THE ROLE OF RETINOIC ACID IN EXPLAINING THE PREVALENCE OF STRABISMUS FOR CHILDREN WITH FETAL ALCOHOL SPECTRUM DISORDER: A LITERATURE REVIEW

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ABSTRACT

Background: Fetal Alcohol Spectrum Disorder (FASD) encompasses a range of neurodevelopmental conditions caused by prenatal alcohol exposure (PAE), affecting up to 5% of the population. Among its comorbidities, strabismus– a misalignment of the eyes– shows a significantly higher prevalence in children with FASD. Retinoic acid (RA), a metabolite of vitamin A, is crucial for extraocular muscle development. PAE disrupts RA metabolism, potentially mediating the relationship between FASD and strabismus.

Aim: To elucidate the biochemical and physiological pathways linking PAE to strabismus and specifically, focusing on the role of disrupted RA metabolism and its impact on extraocular muscle development and ocular alignment.

Methods: 746 articles relating to strabismus, FASD, and RA were identified using 5 databases. Of these, 67 articles were extracted based on relevance and full-text accessibility.

Results: PAE disrupts RA metabolism through competitive inhibition, reducing RA production by up to 87% and altering RA receptor expression. These disruptions may contribute to the development of strabismus by impairing the formation of extraocular muscles and the cerebellum, as supported by findings from both animal models and human studies under FASD-like conditions.

Conclusion: The disrupted RA metabolism caused by PAE provides a plausible explanation for the increased prevalence of strabismus in children with FASD. Further research into genetic and epigenetic markers could enhance clinical assessments and promote earlier diagnosis and intervention, especially for regions with higher FASD prevalence. Understanding these mechanisms is crucial for optimizing medical interventions and mitigating the severity of outcomes following PAE.

INTRODUCTION

1.1 Fetal Alcohol Spectrum Disorder

Fetal Alcohol Spectrum Disorders (FASD) encompass a range of conditions caused by alcohol consumption during pregnancy. Although the prevalence of FASD in North America was historically estimated to be 1% of the population, including in a meta-analysis from 2016, more recent estimates indicate upwards of 5% [1–6]. This increase may be partly due to ascertainment/diagnostic bias, considering its significant growth in attention and therefore diagnosis of FASD. However, considering the worldwide increases in alcohol consumption, there may be some truth to these increases [7–9]. The well-established condition under this spectrum, Fetal Alcohol Syndrome (FAS), requires the presence of three characteristics for a clinical diagnosis: characteristic facial dysmorphology, clinically significant impairments in three domains of the central nervous system (CNS), and prenatal or postnatal growth impairment [10–12]. Unfortunately, this excludes children affected by alcohol in-utero but were otherwise categorized as undergoing 'typical development' due to the absence of characteristic FAS features. To address this, the 5th edition of the Diagnostic and Statistical Manual of Mental Disorders (DSM-5) proposed a new clarifying term for diagnosis

associated with in-utero alcohol exposure, termed Neurobehavioral Disorder Associated With Prenatal Alcohol Exposure (ND-PAE) [13–15]. This term encompasses the full range of developmental disabilities associated with exposure to alcohol in-utero even in the absence of physical atypicalities, and is one this review will focus on. A proposed criterion of ND-PAE includes "more than minimal exposure to alcohol during gestation", defined as consuming more than 13 alcoholic drinks per month of pregnancy or more than 2 alcoholic drinks in one sitting [14]. Additional criteria include exhibition of impaired neurocognitive functioning, impaired self-regulation, and impaired day-to-day adaptive functioning, all of which must be present during childhood. Considering the lack of physical dysmorphologies used to diagnose FAS, ND-PAE is often categorized as a hidden disorder, making it difficult to accurately diagnose [6,16–18]. This characteristic of ND-PAE–or FASD in general–calls for supplementary diagnostic tools to strengthen a diagnosis. For the purposes of this review, the term 'FASD' will be used predominantly, as 'ND-PAE' is a fairly new term that has not been fully implemented nor integrated into the field.

1.2 Strabismus

The eye consists of six extraocular eye muscles that control movement. The six muscles are the superior rectus (elevation), inferior rectus (depression), medial rectus (adduction/medial movement), lateral rectus (abduction/lateral movement), superior oblique (intorsion/medial rotation), and inferior oblique (extorsion/lateral rotation). Strabismus is an eye condition whereby ocular alignment is not achieved due to issues related to eye muscles [19,20]. The global prevalence of childhood strabismus varies from 1.5–3%, by factors such as age and ethnicity, with South Ethiopia reporting up to 17.9% [21–27]. The high prevalence in regions like Ethiopia aligns with the similarly high rates of FASD cases in South African populations, highlighting the possible role of ethnicity and social determinants of health on these conditions [28,29]. The four classifications of strabismus and the resulting physical manifestations are highlighted in Table 1, alongside a diagram of the eye muscles in Figure 1 [30,31].

