Review Article

Investigation of the Effects of Maternal Nutrition during Pregnancy on Cognitive Functions of Toddlers: A Systematic Review

Abstract

Background: Growing the human brain requires all necessary nutrients to form and maintain, so the development of cognitive functions of infants and children depends on adequate nutrition. Children whose mothers had inadequate nutrition are at high risk for cognitive dysfunction. The objective of the present study was to review the studies conducted on "the relationship between nutrient intake during pregnancy and the development of cognitive functions in toddlers". The present study was conducted by systematic review method using PRISMA checklist items. **Methods:** To conduct this study, the keywords "maternal nutrition", "pregnancy diet", "pregnancy supplement", "IQ", "intelligence quotient", "neurodevelopment", "cognitive function", "toddler", "early years" and "infant" were searched based on the Mesh database in scientific databases including Scopus, SID, Google Scholar, PubMed, and Science Direct to find articles related to the effect of nutrition during pregnancy on the development of the cognitive function of toddlers and its components in Persian and English. Finally, 17 articles were selected for review in this study. **Results:** The results showed that taking a supplement of iron, saturated fatty acids, vitamins B and D, and folic acid improved the cognitive functions of toddlers. On the other hand, taking supplements containing iodine and zinc had no significant effect on the development of cognitive functions. Diets containing seafood during pregnancy had a beneficial effect on the cognitive functions of children. **Conclusions:** The study results highlighted the importance of adequate nutrition during pregnancy and showed that maternal nutrition played an important role in the development of cognitive functions of toddlers.

Keywords: *Cognitive function, IQ, micronutrient, nutrition, pregnancy, supplement, toddlers*

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Introduction

Cognitive functions represent a complex set of mental functions that are controlled by the brain and include attention, memory, thinking, learning, and perception. The development of cognitive functions at an early and preschool age predicts academic achievement during and after primary school. As said and heard: "school builds man". Human capital, skills, abilities, and resources are ultimately formed at school. In fact, more education is associated with health and well-being, better jobs, higher incomes, higher socioeconomic status, better access to health care and housing, better lifestyles, and healthier nutrition. All of the above are known as determinants of general health. Accordingly, academic achievement plays an important role in the mental and physical health of a person in the future and is a factor in the general health of society.[1,2]

Cognitive functions are affected by various factors, including nutrition. There are several studies that have investigated the relationship between improving nutritional quality and optimal brain function. Macronutrients (carbohydrates, proteins, and fats) act as building blocks in the total growth of the brain and play an important role in cell proliferation, DNA synthesis, hormone metabolism, and the synthesis of important components of enzyme systems in the brain. Micronutrients, including vitamins and minerals, are involved in the process of myelination, synaptogenesis, and the production of neurotransmitters. Brain growth is faster in the early years of life than in other parts of the body, which may make it more vulnerable to nutritional deficiencies.[1,3,4]

Maternal nutrition during pregnancy is a very important factor in the development of the baby's nervous system, and taking inadequate key nutrients during critical periods can lead to lifelong growth disorder

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as well as impairment in the development of cognitive skills and mental health, which cannot be corrected by nutritional replenishment.[5]

Maternal nutrition plays an important role in planning brain development and, consequently, mental processes. Severe micronutrient deficiencies can also lead to brain dysfunction and neural tube defects (NTDs). Although the beneficial effects of adequate nutrition during pregnancy have been extensively studied over the past decade, many problems remained unsolved, including the most vulnerable periods of pregnancy, the specific effects of malnutrition during pregnancy on the infant, essential nutrients, and what levels of nutrients required to improve neonatal brain development and cognitive intelligence.[6]

Human brain growth and development

Understanding the functional and structural growth of the human brain has been obtained by using a set of methods (clinical lesions, and animal and experimental studies). In recent years, advances in imaging techniques, especially positron emission tomography and magnetic resonance imaging (MRI), have led to a more accurate and complete understanding of brain development at different stages.[1]

Brain growth is considered a complex process, and the brain different parts and their function develop during different periods. Within 5 weeks after fertilization in humans, neural tubes develop and anterior-posterior and dorsal-abdominal axes are formed. The cortex and some neural connections form during 8-16 weeks of pregnancy. From the 24th week of pregnancy to the perinatal period, the neurons in the cortex of the brain die and are replaced by more mature neurons. During this period, significant improvement in neural communication occurs. From 34 weeks after fertilization until the age of 2, there is a peak in brain growth and synaptic development. At preschool age, synaptic density has reached the level of adults. Myelination of parts of the brain (especially those that control higher-level cognitive functions, such as the frontal lobes) continues into adolescence, while myelination of the parts of the brain that most coordinate early functions occurs earlier.

