Selected environmental risk factors and congenital heart defects

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Key words: environmental risk factors; congenital heart defects; maternal illness; lifestyle factors.

Summary. The aim of the article is to review the published scientific literature and epidemiological studies about the effect of selected environmental risk factors on congenital heart defects in infants.

According to recent reports, the prevalence of congenital heart defects is around 1% of live births. Congenital heart malformations are the leading cause of infant mortality. Unfortunately, the majority of the causes of heart defects remain unknown. These malformations are caused by interaction of genetic and environmental factors.

The article reviews selected environmental risk factors: maternal illnesses and conditions associated with metabolic disorder (maternal diabetes, obesity, phenylketonuria), maternal lifestyle factors (alcohol use, smoking), which may increase the risk of congenital heart defects.

Introduction

The prevalence of congenital heart defects (CHDs) is around 1% of live births (1). Mortality from CHDs remains a major cause of death in infancy and childhood (2). The heart and the vascular system are almost fully formed by midgestation, so early months of pregnancy are a critical window of exposure for CHDs (3).

The etiology of most CHDs is unknown; only around 15% of CHDs can be attributed to a known cause (4). Approximately 5–10% are associated with a chromosome abnormality, 3–5% can be linked to defects in single genes, and about 2% are attributed to known environmental factors (5). It is difficult to establish the role of a single factor, because in many cases, the cause of a defect is believed to be multifactorial (6, 7), including environmental teratogens with genetic and chromosomal conditions (4). Most of the causes of these anomalies occur within the fetal–placental–maternal “environment” (8). Maternal illnesses play a significant role in the development of heart defects in fetuses. Although the embryo does not have the disease, prolonged exposure to metabolites of the maternal illness leads to the development of congenital malformations (7). Any of the environmental factors may affect the woman’s organism before pregnancy or development of the fetus.

The article reviews published scientific literature and epidemiological studies on association between CHDs in offspring and selected environmental risk factors: maternal illnesses and conditions (diabetes mellitus, obesity, and phenylketonuria) associated with metabolic disorders and lifestyle factors (alcohol use, smoking).

Methods

Relevant studies were identified by searching computerized Medline database by the following key words: “congenital heart defects,” “environmental risk factors,” “lifestyle factors,” and “maternal illness.” Publications published between 1995 and 2007 were included.

Maternal illnesses and conditions

Maternal diabetes mellitus

Maternal pregestational diabetes mellitus increases the risk of CHDs (9–13). Maternal diabetes mellitus is generally associated with a wide spectrum of CHDs: laterality/looping defects, transposition of the great arteries outflow tract defects with normal great arteries, nonchromosomal atriocentric septal defects, double-outlet right ventricle, tetralogy of Fallot, membranous ventricular septal defects, hypoplastic left heart syndrome, cardiomyopathy (9). Recent studies showed that pre-existing maternal diabetes had an increased risk of cardiovascular congenital abnormalities (10, 11) (Table).

The exact teratogenic mechanism of maternal diabetes is not fully defined and is likely to be multifactorial (4, 14, 15). Abnormalities, including increased
Table. Selected environmental risk factors reported to be significantly associated with congenital heart defects

