Review

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The Impact of Oxidative Stress on the Epigenetics of Fetal Alcohol Spectrum Disorders

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Abstract: Fetal Alcohol Spectrum Disorders (FASD) represent a continuum of lifelong impairments resulting from prenatal exposure to alcohol, with significant global impact. The "spectrum" of disorders includes a continuum of physical, cognitive, behavioral, and developmental impairments, which can have profound and lasting effects on individuals throughout their lives impacting their health, social interactions, psychological well-being and every aspect of their lives. This narrative paper explores the intricate relationship between oxidative stress and epigenetics in FASD pathogenesis and its therapeutic implications. Oxidative stress, induced by alcohol metabolism, disrupts cellular components, particularly in the vulnerable fetal brain, leading to aberrant development. Furthermore, oxidative stress is implicated in epigenetic changes, including alterations in DNA methylation, histone modifications, and microRNA expression, which influence gene regulation in FASD patients. Moreover, mitochondrial dysfunction and neuroinflammation contribute to epigenetic changes associated with FASD. Understanding these mechanisms holds promise for targeted therapeutic interventions. This includes antioxidant supplementation and lifestyle modifications to mitigate FASD-related impairments. While preclinical studies show promise, further clinical trials are needed to validate these interventions' efficacy in improving clinical outcomes for individuals affected by FASD. This comprehensive understanding of the role of oxidative stress on epigenetics in FASD underscores the importance of multidisciplinary approaches for diagnosis, management, and prevention strategies. Continued research in this field is crucial for advancing our knowledge and developing effective interventions to address this significant public health concern.

Keywords: FASD; Epigenetics; Oxidative Stress; Antioxidants; Alcohol

1. Fetal Alcohol Spectrum Disorders (FASD)

Fetal Alcohol Spectrum Disorders (FASD) represent a spectrum of lifelong, debilitating conditions that result from prenatal exposure to alcohol [1–4]. This diverse range of disorders encompasses a continuum of physical, cognitive, behavioral, and developmental impairments, which can have profound and lasting effects on individuals throughout their lives [5–7]. The term "spectrum" reflects the wide variability in the impact of alcohol exposure on fetal development, with some individuals experiencing more severe manifestations than others. The critical period of vulnerability is during pregnancy, particularly during the first trimester when organ systems are

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rapidly developing [8]. The main risk factors for FASD are increased fetal exposure to alcohol and sustained alcohol intake during any trimester of pregnancy, genetic predisposition, maternal lower socioeconomic statuses and smoking, and paternal chronic alcohol use [9–14].

Alcohol is able to freely cross the placenta during pregnancy and enter the growing fetus through the umbilical cord, the different quantity, defense efficiency and excretion of maternal and fetal enzymes allow for alcohol to have a lengthy effect on the fetus [15]. Alcohol is a teratogen substance acting through various methods including direct damage of its metabolites, reactive oxygen species (ROS) generated as byproducts of CYP2E1, decreased endogenous antioxidant levels, mitochondrial damage, lipid peroxidation, disrupted neuronal cell-cell adhesion, placental vasoconstriction, inhibition of cofactors required for fetal growth and development and epigenetic changes (Figure 1. Alcohol interferes with the development of cells and tissues in the fetus [16]. It disrupts the process of cell division and differentiation, leading to abnormal growth and development of various organs, especially the brain. Early observations supported alcohol, rather than acetaldehyde, being the more important teratogen and specific genetic susceptibility differences to alcohol-related birth defects were found (e.g. alcohol dehydrogenase-2*3 allele protects against alcohol-related birth defects) [17].