Gray matter (which contains the body of nerve cells) develops in different regions of the brain by the age of 7-11, and it is also thought that white matter (which represents the axonal nerve ducts) continues to grow even after the age of 20.

The study results have shown that brain maturation in childhood is associated with the development of certain cognitive skills such as language, reading, and memory. The frontal lobes involved in controlling higher-level cognitive skills (including planning and self-regulation skills) develop during the growth spurt, i.e. during the first 2 years of life and then between 7 and 9 years of age, and around 15 years of age. The development of some subcortical structures, including the basal ganglia, amygdala, and hippocampus (the brain multiple systems involved in some higher-level cognitive skills, including memory, executive function, and emotion), continues into late adolescence.[1,7]

In addition, the results of a study confirmed a positive relationship between hippocampal size and memory function during brain development in children and adolescents. The development of the human brain follows a genetic program affected by environmental factors, including nutrition. Environmental factors can change gene expression through epigenetic mechanisms, thereby changing gene function. Epigenetic mechanisms involve a set of processes, including DNA methylation, changes in histone structures, and effects on a variety of non-coding RNAs, leading to the expression and/or non-expression of specific genes without changing the gene sequence in a cell. Epigenetic mechanisms cause long-term or hereditary changes in biological programs. Studies on animals and humans in recent years have shown that nutrition is one of the most prominent environmental factors that can have a direct effect on gene expression.[8]

Evidence shows that scheduling access to nutrients can significantly affect brain development. One of the critical periods is neurulation, which occurs before birth, during which the neural tubes close and finally the central nervous system is completed by the development of neural tubes. The folic acid deficiency between 21 and 28 days after fertilization (when the neural tubes close) predisposes the fetus to a congenital anomaly called neural tube defects (NTDs). Therefore, during a short period of about 22 days of human pregnancy, the supply of folic acid is necessary for the formation of neural tubes. Hence, this is a critical period, if there is not adequate folic acid during this period, an irreversible change in the structure and function of the brain occurs. Accordingly, the critical period is a specific period within a sensitive period and/or a time frame during the growth period during which the brain is more sensitive to specific interventions.[9]

The objective of the present study was to review the studies conducted on the relationship between nutrient intake during pregnancy and the development of cognitive functions in toddlers. According to the Centers for Disease Control (CDC), children between the ages of 1 and 3 are considered toddlers. The main reason for the focus of the present study on this age range is brain plasticity, brain flexibility, and rapid and significant changes in the brain during this period. This age range is also the time to acquire basic cognitive and interpersonal skills.

Meanwhile, children's verbal language developed, motor coordination increased significantly, and children engaged in tasks for longer. Toddler age is considered one of the most difficult stages of life to study because toddler performance is affected by factors that are beyond empirical control. These factors include emotional state, motivation, perseverance, and understanding of instructions. Therefore, few studies have been conducted on toddlers, not only because of age-related diversity but also because of the difficulty of assessing cognitive developmental criteria such as "IQ".

Method

Search strategy

The present study was conducted by systematic review method using PRISMA checklist items. To conduct this study, the keywords "maternal nutrition", "pregnancy diet", "pregnancy supplement", "IQ", "intelligence quotient", "neurodevelopment", "cognitive function", "toddler", "early years" and "infant" were searched based on the Mesh database, scientific databases including Scopus, SID, Google Scholar, PubMed and Science Direct for articles related to "the effect of nutrition during pregnancy on the development of cognitive function of toddlers" and its components were searched in Persian and English. The references of the selected articles were also manually reviewed to find gray literature references that were not found in the search for scientific databases. First, all the resulting articles were reviewed to identify duplicate articles and excluded from the study, then the titles and abstracts of the articles were carefully reviewed to exclude articles that have a title and abstract unrelated to the research topic. Finally, the full text of the articles was reviewed carefully based on the inclusion and exclusion criteria of the study, and the data from selected articles were extracted. The study was conducted in March 2022 and no time limit was set for this study.

