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FETAL ALCOHOL SYNDROME

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This review summarizes the literature on the fetal disorders that arise under the influence of prenatal alcoholism, on the criteria for diagnosis, pathogenesis, behavioral disorders, treatment and prevention of fetal alcohol syndrome (FAS). The main effect of FAS is permanent central nervous system damage, especially to the brain. The development of maturation of brain cells and structures can be impaired by prenatal alcohol exposure; this can cause primary cognitive and functional disabilities (including poor memory, attention deficits, impulsive behavior, and poor cause-effect reasoning) as well as secondary disabilities (for example, predispositions to mental health problems and drug addiction). Alcohol exposure presents a risk of fetal brain damage at any point during a pregnancy, since brain development is ongoing throughout pregnancy.

Key words: *fetal alcohol syndrome, central nervous system.*

Alcohol consumption during pregnancy is a widespread problem which is increasing in the generation of young women. Alcohol consumption, even in moderate amounts, during a pregnancy is associated with an increased risk of spontaneous abortions, especially in the first trimester of pregnancy. It is associated with increased risk of fetal death. The consequences of ethanol action for the survived fetus is associated with the development of fetal alcohol spectrum disorders (FASD) and its marginal manifestation - fetal alcohol syndrome (FAS). FASD and FAS included the physical, cognitive and behavioral disabilities, whose early diagnosis is very important to perform primary prevention with total abstinence from alcohol during pregnancy and secondary prevention in newborns and children for a proper follow up to reduce risk of secondary consequences. In recent years significant efforts have been made to understand the underlying mechanisms of this disease and to identify objective biological and instrumental diagnostic tools, such as alcohol exposure biomarkers in neonatal meconium and advanced magnetic resonance imaging [57, 8, 6].

The severity of the consequences for the posterity ranges from FAS, which is evident in 4–6% of infants of heavy drinking mothers, to minor effects, such as low birth weight (Intra Uterine Growth Retardation (IUGR)), a slight reduction in IQ of the infants and increased rate of congenital anomalies. IUGR as well as postnatal long-term height and weight deficits is well demonstrated among children born from ethanol using women.

The most common, serious and specific syndrome of alcohol effects in pregnancy – FAS has been described only for regular/daily high dose alcohol users. Recognition of the syndrome was made by Dr. David Smith and Dr. Kenneth Jones in 1973 based on the evaluation of eight children born by mothers who were defined as chronic alcoholics. The principal features of FAS were determined as prenatal and postnatal growth deficiency, short stature, developmental delay, microcephaly, fine-motor dysfunction and facial dysmorphism. In addition, there may be cleft palate, joint and cardiac anomalies. The above described facial dysmorphism tends to improve with the advancement in age of the affected individuals [5, 6, 30].

Criteria for Diagnostics of FAS

The criteria of diagnostics are based on the growth deficiency, facial phenotype, central nervous system (CNS) damage and evidence of intrauterine alcohol exposure. The more commonly used scores are the 1996 Institute of Medicine criteria and the Washington criteria [1]. There are revised criteria applicable for pediatric practice by scoring the clinical findings: height <10%; weight <0%; occipito-frontal circumference <10%; inner canthal distance <10%; palpebral fissure length <10%; attention-deficiency/hyperactivity disorder; fine motor dysfunction; mid-facial hypoplasia; railroad track ears; strabismus; ptosis; nonracial epicanthal folds; flat nasal bridge; anteverted nares; long philtrum; smooth philtrum; thin vermilion border of upper lip; prognathism; cardiac murmur; cardiac malformations; hypoplastic nails; decreased pronation/supination of elbow; clinodactyly of fifth fingers; camptodactyly; hockey stick palmar creases and hirsutism. Even several of these clinical findings are sufficient for diagnosis if there is a positive history of alcohol exposure [25, 4, 7, 31, 58, 30].

