cardiac malformations, including Ebstein's anomaly; the magnitude of this effect was smaller than had been previously postulated [112]. ndings from this observational study support a modest increase in the risk of cardiac malformations in infants that are associated with lithium use in early pregnancy. On the basis of the 95% confidence interval around the effect estimates, results were consistent with up to 2 additional cases per 100 births among pregnancies in women who were exposed to lithium during the first trimester as compared with pregnancies in unexposed women with similar characteristics. The relative risk appeared to be higher for right ventricular outflow tract obstruction defects than for other CHD.

This study also suggests that the association of lithium and cardiac malformations in

humans is dose-dependent, with a risk that is increased by a factor of approximately 3 beyond doses of 900 mg per day [112].

9. Organochlorine Pesticides and Organic Solvents

A growing number of studies have indicated the potential role of environmental agents as risk factors in CHD occurrence. In particular, maternal exposure to chemicals during the first trimester of pregnancy represents the most critical window of exposure for CHD. Specific classes of xenobiotics (e.g. organochlorine pesticides, organic solvents, air pollutants) have been identified as potential risk factors for CHD. Nonetheless, the knowledge gained is currently still incomplete as a consequence of the frequent heterogeneity of the methods applied and the difficulty in estimating the net effect of environmental pollution on the pregnant mother [113].

Among the potential environmental risk factors for CHD, pesticides represent one of the most studied. While assessing the possible association between maternal exposure to pesticides and the occurrence of congenital defects, several studies detected an increased risk of congenital anomalies [114]. Frequently, the emerging results could not establish whether the effects observed were valid because of the small number of affected cases and the lack of a control group and more specific information on the type and level of exposure to chemicals [115, 109]. Results of some epidemiological studies, including The Baltimore-Washington Infant Study [119] have suggested that infants of mothers exposed to pesticides had an increased risk of ventricular septal defect [120, 121], whereas others have not detected any association [122]. Few studies have examined the potential correlation between pesticide exposure and specific cardiovascular malformations [115]. The Baltimore-Washington Infant Study, revealed a positive association incidence of transposition of the great arteries with maternal exposures to herbicides and rodenticides [115]. Although there are no data on the specific products to which parents of affected infants were exposed, it is likely that, at least with regard to the herbicide group, some of the chemicals are organochloride pecticides. Specifically, Loffredo et al. [115] showed that for both of the two categories of pesticides, the association with transposition of the great arteries was significant if the exposure occurred during the critical period for cardiovascular development.

Exposure to organic solvents in early pregnancy, both at home and in the workplace, is among the most prevalent sources of concern to CHD development [114].

Studies of maternal occupational exposure to organic solvents showed an increased risk of ventricular septal and conotruncal defects [114,116]. The results from research concerning maternal exposure to trichloroethylene and related compounds, and risk for CHD in the offspring, are inconclusive.

Yauck et al. [117] showed that trichloroethylene is likely to be a risk factor for CHD, reporting a threefold increase in risk for the disease among infants of older mothers presumably exposed to trichloroethylene compared with those of non-exposed mothers. The study suggests that trichloroethylene is a cardiac teratogen. Even though the mechanisms by which trichloroethylene and its metabolites induce heart defects are still largely unknown, it has been suggested that trichloroethylene exposure alters expression of several genes critical for heart development [118].

Due to the frequent heterogeneity of the methods applied, our knowledge is currently still incomplete for some determinants, and ambiguous for others. Nonetheless, increasing evidence suggests that environmental factors having teratogenic properties provide a serious threat for humans at birth and, specifically, may increase the risk of development of one of the most common congenital diseases.

10. Vitamin D Deficiency

Recently a large case control study was conducted in order to investigate associations between periconceptional maternal vitamin D status and CHD in the offspring.

Serum 25(OH)D concentrations as marker of vitamin D status were associated with maternal BMI, the use of multivitamin supplements, ethnicity and season of blood sampling. The results demonstrate that a deficient or moderate maternal vitamin D status is associated with CHD in the offspring, after adjusting for maternal age, BMI, ethnicity, smoking and lipids. When case children were stratified into isolated and complex CHD, only isolated CHD showed a significant association with maternal vitamin D status [123]

Similar to these results, Dilli et al conducted a case control study to measure serum level of micronutrients (including vitamin D) in 108 neonates with CHD and their mothers. They found a significant decrease in vitamin D level in both neonates and their mothers compared to controls. The authors report that maternal and neonatal Vitamin D level were lower in truncal anomalies including truncus arteriosus, tetralogy of Fallot, and D-transposition of great arteries [124].

Another case-control study was conducted to investigate the association between maternal serum vitamin D level & vitamin D receptor gene Fok1 polymorphism and risk of CHD in offspring. There was a significant decrease in maternal vitamin D level and a significant increase in vitamin D deficient status among cases when compared to controls. A significant increase in vitamin D receptor gene Fok1 F/f & f/f genotypes and f allele were observed in cases compared to controls. here was a significant decrease in maternal vitamin D level in neonates with cyanotic CHD compared to those with a cyanotic CHD while there was no significant difference in VDR Fok1 genotype & allele distribution between two groups. The

authors concluded that maternal vitamin D deficiency and vitamin D receptor gene Fok1 F/f, f/f genotype and f allele were associated with increased risk of CHD in the offspring [125].

A reported number of functional single-nucleotide polymorphisms of vitamin D receptor gene have been genotyped. Interestingly, it has been emphasized that certain single-nucleotide polymorphisms were correlated to impaired concentrations of vitamin D in the circulation [126].

A slightly elevated concentration of some nutrients can have a teratogenic effect, vitamin D and others seem beneficial in cardiac development. It is plausible that vitamin D interacts with many other genetic and environmental factors in the complex pathogenesis of CHD. Vitamin D affects cell processes through the binding of its active form 1, 25-dihydroxyvitamin D to the vitamin D receptor. This vitamin D receptor belongs to the nuclear receptor family and is involved in gene regulation [127].

A precise regulation of involved genes is extremely important during embryogenesis and cardiogenesis. Recent studies have demonstrated that components of the vitamin D pathway are involved in cardiogenesis [128-129]. Interestingly, the 1, 25-dihydroxyvitamin D concentration increases by 100–200% during the first trimester, suggesting an increased need during this early pregnancy period [130]. When the 25(OH) D concentration is inadequate, the conversion into active 1, 25-dihydroxyvitamin D might be decreased, resulting in a low vitamin D status, alterations of gene regulation and altered cardiogenesis.

11. Conclusion

Increasing evidence suggests that environmental factors and maternal intrinsic factors have teratogenic properties, provide a serious threat for humans at birth and, specifically, may increase the risk of development of CHD. For an intervention to be effective in the prevention of CHD this should be applied in the critical period of cardiogenesis which takes place between the 3rd and 7th week of gestation. Thus, instructions for future mothers should be to avoid exposures in the periconceptional period and during the first trimester of pregnancy. Future research will clarify the role of potentially preventable risk factors for CHD and will help establish prevention policies and interventions within the community.

12. References

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