Selection of articles

In this study, articles in Persian and English were searched, but no article in Persian was found in this regard. Also, only observational studies such as prospective/retrospective cohort, case-control, cross-sectional, and clinical trials investigating the relationship between nutrition during pregnancy and the brain cognitive function of toddlers (1-3 years old) were identified and reviewed. Review articles such as systematic and meta-analysis, repeated articles, and animal studies were excluded from the study. At later stages of screening, studies related to children older than 3 years and/or less than 1 year were also excluded.

Data extraction

Required data are corresponding author, year of publication of the article, a country in which the study was conducted, type of study, number of participants (number of mother-child pairs), mean or age range of children, a dietary supplement used in the study, The amount of supplement used and the time of use of the dietary supplement.

Finally, the results obtained from the articles were studied and assessed and entered Table 1.

The stages of selecting articles based on the PRISMA checklist are shown in Figure 1.

Results

Dietary supplements studied in the reviewed articles included polyunsaturated fatty acids, especially

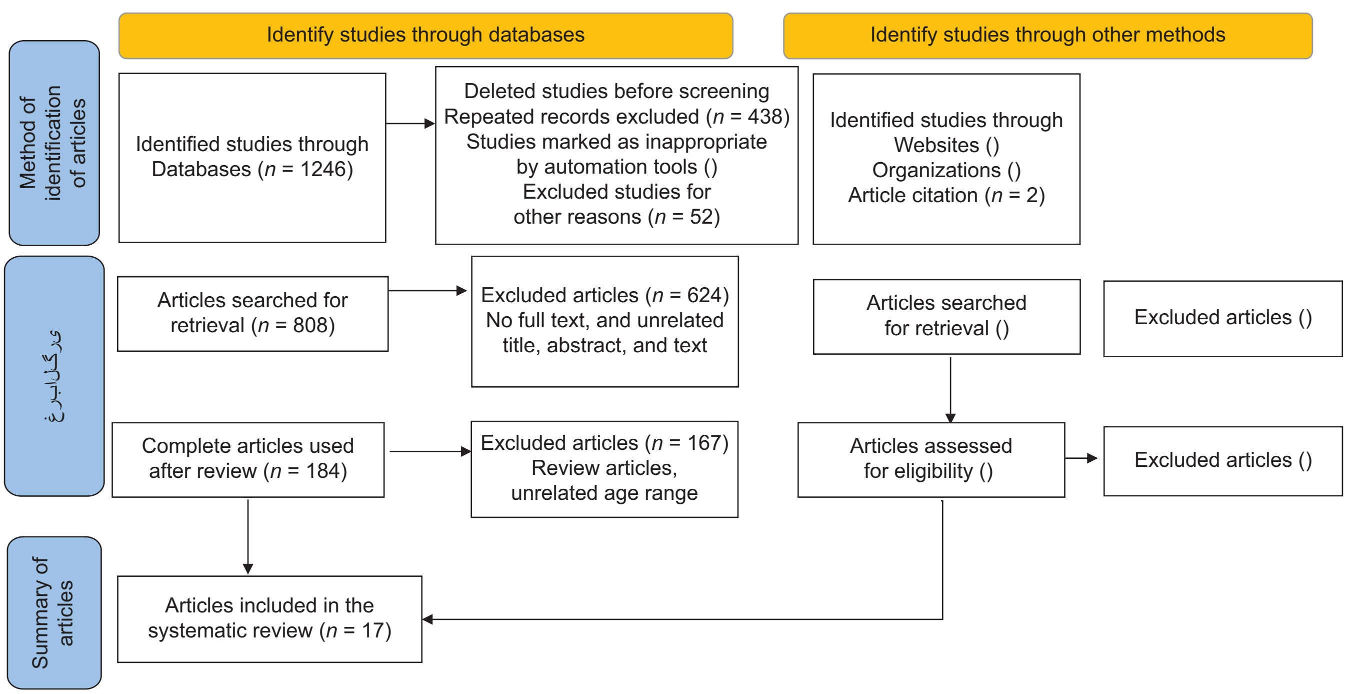

Figure 1: PRISMA 2020

Table 1: Detailed description of the included studies

Year Author Study design Site Number of mother-child pairs	Criteria of measurement	Age of child	Diet type	Results
Valent *et al*. (2013)[10] Prospective cohort study Italy *n*=606	BSID, III Cognitive, linguistic, motor, socio-emotional, and adaptive behavioral subscales	18 months	Diet containing seafood	The mean weekly consumption of fish during pregnancy was less than 2 servings. The mean scores of socio-emotional development of the child were related to the increase in maternal fish consumption during pregnancy. However, the expected beneficial effect of fish consumption during pregnancy (PUFA ω-3) was not observed on other subscales.
Julvez *et al*. (2016)[11] Prospective cohort study Spain *n*=1892	BSID MSCA CAST	14 months	Diet containing seafood	In general, consuming seafood higher than the recommended 340 grams per week was associated with an increase in psychological nerve scores. Consumption of low-fat fish is recommended compared to high-fat fish due to the presence of mercury in adipose tissue.