Mechanisms of Alcohol Teratogenicity

The mechanisms whereby alcohol injures the developing fetus have not been fully elucidated. Indeed, it is not yet clear whether the culprit is alcohol itself or one of its metabolites, particularly acetaldehyde, a highly toxic one. Alcohol and its metabolites cross the placenta and, being lipophilic, enter the developing fetal CNS readily [9,43,42]. Thus, the CNS bears the brunt in injury. The actual outcome of the insult may depend on such factors as the pattern of exposure (i.e., binge drinking as opposed to regular, frequent intake), and the timing (i.e., before conception and at each stage of pregnancy). The use of other agents including nicotine, marijuana, and over the-counter drugs, plus determinants of maternal health such as nutrition, also may influence the final result [19].

Different mechanisms have been offered to explain the teratogenic effects of alcohol on the developing fetus. They include the following:

1) Increased oxidative stress; 2) Disturbed glucose, protein, lipid and DNA metabolism; 3) Impaired neurogenesis and increased cellular apoptosis, especially of neural crest cells; 4) Endocrine effect; 5) Effects on gene expression [21, 46, 59, 26, 32].

Oxidative Stress

Alterations in the redox status in the CNS was supported by studies demonstrating that ethanol - mediated changes in the production and/or activity of endogenous antioxidants in various organs, including the cerebellum and placenta [11, 51, 1]. Ethanol can induces oxidative stress directly by formation of free radicals which react with different cellular compounds, or indirectly by reducing intracellular antioxidant capacity, such as the decreased glutathione peroxidase levels. A significant increase in oxidative stress was demonstrated in placental villous tissue following two hours of ethanol

perfusion, primarily involving the nitric oxide pathway in the trophoblast and DNA damage in the villous stromal cells. Alcohol-induced oxidative stress was also found to increase lipid peroxidation and damage of protein and DNA molecules. However, there is lack of data from human clinical studies. No significant different in urine 2,3-dinor-6-keto-prostaglandin F1α, or 11-dehydro-thromboxane B2 8-isoprostane F2α an oxidative stress markers was found between pregnant women who drank heavily and those who abstained [59, 29, 8, 23].

Disturbed Prostaglandin Synthesis

Alcohol is known to affect prostaglandins, hence, influencing fetal development and parturition [3]. When mice were treated with aspirin (a prostaglandin synthesis inhibitor) prior to alcohol exposure, the alcohol-induced malformations were reduced by 50% in comparison to mice treated with aspirin after alcohol exposure. Urinary 6-keto-PGF1alpha and 2,3-dinor-6 keto PG F1 alpha were higher in heavily drinking mothers and infants who suffered from FAS compare to abstinent mothers and infants. High levels of thromboxane B2 in urine were also found in the infants of the drinking mothers but without correlation to FAS [22].

Effects on Neurons

Several studies in rats and mice have shown that in utero exposure to alcohol caused structural defects in the hippocampus, cerebellum and neural crest cells with increased cell death [55, 20, 41, 39].

Endocrine Effect

An effect of prenatal alcohol exposure on the limbic, hypothalamic pituitary–adrenal axis was shown, when higher cortisol and heart rate levels were found in 5–7 month-old infants during emotional stress. The effect differed among the genders, with boys having higher cortisol levels and girls higher heart rate [14, 28].

Gene Expression

Neural progenitor cells that were isolated from normal second trimester fetal human brains and cultured for up to 72 hours in mitogenic media containing ethanol generated in these conditions neurosphere which diameter correlated positively with the increasing ethanol concentrations. Real-time PCR analysis showed that ethanol significantly altered the expression of genes involved in cell adhesion [2, 40]. There was an increase in the expression of alpha and beta Laminins 1, beta Integrins 3 and 5. Secreted phosphoprotein 1 and Sarcoglycan epsilon. Those changes may underlie aspects of neurodevelopmental abnormalities in FAS. In light of those different mechanisms of action, it is reasonable to presume that alcohol- induced teratogenicity is probably the result of injuries caused by several mechanisms [50].

