A Research Perspective: Can Mental Illness Be Prevented in the Womb?

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March 4, 2017
Financial Disclosures

NONE TO REPORT
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Prevention is the Holy Grail in mental illness.
Maternal folic acid supplements prevent developmental abnormalities

Folic acid, diet, vitamins
Folic acid + vitamins
Good diet + vitamins
No Treatment

Can Mental Illness Be Prevented in the Womb?
Critical Periods in Development and Schizophrenia — SYMPTOMS

Fetal and newborn brain formation
• developmental delay

Childhood—3.5-12 years
• ADD, social isolation

Adolescence—13-18 years
• Anxiety, depression, OCD, school failure, concealed hallucinations, suicide

Early Adulthood—18-30 years
• Chronic symptoms and disability
Prevention of Schizophrenia

**PRIMARY**
- intervention during fetal brain development

**SECONDARY**
- intervention during the prodrome of schizophrenia in adolescence

**TERTIARY**
- enhanced early treatment of first and second episodes
Early brain dysfunction in newborns who will later develop schizophrenia has long been known. Social deficits and problems with neuromotor functioning studied from infancy through adolescence collectively show that schizophrenia is a longitudinal syndrome with premorbid signs already present in childhood.
Many of the same genes that will later malfunction in schizophrenia are also responsible for the development of the brain before birth.
A gene clue: People with schizophrenia smoke more heavily than any other group

They activate alpha-7 nicotinic receptors, which are genetically abnormal in schizophrenia

“Very soon, being without a pack of cigarettes made me very uneasy.”

The brain develops before birth using a series of neurotransmitter “operating systems.” Once installed, the final system is permanent, but it cannot be installed after birth.
Cerebral Inhibition in the Hippocampus

In the fetal brain, alpha 7 nicotinic receptors are more widely distributed than in adults.
Choline activates nicotinic receptors before birth

- Normal ingredient in liver, eggs, and meats.

- Pregnant women often cannot keep up with the demands of the baby.

- Stress, anxiety, depression, infection, and nicotine use during pregnancy all increase the risk for mental illness in the baby and may be overcome by increasing choline.

- The single greatest risk factor, genetic risk, may be overcome by increasing choline as well.

- Phosphatidylcholine (PC) is available as a natural vitamin.
Choline Supplementation

Normal genes and nutrition

Genetic and nutritional deficiencies

Can choline supplements overcome deficiencies?

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Two ways to study choline

- Measure choline levels in mothers during pregnancy and wait 25 years to see if their children become ill.

- A clinical trial. All mothers receive dietary advice but half receive choline supplements and half receive placebo. The baby’s brain development is assessed at birth and then throughout childhood.
100 women fulfilled screening criteria and gave informed consent

50 randomized to placebo
3 withdrew before term
3 infants did not sleep during recording
8 smoked during first trimester
36 infants into outcome analysis

50 randomized to choline
4 withdrew before term
4 infants did not sleep during recording
2 smoked during first trimester
40 infants into outcome analysis
P50 sensory gating as a newborn biomarker of fetal brain development

- Associated with risk for mental illness

- Indicates target engagement of choline supplementation with α7-nicotinic receptors

- Develops during fetal brain development and can be fully assessed in the newborn period

- Predicts future behavior symptoms
Averaged P50 evoked potentials in infants treated in utero with choline or placebo supplementation

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Ross AJP 2013
P50 ratio in infants treated in utero with choline or placebo supplementation

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Ross AJP 2013
Choline enhances P50 inhibition in children of both low and high risk mothers*

* P50 S2/S1 < 0.5, all mothers, p=0.007
Parent rating of child’s behavior at 40 months of age
Newborn P50 predicts 40 month-old behavior

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Parent CBCL Rating

Withdrawn  Attention  Total Problems

P50 S2/S1 > 0.5  P50 S2/S1 < 0.5
Good diet alone does not prevent cleft palate and it will not prevent mental illness.
Like folic acid, choline is effective only before birth; you cannot wait until later when you are already ill.

Folic acid prevents spina bifida, cleft palate and even microcephaly. Choline may have similar broad effect.
What is the goal? Prevention of heart disease as a model

Primary prevention
• better diets, exercise, smoking restrictions.

Secondary prevention
• statins, antihypertensives, weight loss programs

Tertiary prevention
• AED’s, stents

The combined result is that deaths from heart disease have decreased significantly in the U.S.

We need to do the same for schizophrenia.
For more information: PrenatalDoctorAdvice.com
Other trials of choline

- One trial found no difference on 12 month cognition between choline and placebo in highly educated mothers; control women had higher levels of choline metabolites, indicating that they had adjusted their diet.

- Observational studies have uniformly associated higher choline levels or high choline intake with improved child cognition through the first 8 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.
The brain needs to inhibit responses to repeated sounds. This function develops just before birth and requires the effect of choline on nicotinic receptors. People with schizophrenia generally do not develop this capability.
At 30 months of age parents can reliably rate their child’s behavior.

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Perinatal choline

3-4 year old

Adult Schizophrenia