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Folic Acid, Choline Supplementation and FASD

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KEY MESSAGES

Nutrition is an important aspect of a healthy pregnancy. Drinking alcohol during pregnancy increases the risk of nutritional deficiencies and thus vitamin, mineral and essential nutrient supplements may be beneficial. Emerging evidence suggests that the use of certain micronutrient supplements during pregnancy, such as folic acid and choline, may mitigate some effects of prenatal alcohol exposure. While more research is needed to better understand the potential of folic acid and choline supplementation to lessen the teratogenicity of alcohol use during pregnancy and thus improve infant and child outcomes, this issue paper highlights what is known and the role of nutrition in healthy pregnancies, FASD prevention, and improving health equity for women and gender diverse people who use substances during pregnancy.

Issue:

Fetal Alcohol Spectrum Disorder (FASD) is a result of prenatal alcohol exposure; however, many factors influence the effects of alcohol on the developing fetus including nutrition, genetics, age, socioeconomic status (SES), and other substance use, such as tobacco [1-4]. Alcohol can impact the absorption of nutrients into the body and transfer of nutrients via the placenta, and behaviourally, alcohol intake may displace some food and caloric intake [5-8]. Supporting the nutritional status of pregnant women and gender diverse people who use alcohol may be an important and relatively accessible way to support maternal and fetal health.

In addition to a nutrient dense diet, certain vitamins and supplements have been identified as important during pregnancy, such as folic acid, choline, vitamin D, omega-3 fatty acids, iodine, and iron [9, 10]. Physiological changes during pregnancy increase the body's need for certain vitamins, minerals, and essential nutrients and many pregnant women are deficient in important micronutrients [7, 11]. Additionally, alcohol can interfere with the body's uptake of important micronutrients, creating deficiencies [5, 8]. Emerging research suggests that maternal use of nutritional supplements, especially folic acid and choline, may mitigate the effects of prenatal alcohol exposure and support healthy pregnancies [8, 12, 13].

This issue paper seeks to summarize evidence on the impact of maternal nutrition and the role of folic acid and choline supplementation on mitigating the effects of prenatal alcohol exposure.

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Background:

Maternal nutrition, along with alcohol use, age, genetics, SES, and tobacco use, is an important factor in the development of FASD. As with many Canadian women who experience nutritional deficiencies and who may not be getting adequate micronutrients in their diet on a regular basis [14-17], it is common for women who use alcohol to experience nutritional deficiencies, particularly during pregnancy [5]. Pregnancy creates physiological changes to the body that increase the need for certain micronutrients, and alcohol use exaggerates this need by interrupting micronutrient absorption and metabolism, as well as the transfer of nutrients to the developing fetus [5, 6]. Mothers with, or at risk of having, a child with FASD have been found to be deficient in numerous micronutrients, including folate [14] and choline [18], and there may be a risk of FASD associated with lower maternal weight [5, 18]. As a result, researchers have begun to investigate a range of vitamins, minerals, and essential nutrients in relation to alcohol use during pregnancy to explore potential benefits for fetal and infant outcomes [6, 13, 19].

While no alcohol during pregnancy is safest, abstinence is not always possible. For women and gender diverse individuals who continue to use alcohol during pregnancy, interventions that reduce harms are important. Evidence on maternal use of micronutrient supplements, such as folic acid and choline, which are metabolically linked during fetal development [20], are emerging as potentially protective of some of the challenges associated with FASD, including those related to brain differences. Additionally, promoting the nutritional health of all pregnant women and gender diverse individuals, and removing barriers to accessing folic acid, choline supplements, and other nutritional supports are important aspects of health equity.

1. Folic Acid

Folic acid, or folate, is a vitamin found in leafy greens, beef, liver, and whole wheats. In Canada, folic acid supplements are currently recommended during pregnancy or when planning a pregnancy to protect against neural tube development anomalies. While folic acid supplementation is well established as important during pregnancy, little research has investigated the vitamin in relation to prenatal alcohol use, despite the evidence of nutritional deficiencies among women at risk of having an alcohol exposed pregnancy [14, 18]. However, some animal studies have found maternal folic acid supplementation to mitigate growth restriction and cardiac dysfunction in offspring exposed to alcohol in utero [6]. Additional protective effects associated with maternal folic acid supplementation have also been found, such as positive effects on offspring weight [19] and hyperactive behaviour [21].

Heavy or chronic alcohol use may impair placental transport of folate (i.e., the process of the placenta taking up maternal folic acid and circulating it into the fetal bloodstream) [22] and researchers theorize that oxidative stress resulting from lower levels of folic acid may contribute to the development of FASD [23]. Additionally, higher levels of maternal folic acid may mitigate the effect of alcohol on placental transport of folate [22, 23]. These findings are beginning to demonstrate a potential mechanism through which FASD develops, opening the door to innovative prevention interventions involving folic acid transport.

2. Choline

Growing research evidence suggests that maternal choline supplementation may be important for those who use alcohol during pregnancy. Choline is an essential nutrient found in both animal and plant foods, with meat and egg sources containing the highest concentrations [24]. Choline is important for many processes, including brain development, cognitive function and gene expression [25]. Alcohol affects choline-related mechanisms in the body and contributes to choline deficiency [6]. Emerging evidence of an interaction between choline metabolism-related genes and prenatal alcohol exposure-related memory deficits points to the relevance of choline in the development of FASD [26]. Additionally, research evidence on maternal choline supplementation has found mitigating effects of prenatal alcohol exposure in regard to growth restriction, brain structure, learning and memory [12, 13]. Depending on diet, genetics, and amount of alcohol consumption, choline supplementation may mitigate certain behavioural, neurological, cognitive, and growth effects resulting from prenatal alcohol exposure [25, 27, 28].

