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Maternal choline and respiratory coronavirus effects on fetal brain development

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ABSTRACT

Prenatal COVID-19 infection is anticipated by the U.S. Centers for Disease Control to affect fetal development similarly to other common respiratory coronaviruses through effects of the maternal inflammatory response on the fetus and placenta. Plasma choline levels were measured at 16 weeks gestation in 43 mothers who had contracted common respiratory viruses during the first 6–16 weeks of pregnancy and 53 mothers who had not. When their infants reached 3 months of age, mothers completed the Infant Behavior Questionnaire-Revised (IBQ-R), which assesses their infants' level of activity (Surgency), their fearfulness and sadness (Negativity), and their ability to maintain attention and bond to their parents and caretakers (Regulation). Infants of mothers who had contracted a moderately severe respiratory virus infection and had higher gestational choline serum levels ($\geq$7.5 mM consistent with U.S. Food and Drug Administration dietary recommendations) had significantly increased development of their ability to maintain attention and to bond with their parents (Regulation), compared to infants whose mothers had contracted an infection but had lower choline levels ($<$7.5 mM). For infants of mothers with choline levels $\geq$7.5 μM, there was no effect of viral infection on infant IBQ-R Regulation, compared to infants of mothers who were not infected. Higher choline levels obtained through diet or supplements may protect fetal development and support infant early behavioral development even if the mother contracts a viral infection in early gestation when the brain is first being formed.

1. Introduction

The Centers for Disease Control (CDC) anticipate that maternal COVID-19 infection will affect fetal development like other respiratory coronaviruses (Centers for Disease Control and Prevention, 2020). COVID-19 is not usually transmitted directly to the fetus (Kimberlin and Stagno, 2020). Instead, the maternal inflammatory response to the virus is thought to be the pathogenic mechanism underlying effects on the fetus and its support by the placenta (Brown and Meyer, 2018). Common respiratory infections increase the risk for attention deficit disorder, autism spectrum disorder, and schizophrenia, with relative risks ranging from 1.6 to 2.2 (Mednick et al., 1988; Hornig et al., 2018; Dreier et al., 2016). Higher maternal C-reactive protein (CRP) at the beginning of the second trimester is associated with increased risk of schizophrenia in the offspring (Canetta et al., 2014).

We reported that common bacterial and viral infections from 10 to 16 weeks gestation increase maternal inflammation as assessed by elevated maternal CRP levels. Higher maternal choline levels at 16 weeks gestation consistent with U.S. Food and Drug Administration (FDA) dietary recommendations for pregnant women appear to mitigate the adverse effects of the inflammation on the offspring's behavior at 3 months of age (Freedman et al., 2019). We analyzed a subset of the data from that study to examine the effects on infant behavior if the mother had contracted a respiratory virus. The new analysis may provide information relevant to potential COVID-19 effects on fetal brain development and their interaction with higher prenatal maternal choline levels.

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2. Methods

At 16 weeks gestation, mothers were asked if they had experienced illnesses in the preceding 6 weeks including infections. Most of the 43 mothers with viral respiratory infections rated their symptoms as moderate to severe (N = 36, 84%). These self-ratings of symptom severity correlated with the clinical assessment of infection severity in the prenatal clinic medical record (rho = 0.95, $P < 0.001$). A comparison group of mothers (N = 53) reported no infections. Maternal CRP and choline levels were determined at 16 weeks in both groups. CRP levels remain elevated for up to 10 days after onset of a viral respiratory infection (Melbye et al., 2004). Infection reports at 22, 28, 34, and 40 weeks had no significant effects on infant outcomes (Freedman et al., 2019). Choline levels ≥7.5 μM are consistent with diets that meet or exceed the FDA minimum daily requirement for pregnant women, 550 mg (Wu et al., 2012).

