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Teratogenesis of alcohol

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Summary. - Many studies describing the teratogenic effects of alcohol have been published since Fetal Alcohol Syndrome (FAS) was first identified in 1973. Specifically, it has been a widely documented that alcohol is a teratogen that causes brain, craniofacial, and limb abnormalities in children suffering from FAS. These children have also been shown to be at high risk for mental deficiences. Teratogenicity has only been observed in offspring of mothers who consume large quantities of alcohol during pregnancy, while the effects of moderate drinking, though linked with adverse fetal alcohol effects in many reports, are not yet clear. Studies have also shown the teratogenic effects of paternal drinking on newborns. Estimates of prevalence at birth of FAS range from 1.9 to 0.33 per 1,000 births, depending on race, population, socioeconomic status, etc. New hypotheses on the biochemical basis of ethanol-induced birth defects have been recently proposed, contributing to the understanding of alcohol teratogenicity. The following review focuses on major recent findings in this field and describes the current situation regarding FAS.

Key words: Fetal Alcohol Syndrome, mechanism of alcohol damage in utero, occurrence of FAS, fetal alcohol effects.

Riassunto *(Effetti teratogeni dell'alcool).* - Da quando la Sindrome Feto-Alcolica (FAS) è stata identificata per la prima volta nel 1973, sono stati pubblicati molti studi che hanno descritto gli effetti teratogeni dell'alcool. E' stato ormai ampiamente documentato che l'alcool è un teratogeno che causa anomalie cerebrali, craniofacciali e degli arti in bambini affetti da FAS. La teratogenicita è stata dimostrata solo nei neonati di madri che consumavano grandi quantità di alcool in gravidanza, mentre gli effetti dell'assunzione moderata, anche se associata in molti studi con eventi sfavorevoli per il feto, non sono ancora del tutto chiariti e certi. Alcuni studi hanno dimostrato, inoltre, effetti teratogeni nel neonato associati al consumo paterno di alcolici. Le stime sulla prevalenza alla nascita della FAS variano tra 1,9 a 0,33 per 1.000 nati in relazione alla razza, popolazione, stato socioeconomico, ecc. Recentemente sono state proposte nuove ipotesi sulle basi biochimiche dell'induzione di difetti congeniti alcool correlati, contribuendo a chiarire sempre meglio i meccanismi teratogenici dell'alcool. La presente rassegna puntualizza i maggiori e più recenti risultati in questo campo, descrivendo lo stato attuale dell'arte relativo alla FAS.

Parole chiave: Sindrome feto-alcolica, meccanismi di danno alcolico in utero, frequenza di FAS.

Introduction

The teratogenicity of alcohol has been suspected for thousands of years. Since Jones *et al.* (1973) [1] described Fetal Alcohol Syndrome (FAS) as a distinctive result of in utero exposure to maternal alcohol consumption, the effects of maternal drinking during pregnancy have been intensively investigated [2-6].

Fetal Alcohol Syndrome

Fetal Alcohol Syndrome refers to a pattern of birth defects in children born to women who are heavy drinkers [7]. For a diagnosis of FAS to be made, the patient must show three main symptoms: 1) typical abnormal facies (flattened nasal bridge, hypoplastic to absent philtrum, epicanthic folds, narrow forehead, etc.) [8]; 2) pre- and postnatal growth retardation (≥ 2 SD for length and weight); and 3) central nervous system defects, including reduced head circumference and mental retardation.

There is also evidence of immunologic impairment [9, 10], and other major and/or minor congenital malformations are frequently present. The characteristic pattern of minor facial anomalies (facies) is readily reproduced in rodent and non-human primate animal models [5]. A semi-quantitative score system for epidemiologic studies of FAS was proposed by Vitez *et al.* in order to decrease biases in diagnosing the syndrome [11].

The first review of reported cases of FAS was provided by Clarren and Smith (1978) [4]. A 10-year follow-up study showed that, of the 11 patients diagnosed with FAS, two had died and eight had shown growth deficiency and dysmorphic features [12]; of these, four were of borderline intelligence, and the other four were severely mentally handicapped. One patient could not be found for follow-up. Educational evaluation of children showing fetal alcohol exposure suggests that maternal alcohol consumption results in certain behavioral patterns in children (hyperactivity, short attention span, and emotional lability) which is later diagnosed as learning disabilities [13, 14].

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The specific deleterious effects of ethanol on the fetus are dose-related and depend on the stage of gestation, as with other fetotoxic agents. However, the precise timing and dose-effect curves have yet to be established in animal models for most types of ethanol-induced damage [15].

Furthermore, alcohol is not an obligate teratogen: some women who are heavy drinkers produce healty children. Evidently, the teratogenic mechanism is complex, and many other factors may have a bearing on the outcome of these pregnancies.