Classification	Result	Affected Muscle(s)
Esotropia	Eye turned inward	Overaction of *medial rectus* Underaction of *lateral rectus*
Exotropia	Eye turned outward	Overaction of *lateral rectus* Underaction of *medial rectus*
Hypertropia	Eye turned upward	Overaction of *superior rectus* OR *inferior oblique* Underaction of *lateral rectus* OR *superior oblique*
Hypotropia	Eye turned downward	Overaction of *inferior rectus* OR *superior oblique* Underaction of *superior rectus* OR *inferior oblique*

Table 1. Strabismus classifications and affected eye muscles

Current statistics show a robust relationship between FASD and strabismus [16,32–34]. In a cross-sectional, observational study performed by Kavitha et al., researchers revealed that 15.97% of children without

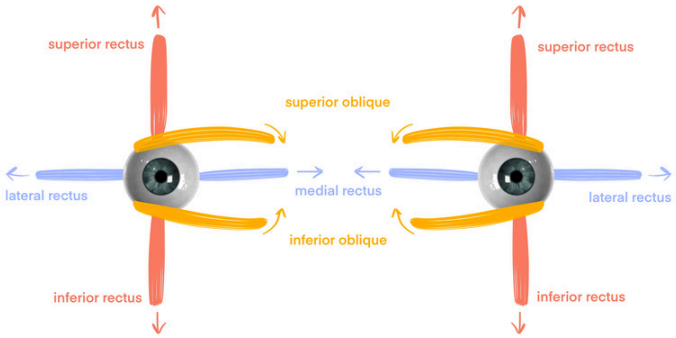

Figure 1. Muscles of the Eye

FASD had strabismus, whereas 41.49% of children with FASD had strabismus [35,36]. In one of their papers, Strömland et al. stated that alcohol was what significantly affected ocular abnormalities, like strabismus [37]. This review attempts to identify how alcohol contributes to this relationship in an effort to explain the significant correlation between FASD and strabismus.

METHODS

Multiple databases, namely Ovid MEDLINE, Ovid EMBASE, Web of Science, JSTOR, and PubMed were used to search for published academic articles in reputable journals. The majority of relevant literature was derived from Ovid as they yielded the most results. To provide an accurate review of the literature, grey literature and searches performed outside of databases were limited to the greatest extent possible unless deemed necessary for certain sections. Three clusters of keywords were used, including any associated abbreviations, truncations, and wildcards to refine the search: 1:['strabismus' OR 'cross eye'], 2:['fetal alcohol spectrum disorder' OR 'fetal alcohol syndrome' OR 'prenatal alcohol exposure'], and 3:['vitamin A' OR 'retinol' OR 'retinoic acid']. Full-text accessible articles both written and translated in English, were included. The initial searches across the databases (n=746) were condensed (n=486) by removing duplicates. Title and abstracts were screened for relevance. Studies exploring eye conditions besides strabismus were excluded, as it was beyond the scope of this review. 67 studies were ultimately selected and synthesized to inform the review, as illustrated in Figure 2.

RESULTS

3.1 Alcohol and its association with FASD

Although the dosage, timing, and duration of alcohol exposure to the prenatal environment may alter the extent of damage, it is unclear how each of these factors directly causes an outcome. Pregnant individuals are therefore strongly discouraged from consuming any amount of alcohol throughout a pregnancy. Unfortunately, the global prevalence of alcohol consumption during

