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The impact of micronutrient supplementation in alcohol-exposed pregnancies on information processing skills in Ukrainian infants

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ABSTRACT

The potential of micronutrients to ameliorate the impact of prenatal alcohol exposure (PAE) was explored in a clinical trial conducted in Ukraine. Cardiac orienting responses (ORs) during a habituation/dishabituation learning paradigm were obtained from 6 to 12 month-olds to assess neurophysiological encoding and memory. Women who differed in prenatal alcohol use were recruited during pregnancy and assigned to a group (No study-provided supplements, multivitamin/mineral supplement, or multivitamin/mineral supplement plus choline supplement). Heart rate was collected for 30 s prior to stimulus onset and 12 s post-stimulus onset. Difference values (ΔHR) for the first 3 trials of each condition were aggregated for analysis. Gestational blood samples were collected to assess maternal nutritional status and changes as a function of the intervention. Choline supplementation resulted in a greater ΔHR on the visual habituation trials for all infants and for the infants with no PAE on the dishabituation trials. The latency of the response was reduced in both conditions for all infants whose mothers received choline supplementation. Change in gestational choline level was positively related to ΔHR during habituation trials and levels of one choline metabolite, dimethylglycine (DMG), predicted ΔHR during habituation trials and latency of responses. A trend was found between DMG and ΔHR on the dishabituation trials and latency of the response. Supplementation did not affect ORs to auditory stimuli. Choline supplementation when administered together with routinely recommended multivitamin/mineral prenatal supplements during pregnancy may provide a beneficial impact to basic learning mechanisms involved in encoding and memory of environmental events in alcohol-exposed pregnancies as well as non- or low alcohol-exposed pregnancies. Changes in maternal nutrient status suggested that one mechanism by which choline supplementation may positively impact brain development is through prevention of fetal alcohol-related depletion of DMG, a metabolic nutrient that can protect against overproduction of glycine, during critical periods of neurogenesis.

Introduction

The negative impact of prenatal alcohol exposure (PAE) on neurodevelopmental functioning has been investigated in both human and animal models for over 40 years (Thomas, Warren, & Hewitt, 2010) but it is only recently that factors that modify the teratogenic impact of PAE have been the focus of research (Guerri et al., 2005; Peadon, Rhys-Jones, Bower, & Elliott, 2009). Such factors include changes to postnatal environmental circumstances (Guerri et al., 2005; Thomas, Sather, & Whinery, 2008), cognitive behavioral interventions (Adnams et al., 2007; Bertrand, 2009; Coles, Kable, & Taddeo, 2009; Coles, Strickland, Padgett, & Bellmoff, 2007; Kable, Coles, & Taddeo, 2007; Loomes, Rasmussen, Pei, Manji, & Andrew, 2008; O'Connor et al., 2006, 2012; Olson & Montague, 2011), pharmacological agents (Incerti, Vink, Roberson, Benassou, et al., 2010; Incerti, Vink, Roberson, Wood, et al., 2010;

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Marche, Danel, & Bordet, 2011; Zhou, Fang, & Goodlett, 2008), and nutritional interventions (Naseer, Lee, & Kim, 2010; Ojeda et al., 2009; Serrano, Han, Brinez, & Linask, 2010; Summers, Rofe, & Coyle, 2009; Thomas, Abou, & Dominguez, 2009).

Maternal nutritional status has been posited as one potential moderator of the teratogenic impact of PAE (Keen et al., 2003, 2010). Women who drink heavily in pregnancy often have poor nutritional status (Guerrini, Thomson, & Gurling, 2007) and poor diets alone have been linked to adverse pregnancy outcomes (Keen, Bendich, & Willhite, 1993; Walker et al., 2011). Maternal drinking during the periconceptual period (Weiss & Chambers, 2013) has also been found to be dose-related to a reduction in multivitamin supplement use. Even among women who maintain adequate diets, moderate and heavy alcohol consumption can interfere with micronutrient absorption (Carter, Jacobson, Molteno, & Jacobson, 2007; Church, Jen, Pellizzon, & Holmes, 1998).

Multivitamin use in pregnancy has been associated with significant improvements in pregnancy outcomes, including lengthening gestation, increasing birth weight and length, reducing miscarriages, and preventing oral clefts (Glenville, 2006). Information on the long-term impact to the development of the offspring has been more limited. Among women from Tanzania who were HIV positive, multivitamin supplementation resulted in improvements in toddler motor functioning but not cognitive development (McGrath et al., 2006). In a U.S. study based on parent ratings of preschool children, multivitamin use in pregnancy was associated with a decreased risk for delays in language and personal/social functioning but was not found to impact overall development (Wehby & Murray, 2008). In another study, multivitamin use was associated with improvements in verbal abilities on standardized tests but was not related to changes in perceptual, quantitative, memory, motor, and executive functioning in 4-year-olds (Julvez et al., 2009).

