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IMPACT OF PRENATAL NUTRITION ON THE CEREBRAL DEVELOPMENT OF THE INFANT

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Abstract

It is well documented that malnutrition in pregnancy is of increasing concern in both the developing and developed world, resulting in poor health of children. Various serious diseases in childhood have been attributed to malnutrition in maternity. Latest research links maternal malnutrition with dysfunction of the higher brain in children. It has been hypothesised from animal trials, that prenatal nutrition has a strong impact on the neurological development of the infant. Especially the content of unsaturated fats and certain phospholipids seem to be essential for the cerebral function of the foetus. There is a strong body of evidence pointing especially to omega 3 fatty acids and choline as one very necessary nutritional component in pregnancy. The consumption of omega 3 in fish has been under controversial discussion because of methyl mercury which can induce food poisonings also affecting the unboorn child. Evidently mother's nutrition is effecting the development of the child even after parturition. However little is only known about the definite supply with choline in different stages of human pregnancy. Considering factors socioeconomically, it can be assumed that choline supply in pregnant woman presently does not meet the required amount for a development of higher brain structures in children. This certainly applies to developing countries with a higher proportion of poverty and malnutrition in low-income households. Epidemiological data has shown, that in so called developed countries such as in Europe or United States the content of choline in prenatal diets is not balanced enough to reach the requirements of the unborn child fully.

From this point of view the prevention of prenatal malnutrition is a main subject for public health concern. We recommend revising the rationale for recommending certain dietary supplements in pregnancy and breastfeeding women.

Key words: *nutrition in pregnancy; impact of malnutrition on intelligence in children; stimulating components in food for the development of intelligence; omega 3 and choline and cerebral development*

REVIEW

INTRODUCTION

It is well documented that malnutrition in pregnancy is of increasing concern in both the developing and developed world, resulting in poor health of children. A large body of evidence proves that pregnancy certainly is a special stage of metabolism requiring a higher amount of macro- and micronutrients. Recommendations have been made on the basis of this observation emphasising the special need for different vitamins. Primary care and National Health Services should be instructed and

well aware about the appropriate diets and supplementation of pregnant women. In some countries the benefit of healthy vitamin starters for pregnant women as supplements including folic acid, vitamins C and D have been widely accepted (NICE 2008).

Supplementation has many potential advantages over fortification and dietary approaches for improving micronutrient intake. Pregnant and lactating women and infants are most likely to benefit from such supplementation. This has been proved for vitamin A, ferum and folate. Even UNICEF has been employing the supplementation in certain programmes aimed at the prevention low birth weight (Shrimpton et al. 2002).

Late discovery about some effects of nutritional compounds in pregnancy on dividing progenitor cells has broaden the approach for finding other critical nutrients. More human studies need to be conducted to increase epidemiological evidence. A better understanding of diet and diet supplement intake during pregnancy and lactation is needed to prove the bioavailability of certain critical nutrients. Also, a deeper understanding of common genetic variations influencing nutrient requirements during these periods is also needed for clarification the premises of sufficient prenatal nutrition. Supplementation of maternal and infant diets calls for more understanding about the risks of having insufficient critical nutrient supply. Whatever the limitations of the current state of knowledge, it is apparent that pregnancy and lactation are periods during which good nutrition is exceptionally important. The infant is not protected from the inadequate diet of the mother (Zeisel 2009).

Supplementation in pregnancy is of utmost concern in Public Health, with no regional exception. Intrauterine growth retardation, which reflects in large part maternal malnutrition, contributes to chronic disease risk through foetal programming. Foetal programming implies that during critical periods of prenatal growth, permanent changes in metabolism or structures result from adverse intrauterine conditions. Observational studies first showed an association between lower birth weights and higher rates of coronary disease in the 80s, in England and Scandinavia. The link between low birth weights, or other indicators of small birth size, and cardiovascular disease was later confirmed in many epidemiological studies, including in the USA and in India. A further factor of non communicable chronic disease such as the metabolic syndrome and diabetes II seem to be related with prenatal intrauterine malnutrition. Insulin resistance associated with small size at birth was frequently shown to be present at a young age. Although there are still controversial areas, there is at present sufficient scientific evidence for foetal programming to be regarded as an additional risk factor for chronic disease, in interaction with genetic and lifestyle risk factors. The fact that intrauterine growth retardation may predispose to nutrition-related chronic disease has serious implications. The challenge is for programmes to simultaneously combat apparently opposite nutrition problems, malnutrition and "over-nutrition". Improving the nutrition of women is even more imperative when considering that it may contribute to preventing chronic diseases in the next generation, in addition to enhancing health and survival of mothers and children (Delisle 2002).

Aspects of prenatal malnutrition in developing and so called developed countries will be discussed in this review socio-epidemiologically and from a point of view of Preventive medicine. Biochemical pathways of critical nutrient components will be discussed and different potions of intervention will be summarized to face the problem of prenatal malnutrition in the interest of public health in future.

Socio-epidemiological aspects of prenatal malnutrition in developing countries

The consequences of food and nutrition shortfalls are enormous. Protein-energy malnutrition can impair the immune system, leaving malnourished children less able to battle common diseases. Again the combination of malnutrition and infectious disease can be particularly in particular pernicious (Tomkins and Watson 1989).