Anomalies of the Organs

Alcohol is known to affect not only the CNS, but also organs that are developmentally related to CNS derivatives, including those developmentally dependent on neural crest cells like the craniofacial complex and the heart [33, 45].

Maternal alcohol consumption early in pregnancy was found to be related to increased risk of neural tube defects. Chen et al. [35] found in the literature nine cases of neural tube defects related to prenatal exposure to ethanol, but speculated that this effect may result from the folate deficiency induced by alcohol abuse. A hazard ratio of 1.6 and 2.1 for neural tube defect was found in women who consumed ethanol during the periconceptual period, less than once and more than once a week respectively [35]. Opposed to these findings, periconceptual maternal alcohol use did not reveal increased risk for neural tube defects using a population based case control study between 1989-1991 in California [11].

Disorders of neurogenesis of cortical and subcortical structures in rat brain limbic system were studied in the offspring of rats that received ethanol during pregnancy. The methods used included the staining of histological sections with cresyl violet, in vitro culture, and electron paramagnetic resonance. Prenatal alcohol intoxication was shown to induce the disturbances in proliferative activity of granular layer cells in the hippocampal dentate gyrus, neuron- and glioblast migration, enhancement of free NO and lipoperoxide production and cell death. This resulted in the changes of the number of neurons in cortical and subcortical structures of rat brain limbic system and in fetal alcohol syndrome formation [7,47].

Evidence of adverse effects on the fetal CNS has come from several studies with, as yet, very little dissenting data. By far the most influential work is the longitudinal study in Seattle, which has examined a birth cohort of children repeatedly over seven years. Analyses on all but the seventh year examination have been reported at 30' 45, 46. Using a battery of developmental and psychological tests, the researchers have demonstrated at rend linking poor performance on some measures to increasing levels of alcohol exposure prenatally. Significant differences were seen only at the highest exposure level (an average of more than two drinks per day). Confirmation of the findings at the preschool evaluation will be difficult to obtain. Many intervening factors could have had an impact on the children's mental and motor development [2].

Diffusion tensor imaging (DTI) of brain development in FASD has revealed structural abnormalities, but studies have been limited by the use of cross-sectional designs. Longitudinal scans can provide key insights into trajectories of neurodevelopment within individuals with this common developmental disorder. This study evaluate serial DTI and T1-weighted volumetric magnetic resonance imaging (MRI) in a human sample of 17 participants with FASD and 27 controls aged 5-15 years who underwent 2-3 scans each, 2-4 years apart (92 scans total). Increases of fractional anisotropy and decreases of mean diffusivity were observed between scans for both groups, in keeping with changes expected of typical development, but mixed-models analysis revealed significant age-by-group interactions for three major white matter tracts: superior longitudinal fasciculus and superior and inferior fronto-occipital fasciculus. These findings indicate altered developmental progression in these frontal-association tracts, with the FASD group notably showing greater reduction of mean diffusivity between scans. Mean diffusivity is shown to correlate with reading and receptive vocabulary in the FASD group, with steeper decreases of mean diffusivity in the superior fronto-occipital fasciculus and superior longitudinal fasciculus between scans correlating with greater improvement in language scores. Volumetric analysis revealed reduced total brain, white, cortical gray, and deep gray matter volumes and fewer significant age-related volume increases in the FASD group, although age-by-group interactions were not significant. Longitudinal DTI indicates delayed white matter development during childhood and adolescence in FASD, which may underlie persistent or worsening behavioral and cognitive deficits during this critical period [13, 24].