The potential of micronutrient supplementation to ameliorate the negative impact of PAE is unknown as no previous human studies have attempted to administer micronutrient supplements during alcohol-exposed pregnancies, and studies using animal models have limited the intervention to only a few discrete minerals or micronutrients (El Banna, Picciano, & Simon, 1983; Rufer et al., 2012; Summers et al., 2009; Thomas et al., 2009). Among these, the use of choline supplementation appears to be the most promising. Using animal models, improvements in behavioral flexibility (Thomas, Idrus, Monk, & Dominguez, 2010), reduced activity (Thomas, Garrison, & O'Neill, 2004), and improved performance on a variety of learning tasks has been found in response to choline supplementation, including tasks of spontaneous alternation (Thomas, Biane, O'Bryan, O'Neill, & Dominguez, 2007; Thomas, Garrison, et al., 2004), discrimination learning (Thomas, La Fiette, Quinn, & Riley, 2000), and trace eyeblink conditioning (Thomas & Tran, 2012). Choline supplementation has also been found to reduce the impact of PAE on the density of muscarinic M(1) receptors in the dorsal hippocampus (Monk, Leslie, & Thomas, 2012) and to reduce hyper-methylation associated with PAE in the hippocampus and prefrontal cortex (Otero, Thomas, Saski, Xia, & Kelly, 2012). Gestational choline supplementation also prevented PAE modulation of histone and DNA methylation in hypothalamic proopiomelanocortin neurons (Bekdash, Zhang, & Sarkar, 2013). In contrast, choline supplementation was not found to alter the impact of PAE on motor coordination deficits (Thomas, O'Neill, & Dominguez, 2004), delayed eyeblink response (Thomas & Tran, 2012), or olfactory habituation (Hunt, Jacobson, & Kim, 2014).

The impact of choline levels and dietary supplementation among humans with PAE is not yet known but has been posited as a potentially helpful agent (Ballard, Sun, & Ko, 2012), particularly for women who may have an inadequate intake of choline in their everyday diets (Zeisel, 2011). The impact of gestational choline in the absence of PAE on child neurodevelopmental outcomes has been ambiguous. Choline was not found to be related to 5-year cognitive status in a population of children in Alabama with a history of poverty and poor nutrition (Signore, Ueland, Troendle, & Mills, 2008). An observational study conducted in the Seychelles also found no relationship between choline concentration and neurodevelopmental outcome in children at 5 years of age but found levels of betaine, a metabolite of choline, were positively associated with language functioning (Strain et al., 2013). In other prospective studies of healthy pregnant women, positive associations were found between infant cognitive functioning as assessed using the Bayley Scales of Infant and Toddler Development, 3rd edition (Bayley, 2006) and maternal plasma free choline and betaine levels collected at 16 weeks of gestation (Wu, Dyer, King, Richardson, & Innis, 2012), and second-trimester intake of choline was associated with modest improvements in visual memory of offspring at 7 years of age (Boeke et al., 2013).

To evaluate the impact of choline supplementation in pregnancy, a double-blind clinical trial was conducted in the United States with healthy pregnant women. In this study, choline supplementation was not found to improve global development, number of words spoken, short-term visuospatial memory, or long-term episodic memory in infants under a year of age (Cheatham et al., 2012). The authors noted that no efforts were made to control dietary intake of choline and its metabolites, and further explorations revealed that gestational betaine levels were negatively related to short-term visuo-spatial memory and global development at 12 months of age.

To assess the impact of micronutrient supplementation on the cognitive functioning of offspring with a history of PAE, a task that assesses early indices of alcohol-related neurodevelopmental damage is needed that also minimizes other environmental factors associated with maternal drinking, such as lower socioeconomic status, environmental chaos (i.e., poor stability in caregivers or the home environment), and exposure to violence, that may adversely impact development (Blair & Raver, 2012). One such index of early cognitive functioning assesses the neurophysiological encoding and memory of environmental events using cardiac orienting responses (Kable & Coles, 2004). Cardiac orienting responses (ORs) to stimuli are characterized by a specific pattern of heart rate deceleration (Graham & Jackson, 1970) in the presence of novel or interesting stimuli and are triggered by mechanisms that enable the heart to gate oxygen away from the periphery to the central nervous system, allowing for higher-level information processing and learning about environmental events. The neural circuitry that supports ORs is present in all mammals and can be reliably elicited within the first few months of life in humans (Sokolov, Spinks, Näätänen, & Lyytinen, 2002).

ORs have been found in response to the onset of both visual and auditory stimuli (Berg, Berg, & Graham, 1971; Brown, Leavitt, & Graham, 1977; Lewis, Kagan, Campbell, & Kalafat, 1966) and measures during the first year of life have been linked to later cognitive functioning at 18 months (O'Connor, 1980) and 5 years (O'Connor, Cohen, & Parmelee, 1984). Characteristics of the OR response, in particular the sustained deceleration or the trough of the OR, reflect the degree of neurophysiological encoding and sustained interest to the stimuli (Lansink, Mintz, & Richards, 2000; Richards, 1995) and have been sensitive to effects of PAE in human (Kable & Coles, 2004) and animal models (Hunt & Phillips, 2004; Morasch & Hunt, 2009).

To evaluate the impact of multivitamin/mineral and choline supplementation, a clinical trial of the impact of prenatal micronutrient supplementation was conducted with a prospective cohort of moderate/heavy drinking pregnant women and low/unexposed comparison women in Ukraine. Estimates of the prevalence of alcohol use among pregnant women in Ukraine (Bakhireva et al.,