Choline: A New Prenatal Supplement to Improve a Child’s Mental Health

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- No financial or commercial or other conflict of interest.

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Randy Ross, MD
August 9, 1961 - December 20, 2016
Objectives

• Explore the developmental origins of health and disease hypothesis (DOHaD) as it pertains to mental health

• Assess genetic and environmental factors that impact fetal brain development

• Describe how choline improves human brain development, starting prenatally
The perinatal experience influences maternal, pregnancy & child outcomes

Adverse Pregnancy Outcomes
- Preterm birth
- Low birthweight
- Perinatal Mood Disorders

Later in the life of the child:
- Mood and anxiety disorders
- Cognition
- Behavioral & Developmental disorders
- Autism Spectrum Disorder
- Schizophrenia
- Chronic diseases of adulthood
- Shortened telomeres

“The things desired by the mother are often found impressed on the child that the mother carries”

- Leonardo Da Vinci 1452-1519
Nature & Nurture

http://www.scientificamerican.com

http://news.sciencemag.org/health/2012/06/sequencing-unborn
Brain function across the Life-Course can be Influenced by:
Genetics, Maternal, & Environmental Factors

Prenatal factors that have the greatest impact on child CNS (brain) development

- Maternal illness, infection
- Maternal alcohol, tobacco and marijuana use
- Maternal nutritional deficits
- Maternal psychosocial stress
- Maternal psychiatric symptoms
- Genetics
- Obstetric complications
Epidemiology of prenatal risk factors for serious mental disorders before birth (including schizophrenia)

- **Genetic (nature)**
  - many genes associated with schizophrenia are expressed at highest levels in the fetus and the placenta
  - Familial risk odds ratio ~ 4.2 (10%)
  - $CHRNA7$ deletion 15.0 (0.05%)

- **Maternal Environment (nuture)**
  - Respiratory infection 2.1 (40%)
  - Sexually transmitted infections (STIs) 5.0 (10%)
  - Cigarette smoking 3.4 (30%)
  - Prenatal Marijuana use OR?
    - decreases childhood cognition, possibly psychosis
  - Malnutrition 2.7
    - rare famines: Holland WWII, China Cultural Revolution
Scientists have understood that early brain dysfunction is identifiable in newborns who will later develop schizophrenia for > 20 years.
**CHRNA7**
- gene that makes α7 nicotinic acetylcholine receptor
- 15q13:
  - deletion in schizophrenia and autism spectrum disorder
  - duplication in ADHD
- **CHRNA7** and the alpha7 nicotinic acetylcholine receptor are involved in inhibitory neuron dysfunction related to sensory gating abnormalities in psychosis.
- A *heritable* defect in families with schizophrenia.
Development of cerebral inhibition in hippocampus

1. GABA is an excitatory neurotransmitter in early gestation
2. Fetuses have MANY MORE $\alpha_7$ nicotinic receptors
3. Stimulation critical for giant depolarizing potentials
4. Receptors more widely distributed (not in synapses)
5. There is little (prenatal) acetylcholinergic innervation
6. Choline is the primary agonist early in development
Prenatal brain develops using a series of neurotransmitter “operating systems”

**OS 2** (early) = primarily driven by choline and CHRNA7 gene

**OS5** (third trimester) = CHRNA7 appears again, leading to GABA becoming **inhibitory** (vs. excitatory)

*Once installed, the final system is permanent & cannot be re-installed after birth.*

-slide courtesy of Randy Ross, MD
Inhibitory Neurocircuits involved in:

- Working memory (prefrontal cortex)
- Somatosensory specificity (somatosensory cortex)
- Associative fear learning (auditory cortex)
- Recognition memory (hippocampus)

- Plus...schizophrenia, bipolar, autism, depression, PTSD, ADHD, Down syndrome, Parkinsons...
Normal genes and good maternal nutrition

Genetic and/or nutritional deficiencies

Scientific Question: Can choline supplements overcome deficiencies?
Causes of choline deficiency in Pregnancy

- **Genetics:**
  - Polymorphism in maternal PEMT (phenylethanolamine transferase)
    - associated with schizophrenia (17p11.2)
- **Dietary deficiency**, tremendous amounts needed for:
  - cell membrane synthesis
  - as one-carbon metabolism, DNA methylation
  - cholinergic agonist prior to cholinergic synapse ingrowth
- **Maternal stress**
  - This leads to liver sequestration in the first trimester
- ~25-50% of women fail to reach optimal choline intake (NA) during pregnancy, an estimated 20% smoke cigarettes
Genetics

Nicotine exposure

Transport
-Slide courtesy of Randy Ross, MD

Synthesis - Genetic

Diet & Gut physiology

Maternal Blood

Stress or Infection
- Cortisol mediated

Storage

Fetal

Genetics

Nicotine exposure
Choline supplementation decreases fetal/neonatal stress exposure

- Higher Maternal choline intake decreased umbilical cord cortisol levels
- No difference in maternal cortisol levels

Placental Corticotropin Releasing Hormone (pCRH) gene methylation increased and gene transcription decreased with increased choline

Jiang X et al, FASEB J 2012
One study found no difference in 5 month cognition related to maternal choline serum levels
  - Average estimated daily intake <400mg

Observational studies have uniformly associated higher choline levels or high choline intake with improved child cognition through the first 7 years of life.