Malnutrition reduces work capacity and the immune system, both of which affect income generation. Women and children who have special nutritional needs are particularly at risk. Food shortages are known to impact most acutely on women during pregnancy.

Maternal malnutrition, poor foetal growth and stunting in the first two years of life lead to increased maternal and child mortality as well as causing irreversible damage throughout the course of life, such as shorter adult height, lower attained schooling, reduced adult income and decreased offspring birth weight among those that survive (Victora et al. 2008).

Such malnutrition in developing countries is strongly linked to poverty. According to the world resources institute approximately 800 million people i.t. one out of every 5 people in the developing world did not have access to enough food for healthy living (FAO 1996).

In developing countries, presently 40 percent of nonpregnant women and 50 percent of pregnant women are found to be anaemic, and 3.6 billion people suffer from iron deficiencies. The problem is most severe in India, where 88 percent of pregnant women are anaemic (The World Health Report 1997).

Overall the number of extremely poor is estimated to have increased by between 130 and 155 million globally between 2005 and 2008, with another 53 million more expected by the end of 2009. It may be assumed that the first response is to save on food costs and cut down on non-staple food consumption in developing countries. These coping strategies affect first the diversity and quality, and then the quantity and safety of diets, with mothers usually the first to make such sacrifices. Distress sales of assets and cutbacks in health expenditures may further jeopardize the nutrition situation. It can be expected that malnutrition of pregnant women increases in developing countries such as Africa and Asian continent in future dramatically.

The risk of poverty and its effects on prenatal nutrition may even increase under the present aspect of the global financial crisis. Food shortages are known to impact most acutely on women during pregnancy. The Dutch famine of 1944–45 showed for instance that even in a previously well nourished population receiving food rations, even minor food restriction during pregnancy produced significant reductions in birth weight, length and head circumference (Stein and Susser 1975).

Recent evidence from developing country settings further confirms that raising food prices contributes to maternal and child malnutrition rapidly. During the Indonesian financial crisis in 1997–98 wasting increased in Javanese women, although without increases in child malnutrition, suggesting that mothers buffered children's food intake. Moreover, increased prevalence of anaemia in mothers and children was associated with a reduction in consumption of high quality foods. The combined effects were particularly severe for cohorts conceived and weaned during the crisis (Block et al. 2004).

Africa, the Andean region of South America, and many parts of Asia are at risk from not only protein energy malnutrition, but also from all three main micronutrient deficiencies because of both poverty and environmental factors. Iron deficiency is the most common micronutrient disorder. Whereas women are usually the last to benefit from increased household income they are usually the first to make sacrifices when the financial situation deteriorates (State of the World's Children 2007).

The Centre for International Health, Division of Health Sciences, Curtin University of Technology, Perth, Western Australia, Australia studied the maternal malnutrition in rural Bangladesh which belongs to the poorest areas in the world. They found that despite high levels of awareness of nutritional dietary requirements, half the women reported unchanged or reduced food intake during pregnancy. Dietary taboos and food aversions were widely practiced. Women consistently received the last and smallest food shares during mealtimes. This data proves that pregnant women although in a special position of nutritional need are often the last members of the food chain in developing countries (Shannon et al. 2008).

The Erasmus University Rotterdam, Netherlands studied the socioeconomic inequality in childhood malnutrition in the developing world, to provide evidence for an association between socioeconomic inequality and the average level of malnutrition. In almost all countries investigated, stunting and wasting disproportionately affected the poor. Socioeconomic inequality in childhood malnutrition existed throughout the developing world. Failure to tackle this inequality is a cause of social injustice. According to the authors reducing the overall rate of malnutrition does not necessarily lead to a reduction in inequality. Policies

should, therefore, take into account the distribution of childhood malnutrition across all socioeconomic groups (Van de Poel et al. 2008).

Another example of malnutrition has been under investigation by the Department of Community Medicine, Medical College, New Delhi, India documenting the current dietary profile of pregnant women in rural areas of Delhi. The mean intake of macronutrients and micronutrients, namely, iron, folic acid and Vitamin C which play an important role in the pathophysiology of nutritional anaemia during pregnancy was calculated from the foodstuffs, using Nutritive Value of Indian Foods. The intake of calories, protein, iron, folic acid and vitamin C was found to be less than the recommended dietary allowance of pregnant women respectively. Folic acid intakes were significantly lower in younger, primiparous and poorly educated women from low-income families. The overall data suggested the presence of food gap rather than isolated deficiency of any particular nutrient (Guatam et al. 2008).

The Department of Paediatrics and Child Health, Ile-Ife University, Nigeria assessed four hundred and seventy three live born neonates for foetal malnutrition and found a relatively high rate Eighty-nine 18.8% of the 473 babies with foetal malnutrition. Severe birth asphyxia, respiratory distress, meconium aspiration, hypoglycaemia, high haematocrit and hypoalbuminaemia were significantly commoner in babies with foetal malnutrition. Infants with foetal malnutrition had significantly higher mortality and neurological sequelae in the first month of life. Finally they concluded that foetal malnutrition is a major health problem in Nigeria with considerable morbidity and mortality (Adebami et al. 2007).

