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Critical Review

An Update on Fetal Alcohol Syndrome—Pathogenesis, Risks, and Treatment

Keshav K. Gupta, Vinay K. Gupta, and Tomohiro Shirasaka

Alcohol is a well-established teratogen that can cause variable physical and behavioral effects on the fetus. The most severe condition in this spectrum of diseases is known as fetal alcohol syndrome (FAS). The differences in maternal and fetal enzymes, in terms of abundance and efficiency, in addition to reduced elimination, allow for alcohol to have a prolonged effect on the fetus. This can act as a teratogen through numerous methods including reactive oxygen species (generated as by products of CYP2E1), decreased endogenous antioxidant levels, mitochondrial damage, lipid peroxidation, disrupted neuronal cell–cell adhesion, placental vasoconstriction, and inhibition of cofactors required for fetal growth and development. More recently, alcohol has also been shown to have epigenetic effects. Increased fetal exposure to alcohol and sustained alcohol intake during any trimester of pregnancy is associated with an increased risk of FAS. Other risk factors include genetic influences, maternal characteristics, for example, lower socioeconomic statuses and smoking, and paternal chronic alcohol use. The treatment options for FAS have recently started to be explored although none are currently approved clinically. These include prenatal antioxidant administration food supplements, folic acid, choline, neuroactive peptides, and neurotrophic growth factors. Tackling the wider impacts of FAS, such as comorbidities, and the family system have been shown to improve the quality of life of FAS patients. This review aimed to focus on the pathogenesis, especially mechanisms of alcohol teratogenicity, and risks of developing FAS. Recent developments in potential management strategies, including prenatal interventions, are discussed.

Key Words: Alcohol, Fetal Alcohol Syndrome, Prenatal Treatment, Teratogenicity.

FETAL ALCOHOL SYNDROME (FAS) was first formally termed in 1973. Jones and colleagues (1973) described a group of characteristic features seen in 8 children born to chronic alcoholics: growth deficiency, defined as pre-/postnatal height or weight below the 10th percentile, and central nervous system (CNS) damage (Hoyme et al., 2005), and 3 craniofacial abnormalities are used in diagnosis (National Center on Birth Defects and Developmental Disabilities at the Centers for Disease Control and Prevention, National Task Force on Fetal Alcohol Syndrome and Fetal Alcohol Effect, 2004).

Estimates of FAS incidence vary considerably, reported in Canada (Farag, 2014) and the United States as 0.5 to 3/1,000 live births (Goh et al., 2008). This is largely due to the variable physical and behavioral effects of alcohol on the fetus, leading to a scale of disorders named fetal alcohol spectrum disorders (FASD) (Bertrand et al., 2005; Sokol et al., 2003). This umbrella term identifies the "range of outcomes from gestational alcohol exposure" (Riley et al., 2011, p. 76) from alcohol-related birth defects (ARBDs), which are hard to diagnose, to FAS.

This review aimed to focus on the pathogenesis, especially mechanisms of alcohol teratogenicity, and risks of developing FAS. Recent developments in potential management strategies, concentrating on prenatal interventions, will also be discussed.

PATHOGENESIS

Alcohol has been a well-established teratogen for many years (Ornoy and Ergaz, 2010). In 1968, a common pattern of birth defects was seen in 127 children born to alcoholic women in France. Both the Institute of Medicine (Stratton et al., 1996) and Washington criteria (Astley and Clarren, 2000) require evidence of gestational alcohol exposure to diagnose FAS. In the United Kingdom, the Royal College of Obstetricians and Gynaecologists (Royal College of Obstetricians and Gynaecologists, 2008) and the National Institute of Clinical Excellence (National Institute for Health and Care Excellence, 2008) both advise against drinking alcohol during pregnancy. Such recommendations have been

From the School of Medicine (KKG), Imperial College London, London, UK; School of Medicine (VKG), University of Birmingham, Birmingham, UK; and Department of Neuropsychiatry (TS), School of Medicine, Sapporo Medical University, Sapporo, Japan.