| Risk factor                    | Study design | Defects                                      | Estimated risk                        | Authors                      |
|-------------------------------|--------------|----------------------------------------------|---------------------------------------|------------------------------|
|                               |              |                                               |                                       |                              |
| Pregestational diabetes       | Case-control | Laterality/looping defects                    | Adjusted OR=8.3 (95% CI, 3.0–23.0)    | Ferencz et al. (1997)        |
|                               | Case-control | Transposition of the great arteries          | Adjusted OR=3.8 (95% CI, 1.4–10.2)    | Ferencz et al. (1997)        |
|                               | Case-control | Outflow tract defects with normal great arteries | Adjusted OR=5.4 (95% CI, 2.5–10.8)    | Ferencz et al. (1997)        |
|                               | Case-control | Nonchromosomal atrioventricular septal defects | Adjusted OR=10.6 (95% CI, 3.7–30.6)   | Ferencz et al. (1997)        |
|                               | Case-control | Membranous ventricular septal defects         | Adjusted OR=2.9 (95% CI, 1.4–6.1)     | Ferencz et al. (1997)        |
|                               | Case-control | Hypoplastic left heart syndrome               | Adjusted OR=3.9 (95% CI, 1.2–13.2)    | Ferencz et al. (1997)        |
|                               | Case-control | Cardiomyopathy                               | Adjusted OR=11.5 (95% CI, 4.4–29.8)   | Ferencz et al. (1997)        |
|                               | Case-control | Cardiovascular malformations                 | OR=5.0 (95% CI, 3.3–7.8)              | Wren et al. (2003)           |
| Obesity                       | Case-control | Transposition of the great arteries          | OR=4.4 (95% CI, 1.1–17.7)             | Quiesser-Luft et al. (1998)  |
| BMI ≥30 kg/m² for risk*       | Case-control | Truncus arteriosus                           | OR=6.3 (95% CI, 1.6–24.8)             | Quiesser-Luft et al. (1998)  |
| BMI ≥27 kg/m²                 | Retrospective cohort | Congenital heart defects                     | OR=6.5 (95% CI, 1.2–34.9)             | Mikhail et al. (2002)        |
| BMI 25.0–29.9 kg/m²           | Case-control | Heart defects in aggregate                   | Unadjusted OR=2.0 (95% CI, 1.2–3.1)   | Watkins et al. (2003)        |
| BMI 25.0–29.9 kg/m²           | Case-control | Left ventricular outflow tract defects       | Unadjusted OR=3.3 (95% CI, 1.6–6.7)   | Watkins et al. (2003)        |
| BMI ≥30 kg/m²                 | Case-control | Heart defects in aggregate                   | Unadjusted OR=2.0 (95% CI, 1.2–3.4)   | Watkins et al. (2003)        |
| BMI >29 kg/m²                 | Case-control | All cardiovascular defects                   | Adjusted OR=1.18 (95% CI, 1.09–1.27)  | Cedergren et al. (2003)      |
| BMI >29 kg/m²                 | Case-control | Ventricular septal defects                   | Adjusted OR=1.14 (95% CI, 1.01–1.28)  | Cedergren et al. (2003)      |
| BMI >29 kg/m²                 | Case-control | Atrial septal defects                        | Adjusted OR=1.37 (95% CI, 1.09–1.72)  | Cedergren et al. (2003)      |
| BMI >35 kg/m²                 | Case-control | All cardiovascular defects                   | Adjusted OR=1.40 (95% CI, 1.22–1.64)  | Cedergren et al. (2003)      |
| Alcohol                       | Case-control | Small muscular ventricular septal defect     | Adjusted OR=2.6 (95% CI, 1.4–4.8)     | Ferencz et al. (1997)        |
osmolarity and abnormal levels of ketones, amino acids, and fatty acids, may contribute to pathogenesis. High blood glucose levels could cause congenital malformations by inhibiting glycolysis, the primary process of energy production during embryogenesis (15). The experimental study showed a positive significant interrelationship between increased malformation and resorption rates and the maternal serum concentrations of glucose, triglycerides, beta-hydroxybutyrate, branched-chain amino acids, and creatinine (16). Hyperglycemia has a direct influence on proliferation and migration of neural crest cells, which are essential in the development of the heart (17). The recent study by Roest et al. showed a high incidence of cardiovascular malformations in embryos, which cardiac neural crest cells were exposed to an elevated glucose level (18). Other study reported that abnormal glucose level in embryos disturbed the expression of Pax-3, a development control gene (19), which is an important transcription factor of cardiac neural crest cells (18, 20).

The influence of preconceptional diabetes begins during embryonic development in the first trimester; it continues to have an influence during the second and third trimesters and into the perinatal and neonatal period (14).

The risk of developing a CHD can be greatly diminished by good blood glucose control (4). Contrarily, duration of mother’s insulin-dependent diabetes and poor glycemic control before and during pregnancy increase the risk of congenital malformations (13).

**Obesity**

A number of recent studies have examined the relation between maternal prepregnancy obesity and CHDs. The findings of these studies have been inconsistent because of variations in categorization of body mass index and methods.

A population-based case-control study by Watkins et al. reported that obese and overweight women were more likely than average-weight women to have infants with heart defects (21). Cedergren et al. observed a positive association between maternal obesity in early pregnancy and CHDs in the offspring. Obese mother and mothers with morbid obesity (BMI >35 kg/m²) had an increased risk for cardiovascular defects compared with the average-weight mothers. There was an increased risk for all specific defects studied among the obese women, but only ventricular septal defects and atrial septal defects reached statistical significance (22). A case-control study from Germany reported

