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REVIEW ARTICLE

Biomarkers in fetal alcohol syndrome

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Abstract Ethanol consumption during pregnancy is a widespread problem and is increasing globally among young women. Development of biomarkers of fetal alcohol syndrome (FAS), which can identify children at risk, may lead to interventions earlier in life. In addition, animal models of fetal alcohol spectrum disorders can help in novel biomarker discovery. Biomarkers of fetal alcohol spectrum disorders include classical biomarkers of alcohol-induced pathology (mean corpuscular volume, γ-glutamyl transferase, aspartate aminotransferase, and alanine aminotransferase), acetaldehyde-derived conjugates, and derivatives of nonoxidative ethanol metabolism (fatty acid ethyl esters, ethyl glucuronide, ethyl sulfate, and phosphatidyl ethanol). Because ethanol and acetaldehyde levels can be measured in blood, urine, and sweat a few hours after ethanol intake, these can be used to detect recent ethanol exposure. Magnetic resonance spectroscopic (MRS) biomarkers include N-acetyl aspartate, an indicator of neuronal density; choline, a precursor of the neurotransmitter; acetyl choline, implicated in learning and memory and in the synthesis of glycerophosphocholine (involved in membrane synthesis); and glutamate that is reduced in FAS. Glutamate is a precursor for the synthesis of γ-amino butyric acid, and creatine is required for high-energy phosphate synthesis. Furthermore, reduced brain-derived neurotropic factor, somatostatin, complexin, taurine, glutathione, myoinositol, leptin, and increased insulin-like growth factor and N-methyl D-aspartic acid receptor toxicity are observed in FAS. Impaired methionine–homocysteine cycle may also have deleterious effects on protein, DNA, and histone methylation in FAS. In addition to meconium fatty acid ethyl esters, magnetic resonance imaging, positron emission tomography, and single-photon-emission computerized tomography facilitate an earlier diagnosis of less alcohol-related disabilities that cannot be confirmed in the absence of a maternal drinking history. Brain volume, cortical volume, and cortical surface area are also reduced following prenatal exposure to ethanol. Hence, discovery of novel biomarkers is needed to define behavioral, physical, and genetic factors for better clinical management of FAS.

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Introduction

Alcohol and several other drugs are frequently abused alone or in combination across the globe.[1] Ethanol is the most widely used drug of abuse and a teratogen whose consumption among women of childbearing age is increasing gradually. Fetal alcohol spectrum disorder (FASD) is a developmental disorder that affects up to 0.2% of births. Because both fetal alcohol syndrome (FAS) and fetal alcohol effect represent preventable causes of mental retardation and birth defects, detection of alcohol abuse during pregnancy is essential to avoid deleterious consequences on fetal brain development. A considerable amount of work is required to extend the knowledge on fetal alcohol effects among women of childbearing age. Moreover, awareness and training among health care professionals may play significant roles in the early diagnosis of these devastating conditions.

Alcohol consumption during the gestational period causes fetal alcohol exposure and is associated with the onset of FASD, including FAS. FASD and FAS can lead to physical, cognitive, and behavioral disabilities, whose early diagnosis is important to accomplish primary prevention with total abstinence from alcohol during pregnancy and secondary prevention in newborns and children with regular follow-ups to reduce the risk of secondary consequences. In recent years, efforts have been made to understand molecular mechanisms of FAS and identify biological and diagnostic tools, such as biomarkers in neonatal meconium and magnetic resonance imaging (MRI). However, further studies are needed to extend the knowledge on fetal effects of ethanol, and multidisciplinary approaches are necessary to raise awareness among women of childbearing age about the dangers of consuming even a small amount of alcohol during pregnancy.[2] Deleterious consequences of FAS are well established; as a leading cause of intellectual impairments, it has social and public health impact as FAS is associated with several neurobehavioral deficits.[3] FAS is the most serious consequence of prenatal ethanol exposure, and individuals who do not meet diagnostic criteria for FAS are also influenced by gestational ethanol exposure. The term FASD is used to cover a spectrum of effects that includes FAS as well as alcohol-related neurodevelopmental disorder and alcohol-related birth defects. The term alcohol-related neurodevelopmental disorder refers to a condition in which individuals, after heavy prenatal alcohol exposure, exhibit neurobehavioral deficits without meeting the physical criteria of FAS.[4,5] Clinical identification of this group is difficult because it does not exhibit typical physical features of FAS, and physiological biomarkers of gestational alcohol exposure have limitations. Hence, determination of a profile, based on the neurobehavioral effects of prenatal alcohol exposure, would allow accurate identification of FAS and affected individuals. The development of such a profile is aimed at identifying and characterizing those who are affected by prenatal alcohol exposure, and not only those who have been exposed to alcohol prenatally.[6,7] Acquiring information about drinking during pregnancy is one of the most challenging areas of the study on FASD, because these children are difficult to differentially diagnose, treat, and confirm whether or not their mothers consumed alcohol during pregnancy. Currently available screening questionnaires to diagnose and confirm FASD are unreliable, and biomarkers are insensitive for pregnant women. Hence, there is a dire need to discover novel biomarkers with better sensitivity and specificity for detecting even moderate drinking during pregnancy. Gestational alcohol consumption is associated with the onset of FASD (including FAS), which can lead to physical, cognitive, and neurobehavioral impairments. Hence, an early diagnosis of FAS is extremely important for primary prevention with total abstinence from alcohol during pregnancy and for secondary prevention to reduce the risk in newborns and children during later life.

The exact molecular mechanism underlying fetal developmental defects caused by maternal ethanol consumption remains enigmatic. Unfortunately, the diagnosis of FAS and fetal alcohol effect is made after birth, when alcohol damage has become irreversible and permanent. Laboratory diagnosis can help prevent this damage and make a valuable contribution to the assessment of prenatal alcohol abuse. Especially, clinical utility of blood/breath alcohol, γ-glutamyl transferase (GGT), mean corpuscular volume (MCV), and carbohydrate-deficient transferrin (CDT) in pregnancy is remarkable. Although none of these biomarkers has adequate sensitivity and specificity, their diagnostic accuracy increases when estimated as a panel, particularly while detecting alcohol abuse in pregnancy where the presence of several positive biomarkers can be correlated in the presence of alcohol-related fetal defects.[8]

This article briefly reviews the recent literature on biomarkers as maternal risk factors for FASD and emphasizes that maternal risk is multidimensional, including factors related to quantity, frequency, timing of alcohol abuse, maternal age, number of pregnancies, mother's frequency of child birth, body size, body mass index, nutritional status, socioeconomic status, metabolism, religion, spirituality, depression, drug abuse, and social relationships. Furthermore, a brief description of various biomarkers is provided as a basic guideline for the clinical management of FAS during the early stages. Although the first trimester is considered to be the most vulnerable period, it is now realized that intrauterine exposure to ethanol may cause fetal damage throughout the entire gestational period. Based on the data obtained from the National Epidemiologic Survey on Alcohol and Related Conditions, Falk et al[9,10] reported that 21.7% of the sampled population abused both alcohol and tobacco and 5.6% abused alcohol along with other drugs. Among women aged 18—24 years, the rates were 25.5% and 12.5%, respectively.

Individually, alcohol, tobacco, and illicit drugs (cocaine or amphetamine) are harmful to the developing fetus. Hence, determining the harm resulting from multiple drug abuse during pregnancy is a challenging task. Unpredictable interactive effects of the drugs abused simultaneously have long-term consequences on the child's health and development. Intrauterine ethanol-exposed adolescents are highly prone to developing drug dependence, and ethanol neurotoxicity is augmented by nicotine in these individuals.