Lv *et al*. (2022)[12] Prospective cohort study China *n*=1178	BSID, III	12 months	Diet containing fish and vegetables	Daily nutrient intake was calculated by multiplying the daily intake, the amount per meal and the nutrient per gram. The study results showed the cumulative effect of the mother's diet on the neural growth of the infant. These findings highlight the optimal effects of adhering to a "aquatic and vegetables" diet pattern during pregnancy.
Makrides *et al*. (2010)[13] Two-way randomized trial Australia *n*=2399	BSID	18 months	Docosahexaenoic acid (DHA)	DHA supplement and capsules containing 800 mg per day plant oil (control sample) were compared from the 21st week to the end of pregnancy. The results showed no significant difference in the two groups based on BSID.
Gould *et al*. (2014)[14] Controlled randomized trial Australia *n*=185	WMIC	27 months	Docosahexaenoic acid (DHA)	800 mg of DHA per day or placebo (control) continued from the 20th week of pregnancy until birth. Maternal DHA supplement during pregnancy does not increase concentration, working memory and inhibitory control in children.
Ramakrishnan *et al*. (2015)[13] Two-way randomized trial Mexico *n*=730	BSID, II	18 months	Docosahexaenoic acid (DHA)	The dose was 400 mg per day in the last half of pregnancy. The results showed that prenatal DHA supplementation in a population with low DHA intake had no effect on the development of cognitive function in children at 18 months of age, although it may be beneficial for infants from low-income and low-quality food families.
Keim *et al*. (2018)[15] Randomized clinical trial America *n*=377	BSID, III Cognitive, linguistic, motor, socio-emotional, and adaptive behavioral subscales	15 months	Docosahexaenoic acid (DHA) + arachidonic acid (AA)	Daily supplement containing 200 mg of DHA and 200 mg of AA for 6 months did not improve cognitive development and early executive function compared with placebo. The results showed that it could even lead to negative impacts on language development and purposeful control in certain subgroups of children.
Khandelwal *et al*. (2020)[16] Randomized trial India *n*=878	DQ	12 months	Docosahexaenoic acid (DHA)	400 mg per day of DHA supplement taken by mothers during pregnancy and even breastfeeding had no effect on neural growth in children at 12 months.
Morales *et al*. (2012)[17] Prospective cohort study Spain *n*=1820	BSID, III Cognitive, linguistic, motor, socio-emotional, and adaptive behavioral subscales	14 months	5-Hydroxyvitamin D3	The mean plasma 25 (OH) D3 in pregnancy was 29.2 ng/ml (37.21-3.8). Higher concentrations of circulating vitamin D3 in pregnancy were associated with increased scores on cognitive and psychomotor development scales in infants.

Contd...

Table 1: Contd...

