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Fetal Alcohol Syndrome and Mental Health

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SUMMARY

Background: Nearly five decades ago, the term fetal alcohol syndrome was documented for the first time. Since then, several studies have been investigating the link between maternal alcohol drinking during pregnancy and its impacts on the mental health of affected individuals. *Aim*: This review aims to provide a narrative approach to the scientific literature on the history, clinical presentation, pathology, pathophysiology, diagnosis, and management of fetal alcohol syndrome from a psychiatry related perspective. *Methods*: an extensive search using the specific keywords was conducted on PubMed, ScienceDirect, Google Scholar, and VU library online databases. Both full text and their abstracts were analyzed in this review, and only records containing related keywords in their abstracts or titles were selected. Date of publication was predominantly refined from 2000 to 2022, however due to the paucity of material focused primarily on this topic, earlier research was also analyzed. *Results*: the studies suggested that mental health problems are the most disabling consequence faced by patients with fetal alcohol syndrome throughout their lifetime. Its diagnosis and management have been stablished and tailored accordingly. *Conclusion*: The mechanism behind the development of neuropsychiatric conditions is still not completely understood, however, morphological damages to certain areas of the fetal brain, as well as the dose, frequency, and trimester of alcohol consumption, can all translate into the functional problems commonly seen in those patients. So far, the traditional diagnostic criteria are still used, and the management, which involves a multidisciplinary team, varies according to each patient's specific needs.

KEYWORDS

Fetal alcohol syndrome, fetal alcohol spectrum disorder, mental health, cognitive disorders, behavioral disorders, secondary disabilities, central nervous system, alcohol, pregnancy.

INTRODUCTION

Prenatal alcohol exposure (PAE) is considered one of the major avoidable causes of developmental disruption and health abnormalities in children worldwide (1). It may lead to irreversible impairments of cognition, development, and behavior, which is, in turn, called fetal alcohol spectrum disorder (FASD), an umbrella term that encompasses other conditions such as partial fetal alcohol syndrome (PFAS), alcohol-related birth defects (ARBD) and alcohol-related neurodevelopmental disorder (ARND). All the terms mentioned, develop as a result of fetal exposure to alcohol during the gestational period, however, they do not present all the required criteria to be diagnosed as fetal alcohol syndrome (FAS) (2).

FAS, in turn, is the most severe presentation of the spectrum, as it requires specific facial dysmorphologies, CNS dysfunctions (both morphological and functional), and growth deficiency to be confirmed (3). Nevertheless, the greater consequences faced by individuals with FAS are thought to arise from the cognitive, behavioral, and mental issues commonly observed in these patients (4). Research is increasingly trying to understand the pathophysiology behind prenatal fetal contact with alcohol and such neuro disruptions, however, a conclusive explanation has not been reached yet.

In fact, several factors are thought to influence determining the extent and severity of alcohol's damage to the developing brain of the fetus. For instance, studies have associated the level of drinking and the trimester of pregnancy to play an important role in the final detrimental aspects of the syndrome, but the specific threshold capable of causing teratogenic effects is currently undetermined (5)(6).

Regarding diagnosis, clinical observations have suggested that early detection is a significant protective factor against secondary mental issues. In addition, given that there is no definitive cure for FAS, the earlier the management begins, the greater the chances of a positive outcome. However, alcohol-related disorders are frequently underdiagnosed because the specific pattern of physical features is usually not entirely displayed, besides, the psychological deficits often vary, and might overlap with other cognitive or mental health issues. Consequently, this prevents affected patients from receiving adequate interventions at early ages, which potentially increases their chances of facing greater difficulties during their lifetime (7).

HISTORY

Alcohol drinking has been referred as an ordinary habit that perpetuates in our society since the most primordial periods. Several sources, dated from as early as the ancient Greek times, until the advent of modern medicine, report its consumption to be questionable due to the possible effects that could be caused to the fetus. That being said, it is surprising that for quite a long time there were hardly any clinical studies designed to scientifically prove the correlation between alcohol intake during the gestational period, and its long-dated impacts on the mental health of the expected child throughout his/her life. In 1899 female alcohol abuse was linked and documented for the first time to fetal negative outcomes (8), and only 49 years ago the term Fetal Alcohol Syndrome (FAS) was officially introduced (9).

Contraindications regarding antenatal consumption of alcohol from ancient Greek writings suggest that the link between drinking and fetal development was somehow understood back

in the 4th century BC. Plato's Laws dialogue stressed: '… it is not right that procreation should be the work of bodies dissolved by excess of wine, but rather that the embryo should be compacted firmly, steadily and quietly in the womb' (Plato, reprinted 1952, 6, 775c–d) (10). Although it seems like they had some awareness, it was believed that drinking affected mostly the male body, therefore to prevent offspring anomalies, paternal alcohol intake should be strongly avoided.

Unlike, in 1899 Dr. William Sullivan, conducted a study with the female population of Liverpool prison to observe the prevalence of infant mortality associated with mothers whose alcohol intoxication was noted throughout pregnancy. During the participant's selection, efforts were made to exclude cases in which alcoholism occurred concomitantly with another degenerative diseases. The results showed that out of 120 women's offspring, 44.2% lived over two years of age while 55.8% died under two years or were dead born. Provided that, the study concluded not only that maternal alcoholism was unfavorable to the fetus's viability, but also that its impact was more significant than that of the paternal side (11).

Likewise, in a nursery home back in 1957, the French pediatrician Jacqueline Rouquette organized a study with 100 children. Out of them, 28 were born to alcoholic mothers, 42 to alcoholic fathers, and the 30 remaining children were born to both alcoholic parents. It was noticed that the majority of children who presented with low birth weight, delayed growth, and severe intellectual disability, were especially linked to maternal exposure to alcohol. Furthermore, Rouquette added: "the alcoholic infant's portrait the head is often small the nose is turned up, its root flat the upper lip is short and retracted, a frontal angioma persists during the first months the infant is irritable, its movements jerky and awkward (postnatal) growth is severely retarded" (14).

A few years later, in 1968 Lemoine and coworkers published a study in which chronic maternal alcoholism was deemed to have teratogenic effects for the embryo. He described four specific alcohol-induced findings: growth retardation, facial anomalies, central nervous system issues, and malformations (visceral, heart, and limbs) (15). Despite their efforts, this study neither reached enough attention from the international medical community nor contributed to the scope of public health awareness policies.

