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Intake of eggs, choline, lutein, zeaxanthin, and DHA during pregnancy and their relationship to fetal neurodevelopment

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Abstract

Background: Maternal intake of eggs and nutrients contained within eggs during pregnancy have the potential to impact fetal neurodevelopment; however, this area is understudied. The purpose of this study was to determine whether maternal egg and choline intake and nutrient interactions between choline, lutein and zeaxanthin (L/Z), and DHA predict fetal neurodevelopment in a large cohort of pregnant women (n=202). NCT02709239

Methods: Food frequency questionnaires were used to assess egg and nutrient intake during pregnancy. Fetal neurodevelopment was measured using fetal biomagnetometry at 32 and 36wks gestation, and fetal autonomic indices (SDNN, RMSSD) and brain maturation indices (fABAS) were calculated. Generalized linear models tested the relationships between choline intake, egg intake, and nutrient interactions with fetal neurodevelopment.

Results: Maternal egg intake predicted RMSSD at 32wks and fABAS at 36wks. The interaction between choline and L/Z intake predicted fABAS at 32wks and 36wks and the interaction between choline intake, L/Z intake, and DHA predicted fABAS at 36wks. At 36wks, SDNN was predicted

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Author Contributions: DNC was the principal investigator and designed the secondary analysis with input from KFG (principal investigator of the parent trial); DH and AS performed the fABAS analysis; LCH completed the statistical analysis; DNC, KFG, and LCH wrote the manuscript but all authors contributed their insights.

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by L/Z intake and interactions between choline and L/Z, L/Z and DHA, and choline, L/Z, and DHA.

Conclusion: Eggs and the nutrients contained within eggs showed synergistic associations with fetal neurodevelopment, and consumption should be encouraged among pregnant women.

Keywords

Maternal diet; egg; choline; DHA; lutein; zeaxanthin; nutrient synergy; fetal neurodevelopment

Introduction

Experts agree choline is essential for proper fetal and infant development; however, nearly all pregnant women in the United States fall short of the Adequate Intake (450 mg/day), with only ~10% of Americans meeting recommendations.[1] Eggs are one of the richest sources of choline in the human diet, providing 115 mg of choline per one yolk, yet most women get their choline primarily from milk which contains fewer mg of choline per serving.[2] Furthermore, eggs contain a variety of nutrients in addition to choline, including lutein, zeaxanthin, and docosahexaenoic acid (DHA), which have been implicated in infant memory and cognition.[3] While each of these nutrients have been studied in isolation in terms of infant outcomes, together they have the potential to act synergistically to promote healthy brain development early in life.

Since direct measures of fetal brain development in humans are limited, researchers have examined the effects of choline supplementation during pregnancy in rodent models and among human infants and children. Rodent studies have consistently shown that choline supplementation during pregnancy has a positive effect on spatial learning, memory, and attention.[4] However, results of human studies examining the effects of maternal choline supplementation during pregnancy and infant attention and cognition are mixed – some show no effect[5] while others show a positive effect[6,7]. Cheatham et al. conducted a randomized controlled trial (RCT) of 140 pregnant women who were supplemented with 750mg/d of choline or placebo from 18w gestation through 90 days postpartum. In this trial, the groups did not differ in global development, language development, short-term or long-term memory at 10 and 12 months of age[5]. Another RCT of choline supplementation (430mg/d vs 930mg/d) by Caudill et al. found that children in the higher dose group had improved information processing and reaction time at 4mo, 7mo, 10mo, and 13mo of age when compared to the lower dose group[8]. Nutrient synergy between choline, lutein, and docosahexaenoic acid (DHA) was demonstrated in a study showing human milk containing higher levels of these three nutrients were associated with improved infant recognition memory.[9] However, these findings have not been examined in terms of the maternal diet and fetal outcomes.

The purpose of this study was to determine whether maternal egg and choline intake during pregnancy predict fetal neurodevelopment at 32 and 36 weeks gestation in a large cohort of pregnant women participating in the Prenatal Autonomic Neurodevelopmental Assessment (PANDA) randomized clinical trial.[10] We also aimed to determine whether the interaction of nutrients present in eggs and other nutrient dense food sources such as seafood and

leafy greens (choline, lutein, zeaxanthin, DHA) would affect fetal neurodevelopment. We hypothesized that lower egg and choline intake during pregnancy would constrain fetal neurodevelopment as evidenced by lower fetal cardiac and brain autonomic indices at 32 and 36 weeks gestation.

