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Original article

Alcohol and pregnancy

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Abstract

Alcohol exerts teratogenic effects in all the gestation times, with peculiar features in relationship to the trimester of pregnancy in which alcohol is assumed. Alcohol itself and its metabolites modify DNA synthesis, cellular division, cellular migration and the fetal development.

The characteristic facies of feto-alcoholic syndrome (FAS)-affected baby depends on the alcohol impact on skull facial development during the first trimester of pregnancy. In association there are cerebral damages with a strong defect of brain development up to the life incompatibility. Serious consequences on fetal health also depends on dangerous effects of alcohol exposure in the organogenesis of the heart, the bone, the kidney, sensorial organs, et al. It has been demonstrated that maternal binge drinking is a high factor risk of mental retardation and of delinquent behaviour. Unfortunately, a lower alcohol intake also exerts deleterious effects on fetal health. In several countries of the world there is a high alcohol use, and this habit is increased in the women. Therefore, correct information has to be given to avoid alcohol use by women in the preconceptional time and during the pregnancy. Preliminary results of a study performed by the authors show that over 80% of pregnant and puerperal women are not unaware that more than 2 glasses of alcohol/week ingested during pregnancy can create neurological abnormalities in the fetus. However, after the information provided on alcoholic fetopathy, all women are conscious of the damage caused by the use of alcohol to the fetus during pregnancy. This study confirms the need to provide detailed information on the negative effects of alcohol on fetal health.

Keywords

Alcohol, ethanol, feto-alcoholic syndrome (FAS), oxidative stress, hypothalamic-pituitary-axis, prevention of FAS.

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Introduction

Feto-alcoholic syndrome (FAS) was firstly described by Jones & Smith in newborns of alcoholic mothers [1]. Growth retardation, phenotipic features and distortions of central nervous system (CNS) are the remarkable deleterious effects provoked by alcohol assumption during the organogenesis [1]. Forty years of studies recognize prenatal alcohol exposition in the pathogenesis of serious damages in several nuclei of CNS causing deleterious consequences in the cognitive, psychological functions and severe disadvantages in the behaviour and social activities.

"Fetal Alcohol Spectrum Disorders"(FASD) is the recent definition of disorders consequent to alcohol exposition during the pregnancy [2]. This classification includes fetal alcohol effects (FAE), partial FAS (PFAS), alcohol related birth defects (ARBD), and alcohol related neurodevelopmental disorders (ARND). Dramatic FAS incidence is reported in South Africa [3] with an estimated incidence between 70 and 80 per 1,000 babies born in the Western Cape, the highest known incidence in the world. A FAS incidence of 0.5-3 per 1,000 newborns is reported in Canada, whereas in the same country FASD is 10 per 1,000 newborns [4]. In Italy, a first pilot study has been performed in 2007: FAS was found in 7.4 babies per 1,000 live newborns. These percentages increase to 40.5‰ and to 20.3‰ if we consider all alcohol related diseases, included the minor pathologies [5].

Alcohol exerts teratogenic effects in all the gestation times, with peculiar feature in relationship to the trimester of pregnancy in which alcohol is assumed. Alcohol itself and its metabolites modify DNA synthesis, cellular division, cellular migration and the fetal development. In a recent review by Brocardo et al. [6] the teratogenic effect of alcohol exposure is explained through the mechanism of oxidative stress. The studies by Brocardo et al. [6] in rodent model show that ethanol exposure can lead to generation of reactive oxygen species (ROS) inside the cells. The exposure to ethanol can also decrease the intracellular antioxidant capacity by reducing the activities of the endogenous antioxidant enzymes [6]. The activity of these enzymes is lower in the brain than in other organs [7] and, mainly, in the fetal life characterized by lower levels of antioxidants enzymes in comparison to adult life [8]. In their review, Brocardo et al. [6] conclude that "it is also possible that the oxidative insults experienced early during development have long-lasting effects, rendering the antioxidant defense system of the offspring ineffective later on in life…". It has also been demonstrated that alcohol induces imbalances in maternal endocrine function with possible disruption in the maternal-fetal hormonal interactions, interfering in the woman's ability to maintain a good outcome of the pregnancy [9]. In particular, Zhang et al. [9] studied the interference of alcohol on the hypothalamus-pituitary-adrenal-axis (HPA) and focused on the hypothesis that a permanent HPA increased activity could justify a bad adult health of subjects alcohol-exposed during their fetal life, though in absence of serious ARBD. In relationship to these studies, alcohol exposure during the fetal life may also impair the immune system and the function of different neuronal function linked with the HPA function [9, 10].

