REVIEW

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Prospects for improving future mental health of children through prenatal maternal micronutrient supplementation in China

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Received: 9 March, 2020
Accepted: 9 May, 2020

ABSTRACT
Prenatal micronutrients in pregnant women's diets, including supplements, have an essential role in fetal brain development and may reduce the risk of mental disorders in offspring. Folic acid, vitamin D, omega-3 fatty acids, and choline have been investigated for this purpose. Folic acid supplementation throughout pregnancy has well-established positive effects. Vitamin D, administered to the mother before birth or to the newborn, has also been shown to reduce the risk of neurodevelopmental disorders. Omega-3 fatty acids during pregnancy have a more uncertain role, with recent trials questioning a beneficial effect on cognition and attention deficit disorder, despite positive effects on prematurity and neonatal wheezing prevention. Choline supplementation is associated with positive effects on cognition and behavior, including early behaviors associated with the development of autism and schizophrenia. There is no experience yet with COVID-19, but adverse effects on fetal brain development of most common coronaviruses are mitigated by higher choline levels. Maternal dietary supplementation of nutrients is a benign and inexpensive intervention in pregnancy to prevent life-long disability from mental illness. Use of dietary supplements in poorer, rural areas of China is below recommendations. Physicians, midwives, and public health officials in China can promote prenatal nutrient supplementation to reduce the future burden of mental illnesses that might be prevented before birth.

KEYWORDS
Folic acid, Vitamin D, Omega-3 fatty acids, Choline, Pregnancy, Coronavirus

Introduction

Prenatal development of the fetus has long-lasting consequences for the future health of the child. Children who are born small for gestational age have increased risk for a variety of future illnesses, including cardiovascular, pulmonary, and mental disorders.[1,2] Poor fetal development is associated with decreased executive function, ability to focus attention and control impulses; poorer educational achievement; and depressive symptoms.[3,4] Many children who show evidence of poor fetal development at birth are subsequently diagnosed with attention deficit disorder (ADD) or autism spectrum disorder (ASD) in childhood.[5,6]

Epidemiological evidence from the 1944–1995 Dutch Hunger Winter and the 1959–1961 Chinese famines is the most dramatic example of the effect of adverse maternal factors during pregnancy on the child's future mental wellbeing. Children conceived or in early gestation during the famines have a 2-fold increased risk of schizophrenia

DOI: 10.1002/ped4.12199

in adulthood.[7,8] Xu et al[9] provided further evidence that confirms these results from population in Guangxi, China.

Common factors adversely impacting fetal development include maternal infections, substance abuse, stress, and depression. COVID-19 infection in pregnancy is currently being assessed, but the virus does not seem to invade the amniotic space or be transmitted directly to the fetus.[10] However, viruses that do not directly infect the fetus may nonetheless increase the risk of future mental illness by causing maternal inflammation that adversely affects the placenta's ability to support fetal development.[11-14]

Positive steps that protect fetal brain development and mitigate the effect of these risks include increasing the maternal level of micronutrients, specifically folic acid, vitamin D, and choline, promoting full-term development through nutrients such as docosahexaenoic acid (DHA), as well as evaluation and treatment of maternal stress and depression. In this article, we review the evidence for these interventions with specific recommendations for expectant mothers, clinicians, and public health authorities responsible for population-wide preventive initiatives. Methodologically, we use a recent review of prenatal prevention of mental illness[15] supplemented with a Medline search [key words (folic acid OR vitamin D OR choline OR omega-3 fatty acids) AND pregnancy AND China].

Folic acid

Folic acid is a classic example of the positive effects of prenatal micronutrient supplementation on preventing serious fetal developmental problems. Neural tube defects, such as mental illnesses have various causes including maternal infection and familial, most likely genetic factors. After initial observations of folic acid deficiency, a randomized controlled trial evaluating folic acid supplementation was conducted with women who already had one child with a neural tube deficit and had decided to have another child. The study found that supplements of folic acid in early pregnancy reduced the risk of neural tube defects.[16] As a result of this study, folic acid supplementation in pregnancy has become one of the most important public health advances of recent years.