When the infant reached 3 months of age, mothers completed the Infant Behavior Questionnaire-Revised Short Form (IBQ-R; Gartstein and Rothbart, 2004), a parent-report measure of infant behaviors indicative of temperamental reactivity and self-regulation. Mothers rated 91 infant behaviors on Likert scales ranging from 1 (never) to 7 (always). The ratings were then averaged into 14 scales of infant temperament and behavior. Factor weightings from Gartstein and Rothbart (2004) original report grouped these 14 scales into 3 dimensions: Orienting/Regulation (Regulation), Negative Affectivity (Negativity), and Surgency/Extraversion (Surgency). Regulation includes duration of attention, enjoyment of quiet play, cuddliness and engagement with parents, and soothability; Surgency includes general level of activity and perceptual sensitivity, pleasure in high-intensity activities, vocal reactivity, and smiling and laughter; Negativity includes fearfulness, sadness, and recovery after exposure to a stressor.

This research was approved by the Colorado Multi-Institutional Review Board and conducted in accordance with the Helsinki Declaration as revised 1989. Detailed methods have been previously reported (Freedman et al., 2019). Full statistical analyses are in the Supplement (Tables S1–S6).

3. Results

Mothers with respiratory viral infections in early gestation were younger and more likely to be depressed and anxious (Table 1). Viral infection was associated with increased CRP, 11.0 mg/L (SEM 1.4) in infected women versus 7.5 mg/L (SEM 1.2) in uninfected women, $F_{df1,82} = 4.06$, $P = 0.047$. The range in infected women in our sample was 0.6–38.8 mg/L. In a case series of 9 COVID-19 infected mothers from Wuhan, China, CRP levels ranged from 3.3 to 33.4 mg/L (Chen et al., 2020).

Infants of mothers who contracted viral infections and had choline levels ≥7.5 μM had significantly increased 3-month IBQ-R scores on the Regulation dimension and specifically the Attention scale in the Regulation dimension, compared to infants of mothers who had viral infections and had choline levels <7.5 μM (Table 2). For infants of mothers with choline levels ≥7.5 μM, there was no effect of viral infection on infant IBQ-R Regulation and Attention, compared to infants of mothers who were not infected. The increased maternal anxiety and depression in the viral-infected mothers were not associated with their infants' IBQ-R Regulation.

Table 1
Demographic differences related to respiratory viral infection by 16 weeks gestation.

Parameter	Mother with respiratory viral infection N = 43	Mother with no infection[a] N = 53	[b]P =
Maternal status			
Maternal age, mean (SD), yrs	28.8 (5.9)	31.6 (5.5)	0.02
European-American N (%)	32 (74)	42 (79)	0.8
African-American N (%)	6 (14)	8 (15)	>0.9
Native-American N (%)	5 (12)	3 (6)	0.7
Hispanic N (%)	16 (37)	23 (45)	0.7
Maternal education, mean (SD), yrs	13.5 (2.9)	14.6 (3.2)	0.4
Lifetime American Psychiatric Association DSM-5 Depressive disorder N (%)	11 (24)	4 (6)	0.015
Center for Epidemiological Studies of Depression (CESD) 16 weeks gestation, mean (SD)	16.9 (10.4)	10.7 (8.3)	0.002
State-Trait Anxiety Inventory-State 16 weeks gestation, mean (SD)[c]	37.6 (12.1)	32.3 (9.6)	0.02
Perceived Stress Scale 16 weeks gestation, mean (SD)[c]	21.4 (7.7)	24.7 (9.6)	0.07
Maternal Adverse Childhood Experiences scale, mean (SD)	3.22 (2.38)	2.26 (2.36)	0.1
Antidepressant use N (%)	10 (24)	3 (6)	0.015
Acetaminophen N (%)	36 (85)	42 (80)	0.5
Obesity BMI > 30 N (%)	6 (16)	15 (30)	0.14
Gestational diabetes N (%)	1 (2)	5 (12)	0.06
Prenatal vitamins with folate N (%)	37 (88)	48 (92)	0.5
Maternal serum 16 weeks gestation choline, mean (SD), μM	6.13 (1.79)	6.54 (2.11)	0.3
Maternal postnatal PSI Parenting Stress Index, mean (SD)	25.0 (9.6)	24.8 (9.0)	>0.9
Pre-eclampsia N (%)	4 (10)	4 (10)	>0.9
Vaginal delivery N (%)	29 (71)	32 (67)	0.7
Neonate status			
Male sex N (%)	24 (58)	26 (48)	0.6
APGAR 5 min, mean (SD)	8.82 (0.80)	8.63 (0.96)	0.2
Gestational age, mean (SD), days	273 (13)	272 (16)	0.8
Large for gestational age N (%)	9 (21)	7 (13)	>0.9
Small for gestational age N (%)	1 (2)	2 (4)	>0.9
Birth weight, mean (SD), grams	3166 (528)	3071 (544)	0.5
Birth head circumference, mean (SD), cm	34.3 (1.5)	34.5 (3.0)	0.6