Features of subjects affected by FAS

The characteristic facies of FAS-affected baby depends on the alcohol impact on skull facial development during the first trimester of pregnancy [4]. In association there are cerebral damages with a strong defect of brain development up to the life incompatibility [4]. Serious consequences on fetal health also depends on dangerous effects of alcohol exposure in the organogenesis of the heart, the bone, the kidney, and sensorial organs. The complete list of ARBD is reported by several authors [11-13].

Main neuronal defects in relationship to gestational age of alcohol exposure

As before reported, the effects of alcohol exposure can be different throughout the trimester of gestation.

First trimester

During the first trimester of human gestation, alcohol exposure can alter the normal development of the neural tube and crest, leading to microcephaly as demonstrated by the studies of Miller [14] in the rats. Miller [14] reported that the alcohol fetal exposure induces a delay in the generation of cortical neurons, with a reduction in their number and their distribution. Ocular malformations and the characteristic facial dysmorphology are associated with the brain malformations [15].

Second trimester

During the second trimester, alcohol exposure still affects the proliferation of glia and neuronal precursors [16], with a strong modification in the migration of cortical neurons [16]. These abnormalities are likely the cause of the agenesis or the malformation of corpus callosum, of ventriculomegaly, of a small cerebellum. All these abnormalities have been evidenced in autopsies of newborns exposed to alcohol during the second trimester of their fetal life [17]. The alcohol exposure in the second trimester of pregnancy may reduce both the intrauterine and the postnatal growth [18]. In the study of Aros et al. [19] the cause of this feature could depend on low leptin levels shown in children exposed to alcohol during their fetal life [19].

Third trimester

During the third trimester of human gestation, the neurons are more susceptible to the apoptotic effects of alcohol [20]. Through this mechanism there is a injury on neuronal plasticity, the ability of brain to be changed in relationship to previous experiences. During the development, the neuronal plasticity plays an essential role in the processes of learning and memory [21]. A recent review of Morris et al. [22] emphasizes the role of microglia in the process of neuronal plasticity, suggesting that the lack of dynamic activity of microglia plays an important role in the pathogenesis of inflammatory neuronal diseases such as the Alzheimer and Parkinson diseases. The proposed oxidative stress alcohol induced [6] can explain the mechanism through which alcohol can exert deleterious teratogenic effects on the brain also during the third trimester of pregnancy.

Alcohol amount related to FAS

The question about the threshold of alcohol allowed during pregnancy is unknown. It is recognized that the FASD risk dramatically increases in the presence of frequent drinkings, equal to six or more alcohol glasses by occasion. However, a lower amount of alcohol glasses, for example 1-3 by occasion, can also induce cognitive and learning impairments in children [23, 24]. The excessive drinking per occasion, mainly if uncontrolled, is called binge drinking. In this case, the high alcohol peak in the blood can be more dangerous in the fetus development than the same amount divided in several days [25]. Therefore, the pattern of fetal alcohol exposure also seems to play a key role in the negative outcome of cognitive and behavioral health. Bailey et al. [26] demonstrated that the children exposed to binge drinking during their fetal life have a higher risk of mental retardation and of delinquent behaviour [26].