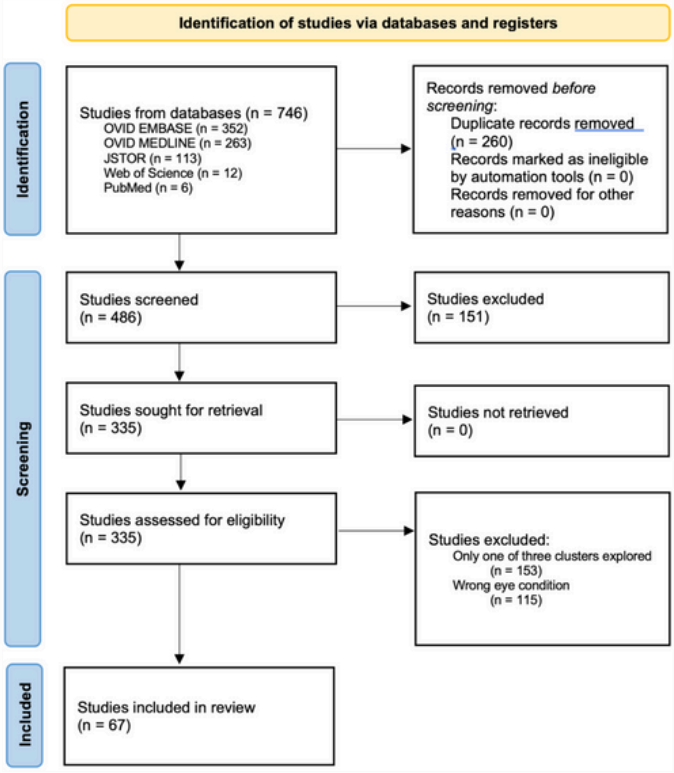

Figure 2. PRISMA flow diagram

pregnancy was estimated to be 9.8% as reported by a 2017 meta-analysis [38]. Alcohol is able to readily cross the placenta to reach the fetus, affecting fetal development [6]. In a prospective longitudinal study, researchers revealed that alcohol consumption also changes the expression of certain genes related to the growth and production of red blood cells (erythropoiesis) and blood vessels (angiogenesis), and iron homeostasis in the fetus [39]. The interference with these systems compromises proper fetal growth and neurodevelopment [40–42].

3.2 Alcohol and its association with retinoic acid levels

Retinol, commonly known as Vitamin A, was found to be a potential mediator of this relationship. The presence of alcohol arrests retinol metabolism, which may ultimately contribute to strabismus. Retinol, when metabolized, becomes Retinoic Acid (RA) using retinaldehyde as an intermediate (Figure III) [43,44]. RA regulates transcription factors, mediates embryogenesis and differentiation, develops the eye and its muscles, and acts as a morphogen that shapes the developing eye [44,45]. This metabolism is done by the enzyme Retinaldehyde Dehydrogenase (RDH). Alcohol is a potential molecule that is hypothesized to interrupt this interaction, as the ethanol in alcohol competitively inhibits RDH to convert ethanol into acetic acid instead of retinol into RA [46–48]. This is due to the similar molecular structures of retinol and ethanol. Another possible mechanism is the downregulation of the retinoic acid receptor β (RARβ) via ethanol [49–50]. Ethanol was found to change the expression of RARβ mRNA, possibly inferring that even if retinol were effectively

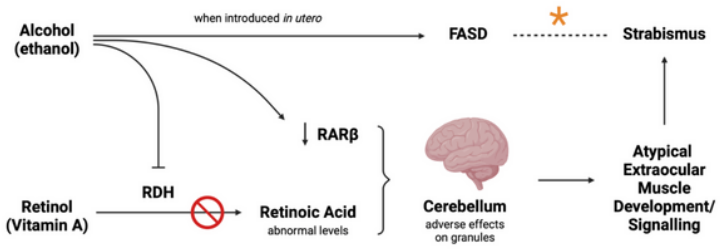

Figure 3. Visual Relationship between FASD and Strabismus (denoted by the dotted line)

converted to RA in the presence of ethanol, RA may not be able to induce adequate downstream effects due to the limited receptors.

Although the biochemical mechanism is still hypothetical, the impact of ethanol on RA levels is well-supported by the literature. Molotkov *et al*. recorded an 87% reduction in RA production when ethanol was introduced in mice, which is a significant drop [51]. Furthermore, Gray *et al*. demonstrated that, in an *in-vitro* experiment, the adverse effects of alcohol in development could be ameliorated by introducing RA into the culture [52]. Another study using rats demonstrated that alcohol consumption in pregnant mice not only decreased RA levels but increased retinol levels in the fetal heart [53]. This further supports the potential mechanism of retinol metabolism being inhibited by the presence of ethanol, therefore causing a build-up of retinol. This accumulation of retinol is also harmful to the fetus, as it is linked to developmental defects in the CNS [54–56]. In fact, a cross-sectional study found that 19% of children with FASD exhibited significantly elevated serum levels of retinol [57]. The researchers concluded these children may have a completely altered retinol metabolism, meaning the effects of prenatal alcohol exposure on a fetus' micronutrient balance may have sustained effects throughout child development. It is interesting to note that prenatal exposure to alcohol could also result in a significantly deficient serum vitamin A level, which then could also lead to developmental defects in the CNS, as presented in a case study by Goez *et al*. [58]. Perhaps this means that there is an optimal level of retinol and RA for typical development, and deviations from this optimum can have adverse effects on CNS development.