[a] These mothers had no bacterial or viral infections in any body system.
[b] From *t*-test or Fisher's exact test.
[c] Correlation with CESD r > 0.7, $P < 0.001$.

4. Discussion

Our results show that higher prenatal choline levels may help protect the fetus's developing brain even if the mother contracts a viral respiratory infection in early pregnancy. The timing of the effect on viral infection at the beginning of the second trimester on the development of infant behavior is consistent with investigations in human fetal brain. Inhibitory interneurons are being formed in the hippocampus in this gestational window, when they are most vulnerable to maternal inflammation (Vasistha et al., 2019). Fetal development of inhibitory interneuron function, as measured by cerebral evoked potential inhibition in newborns, is associated with the development of infant attention and other self-regulatory behavior as measured with the IBQ-R Regulation dimension (Freedman et al., 2019).

The IBQ-R is a widely used indicator of the development of behavior in infants. Parental ratings have been shown to be similar across different populations (Gartstein and Rothbart, 2004; Bosquet Enlow et al., 2016). There are no normal or abnormal values established, but IBQ-R ratings are significantly related to scores on other rating scales as infants reach early childhood (Putnam et al., 2008). Regulation scores predict the child's ability to succeed in early schooling. Lower IBQ-R Regulation at 1 year of age is associated with decreased reading readiness at age 4 years and with problems in concentration, and conscientiousness in children through 7 years of age (Gartstein et al., 2016; Slobodskaya and Kozlova, 2016). In addition, Regulation modulates the child's Surgency and Negativity to meet cultural expectations as the child develops (Ahadi and Rothbart, 1993). Poor attention and social interactions in early childhood are early signs of psychopathology in individuals who later develop severe mental illness as adults (Rossi et al., 2000).

Table 2
Effects of prenatal viral respiratory infection and maternal choline level on Infant Regulation at 3 months of age.[a]

IBQ-R Regulation		Choline < 7.5 μM 16 weeks	Choline ≥ 7.5 μM 16 weeks	[b,c]Choline P =
3 months, mean (SE)	No infection by 16 weeks	5.67 (0.18)	5.34 (0.22)	0.34
	Viral infection by 16 weeks	4.55 (0.25)	5.23 (0.30)	0.002
	[b]Viral P =	0.005	0.82	
IBQ-R Attention Duration	No infection by 16 weeks	5.00 (0.45)	4.47 (0.57)	0.25
	Viral infection by 16 weeks	2.64 (0.64)	4.21 (0.77)	0.006
3 months, mean (SE)	[c]Viral P =	< 0.001	0.48	

LSD for marginal means.

[a] Lower scores for the Regulation dimension and Attention Duration scale indicate that the viral infection has adversely affected the infant's ability to concentrate, to interact with caregivers, and to maintain attention.

[b] Regulation: viral infection*choline ≥ 7.5 μL, $F_{df1,73}$ = 13.22, P = 0.001.

[c] Attention Duration: viral infection*choline ≥ 7.5 μL, $F_{df1,73}$ = 7.24, P = 0.009.