Finally, in 1973 Jones and coworkers introduced the name fetal alcohol syndrome (FAS) through a published scientific report, in which eight children of different ethnic backgrounds were evaluated. They were all born to mothers whose alcohol consumption level during

pregnancy was exaggerated. Surprisingly, a specific pattern was observed in those children: cardiovascular defects, brain structure defects, facial and limb anomalies, associated with antenatal growth retardation, and delayed development (9).

Since the reports published by Lemoine et al. and Jones et. al, a number of other studies have successfully documented that maternal alcohol consumption can cause a constellation of abnormalities and disabilities for the developing fetus. Remarkably, a few studies were conducted particularly aiming to investigate those impacts on mental health. For instance, the results from a study performed in 1988, suggested that patients diagnosed with FAS are likely to have some mental disorders. In this analysis, 25 patients underwent a coordinated clinical interview to illustrate the type and frequency of mental issues they had. It was found that out of them, 15 patients had alcohol/drug dependence and 11 had depression (16).

At present, the harmful effects caused by alcohol are known to encompass a broad range of conditions including neurobehavioral, neurodevelopmental, neurocognitive, and physical problems. Such conditions are grouped under the umbrella term Fetal alcohol spectrum disorders (FASDs), and Fetal Alcohol Syndrome is the most severe of them (17). Currently, FAS is the only form of gestational alcohol consumption outcome officially seen as an ICD-10 diagnosis.

Overall, due to the awareness raised by studies and clinical experience, nowadays it is notable that mothers are strongly recommended to abstain from alcohol during gestation, not only because of the morphological impairments that might be caused to the fetus, but also taking into account the possible long-lasting mental health issues that could potentially threaten the quality of life of children and their families.

CLINICAL PRESENTATION

Alcohol is known to provoke devastating consequences to the physical and neural development of the fetus if consumed during the gestational period. Growth retardation and craniofacial abnormalities represent two fundamental criteria for the recognition of FAS. Moreover, CNS damage, both structurally and functionally is regularly seen, and their effects can lead to cognitive, behavioral, and developmental patterns of manifestation co mpatible with mental health conditions. These presentations can differ along with the lifespan, as well as range from milder to more severe; and they tend to persist into adulthood, which over time combined with environmental factors may potentially lead to secondary disabilities (18).

Children born to mothers who ingested alcoholic beverages during pregnancy, frequently display growth deficiency, manifested as weight or height/length restriction, detected either prenatally or directly after birth. Several studies have attempted to investigate the trajectory of growth of FAS children, whereas some suggest they catch up along the aging process (19), while others believe such deficiency to be long-lasting. For instance, a study conducted with ninety-four heavy drinking women compared to sixty-three controls, found out that more than 50% of alcohol-exposed kids were small for gestational age at birth, compared to less than 20% of control participants. In addition, out of the 18 children classified as having restricted growth without catch-up through age 13, seventeen were heavily exposed to alcohol in contrast to only one from the control group. In essence, the results of this research evidenced that a significant percentage of FAS-diagnosed children exhibit retarded intrauterine growth that is not compensated throughout maturation; besides, it was also noticed that the kids with persistent undergrowth are at particularly greater risk of developing neurocognitive disabilities (20).

Although craniofacial dysmorphologies have been considered as one of the key clinical presentations of FAS, only a small proportion of affected kids, teenagers, and adults are identifiable due to their atypical face features (18). The three main facial characteristics observed are: short palpebral fissure, thin upper lip, and smooth philtrum. Their expression magnitude may vary, especially in older patients, as these facial elements tend to diminish over time. Less often, other anomalies such as strabismus, ptosis, microphthalmia, and midface hypoplasia can also be seen, however, they are not regarded as pathognomonic for FAS (21). At the structural central nervous system level, the most common abnormality found is decreased head circumference, which possibly indicates microcephaly, and is detected right after birth (22). Interestingly, a linear correlation was found between the severity of dysmorphic features and the degree of CNS damage (18).

Notwithstanding, the impacts of prenatal alcohol exposure to CNS escalate further beyond morphological damages. In fact, they encompass a constellation of functional alterations resulting in neuropsychiatric disabilities, that unlike dysmorphic abnormalities, which are thought to become less apparent with age, they are generally persistent and may progress (4). Furthermore, such disabilities affect both children, and adults, as reported by Lemoine et al., whose research suggested mental health to be the most severe characteristic of FAS during adulthood (4,15). Although efforts have been made to standardize the "psychological/psychiatric manifestations" of FAS, studies have shown that individuals exhibit a set of different presentations, which may vary in severity, type, time of onset, etc.

Executive functions are a set of cognitive skills involved in behavior controlling and management (23). FAS patients have been reported to frequently present impairments in areas of executive functioning, such as planning and strategy use, verbal reasoning, cognitive flexibility, fluency, inhibition, working memory, set-shifting, and emotion-related learning. For instance, a study recruited two groups of children, the first group had a diagnosis of FAS/partial FAS, and the second was healthy controls with no exposure to alcohol. All participants were assessed on cognitive flexibility, response inhibition, planning ability, concept formation, and verbal reasoning, but the first group showed a reduction in all assessed executive functions compared to the second group (24). Furthermore, Schonfeld et al. conducted a study aimed at gaining insight into fluency deficits, in both verbal and nonverbal domains, among controls and children whose mothers were heavy drinkers during pregnancy. As expected, their performance was lower, thereby it was concluded that such children appear to be particularly susceptible to disruptions in the fluency area of executive functions (25).

Other cognitive abilities have also been well documented to show clinical signs of impairment, and it was noticed that one deficit may aggravate another. Children experience the most significant problems in the following areas: intelligence, language, attention, memory, learning, general cognitive performance, visual-spatial perception, social ability, and emotional processing. Intellectual disability is commonly assessed through a standardized test of intelligence quotient (IQ), which has demonstrated below-average marks (around 70) for children with FAS, although not all of them suffer from it (26). Regarding language competence, the most frequent impairments observed are speech problems and delays, comprehension difficulties, reduced capacity to process and store linguistic elements, and semantics confusion (27). Likewise, impairment in verbal memory is also detected, and since it is interconnected to learning, individuals with FAS may lack the capacity of learning and retrieving information from long-term memory (18). Further, kids may struggle to recall formerly viewed spatial arrangements and wrongly describe them, thus characterizing disabilities in space perception and recalling. Moreover, caretakers have reported disruptions in social cognition and emotional recognition, that are thought to be attributed to language and executive functions disabilities, which could lead to unstable interpersonal relationships and poor social skills for individuals in the future (18,28). Overall, cognitive functions impairments are known to persist into adulthood, thus negatively influencing the mental health of patients and their quality of life.

