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Alcohol and cardiac abnormalities in embryos

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Consuming alcohol during pregnancy poses risks to the fetus, namely the manifestation of fetal alcohol syndrome or fetal alcohol spectrum disorders (FAS/FASD). In the present paper, alcohol-related congenital heart abnormalities are examined. Congenital heart defects are morphological and functional abnormalities of the heart, which are present at birth and can disrupt the normal blood flow of the heart or great arteries. The most critical cardiac abnormalities due to alcohol consumption during pregnancy are d-transposition of the great arteries, tetralogy of Fallot, pulmonary stenosis, as well as ventricular, atrial, and atrioventricular septal defects. The first clinical presentation in the immediate neonatal period is usually cyanosis (cyanotic heart diseases), without a standard occurrence. The treatment can be conservative or surgical, depending on the type and degree of the abnormality. Informing the public about the complications of alcohol consumption during pregnancy is essential to prevent the birth of children with abnormalities. Last but not least, early prenatal diagnosis is imperative for applying the best treatment.

Αλκοόλ και καρδιακές ανωμαλίες στο έμβρυο

Περίληψη στο τέλος του άρθρου

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1. INTRODUCTION

Alcohol is a teratogenic substance, meaning it can cause various problems if consumed during pregnancy. Yet, alcohol consumption advice during pregnancy varies, from complete abstinence to moderate consumption (usually defined as no more than 1 to 2 units, once or twice a week).[1] Alcohol intake during pregnancy is estimated to be between 28% and 72% in Australia, according to prospective cohort studies and national surveys. In another cohort study of 1,570 pregnant women, 59% said they drank alcohol while pregnant, with 32% stating that they did so in the second or third trimester. Likewise, according to a national study conducted in 2016, half of the pregnant women drank alcohol before realizing they were pregnant, and 25% continued to drink alcohol after discovering their pregnancy. Most women who drank alcohol during pregnancy consumed monthly or less frequently (81%), with an average of one to two standard drinks per occasion (97%).[2] In all of the above mentioned cases, alcohol reaches the fetal bloodstream through the placenta and has the same concentrations in the mother's blood as in the embryos; however, it takes twice as long to be digested due to the incomplete development of the fetus's liver and kidneys.[3] As a result, it may lead to the manifestation of fetal alcohol syndrome or fetal alcohol spectrum disorders (FAS/FASD).

The acronym FASD describes a wide range of disorders in babies and children caused by mild to excessive prenatal alcohol exposure (PAE). FAS, partial FAS (pFAS), alcohol-related birth defects (ARBD), and alcohol-related neurodevelopmental disorders (ARND) are also included. FASD is the most common cause of mental retardation in children. At the same time, structural involvement of other systems (cardiovascular, renal, musculoskeletal, ocular, and auditory systems) has been related to this disorder as well. According to a meta-analysis conducted by Yang et al, prenatal binge drinking was linked to 1.49 times rise in

overall congenital heart defects' (CHD) risk compared to not drinking at all.[4] Another relevant study conducted by Zhang et al made evident that the probability of total CHDs in offspring increased by 42% when maternal alcohol intake exceeded 116 g per day.[5] Likewise, when paternal alcohol intake was more significant than 375 g per day, the risk of total CHDs in offspring was increased by 47%.[5]

As for the size of the impact of alcohol consumption, a study made by Denny et al showed that FASD is estimated to affect 33.5 out of 1,000 children in the United States of America (USA) and 22.8 out of 1,000 globally.[6] Specifically, according to Abel et al (1996), approximately 54% of FASD patients have alcohol-related CHDs, making the heart a common organ affected by fetal alcohol exposure, while being the leading cause of perinatal mortality at the same time.[7] As for FAS, it is estimated to impact 0.3 to 0.8 out of 1,000 children in the USA and 2.9 out of 1,000 worldwide.[6]

The present paper examined the alcohol-related CHD caused in the fetus, described as structural abnormalities of the heart or great intrathoracic vessels during embryonic development. More in detail, these are d-transposition of the great arteries, tetralogy of Fallot (TOF), pulmonary stenosis,[8] and ventricular, atrial, and atrioventricular septal defects,[4] as well as arrhythmic disorders.[9]

2. ALCOHOL-RELATED CONGENITAL HEART DISEASES

Many CHDs have been documented in the literature so far, regarding the consequences of alcohol consumption in this particular group of patients. More specifically, individuals born with FASD, apart from abnormalities in the development of the heart, may have abnormalities in other systems as well, such as intrauterine growth restriction (IUGR), deformities of the face, limbs, central nervous system anomalies, visual, auditory, and learning disabilities, social, behavioral issues in a state of crisis, and abnormalities in the development of the heart, genital, renal, musculoskeletal system, and high mortality rate (tab. 1).[6,9] As for the manifestation of CHD after parental alcohol consumption during gestation, it is proven that drinking alcohol while pregnant can affect the fetus' cardiovascular system, but only CHDs have been reported so far.