Year Author Study design Site Number of mother-child pairs	Criteria of measurement	Age of child	Diet type	Results
Thomas *et al*. (2019)[18] Randomized trial India n=218	BSID, III Cognitive, linguistic, motor, socio-emotional, and adaptive behavioral subscales	30 months	Vitamin B12	Vitamin B12 continued throughout pregnancy until 6 weeks after delivery. The study results showed that children whose mothers received 50 micrograms per day of vitamin B12 had better cognitive function on the language subscale than children whose mothers received placebo.
Chatzi *et al*. (2012)[19] Prospective cohort study Greece n=58	BSID, III Cognitive, linguistic, motor, socio-emotional, and adaptive behavioral subscales	18 months	Folic acid	The dose of folic acid supplementation was 5-15 mg per day. Folic acid was taken by the mother during the 14-18th weeks of pregnancy. The results showed that taking high doses of folic acid supplement in early pregnancy can be associated with strengthening the vocabulary, communication skills and verbal comprehension of the child at 18 months.
Chang *et al*. (2013)[20] Two-way randomized trial China n=850	MDI	18-24 months	Folic acid supplement Iron/folic acid supplement Supplement of composition of micronutrients	Folic acid, iron/folic acid (60 mg of iron), and several micronutrients (30 mg of iron) supplement was taken during pregnancy. Accordingly, adequate iron supplement before birth protects the growth and development of the child's brain, even when the mother and fetus are iron deficient.
Velasco *et al*. (2009)[21] Meta-analysis Spain n=194	BSID	18 months	iodine	The objective of this study was to investigate the mental development of 18-month-old infants whose mothers received 300 micrograms of potassium iodide in the first trimester of pregnancy and compared with infants whose mothers did not receive iodine supplement. Dietary iodine supplement not only had no detrimental effect on children's nervous development, but also improved the development of children's cognitive skills.
Murcia *et al*. (2011)[22] Prospective cohort study Spain n=691	BSID	12 months	Supplement containing iodine	Infants (especially girls) whose mothers took multivitamin supplement high in iodine (1-149 micrograms per day) during pregnancy had less motor development than infants whose mothers took less iodine supplement (less than 100 micrograms per day).
Rebagliato *et al*. (2013)[23] Prospective cohort study Spain n=1519	PDI	14 months	iodine	The amount of iodine received by the mother was in the range of 400-150 micrograms per day. Iodine was consumed in 10-13 and 28-32 weeks of pregnancy. Consumption of more than 150 micrograms per day by the mother, compared to consumption of less than 100 micrograms per day iodine, increased PDI in children by 1.8 times.
Zhou *et al*. (2019)[24] Prospective cohort study Australia n=699	BSID, III Cognitive, linguistic, motor, socio-emotional, and adaptive behavioral subscales	18 months	iodine	Iodine supplementation was used during the 20-20 weeks of pregnancy and the dose was 391-220 mg per day. The results showed no significant relationship between iodine supplement during pregnancy and the development of cognitive functions in children. In some cases, low or high iodine intake during pregnancy was associated with poorer childhood neurodevelopment in this population with adequate iodine.
Hamadani *et al*. (2002)[41] Controlled randomized trial Bangladesh n=559	BSID-II	13 months	zinc	Pregnant mothers were randomly assigned to receive 30 mg of zinc supplement or cellulose placebo from the fourth month of pregnancy until delivery. Infants in the placebo group had higher scores on mental growth index and psychomotor development index than those in the zinc supplement group.

docosahexaenoic acid, arachidonic acid, vitamin D, vitamin B12, folic acid, iron, iodine, and aquatic diets. To investigate the cognitive function of toddlers, standard scales have been used, including Bayley-I, II, and III Scales of Infant and Toddler Development, McCarthy Scales of Children's Abilities (MSCA), Childhood Asperger Syndrome Test (CAST), Working Memory and Inhibitory Control (WMIC), decency quotient (DQ), Mental Development Index (MDI), Psychomotor Development Index (PDI) and subscales of cognitive, language, motor, socio-emotional and adaptive behavior in reviewed articles.

The study results are as follows:

Polyunsaturated fatty acids

In recent years, several studies have been conducted on the effect of essential fatty acids, especially long-chain polyunsaturated fatty acids (LCPUFA), on brain cognitive function. 60% of the dry weight of the human brain is made up of lipids, 20% of which are docosahexaenoic acid (DHA; which is an omega-3 fatty acid) and arachidonic acid (AA; omega-6 fatty acid). Docosahexaenoic acid and arachidonic acid are the two main fatty acids in the gray matter of the brain.[25]

Essential fatty acids play a functional role in the brain tissue. They are not only the main components of nerve membranes but also modulate the fluidity and volume of the membrane. As a result, in addition to ion channels, they affect the activity of receptors and enzymes. Essential fatty acids are also precursors of active mediators that play a key role in inflammatory and immune responses. They affect the development of nerve cells and spinal dendrites, the synthesis of synaptic membranes, and thus the processing and transmission of nerve signals. In addition, essential fatty acids regulate gene expression in the brain. The results of existing literature showed that fatty acids are essential for brain development and function. Researchers have suggested that the rapid growth of the human cerebral cortex over the past two million years has been strongly linked to a balanced diet containing LCPUFAs, especially those containing equal proportions of omega-6 and omega-3 fatty acids.[1,3]