While this epidemiological data on pregnant women proves a lack in vitamin intake in developing countries only little is known about the supply with essential fats in such population. A study from the Human Nutrition and Food Science Department, California Poly Pomona revealed an insufficient supply with phosphatidylcholine in African American women lately, which was associated also with lower folate status (Hung et al. 2008).

The Department of Basic Medical Sciences of the University of the West Indies, Kingston Jamaica, examined the dietary intake of choline in groups of students at the University of the West Indies. Sixty-two medical students (first and second years) and biochemistry students (final year) were recruited The analysis revealed that 86.2% of the females and 90.9% of the males reported diets that delivered less daily choline than the adequate intake quoted by the Institute of Medicine of the National Academy of Sciences, USA (425–550 mg/day). The dietary intake of choline in the majority of students were below adequate intake. It can be concluded that the part of population at a special need such **as** pregnant women have to face even a greater gap of choline supply (Gossell-Williams and Benjamin 2006).

This data highlights the need to address traditional dietary taboos and preferences, and actively target key household decision makers, namely, husbands and mothers-in-law, in nutrition behaviour change communication.

Socioepidemiological aspects of prenatal malnutrition in developed countries

Chronic diseases are the main public health problem in Western countries. There are indications that these diseases originate in the early childhood or even have prenatal roots. It is thought that malnutrition of the fetus during critical periods of development would lead to adaptations in the structure and physiology of the fetal body, and thereby increase the risk of diseases in later life.

Although a lot has been undertaken to cope with nutritional needs of pregnant women by social public health systems epidemiological data still refers to a resisting lack in this regard. This tendency may even increase under the aspect of further economic depression.

European records have shown that malnutrition during gestation affects health in later life. This was proven by the historical disaster of the Dutch famine. According to this epidemiological data, the effects of malnutrition, were depending upon the specific time of gestation. adult health without affecting the size of the baby at birth (Roseboom et al. 2001).

Studies clearly proved that small variations within the normal range in the micronutrient content of maternal diets and/or maternal micronutrient status during pregnancy are associated with significant differences in foetal and infant growth.

This was shown by randomized controlled trials in Cleveland Ohio, USA which increased mean birth weight by 200 g in a iron-folate supplementation versus a true placebo in non-anaemic women during the latter part of pregnancy. It was concluded that even in so called developed countries maternal malnutrition and the premature introduction of complementary foods with low energy-nutrient density lead to low birth weight, impaired growth and intellectual development, and high mortality. Finally more than 5 million of the 10 million annual child deaths are attributed to malnutrition (Friis 2006).

A survey of the actual nutrition status of the urban population of the Primorsky Krai Territory (Russia) revealed the under-consumption of choline containing milk and its products, eggs, meat and its products, and in contrast overconsumption of fish and its products, bread and bakery products, and vegetable oil. The assessment of the nutrient composition of foodstuffs indicated that all the population groups showed the varying levels of vitamins A, D, B_{12}, beta-carotene and the inadequate content of pantothenic and folic acids, choline, calcium, magnesium, iodine, zinc, selenium. Although such surveys can not fully represent the nutritional status in developed countries, it may be assumed that certain parts of the population have to cope with a lack of choline supply in pregnancy (Lapardin and Kiku 2008).

Essential components of adequate nutrition in maternity

Malnutrition has often been linked with a shortage of energy consumption. From the viewpoint of energy, pregnancy is a physiological stage of high turnover in energy. It has been calculated that the total energy cost of pregnancy is about 85,000 kcal. Three components comprise the total cost: the energy equivalent of the fat and protein gained in the fetus and added maternal tissues, the energy required to support metabolism of these added tissues, and an allowance for efficiency of conversion of dietary to tissue energy.

If averaged over 280 days, the cumulative energy cost of pregnancy is about 300 kcal per day. However during the first quarter there is relatively little gain of fetal or maternal tissue and the daily additional need is thought to be only about 115 kcal per day. During the next two quarters extra energy is needed primarily for maternal tissue accretion which is primarily fat. This averages about 380 and 420 kcal per day in the second and third quarter, respectively. Fetal tissue gain is great in the fourth quarter, but since maternal gain is considerably reduced, the average daily cost is only about 320 kcal. Data compiled from several studies of basal energy expenditure (BEE) during pregnancy show an average increase of approximately 20% over non pregnant rates, with a range of 13 to 48 percent (King 1981).

Despite these calculations present studies have shown that healthy pregnancy and the development of the foetus require more than mere energy consideration. Vitamins, minerals and trace elements are known to be essential in pregnancy. Sufficient supply with critical nutrients is linked to some degree with the density of energy consumption. However amino acids and proteins as well as essential fats and phospholipids need a separate consideration.

To guarantee optimal supply with essential food components during pregnancy prenatal nutrition should not be limited to calculations based on a caloric scale. Later data has shown that the quality of food, measured by the contents of minerals, trace elements and vitamins are of utmost importance for the developing the foetus.