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Reprint requests: Keshav K. Gupta, BSc, Imperial College London South Kensington Campus London, SW7 2AZ UK. Tel.: +44(0) 7824859131; Fax: +44(0)01216272667; E-mail: keshav.gupta11@imperial.ac.uk

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established much longer with the U.S. Surgeon General also advising against consuming alcohol during pregnancy in 1981 (Food and Drug Administration, 1981).

Alcohol and the Placenta

Both animal and clinical studies have shown that ethanol (EtOH) diffuses through the placenta and distributes rapidly into the fetal compartment (Brien et al., 1983, 1985; Idanpaan-Heikkila et al., 1972) where EtOH also has a slower elimination rate (3 to 4% of maternal rate; Heller and Burd, 2014)—accumulating in the amniotic fluid (Brien et al., 1983). This reservoir causes greater fetal exposure to EtOH and is compounded by fetal swallowing, caused by the fetal kidneys excreting xenobiotics into the amniotic fluid, which the fetus then swallows (Morgan, 1997; Underwood et al., 2005).

Oxidative and nonoxidative processes govern regular alcohol metabolism (Agarwal, 2001). Cytosolic alcohol dehydrogenase (ADH) mediates the major, and hepatic CYP2E1 the minor, biotransformation of EtOH to acetaldehyde (Gemma et al., 2007). The CYP2E1 pathway normally accounts for only 10% of EtOH metabolism but becomes more significant during ingestion of higher alcohol concentrations, due to ADH saturation (Howard et al., 2003). This is explained by the enzyme kinetics—the KM for ADH is 4.5 mg/dl (Tran et al., 2007) compared to 74 mg/dl for CYP2E1 (Lands, 1998). Therefore, once blood alcohol concentrations (BAC) exceed 4.5 mg/dl, EtOH follows saturation (zero order) elimination kinetics by ADH and therefore favors metabolism by CYP2E1 (Tran et al., 2007; Wagner et al., 1976).

The situation in the fetus is different. The placenta has metabolic functionality due to enzymatic expression, particularly in the first trimester (when the liver is developing) (Myllynen et al., 2005). Here, CYP2E1 is the major metabolizing enzyme (Cummings and Kavlock, 2004), because CYP2E1 is induced by alcohol and EtOH has a higher affinity for placental CYP2E1 than ADH (Rasheed et al., 1997). The fetal liver contains CYP2E1 earlier in gestation (16 weeks) (Hines and McCarver, 2002) compared to ADH (26 weeks) (Arfsten et al., 2004). Significant levels of CYP2E1 activity and mRNA have also been found in fetal brain tissue between 45 and 113 days' gestation (Brzezinski et al., 1999).

Alcohol therefore has a prolonged effect on the fetus due to amniotic accumulation, reduced concentrations of fetal metabolic enzymes (CYP2E1 levels remain relatively low throughout pregnancy, gradually increasing to a maximum of 30 to 40% of adult hepatic levels 1 year postdelivery; Zelner and Koren, 2013), and reduced elimination.

Mechanisms of Alcohol Teratogenicity

There are many different proposed mechanisms of alcohol teratogenicity. Such putative mechanisms are illustrated in an earlier review by Goodlett and colleagues (2005). EtOH can compromise endogenous antioxidant capacity, for example, by decreasing glutathione peroxidase levels, or generate free radicals as by products of its CYP2E1 metabolism (Ornoy and Ergaz, 2010). The presence of CYP2E1 in brain tissue is significant as it overlaps with the start of organogenesis (days 50 to 60) (Brzezinski et al., 1999; Zelner and Koren, 2013). When CYP2E1 oxidizes EtOH, it generates a hydroxyethyl or superoxide radical, which target polyunsaturated fatty acids side chains in brain tissue membranes. These lipid peroxidative processes may damage fetal brain tissue during organogenesis, manifesting as CNS dysfunction after delivery (Gemma et al., 2007).