Most studies of prenatal folic acid are now retrospective because of general acknowledgement of its positive effects. These studies compare the effects of folic acid in women who did and did not decide to follow supplementation recommendations. Studies have found that preconception initiation is superior to initiation after 10 weeks gestation; supplementation is more effective than good diet, although the effects are additive; and the positive effects of supplementation extend beyond neural tube deficits to include facial clefts and other midline defects, and general cognition.[17,18] One of the few remaining randomized studies reported that folate supplementation during pregnancy, rather than fish oil and fish oil plus 5-methyltetrahydrofolate supplementation, improves children's ability to solve response conflicts.[19]

The positive data led public health authorities in many countries to mandate folic acid supplementation of processed foods, which has led to more recent studies showing less impressive effects. No adverse effects of taking recommended folic acid supplements, in the context of food supplementation, have been found.[20]

Folate supplementation in early pregnancy might also reduce the risk of mental health problems in children.[21] Folate is important in neurogenesis, cell growth and proliferation, and myelination. It has been associated with catecholamine neurotransmitters and serotonin synthesis.[22] Higher birth weights in children of mothers who had folic acid supplementation also may mediate the effect.[23,24]

The current recommendation from the U.S. Prevention Studies Task Force is a daily supplement containing 0.4 to 0.8 mg (400–800 μg) of folic acid, initiated pre-conception or as soon as possible in gestation.[25] Women who must take valproate and other anti-epileptics for seizure control, despite potentially harmful fetal effects, take higher doses.[26] In a Chinese Ministry of Health study in 21 counties in southern (Zhejiang and Jiangsu provinces) and northern (Hebei province) China in 1993–1996, only 41% of pregnant women used folic acid supplements.[27-29]

Vitamin D

Vitamin D is ingested or produced by skin exposure to ultraviolet light.[30] Emerging data suggest that gestational 25-hydroxyvitamin D (25(OH)D) status is associated with brain development in childhood and adolescence.[31-33] In humans, 25(OH)D levels during pregnancy are positively associated with neurocognitive development.[34,35] A large prospective study found that early childhood language development is positively associated with gestational 25(OH)D levels.[36]

An increasing amount of evidence links gestational vitamin D deficiency with neurodevelopmental disorders such as schizophrenia and ASD.[37,38] A Dutch birth cohort study reported an association between developmental vitamin D deficiency and autism traits.[39] Vitamin D supplements either prenatally or initiated within in the first month after birth may reduce the incidence of schizophrenia.[40-42] Some studies have linked ASD with neuronal migration, which starts at 6 weeks' gestation and ends around 24 weeks' gestation.[43] Expression of vitamin D receptor in the mammalian brain occurs as early as day 12 of gestation, and then increases throughout pregnancy.[44] Neonatal vitamin D deficiency might be associated with altered neuronal migration. A general mechanism might be alterations in the calcium flux associated with vitamin D-sensitive ion channels.[45] The active form of vitamin

D (1,25-dihydroxyvitamin D) affects the function of voltage-gated calcium channels.[46] Genes that code for the subunits of calcium channels are associated with the risk of schizophrenia and ASD.[47] In addition to these effects in the brain, cord-blood levels of 25(OH)D negatively associated with risk of respiratory infection and childhood wheezing.[48]

Currently manufactured prenatal multivitamins contain vitamin D in safe, recommended amounts and consider the amounts obtained via diet and sunlight. The usual recommended dose is 600 IU/day (Table 1).[49] The most robust effects of supplements have been found in Northern European and Nordic countries, where winter sunlight is restricted. Summer gestations in these countries are less likely to benefit from vitamin D supplements. In southern China between 2016 and 2019, 35% of pregnant women were vitamin D deficient. Deficiency was significantly associated with pre-term birth.[50] For example, in 2014 and 2015, 90% of pregnant women in Guizhou were deemed vitamin D insufficient[51] and low birth weight neonates and other birth complications were observed.[52] In the China-Anhui Birth Cohort Study, the incidence of small for gestational age was significantly reduced if mothers took recommended vitamin D supplements for at least 2 months.[53]

TABLE 1 Vitamin D daily intake recommendations for pregnant women

Society	Recommended daily intake (IU)
Chinese Nutrition Society	600
European Food Safety Authority	600
Global Consensus Recommendations on Prevention and Management of Nutritional Rickets	600

Choline

Choline, a micronutrient grouped with B vitamins, is an essential nutrient involved in many metabolic pathways, including the rapid cellular growth during fetal brain development. Choline is required for the biosynthesis of phosphatidylcholine, the main component of cell membranes. There is higher demand for choline during pregnancy because of accelerated one-carbon metabolism and the formation of new membranes as cells undergo division.[54] The neurotransmitter, acetylcholine, is produced directly from free choline in cholinergic neurons.[55] Earlier in fetal development, choline acts as the agonist at cholinergic receptors before they receive cholinergic synapses.[56] Animal studies indicate that perinatal choline supplementation or restriction fundamentally changes fetal brain development, particularly in the hippocampus, which can result in changes in attention and spatial memory abilities during adulthood.[57] *CHRNA7*, the gene for the a7-nicotinic acetylcholine receptor, which is activated by choline, has been associated with schizophrenia, ASD, and attention deficit-hyperactivity disorder.[58] However, mouse *CHRNA7* null mutants do not benefit from choline supplementation during gestation.[56]