Motor functioning, which is subclassified into fine and gross skills, reflects one more sphere of development that shows signs of delay due to prenatal alcohol exposure. Deficits in fine motor skills may hinder basic everyday activities such as grasping an object or teeth brushing, while imbalance, unusual gait, and posture may be disturbed by underdeveloped gross motor skills. Children with FAS present impairments in both skills; however, the most severe and frequent issues are significantly more expressed in fine motor skills (26,29). Furthermore, oculomotor dysfunction has also been seen in FAS patients; it causes reduced control of eye movements and consequently increased mistakes on visual tasks (18).

The most often recognized behavioral disorder in fetal alcohol syndrome is attention deficit hyperactivity disorder (ADHD) (30). Research evidenced that males are affected more often than females (31). Notably, children start manifesting symptoms during infancy, that become apparent as sleep disturbances, excessive crying, and dysphagia. As they age, the presentation translates into hyperactivity, lack of concentration, impulsivity, and poor performance at school. Once they reach adolescence and adulthood, hyperactivity may ease, and the main concern goes to impulsivity and the inability to concentrate for long periods (18).

Individuals diagnosed with FAS are known to be lifelong affected, and its cluster of presentations may vary according to each developmental stage along with the lifespan. In infancy, apart from the symptoms already mentioned previously, newborns may display signs of alcohol withdrawal (i.e.: irritability, tremors, agitation), muscle hypotonia, and greater susceptibility to infections. In preschool age, developmental delays such as lack of weight/height gain, abnormal social interaction, hyperactivity, and poor language skills are the most common presented signs. At school age, frequently reported problems are impulsivity, aggressiveness, poor memory, short attention span, and no sense of space and time. During late childhood and adolescence, if FAS has not been diagnosed yet, the presented clinical signs (e.g.: less pronounced face dysmorphology, school failure, inappropriate sexual behavior, criminal behavior, lack of independency) might not be interpreted as a result of prenatal alcohol exposure, and teenagers tend to become increasingly isolated from their peers and to deny support. For adults, despite the reduced presentation of clinical symptoms, they still show signs of behavioral and intellectual issues, mostly accompanied by secondary disabilities (18).

In fact, secondary disabilities as suggested by the name, are not directly caused by prenatal alcohol injury, but instead are the result of different interactions between primary disabilities (e.g.: low IQ, poor reading/spelling skills, etc) and environment (4). Mental health disorders

are by far the most predominant secondary disability found in FAS, with depression occurring in at least 50% of adult patients. Further psychiatric problems encountered are: suicide threats, panic attacks, psychotic behavior, conduct problems, anxiety, and alcohol/drug addiction (4,32). In addition, other common issues have been documented including disrupted school experience, trouble with the law, confinement, inappropriate sexual behaviors, dependent living, and problems with employment (33).

Overall, adults and children diagnosed with FAS present with both physical and neural disturbances. What can be suggested based on evidence, is that those presenting with the classical phenotypical signs are simply the tip of the iceberg, as such symptoms are thought to regress over time. However, the cognitive and behavioral manifestations are commonly persistent; although they differ individually, depending on genetic inclination, period of exposition, and dosage, their effects are claimed to cause life-long primary and secondary disabling consequences, which can drastically reduce the quality of life of FAS individuals.

MECHANISM AND PATHOLOGY

Level of alcohol consumption and risk/severity of FAS

Ever since the first correlations between prenatal alcohol exposure and subsequent fetal damage, the quantity of alcohol that is safe to ingest has been under discussion. Up to now, several studies have successfully linked the most negative outcomes to be a result of maternal heavy and/or binge drinking (5), however, the effects of low to moderate alcohol use are still surrounded by conflicting speculations. For this reason, the current guidance recommends women to abstain completely from drinking during pregnancy, as no safe amount has been revealed so far (22).

For instance, the results of a meta-analysis showed that heavy consumption of alcoholic drinks is associated with increased risk of small size for gestational age, preterm, and low birth weight; while low consumption did not seem to affect such outcomes (5). On the other hand, another study compared the effects of maternal light drinking (i.e., up to ~32 g/week) with absolute abstaining during pregnancy, and a 10% increased risk of premature delivery was found among the mothers who consumed alcohol (34). In essence, it could be said that both studies showed that low consumption appears to add up little value to the risk of detrimental fetal effects, however, such evidence is inconclusive, therefore this should not encourage women to drink at these levels during gestation (35).

Another meta-analysis reviewed searches regarding the effects of gestational binge drinking on the neuropsychological development. Binge alcohol consumption was defined as having 4 drinks or more per occasion, and its consequences were strongly associated with dysfunction in diverse aspects of cognition among children from 6 months through 14 years old, although such dysfunctions are thought to extend to older children and adults as well (36).

As expected, the consequences of drinking escalate further beyond when larger amounts are consumed, and it is well known that heavy drinking can cause serious outcomes to the neuro and physical development of the exposed children. The distinction between low consumption and abstinence seems to be the most misunderstood point, which leads to confusion for both pregnant women and health workers. This contributes to unreliable guidance, given that there is no consensus regarding the safe level of alcohol intake during pregnancy (37). For this reason, even though little evidence has correlated light consumption to adverse outcomes, complete abstinence from alcohol should be recommended to all pregnant women without distinction.

Trimester related alcohol damage

The extent to which alcohol affects fetus has been largely attributed to the time during pregnancy that maternal drinking occurs. Throughout the three trimesters, different parts of the body and brain might be irreversibly damaged depending on their current developmental stage. For this reason, some studies have tried to examine the pattern of malformations found in FAS and their correlation with the timing of alcohol exposure, as well as other additional factors that could potentialize those negative outcomes.

Fetal organs and organ systems are known to follow a gradual development timeline, alcohol consumption during the first trimester, for instance, can lead to serious adversities especially in the face and brain, such as microcephaly during early embryogenesis (4^{th} week of gestation) (38) (6). Other physical anomalies have also been reported to happen onward the first three months, such as congenital heart defects and cleft palate (18). Nevertheless, since most pregnancies are discovered around the 8^{th} week, it is important to notice that damage at this period could occur even before gestation is confirmed.