Kay and colleagues (2006) showed markers of oxidative stress (nitrotyrosine and 4-hyroxy-2-nonenal) were present in trophoblasts and stroma, after perfusing placental villous tissues with EtOH. This was contradicted by another study (Signore et al., 2008) showing no increase in urinary eicosanoid markers of oxidative stress between pregnant drinkers and abstainers. However, here, only 29 pregnant drinkers were enrolled, of which only 1 had a child diagnosed with FAS. Furthermore, the presence of eicosanoid markers localized to the placenta, where the oxidative stress is likely to occur, was not investigated.

Free radicals and reactive oxygen species (ROS) may result in cellular damage in the fetal brain by inducing uncontrolled apoptosis (Cohen-Kerem and Koren, 2003; Guerri et al., 1994). Animal trials showed EtOH increased components of the intrinsic apoptotic pathway (cytochrome c and capsase 3) (Ramachandran et al., 2001) and in vitro studies demonstrated apoptosis following cellular (Ramachandran et al., 2001) and mitochondrial (de La Monte and Wands, 2001) DNA damage. This is summarized in Fig. 1.

Applying this to FAS, it has been suggested that its characteristic facial morphology is linked to the apoptotic effects of alcohol on cranial neural crest cells (Cartwright and Smith, 1995a,b). The neuropsychiatric effects of FAS may be explained by EtOH favoring apoptosis of serotonergic neurons in mice (Sari and Zhou, 2004). Clearly, animal studies have a limited translatable potential to humans, especially when concerning fetal development. However, functional imaging of children with FAS has confirmed lower levels of serotonin in the cortex and increased dopamine binding in the basal ganglia (Riikonen et al., 2005), suggesting the same apoptotic effects are observed in humans. However, other studies have shown that this observation may be a result of different mechanisms, such as serotonin transporter alterations (Zafar et al., 2000).

It is important to note that the functional imaging was conducted on only 12 children with FAS (Riikonen et al., 2005) reducing the validity of the conclusions. Furthermore, all children had attention-deficit/hyperkinetic disorder (ADHD) making it unclear as to whether the reduced effects of serotonin and/or dopamine at the synaptic level are more related to a diagnosis of ADHD or FAS. Future studies involving children exclusively with FAS are required to establish an independent relationship.

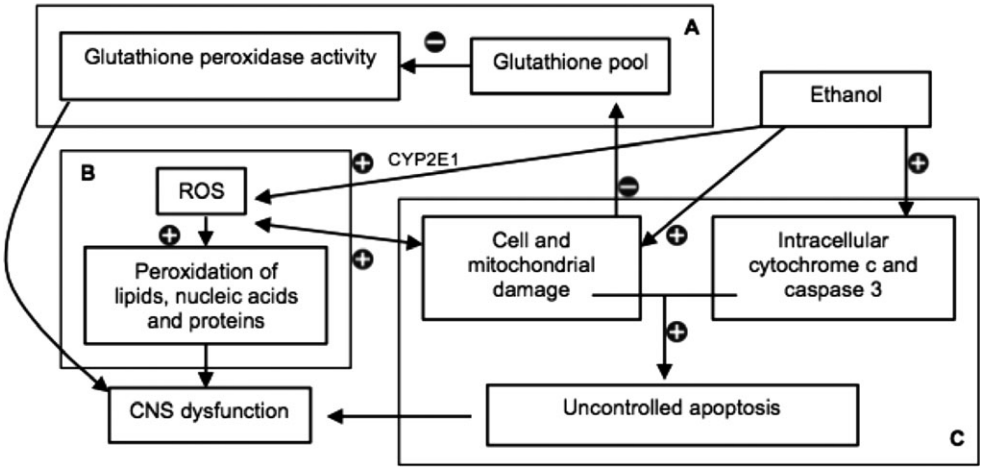

Fig. 1. Summary of ethanol (EtOH)-induced mechanisms of central nervous system (CNS) dysfunction. (**A**) Shows the indirect pathway for EtOH-induced oxidative stress with an overall reduction in glutathione peroxidase activity (an endogenous antioxidant). (**B**) Shows the direct pathway for EtOH-induced oxidative stress with peroxidation of lipids, nucleic acids, and proteins through free radicals and reactive oxygen species (ROS) generated as byproducts of alcohol metabolism by CYP2E1. Free radicals include hydroxyethyl and hydroxyl groups. (**C**) Other ways in which EtOH affects cells leading to damage to the fetus culminating in uncontrolled apoptosis via cell and mitochondrial damage and cytochrome c and caspase 3.