Materials and Methods

This study was a secondary analysis of a NIH funded randomized controlled clinical trial examining the effects of 2 doses (200 mg and 800 mg) of DHA on fetal and infant neurodevelopment and cognition (NCT02709239). Results of the primary outcomes and methods of the parent study have been recently published.[10] The following methods are specific to this secondary analysis of egg and choline intake on fetal neurodevelopment.

Diet survey.

The National Cancer Institute Diet History Questionnaire II (DHQ-II) is a food frequency and portion size questionnaire. The database associated with the DHQ versions are based on the National Health and Nutrition Examination Surveys (NHANES) data collection from 2001–2006. At 32 weeks, participants completed version 3 (past month, with portion size) to determine diet during pregnancy. The survey was completed online by all participants. Diet*Calc analysis software was used to extract choline intake (mg/d) and lutein and zeaxanthin (L/Z) intake (mg/d) from all food sources.[11] The *DHA-rich foods questionnaire* is a non-standardized DHA-rich food questionnaire that was administered at the enrollment study visit (12–20 weeks gestation).[12] In this survey, women were asked to identify from a list of DHA-containing foods which they consume (including eggs) and the approximate frequency and portion size of each. Egg intake included eggs used in mix-dishes or baked goods. Egg preparation (e.g. scrambled, hardboiled, raw) was not specified.

DHA Status.

Maternal blood samples were collected at 32 weeks in EDTA tubes (BD Vacutainer, Franklin Lakes, NH), placed on wet ice, and processed within 24 hours. Following centrifuging (3000g, 10 minutes, 4°C) to separate the plasma, buffy coat, and RBCs, samples were stored at −80°C in barcoded vials until analysis. RBC phospholipid fatty acids were assessed by gas chromatography using an Agilent 6890N gas chromatograph and Agilent OpenLab CDS ChemStation software, Edition c.01.09. RBC DHA is reported as weight percent of total fatty acids (wt% TFA). Greater details of the fatty acid analysis methodology are described in a recent report.[13]

Magnetocardiogram (MCG).

Fetal MCGs of 30 minutes duration were recorded using an 83 channel, large array dedicated fetal biomagnetometer system (CTF Systems, VSM MedTech, Vancouver, Canada) at 32 and 36 weeks gestation. Participants were tested in a magnetically shielded room with an adjustable, reclining chair designed to support pregnant women, made comfortable with arm rests and pillows in a slightly reclined position. The women were monitored via video camera and microphone.

Fetal Neurodevelopment.

Data from the MCG recordings were used to calculate fetal heart rate variability (HRV) using Kubios software (version 3.4.2; Kuopio, Finland).[14] Two standard time-domain metrics of HRV were utilized in this study: the Standard Deviation of Normal to Normal interbeat intervals (SDNN), and the Root Mean Square of Successive Differences (RMSSD). SDNN is an index of overall HRV capturing long-term fluctuation amplitude from vagal (parasympathetic), sympathetic and slower neuro-humoral sources.[15] RMSSD is an index of short-term fluctuation amplitude, largely under vagal control.[15]

We also analyzed a comprehensive metric of fetal neurodevelopment known as the fetal autonomic brain age score (fABAS).[16] This universal system-theory approach to HRV analysis results in a proxy for the neural integration of the developing fetus, mediated by the autonomic nervous system. The measure enables the characterization of important maturational periods during the 2nd and 3rd trimesters using HRV-derived measures related to increasing fluctuation amplitude, complexity, and pattern formation, thereby serving as an index of fetal neurodevelopment . The fABAS score, reported as gestational age in weeks, has proven to be a sensitive indicator of maternal and fetal factors influencing development, including maternal DHA supplementation.[17]

Statistical Analysis.