The demands of pregnancy cause a pronounced reduction of choline pools, as first studied in animal models.[59] Many pregnant women cannot maintain adequate choline levels through dietary intake and endogenous synthesis. Nucleotide variants in PEMT, the gene for phosphatidylethanolamine N-methyltransferase, are associated with lower choline levels. This gene is also associated with schizophrenia in Asians.[60] Compounding the biological mechanisms, most pregnant women in North America have inadequate dietary consumption of choline, despite recommendations of a minimum of 500 mg/d. Egg yolks, liver, and red meats are the richest sources of choline, and soybeans, fish, and other meats also contain choline. Higher choline levels during gestation and increased dietary intake have been associated with improved cognition lasting as long as 8 years after birth.[61] Dietary intake and gestational choline levels in China have not been studied.

Four double-blind, placebo-controlled trials have investigated the effect of choline supplementation during gestation; the timing and dosage of supplementation varied in the studies.[62-65] The Ross et al[65] trial used high doses of phosphatidylcholine, which is the form found in most foods. An advantage of using phosphatidylcholine is that it is not metabolized by most intestinal bacteria, which can metabolize choline to trimethyl-urea or the cardiotoxic trimethyl-amineoxide. They found positive effects of early gestational phosphatidylcholine (6300 mg, equivalent to 900 mg free choline) on the development of cerebral inhibition, measured electrophysiologically in the newborns. This amount triples the minimal amount recommended in the diet. An early benefit on cerebral inhibition was found in the phosphatidylcholine-supplemented group compared with the placebo group. The positive effects extended to 3.5 years of age; early cerebral inhibition was associated with fewer problems in attention and social behavior.[65] It is possible that the benefits of supplementation could last even longer because these problems in childhood are associated with later mental illnesses, including schizophrenia.[66] In the Ross et al trial, positive outcomes were related to variants in the child's *CHRNA7* genotype. Benefits were also found in women at higher risk for an offspring with mental illness, including women who had mental illnesses themselves.

Other trials have found beneficial effects of choline supplementation in women who were heavy drinkers of alcoholic beverages and in average-risk women.[63,64] One trial failed to find a benefit of choline supplementation on infant cognitive function; this study used a single cognitive test to evaluate the benefit in offspring.[62] None of the four trials have found adverse side effects.

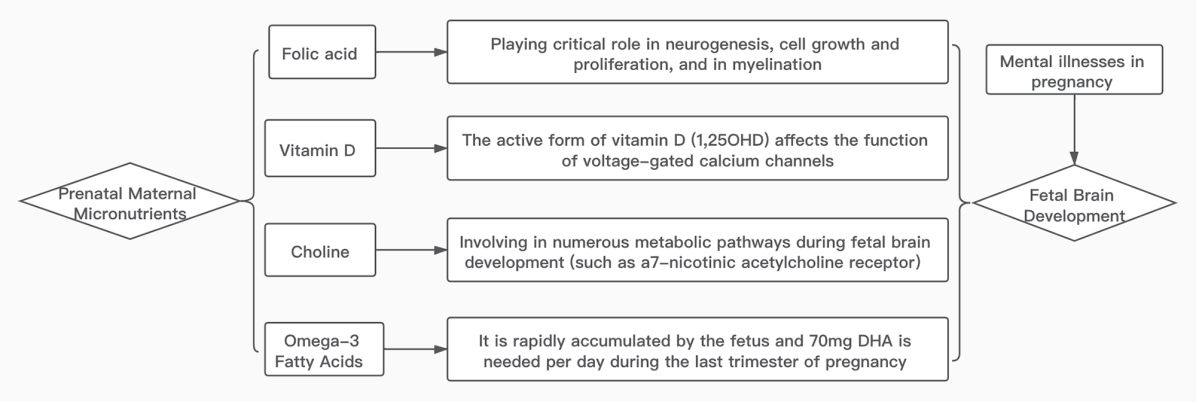

FIGURE 1 The association between the maternal nutrients and fetal brain development