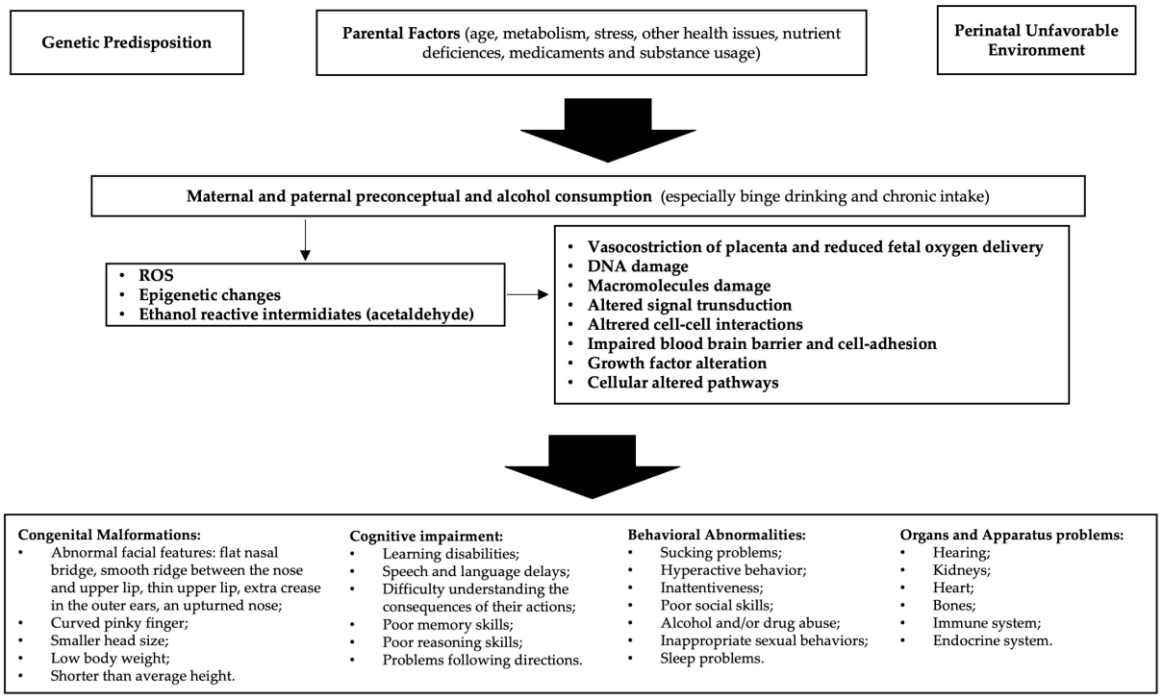

Figure 1. Etiopathogenesis of FASD: In predisposed individuals, the risk of FASD is high in the case of alcohol abuse. Decreased endogenous antioxidant levels and mitochondrial damage may result in reduced compensation for the increased reactive oxygen species (ROS) generated by alcohol metabolism. Furthermore, epigenetic changes due to oxidative stress and acetaldehyde activity lead to cellular alterations that ultimately cause manifestations of FASD. FASD stands for fetal alcohol spectrum disorders, and ROS stands for reactive oxygen species.

So, prenatal exposure to alcohol can interfere with the normal growth and development of the fetus, leading to a myriad of challenges that may manifest in infancy, childhood, adolescence, and adulthood. The severity of FASD can be influenced by factors such as the timing, amount, and pattern of alcohol consumption. Individual genetic and environmental factors also play a significant role [18]. The hallmark features of FASD include physical anomalies, cognitive deficits, and behavioral issues [19]. Physical characteristics may include facial abnormalities, growth deficiencies, and organ malformations [20]. Cognitive impairments often encompass difficulties in learning, memory, attention, and problem-solving skills [21]. Behavioral challenges can range from hyperactivity and

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impulsivity to social and emotional difficulties [22]. The intricate interplay of these components makes the diagnosis and management of FASD a complex and multidisciplinary task. Prevention is paramount, and education about the risks of alcohol consumption during pregnancy is crucial [23]. Unfortunately, FASD remain a significant public health concern globally, affecting individuals from all walks of life [19].