High amounts of alcohol consumption during the second trimester are related to an increased incidence of miscarriage (39). Moreover, concerns are also directed at the brain growth sprout that is thought to initiate around the $25\text{-}26^{th}$ week of pregnancy and extend into the postnatal period. During this phase, recently differentiated neurons involved in synaptogenesis are highly

vulnerable to damage from external factors, like alcohol, nicotine, and other drugs (40). Thereby, they could induce exaggerated apoptosis and end up causing some of the neuro-morphological and neurocognitive disorders observed in FAS (41).

During the third trimester, fetal growth and weight are not completely developed yet, therefore alcohol intake could impair their normal maturation process (39). Furthermore, damage to different brain structures such as the prefrontal cortex, hippocampus, and cerebellum have been linked to neuropsychiatric deficits (42), and some studies have pointed them to be at particular risk across the last months of intrauterine development.

Based on the findings correlating the physical and neurological issues, and the timing of fetal alcohol exposure met in children and adults with FAS, it can be argued that the degree of damage is associated with the maturation process happening in the fetus during the time of exposure. However, the fetal brain is claimed to be the main target of alcohol teratogenicity during all gestational periods. Yet, it is still debatable how other factors such as nutrition, drugs consumption, and genetics could potentialize the final adverse outcomes, therefore full alcohol withdrawal is highly recommended during pregnancy.

Pathophysiology of fetal alcohol toxicity

Alcohol itself, as well as its metabolites, are teratogenic agents known to interfere with the pathophysiology of embryogenesis, as demonstrated in multiple animal and human studies (43). Fetal alcohol syndrome, in turn, is established to be caused as a result of maternal alcohol intake during gestational period. Its pharmacokinetic effects on the placenta (44), amniotic fluid, and liver of embryo/fetus are postulated to be significantly important, since it may explain to a certain extent, the reason why there is such a great variability between the toxic response alcohol cause to fetal organism, particularly the central nervous system, when compared to adults.

First, the placenta of humans contains small amounts of one isoenzyme of alcohol dehydrogenase, which is responsible for catalyzing the oxidation of alcohols (44). This enzyme when found in the placenta, is able to oxidize ethanol and its noxious metabolites, such as acetaldehyde, if their concentrations are highly detectable (43). Yet, the action of alcohol dehydrogenase was found to be so slow that its relevance to pregnant women is nearly nonexistent, thereby alcohol can be almost freely transferred from the mother through the placental barrier, reach fetal compartment, and ultimately disrupt the regular development and organization of fetal systems, at a cellular level (44).

Second, amniotic fluid is constantly in contact with the fetus throughout pregnancy. Apart from serving as physical space for the fetus to move, its swallowing and breathing also contribute to gastrointestinal tract and lungs development, respectively (45). In the setting of fetal alcohol syndrome, amniotic fluid is thought to act as a potential reservoir for alcohol and its end products (43). Notably, one study was conducted to clarify the disposition of ethanol and acetaldehyde in the amniotic fluid, as well as in the venous blood of six healthy pregnant women between the 16^{th} and 18^{th} weeks of gestation (46). The concentration of ethanol was analyzed 3.5 hours after ingestion of 0.3 gm/kg, and it was noticed that even though there was hardly any detectable ethanol in maternal venous blood, its level was still measurable in amniotic fluid. Likewise, the elimination rate of this substance from venous blood was twice as fast as its elimination rate from amniotic fluid. Moreover, acetaldehyde was found in the amniotic fluid of one out of the six women participating in the research, and its detected levels were higher than in blood (46). Hence, the findings of this study suggest that despite the presumed efficient metabolism of ethanol in pregnant women (43), alcohol concentration persists for longer periods in amniotic fluid than it would in maternal venous blood. Consequently, the fetus is exposed to such a hazardous environment for a prolonged time (46), which could likely be a risk factor for the incidence of developmental abnormalities.

Third, alcohol elimination from fetal system is particularly challenging due to their decreased hepatic metabolic capacity, which ranges from 5% to 10% of a healthy adult's capability (47). Ethanol metabolism is accomplished in two different ways: by both alcohol dehydrogenase (ADH) plus cytochrome P450 2E1(CYP2E1) and minimally by catalase (CAT) (48). Several studies have shown that such enzymes are not present during the first weeks of fetal life, whereas CYP2E1 starts to show signs of activity from the 16^{th} week, and ADH only from the 26^{th} week (33). Notwithstanding, their levels are much lower than in grownups (48). Due to all these factors, fetal liver is unable to efficiently act as a detoxifying organ, which leads to accumulation and subsequently increased concentration of ethanol in the fetal surroundings. In effect, the role of cleaning up fetal systems from alcohol and its metabolites, remains predominantly dependent on maternal metabolic capacity (47).

Overall, following maternal ingestion of alcohol, it travels almost freely from mother's circulation into fetal circulation through placenta. Once mixed with amniotic fluid, ethanol and its end products are kept recirculating in and out of fetal system, via swallowing, breathing, and urinating. Moreover, alcohol metabolic clearance of the fetus is decreased compared to adults, not only due to delayed liver enzymes activation, but also due to their significantly low

levels. Despite such findings, mainly because of ethical reasons, nowadays there is not enough evidence to fully clarify the pathophysiology behind the adversities caused by FAS.

Mechanism of alcohol toxicity to fetal central nervous system

Alcohol constitutes an important set of negative irreversible consequences to the normal maturation of fetus's nervous system. The processes by which this agent causes the specific adversities found in fetal alcohol syndrome are not completely understood yet, but some studies have suggested a few mechanisms to be involved (50) including neuroimmune activation (51), abnormalities in glial cells (52), oxidative stress (53), apoptosis of neurons and oligodendroglia (40), and polymorphism of alcohol metabolizing enzymes (54,55).

Immune activation in the developing central nervous system is suggested to be provoked by maternal alcohol consumption, and its consequences could lead to mental health-related issues. Microglia, the immune cells of the CNS, are known to play a critical role in homeostasis of the brain. Differently from adult brains, proinflammatory cells produced by microglia, as cytokines and chemokines, take part in CNS development of fetus, therefore they are expressed at significantly increased levels, independently of inflammatory events. However, alcohol exposure during gestation has been proposed to interfere with the beneficial roles played by microglia, and consequently lead to neuroimmune activation. To clarify, a review analyzed correlations between animal and human models, and it was pointed out that alcohol triggers inflammation in the developing brain of rodents, which subsequently causes microglial cells activation and altered pro-inflammatory cells production. Such events have been associated to incite cognitive deficits and behavioral disorders later in life. Yet, further studies are needed to prove whether neuroimmune activation is directly linked to the mental health outcomes seen in fetal alcohol syndrome (51).

