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RISK FACTORS IN CHILD CONGENITAL MALFORMATIONS

Theoretical
Article

Keywords

Teratogenic,
Pregnancy heart malformation,
Prevention

JEL Classification I18

Abstract

Congenital heart malformations are among the most common congenital malformations. Congenital heart malformations occur due to genetic and environmental factors during embryonic morphogenesis period of the heart. About 25% of these malformations are severe, requiring intervention immediately after birth or in infancy.

Abnormalities of structure and function of the heart and great vessels are the consequence of teratogenic factors occurring between day 19 and 45 of gestation. (Yagel et al, 2002; Socoteanu, 2010)

According to WHO, global incidence of congenital heart diseases (MCHC) is 8 per 1,000 live births and show an upward trend. In the US, an incidence of 6 cases per 1000 live births was reported in 1968 (Hoffman, 1968) and it is much higher nowadays, more than 12-14 cases per 1000 live births. (Hoffman, 1995)

Differences could be observed by region. Two different studies conducted in the UK and Denmark over a long period of 20 and 28 years, respectively, reported a significantly different incidence of 6.5 cases, 10.3 cases per 1,000 live birth, respectively. (Wren et al., 2008; Øyen et al., 2009)

1. The most common form of cardiac malformation is ventricular septal defect (VSD) found in 30-40% of cases, followed by the persistence of the ductus arteriosus (DSA) and atrial septal defect in 6-10% of cases. (Yagel et al, 2002; Hoffman et al., 2004) Both genetic and environmental factors are involved in congenital heart diseases etiology. Only 5-8% of MCC are due only to congenital anomalies and only 2% to environmental factors. (Yagel et al, 2002; 24) There is a genetic predisposition favoring the effects of teratogenic compounds, thus about 80% of MCC have a plurifactorial etiology. (Pierpont et al., 2007; www.usmf.md)

Certain drugs given to mother during pregnancy are directly involved in the increased risk of MCC.

Anticonvulsant medication, especially phenytoin, hydantoin, carbamazepine, phenobarbital and valproic acid increases three times the risk of malformations due to toxic or teratogenic effects on the embryo. (Holmes et al., 2010)

In particular, fetal exposure to hydantoin is associated in 4-7% of the cases with hydantoin syndrome characterized by craniofacial dysmorphism, disorders in the development of neural tube associated with cardiovascular malformations: coarctation of the aorta, atrial septal defect or ventricular persistence of ductus arteriosus. (Yagel et al, 2002; Holmes et al., 2010) Hydantoin inhibits the absorption of folic acid, the created deficiency being involved in the etiology of this syndrome. Taking folic acid supplements before conception based and during pregnancy can reduce up to 70% the incidence of malformations among infants at risk. (Holmes et al., 2010; Nicolai et al., 2008)

Lithium salts are used successfully in the treatment of people suffering from depression, bipolar disorder or manic states. Their risk - benefit ratio should be assessed when administered to pregnant women, these being involved in abnormalities of the tricuspid valve or anomaly Ebstein's anomaly. (Bergink & Kushner, 2014)

Retinoic acid and its isomer, *isotretinoin*, are used in the management of acne resistant to treatment. Exposure in the first trimester of pregnancy increases by 30% the risk of congenital heart defects (Kenneth et al., 2001), strong teratogenic effect on the fetus was demonstrated back in 1982. It is frequently associated with transposition of great arteries or abnormalities of

the aorta. Contraception is recommended during treatment and at least 1-2 months after it. (Yagel et al, 2002 Malvasi et al., 2009)

Betasympaticomimeticile, *corticosteroids*, *nonsteroidal anti-inflammatory drugs*, *angiotensin converting enzyme inhibitors* should be avoided during pregnancy because of proven teratogenic effects. (Yagel et al, 2002; May et al., 2013)

Diabetes during pregnancy is associated with an increased risk of fetal neonatal and long-term complications. Diabetes can be pre-existing (diabetes type 1 or type 2) or gestational identified during pregnancy with a prevalence of 7.5%. The risk of developing congenital malformations in children of diabetic mothers is between 2.5 - 12%, being most affected infants of mothers who were diagnosed with preconception insulin-dependent diabetes. (Yagel et al, 2002; Riskin et al., 2007) Maintaining an elevated glycosylated hemoglobin during pregnancy is associated with an increased risk of birth defects, particularly of the heart. The most common MCC in children of mothers with unbalanced diabetes are transposition of great arteries, ventricular septal defect, hypoplastic left heart. Despite strict glycemic control, septal hypertrophic cardiomyopathy occurs in 30% of the cases. It has a benign evolution with spontaneous resolution in most cases. There are, however, rare cases evolving to severe heart failure. (Narchi & Kulaylat, 2000; Hornberger, 2006) A strict glycemic control with a balanced diet during pregnancy is enough for significant decrease of intrauterine fetal damage.