3.3 Retinoic acid levels and its association with strabismus

It has been established that ethanol exposure in the prenatal environment causes dysfunctional development of the CNS, contributing to outcomes like FASD. Of the CNS, the cerebellum, specifically the cerebellar granules, were most affected when animal models were exposed to third trimester-equivalent ethanol exposure [59]. Abnormal levels of RA, both excessive and deficient, were shown to also significantly impact cerebellar granules [60,61]. A study by Comai et al. demonstrated that RA plays a predominant role in initiating the establishment of extraocular muscles, which are

necessary for the fine displacement of the eyeball [62]. Problems and trauma to the extraocular muscles cause ocular motility disorders, like strabismus [63]. The cerebellar granules play a crucial role in eye coordination, and damage in this area can cause outcomes like strabismus. In fact, strabismus is one of the characteristic clinical features of an autosomal recessive disorder that causes degeneration of the cerebellar granules, called 'Primary Degeneration of the Granular Layer of the Cerebellum' [64]. A study by Kumar et al. confirms this relationship, as they demonstrated that high levels of ethanol affect RA receptor expression, impairing the survival and differentiation of cerebellar granules [49]. Furthermore, a systematic review of magnetic resonance imaging (MRI) studies of brains in subjects exposed to alcohol prenatally found that the physical cerebellar volume was consistently smaller when compared to controls [65–67]. In addition, lesions of the cerebellar vermin in three monkeys caused esodeviation, a loss of comitancy, and defects in phoria adaptation, which are all examples of ocular misalignments that are closely associated with strabismus [68,69]. Accordingly, it can be inferred that the cerebellum has a prominent role in ocular alignment, and therefore in preventing strabismus.

RA contributes significantly to the intricate processes of embryonic development, serving as a vital signaling molecule governing cellular differentiation and morphogenesis. An experimental research study conducted by Kahana et al. highlights the mediating behavior of RA in extraocular muscle (EOM) organization in zebrafish, supporting data from relative mammalian models [70]. Specifically, RA is observed to support the regulation of neural crest-derived periocular mesenchyme (POM), the tissue surrounding the optic cup, directing the formation of EOM-associated connective tissues [62]. The precise organization and structural integrity of EOMs, mediated by RA signaling, are essential for maintaining eye alignment during embryonic development and ensuring proper binocular vision. Consequently, disruptions in the RA signaling pathway can have profound consequences, leading to conditions impacted by the misarrangement of EOM, such as strabismus.

In a zebrafish model of FASD, Marrs et al. showed that the extent of FASD manifestations caused by ethanol could be alleviated by retinoic acid [71]. This further supports the hypothesis that retinoic acid, or the lack thereof, has a role in both strabismus and FASD, making it a prominent mediator of this relationship.

DISCUSSION

The relationship between FASD and strabismus is an important one. Although the relationship is multifaceted, elucidating these relationships can help healthcare providers, such as optometrists, ophthalmologists, and pediatricians, to accurately diagnose and inform patients of potential comorbidities. An example of this relationship in practice is the application of the FASD eye code (see below). As alluded to earlier, FASD is a hidden disorder, meaning that FASD cannot be diagnosed with a single test. There are also currently no standardized tools for FASD [72]. Instead, diagnosis is based on a combination of evidence, including the FASD eye code, whereby four vision assessments, one of them being strabismus, are completed to supplement a diagnosis. This complementary diagnostic tool for FASD was developed in 2021 by Aring *et al.*, which was demonstrated to have 38–52% sensitivity and 95–100% specificity [73,74]. Although the low sensitivity means that many true FASD cases will be missed (false negatives), its high specificity means that a positive result can be useful in ruling in FASD. Whilst the FASD eye code is helpful in theory, its practical adoption remains limited due to its novelty and the relatively low prevalence of FASD. It may be interesting to see if the FASD eye code will be implemented more effectively in regions where FASD and strabismus are significantly more prevalent, like Africa [1–6,28,29].