Likewise, the effects of alcohol on another glial cells during brain development have been documented. For instance, radial glial cells, precursors of oligodendrocytes and astrocytes, when damaged due to excessive prenatal alcohol exposure, may have their maturation disrupted, leading to abnormal migration of neurons and other glial cells throughout the CNS, and also impairing the normal formation of cerebral cortex. Furthermore, astrocytes were suggested to cause neural loos upon decreased release of cerebral antioxidants and neurotrophic factors, and activation of inflammatory pathways. Oligodendrocytes, in turn, are known to play a crucial role in the myelination of neuronal axons in the CNS, thereby early contact of fetus with alcohol is thought to interfere with the integrity of white matter

(myelin/oligodendrocytes), as seen in individuals who were exposed to antenatal alcohol hazards. Despite the possible links summarized in this review, there is still no defined correlation between glial cells adversities caused by alcohol exposure, and the overall mental health presentations found in children and adults diagnosed with fetal alcohol syndrome (52).

Enhanced oxidative stress is another mechanism believed to cause abnormal CNS development. Exposure to ethanol and its metabolites can generate reactive oxygen species (ROS) and creates a disbalance in the redox state of the cells, particularly in the fetal brain, since it is more sensitive to ROS than other organs. The pathway of ethanol metabolism involves mainly ADH and CYP2E1 enzymes; the latter has been detected in the brain cells of human fetuses, and it is believed to produce ROS as a side product during oxidation of ethanol. Under alcohol-free conditions, the production of ROS is equilibrated, and they can fulfill some physiological roles accordingly. But under uncontrolled production, they can oxidate and cause damage to lipids, proteins, and DNA. In the setting of CNS injury, damage to DNA can trigger apoptosis and ultimately contributes to neurodegeneration, which has been associated with decreased brain volume and cortex abnormalities. Nevertheless, this is suggested to somehow correlate to the behavioral and cognitive alternations met in patients exposed to alcohol prenatally, however, due to the non-systemically organization parameters of the studies analyzed, it has been difficult to establish a precise comparison between their results, which complicates the construction of a solid conclusion (48,53)

As previously mentioned, alcohol is claimed to prompt serious damages at a cellular level. Several animal studies have gathered evidence to support the theory that alcohol causes generalized apoptosis of nerve cells and oligodendroglia during a period equal to the third semester of human gestation. Such cell death response is suggested to change the brain formation of the developing fetus, leading to overall and regional CNS disturbances (40). For instance, a study involving infant rats (equivalent to the third trimester and onward) found that administration of high doses of alcohol during this period, could result in apoptotic degeneration of neurons, leading to potential reduction in brain mass (41). Another study has documented apoptotic reactions in the caudate and putamen structures of basal ganglia, following a single administration of alcohol in fetal monkeys throughout the third trimester (56). In addition, the area of white matter separating these two structures, called internal capsule, was also found to lose mass due to alcohol-induced apoptosis of its oligodendrocytes. In either case, focal or generalized apoptosis of brain cells is believed to highlight the

probability that alcohol is able to induce neuronal deletion, which could strongly translate into a spectrum of long-lasting neurobehavioral disorders (40).

The development of molecular science has deepened the understanding of the involvement of genetics in the mechanism of fetal alcohol syndrome. Nowadays, it is well known that the outcomes caused by alcohol do not follow a hereditary pattern of acquirement, but they arise as a consequence of early exposure of fetal brain to ethanol and its toxic metabolites. However, some studies have argued that the enzymes involved in the metabolism of alcohol seem to be coded by polymorphic genes, thus the severity of damage can be susceptible to changes depending on each individual's allelic expression. Although several classes of the enzyme alcohol dehydrogenase (ADH) have been discovered, ethanol is mostly metabolized by class I (ADH1A, ADH1B, ADH1C) and class II enzymes (ADH4). Moreover, studies have shown that ADH1B presents three different polymorphic variations, wherein ADH1B*2 was found to have the greatest binding affinity to alcohol and maximal velocity when compared to the other two allele variations. This suggests that the occurrence of ADH1B*2 allele, could result in an increased rate of ethanol metabolism, in either mother or fetus, thus providing a protective role against fetal alcohol-induced injuries. In addition, polymorphism of other genes, such as human CYP2E1 and 5-HTTLPR has been under investigation for their possible involvement with alcohol teratogenicity predisposition (54,55).

Central nervous system structural malformations

With the advances in the field of neuroimaging techniques, different modalities have been used to investigate the pattern of changes in the brain of individuals exposed to alcohol before birth (57). In fact, some studies have found variations such as shape irregularities, decreased white matter density, and surface area reductions (58) in certain areas as corpus callosum (CC), basal ganglia, hippocampus, cerebellum, and cerebral cortex. In addition, such changes are thought to be heterogeneous, thus, some areas and cell populations are found to be more vulnerable, thereby they could be more severely affected than others (57).

Corpus Callosum (CC) abnormalities have been considered a consistent sign of offspring contact with ethanol. The most commonly documented structural changes are partial and complete agenesis (59), hypoplasia, and posterior region displacement anteriorly and inferiorly (60). These structural abnormalities are thought to develop gradually, since the greater the exposure to alcohol during prenatal period, the more pronounced the expression of defects. A cross-sectional study was conducted to compare the brain structural MRI of children born to

mothers who consumed alcohol antenatally, and of children whose mothers have not consumed alcohol antenatally. Notably, a significant reduction in the midbody size of corpus callosum was found in kids who were exposed to alcohol before birth, even when they did not have the clinical phenotypical features associated with FAS (61). Likewise, another study employed diffusion tensor imaging (DTI) to analyze 6 white matter tracts of corpus callosum on 33 participants with FASD (2 static encephalopathy, 8 FAS, and 23 partial FAS) and 19 controls, with ages ranging from 10 to 17 years old. The scan findings showed that 3 posterior tracts of corpus callosum (splenium, isthmus, and posterior mid-body) displayed significant abnormalities in the individuals with FASD (62). The results of both MRI and DTI studies have great relevance in clinical backgrounds, as corpus callosum defects induced by alcohol are believed to play an important role in the development of cognitive deficits.