Prenatal alcohol exposure is responsible for a broad range of brain structural malformations, which can

be studied using MRI. Advanced MRI methods have emerged to characterize brain abnormalities, but the teratogenic effects of alcohol on cortical morphology have received little attention to date. Twenty-four 9-year-old children with fetal alcohol spectrum disorders (9 with fetal alcohol syndrome, 15 heavy exposed non syndromal children) and 16 age-matched controls were studied to assess the effect of alcohol consumption during pregnancy on cortical morphology. An automated method was applied to 3D T1-weighted images to assess cortical gyrification using global and regional sulcal indices and two region-based morphological measurements, mean sulcal depth and fold opening. Increasing levels of alcohol exposure were related to reduced cortical folding complexity, even among children with normal brain size, indicating a reduction of buried cortical surface [16, 10].

A number of reports addressed a potential correlation between alcohol consumption and oral clefts [25].

It is accepted that about one third of children with alcohol embryopathy will also have congenital cardiac problems. A higher risk of heart defect and coarctation and hypoplastic aortic arch were associated with maternal alcohol consumption [27, 34,52,56].

Binge drinking during the second month of pregnancy was associated with bilateral renal agenesis or hypoplasia among infants [6].

Behavioral and Developmental Changes

Alcohol is considered one of the risk factors for Attention Deficit Hyperactivity Disorder (ADHD), independently of prenatal nicotine exposure or other familial risk factors. A positive correlation between alcohol and ADHD was reported in 26 prenatally alcohol exposed children. Discontinuation of the alcohol consumption by the 12th week resulted in normally developed children, demonstrating the fact that the cerebral cortex is more vulnerable to these effects of ethanol from the second trimester of pregnancy, post the organogenetic period. Moreover, consumption of less than one alcoholic drink per day in the last three months of pregnancy, in spite of heavier drinking earlier, did not result in ADHD, learning disabilities or cognitive impairment at the age of 14 years. Among 10 alcohol dependent adults who had maternal and paternal history of alcoholism, 8 had ADHD; seven of them were at risk of suicide, and all had a history of violence during intoxication [1]. When compared to a group of 185 matched control alcohol addicts without a family history of alcoholism, none of the controls had ADHD, one had a risk of suicide and two were violent when drunk [12].

It has been difficult to define and characterize developmental risks associated with binge drinking or moderate drinking in pregnancy and some studies failed to demonstrate an association between alcohol exposure and sustained attention performance in school age children. Alcohol in pregnancy may affect intellectual ability that together with attention span and behavior are being considered higher functions of the cerebral cortex. Studies in 7 year-old school children following prenatal exposure to moderate amount of alcohol showed a decrement of 7 points in IQ. Nine years old participants with FAS were significantly weaker than control children in reading, spelling, addition, subtraction, phonological awareness, and other tests of early literacy. A deficit in phonological awareness, a key pre-function for reading may be a primary cognitive phenotypic characteristic in children with FAS. Syllable manipulation, letter sound knowledge, written letters, word reading and non-word reading and spelling were improved after nine months manipulation class [46].

Delayed motor functions, mostly fine motor skills were found in 22–68 months old FAS children. In addition, alcohol may also affect the cerebellum. In the human cerebellum, Purkinje cell migration is completed and their dendritic outgrowth begins around gestational week 26 extending to the third trimester of pregnancy. Consequently, a period of enhanced vulnerability of Purkinje cells to binge alcohol exposure in humans would be predicted near the end of the second trimester and may extend over the third trimester [17,36,44].

Children with FAS were found to have the frontal lobes smaller with lower choline concentrations in MR spectroscopy as a marker of cell membrane stabilizer and myelinization. The caudate nucleus was found disproportionately smaller in children with neuropsychological impairment. Decreased cerebellar growth and decreased cranial to body growth in fetuses of alcohol abusing mothers was also observed on fetal ultrasound performed on the 18 week of gestation. If the mothers stopped drinking at the beginning of pregnancy, cerebellar growth was normal [2].