Maternal immune activation models the inflammatory effect of infection in pregnancy in laboratory models. Mice are injected with double-stranded RNA to mimic viral infection or lipopolysaccharide to mimic bacterial infection (Wu et al., 2015; Zhang et al., 2018). Both insults produce maternal inflammatory responses with increased Interleukin-6 (IL-6) that reaches the fetal brain (Smith et al., 2007). The offspring's behavioral deficits include fearfulness, hyperactivity, and decreased learning. Maternal choline supplementation decreases inflammation from maternal immune activation. Fetal brain IL-6 is decreased, and behavioral effects are reversed (Wu et al., 2015; Zhang et al., 2018). Choline is an agonist at α7-nicotinic receptors, which are expressed in large amounts in both fetal brain and placenta (Frazier et al., 1997; Birnbaum et al., 2014; Lips et al., 2005). *CHRNA7*, the gene that produces the α7-nicotinic receptor, is expressed in fetal neurons, mescenchymal placental cells, and Hofbauer activated fetal placental macrophages (Lips et al., 2005; Kunii et al., 2015). α7-nicotinic receptors regulate activation of Nuclear Factor-κβ (NF-kB) and Protein kinase B (AKT) (Zhang et al., 2018; Freedman, 2014). Choline supplementation alters α7-nicotinic receptor expression in the placenta and activates the nF-kB and AKT pathway (Wu et al., 2015; Zhang et al., 2018). Null mutation of *CHRNA7* increases the effect of maternal inflammation and blocks choline's promotion of cerebral development (Wu et al., 2015; Wang et al., 2003). The effects of choline supplementation in human pregnancy are also associated with *CHRNA7* genotype (Ross et al., 2016).

Many pregnant women have inadequate dietary choline intake and therefore supplements may be indicated (Moore et al., 2019). Of the four double-blind placebo-controlled studies of choline or phosphatidylcholine supplementation in pregnancy, three have found significant effects on infant cognition or behavior (Ross et al., 2016; Jacobson et al., 2018; Caudill et al., 2018); one did not (Cheatham et al., 2012). None reported serious adverse effects. Two of the studies found positive effects of supplementation in women who were not selected for adverse risk factors such as infection (Ross et al., 2016; Caudill et al., 2018). Daily 6300 mg phosphatidylcholine supplements containing 900 mg choline have been used safely during pregnancy from 15 weeks gestation until delivery with subsequent positive effects on the child's attention and social behavior through 3.5 years of age (Ross et al., 2016). The increased significance of effects in mothers with infection in this study likely represents an interaction between the adverse effect of the infection and the positive effect of higher choline levels.

Effects of choline in COVID-19 infection on infant development are as yet unknown, and no mother in this study had an infection requiring intensive care medical support or COIVD-19. CRP levels in this study indicate a wide variance in inflammatory reactions in pregnant women in this study, but the range is similar to the range of CRP levels in Chinese pregnant women who were infected with COVID-19. The key finding of this study is that higher prenatal choline levels are associated with decreased adverse effects on the infant's development if the mother has a moderately severe respiratory virus infection. In conjunction with the CDC's current advice on COVID-19's effects in pregnancy, phosphatidylcholine or choline supplements along with other prenatal vitamins may help buffer the fetal brain from the possible detrimental impact of the current pandemic and decrease the risk of the children's future mental illness.

Data sharing

De-identified data will be share on request to the authors.

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CRediT authorship contribution statement

Robert Freedman: Conceptualization, Methodology, Formal analysis, Writing - original draft, Funding acquisition. **Sharon K. Hunter:** Conceptualization, Methodology, Data curation, Validation, Writing - review & editing. **Amanda J. Law:** Conceptualization, Methodology, Data curation, Writing - review & editing. **Angelo D'Alessandro:** Methodology, Data curation, Writing - review & editing. **Kathleen Noonan:** Investigation, Methodology, Data curation, Validation, Writing - review & editing. **Anna Wyrwa:** Investigation, Methodology, Data curation, Writing - review & editing. **M. Camille Hoffman:** Conceptualization, Funding acquisition, Writing - review & editing.

Declaration of competing interest

None.

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The late Randal G. Ross conceived the initial study.

Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.jpsychires.2020.05.019.

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