Growth restriction

Researchers have found protective effects of choline regarding growth restriction among infants prenatally exposed to alcohol. Specifically, maternal dietary intake of choline, energy (i.e., calories), and iron in addition to gestational weight gain was found to protect against growth restriction outcomes associated with prenatal alcohol exposure [29]. The authors of another study found that 2 grams of daily maternal choline supplementation from mid-pregnancy to delivery mitigated the effects of alcohol exposure on growth restriction at 6.5 and 12 months [30]. The authors of an animal study that investigated preconception and maternal supplementation of folic acid, choline, betaine and vitamin B12, found reduced incidence and severity of growth restriction, brain malformations, and skeletal delays among offspring [31].

Brain Structure

There may be protective effects of maternal choline supplementation for the effects of prenatal alcohol exposure on brain structure. The authors of a study from South Africa found that 2 grams of daily maternal choline supplementation protected against brain volume reductions in infants prenatally exposed to alcohol and resulted in increased brain volume in the putamen (i.e., a part of the brain involved in learning and motor control) and corpus callosum (i.e., a region of the brain consisting of white matter tracts that connect the two hemispheres of the brain) that was associated with improved recognition memory [32].

Learning and memory

While the findings are mixed, maternal choline supplementation may also mitigate the effects of prenatal alcohol exposure on certain cognitive outcomes. One randomized placebo-controlled clinical trial found that at 6.5 months, infants born to mothers who drank 1 – 2 days a week (and had 8 – 9 drinks per occasion) throughout their pregnancy and received 2 grams of daily choline supplementation, performed better in eyeblink conditioning, a measure of memory and learning. At 12 months, infants born to mothers who supplemented with choline had improved visual recognition memory compared to those born to mothers who used alcohol and received the placebo. However, there was no significant difference between the two groups in infant information-processing speed. There also was no significant difference in FASD diagnosis [30].

Additional research has found mixed impacts of maternal choline supplementation with multivitamins (MVM). For instance, while the authors of one study found that MVM supplementation alone was associated with improved cognitive outcomes, MVM supplementation in combination with choline (750 mg per day) was not [33]. The authors of another study found that compared to MVM supplementation alone, improved infant outcomes were found when paired with choline supplementation (750 mg per day) in regards to basic learning mechanisms related to memory [34]. The authors of this study also found MVM combined with choline to benefit all infants, regardless of alcohol exposure [34].

While the research on choline's effects on infant cognition after prenatal alcohol exposure are mixed [24], the effects on growth outcomes may be more robust [20]. More research is needed to understand other possible effects into childhood. For example, it has been found that higher maternal choline concentrations may be associated with decreased attention problems and social withdrawal among 4-year-old children, especially boys, when prenatal cannabis exposure or maternal infection are of concern [35]. Nonetheless, choline supplementation may be especially supportive for pregnant women and gender diverse people with choline deficiency, either due to heavy alcohol use, inadequate dietary intake or genetic variation that impedes choline synthesis [30], and there is no evidence to suggest that choline supplementation can be harmful [24], although a small increase in nausea has been reported to be a side effect [36]. Screening for choline intake paired with dietary education and access to supplements can be supportive to FASD prevention [37].

Recommendations and Implications:

- Given the importance of nutrition and the heightened nutritional vulnerability of pregnant women and gender diverse individuals who use alcohol, it is important to identify those who may benefit from supplements as well as providing nutrition and supplementation programs tailored to their needs.
- It is crucial to continue to provide funding for Community Action Programs for Children (CAP-C) and Canada Prenatal Nutrition Programs (CPNP), which are designed to ensure pregnant and parenting women have access to nutrition supports and supplementation, such as the provision of folic acid and choline.
- More support for existing wraparound programs and enhanced opportunities are needed for pregnant women with substance use concerns to access holistic support, such as Level 3 and Level 4 FASD prevention programs that integrate nutrition and related social and health services with substance use treatment.
- Additional research is needed that further explores the benefits of maternal micronutrient supplementation as it affects prenatal alcohol exposure and maternal health, including longitudinal studies and community-based research. This research should address the multiple variables that influence the development of FASD that can be difficult to control for, and small sample sizes have been used in research to-date. Research with larger samples and with follow-up measurements over time will contribute to a better understanding of the effects of maternal supplement use when alcohol use is present. As available, this research needs to be translated and communicated to healthcare providers.

Conclusion:

Nutrition is an important factor for healthy pregnancies. For women and gender diverse individuals who use alcohol, nutrition is an often overlooked avenue for support and intervention, and may be especially important for those who use alcohol during pregnancy. Micronutrient supplementation is

emerging as a low risk, relatively accessible opportunity to support the health and pregnancies of women who use alcohol and may help prevent FASD. While more research is needed to better understand the extent and circumstances under which choline may mitigate the effects of prenatal alcohol exposure, deficiency in this nutrient is common and many may benefit from supplementation. Additionally, while folic acid is already a recommended supplement during and prior to pregnancy, alcohol use may create a need for more of the vitamin to reap the same benefits, and therefore conversations with informed and trusted healthcare providers are key.

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