Simple descriptive statistics (means/standard deviations or frequencies/percentages) were tabulated for all variables. Scatter plots and histograms were used to investigate the adequacy of the model assumptions. Fetal HRV metrics, SDNN and RMSSD, showed strongly right-skewed distributions and were log transformed to normalize the model residuals and improve model fit. Generalized linear models were used to test the relationships between choline intake (mg/d) or egg intake (eggs/day) and each outcome variable (fABAS at 32 and 36 wks and fetal HRV (SDNN, RMSSD) at 32 and 36 wks), with maternal dietary L/Z intake and maternal RBC DHA status as covariates. We also tested for potential interactions between maternal dietary L/Z intake and maternal RBC DHA status with choline or egg intake on fetal neurodevelopmental outcomes[18]. For each model, main effects for each predictor (either choline or egg intake with dietary L/Z intake and RBC DHA) and all two- and three-way interaction terms were estimated, and nonsignificant interaction terms were serially removed to define the final models. To compare the magnitude of the main and interaction effects for each predictor and interaction on the outcome variables, standardized regression coefficients were calculated by conducting a z-score transformation on all predictors and re-estimating the generalized linear models with the transformed variables.

Results

Of the 300 women enrolled in the trial, 227 women completed their 32 and 36 week fetal visits. Of those, there were 202 women with data for dietary intake, fABAS, and fetal HRV metrics at 32 and 36 weeks gestation and were thus included in the analysis. Descriptive statistics for the women included in the secondary analysis are listed in Table 1. A CONSORT is available for the parent study.[10]

Table 2 summarizes the regression results for each choline intake model. The interaction between choline intake and L/Z intake significantly predicted fABAS at 32wks (p=0.0284) and 36wks (p=0.0346). Furthermore, the interaction between choline intake, L/Z intake, and RBC DHA predicted fABAS at 36wks (p=0.0410), suggesting a synergistic effect of nutrients contained in eggs on fetal neurodevelopment. At 36 weeks, fetal overall HRV (SDNN) was predicted by L/Z intake as a main effect (p=0.0020) and the two- and three-way interactions between choline and L/Z (p=0.0077), L/Z and DHA (p=0.002), and choline, L/Z, and DHA (p=0.0079). In general, the standardized regression coefficients revealed substantially greater magnitudes of effect for interaction effects compared to main effects. Choline and L/Z intake had the greatest effect on fABAS at 32 weeks compared to RBC DHA, while interactions involving L/Z intake showed the greatest effects on both fABAS and SDNN at 36 weeks. No main effects were statistically significant for any outcomes at 32 weeks.

Table 3 summarizes the regression results for the egg intake models. Maternal egg intake predicted fetal vagally-mediated HRV (RMSSD) at 32 weeks (p=0.0239), such that higher intake of eggs resulted in higher fetal RMSSD. No other main or interaction effects were statistically significant at 32 weeks. Egg intake also predicted fABAS at 36wks (p =0.0353), such that higher egg intake resulted in a more developmentally advanced fABAS score at 36 weeks. The standardized regression coefficients showed variation in the relative importance of each main effect across models, with egg intake showing a consistently stronger effect in fABAS and SDNN models and a stronger effect of RBC DHA on RMSSD at both 32 and 36 weeks.

Discussion

We examined the effects of choline and egg intake on fetal neurodevelopment using highly novel methods and found that egg intake alone and the interaction between nutrients commonly found in eggs have a positive effect on fetal neurodevelopment as indexed by fABAS and fetal HRV (RMSSD, SDNN). Maternal nutrition during pregnancy has been associated with many outcomes of health in the infant and child; however, this is the first study of its kind to examine the effect of maternal egg and choline intake on fetal neurodevelopment. Specifically, the approach we used allowed us to quantify the influence of maternal nutrition on the development of the fetal autonomic nervous system. Of the metrics employed, the effect of nutrient synergy is most reliably represented by fABAS. Because fABAS considers the coordinated behavior of different aspects of fetal autonomic control, i.e., fluctuation amplitude, signal complexity and pattern (accelerations and decelerations reflected in the skewness measure), it may serve as a more sensitive indicator of complex nutrient effects than standardized time-domain measures of HRV.