Choline is the only micronutrient to be evaluated specifically in women who have early gestational infections.[14] When women are infected before 16 weeks' gestation, Zika virus and cytomegalovirus invade the fetal brain, where the damage can be catastrophic. Conversely, most common viral and bacterial infectious agents, including influenza and coronaviruses, do not invade the fetal brain when infections occur in early pregnancy. These pathogens elicit a maternal inflammatory response that is thought to be most damaging to the placenta. Cytokine-activated macrophages, called Hofbauer cells, invade the chorionic villi, which they treat as a foreign body. The resultant compromise in placental function causes problems in ongoing fetal development. The most vulnerable gestational period, between 12 and 18 weeks, is when neurogenesis occurs. In this period, the immature neurons migrate into the embryonic cerebral layers and begin differentiation into mature neurons, which includes development of neurotransmitter receptors and formation of synaptic connections.[67]

Higher choline levels during early gestation mitigate the effects of these common bacterial and viral infections. Inhibitory cerebral neurons appear to be the most sensitive to the effects of inflammation. Choline's beneficial effects are initially observed as enhanced cerebral inhibition in newborns with infected mothers. By 3 months of age, the infants whose mothers were infected by common viruses have higher self-regulation as assessed on the Infant Behavior Questionnaire–Revised (IBQ-R), a standard instrument for rating behavior in infants up to 1 year of age that has been studied in both the United States and China.[68] The Self-Regulation Index is associated with later social behavior and reading readiness up to 4 years of age.[69,70] Comparing with betaine supplementation, choline supplementation significantly changed the percentage of scores on the Self-Regulation Index and sub-components in 3-month-old infants whose mothers had viral infection during early pregnancy (Table 2). Infants whose mothers had higher choline levels (at least one standard deviation above the mean) early in pregnancy had fewer problems in distractibility and better ability to regulate their behavior in several dimensions than those with lower choline levels. These choline levels can be achieved by diets rich in eggs and meats or by a daily supplement containing 500–1000 mg choline or 3500–7000 mg phosphatidylcholine.[62-65]

TABLE 2 The percentage change of scores on behavior ratings in 3-month-old infants whose mothers take choline supplementation after viral infection in early pregnancy compared with betain supplementation

Behavior (n = 33)	Effect of 16 weeks maternal with gestation choline >8.4 μM
Distractibility†	–37%
Pleasure in quiet play†	25%
Soothability†	32%
Recovery from distress†	34%
Self-Regulation Index†	23%

A re-analysis of data that were published in our previous study.[14]

† Infant Behavioral Questionnaire-R-short form $P < 0.01$.

Common viral infections experienced by women in the study were likely coronaviruses, based on their having symptoms of a severe cold. If COVID-19, like other coronaviruses, primarily causes a maternal inflammatory response that affects the placenta,[71] then choline supplementation along with other prenatal micronutrients and a good diet, will likely be helpful in reducing future mental problems in the offspring of infected women. Of course, women should be counseled to avoid infection if possible. To date, COVID-19-infected pregnancies have not been found to involve infection of the fetus.[10]

Prenatal studies of choline supplementation directed to *CHRNA7* and its nicotinic receptor were initiated with the aim of preventing brain developmental problems associated with *CHRNA7* gene variants. *CHRNA7* polymorphisms are associated with schizophrenia, and microdeletions that include *CHRNA7* are considered to be a genetic risk factor.[56] Schizophrenia is impacted by many risk factors, some prenatal and some postnatal.

However, epidemiological evidence points to prenatal risk factors including maternal infection and inflammation playing a major role.[11] To the extent that higher choline levels mitigate these risk factors, prenatal choline supplementation may be one factor in preventing future cases of schizophrenia.

Higher choline levels have other positive effects as well as those discussed above. For example, dietary choline intake and midgestation maternal serum total choline have been found to have inversely associated with the risk of neural tube defects in offspring.[72,73]

The American Medical Association recommends prenatal choline supplementation, but commercially available prenatal vitamins do not currently contain adequate amounts of choline, at least not in the United States. It is estimated the choline intake of individuals in the United States, including children, men, women, and pregnant women, is far below the recommended adequate intake.[74] The current FDA recommendation for pregnant women is 550 mg/d.[75] On the basis of our review of the current research, we recommend a supplement contain 1000 mg choline or 7200 mg phosphatidylcholine per day. The safe upper limit, according to the FDA, is 36 000 mg of phosphatidylcholine. Although it is possible to achieve adequate amounts from diet, as it is for all the micronutrients, the higher levels that are maximally effective for preventive efforts generally require supplementation. In China, to our knowledge, there are no data or recommendations about choline intake.

