

## FETAL ALCOHOL SPECTRUM DISORDERS (FASD)

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# Fetal Alcohol Spectrum Disorders and Nutrition

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### Introduction

The consequences of prenatal alcohol exposure vary widely, and a number of factors, including prenatal nutrition, contribute to variation in the expression of fetal alcohol spectrum disorders (FASD). While nutrient deficiencies may exacerbate FASD, nutrient supplementation may decrease risk by ameliorating inadequate nutritional state or by acting via pathways that positively influence development. Thus, manipulations of nutritional status either during or after pregnancy may serve as potential interventions for FASD.

### Subject

Elucidation of risk and protective factors for FASD is critical for the development of effective prevention and intervention strategies. Nutritional factors interact with alcohol, potentially exacerbating or protecting against FASD. Poor maternal nutrition is a significant problem in FASD, as the nutrients essential to support fetal development and preserve maternal health are often deficient with heavy alcohol use.<sup>1,2</sup> Heavy alcohol consumption is one of the leading causes of both primary and secondary malnutrition,<sup>2,3</sup> and undernutrition is a common characteristic of mothers in a majority of cases of FASD.<sup>4</sup> Not only may a woman who drinks during pregnancy

consume inadequate nutrition, but alcohol itself can compromise nutrient absorption and utilization,<sup>5</sup> including thiamin, folate, pyridoxine, vitamin A, vitamin D, magnesium and zinc.<sup>6-9</sup> These insufficiencies are only compounded as alcohol is placentotoxic, impairing the ability of the placenta to deliver essential nutrients to the fetus.<sup>10</sup>

Research using animal models has shown that nutritional factors influence the *teratogenic* effects of prenatal alcohol exposure.<sup>4</sup> Studies report that diets low in important nutrients exacerbate alcohol's teratogenic effects in the offspring,<sup>11-14</sup> such as low birth weight,<sup>12</sup> physical anomalies,<sup>14</sup> brain damage,<sup>15</sup> and reductions in growth factors.<sup>16</sup> Some of these effects are due to slower rates of alcohol metabolism and resultant increases in blood alcohol level (BAL),<sup>17-19</sup> but some are independent of BAL. The effects of nutrient deficiencies not only cause short-term effects but long-lasting problems due to *epigenetic* changes in fetal gene expression, which are enduring and pervasive.<sup>20</sup>

On the other hand, some nutritional factors may be protective.<sup>21-24</sup> The possibility that certain nutrients may reduce alcohol's teratogenicity provides an exciting opportunity to intervene in this clinical population. As such, the identification of effective nutritional supplements that reduce the severity of FASD is essential as micronutrients are relatively easy to implement, inexpensive, and safer to administer than other pharmacologic agents.

## **Problems**

Although the damaging effects of alcohol on the fetus have been recognized for almost 40 years, there is still a need to identify effective interventions to reduce these effects. However, the interactions of nutritional factors and ethanol in pathophysiology of FASD are still not well understood. The complexity of nutrient assessment is a challenge to understanding nutrient deficiencies in FASD. Dietary recall studies often underestimate the incidence of deficiency. Furthermore, clear biomarkers of nutrient status are not always present, and they may be unreliable. For instance, a variety of biomarkers may be potentially useful in determining zinc status, such as urinary excretion and hair concentration; however, interpretation of these markers as indices of zinc *nutriture* are often inconsistent.<sup>25,26</sup> Moreover, assessment of maternal nutritional status is hampered by the potential for diverse responses in nutrient metabolism in pregnant women.<sup>27,28</sup> In fact, nutritional requirements during pregnancy are considerably different than those for non-pregnant women, and these levels can vary greatly depending on many factors. For example, plasma zinc concentrations may vary with infection, vigorous exercise, food

intake, and proportion of plasma volume increase during pregnancy. Thus, inattention to these variables at the time of measurement may lead to inaccurate conclusions about maternal nutritional status. As such, assessing nutrient status in these women and understanding the effect of specific nutrient deficiencies in children prenatally exposed to alcohol is particularly challenging.

In addition, simple nutrient supplementation and fortification may not be the straightforward solution to prenatal nutrient deficiency in FASD. Complex interactions among micronutrients can facilitate or hinder absorption and bioavailability through a variety of different mechanisms, competing for transport proteins,<sup>29,30</sup> *chelating* organic substances, or other uptake mechanisms. Iron, copper and zinc competitively interact with each other under certain conditions, and supplements with one may lead to deficits in another.<sup>31,32</sup> Clinical groups with higher zinc requirements, such as pregnant and lactating women, may even be more sensitive to iron-zinc interactions.<sup>33</sup> Thus, potential risks associated with interactions need to be thoroughly considered and care must be taken to ensure proper levels and ratio of each mineral to facilitate the most beneficial effects.

## **Research Context**

Many of the studies examining the effects of nutritional supplements on outcome following prenatal alcohol exposure rely on animal model systems, which allow nutritional variables as well as other potentially confounding factors such as genetics and environment to be controlled. Epidemiological and clinical studies have assessed nutritional state of pregnant women who drink alcohol, but data are limited, as are data on the nutritional status of individuals with FASD. Moreover, studies on nutritional interventions, both during pregnancy and in individuals with FASD, have only recently been initiated.