Table 1. Side effects of alcohol intake during pregnancy.

Intrauterine growth restriction	
Deformities of the face	Short palpebral fissures
	Thin vermillion border
	Smooth philtrum
Deformities of the limbs	
Central nervous system anomalies	Intellectual disability
	Neuropsychiatric disorders
Visual anomalies	Optic nerve hypoplasia
	Ptosis
	Retinal vascular anomalies
	Strabismus
Auditory anomalies	Conductive or neurosensory hearing loss
Learning disabilities	
Social, behavioral issues in a state of crisis	
Abnormalities of the heart	Dextro transposition of the great arteries
	Tetralogy of Fallot
	Pulmonary stenosis
	Ventricular septal defects
	Atrial septal defects
	Atrioventricular septal defects
	Arrhythmic disorders
Genital deformities	Hypoplastic labia majora
	Uterine hypoplasia
Renal deformities	Aplastic, dysplastic, hypoplastic kidneys
	Horseshoe kidney
	Ureteral duplication
	Hydronephrosis
Musculoskeletal system	Flexion contractures
	Radioulnar synostosis
	Scoliosis
	Vertebral segmentation defects
High mortality rate	

2.1. Arrhythmic disorders

Arrhythmic disorders, such as premature ventricular contractions (PVCs), sinus rhythm with frequent premature atrial contractions (PACs) and short runs of ectopic atrial tachycardia, as well as supraventricular tachycardia (SVT) were documented in this group of patients. As for the occurrence of asymptomatic arrhythmic irregularities in the absence of structural cardiac defects, this may be

explained by a toxic effect of the alcohol on the autonomic nervous system. A case report made by Onesimo et al, on two children with FASD, showed that the severity of FASD can be influenced by several factors, including the onset of alcohol dependence during pregnancy, regular dosage, and maternal comorbidities. They concluded that arrhythmic disorders are a coincidental correlation or a trait that may broaden the FAS spectrum and that a cardiac treatment was not necessary; however, a follow-up with ECG, 24-hour Holter monitoring and exercise stress testing is needed.[9]

2.2. Pulmonary stenosis

Pulmonary stenosis is present in 8% of all congenital heart defects.[10] Valvular pulmonary stenosis is typically an isolated defect, although it can sometimes be linked to CHDs, such as atrial septal defect (ASD), ventricular septal defect (VSD), and persistent ductus arteriosus. Combined valvular and infundibular pulmonary stenosis can be part of the TOF.[11] In more detail, pulmonary stenosis is a condition in which blood flow from the right ventricle to the pulmonary artery is obstructed. This obstruction is caused by the stenosis of one or more points between the right ventricle and the pulmonary artery. The right ventricle must work harder to eject blood into the pulmonary artery when the pulmonary valve is obstructed. The right ventricle muscle gradually hypertrophies to compensate for the increased workload. These patients may have heart failure and be frequently duct-dependent. Most people with ranging from mild to moderate pulmonary stenosis are asymptomatic and are diagnosed with a murmur during a typical physical examination during childhood. Mild exertional dyspnea and tiredness are known symptoms. The inability to improve pulmonary blood flow during exercise in untreated severe pulmonary stenosis might cause chest pain or syncope.[11] According to the literature, pulmonary stenosis and septal defects can be attributed to low levels of PAE, such as a single dose and can lead to developmental abnormalities, continuous medical treatments and death.[8] Balloon pulmonary valvuloplasty, replaced by surgical valvotomy is the preferred treatment. However, if there is a hypoplastic pulmonary annulus, a severely dysplastic valve, an infundibular stenosis, surgical treatment may often be inevitable.[11]

2.3. Conotruncal defects

Conotruncal defects (CTDs) (TOF and dextro transposition of the great arteries [dTGA]) are heart malformations caused by developmental damage to the branchial arch and arteries in the outflow tract. It is known that TOF is a four-part CHD: (a) A large VSD; (b) pulmonary stenosis (a narrowing in the blood vessel leading to the lungs); (c) aortic overriding (the aorta is located right above the VSD); and (d) the right ventricle hypertrophies as a result of these cases. Children with this condition may become cyanotic because of under-oxygenated blood circulating the body. The presence of pulmonary stenosis and large VSD result to low blood flow towards the pulmonary artery and right to left shunt; therefore symptoms like hypoxemia and cyanosis are common. Minimal obstruction to pulmonary blood flow may provoke a not easily evident cyanosis, known as acyanotic or "pink" TOF. With severe obstruction and saturations <80%, severe cyanosis, difficulty in feeding, hypercyanotic spells, clubbing, fatigue and erythrocythemia are present. TOF's treatment is the creation of a temporary shunt soon after birth and open-heart surgery later in infancy.[12]