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**Table continuation**

| 1          | 2                        | 3                          | 4                        | 5                         |
|------------|--------------------------|-----------------------------|--------------------------|----------------------------|
| Smoking    | Case-control             | Pulmonic stenosis           | Adjusted OR=12.5 (95% CI, 3.2–49.4) | Ferencz et al. (1997)      |
| Case-control| Transposition with ventricular septal defect | Adjusted OR=2.1 (95% CI, 1.2–3.9) | Ferencz et al. (1997)      |
| Case-control| Transposition with ventricular septal defect | Adjusted OR=4.5 (95% CI, 1.4–14.9) | Ferencz et al. (1997)      |
| Case-control| Atrioventricular canal defects | OR=2.3 (95% CI, 1.2–4.5) | Torfs and Christianson (1999) |
| Case-control| Tetralogy of Fallot       | OR=4.6 (95% CI, 1.2–17.08) | Torfs and Christianson (1999) |
| Case-control| Atrial septal defects without ventricular septal defect | OR=2.2 (95% CI, 1.1–4.3) | Torfs and Christianson (1999) |
| Retrospective cohort | Cardiovascular system abnormalities | Adjusted RR=1.56 (95% CI, 1.12–2.19) | Woods and Raju (2001)      |
| Case-control| Heart defects in aggregate | Adjusted OR=1.88 (95% CI, 1.21–2.92) | Dulskenė and Gražulevičienė (2005) |

*Reference group, BMI <30 kg/m².
**Reference group, BMI <27 kg/m².
***Reference group, BMI 18.5–24.9 kg/m².
****Reference group, BMI=19.8–26 kg/m².

21–39 cigarettes/day.

40+ cigarettes/day.
Maternal lifestyle factors

Alcohol use and cigarette smoking

A limited number of studies have examined the relationship between maternal lifestyle factors and risk of CHDs. Maternal alcohol use during pregnancy is associated with birth defects in children (6, 33, 34). The adverse effects of alcohol on the developing human comprise a spectrum of structural anomalies and behavioral disabilities (34) and leads to an increased number of neonates with fetal alcohol syndrome (6, 34, 35). Shillingford et al. reported that atrial septal defects were the most frequent cardiac anomalies in these neonates (35). Ferencz et al. reported only association between heavy maternal alcohol consumption and small muscular ventricular septal defect. Authors explained that analysis by the greatest number of alcoholic beverages consumed at any occasion during critical period did not reveal any associations of the trend in the risk of CHD with exposure (9) (Table).

In Spain, a case-control study by Martinez-Frias et al. reported that higher risk of developing CHDs was in the group with the highest-level prenatal exposure to alcohol (the absolute alcohol ingestion was more than 92 gm per day) (36).

Few epidemiological studies investigated the association between maternal smoking during their pregnancies and CHDs. These studies are difficult to compare because of differences in sizes, classifications, and methods of population-based studies. In the Baltimore–Washington Infant Study, maternal cigarette smoking of more than one pack per day was associated with two cardiac diagnoses: transposition with ventricular septal defect and pulmonic stenosis (women who were more than 34 years old) (9). In study by Torfs and Christianson, an association between mother’s cigarette smoking and specific defects (atrioventricular canal and atrial septal defects without ventricular septal defect, tetralogy of Fallot) was reported (37). The case-control study conducted in Lithuania indicated that maternal smoking increased the risk of having infant with CHD almost two times (38) (Table). Kallen found no association between all heart defects combined and maternal smoking (39). In a retrospective different cohort study, Woods and Raju reported that of the 22 categories of congenital defects, only cardiovascular system abnormalities were significantly associated with maternal smoking (40). In a recent study, Scherbak et al. did not detect any dependence between smoking and probability of having a newborn with birth defects in the cardiovascular system (41).

Lifestyle factors such alcohol consumption and
Selected environmental risk factors and congenital heart defects

Kai kurie aplinkos rizikos veiksniai ir įgimtos širdies ydos

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Raktas
Aplinkos rizikos veiksniai, įgimtos širdies ydos, motinos liga, gyvensenos veiksniai.

Santrauka
Straipsnio tikslas. Apžvelgti mokslinę literatūrą ir epidemiologines studijas apie pasirinktų aplinkos veiksniių poveikį įgimtoms širdies ydoms. Moksliniai tyrimai duomenimis, apie 1 proc. gyvų gimų su įgimtais širdies ydomais. Šiame straipsnyje apžvelgiame kai kurie aplinkos rizikos veiksniai: motinos ligos ir būklės, susijusios su sutrikusia medžiaga apykleita (cukrinis diabetas, nutukimas, fenilketonuriija), motinos gyvensenos veiksniai (alkoholinës gėrimų vartojimas, rūkymas), turintys įtakos įgimtoms širdies ydoms formavimui.

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