Phenylketonuria (PKU) is a genetic metabolic disease in which the phenylalanine hydroxylase enzyme involved in the metabolism of phenylalanine is in very little quantity or is absent in blood. The only available treatment is natural proteins restriction in diet that contain phenylalanine. If this diet is not followed, children have low birth weight, mental retardation, microcephaly, congenital heart. (Harvey, 1996; Kimberlee et al., 2003) Cardiac malformations are found in about 12% of the cases. (Kimberlee et al., 2003) Strict adherence to the diet for at least 3 months before conception and throughout pregnancy drops significantly almost to zero the risk of developing embryopathy. (Maillot et al., 2008)

Although *rubella infection* is a viral eruptive disease, benign in most cases, it can be devastating in pregnant women not previously immunized, with a high embryofetal teratogenic effect. (Robertson et al., 2003) The consequences of maternal infection can be miscarriage, premature birth, fetal malformations by congenital rubella. Their risk decreases with gestational age, the consequences of the severe fetal and neonatal

occurring when the infection has been contacted within the first 2 months of pregnancy. Deafness, eye damage (cataracts, microphthalmia) are given by cardiac malformations. Cardiac malformations are found in at least 2/3 of children affected in the first 16 weeks of gestation and are given by the persistence of the ductus arteriosus, pulmonary stenosis, pulmonary vein stenosis, atrial septal defect and ventricular tetralogy of Fallot. (Yagel et al, 2002; Robertson et al., 2003) Breast screening is required for checking the immune status. Immunoprophylaxis with rubella vaccine is given in the absence of pregnancy at least 3 months before conception. In case of non-immunized pregnant women, careful monitoring is recommended in early pregnancy and repetition of specific antibodies during pregnancy to check the immune status. (Robertson et al., 2003; Cutts et al., 2000)

Other maternal-fetal infections involved in cardiac malformations are *infection with toxoplasma gondii, Coxsackie virus A and B or cytomegalovirus infection*. (Yagel et al, 2002; May et al., 2013)

Alcohol drinking during pregnancy is associated with toxicity, teratogenic fetus from miscarriage, premature birth up to fetal alcohol syndrome. Fetal alcohol syndrome occurs after heavy drinking of alcohol during pregnancy and is characterized, depending on severity, by specific craniocerebral malformations, skeletal malformations of the central nervous and cardiovascular systems. There is no certain minimum level of alcohol consumption for a pregnant woman; there have been reported cases of fetal impairment even in occasional drinking. Mother's abstinence from alcohol drinking is the only prevention method. (Cutts et al., 2000)

2. *Maternal smoking* is a public health issue, about 25% of pregnant women being smokers. Nicotine and carbon monoxide are the main teratogenic factors affecting the development of the embryo and fetus. Besides being involved in the bioavailability of vitamin B12, folic acid and zinc favor intrauterine growth restriction, congenital malformations and prenatal mortality increase. Right heart obstructive impairment, septal defects, transposition of great arteries are associated with maternal smoking, especially in the first quarter. (www.usmf.md) Reduction of the number of cigarettes during pregnancy does not decrease the risk of teratogenicity. Quitting smoking at least 2 months before conception, avoiding smoking and exposure to tobacco smoke during pregnancy are the only methods for significant decrease of fetal damage. (www.usmf.md; May et al., 2013)

Maternal exposure to *toluene* is closely linked with heart malformations in children, especially in hypoplastic left heart, coarctation of

the aorta, pulmonary stenosis. Also, in chronic exposure, there have been reported cases of alcohol-like fetal syndrome. Products containing toluene are nail polish, paint, glue or different solvents. (May et al., 2013)

Since one third of infants leave maternity undiagnosed with MCC, a thorough medical history is essential for identifying potentially teratogenic factors.

Understanding risk factors affecting the normal development of the cardiovascular system is important due to the increased incidence of cardiovascular malformations and their negative impact on patients' quality of life. If genetic factors are factors that cannot be changed, environmental factors could be influenced, known and avoided as much as possible during pregnancy.

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