A recent study by Sayal et al. [27] evaluates if a low amount of alcohol drinking (not more than 1 unit/week) can impair the cognitive development of children evaluated at 11 years, mainly in the school efficiency. Low amount of drinking in pregnancy does not induce adverse effects for mental health and scholastic outcomes [27]. However, a low drinking intake during pregnancy should not be promoted. Sufficient studies on individual alcohol metabolism are not available, so that a low drinking can be deleterious in a woman with a low metabolization. Environmental factors can induce the pregnant women to increase the alcohol intake, with the incorrect persuasion of the harmlessness of the minimum amount of alcohol. Increased alcohol intake can also favour the use of other unhealthy habits, such as smoking, cannabis abuse, illicit drug use [27]. In these cases, the deleterious effects on the fetal health depends on more than one factor.

Therefore, the goal of public health is to diffuse to the public the serious health consequences to infants of alcohol consumption during pregnancy, to locate the average consumption of alcohol during pregnancy, to identify the populations at high risk and to inform that the consumption of alcohol during pregnancy has to be abolished.

Consumption of alcohol in the Italian population

The investigations on the consumption of alcohol in our Italian population are presented in the report of the National Plan Alcohol and Health

(Year 2009) [28]. The report is a centralized collection and analysis of information flows and data for monitoring the impact of the use and abuse of alcohol on health in Italy. The report was produced by the Working Group CSDA (Centro Servizi Documentazione Alcol) of the National Observatory of Alcohol CNESPS in collaboration with: WHO Collaborating Centre for Research and Health Promotion on Alcohol and Alcohol-related Health Problems; Società Italiana Alcologia (SIA); Alcohol Regional Center of Tuscany, Region of Tuscany; Associazione Italiana dei Club degli Alcolisti in Trattamento (AICAT); Eurocare Italy. The overall data of the study show an increase in alcohol consumption, especially among young people and among women. This habit is very worrying, not only in relation to the harm that alcohol induces both on individual health and on the state of intoxication that reduces alertness and, therefore, the risk of accidents affecting the life and/or vitality of its own and others, but also in relation to the reduction of the state of vigilance regarding the use of contraception and the risk of unwanted pregnancy and, unfortunately, of the risk of the consequences of alcohol on fetal health. The Italian situation in the young population is alarming in relation to the use and abuse of alcohol in pregnancy. It will be difficult to persuade a young pregnant woman accustomed to drink alcohol to stop this habit both before conception and during pregnancy. Therefore, it is necessary to conduct an anti-alcohol campaign both in the general population and in women during pregnancy.

Knowledge of pregnant and puerperal women for fetal damages by alcohol use during pregnancy

We have recently carried out a study to identify the consumption of alcohol in the female population, including pregnant women and in the postnatal period, indicating the amount of alcohol consumed during the week, any excessive use of alcohol and uncontrolled conditions related to the use of alcohol, such as the subject's age, family status, emotional, social, professional, racial, psychological, pathological, others. The purpose of the study was also to identify the real knowledge of FAS with specific questions. The subjects participating in the study (pregnant women and puerperal women related to the Department of Obstetrics and Gynecology of the University of Cagliari) were invited to respond to several questions before and after the information on the consequences on fetal health deriving by maternal alcohol use during all trimesters of pregnancy. This was done with a questionnaire (**Attach. 1**) in which the subjects answered in anonymity after being educated on the purpose of research. All subjects had to give their informed consent to complete the questionnaire. Later, after the completion of the baseline questionnaire, detailed information on the adverse impact of alcohol on fetal health was given. Thus, the questionnaire relating to the notions on the alcohol fetopathy has been confirmed in order to identify how the information on deterrence interferes in alcohol use in pregnancy, so that the last questions of the questionnaire were placed on the behavior that the subject would take in terms of pregnancy of a joint or of the same subject interviewed (**Attach. 1**).