Prenatal alcohol exposure can have serious and permanent adverse effects. The developing brain is the most vulnerable organ to the insults of prenatal alcohol exposure. A behavioral phenotype of prenatal alcohol exposure including conduct disorders is also described. This study on a sample of Brazilian adolescents convicted for criminal behavior aimed to evaluate possible clinical features of FAS. These were compared to a control group of school adolescents, as well as tested for other environmental risk factors for antisocial behavior. A sample of 262 institutionalized male adolescents due to criminal behavior and 154 male students aged between 13 and 21 years comprised the study population. Maternal use of alcohol was admitted by 48.8% of the mothers of institutionalized adolescents and by 39.9% of the school students. The signs suggestive of FASD were more common in the institutionalized adolescents. Social factors like domestic and family violence were frequent in the risk group, this also being associated to maternal drinking during pregnancy. The inference is that in this sample, criminal behavior is more related to complex interactions between environmental and social issues including prenatal alcohol exposure [28].

To evaluate the visual pathway by a coherent motion perception test in children with FAS [49] eighty-nine children (49 with verified FAS and 40 without FAS) aged from 10 to 16 years were included into the study. Both the study and the control group were children living in orphanages. A coherent motion perception test was used. The test consisted of 150 white moving dots on a black background presented in different signal-to-noise ratio conditions. The task was direction detection of the coherently moving dots whose percentage decreased at each step. A significant difference between the two groups was found ($p = 0.018$). Children with FAS had lower coherent motion perception ability in all the signal-to-noise ratio conditions. A significant difference between difficulty levels ($p < 0.001$) was found for all subjects in both groups - decreasing the stimulus signal-to-noise level decreased the motion perception score. In both groups, the motion perception score differed for vertical and horizontal stimuli ($p = 0.003$) with better performance with vertical stimuli. Impaired motion perception in FAS children could be indicative of a dorsal stream developmental dysfunction resulting from alcohol brain damage [48, 14].

Adults exposed to binge drinking while in utero were found to have increased rate of somatoform

disorders, substance dependence, paranoid, passive aggressive, antisocial and other personality disorders [5].

Prevention and Treatment of FAS in human

Unfortunately, there are only few reports demonstrating success in reducing drinking of alcohol in pregnancy, and these reports even declined from 1995–1999. The rate of binge-drinking and of chronic heavy drinking remained unchanged, suggesting that the education programs were not effective. Preventing alcohol abuse must, therefore, start with educational programs in schools. Preventing programs need to be primarily addressed towards high risk individuals and groups. Lately a motivational intervention to reduce the risk of an alcohol-exposed pregnancy in preconceptional women by information plus a brief motivational intervention or information resulted in twofold reduced risk of fetal alcohol exposure across the follow-up period [55, 1].

Assuming that oxidative stress is one of the major routes of ethanol-induced damage, it is reasonable to supplement antioxidants, in effort to attenuate this damage. Antioxidants, such as Vitamin C, Vitamin E, folic acid, beta-carotene and flavonoids can be supplemented by food, therefore, reversing other nutritional deficits common among this population [46, 15].

Alcohol is transferred to human milk, reaching levels similar to those in maternal serum, hence, women with heavy drinking should refrain from nursing. However, according to the American Academy of Pediatrics lactation is allowed, apparently depending on the daily dose of alcohol. The known side effects includes: drowsiness, diaphoresis, deep sleep, weakness, decrease in linear growth, abnormal weight gain and decreased milk ejection reflex with high maternal ingestion. If nursing mothers drink only small to moderate amounts of alcohol, they should wait 2-3 hours before nursing their infants [3, 5].

Early Recognition of Fetal Alcohol Exposure

Over time, as subsequent research and clinical experience suggested that a range of effects (including physical, behavioral, and cognitive) could arise from prenatal alcohol exposure, the term FASD was developed to include FAS as well as other conditions resulting from prenatal alcohol exposure.