EtOH also disrupts neuronal cell–cell adhesion (Pruett et al., 2013) by increasing alpha- and beta-laminins 1, beta-integrins 3 and 5, and secreted phosphoprotein-1 and sarcoglycan epsilon expression (observed as increased neurosphere sizes). Several studies have linked the importance of these molecules in normal brain development (Minana et al., 2000; Vangipuram et al., 2008) and other neurodevelopmental disorders such as microcephaly and mental retardation (Charness et al., 1994; Minana et al., 2000; Wilkemeyer et al., 1999). Neurosphere usage brings limitations to the study, as their variable formation leads to differences in composition. They contain cells at multiple stages of differentiation, which makes it harder to pinpoint the most vulnerable time of alcohol-induced effects on cell adhesion molecules.

Other proposed mechanisms include the transport inhibition of critical cofactors necessary for fetal growth and development, such as biotin (Schenker et al., 1993) and vitamin B6 (Schenker et al., 1992). Such theories on impaired placental transfer of essential nutrients have been suggested since the 1980s (Randall, 1987). EtOH also causes rapid placental vasoconstriction (Acevedo et al., 2001; Burd et al., 2003), possibly leading to the growth retardation seen in FAS through impaired oxygen and nutrient fetal delivery (Siler-Khodr et al., 2000; West et al., 1994). This occurs via oxidative stress decreasing nitric oxide (a known vasodilator) availability (Kay et al., 2000), or by dysregulating the thromboxane (vasoconstrictor)–prostacyclin (vasodilator) balance (Burd et al., 2003; Siler-Khodr et al., 2000).

More recently, pre- and postnatal alcohol exposure has been shown to cause a significant increase in DNA methyltransferase activity (Ponomarev, 2013) without affecting histone deacetylase activity (Perkins et al., 2013). These epigenetic changes can impact the brain structure and function for the remainder of the organism's life (Nestler, 2014; Ungerer et al., 2013). EtOH can also disrupt intercellular communication necessary for trophoblast growth and cellular differentiation—important steps in fetal development. Interleukins 6 and 13 are specifically involved in neuroepithelial/radial glial cell renewal (Deverman and Patterson, 2009) and are significantly reduced following alcohol exposure (Roberson et al., 2012) leading to potential adverse effects on CNS development.

FACTORS INCREASING RISK OF FAS DEVELOPMENT

The risk of developing FAS is related to timing and amount of alcohol consumption (dose-dependent) (Abel and Hannigan, 1995), as well as other factors. BAC is the most relevant tool when assessing risk as binge drinking, producing the highest BAC, which carries the highest risk of fetal damage (Livy et al., 2003; Maier and West, 2001; Pierce and West, 1986). This is backed up by studies showing populations with higher binge-drinking rates, having a greater FAS to partial FAS ratio, such as South Africa (May and Gossage, 2011).

A recent trial looked at different variables concerning maternal alcohol consumption (May et al., 2013). Greater numbers of drinking days per week and sustained drinking throughout all trimesters increase the risk of having a child with FAS. The first trimester is the most vulnerable time period with a 12-times increased risk. However, the study was based in South Africa, where binge drinking is a known cultural norm, perhaps making it unreasonable to extrapolate these conclusions to other populations. Additionally, large standard error overlaps in analysis demonstrate large maternal drinking variance in the FAS group, meaning it is likely that other factors also contribute to the increased risk of FAS development.