Preliminary results of the study

So far, the study was carried out in 60 pregnant women related to Obstetrics and Gynecology of Cagliari and in 30 women mothers who gave birth at the same clinic. These preliminary data show that over 80% of respondents are not unaware that more than 2 glasses of alcohol/week ingested during pregnancy can create neurological abnormalities in the fetus. However, after the information provided on alcoholic fetopathy, all women became conscious of the damage caused by the use of alcohol to the fetus during pregnancy.

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Declaration of interest

The Authors declare that there is no conflict of interest.

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Attachment 1. Questionnaire.

Anonymous Questionnaire after having had oral informed consent from the subject to be interviewed.
Interview subjects: pregnant women during the first, second, third trimester of pregnancy and women during the postpartum period (by the third day after birth).

Interview No. .....

For the filling: Please tick the relevant voice

- Age of the interviewee:
  16-18 years 19-25 years 26-35 years 36-45 years
- Pregnant or postpartum woman:
  Pregnant woman, first trimester | Pregnant woman, second trimester | Pregnant woman, third trimester | Postpartum woman by the third day after birth
- Ethnicity:
  Caucasian Hispanic African African-American Eastern
- Marital Status:
  Free Conjugated Separated
- Previous children:
  Yes No
  If yes, how many? Indicate the number: .....
- Occupation:
  Yes No
  - If yes, indicate your occupation:
    Housewife Worker Employee
    Officer Teacher Dealer
    Other, specify: .....
- The occupational area corresponds to your objectives?
  Yes No
- Student:
  Yes No
- Title of study:
  None Elementary school graduation Middle school graduation
  High school graduation University degree Other, specify: .....
- Do you suffer from any psychiatric illness?
  Yes No
  - If yes, specify:
    Depression Anxiety Other, specify: .....
- Do you suffer from chronic non-psychiatric illness?
  Yes No
  - If yes, specify:
    Heart disease Kidney disease Lung disease Lliver disease
    Autoimmune disease Blood disorders Other, specify: .....
- In your family, are there psychiatric disorders?
  Yes No
  - If yes, specify:
    Depression Anxiety Other, specify: .....

Attachment 1 (continued). Questionnaire.

- Are chronic non-psychiatric illness present in your family?
  Yes No
  - If yes, specify:
    Heart disease Kidney disease Lung disease Lliver disease
    Autoimmune disease Blood disorders Other, specify: .....
- Do you smoke?
  Yes No
  - If yes, specify:
    < 5 cigarettes a day 5-20 cigarettes a day > 20 cigarettes a day
- Do you usually drink alcohol with meals?
  Yes No
  - If yes, specify:
    Wine Beer
  - How many glasses per meal?
    Half One Two More than two
- Do you drink liquor?
  Yes No
  - If yes, specify:
    Habitually Occasionally
- Have you ever drunk excessively?
  Yes No
  - If yes, on what occasion?
    Party Disco I felt sad I felt anxious
    I could not solve my problems Other, specify: .....
- Would you care to get information on alcohol taken by the mother during pregnancy on child health?
  Yes No
  - If yes, the following questions are proposed by adequate information on damages to fetal health deriving from maternal alcohol use during pregnancy
- Do you think that drinking alcohol is injurious to health?
  Yes No
  - If yes, please indicate for which diseases:
    Cardiovascular Tumor Brain Liver Kidney
    Blood Other, specify: .....
- What do you think of drinking alcohol by a pregnant woman?
  She should not drink She should drink moderately There is no problem if she drinks a lot, but only occasionally There is no problem if she drinks a lot, even habitually
- Do you know the damage induced in the fetus when the mother drinks alcohol during pregnancy?
  Yes No
  - If yes, which do you think are the damages caused to the fetus from maternal consumption of alcohol during pregnancy?
    Neurological damage Behavioral damage Cardiac damage
    Kidney damage Damage to the sense organs Damage to the characteristics of the face
    Other, specify .....
- Do you advise to stop drinking for a woman who want to become pregnant?
  Yes No

Thanks for your cooperation