To address the complexities of FASD, a comprehensive approach is required. This involves collaboration among healthcare professionals, educators, policymakers, and community support systems. Early intervention and appropriate support services can enhance the quality of life for individuals with FASD, providing them with the tools they need to navigate the challenges associated with their unique conditions. As our understanding of FASD continues to evolve, ongoing research and advocacy efforts are essential to raise awareness, improve diagnostic methods, and develop effective interventions to mitigate the impact of prenatal alcohol exposure on individuals and their families.

2. FASD Epigenetics

Epigenetics, a captivating and rapidly advancing field within the realm of genetics, unveils the intricate dance between genes and the environment, fundamentally shaping the destiny of living organisms [24]. At its core, epigenetics explores the heritable changes in gene activity that occur without alterations to the underlying DNA sequence. This field revolutionizes our understanding of how external factors, spanning from lifestyle choices to environmental exposures, can imprint molecular marks on the genome, influencing gene expression and, consequently, the phenotype.

The term 'epigenetics' itself underscores the pivotal role of these processes. It translates to 'above' or 'on top of' genetics [25]. Unlike the unalterable DNA code, epigenetic modifications act as dynamic regulators, orchestrating the symphony of gene expression in response to various internal and external cues. These modifications include DNA methylation, histone modification, and non-coding RNA molecules, collectively influencing the accessibility of genes to the cellular machinery responsible for transcription [26,27]. The impact of epigenetics extends far beyond the individual organism, as these marks can be passed down through generations, heralding the era of transgenerational inheritance [4,28]. This phenomenon challenges the conventional view that genetic information flows strictly through the DNA sequence, introducing a dynamic layer of complexity to our understanding of heredity.

Consequently, the study of epigenetics not only elucidates the molecular intricacies governing development and cellular function but also sheds light on the potential intergenerational consequences of environmental exposures. In this expansive landscape, researchers delve into the epigenetic mechanisms underpinning health and disease. From the early stages of embryonic development to the intricate regulation of tissue-specific gene expression, epigenetic processes play a pivotal role in determining cellular identity and function [29]. Moreover, aberrations in epigenetic regulation have been implicated in a myriad of diseases, including cancer, neurodegenerative disorders, and metabolic conditions, providing a new avenue for therapeutic exploration. As scientists continue to unravel the epigenetic tapestry, they grapple with the ethical implications and societal ramifications of this knowledge.

The dynamic nature of epigenetic modifications prompts questions about the potential reversibility of epigenetic changes and the development of interventions to modulate these processes for therapeutic purposes [30,31]. The intersection of science, ethics, and medicine in the realm of epigenetics underscores the need for careful consideration and responsible stewardship as we navigate the uncharted territories of this revolutionary field.

The epigenetics of FASD represents a compelling area of research that delves into the molecular mechanisms underlying the long-term effects of prenatal alcohol exposure on gene regulation [32,33]. Furthermore, FASD, resulting from maternal alcohol consumption during pregnancy, encompass a range of developmental, cognitive, and behavioral abnormalities. Understanding how alcohol-induced epigenetic changes contribute to the varied and often severe phenotypic outcomes is crucial for developing targeted interventions and therapies [34–39]. Most of the studies on FASD epigenetics

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have been published in the last decades and the majority have been conducted on animal models [40]. One of the key epigenetic modifications associated with FASD is DNA methylation [15,40–42]. Studies have revealed alterations in the methylation patterns of specific genes involved in neural development and function in individuals with FASD.

For instance, genes related to neuronal migration, synaptogenesis, and neurotransmitter regulation may undergo abnormal DNA methylation, leading to disruptions in neural circuitry and function [43,44]. The dynamic nature of DNA methylation makes it a potential biomarker for assessing the severity and persistence of FASD-related impairments. Histone modifications, another critical facet of epigenetics, play a role in orchestrating the three-dimensional structure of chromatin and regulating gene accessibility [45]. Prenatal alcohol exposure has been linked to changes in histone acetylation and methylation patterns, particularly in genes associated with neurodevelopment [46].