Therefore, the identification of biomarkers that can reliably reflect fetal alcohol exposure and/or injury is of high priority, especially because such markers may be useful for early case recognition and thereby early intervention. Although metabolites of tobacco or other drugs often are used as biomarkers of their respective use, the prime oxidative metabolites of alcohol are carbon dioxide and water, both of which are present in such abundance that they cannot serve as a marker of alcohol use. However, there also are less prominent nonoxidative routes by which alcohol is eliminated from the body. This includes the formation of esters with the body's fatty acids to make fatty acid ethyl esters (FAEEs). The FAEEs, which can accumulate in hair, are a potential marker for prior alcohol use. FAEEs also may be found in the meconium from newborns and can indicate exposure to alcohol in the last few weeks or months of pregnancy. Other nonoxidative metabolites of ethanol include ethyl glucuronide, which already has been used as a clinical marker to reflect alcohol exposure within the past 3 days, and phosphatidyl ethanol, a marker that may indicate alcohol use for up to 1 to 2 weeks. Newer technologies in the fields of proteomics and metabolomics, and even epigenetic alterations of histone proteins and DNA methylation eventually may provide meaningful indications of alcohol exposure via biological fluids from either maternal or infant sources. Markers that can reliably indicate level and timing of alcohol exposure would greatly improve the ability to identify individuals with FASD [2].

Early detection of neonates who had intrauterine alcohol exposure may enable effective social and educational intervention programs. The meconium FAEEs, ethyl palmitate (E16:0), ethyl palmitoleate (E16:1), ethyl stearate (E18:0), ethyl oleate (E18:1), ethyl linoleate (E18:2), ethyl linolenate (E18:3), and ethyl arachidonate (E20:4) products of nonoxidative ethanol metabolism, have been established as a biomarker of fetal ethanol exposure. Among 682 meconium specimens anonymously collected in Canada FAEE analysis detected fivefold more ethanol-exposed pregnancies than reported by standard postpartum questionnaires in this population [18].

Treatment of Alcohol Exposed Pregnant Animals

There seem to be no human studies trying to prevent the teratogenic effects of alcohol during pregnancy. However, there are several animal studies which demonstrated that antioxidants, as well as some other agents, may be effective in reducing ethanol–induced embryotoxicity. Alcohol exposed C57BL/6J mice were injected twice with 2.9 g/kg, four hours apart of EUK-134 (a potent synthetic superoxide dismutase plus catalase mimetic) on their 9th day of pregnancy. EUK-134 supplementation induced a notable reduction in cell death of apical ectodermal ridge of the newly forming limb buds in ethanol exposed embryos and reduced the forelimb malformations by half (67.3% to 35.9%)[61, 43].

Metadoxine accelerates ethanol metabolism by increase the ethanol and acetaldehyde plasma clearance and urinary elimination of ketones. A faster rate of ethanol elimination was found in patients with acute alcohol intoxication. Reports on the safety of metadoxine in pregnant rats in therapeutic dosage were published in the Chinese literature and may be a promising therapy for binge drinking during pregnancy [7,11].

Exposure to ethanol during developmental stages leads to several types of neurological disorders. Apoptotic neurodegeneration due to ethanol exposure is a main feature in alcoholism. Exposure of developing animals to alcohol induces apoptotic neuronal death and causes fetal alcohol syndrome. It was found that the possible protective effect of pyruvate against ethanol-induced neurodegeneration. Exposure of developing mice to ethanol (2.5 g/kg) induces apoptotic neurodegeneration and widespread neuronal cell death in the cortex and thalamus. Co-treatment of pyruvate (500 mg/kg) protects neuronal cell against ethanol by the reduced expression of caspase-3 in these brain regions. Immunohistochemical analysis and TUNEL at 24 h showed that apoptotic cell death induced by ethanol in the cortex and thalamus is reduced by pyruvate. Histomorphological analysis at 24 h with cresyl violet staining also proved that pyruvate reduced the number of neuronal cell loss in the cortex and thalamus. The results showed that ethanol increased the expression of caspase-3 and thus induced apoptotic neurodegeneration in the developing mice cortex and thalamus, while co-treatment of pyruvate inhibits the induction of caspase-3 and reduced the cell death in these brain regions. These findings, therefore, showed that treatment of pyruvate inhibits ethanol-induced neuronal cell loss in the postnatal seven (P7) developing

mice brain and may appear as a safe neuroprotectant for treating neurodegenerative disorders in newborns and infants [53].