No study has found any adverse effects. The maximum tolerated dose of choline is 7 grams, equivalent to 49 grams of phosphatidylcholine.

University of Colorado RCT: Phosphatidylcholine vs. Placebo

Primary outcome: CBCL at 40 months of life

Study timeline

Enrollment, Capsule trial ≤ 15 weeks
Randomization 16 weeks
18-22 weeks
32-34 weeks
Birth/PP
1 month PP → 6, 12, 18... 40 months

- Hair collection
- Blood draw
- Fetal Ultrasound
- Surveys
- Heart Rate Variability
- P50 assessment
Choline administration

- Phosphatidylcholine 3600 mg q am and 2700 (3600) mg q pm administered to pregnant women,
  - ~900 mg choline or 3-4 extra large eggs per day
  - Placebo is identical

- Women on both placebo and choline received dietary instruction (eggs, salmon, red meat, liver) and good prenatal care.

- Prenataldoctoradvice.com
Infant treated with choline at 1 month, EEG (P50) S2/S1 < 0.5

Infant treated with placebo at 1 month, EEG (P50) S2/S1 > 0.5

Example of P50 study in adult control versus adult with schizophrenia

Pilot RCT: Choline improves Newborn EEG

Ross Am J Psychiatry 2013
Pilot RCT Data: Choline Improves Newborn EEG, which predicts Child Behavior at 40 months

Prenatal choline enhances P50 inhibition in newborns of both low and high risk mothers*

Ross et al, Am J Psychiatry 2013

*% P50 S2/S1 < 0.5, all mothers, p = 0.007

Newborn P50 predicts 40 month-old behavior on Child Behavior Checklist (CBCL)

Prenatal choline (also) enhances P50 inhibition and regulation in infants of mothers with second trimester infections

Freedman et al, J Pediatrics 2019
Prenatal choline (also) enhances P50 inhibition in newborns of mothers with marijuana use

Hoffman et al, Psychol Med 2019
Prenatal choline (also) enhances infant regulation at 1 month of age in mothers with marijuana use.

Hoffman et al, Psychol Med 2019
Proximity of α7 (CHRNA7) and Cannabidiol 1-CB1 interneurons

Fig. 1. From Morales et al., 2008. Double labeling of interneurons in rat dorsal hippocampus CA1 for CHRNA7 and CB1 (CNR1) by riboprobe in situ hybridization. The study also found double labeling of CHRNA7 positive interneurons with riboprobes for GAD 65, GAD 67, and CCK, proving that the labeled neurons are inhibitory interneurons. The width of each photomicrograph is 1870 μm.
**Prenatal Choline:**
- Improves cognitive function into adulthood
- Decreases risk of impaired neural programming & development in relation to:
  - Schizophrenia, psychosis
  - ADHD
  - Down syndrome
  - Fetal alcohol exposure
  - Prenatal infection (2nd tri)
  - Maternal MJ use

Freedman, Hunter, Hoffman, AJP 2018
Ross et al, AJP 2016
Bell et al, Psych Serv 2015
Choline dosing

- We aim for 900-1000 mg of choline, equivalent to about 9000 mg of phosphatidylcholine.

- Pure phosphatidylcholine costs about $1000 per pregnancy and was required by the US FDA.

- Common retail capsules or liquid cost about $260-$300 per pregnancy.

- Soy lecithin in granular form is available as a health food supplement for about $260 per pregnancy. It should be mixed with food, such as a soup.
Foods Rich in Choline (mg/100g)

- Salmon – smoked – 220mg/100g
- Chicken – roasted – 79mg/100g
- Salmon – cooked – 91mg/100g
- Tilapia – 83mg/100g
- Soy protein powder – 86mg/100g
- Peanut Butter – 66mg/100g
- Cocoa powder – 115mg/110g
- Skim Milk – 38mg/cup

- Fried egg – 270/100g
- Hard-boiled egg – 230/100g
- Large Egg (one) – 120mg
- Beef Liver – 350mg/100g
- Chicken Liver – 330mg/100g
- Almonds – 52mg/100g
- Broccoli – 40mg/100g
- Brussels sprouts – 41mg/100g
- Cauliflower – 39mg/100g

Standard Prenatal Care

Incorporates:

- Genetics
- Nutrition
  - ☑ Folate
  - ☐ Choline
- Environmental health
- Lifestyle
- Infections
- & Immunology
- Psychosocial factors
Standard Prenatal Care

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- Genetics
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- Psychosocial factors
Pre-quel: Maternal folic acid supplements & dietary fortification prevent open neural tube defects (spina bifida)

cdc.gov/ncbddd/birthdefectscount/data.html
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Denver Health Women’s Care Staff & Patients
Take Away Points:

1. Choline buffers the fetal brain from adverse genetics and environmental exposures that can predispose to mental illnesses and/or behavioral issues