A number of epidemiological studies have shown a positive relationship between maternal consumption of fish (a rich source of omega-3 fatty acids) during pregnancy and the development of the cognitive function in children. The results of the present study showed that the mean scores of socio-emotional development of toddlers were associated with increased maternal consumption of fish during pregnancy. However, the expected positive effect of fish consumption during pregnancy was not observed on all subscales of cognitive function, which can be attributed to the consumption of fish less than the required amount due to the presence of mercury in aquatic tissue. On the other hand, the consumption of low-fat fish is recommended compared to higher-fat fish due to the presence of mercury in adipose tissue.[10-12]

The study results investigating the relationship between docosahexaenoic acid and arachidonic acid supplements and the cognitive function of toddlers showed that DHA supplements during pregnancy did not significantly increase subscales of the cognitive function of children. Given that these two fatty acids are the main fatty acids in the gray matter of the brain, the optimal level of these two substances is maintained by maternal reserves in the fetus. Accordingly, due to the protection of intrauterine brain growth, transfer of maternal DHA reserves to the fetus, positive regulation of DHA synthesis, and preferential transfer of DHA from the placenta during pregnancy, the fetal nervous structures are protected against abnormal growth and DHA supplement shows no effect (Ramakrishnan *et al*., 2015).[13-17]

Vitamin B12 and folic acid

B12 and folic acid deficiency lead to anemia around the world. This is seen in both developing and developed countries in those with absorption problems, vegetarians, and especially the elderly. For this reason, fortification of bakery products with folate has become mandatory in Australia and many other countries and has significantly reduced the deficiency of this nutrient. In recent years, there has been a growing interest in investigating the relationship between vitamin B12 and folic acid and the development of cognitive brain function (Brown *et al*., 2011).[19]

Folic acid as an important water-soluble nutrient plays an important role mainly in the metabolism of non-essential amino acids, proliferation and differentiation of neuronal stem cells, reduction in apoptosis (programmed cell death as a conserved method, controlled by genes, and remove of unwanted or unnecessary cells in living organisms), changes in DNA biosynthesis, homocysteine biosynthesis, and S-adenosyl methionine. In addition, the metabolism of folic acid and vitamin B12 are linked in the homocysteine-methionine-S-adenosyl methionine pathway. S-adenosyl methionine is one of the major donors of methyl in methylation reactions, including DNA methylation. Therefore, folic acid deficiency leads to DNA hypomethylation and thus changes gene transcription.[26,27]

Vitamin B12 is one of the essential vitamins for the human body. This vitamin plays an important role in DNA synthesis and maintenance of genome stability and acts as a cofactor for the enzyme methionine synthase in the methylation process. Homocysteine (Hcy) is a sulfur-containing amino acid that is converted to methionine during the methylation process by the enzyme methionine synthase and is involved in the conversion of 5-methyl tetrahydrofolate to tetrahydrofolate.

Vitamin B12 is involved in axonal myelination, which is important for conducting nerve pulses from cell to cell as well as protecting neurons from destruction. Vitamin B12 can also alter the synthesis of various cytokines, growth factors, and oxidative energy metabolites such as lactic acid.[28]

The relationship between vitamin B12 deficiency and lack of development of cognitive functions had been observed mainly in infants born to vegetarian mothers or mothers on a macrobiotic diet. These diets can lead to vitamin B12 deficiency, as vitamin B12 is found in large amounts in animal products. In a review study consisting of 48 articles, the issue of vitamin B12 deficiency in infants was investigated. A variety of abnormal clinical and radiological symptoms, including hypotonic muscle, involuntary muscle movements, cerebral indifference, and myelin destruction of neurons were observed in infants with vitamin B12 deficiency. After treatment with vitamin B12, rapid improvement in neurological symptoms was reported in deficient infants, but many of these infants were severely delayed in developing long-term cognitive and language functions.[28]

The results of articles investigating the relationship between vitamin B12 and folic acid intake during pregnancy and the development of cognitive function in toddlers showed that taking high doses of folic acid supplement early in pregnancy and vitamin B12 during pregnancy were associated with vocabulary, communication, verbal comprehension and expression skills of children.[18,19]