## **Key Research Questions**

While research has shown that suboptimal maternal nutritional status interacts with alcohol to interfere with healthy fetal development, the contribution of select nutritional factors in moderating FASD risk in humans is still not well understood. To what extent and by what mechanism do nutritional deficiencies during pregnancy influence alcohol's teratogenicity? How persistent, specific and important are the effects? What is known of the nutritional status of individuals with FASD? And finally, how can nutritional manipulations during the lifespan influence

outcome, whether by compensating for a deficiency or by influencing developmental processes independent of baseline nutrient status? Understanding the mechanism through which nutrients may moderate or mediate the degree of alcohol damage will help inform the development of nutritional interventions for children affected by prenatal exposure to alcohol.

## Recent Research Results

Early in FASD research, alcohol-nutritional interactions were investigated using animal models to determine how dietary factors might influence alcohol's teratogenic effects. Interest in this interaction has re-emerged given the increased risk of FASD in countries with poor nutrition.<sup>34</sup> Animal studies have clearly demonstrated that undernutrition increases ethanol-related fetal toxicity and changes in gene expression.<sup>35</sup> Several groups have examined the interactive effects of specific nutritional deficiencies and developmental alcohol exposure. For example, in combination with prenatal alcohol exposure, the teratogenic effects of alcohol and low dietary zinc are synergistic, much greater than the effects of either alone.<sup>36</sup> The data also suggest that the relationship between alcohol exposure and zinc deficiency cannot be simply explained by an alcohol-induced zinc deficiency, but rather to independent but overlapping effects of each condition.<sup>1,37,38</sup> These findings are of great concern, given that insufficiencies of these same nutrients have been well documented in alcoholics.<sup>39-43</sup> Similarly, even moderate inadequacies of iron<sup>4</sup> or *choline*<sup>44</sup> during prenatal development exacerbate ethanol's adverse effects on physical and behavioural development.

In contrast, nutritional supplementation during prenatal alcohol exposure may reduce the severity of FASD. For example, antioxidants, including vitamin C, vitamin E and B-carotene, have also shown to provide significant protection against alcohol-induced neurotoxicity in animal models of FASD,<sup>46,47</sup> although one clinical study<sup>48</sup> using megadoses of vitamins C and E was terminated because of safety concerns. Animal studies also show that zinc supplementation during prenatal alcohol exposure reduces the severity of alcohol's damaging effects on physical development<sup>22</sup> and on learning deficits,<sup>21,23</sup> but not *cerebellar* cell loss.<sup>49</sup> Not only is zinc supplementation of value in modulating FASD risk in the offspring, it also confers beneficial effects for the mother.<sup>50</sup> Similarly, folate supplementation reduces the incidence of cardiac abnormalities.<sup>51</sup> Choline supplementation can also reduce the severity of physical, neuropathological and behavioural alterations associated with developmental alcohol exposure.<sup>52,53</sup>

What is particularly exciting is that nutritional supplements may effectively reduce the severity of FASD, even when administered during the postnatal period and after alcohol exposure has ceased. Postnatal choline supplementation in rodents reduces the severity of hyperactivity,<sup>54</sup> deficits in trace conditioning of fear responses<sup>55</sup> and eyeblink conditioning,<sup>56</sup> spatial memory,<sup>57,58</sup> working memory,<sup>59</sup> and reversal learning.<sup>54</sup> Importantly, in all of these studies, the beneficial effects of choline on behavioural performance was evident even after choline treatment had ceased, indicating that choline leads to long-lasting changes in brain function. Choline acts as a precursor to the neurotransmitter acetylcholine and to cell membrane components, but, like folate, it also affects the *homocysteine/methionine cycle* and *DNA methylation*; thus, its actions may influence multiple pathways important for brain development and function. Although it is not yet known if prenatal alcohol influences long-lasting choline status, these data suggest that nutritional supplements may be effective even if they are not compensating for a nutritional deficiency.

## Research Gaps

Despite the existence of animal data suggesting the feasibility of nutrient supplementation as a potential intervention for individuals with FASD, these studies are only now being implemented in human clinical populations. Clinical trials are needed to translate experimental findings in children with FASD. Furthermore, a formidable limiting factor in understanding the role of maternal nutritional status in FASD is the availability of the nutritional status of women who have been drinking and their children. Longitudinal prospective studies are needed to examine maternal nutritional status and its modulation of FASD risk, as well as the long-lasting effects of prenatal alcohol exposure on the nutritional status of the individual with FASD.

## Conclusions

Although it is clear that nutritional state influences alcohol's damaging effects on the fetus, the specific interactions are not well understood. Elucidation of how nutritional factors moderate and mediate alcohol's teratogenic effects not only can help target prevention efforts to high-risk populations, but nutritional supplements may serve as effective interventions. In addition, given the role of nutrients on brain and behavioural development, nutritional supplements may effectively reduce the severity of symptoms in children with FASD, whether compensating for nutritional deficiencies or by acting on pathways that enhance behavioural and cognitive functioning.

## Implications

The potential of nutritional interventions, either during pregnancy or in the individual with FASD, to reduce the severity of FASD and improve the quality of life of individuals who have been exposed to alcohol prenatally is promising.

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