Altered histone modifications can influence the expression of genes involved in learning, memory, and behavioral regulation, contributing to the cognitive and behavioral deficits observed in individuals with FASD. Non-coding RNAs, such as microRNAs, also emerge as key players in the epigenetic landscape of FASD [47,48]. These small RNA molecules can post-transcriptionally regulate gene expression, and their dysregulation has been implicated in the pathogenesis of neurodevelopmental disorders. Studies suggest that alcohol exposure during pregnancy can disrupt the expression of specific microRNAs, potentially contributing to the aberrant gene expression patterns associated with FASD [47].

The transgenerational aspect of epigenetics adds an additional layer of complexity to the study of FASD [11,27]. Emerging evidence suggests that prenatal alcohol exposure can induce epigenetic changes that persist across generations, influencing the susceptibility of offspring to FASD-related outcomes [4]. This transgenerational epigenetic inheritance underscores the importance of considering not only the immediate consequences of prenatal alcohol exposure but also its potential impact on future generations.

Understanding the epigenetic landscape of FASD holds promise for the development of targeted interventions and therapeutic strategies. By unraveling the molecular mechanisms through which alcohol exposure induces lasting epigenetic changes, researchers aim to identify potential targets for intervention and prevention, ultimately improving the quality of life for individuals affected by FASD and potentially mitigating the risk of FASD in future generations.

3. Oxidative Stress and FASD

Alcohol causes FASD by interfering during fetal development with molecular pathways associated with increased oxidative stress, altered organ development, and change of epigenetic gene expression control [49]. Oxidative stress, characterized by an imbalance between reactive oxygen species (ROS) and the body's ability to neutralize them, plays a significant role in the pathogenesis of FASD leading to potential damage to key cellular components during the development phase of the fetus [50,51]. When alcohol is metabolized in the liver, it generates ROS as byproducts (including superoxide radicals and hydrogen peroxide), leading to elevated levels of ROS that can overwhelm the body's antioxidant defense systems and result in oxidative stress [52,53]. ROS can cause damage to cellular structures such as lipids, proteins, and DNA of developing fetal tissues, including the brain, which is particularly vulnerable to oxidative stress because of the rich lipid composition and the high metabolic rate. Furthermore, oxidative stress can impact mitochondrial function, trigger inflammatory responses and disrupt normal cellular processes, including neuronal migration, synaptogenesis, and myelination [54,55].

In fact, the fetal body has defenses against ROS. Specifically, it can produce endocrine antioxidative enzymes, such as catalase, providing critical protection. It can also activate mechanisms to repair damaged cellular and genetic components, such as oxoguanine glycosylase 1 (OGG1) activated in the case of DNA. Additionally, the fetal body can reduce the risk of damage by producing products like the fetal nuclear factor erythroid 2-related factor 2 (Nrf2), a ROS-sensing protein that upregulates an array of proteins, including antioxidative enzymes and DNA repair proteins [53].

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In particular, oxidative stress plays a major role in the epigenetic changes associated with FASDs [53,56]. In fact, it has been associated with alterations in DNA methylation patterns and miRNAs expression, as well as histone modifications shifting gene accessibility and expression in patients affected by FASD and neurodevelopmental disorders. Furthermore, as stated before, oxidative stress can directly cause damage to DNA and its components leading to mutations potentially affecting the expression of genes critical for brain development and function. Mitochondrial dysfunction also may contribute to epigenetic changes, as mitochondria play a key role in providing the intermediate metabolites necessary to generate and modify epigenetic marks in the nucleus, which in turn can regulate the expression of mitochondrial proteins [57]. In the context of FASD, neuroinflammation may contribute to epigenetic changes that modulate the expression of genes involved in neurodevelopment.

Studying the impact of oxidative stress on FASD epigenetics holds great potential for advancing our understanding of the disorder, identifying diagnostic markers, and improving the management of this incurable disease.