Vitamin D

Over the past decade, the focus has shifted to the effect of vitamin D deficiency during pregnancy on the growth and function of children's brains. The discovery of vitamin D receptors in several regions of the brain and central nervous system in infants and adults indicates the importance of vitamin D in the development of the brain and nervous system. Further studies demonstrated the importance of vitamin D in brain growth and function mechanisms, including nerve cell differentiation, axonal binding, dopamine synthesis, immune modulation, transcription, and gene expression.[29] Vitamin D has a variety of anti-inflammatory effects on the brain, including the reduction in harmful inflammatory cytokines and neuro-inflammation caused by oxidants and toxins. Increased DNA repair mechanisms, autoimmune effects, increased seizure threshold, increased number of T regulatory cells, glutathione regulation, and protection of neuronal mitochondria are the effects of vitamin D on the brain (García-Serna and Morales, 2020).[33]

In addition, vitamin D activates the enzymes that limit the rate of serotonin (a neurotransmitter that forms brain networks during growth and plays a vital role in brain function). Vitamin D also activates a gene that makes the enzyme tryptophan hydroxylase. This enzyme converts the amino acids tryptophan to serotonin in the brain. This vitamin is involved in regulating the expression of the tyrosine hydroxylase (TH) gene and thus the biosynthesis of dopamine.[31]

The critical period of access to vitamin D is the first and second trimesters of pregnancy. The study results showed that the protective effects of vitamin D occur during early prenatal development when brain structures begin to form and are more vulnerable to destructive effects.[32]

The study results of Morales *et al*. (2012)[17] investigating the relationship between vitamin D intake during pregnancy and the development of cognitive function showed that higher concentrations of circulating vitamin D during pregnancy were associated with increased scores on cognitive and psychomotor development scales of toddlers.

Iron

Iron deficiency is one of the most common nutritional deficiencies in developing and developed countries. In some parts of the world, such as sub-Saharan Africa and Southeast Asia, the prevalence of iron deficiency is over 40%. In developed countries, including Australia, the prevalence of iron deficiency is 20%. Iron deficiency is more common in pregnant women and children. Over the past decades, many articles have been published on the relationship between iron/anemia and the development of cognitive functions children. Iron is involved in various enzymatic systems in the brain, including cytochrome c oxidase enzyme system for energy production in mitochondria, tyrosine hydroxylase for dopamine receptor synthesis, delta-9-desaturase for myelin synthesis, fatty acid biosynthesis and ribonucleotide reductase for the brain growth regulatory. In addition, it seems that iron changes growth processes in hippocampal neurons by changing the growth of dendritic cells.[33]

There are few studies that have investigated the relationship between iron or iron supplements in the diet during pregnancy and the development of cognitive functions in children. The results of one of these studies showed that in 5-year-old children whose umbilical cord ferritin level was the lowest; poor performance in language skills, motor skills, and decentralization (as well as lower but not significant scores on other tests) was observed. In this study, cognitive function was measured using the Wechsler Intelligence Test for Scale for Children-Revised (**WISC-R**, Wechsler, 1974) and the Test for Auditory Comprehension of Language.[36]

Chang *et al*. (2013)[20] in a study investigated the relationship between iron supplements during pregnancy and the mental development index (MDI) of toddlers. In this study, women were randomly divided into three groups to receive different supplements daily: folic acid, iron/folic acid (60 mg of iron), and several micronutrients (30 mg of iron). The children were divided into two groups with iron deficiency and healthy based on the maternal blood hemoglobin in the third trimester. The results showed that the MDI of children with iron deficiency and healthy children whose mothers took iron/folic acid supplements was the same. While taking a folic acid supplements or multi-micronutrient supplements had no effect on increasing the MDI of children with iron deficiency. Accordingly, adequate iron supplement before birth protects the growth and development of the child's brain, even when the mother and fetus are iron deficient.

Iodine

Iodine deficiency is an important general health issue, especially in children and pregnant women around the world. Soil iodine deficiency has led to nutrient enrichment in many countries, and iodized salt is commonly used.