Prenatal alcohol exposure is known to induce fetal brain growth deficits at different embryonic stages. The neuroprotective effects against alcohol-induced apoptosis at midge station using activity-dependent neurotrophic factor (ADNF)-9, a peptide (SALLRSIPA) derived from activity-dependent neurotrophic factor, and NAP, a peptide (NAPVSIPQ) derived from activity-dependent neuroprotective protein have been investigated. On embryonic day 7 (E7), weight-matched pregnant females were assigned to the following groups: (1) ethanol liquid diet (ALC) group with 25 % (4.49 %, v/v) ethanol-derived calories, (2) pair-fed (PF) control group, (3) ALC combined with i.p. injections (1.5 mg/kg) of ADNF-9 (ALC/ADNF-9) group, (4) ALC combined with i.p. injections (1.5 mg/kg) of NAP (ALC/NAP) group, (5) PF liquid diet combined with i.p. injections of ADNF-9 (PF/ADNF-9) group, and (6) PF liquid diet combined with i.p. injections of NAP (PF/NAP) group. On day 15 (E15), fetal brains were collected, weighed, and assayed for TdT-mediated dUTP nick end labeling (TUNEL) staining. ADNF-9 or NAP was administered daily from E7 to E15 alongside PF or alcohol liquid diet exposure. The results show that NAP and ADNF-9 significantly prevented alcohol-induced weight reduction of fetal brains. Apoptosis was determined by TUNEL staining; NAP or ADNF-9 administration alongside alcohol exposure significantly prevented alcohol-induced increase in TUNEL-positive cells in primordium of the cingulate cortex [45].

To better understand the cellular pathogenetic mechanisms of FASD and the therapeutic benefit of stem cell treatment, pregnant rats were exposed to ethanol followed by intravenous administration of neural stem cells (NSCs) complexed with atelocollagen to the newborn rats and studied recovery of GABAergic interneuron numbers and synaptic protein density in the anterior cingulate cortex, hippocampus and amygdala. Prenatal ethanol exposure reduced both parvalbumin-positive phenotype of GABAergic interneurons and postsynaptic density protein 95 levels in these areas. Intravenous NSC treatment reversed these reductions. Furthermore, treatment with NSCs reversed impaired memory/cognitive function and social interaction behavior. These experiments underscore an important role for synaptic remodeling and GABAergic interneuron genesis in the pathophysiology and treatment of FASD and highlight the therapeutic potential for intravenous NSC administration in FASD utilizing atelocollagen [37, 2,51].

It has been elucidated that psychiatric disorders are associated with impairment of the brain neural network. Reduction in brain size and hypoplasia of the basal ganglia and corpus callosum have been reported in FASD. It is believed that the formation of the neural network is influenced by alcohol exposure during the fetal period. Additionally, it is well known that the functional expression of CNS consequences of prenatal alcohol exposure includes cognitive and attentional processes, as well as social behavioral problems. It has also been reported that abnormal 5-HT neuron development can be reversed by treatment with a 5-HT1A agonist in a prenatal alcohol exposure model. However, these treatments are prophylactic. Without early intervention, the consequences of FASD are permanent. Recently, emerging evidence suggest that many clinical symptoms observed in psychiatric disease are likely related to neural network disruptions including neurogenesis dysfunction [37].