Occurrence

Estimates of the prevalence of FAS vary considerably with the population studied. Among the general population, estimated incidence ranges from one in 300 to one in 2,000 live births (between 0.4 and 3.1 per 1,000) [16-20]. Incidence is considerably higher among alcoholic women: approximately 30-40% in infants of alcoholic mothers [5, 16, 18, 19]. Estimates of the incidence of FAS vary from 1/1,000 live births in France [21], to 1/600 births in Sweden [17], to 1/750 births in Seattle (USA) [5].

Though FAS occurs, among various populations worldwide, disproportionately high levels have been found among American Indians [22, 23], lower socioeconomic groups, and children of older mothers. This may be due to possible higher levels of alcoholism and alcohol abuse among these groups [24].

Recent estimates based on 20 studies carried out in Australia, North America, and Europe show an incidence of 1.9/1,000 live births and suggest that FAS is one of the leading causes of mental retardation in the western world [25]. The same authors, based solely on the prospective studies in which consecutive pregnancies were followed, proposed a more conservative estimate of FAS incidence in the western world: 0.33/1,000 [26]. The range in rates in these studies varies from 0 to 1.58 per 1,000, depending on ethnic background and socioeconomic status of the population studied.

Other congenital malformations related to alcohol consumption

Sex organ malformations and all genito-urinary malformations have been associated with increased alcohol consumption. However, total malformation rates were not significantly higher among offspring of moderate drinkers compared to non-drinkers [27].

In a recent prospective epidemiological study [28], congenital heart disease was sometimes associated with alcohol consumption, smoking, and maternal age. Father's alcohol consumption has been positively related to the offspring's risk of ventricular septal defect [29]. In a retrospective study, maternal alcohol consumption during the first trimester of pregnancy was more common among mothers of infants with cardiovascular malformation (45.9%) than those of the control group (39.6%), but neither association was significant when adjusted for maternal age [30].

The association of holoprosencephaly with alcohol exposure during pregnancy in humans has also been recently reported [31]; this malformation has also been induced by alcohol in animals. Musculoskeletal defects in infants born to women who drank one or more alcoholic drinks a day was reported [32].

Measuring levels of exposure

Most studies have used questionnaires to assess the relation between pregnancy outcome and alcohol consumption.

Biochemical tests, which are more objective than questionnaires, have also been used, mainly in British studies. However, specifity of these tests is very low. The most commonly used laboratory tests are those that measure blood alcohol levels for recent drinking, or mean corpuscular volume and serum gamma glutamyl transferase for long term excessive drinking. Results obtained using the latter two techniques are influenced by factors other than alcohol intake; thus, they are not effective in measuring alcohol consumption in epidemiologic studies [33-37]. Since no completely accurate biological markers of alcohol consumption exist, we must rely on the information provided by the women themselves. Methods for obtaining and interpreting data on maternal drinking vary among studies. Definition of "a drink" and drinking patterns have not been standardized, and the level of alcohol consumption chosen to define heavy or moderate drinkers also varies (cl/day of wine, ml/day or g/week of absolute alcohol, ounces on occasion, number of drinks/day or drinks/week).

Detailed interviews regarding type of alcoholic beverage consumed and daily consumption improve the quality of data. In most studies, alcohol consumption has been measured prospectively, however, which eliminates the risk of recall bias and allows for a more precise evaluation.

Toxic mechanisms

The mechanism of alcohol's toxic effect on the fetus is not well understood. While it is clear that alcohol can pass freely through the placental barrier [38], it is not known whether alcohol itself or one or more of its metabolites (e.g. acetaldehyde) is the primary cause of FAS [39].

As a result of the kinetics of amniotic fluid circulation, and because the enzymes necessary for drug biotransformation are absent in the embryo and present only in small amounts during later fetal development [40, 41], the amniotic fluid acts as a reservoir for unchanged alcohol and acetaldehyde [42]. Thus, the embryofetus is exposed to both compounds long after they have been cleared from the maternal organism.

Despite numerous studies on ethanol embryotoxicity in humans, rodents, and other vertebrates, no single underlying mechanism for the teratogenic action of ethanol has been proposed [43-47]. The etiology of FAS has alternatively been ascribed to the mutagenic potency of acetaldehyde, a primary metabolite of ethanol [48, 49]; to the ability of ethanol to alter the fluidity of cell membranes [50]; to the onset of alcoholic cirrhosis in the pregnant mother [51] and to maternal hormonal changes induced by alcoholism [5]. The mechanisms of action have included abnormal prostaglandin metabolism [52, 53], chromosomal alterations [54], placental dysfunction [55, 56], hypoxia [57], interference with protein synthesis [58, 59], altered growth signalling [60], interference with neurotransmitter production which can lead to neuroendocrine abnormalities [10, 61] and alteration of enzymes which regulate glycogen synthesis and degradation [62, 63].