Omega-3 fatty acids

The n-3 long-chain polyunsaturated fatty acid (LCPUFA), docosahexaenoic acid (DHA 22:6n-3), is rapidly accumulated by the fetus during the last trimester of pregnancy. During this last trimester, the fetal brain undergoes a significant growth spurt, and nearly 70 mg DHA is needed per day. Low maternal intake of DHA is associated with lower verbal IQ, diminished prosocial behavior, suboptimal fine motor ability, and impaired social and verbal development.[76] Supplementation with fish oil rich in DHA during pregnancy has been found to increase the offspring's neurocognitive functioning.[77-79] However, not all studies have had positive findings.[80,81] A double-blind supplementation trial found a lack of benefit of prenatal DHA supplementation on IQ at the seven-year follow-up.[82] Fatty acid desaturase (FASD2) polymorphisms have been found to be associated with lower n-3 LCPUFA levels in a genome-wide association study[83] and with blood EPA and DHA levels during pregnancy.[84] Genetic effects might partially explain the inconsistent effects observed. Another possible mechanism is that DHA lowers the incidence of premature birth, which, in turn, is associated with lower IQ scores.[85]

The risk of schizophrenia is increased in mothers with higher overall levels of fatty acids, and autistic traits are associated with higher levels of n-6 LCPUFA.[86,87] Thus, it is doubtful that omega-3 fatty acid supplementation would have a positive impact on mental illness. Positive effects of supplementation with fish oil in the third trimester of pregnancy include reduction in persistent wheeze or asthma and infections of the lower respiratory tract in offspring.[88] Current recommendations for intake of omega-3 fatty acids during pregnancy from dietary sources such as fish are 200–300 mg/d (Table 3).

TABLE 3 Dietary Omega-3 fatty acids daily intake recommendations during pregnancy

Society	Recommended daily intake (mg)
European Commission	200
International Society for the Study of Fatty Acids and Lipids	300
National Institutes of Health U.S.	200
World Association of Perinatal Medicine	300
Chinese Nutrition Society	200

A study in China found higher DHA and eicosapentanoic acid dietary intake in pregnant women from inland and river/lake regions compared with women from coastal regions. Women without access to marine fish may need fish oil supplements for adequate intake. However, there were no differences in umbilical cord erythrocyte membrane levels at birth in the neonates from the three regions.[89]

Mental illnesses in pregnancy

Women who experience mental health issues during pregnancy often have sub-optimal birth outcomes, including increased mortality and morbidity, shorter gestation, and lower birth weight.[90] Depression is one of the most common mental health conditions experienced by women during pregnancy and the childbearing years. The prevalence of major depressive disorder during pregnancy is 12.7%, while 37% of women report experiencing depression symptoms at some point during pregnancy.[91] Depression during pregnancy may not only have physiological consequences, including low birth weight, intrauterine growth restriction, and preterm birth, but may also expose women to an increased risk of poor psychological postnatal adjustment and postnatal depression.[92] A meta-analysis suggested that psychotherapy might benefit the mental health of mothers which has positive impacts on their children and parenting skills.[93] Antidepressants generally have more robust effects than psychotherapy, and do not adversely affect fetal development.[94,95] Assertions of risk for future autism spectrum disorders have discouraged clinicians from prescribing antidepressants to depressed pregnant women;

however, the risk may be due to maternal depression itself rather than its treatment.[96]

Conclusion

Widespread dietary supplementation with the nutrients discussed in this paper (Figure 1), most of which are benign and inexpensive, is a potential intervention in pregnancy to prevent life-long disability from mental illness for individuals and families, and to lessen the burden of mental health on society. Currently, folic acid supplementation is widely promoted to prevent neural tube defects; however, the uptake of this recommendation remains less than 70%.[97] Multivitamins with folic acid, which contain vitamins A, B_{12}, and D are also available. Choline supplements are available, but there are currently no public health recommendations or advocacy promoting their use. Public health officials, especially in China, should consider the value of prenatal nutrient supplementation for reducing the burden of future mental disorders.

CONFLICT OF INTEREST

None.

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How to cite this article: Li Y, Freedman R. Prospects for improving future mental health of children through prenatal maternal micronutrient supplementation in China. Pediatr Invest. 2020;4:118-126. https://doi.org/10.1002/ped4.12199