Basal ganglia is another area of the brain reported to be extremely sensitive to prenatal alcohol insult (58). Several research has used MRI techniques to further investigate the pattern of changes in mainly two measures of caudate structure: volume and symmetry. In particular, a study targeting to analyze brain dysmorphologies in individuals exposed to severe prenatal exposure, recruited 14 participants with FAS, 12 with PAE (prenatal alcohol exposure) and 41 controls, all within the same age group (11 to 15 years old). Upon analysis of the structural magnetic resonance images, disproportionality reduction in the basal ganglia volume, specifically in the caudate nucleus, was confirmed in the FAS group when compared to controls (63). Furthermore, an MRI study from 2010 identified asymmetrical changes in caudate of offspring whose mothers consumed light to moderate levels of alcohol at different periods of gestation. Data analyses showed that for the maternal group with a positive alcohol-use history during all three trimesters of pregnancy, there was a statistically relevant predisposition in caudate asymmetry towards the left side, compared to the group of mothers who consumed zero alcohol. Although the exact location of this change in caudate has not been identified yet, asymmetrical anomalies between interconnections can lead to disturbances in neural circuity, which could end in inadequate coordination among brain areas, and result in deficient processing speed, thus contributing to the development of neuropsychological related consequences (64).

Neuroanatomy studies have extensively attempted to recognize whether the teratogenic effects of prenatal exposure to ethanol can cause abnormalities in the shape and size of the hippocampus. However, a unique consensus has not been reached yet, and there is still ambiguity regarding the evidence found up to now. A study sought to assess regional variations

in the shape of hippocampus of 31 children, 12 diagnosed with FAS/partial FAS and 19 controls, using surface deformation-based methods that were documented through high-resolution structural MRI. The results demonstrated not only visible alterations in the shape of hippocampus between subjects diagnosed with FAS/PFAS and control group, but also the specific locations where these changes were spotted (65). Moreover, another study succeeded to document significant volume decrease in the left half of hippocampus, in 19 children diagnosed with FASD compared to 18 healthy controls (66). Conversely, this result diverges from the findings of a study published in 2001, where no signs of reduction were seen, and disproportionate sparing of hippocampus volume was found in the overall hypoplastic brain of kids presenting with FAS diagnosis criteria (63). The reason behind the disparity between the reports remains controversial, since the mechanism underlying changes in hippocampus volume are yet not completely understood. Therefore, at the present moment it is unknown whether children exposed to alcohol prenatally, display a specific pattern of hippocampal volume abnormality or not (67).

The cerebellum has also shown vulnerability to the hazardous effects of antenatal alcohol exposure. Volume reduction was suggested to be the most prominent morphological alteration found in the cerebellum of individuals diagnosed with FAS. A study recruited 17 children with a mean age of 13 years old, whose 5 kids had exposure to heavy maternal alcohol ingestion limited to the first trimester of pregnancy; 4 kids were exposed during the first and second trimester; and 8 kids were exposed all over the three trimesters. Hypoplasia of variable severity in the cerebellar vermis was the most common visual finding, and it was observed in 10 children in total (68). This was not the first time that such finding had been reported; in 1996 Sowell et. al were the pioneers to publish a work, developed with human models of children exposed to large amounts of alcohol prenatally, that successfully documented a significant decrease in size of the anterior region of vermis compared to controls (69). Besides, following this pattern, more recent studies have found significant displacement in the superior and anterior edges of the anterior vermis in subjects diagnosed with FAS (58). Indeed, volume reduction of cerebellum is such a remarkable finding that its degree of hypoplasia has been suggested to exceed the degree found in cerebral areas (63). Furthermore, other dysmorphic changes, such as decreased cerebellar surface area (70), have also been detected in a great number of individuals whose mothers consumed alcohol during pregnancy, and their consequences can cause serious outcomes to the affected children and adults.

The cerebral cortex seems to be another target of alcohol teratogenesis. Numerous studies have tried to recognize the degree, and types of damage granted to cortical morphology, and in fact, some patterns have been named, but the most frequent documented changes refer to cortex volume, composition, and shape. To start with, volumetric alterations of the cerebral cortex have been suggested to preferentially affect some specific areas, however, there are controversies regarding such changes, since both increase and decrease in cortical thickness have been reported. Notably, a study was conducted a decade ago aiming to examine the pattern of hypoplasia noticed in the brain of young adults exposed to alcohol before birth. Structural MRI images of the brain were automatically segmented into 68 cortical regions of interest, and subsequently evaluated through both parametric and group difference approaches. Following normalization by the whole brain volume, several zones of the temporal and occipital lobes exhibited volume reduction in the group of difference approaches (71). Similarly, during the course of a study to comprehend the dysmorphologies among adolescents who were also exposed to alcohol prenatally, Archibald et al. revealed that compared to controls, the parietal lobe of individuals with FAS was found to be disproportionately reduced in volume (63). Additionally, newer research from 2009 divided children with FASD into four distinct groups, according to their spectrum subclassification: FAS/Partial FAS, Static Encephalopathy/Alcohol Exposed, Neurobehavioral Disorder/Alcohol Exposed, and healthy participants. The most notable discovery was a considerable decrease in relative and absolute volume of the frontal lobe in children diagnosed with fetal alcohol syndrome and partial FAS, in comparison to the other groups (72). On the other hand, some studies have found results that contradict the ones described above. For instance, increased cortical thickness has also been documented in the lateral brain surface in frontal, temporal, occipital, and parietal lobes of subjects with FAS when compared to controls (73), and it is likely indicative of brain immaturity, given that the cortex has been ordinarily observed to thin throughout the development of healthy children (67). Regarding the composition of the cerebral cortex, further studies have gathered evidence that shows severe reduction in the white matter located at the parietal lobe in participants with FAS. This could be a result of unorganized myelination, or damage to precursor radial glial cells, which would end up causing dysmorphologies to white matter regions in the brain (63). Lastly, decreased gyrification in fetal alcohol syndrome kids was documented by De Guio et al. Such reduction in cortical folding was surprisingly found to not be attributed uniquely to the generalized microcephaly commonly seen in FAS, since it could happen even in the absence of global reduced cerebral volume (74).