On the other hand, due to dTGA, the aorta and pulmonary arteries, which carry blood away from the heart, become reversed. Consequently, the aorta is connected to the right ventricle and the pulmonary arteries are connected to the left ventricle, causing oxygenated blood to flow through the lungs while deoxygenated blood flows through the body. The lack of oxygen in the body caused by dTGA leads to severe damage to the heart muscles. The presence or absence of a patent ductus arteriosus (PDA), ASD(s) or VSD(s) must be present to sustain postnatal life. Symptoms like severe hypoxemia, cyanosis, tachypnea, metabolic acidosis and heart failure are determined by the degree of cyanosis.[13] Two types of surgery are known to repair d-TGA; arterial switch operation and atrial switch operation.[14]

According to a meta-analysis conducted by Caputo et al in 2016, only the CTDs subtypes were significantly correlated with prenatal alcohol exposure.[15] Mothers who drank during pregnancy had a 1.64 times higher chance of having a baby with dTGA, a subtype of CTDs.[4] Continuing with a study mentioned above, conducted by Yang et al, TOF was also one of the CTDs subtypes present in the effects of PAE. However, according to the study, there was no considerable risk of TOF associated with prenatal alcohol use.[4]

2.4. Ventricular septal defects and atrioventricular septal defects

A substantial correlation between alcohol exposure, VSD and ASD has been discovered in the meta-analysis conducted by Yang et al. An ASD is a cardiac birth defect

wherein the heart's upper chambers (atria) have an opening in the wall dividing them (septum). This opening increases the amount of blood flowing into the lungs, by the presence of a left-to-right shunt, causing pulmonary hypertension and heart failure. The decision to repair an ASD is based on clinical and anatomic evidence, size and location of the defect, significance of the hemodynamic impact of the shunt, and the presence and degree of pulmonary arterial hypertension. Small ASDs may close naturally in children; however, if left untreated, wider defects may cause hemodynamic irregularities and clinical signs, such as right heart failure, arrhythmias and pulmonary hypertension. Asymptomatic patients with a significant left-to-right shunt and evidence of right heart enlargement also benefit from closure, given that continued over-circulation in an already dilated right heart increases the risk of late clinical complications, such as reduced functional capacity, atrial arrhythmia and pulmonary arterial hypertension.[16] Yang et al pointed out that the connection between maternal alcohol consumption and ASDs was also considered. However, the ultimate finding was that maternal alcohol consumption was not significantly linked to the risk of ASDs.[4]

A VSD is an irregular opening between the lower chambers of the heart (ventricles). This leads blood that is oxygen-rich to mix with oxygen-depleted blood. As pressure in the right side of the heart decreases, blood flows to the path of the smallest resistance, causing a left-to-right shunt. This will gradually lead to symptoms of congestive heart failure. The significance of the VSD is determined by the size, location of the opening, and pulmonary vascular resistance. Small VSDs present an insignificant hemodynamic impact on infants, who remain asymptomatic and will not need any intervention. Medium to large VSDs present an important hemodynamic impact, leading to symptoms like tachypnea, dyspnea, poor eating, easy tiring and sweating during feeding, reoccurring infections. To prevent long-term complications such as pulmonary hypertension, closure of VSD beyond infancy is recommended in patients with hemodynamically significant left-to-right shunts.[17] The same study showed that VSDs were significantly linked with prenatal alcohol consumption.[4]

Furthermore, the combined findings of the two studies, conducted by Yang et al, that looked into the correlation between prenatal alcohol exposure and atrioventricular septal defects (AVSD), showed no evidence of a link.[4]

3. DISCUSSION

To our knowledge, the present study consists of all the possible defects that prenatal alcohol consumption by both parents can cause to the embryonic heart. Even though the teratogenic effect of alcohol on the cardiovascular system and cardiac rhythm is already fully proved, the actual mechanisms by which alcohol intake can cause CHDs, and pro-arrhythmic impact remain unclear.[8]