The relationship between iodine and the development of cognitive function has been widely investigated. The study results showed that severe iodine deficiency during pregnancy can cause "cretinism" in children (a complication of mental retardation). The clinical manifestations of cretinism depend on the severity of iodine deficiency, including mental retardation, speech and hearing impairment, lesions of the upper motor neurons, and complications of the extra-pyramidal system. The presence of iodine is essential for the production of thyroid hormones in the body, 70-80% of which is found in the thyroid gland. Iodine deficiency occurs in hypothyroidism and reduces the production of thyroid hormones including triiodothyronine (T3) and thyroxine (T4). Thyroid hormones play an important role in the development of the nervous system and regulate several neural processes including neuronal cell differentiation, neuronal maturation and migration, myelination, neuronal transmission, and synaptic plasticity. In addition, in animal models, hypothyroidism neurogenesis changes the development and function of synapses in the hippocampus.[1,4,35]

Qian *et al*. (2005)[36] investigated the effect of iodine deficiency in pregnant mothers on the child's IQ. The study was conducted in various sites in China where the soil was severely iodine deficient. The results showed that the IQ scores of children whose mothers lived under iodine-deficient conditions were about 12.3 lower than those whose mothers lived in sites with sufficient iodine.

In the studies reviewed in the present study, the results were divided into two parts. Some results have shown that taking dietary iodine supplements not only had no detrimental effect on children's neurodevelopment but also improved the development of children's cognitive skills.[21,23]

While some results showed no significant relationship between iodine supplements during pregnancy and the development of cognitive functions in children. In some cases, low or high iodine intake during pregnancy was associated with poorer neurodevelopment in childhood.[22,24] The difference in the results can be attributed to the type of family diet. For mothers who have a poor diet and are poor in minerals such as iodine, even taking iodine supplements during pregnancy cannot compensate for iodine deficiency in the fetus and the supplement has no effect on the development of cognitive functions of the child.

Zinc

Zinc is present as an important catalytic component in the structure of more than 200 enzymes. It can also be found in the structure of several nucleotides, proteins, and hormones. It plays an important role in most biochemical reactions including protein synthesis, nucleic acid metabolism, cell division, gene expression, antioxidant defense, wound healing, neurological function, and immunity (Ota *et al*., 2015; Musa *et al*., 2019).[37,38] In addition, zinc is involved in neurogenesis, maturation, and migration of neurons, and the formation of synapses. Zinc is found at high concentrations in the synaptic vesicles of hippocampal neurons (involved in learning and memory) and it seems that it controls the synthesis of some neurotransmitters, including glutamate and gamma-aminobutyric acid (GABA) receptors.[1]

Zinc is found in most foods. Meat, seafood, milk, and nuts have higher levels of this mineral, while diets high in fiber or phytate reduce the bioavailability of zinc. However, about 82% of pregnant women receive inadequate zinc during pregnancy. The allowable level of zinc in the second and third trimesters of pregnancy is 15 mg per day, but most pregnant women consume about 9.6 mg of zinc per day. Zinc deficiency causes the annual death of half a million mothers and fetuses, especially in developing countries. Zinc deficiency in pregnancy causes immunodeficiency, prolonged labor, preterm labor, fetal growth retardation, and maternal hypertension. One of the rare complications of severe zinc deficiency that results from inherited defects in zinc absorption (acrodermatitis enteropathica) is congenital malformations and miscarriage (Chaffee and King, 2012).[40]

A randomized placebo-controlled trial of zinc supplements on poor Bangladeshi mothers found that 13-month-old infants whose mothers received zinc supplements scored lower on BSID than infants whose mothers received placebo. To explain the results, the researchers argued that since micronutrients interact with each other, zinc supplement alone causes an imbalance or even deficiency of other micronutrients that are important for brain growth (Hamadani *et al*., 2002).[41]

Conclusions

Pregnancy is a time of rapid and profound physiological changes from fertilization to childbirth. During pregnancy, nutritional needs increase in order to maintain the metabolism of the mother's body while supporting fetal growth and development. Poor diet or lack of key macro- and micronutrients can have a significant effect on maternal and infant health during pregnancy. The effects of nutrition on the fetus continue to adulthood. Even malnutrition has potential intergenerational effects.

Several studies investigating the relationship between nutrition and the cognitive development of children have focused on micronutrients including omega-3 fatty acids, vitamin B12, folic acid, vitamin D, zinc, iron, and iodine. The study results showed that these micronutrients played an important role in the development of children's cognitive functions.

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Nil.

Conflicts of interest

There are no conflicts of interest.

Ethical Considerations

Nil.

Code of Ethics

Nil.

Author contributions

All authors contributed to the study's conception, design, and data collection. The authors have seen and approved the final version of the manuscript.

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Authors' Contributions

All authors contributed to the studys conception, desighn, and data collection.the authors have seen and approved the final version of the manuscript.

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