The advances in the field of neuroimaging, especially structural MRI, have contributed to further the perceptions about the influence of maternal drinking on central nervous system morphology development. Based on the identified causal links between FAS and cerebral malformations presented in the studies mentioned in this subtopic, it is notorious that brain volume of fetus seems to be the main target of alcohol, and its effects are translated into generalized and regional hypoplasia, with some areas and lobes showing greater vulnerability than others. Such alternations require further investigations to be clearly addressed to a specific functional abnormality, however its impacts may be the likely neural substrate for various mental deficits found in individuals diagnosed with FAS.

Central nervous system functional disorders

Fetal alcohol syndrome, as well as overall fetal exposure to alcohol during gestation have been proved to cause neuro-morphological damages. So far, most of the evidence has shown that interactions between factors as genetics, exposure time and dose are also extremely relevant to determine the resulting functional disorder caused to the developing fetal brain. Despite that, further investigations have focused on trying to link how those specific structural changes are associated to some of the behavioral, cognitive, and mental disturbances commonly presented by patients with FAS.

Abnormal morphology of corpus callosum, which greatly differs among affected individuals, has been implicated in neuropsychological deficits. For instance, agenesis is linked to contributing to poor bimanual coordination and executive function deficits. While hypoplasia, disturbs both cognitive competencies and motor functions, depending on what part of CC is dysmorphic. Defects in midbody and splenium, have been considered targets for the maldevelopment of somatosensory perception and motor visual coordination (51). In addition, the degree of CC displacement has been associated with verbal learning ability impairments (60).

Children and adults diagnosed with FAS often present signs of memory deficits. Based on animal and human studies, most of those problems have been correlated to hippocampus insult, particularly loss of its volume (66). Declarative memory seems to be affected more frequently, therefore restraining various everyday processes that depend on conscious recollection of information, experiences and concepts. Indeed, some studies have suggested that the degree of memory deficit is proportional to the amount of hippocampal volume reduction in humans (30). Moreover, damages to the right hippocampal area have been linked to spatial deficits seen in

kids, since these deficits were also exhibited by patients with non-alcohol-related lesions in the same area (66,75).

As one of the most susceptible regions of the CNS to alcohol toxicity, it is expected that cerebellar damage contributes to the serious negative outcomes in the setting of neuro-related disabilities. Given that motor functions as posture, coordination, and balance are controlled by the cerebellum, its volume decrease may help to understand how such structural change connects to the motor dysfunctions commonly observed in FAS individuals (58). Moreover, the impairments in classical coordinated eyeblink response seen in children, are also attributed to cerebellar structural damages (52). As well as memory and verbal learning deficits, which are associated with displacement of the anterior vermis of cerebellum (67).

MRI investigations have reported a disproportionate reduction in basal ganglia volume, particularly in the caudate nucleus. This abnormality can disrupt the general network between cerebral regions that are known to play a role in higher cognitive functions, and ultimately affect the speed of processing. This in turn, has the potential to negatively influence some of the executive functions that require high involvement of processing speed in order to keep operating (64). Children with FAS are observed to manifest particular difficulties with such functions as well as lower processing speed, and attention deficits, compared to other healthy groups (76). In part, this could enlighten one of the reasons behind the poor performance at school and later on in life, displayed by those who were exposed to alcohol prenatally.

Cerebral cortex is associated with complex mental capabilities in the human brain, and a variety of disabilities can result from alcohol-related injuries. Pediatric patients with FAS often demonstrate troubles with behavioral control, executive functions, and response inhibition, all of which are known to be directly related to frontal lobe functioning (77). In terms of cortical thickness, increase in right dorsal frontal areas and left occipital areas, have been associated with verbal recalling impairment and visuospatial functioning, respectively (73). Moreover, global white matter changes have recently been linked to dysfunctions in different behavioral spheres including arithmetical abilities, intelligence, and working memory (30).

Depression and anxiety are secondary disabilities linked to dysregulated hypothalamic–pituitary–adrenal (HPA) axis. Likewise, prenatal alcohol exposure has been demonstrated to increase HPA tone, and cause axis dysregulation across life. As depression and anxiety are frequently encountered in patients with FAS, some studies have hypothesized that fetal programming of the HPA axis modifies some mechanisms of neuroadaptation to stress, which

consequently might lead to early enhanced susceptibility to future life stressors, thus increasing the vulnerability to those depressive and anxiety disorders throughout life (78).

In general, understanding the connections between structural alcohol-related brain damage, and its subsequent outcomes to neuropsychology of individuals, is critical for discriminating the impairments caused by FAS from those caused by other disorders. Despite numerous studies aiming to clarify this matter, the links observed so far are diverse, and might occur in widespread regions of the brain. Some areas have been observed more frequently than others, but there are still no definite conclusions underlying the specific brain-damage-behavior relationship.

DIAGNOSIS

Since 1973, when the term fetal alcohol syndrome was mentioned for the first time by Jones and coworkers (9), clinical observations and other studies have established that a variety of outcomes can result from prenatal alcohol exposure. For this reason, the umbrella term FASD was created to encompass the full range of manifestations including physical, mental, behavioral, and cognitive abnormalities associated with maternal drinking during gestation (18). FAS is the most severe presentation of the spectrum, where the triad of specific facial dysmorphologies, growth retardation, and CNS dysfunctions (morphological/functional) are expressed, however its confirmation is still challenging due to lack of diagnostic precision (31).

It is recommended that FAS should be diagnosed by clinicians with vast experience in prenatal alcohol exposure, and preferentially in a multidisciplinary team setting (79). Assessment of alcohol drinking during pregnancy should be searched meticulously, this includes frequency, timing, and quantity of consumption. To obtain such data is often difficult, either due to lack of information about the birth mother, or if there is contact with her, alcohol intake is usually denied. Nevertheless, in case the characteristic triad is present, alcohol use confirmation is not needed to establish a diagnosis. However, if alcohol abstinence is confirmed, FAS suspicion can be discarded (80).

The typical facial dysmorphologies associated with FAS are short palpebral fissure (equal or below 10^{th} centile for age and racial range), smooth philtrum, and thin vermilion of the upper lip (rank 4 or 5 on a racially normed lip/philtrum guide). At least two of those three minor facial anomalies must be identified for diagnosing FAS. Prenatal and/or postnatal growth deficiency is defined as height and/or weight ≤10th centile (race and ethnicity adjusted growth curve), and it is a mandatory feature for confirming the diagnosis (3).