A sufficient prenatal nutrition can be defined only on the basis of a balanced energy intake and an adequate supply with micronutrients essential for the intrauterine development. To date, however there is still only very small clinical data about essential amino acid phospholipids needs during pregnancy.

It has been estimated that the cumulative total gain of protein in the fetus and maternal body is about 925 g. Since fetal growth occurs primarily in the last half of gestation, predicted nitrogen accretion is considerably greater the last 20 weeks than the first 20 weeks. The

mean nitrogen retention during the last half of gestation is 860 mg per day; retention over all of gestation averages 530 mg N per day. In conclusion, it seems that in the first half of gestation measured N storage is three to six times greater than the predicted gain. At least 36 kcal per kg are required during pregnancy for support of N retention (Oldham and Sheft 1951). Until further data are available, it seems prudent to assume that the rate of N storage is constant throughout gestation and is at least 1.0 g per day (Hitten 1980).

To support a gain of 1.0 g N or 6.25 g protein per day with a 30 percent efficiency of utilization, 20 additional g protein are needed in the diet. If an additional 30 percent is added to cover individual variability, the incremental dietary protein need for pregnancy is about 25 g. Thus, a reference pregnant woman consuming a diet with a protein score of 70 should add 25 g protein to the 41 recommended for the nonpregnant state bringing the total to 66 g protein per day. Latest recommendations from the D-A-CH organisation now even referred to 1,3 g/kg body weight as a sufficient protein supply from the 4. month of pregnancy. This corresponds with 78 g protein in pregnant women with 60 kg (Joint FAO/WHO... 1973).

Several nutritional components have been traced to be essential for pregnant woman. Folic acid, vitamin B_{12}, vitamin B_6 vitamin D are regarded among other substances vital for the cerebral development of the unborn child (see Table 1 below). The body's folic acid increases during pregnancy. Folic acid deficiencies during pregnancy have been linked to low birth weight and to an increased incidence of neural tube defects (such as spina bifida) in infants. Most healthcare professionals recommend that women of childbearing age supplement with 400 to 800 mcg per day. Folic acid should be taken even before a woman knows she is pregnant and throughout the entire pregnancy. Folic-acid supplementation is important prior to conception because it provides its protection in the first weeks of pregnancy before a woman knows she has conceived. Vitamin B_{12} can cause anaemia and irreparable damage to the nervous system. Vegans (people who eat no animal products), including those who are pregnant, should take a daily vitamin B12 supplement. Low maternal vitamin B_{12} levels are more commonly seen in smokers and are associated with low birth weights and premature birth. The recommendation of daily allowance (RDA) of vitamin B_{12} for pregnant women is 2.6 mcg per day from all sources. Lactating women require 2.8 mcg per day (Böhm et al. 2003, Böhm and Muss 2011).

Women who have taken oral contraceptives during the months prior to pregnancy may be also at increased risk of vitamin B_6 deficiency. Vitamin B_6 is essential for neurotransmitter synthesis and is a coenzyme of many enzymes related to cerebral functions (Böhm et al. 2003, Böhm and Muss 2011).

Table 1. Vitamins needed in non pregnant and pregnant woman according to D-A-CH recommendations

Vitamin	Non pregnant women	Pregnant women
Vitamin A	0,8 mg	>1.1 mg
Vitamin D	5 µg	5 µg
Vitamin E	12 mg	>13 mg
Vitamin B_1	1 mg	1.2 mg
Vitamin B_2	1,2 mg	1.5 mg
Vitamin B_3	13 mg	15 mg
Vitamin B_6	1.2 mg	1.9 mg
Vitamin B_{12}	3 µg	3.5 µg
Folic acid	0.4 mg	0.8 mg
Vitamin C	100 mg	110 mg

Among minerals calcium, iron and zinc, were described to have an essential impact on gestation (see Table 2). The highest risk for iron deficiency occurs in the last weeks of pregnancy. Healthy nonpregnant women should not supplement with iron unless they have an iron deficiency proven by a blood test. Many, but not all, pregnant women eventually require iron supplementation during pregnancy, usually around 45 mg per day. Pregnant women may help increase the birth weight of their babies by taking iron supplements before 20 weeks' gestation. However it should be kept in mind that heavy supplementation of iron diminishes zinc bioavailability. Women may become marginally zinc deficient during pregnancy, particularly if they are supplementing with greater than 30 mg per day of iron. Studies conflict as to whether zinc supplementation is effective or necessary in well-nourished pregnant women (Böhm et al. 2003, Böhm and Muss 2011).

Vegetarians may have subtle nutritional deficiencies which have been related to the occurrence of an unrecognized malabsorption syndrome. The excess phytate content in cereals, nuts, legumes and oilseeds which represent the mainstay of their food intake, seems to play a central role in the pathogenesis of this malabsorption syndrome as an inverse relationship has been shown to link the phytate content of the diet with the intestinal absorption of zinc and proteins (Krebs 2000, Böhm et al. 2003, Böhm and Muss 2011).