The connection between maternal alcohol exposure and the risk of CHDs is assessed by a theory of genetic changes caused by the teratogenic effect of alcohol, which increases the risk of CHDs. Serrano et al found that maternal alcohol exposure affects the Wnt/b-catenin signaling pathway, designed to induce normal gene activation and cardiogenesis.[5] Strandberg-Larsen et al, for instance, found that mothers who had been exposed to alcohol had a considerably higher risk of CHDs in their offspring if they had these variant alleles.[18] Furthermore, it has been proposed that maternal alcohol exposure might affect fetal heart development by leading to abnormal conversion of retinol to retinoic acid, antagonism of the N-methyl-d-aspartate (NMDA) receptor, disruptive vascular events, or compromised nutritional status.[19] In addition, paternal alcohol exposure has been shown to affect DNA transmission methylation in spermatozoa, significantly reduce the activity of DNA methyltransferase, induce CG hypomethylation, and then activate the normal silencing gene, resulting in congenital defects in the offspring.[20] Histone alteration has also been proven to control gene expression and modify sperm activity, resulting in defective offspring phenotypes in certain studies.[18,21] Moreover, the pathway review revealed that miRNA expression could regulate many cardiovascular pathways, potentially contributing to cardiac development defects.[22]

It is concluded that parental alcohol exposure and the risk of CHDs have a nonlinear dose-response relationship. As parental alcohol intake increased, the likelihood of CHDs in offspring increased as well.[5] However, given the results of the various studies discussed above, PAE was not significantly associated with overall CHDs. In contrast, there was a statistically significant link with dTGA, a subtype of CTDs. Likewise, studies with arrhythmic disorders in individuals affected by FASD are scarce in the literature and need to be studied in more depth. A measure that several countries found imperative to release was national guidelines advising women who are expecting or considering getting pregnant to avoid consuming alcohol. Even with these guidelines, nearly 10% of women worldwide drink alcohol at some point during their pregnancy, with higher prevalence levels documented in countries with high overall alcohol consumption rates (e.g., Ireland: 60%; Denmark: 46%; United Kingdom: 41%).[2] In addition, unfortunately, FAS is

diagnosed at an average age of 48.3 months, but it is often ignored or misdiagnosed, delaying the provision of needed treatment to affected children.[6] Therefore, further research is required to determine the underlying mechanisms that link parental alcohol intake to offspring's risk of CHDs.

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The corresponding author attests that all listed authors meet authorship standards and that no others meeting the criteria have been omitted.

ΠΕΡΙΛΗΨΗ

Αλκοόλ και καρδιακές ανωμαλίες στο έμβρυο

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Η κατανάλωση οινοπνεύματος κατά την κύηση εγκυμονεί κινδύνους για το έμβρυο, όπως η πρόκληση εμβρυϊκού αλκοολικού συνδρόμου ή φάσμα διαταραχών εμβρυϊκού αλκοολισμού. Στην παρούσα εργασία εξετάστηκαν οι προκληθείσες από το οινόπνευμα συγγενείς καρδιακές ανωμαλίες. Οι συγγενείς καρδιακές βλάβες είναι μορφολογικές και λειτουργικές ανωμαλίες της καρδιάς, οι οποίες είναι παρούσες κατά τη γέννηση και ενδέχεται να διαταράξουν τη φυσιολογική ροή του αίματος της καρδιάς ή των μεγάλων αγγείων. Οι κυριότερες καρδιακές ανωμαλίες που οφείλονται στην κατανάλωση οινοπνεύματος κατά την εγκυμοσύνη είναι η d-μετάθεση μεγάλων αγγείων, η τετραλογία του Fallot, η πνευμονική στένωση και τα ελλείμματα του κολπικού, του κοιλιακού και του κολποκοιλιακού διαφράγματος. Η πρώτη κλινική εκδήλωση στην άμεση νεογνική περίοδο συνήθως είναι η κυάνωση (κυανωτικές καρδιοπάθειες), χωρίς αυτό να αποτελεί τον κανόνα. Η θεραπεία μπορεί να είναι συντηρητική ή χειρουργική, ανάλογα με το είδος και τον βαθμό της ανωμαλίας. Η ενημέρωση των πολιτών ως προς τις επιπλοκές της κατανάλωσης οινοπνεύματος κατά την εγκυμοσύνη είναι πρωταρχικής σημασίας, ώστε να προλαμβάνεται η γέννηση παιδιών με ανωμαλίες της καρδιάς. Τέλος, εξ ίσου σημαντική είναι η έγκαιρη προγεννητική διάγνωση για την ορθή αντιμετώπισή τους.

Λέξεις ευρετηρίου: Εγκυμοσύνη, Εμβρυϊκό αλκοολικό σύνδρομο, Οινόπνευμα, Προγεννητική έκθεση στο οινόπνευμα, Συγγενείς καρδιακές ανωμαλίες, Φάσμα διαταραχών εμβρυϊκού αλκοολισμού

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