There is a potential genetic link with FAS, as alcohol is known to affect multiple genetic loci (Johnson et al., 2006). This is compounded in pregnancy as alterations in maternal loci can influence gene expression of the developing fetus and

the fetal environment, for example, via maternal hormones (Mead and Sarkar, 2014). Genes from the ADH family have also been investigated. One study demonstrated the absence of *ADH1B*3* allele to be protective for FAS (Stoler et al., 2002), while 2 others showed its presence to be protective (Jacobson et al., 2006; McCarver et al., 1997). Building on this, nonsynonymous variants at the *ADH1B* locus (*ADH1B*2* and *ADH1B*3)* have been shown to have a mild protective effect by various case–control and cohort studies across South African (Viljoen et al., 2001) and European populations (Zuccolo et al., 2009). Genetic influences may also tie directly in with teratogenesis. Many global gene expression studies after in utero alcohol exposure showed key genes being either up- or down-regulated to the detriment of functional pathways involved in cell proliferation, differentiation (Hard et al., 2005), and signaling (Green et al., 2007). At this stage, such studies are limited to mouse models and utilize varying experimental designs making it difficult to draw valid comparisons between the studies.

Interestingly, altering paternal gene expression can also influence fetal susceptibility to FAS. Paternal chronic alcohol use demonstrated a correlation with demethylation of normally hypermethylated sperm DNA-imprinted regions. Transmission of these epigenetic alterations in fertilization may alter "critical gene expression dosages required for normal prenatal development," thereby increasing the risk of FAS (Ouko et al., 2009, p. 1615). Importantly, the study enrolled only 16 males, reducing the diversity of the genetic pool sampled, which is especially relevant in this genetic study. Caution must be applied when extrapolating these results to the population. Furthermore, drinking patterns were self-reported and therefore may be under reported due to the social stigma attached to drinking heavily.

Various maternal characteristics also influence FAS risk (May and Gossage, 2011). A smaller body profile (height, weight, and body mass index [BMI]) was associated with an increased incidence of FAS. However, the pooling of these results from independent studies in different countries may not be valid due to differences in methodology and protocol. Additionally, a poor nutritional status (especially riboflavin, calcium, and zinc deficiencies; Keen et al., 2010) increases FAS risk for reasons other than their effect on BMI. A lower socioeconomic status and smoking are also more common in mothers of FAS children (May and Gossage, 2011).

Therefore, many factors are seen to influence incidences of FAS. Therein lie the limitations of such studies. Differences in body size, genetic polymorphisms, and paternal alcohol consumption can never be fully measured and controlled, leading to each trial having multiple confounding factors that can skew results and conclusions.

TREATMENT

Clearly, the most effective method of FAS prevention is to stop maternal alcohol consumption during pregnancy; however, considering current incidence rates, this seems largely ineffective thus far. In 2011/2012, 40 to 52% of women were reported to drink alcohol during pregnancy in the United Kingdom (Nykjaer et al., 2014) and 52.5% in the United States with 17.2% bingeing (4+ drinks/occasion) (CDC, 2012). This does not, however, advocate the discontinuation of programs used to educate mothers on the dangers of drinking during pregnancy.

Prenatal methods to reverse or prevent alcohol's teratogenicity mechanisms are being explored although none are currently approved for clinical use. Many trials have examined the effects of antioxidants on alcohol-exposed fetuses (Cohen-Kerem and Koren, 2003; Joya et al., 2014). For example, vitamins C (Peng et al., 2005) and E (Heaton et al., 2000; Wentzel et al., 2006), resveratrol (Kumar et al., 2011; Yuan et al., 2013), astaxanthin (Zheng et al., 2014), and curcumin (Tiwari and Chopra, 2013) have been administered to cell or animal models and shown to counter EtOH-induced oxidative stress. Treating women with antioxidants as food supplements may also help reverse nutritional deficiencies commonly seen in FAS mothers (Cohen-Kerem and Koren, 2003).