4. Epigenetics and Oxidative Stress

FASD risk is likely increased in children who are genetically and environmentally predisposed, especially in the case of enhanced pathways for ROS formation and/or deficient pathways for ROS detoxification or DNA repair [58].

As stated before, alcohol has the potential to alter gene expression by impacting DNA methylation processes [59,60]. This occurs by enhancing the breakdown and reduction of methyl groups, leading to the disruption of subsequent SAM-dependent transmethylation reactions in the folate pathway, which are crucial for DNA methylation [8]. Additionally, alcohol influences nucleosomal remodeling by initiating histone modifications. It also impacts the expression of microRNA. Furthermore, both maternal and paternal preconceptual alcohol exposures induce mitochondrial dysfunction and a heightened response to oxidative stress in developing organs. This is achieved by metabolizing ethanol into acetaldehyde, facilitated by enzymes like alcohol dehydrogenase, cytochrome P450-CYP2E1, or catalase [50,53,61]. This process generates ROS and reactive nitrogen species (RNS), altering the cell's internal redox balance, leading to neuronal cell death and modified gene expression due to DNA oxidation. Mitochondrial dysfunction and mitochondrial DNA (mtDNA) damage, which are also hallmarks of aging, are key events in FASD [62,63].

Indeed, alcohol can induce mtDNA damage, resulting in increased oxidative stress and alterations in the mtDNA repair protein 8-oxoguanine DNA glycosylase-1 (OGG1) [64]. Therefore, pregnancy inherently heightens susceptibility to oxidative stress, and this risk is further increased by alcohol consumption, leading to various adverse outcomes. These include impaired development, abnormal placental function, and several complications such as pre-eclampsia, recurrent pregnancy loss, fetal anomalies, intrauterine growth restriction, and, in severe cases, fetal demise [65]. In response to the uncontrolled rise in RNS/ROS levels, the body relies on trace elements involved in both non-enzymatic and enzymatic defense mechanisms.

These elements, namely copper (Cu), zinc (Zn), manganese (Mn), and selenium (Se), play a crucial role. Assessing ROS may benefit from the use of marker proteins like malondialdehyde (MDA), superoxide dismutase (SOD), glutathione peroxidase (GPx), glutathione reductase (GR), catalase (CAT), and glutathione (GSH) [66]. These markers serve as indirect indicators of the intensity of oxidative stress and can provide insights into potential pregnancy complications. Prenatal alcohol exposure can alter the Mammalian Target of Rapamycin (mTOR) signaling pathway resulting in increased oxidative stress [67]. mTOR plays a major role in modulating protein synthesis and autophagy necessary for proper fetal development. In fact, mTOR alterations have recently been implicated in FASD etiology as long-lasting effects following alcohol exposure include impaired hippocampal and synapse formation, reduced brain size, as well as cognitive, behavioral, and memory impairments [68].

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The brain is particularly susceptible to generating ROS, including superoxide anions, hydrogen peroxide, and hydroxyl radicals [69]. This susceptibility arises due to the brain's elevated metabolic rate for oxygen consumption. Its cells utilize about 20% of the oxygen consumed by the entire organism. Additionally, brain tissues contain high levels of unsaturated fatty acids, which serve as substrates for the production of ROS. Moreover, certain brain regions contain elevated levels of iron, and various neurotransmitters, such as dopamine, levodopa, serotonin, and norepinephrine, have a tendency to react spontaneously with oxygen [70].

It's important to note that antioxidant enzyme activity, including superoxide dismutase, catalase, and glutathione peroxidase, is generally lower in the brain than in organs like the liver or kidney [71,72]. Furthermore, even though oxidative stress plays a role in normal fetal development, its imbalance caused by alcohol consumption and the higher susceptibility of fetal cells leads to neurotoxic effects. Hence, antioxidants such as vitamin E, vitamin C, and glutathione play a crucial role in FASD treatment. Their ability to counteract the harmful effects of oxidative stress has the potential to mitigate or prevent some of the neurological and developmental issues caused by prenatal alcohol exposure. (Figure 2).