An association between FAS and maternal zinc deficiency has been reported [64-71].

Excessive consumption of alcohol may lead to severe zinc deficiency, probably via hyperzincuria. Maternal zinc deficiency may be one of the primary underlying mechanisms in alcohol-induced fetal dysmorphogenesis. However, some women who have produced children with this syndrome showed normal plasma zinc levels [67, 72].

Recent hypotheses have proposed that FAS is primarily caused by ethanol inhibition of retinoic acid synthesis [73-75]. Other recent studies on the molecular basis of vertebrate embryonic development have revealed that the vitamin A metabolite retinoic acid plays a major role in the specification of spatial patterns during the morphogenesis of the nervous system and limb tissue. The controlled conversion of vitamin A (retinol) into retinoid acid by specific embryonic tissues has been proposed as a major regulatory step in the morphogenetic process. The effect of ethanol on retinoic acid synthesis may not explain all of the defects documented in cases of FAS, but it should be considered as a major factor in the pathogenetic mechanism.

Paternal drinking

Results of some studies on animals indicate that paternal alcohol ingestion prior to conception may have adverse effects on the newborn, but the data are far from conclusive [76, 77]. Despite wide recognition that it is unusual for a woman to drink more than her mate and documentation of mating between alcoholics [78, 79], the role of paternal drinking in alcohol-related birth defects began to receive attention only recently [27, 80-82], and few prospective studies on prenatal alcohol exposure have investigated paternal drinking [83]. As mentioned above, father's alcohol consumption has been found to be associated with ventricular septal defect [27]. An association between indications of maternal problem drinking and cognitive development was observed after controlling for paternal drinking [84].

Moderate drinking and fetal alcohol effects

Even moderate drinking can result in adverse effects on the fetus, ranging from spontaneous abortion to intrauterine growth retardation. Many studies on birthweight have also been carried out [85-95]: consumption of two or more drinks per day is related to a decrease in birthweight, while for lower levels of consumption, findings are inconsistent.

By contrast, studies of moderate drinking mothers have not shown alcohol to have a significant impact on fetal growth. These studies used several different methodologies, particularly in relation to alcohol quantitation, timing of interview, and the way in which potential confounding factors were treated [96-108]. However, other authors have reported that alcohol also affects the offspring of moderate or socially drinking mothers, with diminished fetal growth and increased neonatal risk factors such as respiratory distress [16, 86, 96, 109-112]. Moderate drinking has also been linked to increased rates of spontaneously aborted: women who regularly consumed 1-2 drinks daily in the first trimester were twice as likely as non-drinkers to have spontaneous abortion in the second trimester [113-116].

Many confounding variables that are associated to various drinking habits, such as maternal smoking, parity, ethnicity, gestosis, socioeconomic status, weight at conception, diet, drug use, and medical and obstetric history have been recently reported and discussed [86, 117-121]. An increase (ranging from (1.3 to 3.8) in the risk of complex febrile seizure associated with prenatal maternal intake [122] was recently reported, and a strong dose-response relation was present. This association could not be explained by maternal age, race, level of education, or cigarette smoking.

Prevention

Preventive measures should be strengthened, especially in light of clinical studies which have shown that reduction of alcohol intake during pregnancy, particularly if started in the first trimester, results in improved fetal growth [17,123-129].

The prevention of FAS and other alcohol-related birth defects can only be accomplished through multilevel, articulated multisystem intervention strategies, including community education, therapeutic interventions with the alcohol-abusing mothers, education of parents, and early identification and intervention with respect to the alcohol-affected child [26, 130].

Conclusions

The association between alcohol consumption during pregnancy and an increased incidence of developmental abnormalities in the offspring has been well established in humans and in many other species of mammals. Human FAS is comprised of a cluster of minor physical malformations that vary greatly with respect to frequency and severity of expression.

Many studies in human beings, including both prospective studies and follow-up of children, have been conducted, as have animal and biochemical laboratory studies, helping to better clarify the teratogenic role of alcohol. However, it still must be determined whether there exists a level of maternal alcohol consumption below which embryotoxic and teratogenic effects attributable to alcohol are virtually nonexistent.

Defining and determining quantity and type of alcohol consumed is problematic in that methods often vary among studies, not allowing for definitive conclusions.

Further research may contribute not only to our understanding of alcohol teratogenicity, but also to understanding normal embryonic and fetal developmental, as well as teratogenicity in general. Alcohol-related birth defects represent one of the major public health problems in most countries of the world, and renewed focus is needed to increase our understanding of alcohol teratogenicity and to support the development of effective early identification and prevention strategies.

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