Future research should focus on the exact mechanism of antioxidant action as vitamin C effects were observed as a reduction in hydrogen peroxide and malondialdehyde, which are not representative of all ROS involved in EtOH teratogenicity (Peng et al., 2005). Additionally, not all studies have found a beneficial effect. High-dose vitamin C and E given throughout gestation have potential adverse effects such as low birth weight (Boskovic et al., 2005; Goh et al., 2007), not explained by variables such as maternal age. However, another trial showed that modified vitamin E promoted cell survival at much lower concentrations than natural vitamin E (Siler-Marsiglio et al., 2005).

Other supplements, such as folic acid, L-glutamine, boric acid, and choline, can also reduce the severity of EtOH-induced toxicity (Eskes, 1997; Scholl and Johnson, 2000; Yanaguita et al., 2008). Several studies using guinea pigs and mice showed the beneficial effects of folic acid including restoration of normal embryogenesis, preventing alcohol-induced intrauterine growth restriction (Han et al., 2012) and reducing the effects of EtOH-mediated oxidative stress (Cano et al., 2001). When administered alongside selenium in rats, there was also an improved balance among oxidative enzymes (Ojeda et al., 2009). Maternal ovine L-glutamine supplements were found to prevent alcohol-induced growth restriction on developing fetuses, while increasing amino acid availability (Sawant et al., 2015). Boric acid acted to reduce oxidative stress in prenatally alcohol-exposed rats (Sogut et al., 2015). Zinc has also been shown to have positive effects in reducing physical abnormalities when administered at the time of EtOH exposure in mice (Carey et al., 2003).

Choline has been shown to reduce the severity of certain neurobehavioral events and increases brain weight in animal models (Thomas et al., 2009, 2010). However, this finding was collected from litters with 11 or more pups and thus may over represent larger litters, where there is more competition