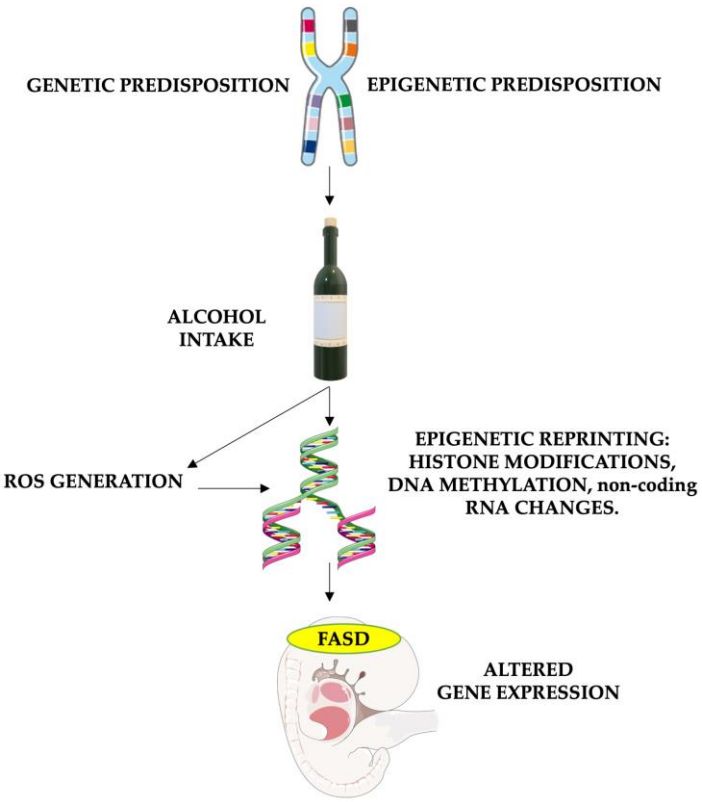

Figure 2. The Role of Oxidative Stress in Causing Epigenetic Modifications in FASD Patients: The risk of FASD is increased in children genetically and environmentally predisposed. Alcohol intake in these patients leads to particularly high damage, enhancing reactive oxygen species (ROS) formation and altering DNA repair. Furthermore, both alcohol and oxidative stress have the potential to alter gene expression by impacting histone methylation and acetylation, DNA methylation processes (through the reduction of methyl groups and disruption of SAM-dependent transmethylation reactions in the folate pathway), and non-coding RNA expression. These epigenetic changes cause altered gene expression, leading to fetal abnormalities associated with FASD. FASD stands for fetal alcohol spectrum disorders, and ROS stands for reactive oxygen species. Parts of the figure were drawn using pictures from Servier Medical Art and Microsoft PowerPoint 365 Version 2112 (https://www.microsoft.com/microsoft-365). Servier Medical Art by Servier is licensed under a Creative Commons Attribution 3.0 Unported License (https://creativecommons.org/licenses/by/3.0/).

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Ethanol-induced oxidative stress can also cause damage to DNA, resulting in genetic mutations within individual cells [58]. This damage can lead to the immortalization and multiplication of cells, potentially resulting in cancer development after birth. Alternatively, ethanol-induced oxidative stress can lead to direct or indirect alterations in the epigenetic makeup of DNA, histones, or RNA across multiple cells

These modifications can influence the expression of genes and contribute to teratogenesis, leading to birth defects and abnormalities in neurodevelopment after birth. Moreover, paternal consumption of alcohol before conception triggers epigenetic alterations in male sperm. This is facilitated by ROS generation and accelerated breakdown of substances, leading to the loss of methyl groups. These changes disrupt SAM-dependent transmethylation reactions in the folate pathway, crucial for DNA methylation. Additionally, there is restructuring of nucleosomes via modifications to histones and abnormal expression of microRNAs [4].