2. Primary prevention for the child

3. Improved health for society. More thriving, less struggle
Infant P50 sensory gating ratios are stable across early childhood
Study timeline

- Hair collection
- Blood draw
- Fetal Ultrasound
- Heart Rate Variability
- Questionnaires
## Participant Characteristics

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>Term N=181</th>
<th>Preterm N=23</th>
<th>P-value</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Maternal Age (years) mean (std)</strong></td>
<td>28.5 ± 6.0</td>
<td>32.3 ± 6.1</td>
<td>0.04</td>
</tr>
<tr>
<td><strong>Gravidity mean (std)</strong></td>
<td>3.0 ± 0.23</td>
<td>3.85 ± 0.61</td>
<td>0.007</td>
</tr>
<tr>
<td><strong>Parity mean (std)</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Term</td>
<td>1.82 ± 0.11</td>
<td>1.71 ± 0.21</td>
<td>NS</td>
</tr>
<tr>
<td>Preterm</td>
<td>0.23 ± 0.05</td>
<td>0.58 ± 0.15</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Abortions/Ectopics</td>
<td>1.03 ± 0.09</td>
<td>1.32 ± 0.19</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Living children</td>
<td>2.00 ± 0.10</td>
<td>1.93 ± 0.23</td>
<td>0.003</td>
</tr>
<tr>
<td><strong>Mode of Delivery n(%)</strong></td>
<td></td>
<td></td>
<td>0.06</td>
</tr>
<tr>
<td>Vaginal Delivery</td>
<td>127 (70)</td>
<td>13 (56)</td>
<td></td>
</tr>
<tr>
<td>Cesarean Delivery</td>
<td>54 (30)</td>
<td>10 (44)</td>
<td></td>
</tr>
<tr>
<td><strong>Pre-pregnancy BMI (kg/m2) mean (std)</strong></td>
<td>27.9 ± 0.55</td>
<td>28.3 ± 0.87</td>
<td>NS</td>
</tr>
<tr>
<td><strong>Gestational Age at delivery (weeks) mean (std)</strong></td>
<td>38.7 ± 0.20</td>
<td>35.6 ± 0.47</td>
<td>0.001</td>
</tr>
<tr>
<td><strong>Birthweight (grams) mean (std)</strong></td>
<td>3225 ± 46.6</td>
<td>2702 ± 705</td>
<td>0.01</td>
</tr>
<tr>
<td>Female fetus n(%)</td>
<td>83 (46)</td>
<td>15 (66)</td>
<td>0.05</td>
</tr>
</tbody>
</table>
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<th>P-value</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Race/ethnicity n(%)</strong></td>
<td></td>
<td></td>
<td>0.03</td>
</tr>
<tr>
<td>White/Caucasian</td>
<td>132 (72)</td>
<td>12 (52)</td>
<td></td>
</tr>
<tr>
<td>African American</td>
<td>17 (9)</td>
<td>6 (27)</td>
<td></td>
</tr>
<tr>
<td>Native American</td>
<td>17 (9)</td>
<td>3 (11)</td>
<td></td>
</tr>
<tr>
<td>Biracial</td>
<td>14 (8)</td>
<td>2 (6)</td>
<td></td>
</tr>
<tr>
<td>Asian/Other</td>
<td>1 (&lt;1)</td>
<td>0 (0)</td>
<td></td>
</tr>
<tr>
<td>Hispanic ethnicity</td>
<td>96 (53)</td>
<td>10 (44)</td>
<td></td>
</tr>
<tr>
<td><strong>Years education n(%)</strong></td>
<td></td>
<td></td>
<td>0.001</td>
</tr>
<tr>
<td>Less than high school diploma</td>
<td>51 (28)</td>
<td>5 (24)</td>
<td></td>
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<tr>
<td>High school diploma/GED</td>
<td>68 (38)</td>
<td>13 (59)</td>
<td></td>
</tr>
<tr>
<td>Associates or certificate</td>
<td>19 (11)</td>
<td>2 (8)</td>
<td></td>
</tr>
<tr>
<td>Bachelors</td>
<td>19 (11)</td>
<td>1 (&lt;1)</td>
<td></td>
</tr>
<tr>
<td>≥ Masters</td>
<td>24 (14)</td>
<td>2 (8)</td>
<td></td>
</tr>
<tr>
<td><strong>Marital status n(%)</strong></td>
<td></td>
<td></td>
<td>0.01</td>
</tr>
<tr>
<td>Single/divorced/separated</td>
<td>47 (26)</td>
<td>7 (32)</td>
<td></td>
</tr>
<tr>
<td>Lives with partner</td>
<td>43 (24)</td>
<td>8 (35)</td>
<td></td>
</tr>
<tr>
<td>Married</td>
<td>91 (50)</td>
<td>7 (32)</td>
<td></td>
</tr>
</tbody>
</table>
Other effective prenatal interventions

- Folic acid
- Vitamins A and D
- Tobacco cessation
- Antidepressant treatment
- Decrease acetaminophen use
- Prevention of post partum depression and mania
- Parenting classes
Infant P50 Sensory Gating Ratios predict an increased risk for later emotional and behavior symptoms.