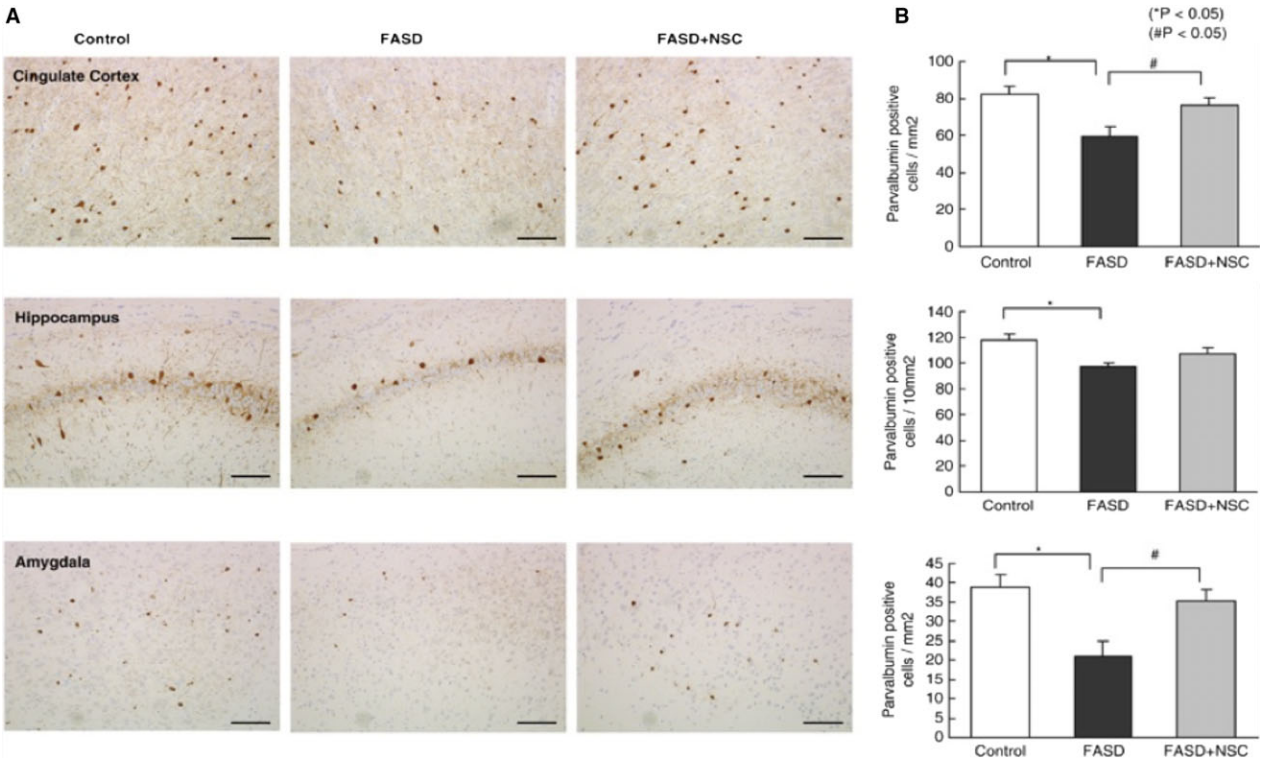

Fig. 2. Decreased number of parvalbumin (PV)-positive GABA interneurons and their area-dependent reverses by neuronal stem cell (NSC) treatment. (**A**) PV-positive cells were counted in coronal sections from control, fetal alcohol spectrum disorder (FASD) and FASD+NSC rats. (**B**) The amount of PV-positive cells significantly decreased in anterior cingulate cortex, hippocampus, and amygdala in FASD rats (*$p < 0.05$). NSC treatment reversed these reductions in anterior cingulate cortex and amygdala (#$p < 0.05$) but not in the hippocampus. Scale bars: 100 μm. Taken with permission from T Shirasaka (co-author) (Shirasaka et al., 2012).

for prenatal nutritional factors. A recent double-blind placebo-controlled clinical trial showed postnatal choline given to children with FASD aged between 2.5 and 5 years was well tolerated but had mixed effects on memory recall and other measures of early learning (Wozniak et al., 2015). This was, however, a pilot study. Perhaps future work could focus on a narrower age range and earlier intervention.

Recently, the use of neuroprotective peptides to influence cytokines and chemokines involved in developmental cellular signaling has been studied. The EtOH-induced reduction of important signaling molecules, interleukins 6 and 13, was reversed with neuroprotective peptides NAPVSIPQ and SALLRSIPA (Roberson et al., 2012). They also reduced inhibition on L1 cell adhesion. Neurotrophic and growth factor administration also have similar effects, with insulin-like, nerve, and heparin-binding EGF-like growth factors (respectively, IGF-1, NGF, and HB-EGF), reducing EtOH-induced adverse effects on insulin-dependent signaling pathways (Barclay et al., 2005; Rahman et al., 1994) and apoptosis. This is perhaps due to high HB-EGF expression during early development, which helps to promote cell survival (Das et al., 1994; Kilburn et al., 2006; Leach et al., 1999). Omega-3 and betaine have also shown to reduce the neurodegeneration triggered by EtOH in rat brains (Ol et al., 2016).

Thus far, the potential treatment options have focused on reversing the mechanisms of alcohol teratogenicity. Regenerative method, such as stem cell use, is a newer avenue of exploration (Muralidharan et al., 2013). A recent paper used fetal rat brain-derived neuronal stem cells (NSCs), which reversed the actions of EtOH-induced reductions of GABAergic interneurons (Fig. 2) (Shirasaka et al., 2012). The rats were either treated with EtOH or an equal volume of physiological saline as a control, for 4 days every 12 hours between days 10 and 13 of gestation. Rats were then injected intravenously with a NSC suspension at postnatal day 45, or received saline alone. Importantly, rats receiving the NSC injection correlated with a reversed impairment of memory/cognitive function and social behavior seen in FAS.