NSC transplantation has been investigated in areas such as brain injury, stroke and neurodegenerative diseases and may be a way to reverse neurogenesis dysfunction. In the present work, authors evaluated the usefulness of intravenous transplantation of NSCs in the FASD model rat focusing on the possibility of regenerative therapy, particularly regarding behavioral abnormalities, for FASD rats. Abnormal behaviors FASD model rats suggest that reduced social activity, and cognitive dysfunction are major symptoms in FASD patients. Intravenous NSC transplantation appeared to partially correct these behavioral abnormalities in FASD model rats. In the amygdala areas intravenous NSC transplantation appears to have partially regenerates expression of PSD95 in FASD model rats.

The results suggest that intravenous NSC transplantation may be an advanced approach to recover neural network damage and CNS dysfunction in FASD and possibly other psychiatric disorders [46, 17]. Exposure to ethanol during early development triggers severe neuronal death by activating multiple stress pathways and causes neurological disorders, such as fetal alcohol effects or FAS. This study investigated the effect of ethanol on intracellular events that predispose developing neurons for apoptosis via calcium-mediated signaling. Although the underlying molecular mechanisms of ethanol neurotoxicity are not completely determined, mitochondrial dysfunction, altered calcium homeostasis and apoptosis-related proteins have been implicated in ethanol neurotoxicity. The present study was designed to evaluate the neuroprotective mechanisms of metformin (Met) and thymoquinone (TQ) during ethanol toxicity in rat prenatal cortical neurons at gestational day 17. Met and TQ treatment inhibited the apoptotic cascade by increasing Bcl-2 expression. These compounds also repressed the activation of caspase-9 and caspase-3 and reduced the cleavage of PARP-1. Morphological conformation of cell death was assessed by TUNEL, Fluoro-Jade-B, and PI staining. These staining methods demonstrated more cell death after ethanol treatment, while Met, TQ or Met plus TQ prevented ethanol-induced apoptotic cell death. These findings suggested that Met and TQ are strong protective agents against ethanol-induced neuronal apoptosis in primary rat cortical neurons [54,51,38].

Conclusions

Maternal alcohol consumption in pregnancy may have deleterious effects on the CNS and other organs of the developing embryo and fetus, depending on the dose, duration and developmental stage of the embryo at exposure. These embryotoxic effects of alcohol were observed in many animal species. It is therefore important to reduce alcohol drinking during pregnancy to the minimum. However, as of today, it is still difficult to define the minimal dose that will affect the developing embryo and the exact dose - response relationship. Educational interventions should start at school and in adolescents and young adults it should start before pregnancy [1]. Early recognition of intrauterine alcohol exposed children may allow nutritional, behavioral and schooling support. Several studies on ethanol exposed pregnant animals are promising in regards with the possible amelioration of alcohol-induced embryotoxicity.

Forty years ago, alcohol was not commonly recognized as a teratogen. Today, not only has public policy changed, but we also have a better understanding

of the consequences of prenatal alcohol exposure and the prevalence and mechanisms of alcohol-related damage. Better identification and diagnosis of the full range of FASD are needed, which could be improved with the development of biomarkers that aid in detection and accurate quantification of prenatal alcohol consumption.

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АЛКОГОЛЬНЫЙ СИНДРОМ ПЛОДА

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В обзоре обобщены данные литературы о нарушениях в организме плода, возникающих под воздействием пренатальной алкоголизации, о критериях диагностики, патогенезе, нарушениях поведения, о лечении и профилактике фетального алкогольного синдрома (ФАС). Основным проявлением ФАС является повреждение центральной нервной системы, особенно головного мозга. Развитие и созревание клеток и структур мозга нарушается при пренатальном воздействии алкоголя, и это может стать причиной первичных когнитивных и функциональных нарушений (в том числе нарушений памяти, дефицита внимания, импульсивного поведения и логического мышления), а также вторичных нарушений (например, предрасположенности к проблемам психического здоровья и наркомании). Воздействие алкоголя представляет угрозу повреждения мозга плода на любом сроке беременности, так как развитие мозга продолжается в течение всей беременности.

Ключевые слова: *фетальный алкогольный синдром, центральная нервная система.*

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