The autonomic nervous system is a basic neural system that is affected by choline by way of acetylcholine[19] and a system through which choline affects both physiological and behavioral outcomes[20]. Early in development, fetal heart rate is largely under sympathetic control[21]. At about 30 weeks gestational age (GA), increasing vagal influence results in lower HR, greater HRV and the emergence of distinct HR patterns attributable to fetal activity states[22]. This developmental shift to greater cardiac vagal activity reflects the

ability of the integrated nervous system to mediate physiological and *in utero* behavioral and regulatory activity. The ability to flexibly adjust HR and other complex, integrated oscillatory systems (breathing, suck/swallow) in response to challenges during the transition to life outside the womb, gives the newborn an adaptive advantage. A newborn with more mature autonomic-central nervous system integration is better able to maintain homeostasis, coordinate sucking and breathing, have more optimal sleep-wake state profiles and in general, experiences a smoother transition to extrauterine life[23].

We chose to include L/Z and DHA in our models to account for possible additive effects of nutrient synergy on fetal neurodevelopment. The latest nutrition research has shifted focus from single nutrients to combinations and patterns of nutrients in order to reflect the mixed-nature of human diets.[24] Our results are in line with work by Cheatham et al. showing nutrient synergy between choline, lutein, and DHA in human milk was positively associated with infant memory at 6 months of age.[9] Adding to this work, we aimed to assess how maternal diet affects development *in utero*, when the dietary intake variables are closer in time to the fetal outcome variables, and found a similar relationship between choline, L/Z and DHA and fetal neurodevelopment. In terms of our findings, nutrient synergy is relevant because choline serves as the major carrier of DHA, as well as increasing the bioavailability of DHA to the fetus through upregulation of the PEMT pathway.[2,25] DHA is also reliant on phosphatidylcholine for transport to the brain and early neurodevelopment. Further, L/Z are the only carotenoids that can cross the blood brain barrier and have been shown to preferentially accumulate in the infant's brain.[26] A recent secondary analysis of the Project Viva cohort showed higher L/Z intake during pregnancy was associated with offspring cognition, including verbal intelligence and behavior regulation.[3] Post-mortem studies in human infant brains found that L/Z concentrations were highly correlated with lipid pathway intermediates[27],which could explain our findings linking L/Z with DHA and choline in terms of neurodevelopmental outcomes.

The greatest strength of this study is the use of a highly sensitive and novel method of measuring fetal neurodevelopment. The relatively large sample size and ability to assess dietary intake of both food (eggs) and nutrients (choline, L/Z) during gestation are additional strengths. The main limitation of this work includes the inability to determine cause and effect due to the observational nature of a secondary analysis. The parent clinical trial was not powered to detect differences in fABAS or fetal HRV based on maternal dietary intake; although, our results suggest the sample size was sufficient. Another limitation includes the inherent issues with relying on self-reported measures of dietary intake; however, the DHQ-II has been shown to provide excellent rank order estimates of nutrient intake suggesting an accurate representation of dietary intake relatively within a sample and has been used effectively in pregnant populations.[28] Additionally, the nutrients analyzed within this paper are contained within many different foods in addition than eggs (e.g. seafood, leafy greens, etc.), and these food sources should be considered when conducting future analyses. We included biomarker assessment of DHA status in this study, but future trials would be strengthened by the inclusion of choline and L/Z biomarker status of the mother, in addition to dietary intake.

While consumption of choline during pregnancy is thought to be crucial for neonatal brain development, most prenatal vitamins contain no or very little choline. Furthermore, L/Z is never found in prenatal vitamins. Therefore, dietary intake from food is necessary and guidelines regarding choline and egg intake during pregnancy are profoundly needed. Future research should focus on examining relationships between maternal choline, L/Z, and DHA intake and serum markers on fetal and infant neurodevelopmental outcomes through randomized controlled trials in diverse cohorts.

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Biographies

Dr. Danielle Christifano is an Assistant Professor at the University of Kansas Medical Center. Dr. Christifano is a nutrition scientist whose work aims to incorporate diet and lifestyle interventions that impact maternal and infant autonomic nervous system function and development. In addition, her lab collaborates with neurocognitive scientists in order to answer questions regarding the impact of dietary interventions on infant health and cognition.