CNS dysfunctions can be manifested both morphologically and functionally. The former is characterized by deficient brain growth, abnormal morphogenesis, or abnormal neurophysiology, and must include at least 1 of the following: head circumference ≤10th percentile, structural brain anomalies, or recurrent nonfebrile seizures (other causes must have been excluded). The latter includes neurobehavioral impairment, and it is determined according to the age of the child with the aid of standardized testing. For children older than 3 years old and without signs of cognitive impairment, confirmation is evidenced through behavioral deficit in at least one domain ≥1.5 standard deviations (SD) below the mean in self-regulation areas, such as mood regulation impairment, impulse control, or attention deficit. For those with signs of cognitive impairment, confirmation can be evidenced in two ways: ‘‘global impairment (general conceptual ability ≥1.5 SD below the mean, or performance IQ or verbal IQ or spatial IQ ≥1.5 SD below the mean), or cognitive deficit in at least 1 domain ≥1.5 SD below the mean (executive functioning, specific learning impairment, memory impairment or visual-spatial impairment)’’. For children younger than 3 years, neurobehavioral dysfunction can be evidenced by developmental delay ≥1.5 SD below the mean (3).

Altogether, FAS is diagnosed when CNS dysfunctions, both morphological and behavioral, are detected together with specific facial features and growth retardation. The confirmation of alcohol drinking during pregnancy may be dismissed if the characteristic presentation is detected. Diagnosis signs are most detectable in patients between 4 and 14 years of age, therefore early recognition of FAS is crucial to increase the chances of successful intervention (31).

MANAGEMENT

CNS dysmorphologies and facial abnormalities encountered in patients diagnosed with FAS are known to be irreversible. For this reason, the main focus of the treatment is the neuropsychological conditions associated with prenatal alcohol exposure, as well as the prevention of secondary disorders. Factors that increase the chances of favorable outcomes should also be considered, such as early diagnosis, supportive behavior towards the child, and safe environment.

Although no medications have been created specifically targeting FAS symptoms, some studies have gathered evidence that some pharmacotherapies are beneficial to improving neuropsychological issues in this population. For instance, many children with FAS are found to meet the diagnosis criteria for ADHD, and are often treated with psychostimulant

medications such as methylphenidate or dexamphetamine (81). Some studies have suggested that such medications are effective to ameliorate hyperactivity/impulsivity and defiance/opposition symptoms, however they had no positive effects on attention-deficit (82).

In addition, a few recent studies have attempted to identify the efficacy of different approaches to addressing behavioral, cognitive, and emotional problems (80). Despite the limited data regarding this issue, some interventions have been observed, such as cognitive control therapy, which is associated with improved behavior; attention process training, as it may improve non-verbal reasoning skills and attention; and language/literacy therapy, which has been linked to increased reading spelling and pre-literacy abilities (83). Moreover, parent/caregiver education is another important domain, as it focus on enhancing the relationship between child and caregiver, positive behavior support, and psychoeducation strategies (82).

So far, FAS management is still an obstacle to health professionals in charge of such patients. Little evidence is available on how to direct recommendations for optimal treatment, therefore currently the pillars of management are based on addressing cognitive and behavioral issues, avoiding/treating secondary disorders, distributing care among a multidisciplinary team, educating patients and caregivers, and so on. It is crucial to intervene as early as possible, and to achieve that, efforts would be needed to spread awareness of maternal alcohol intake consequences, as well as more professionals should be qualified and trained in order to mitigate FAS underdiagnosis.

CONCLUSION

Maternal consumption of alcohol during pregnancy is known to have teratogen effects; the most severe presentation, known as fetal alcohol syndrome, encompasses specific dysmorphic facial traits, and growth retardation. However, the most prevalent feature seems to result from central nervous system damage (morphologically and functionally), which may manifest as cognitive, behavioral, and mental problems, and greatly vary from person to person.

The vulnerability of central nervous system structures and neuropsychological functions to alcohol is thought to be variable depending on timing, severity, and frequency of consumption. In addition, some studies indicate that a few brain areas are more commonly affected than others, therefore it could predispose to a certain pattern of changes directly linked to mental health problems.

Currently, the syndrome's management is planned by a multidisciplinary team, focusing on controlling behavioral and cognitive issues, avoiding/treating secondary mental problems, and setting favorable backgrounds to minimize adverse events. This is often done through a combination of psychopharmacological drugs (when needed), psychotherapy, patient's or patient's caregivers' education, etc. It is especially important to individualize the treatment plan, since each patient's demands are often very particular.

In conclusion, different studies have been carried out attempting to understand the impacts of fetal alcohol syndrome on central nervous system. Given that mental health issues are thought to be the most life-long disabling outcomes of this syndrome, raising awareness about the devastating consequences of fetal alcohol exposure, as well as advocating complete abstinence from alcohol during pregnancy would hold countless long-lasting benefits to the prevention and understanding of the possibilities in all spheres of the affected people's lives.

RECOMMENDATIONS

The majority of the studies have approached the consequences of prenatal alcohol exposure to mental health in the setting of fetal alcohol spectrum disorder, which encompasses different conditions associated with maternal drinking. However, limited amount of information was found targeting fetal alcohol syndrome itself and its psychiatric-related aspects such as clinical presentation, pathophysiology and management. For this reason, further research focused on patients primarily diagnosed with fetal alcohol syndrome would be beneficial to expand the comprehension about this topic.

Furthermore, the link between dosage, trimester, structural damages, and functional outcomes is another area where precise information is still insufficient. In this review some links were discussed, however future investigation is needed to clarify how those factors correlate among themselves, and to which extent they predispose to the development of mental health issues.

In addition, according to the data highlighted in this review, fetal alcohol syndrome is still underdiagnosed. One of the causes, is the strict criteria for facial dysmorphology recognition, which is commonly not fully encountered in patients despite their cognitive, behavioral and mental health issues. To address this problem, heath care practitioners, as a multidisciplinary team, could revise the current diagnostic requirements to make it more flexible and adjustable depending on each patient's presentation. Moreover, diagnosis uncertainty becomes even more challenging when combined with a lack of verified gestational alcohol intake. Based on that,

programs aiming to facilitate the detection of mothers that consumed alcohol during pregnancy could bring significant advantages.

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