Research has specifically focused on several neurotransmitters, insulin resistance, alterations of the hypothalamic-pituitary-adrenal (HPA) axis, abnormal glycosylation of several proteins, oxidative stress, nutritional antioxidants, and various epigenetic factors [73]. Prenatal alcohol consumption is also associated with a widespread increase in the neuroendocrine stress response, regulated by the HPA axis [74,75]. This response influences drinking behavior and is linked to epigenetic changes in neurotrophins and POMC genes, impacting pathways that regulate mood, emotion, and serotonergic function. **R**ecent studies found a correlation between mtDNA damage and phenotypical abnormalities associated with FASD. This suggests that the amount of damaged mtDNA in fetal brain-derived exosomes may serve as a marker to predict FASD risk in fetuses [64]. Moreover, IGF-1 might reduce alcohol-caused mtDNA damage and neuronal apoptosis.

4. Therapeutic Implications

Early diagnosis and intervention can help manage the symptoms and improve the quality of life for individuals affected by FASD but a cure is not available for this disease [76,77]. Antioxidants are commonly employed to protect the fetus against ethanol teratogenicity [78,79]. Indeed, while the optimal therapeutic strategy is complete abstinence from alcohol during pregnancy, various substances have been shown to reduce the production of ROS in these patients and lessen the frequency of severe FASD manifestations[61,80–84]. On the other hand, considering that epigenetic changes are potentially reversible through pharmaceutical interventions, there is an opportunity to develop drugs targeting specific epigenetic mechanisms involved in regulating gene expression. This could have significant clinical relevance [85].

Mitigating oxidative stress through strategies like antioxidant supplementation or lifestyle modifications may potentially modulate FASD-associated epigenetic modifications, improving clinical outcomes. In a recent study, glutathione supplementation was shown to inhibit the effects of prenatal alcohol exposure. This led to improved survival, reduced incidence of morphological defects (especially congenital heart abnormalities), and prevention of global hypomethylation of DNA in heart tissues [86]. Moreover, targeting the effects of oxidative stress on epigenetics, along with the ROS-generating pathways, may offer new avenues for therapeutic interventions in FASD [87].

However, currently, the best therapeutic approach for patients affected by FASD remains unclear. It often involves prenatal administration of antioxidants, food supplements, folic acid, choline, neuroactive peptides, and neurotrophic growth factors. Studies have shown that avoiding comorbidities and addressing the family system can significantly improve the quality of life for individuals with FASD [15,88]. Moreover, many other products with antioxidant activity have been effectively tested. Particularly, those that act on the methionine metabolic cycle have taken the spotlight in recent years [89,90].

Therapies targeting specific epigenetic pathways affected by prenatal alcohol exposure may also help alleviate FASD-related impairments. Unfortunately, most evidence supporting the beneficial effects of therapeutic approaches acting on both ROS and epigenetic pathways comes from murine models, with human clinical trials still being notably scarce. Additional clinical trials are needed to determine the extent to which antioxidants contribute to mitigating FASD damage and to assess the

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actual impact of their epigenetic modulatory effects on the management and efficacy of treating these patients [81].

The role of oxidative stress on epigenetics in FASD underscores the complex interplay between environmental exposures, genetic predisposition, molecular mechanisms, and clinical outcomes. Further research in this area is necessary to fully comprehend the implications for the diagnosis, prognosis, and treatment of FASD.

5. Discussion

The primary objective of the study discussed in this paper was to explore the intricate relationship between oxidative stress and epigenetics in the pathogenesis of FASD and its therapeutic implications. FASD represents a spectrum of lifelong impairments resulting from prenatal exposure to alcohol, presenting significant challenges due to their diverse manifestations, ranging from physical abnormalities to cognitive and behavioral deficits [91]. Prenatal exposure to alcohol disrupts normal fetal development, leading to a myriad of health problems, including facial abnormalities, growth deficiencies, and organ malformations [92].