Zinc is also regarded an essential catalytic or structural element of many proteins, and a signalling messenger that is released by neural activity at many central excitatory synapses. It serves as a catalytic component of over 200 enzymes and as a structural component of various proteins, hormones, and nucleotides. Growing evidence suggests that zinc may also be a key mediator and modulator of the neuronal death associated with transient global ischemia and sustained seizures, as well as perhaps other neurological disease states (Hurley and Swenerton 1966, Hambidge et al. 1986, Valle and Falchuk 1993, Choi and Koh 1998, Krebs 2000).

Zinc deficiency alters autonomic nervous system regulation and hippocampal and cerebellar development (Georgieff 2007). Zinc deficiency has been related to hyperactivity in children (Mehmet et al. 2006).

In summary, the data strongly suggest that zinc supplementation improves the pregnancy outcome in at least some pregnant women, and the inclusion of zinc in prenatal mineral tablets should be approved. The minimum dosage of zinc for any population of pregnant women is not known, although in the present study beneficial effects were demonstrated with a daily supplement of 25 mg. Zinc supplementation should be under a control of medical experts (Böhm et al. 2003, Böhm and Muss 2011).

Beside these critical components in prenatal nutrition also fats play a decisive role in protection brain functions of the child in pregnancy. Especially brain development seems to depend on a sufficient supply with lipid vital substances. However as shown above only little is known about the supply with these substances in pregnancy epidemiologically. To our opinion, this matter of prenatal nutrition has not been regarded with enough emphasis in the past.

Table 2. Minerals needed in non pregnant and pregnant woman according to D-A-CH recommendations

Mineral	Non pregnant women	Pregnant women
calcium	1000 mg	1200 mg
magnesium	300 mg	310 mg
ferum	15 mg	30 mg
iodine	200 µg	230 µg

Omega 3 fatty acids

It is becoming common knowledge that omega3 fatty acids are exceptionally important for human health.

Omega3 and omega6 fatty acids are labelled 'essential' because the body cannot synthesize them on its own. During foetal development, omega3 fatty acids are especially important for neural development and cell growth. Throughout pregnancy, omega3's supply essential lipids to the foetus, as important brain and eye development takes place during foetal development, continuing well into the child's infant years. Omega3 fatty acids during pregnancy and during the formative years after birth have been discovered to be a critical element for both the neurological and visual development of the baby. DHA is especially vital, as foetus cannot produce DHA efficiently independently.

Studies have proven that supplementation with very-long-chain n-3 fatty acids during pregnancy and lactation can even augment children's IQ in early years of age (Helland et al. 2003).

Unfortunately in most Western lifestyles our diets include dangerously low levels of omega3s and a level of omega 6 fatty acids that is far too high. Fish is known to contain a higher amount of omega 3 fatty acids. Over the past thirty years, the focus of this research has turned to omega 3 fatty acids and their role in the behavioural development and learning skills. ADHD, in particular, has been very closely associated with omega 3 fatty acid deficiency both in terms during pregnancy and in the infant's diet until at least the age of four. Research has shown that infants with lower omega 3 levels are more likely to suffer behavioural problems including hyperactivity, impulsivity, anxiety, temper problems and unsettled sleep patterns (Kodas et al. 2004).

This tendency was proved by another study group showing that abnormal essential fatty acid profiles were often observed in younger children and distinctly different from normal controls of similar age. Further fatty acid differences were not explainable by differences in intake. The group suggested that there are metabolic differences in fatty acid handling between ADHD adolescents and normal controls (Colter et al. 2008).

On the other side it has been criticized, that evidence from intervention trials was yet too weak, as most of the studies reviewed had small sample sizes and were conducted in clinically diagnosed samples, with no placebo-controlled groups (Ramakrishnan et al. 2009).

Recommendation for fish consumption in prenatal diets is presently strongly debated, as it seems that a larger fish consumption is associated with a higher risk of food poisoning by methylmercury. Excessive toxic metal absorption seems to be liable with higher fish consumption as fat depots of sea fish are often loaded with heavy metals (Department of Environment Food... 2006).

Soluble methylmercury has been shown to invade fatty tissues and long-term foetal exposure during pregnancy and may therefore contribute to irreversible developmental disorders. Transplacental transmission of cadmium, lead and mercury have been proven in the past also in humans (Semczuk and Semczuk-Sikora 2001).

Officially pregnant woman have been warnde by the US Department of Health and Human Services, US Environmental Protection Agency not to exceed their fish consumption above 340 g/week (The US Department of Health... 2004, Myers and Davidson 2007).

In contrast to the recommendation of US Department of Health the ALSPAC study produced only results in favour of higher fish consumption in pregnancy. Maternal seafood consumption of less than 340 g per week in pregnancy did not protect children from adverse outcomes; rather, beneficial effects on child development with maternal seafood intakes of more than 340 g per week were recorded. This suggests that limiting seafood consumption could actually be detrimental. These results show that risks from the loss of nutrients were greater than the risks of harm from exposure to trace contaminants in 340 g seafood eaten weekly (Hibbeln et al. 2007).