Another paper showed similar outcomes where behavioral abnormalities in fetal alcohol-affected rats were reduced with NSC treatment (Yoshinaga et al., 2007). However, the ethical concerns related to harvesting fetal brain-derived NSCs may require the need for other potential sources such as induced pluripotent stem cells or postmortem human CNS tissue. The possible risks of teratoma formation, immune rejection, and inappropriate stem cell migration (Master et al., 2007) along with limited information about transplantation of stem cells clinically, and their long-term effects, suggest more clinical trials are required surrounding these issues (Poulos et al., 2014).

Further research into the $GABA_A$ receptor has shown a flavonoid compound, dihydromyricetin (DHM), which

Table 1. Psychological Deficits and Secondary Disabilities Seen in Fetal Alcohol Syndrome (FAS)

Summary of psychological deficits in FAS (Jacobson and Jacobson, 2002)
• Hyperactivity
• Attention deficits—sustained and focused attention
• Planning difficulties
• Learning/memory problems
• Poor consolidation of new memories
• Lower IQ—arithmetic, receptive language, and verbal processing problems
• Social difficulties
Common secondary disabilities in FAS (Mukherjee et al., 2006)
• Psychiatric problems
• Disrupted school experience
• Trouble with the law
• Confinement
• Inappropriate sexual behaviors
• Alcohol/drug problems

selectively antagonizes the effects of EtOH at the $GABA_A$ receptor with few side effects. Administration of DHM with EtOH in pregnant rats was found to prevent all the physiological and behavioral changes observed in rats that had been exposed to alcohol in utero (Liang et al., 2014).

There is a wide range of secondary disabilities associated with FAS (Jacobson and Jacobson, 2002; Mukherjee et al., 2006), which are summarized in Table 1. Managing such disabilities does not treat FAS directly but can improve the patient's quality of life—a key part of management. Stabilizing the family system (Olson et al., 2009), improving executive function via the Alert program for self-regulation (Nash et al., 2015; Soh et al., 2015), and using existing treatment plans for common comorbidities seen in FAS, such as ADHD (Doig et al., 2008), are examples of how this can be performed. However, FAS-ADHD differs slightly to ADHD; thus, the response to treatment is variable (Pruett et al., 2013). Therefore, there is a need for novel pharmacological agents, such as fenofibrate, to reduce hyperactivity in FAS (Marche et al., 2011).

LIMITATIONS AND FUTURE WORK

A consistent limitation found in all research was the lack of clinical evidence. In vitro and animal studies produce limited translatable data when studying cellular mechanisms of teratogenicity. This is because in humans, simultaneous chemical reactions and genetics can influence the final outcome of the mechanisms in question.

Furthermore, those clinical trials that were conducted generally had low "n" numbers, limiting their ability to detect an increased risk for specific adverse outcomes. It is clearly unethical to administer alcohol to pregnant women and therefore unreasonable to expect gold standard randomized controlled trials to replace the retrospective case reports commonly used.

Recently, however, the use of zebra fish is coming to the fore. The benefits of hundreds of optically clear eggs laid externally enable accurate analysis of cellular processes, helping the assessment of the impacts of EtOH on developmental embryological sequences (Barclay et al., 2005). Importantly, there is good conservation of major developmental signaling pathways including neural and craniofacial development—particularly relevant for FAS (Eberhart et al., 2008; Ingham, 2009). Embryonic alcohol exposure has been shown to impair zebra fish social behavior due to alcohol-induced dysfunction of the dopamine-controlled reward systems (Fernandes et al., 2015). A recent paper involving zebra fish has shown that alterations to miRNA miR-9 are related to EtOH-induced tetralogy. They found that EtOH transiently inhibited miR-9 and disrupts its interactions with its target genes (Pappalardo-Carter et al., 2013). However, there has been an issue surrounding the agreement of tissue EtOH levels in exposed zebra fish (Barclay et al., 2005).

CONCLUSIONS

The complex interactions of pathogenesis and risk factors for FAS make the current search for a definitive treatment tricky. Addressing existing research limitations may prove beneficial in determining precise mechanisms of alcohol teratogenicity and therefore may help achieve a more effective treatment for FAS.

CONFLICTS OF INTEREST

There are no conflicts of interest.

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