Additionally, cognitive impairments, such as difficulties in learning, memory, attention, and problem-solving skills, are common among individuals with FASD [20,93]. Behavioral challenges may include hyperactivity, impulsivity, and social/emotional difficulties. These issues not only affect the individuals with FASD but also have broader implications for their families and communities, highlighting the urgent need for effective prevention and intervention strategies. The projected lifespan for individuals with FAS is approximately 34 years (with a 95% confidence range of 31 to 37 years), with external causes contributing significantly (44%) to mortality. These external causes encompass suicide (15%), accidents (14%), and substance-related fatalities involving illegal drugs or alcohol poisoning (7%), among other factors [94].

As a safe dose of alcohol use during pregnancy has not been established, it is recommended that pregnant women abstain completely from alcohol to prevent FASD. Unfortunately, identifying women at risk remains challenging, and the diagnosis tends to be overlooked or delayed, lacking adequate public acknowledgment [51,95]. This oversight in diagnosing has substantial social and economic repercussions, escalating challenges in education, employment, and social interactions and leading to increased dependency on social services and healthcare systems [96].

Fetal cellular epigenetic mutations and susceptibility to reactive oxygen species (ROS) appear to play a major role in causing fetal changes. The molecular bases of FASD involve oxidative stress, characterized by an imbalance between ROS and antioxidant defense systems induced by alcohol metabolism. This oxidative stress leads to cellular damage, particularly in the vulnerable fetal brain, resulting in disruptions in development. Moreover, oxidative stress is implicated in epigenetic changes, including alterations in DNA methylation, histone modifications, and microRNA expression, influencing gene regulation in individuals with FASD [53,58].

These epigenetic changes can influence gene regulation, contributing to the varied phenotypic outcomes observed in individuals with FASD. It has been suggested that the risk of FASD is increased in genetically predisposed progeny, particularly in cases of heightened oxidative stress [58].

Prevention should be the primary focus to reduce this preventable disease. Unfortunately, deterrence and educational campaigns appear to have failed in definitively reducing alcohol use during pregnancy [97]. The role of oxidative stress on epigenetics in FASD has significant implications for prevention and treatment.

Early diagnosis and prompt treatment significantly enhance the quality of life for FASD patients [15]. Current treatment options for FASD involve supportive approaches such as motivational interviewing and the community-reinforcement approach. There is potential for proactive maternal nutritional intervention, including prenatal administration of antioxidant supplements, folic acid, choline, neuroactive peptides, and neurotrophic growth factors [20,98,99]. Recent suggestions indicate that targeting specific epigenetic mechanisms involved in regulating gene expression could hold significant clinical relevance for individuals with FASD [85]. Additionally, emerging epigenetic tools might be utilized as preventive, diagnostic, and therapeutic markers.

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Understanding these mechanisms presents opportunities for targeted therapeutic interventions, such as antioxidant supplementation and lifestyle modifications, to alleviate the detrimental impact of alcohol on fetal development and mitigate FASD-related impairments [86]. Further clinical trials are essential to validate the efficacy of these interventions in humans and assess their impact on epigenetic modifications associated with FASD.

6. Conclusion

In conclusion, the study of oxidative stress and epigenetics in FASD provides valuable insights into the intricate interplay between environmental exposures, genetic predisposition, molecular mechanisms, and clinical outcomes. By unraveling these mechanisms, researchers aim to develop targeted interventions and therapeutic strategies to mitigate the impact of prenatal alcohol exposure on individuals and their families. Continued research in this field is essential for advancing our understanding of FASD and for developing effective prevention and treatment approaches to address this global health challenge.

Future approaches to FASD prevention and treatment may involve multidisciplinary strategies targeting both oxidative stress and epigenetic pathways. Therapeutic interventions aimed at modulating epigenetic changes associated with prenatal alcohol exposure hold promise for improving clinical outcomes and enhancing the quality of life for individuals affected by FASD. Additionally, efforts to raise awareness, improve diagnostic methods, and develop effective interventions are essential for addressing this significant public health concern on a global scale.

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