Recent studies in the Seychelles have focused on nutrients in fish that might influence a child's development, including long-chain polyunsaturated fatty acids, iodine, iron, and choline. Preliminary findings from this study suggest that the beneficial influence of nutrients from fish may counter any adverse effects of MeHg on the developing nervous system (Myers et al. 2007).

It is important to remember that it is easier for pregnant women to experience a deficiency in omega 3 fatty acids because more essential fatty acids are required to build a growing baby. This deficiency can be compounded in subsequent pregnancies due to the fact that maternal stores can become further depleted with each pregnancy, rarely returning to pre-pregnancy levels (Scientific Advisory Committee on Nutrition... 2004).

Insufficient intakes of omega-3 fatty acids during pregnancy have been associated with intrauterine growth retardation, delayed or suboptimum depth perception, adverse neuro development, residual deficits in fine motor skills, speed of information processing in infants, and irreversible deficits in serotonin and dopamine release. Studies show that maternal dietary n-3 fatty acid deprivation impairs foetal brain DHA accretion and PS metabolism; altered PS metabolism may change release of lipid mediators and neurotransmitter precursors important in brain function (Salem et al. 2001, Calderon and Kim 2004, Daniels et al. 2004, Scientific Advisory Committee on Nutrition... 2004, Tom and Innis 2006).

Table 3. Nutritional sources of Omega 3

• Krill Oil
• Walnuts & Oil
• Flax & Oil
• Wild Alaskan Salmon
• All oily fish
• Chia Seeds
• Hemp
• Marine algae

Choline

Choline, a dietary component of many foods, is part of several major phospholipids (including phosphatidylcholine – also called lecithin) that are critical for normal membrane structure and function. As a major precursor of betaine, it is used by the kidney to maintain water balance and by the liver as a source of methyl-groups for methionine formation. Also, choline is used to produce the important neurotransmitter acetylcholine. In the body choline is mainly found in phospholipids, such as lecithin (phosphatidylcholine) and sphingomyelin. The outer leaflet of plasma membrane is rich in these choline-phospholipids whereas the inner leaflet is dominated by phosphatidylethanolamine, phosphatidylserine, and phosphatidylinositol.

Phosphatidylcholine, the predominant phospholipid (>50%) in most mammalian membranes, not only contributes to the structure of the membrane bilayer, but products of receptor-mediated lecithin hydrolysis also serve as important second messengers in signal cascades that control cell growth and gene expression.

Phosphatidylcholine, which is a polar lipid, is present in commercial lecithin in concentrations of 20 to 90%. Most of the commercial lecithin products contain about 20% phosphatidylcholine.

Choline is an essential nutrient that is critical during fetal brain development. Choline deficiency may alter DNA methylation and thereby influence neural precursor cell proliferation and apoptosis. This results in long term alterations in brain structure and function, specifically memory function. The choline requirement can be met via endogenous de novo synthesis of phosphatidylcholine catalyzed by phosphatidylethanolamine N-methyltransferase (PEMT) in the liver. Though many foods contain choline, many humans do not get enough in their diets. This evidently applies especially for pregnant women (Fischer et al. 2007).

The definite amount of choline needed in nutrition can not be determined and it has to be anticipated that there is an individual need for choline. The adequate intake recommendation of 550 mg choline/d was established for the prevention of liver dysfunction in men, as assessed by measuring serum alanine aminotransferase concentrations (Veenema et al. 2008).

However further studies have shown that the amount of endogenous choline supply varies according to the activity of hormones and the genetic influence. Estrogen induces expression of the PEMT gene and thereby allows premenopausal women to increase choline supply endogenously. This might explain a certain protection in pregnancy. However a significant variation in the dietary requirement for choline can be explained by common genetic variants (single nucleotide polymorphisms; SNPs) in genes of choline

and folate metabolism. Some of these increase the risk of choline deficiency many-fold. These variations in choline requirement could have important implications for brain development (Resseguie et al. 2007, Zeisel 2008).

Choline tresspasses diaplacental into fetal blood circulation. Choline is concentrated in fetal blood 14× more than in maternal blood stream. Breast milk contains choline concentrated by factor 100 in comparison to maternal blood. Weaned babies are supplied by breastmilk naturally from the mother with 20 mg choline/kg/d. Choline helps to increase the number of cells in the memory center during a critical period of brain development in pregnancy.

Study results from the Department of Nutrition, School of Public Health and School of Medicine, University of North Carolina USA revealed that a choline-deficient diet increased DNA damage also in humans. Assessment of DNA damage and apoptosis in lymphocytes appeared in choline deficiency (Da Costa et al. 2006).

Evidence is growing that optimal dietary intake of choline and folate (both involved in one-carbon transfer or methylation) is important for successful completion of fetal development. Significant portions of the population are eating diets low in one or both of these nutrients. As it is well documented, folates are important for normal neural tube closure in early gestation, and the efficacy of diet fortification with folic acid in reducing the incidence of neural tube defects is a major success story for public health nutrition. Similarly, maternal dietary choline is important for normal neural tube closure in the fetus and, later in gestation, for neurogenesis in the fetal hippocampus, with effects on memory that persist in adult offspring; higher choline intake is associated with enhanced memory performance. Although both folates and choline have many potentially independent mechanisms whereby they could influence fetal development, these 2 nutrients also have a common mechanism for action: altered methylation and related epigenetic effects on gene expression (Davison et al. 2009, Zeisel 2009a).