Clinically, these findings between FASD and strabismus highlight the importance of preventative counselling for pregnant individuals and families, particularly regarding the risks associated with PAE. Healthcare providers should receive education on the effects of disrupted RA metabolism, and its role in ocular abnormalities such as strabismus in children with FASD. Enhanced screening protocols and early intervention strategies could help reduce the developmental impact and improve long-term outcomes for affected individuals.

Moreover, incorporating FASD-related ocular conditions into medical education curricula would significantly enhance the ability of healthcare providers to identify and manage these cases effectively. Further, policy-level interventions could reinforce clinical practices by advocating for the integration of ocular screening in routine pediatric assessments. Together, these initiatives may lead to more standardized diagnostic procedures, improving both the accuracy and timeliness of FASD diagnosis and intervention.

While clinical and policy-level strategies are essential, understanding the broader genetic, environmental, and epigenetic contexts remains critical for fully addressing the complexities of FASD and strabismus. Maternal hypovitaminosis A, characterized by vitamin A deficiency, has been linked to various ocular malformations during embryonic development. The type and severity of these malformations depend on the stage of pregnancy during which the deficiency occurs [76]. Since ocular development is vulnerable to both vitamin A deficiency and PAE, findings from research in these areas may be transferable, offering deeper insights into external influences on eye development. Within the context of FASD, further research could explore how the timing and severity of alcohol exposure influences the manifestation of FASD comorbidities, such as abnormal

eye developments. It could be possible that the severity of PAE at different stages of gestation could result in a spectrum of abnormalities, ranging from complete deformation of the eyes to conditions like strabismus [77].

The nuances in the relationships between FASD and strabismus highlight its multifaceted nature. Ethanol and its effect on retinoic acid deficiency cannot be concluded as the sole factor that correlates the two. Genetic or environmental factors may predispose a child to these conditions, both pre- and post-natally, while others may possess protective factors [78]. On the other hand, epigenetic changes (alteration in gene expression without DNA sequence modification) induced by PAE could play a critical role in shaping the development of FASD and strabismus [79–81]. For example, a study by McKay *et al*. investigated the presence and expression of resilience alleles, which could serve as potential factors that protect against PAE-driven RA deficiency [78]. The role of genetic and epigenetic variables must be further explored to deepen our understanding of these complex relationships. Identifying and evaluating potential genetic and epigenetic biomarkers could then provide valuable tools for the clinical assessment of children with PAE. This could promote earlier diagnosis of FASD, enabling timely interventions and improved care. However, these areas remain underexplored, with some aspects yet to be investigated.

It is important to acknowledge the limitations that may hinder the strength of the literature review conducted. Firstly, the methodological approach of this study included papers exclusively published in the English language, narrowing the full scope of research that may provide relevant publications in other languages. Additionally, the heterogeneity in study designs, including sample populations, could limit the generalizability and comparability of findings. Many of the findings discussed are derived from animal models or in vitro studies, which warrant caution when applying these findings to human populations. Furthermore, future systematic reviews and meta-analyses could benefit from a more inclusive approach and rigorous quality assessment protocols to better validate the conclusions drawn in this review. Finally, although this review offers potential in explaining the relationship between FASD and strabismus, future research can focus on experimenting with these findings directly, drawing more conclusive results for this field of research.

CONCLUSION

Ultimately, the relationship between FASD and strabismus is complex, with disrupted RA metabolism highlighting the intricate interplay between PAE and ocular developmental outcomes. PAE significantly impacts RA metabolism, reducing its availability and altering receptor expression. This impairs the development of extraocular muscles and the cerebellum, leading to ocular misalignment. In support, evidence from animal models display the works of these mechanisms, explaining the prevalence of strabismus in children with FASD. Advancing the understanding of these multifactorial relationships is crucial for enabling early diagnosis and optimizing medical interventions. Further research should focus on investigating genetic and epigenetic biomarkers that elucidates and links the various factors outlined in Figure I. This could lead to the development of more robust assessment tools, mitigating the severity of outcomes following PAE.

Beyond advancing clinical understanding, public health initiatives may play a crucial role in reducing the prevalence and severity of FASD and its associated conditions, like strabismus. Raising awareness about the risks of PAE, alongside provision of additional support and education for at-risk populations, could significantly reduce the incidence of these outcomes. Additionally, implementing screening programs for early detection of FASD in high-prevalence regions could enable timely interventions, alleviating some of the downstream comorbidities. Collaboration between researchers, healthcare providers, and policymakers is essential to integrate these findings into effective prevention and care strategies, ultimately improving outcomes for affected children and their families.

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