Dr. Lynn Chollet Hinton is an Assistant Professor in the Department of Biostatistics Data Science at the University of Kansas Medical Center and an Associate Member in the Cancer Prevention and Control program at the University of Kansas Cancer Center. Dr. Chollet Hinton's research involves multidisciplinary data science work that combines epidemiology, statistics, and biology for a holistic approach to population health.

Dr. Dirk Hoyer is the Head of Research Group Systems Analysis at the Biomagnetic Center at the Jena University. He is an expert in fetal magnetocardiographic recordings and a resulting unique methodology of prenatal diagnosis with regard to the identification of fetal maturation disturbances with instantaneous prenatal consequences as well as the "fetal programming" of diseases in later postnatal age, such as cardiovascular, metabolic, hyperkinetic, cognitive and behavioral problems.

Alexander Schmidt is a Scientific Assistant in the Hans Berger Clinic of Neurology, Biomagnetic Center, University of Jena, Germany. He works closely with Dr. Dirk Hoyer in fetal biomagnetic research.

Dr. Kathleen Gustafson is a Research Associate Professor in the Department of Neurology at the University of Kansas Medical Center. Her research is focused on the Developmental Origins of Health and Disease (DOHaD). She is an expert in electrophysiology and her

research utilizes a dedicated fetal biomagnetometer to measure naturally occurring magnetic fields that surround bioelectric currents in the maternal and fetal bodies. Development and maturation of fetal cardiac autonomic control not only gives us insight into cardiac regulation, but also brain development.

Data availability statement:

The authors will make data and materials supporting the results or analyses presented in their paper available upon reasonable request

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Table 1:

Descriptive Statistics

Maternal	
Age at enrollment (yrs)	30.3 ± 4.9
Maternal Education, n (%)	
Less than high school graduate	6 (2.0)
HS graduate or GED	29 (9.7)
Some college or tech school	73 (24.3)
Bachelor's Degree Obtained	105 (35.0)
Master's Degree Obtained	72 (24.0)
Doctorate	15 (5.0)
Family Income, n (%)	
Less than $15,000	22 (7.3)
$15,000 – $24,999	16 (5.3)
$25,000 – $49,999	39 (13.0)
$50,000 – $99,999	102 (34.0)
$100,000 – $149,999	81 (27.0)
At least $150,000	38 (12.7)
Unknown	2 (0.7)
Ever Smoker, yes n (%)	75 (25.0)
6 Months prior, yes n (%)	36 (12.0)
Current Smoker, yes n (%)	12 (4.0)
Egg intake at baseline (eggs/wk)	4.7 ± 4.4
L/Z intake at 32wks (mg/day)	2.7168 ± 3.3529
Choline intake at 32wks (mg/day)	275.1 ± 137.8
RBC DHA at 32wks (%wt TFA)	10.1 ± 2.6
Fetal Neurodevelopment	
fABAS at 32wks	31.7 ± 2.1
SDNN at 32wks	23.4 ± 8.2
*Log*SDNN at 32wks	3.1 ± 0.3
RMSSD at 32wks	5.5 ± 2.3
*Log*RMSSD at 32wks	1.6 ± 0.4
fABAS at 36wks	33.1 ± 2.1
SDNN at 36wks	24.9 ± 7.7
*Log*SDNN at 36wks	3.2 ± 0.3
RMSSD at 36wks	6.0 ± 2.4
*Log*RMSSD at 36wks	1.7 ± 0.4

Data are presented as mean ± standard deviation or n(%)

Table 2:

Relationships between choline, nutrient interactions, and HRV and fABAS outcomes

	fABAS			LogSDNN			LogRMSSD		
	Beta (SE)	**p-value**	**Standardized coefficient**	**Beta (SE)**	**p-value**	**Standardized coefficient**	**Beta (SE)**	**p-value**	**Standardized coefficient**
32 week fetal metrics									
Choline Intake (mg/day)	0.0030 (0.0016)	0.0610	0.2358	0.0002 (.0002)	0.2568	0.0298	−0.00003 (0.0002)	0.9001	−0.0039
L/Z Intake (mg/day)	0.1698 (0.1122)	0.1319	0.1399	−0.0082 (0.0078)	0.2933	−0.0274	0.0008 (0.0092)	0.9306	0.0027
DHA status (% TFA)	0.020 (0.0572)	0.7262	0.0527	0.0071 (0.0083)	0.3921	0.0188	0.0074 (0.0099)	0.4544	0.0194
Choline*L/Z	−0.0005 (0.0002)	**0.0284**	−0.2154	N/A			N/A		
Choline*L/Z*DHA	N/A			N/A			N/A		
36 week fetal metrics									
Choline Intake (mg/day)	0.0035 (0.0058)	0.5520	−0.0129	0.00003 (0.0009)	0.9734	−0.0063	−0.0001 (0.0002)	0.7146	−0.0119
L/Z Intake (mg/day)	0.8835 (0.5127)	0.0865	0.0870	0.2385 (0.0763)	**0.0020**	0.0321	0.0078 (0.0095)	0.4128	0.0261
DHA status (% TFA)	0.1383 (0.1639)	0.3999	−0.0780	0.0340 (0.0245)	0.1670	−0.0007	0.0142 (0.0104)	0.1733	0.0373
Choline*DHA	−0.0003 (0.0006)	0.6143	0.0592	0.0000004 (0.000088)	0.9961	0.0326	N/A		
Choline*L/Z	−0.0019 (0.0009)	**0.0346**	−0.1002	−0.00037 (0.00014)	**0.0077**	−0.0135	N/A		
L/Z*DHA	−0.0789 (0.0466)	0.0919	−0.2842	−0.0218 (0.0070)	**0.0020**	−0.1120	N/A		
Choline*L/Z*DHA	0.0002 (0.0001)	**0.0410**	0.2059	0.00003 (0.00001)	**0.0079**	0.0402	N/A		

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Table 3.

Relationships between egg, nutrient interactions, and HRV and fABAS outcomes

	fABAS			LogSDNN			LogRMSSD		
	Beta (SE)	**p-value**	**Standardized coefficient**	**Beta (SE)**	**p-value**	**Standardized coefficient**	**Beta (SE)**	**p-value**	**Standardized coefficient**
32 week fetal metrics									
Egg Intake (eggs/day)	0.0210 (0.0327)	0.5210	0.0915	0.0064 (0.0064)	0.3150	−0.0144	0.0478 (0.0210)	**0.0239**	−0.0212
L/Z Intake (mg/day)	−0.0269 (0.0460)	0.5583	−0.0903	0.0181 (0.0121)	0.1366	0.0047	0.0033 (0.0075)	0.6601	0.0110
DHA status (% TFA)	0.0207 (0.0575)	0.7194	0.0545	0.0080 (0.0083)	0.3379	0.0211	0.0334 (0.0146)	**0.0232**	0.0241
Egg*DHA	N/A			N/A			−0.0052 (0.0022)	**0.0176**	−0.0598
Egg*L/Z	N/A			−0.0036 (0.0018)	0.0432	−0.0524			
Egg*L/Z*DHA	N/A			N/A			N/A		
36 week fetal metrics									
Egg Intake (eggs/day)	0.3288 (0.1551)	**0.0353**	−0.1741	−0.0088 (0.0050)	0.0786	−0.0385	0.0051 (0.0079)	0.5153	−0.0197
L/Z Intake (mg/day)	0.3473 (0.3580)	0.3333	−0.1250	0.0006 (0.0063)	0.9228	0.0021	0.0281 (0.0145)	0.0536	0.0386
DHA status (% TFA)	0.1590 (0.1100)	0.1501	0.0683	0.0087 (0.0086)	0.3149	0.0228	0.0161 (0.0103)	0.1186	0.0424
Egg*DHA	−0.0336 (0.0166)	**0.0438**	−0.1066	N/A			N/A		
Egg*L/Z	−0.1015 (0.0613)	0.0997	−0.1526	N/A			−0.0036 (0.0021)	0.0925	−0.0521
L/Z*DHA	−0.0332 (0.0340)	0.3293	0.0759	N/A			N/A		
Egg*L/Z*DHA	0.0090 (0.0054)	0.0971	0.3459	N/A			N/A		