Via its metabolite betaine, choline serves as a donor of methyl groups used in fetal development to establish the epigenetic DNA and histone methylation patterns. Supplementation with choline during embryonic days in rats improves memory performance in adulthood and protects against age-related memory decline, whereas choline deficiency impairs certain cognitive functions. It was previously reported that global and gene-specific DNA methylation increased in choline-deficient fetal brain and liver, and these changes in DNA methylation correlated with an apparently compensatory up-regulation of the expression of DNA methyltransferase Dnmt1. In a further study, pregnant rats were fed a diet containing varying amounts of choline. The mRNA and protein expression of histone methyltransferases G9a and Suv39h1 were directly related to the availability of choline. DNA methylation of the genes was up-regulated by choline deficiency, suggesting that the expression of these enzymes is under negative control by methylation of their genes. These data show that maternal choline supply during pregnancy modifies fetal histone and DNA methylation, suggesting that a concerted epigenomic mechanism contributes to the long term developmental effects of varied choline intake in utero (Zeisel 2009b).

The effects of prenatal choline availability on Pavlovian conditioning were assessed in a study with adult male rats. Prenatal choline availability significantly altered the contextual control of these learned behaviors. Both control and choline-deprived rats exhibited context specificity of conditioned excitation as exhibited by a loss in responding when tested in an alternate context after conditioning; in contrast, choline-supplemented rats showed no such effect. When switched to a different context following extinction, however, both choline-supplemented and control rats showed substantial contextual control of responding, whereas choline-deficient rats did not. These data support the view that configural associations that rely on hippocampal function are selectively sensitive to prenatal manipulations of dietary choline during prenatal development (Lamoureux et al. 2008).

Another animal trial proved the effects of choline supplementation on the interval-timing ability and temporal memory of the offspring. Psychometric response functions indicated that prenatal-choline supplementation systematically increased

sensitivity to auditory signals relative to visual signals, thereby magnifying the modality effect that sounds are judged to be longer than lights of equivalent duration. In addition, sensitivity to signal duration was greater in rats given prenatal-choline supplementation, particularly at low intensities of both the auditory and visual signals. Overall, these results suggest that prenatal-choline supplementation impacts interval timing by enhancing the differences in temporal integration between auditory and visual stimuli in aged subjects (Cheng et al. 2008a).

An animal trial with rats further showed how increased choline availability during the second half of gestation presumably produces long-lasting cognitive effects. Rats that obtain supplemental choline during embryonic day had enhanced depolarization-evoked acetylcholine (ACh) release from hippocampal slices, whereas choline deficiency during this time reduced this release. Rats whose mothers consumed a choline-supplemented diet had a higher level of insulin-like growth factor II (IGF2) mRNA. IGF2 is known to stimulate endogenous ACh release (Napoli et al. 2008).

A further animal experiment showed that choline supplementation increases striatal nerve growth factor expression in mice, suggesting that neuronal proliferation and survival may contribute to improved motor performance (Nupur et al. 2008).

To further delineate the impact of early nutritional status, the Department of Psychology and Neuroscience, Duke University, North Carolina USA examined effects of prenatal-choline supplementation on timing, emotion, and memory performance of adult male and female rats. In summary, long-lasting effects of prenatal-choline supplementation were exhibited by reduced frustrative responding in conjunction with the persistence of temporal memory and enhanced temporal exploration and response efficiency (Cheng et al. 2008b).

Besides these data from neurophysiologic studies we were able to prove in own studies an anti-inflammatory effect of i.v choline citrate infusions in patients with multiple sclerosis in an earlier clinical trail. We hypothesized that choline citrate may increase ATP and perfusion in CNS and regulates lymphocyte activity. Our patients showed significant response to choline i.v. treatment by lymphocyte reaction (Lymphocyte Transformation Test LTT) (Muss et al. 2009).

This is in concordance with further results from studies investigating the association between dietary choline and betaine consumption and various markers of low-grade systemic inflammation. Participants who consumed a higher amount of choline enriched food had lower signs of inflammation in this trial. These results support an association between choline intakes and the inflammation process in free-eating and apparently healthy adults (Detopoulou et al. 2008). In vertebrates choline supplementation even contributed to restoration of defective myelination (Szalay et al. 2001).

Table 4. Nutritional sources of choline

• beef liver
• chicken liver
• eggs
• wheat germ
• bacon
• pork
• dried soybeans

Recommendations for choline reach food for pregnant woman have to consider that fatty acid makeups of phosphatidylcholine from plant and animal sources differ. Cattle liver, cooked beef contains 400 mg per 100 grams on an average, cornflakes contain 170 mg per 100 grams listed and an egg contains 125 mg. Saturated fatty acids, such as palmitic and stearic, make up 19 to 24% of soya lecithin; the monounsaturated oleic acid contributes 9 to 11%; linoleic acid provides 56 to 60%; and alpha-linolenic acid makes up 6 to 9%. In egg yolk lecithin, the saturated fatty acids, palmitic and stearic, make up 41 to 46% of egg lecithin, oleic acid 35 to 38%, linoleic acid 15 to 18% and alpha-linolenic 0 to 1%. Soya lecithin is clearly richer in polyunsaturated fatty acids than egg lecithin. Also poppy-seed oil (5%) contains considerable amounts of lecithin (choline) (Roeytenberg et al. 2007).

CONCLUSIONS

In pregnancy there is evidently a higher risk for malnutrition especially in poverty and for

women living in regions with less structured public health systems. Children born under such circumstance seem to gain a higher risk for cerebral dysfunction as certain nutritional components definitely bear a strong impact on the cerebral development.

This review encourages public health systems in general to focus on prenatal nourishment of pregnant women in order to avoid possible impairment of cerebral development in children.

Brain consists of 60 percent fat. Omega 3 fatty acids are essential, but unfortunately are associated with a certain risk of heavy metal exposure. Choline supplements are also very essential for the development of the child's brain and have no serious side effects when consumed in pregnancy (Hunter et al. 2008).

Besides certain vitamins i.t. folic acid and vitamin B12 pregnant women should therefore be advised to focus on minerals (zinc) and to make sure, that the eat enough essential fats and phospholipids. After parturition baby food should be also enriched with choline containing least 10–30 mg/150 ml choline.

Prior to pregnancy or at least as early as possible within pregnancy the individual health status should be determined by professional experts. In case of signs of malnutrition we suggest to control the following parameters by blood work (Table 5):

Table 5. Blood parameters suggested in malnutrient pregnancy (Böhm et al. 2003)

Parameter of malnutrition	Material	Normal range
Folic acid	Serum	4–17 g/l
Ferritin	Serum	Male: 60–160 g/dl; Female: 40–140 g/l
Homocysteine	Serum	Serum <12 µmol/l
Zync	Full blood (Erythrocytes)	4–7.5 mg/l (0.09–0.11 mmol/l)

A steady increase in plasma choline meets an inverse tendency of Homocysteine levels advancing in gestation. There seems to be a concurrent attenuation of the Folate-Homocysteine relation, especially in midtrimester. Thus, both mobilization of maternal choline stores and enhanced de novo choline synthesis may cause maternal plasma choline concentrations to rise. However, the net effect may be the diminution of maternal choline reserves in the second half of pregnancy. The steady increase in plasma choline throughout gestation may ensure choline availability for placental transfer, with subsequent use by the growing fetus. This relation also points to the possibility that a low betaine and choline status may predispose to pregnancy complications associated with high Homocysteine (Holm et al. 2005).

We therefore recommend to control choline status in pregnancy by measuring Homocysteine levels. Homocysteine levels may rise in choline deficiency (Shaw et al. 2004). Measuring Homocysteine is well established and Homocystein measuring kitts are provided commercially. In turn rising choline levels contribute to an attenuation of Homocysteine levels (Selhub 1999, Ozarda et al. 2002). Other critical factors of malnutrition such as folic acid, zinc and ferritin should also be under the control in pregnancy to implement an individual tool of prophylaxis for cerebral dysfunction in the infant.

We encourage further epidemiological studies in this regard to add more evidence to our hypothesis of the beneficial effects of choline supplementation in pregnancy. Such study design should also enhance the understanding on Homocysteine levels and choline supply in pregnant women clinically.

Nutrition has a strong impact on the development of the infant and according to the revealed evidence therefore should be considered the basis for prevention of neurological dysfunction in infants. The data presented, proves that nutrition has a long-lasting decisive impact on the development of the intelligence of children. Prenatal diets should therefore not only be assessed on the

basis of caloric sufficiency. Pregnant women should consult with their doctor at the beginning of prenatal care to determine how best to meet their specific nutritional needs. Besides well known effects of folic acid and zinc pregnant woman should regard special fatty acids such as omega 3 and other products (phospholipids) containing choline for themselves and there babies as very essential. Vegetarians who renounce milk and eggs have a risk of choline deficiency. These women should consider soybean food to satisfy their needs.

Soybean, sunflower and rapeseed are the major plant sources of commercial lecithin. Soybean however is the most common source. Plant lecithins are considered to be GRAS (generally regarded as safe). Egg yolk lecithin is not a major source of lecithin in nutritional supplements. Eggs themselves naturally contain from 68 to 72% phosphatidylcholine, while soya contains from 20 to 22% phosphatidylcholine.

For the sake of omega 3 supply fish is a very important component of prenatal diets. Pregnant woman are further recommended to feed on milk, eggs or meet to satisfy their daily choline supply if possible. Alternatively on behalf of public health concern we suggest to offer pregnant woman soybean extracts in order to avoid deficient choline supply. Lecithin preparations in tablet form show on average 13% of choline content. Side effects may not be expected from oral choline supplementation. Recommended dosage of choline is about 3,5 grams per day. This may combined with Vitamin B_{12} and folic acid. Public Health Institutions should revise their recommendations for supplementation in pregnancy including the above mentioned features for the benefit of the cerebral development of the infant in future generations.

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