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Analysis of selected nutritional and environmental factors leading to the development of neural tube defects

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Abstract

Neural tube defects represent the most common type of congenital central nervous system malformations. This study focuses on analyzing selected nutritional and environmental factors influencing neural tube development and their roles in the pathogenesis of these defects. A review of the literature, along with an analysis of clinical and experimental research results, has enabled the identification of molecular mechanisms such as the regulation of DNA methylation processes, homocysteine metabolism, and the teratogenic effects of environmental factors. A clinically significant association has been observed between the prenatal administration of vitamin B12 and folic acid and the risk of neural tube defects. The study also examines prenatal exposure to valproic acid, which carries the risk of neural tube defects, and discusses the role of choline, which appears to be important in supporting neurogenic processes. The work emphasizes the necessity of an interdisciplinary approach to the prevention of neural tube defects through the optimization of maternal nutrition and the elimination of harmful environmental factors.

Keywords: neural tube, folic acid, vitamin B12, pregnancy, fetal development, diet during and after pregnancy, neural tube defects, teratogenic factors, valproic acid, choline

1. Introduction

A. Background:

Neural tube defects (NTDs) are congenital malformations resulting from improper closure of the neural tube during early embryonic development. One of the earliest stages of brain formation is the development of the neural tube, which gives rise to the ventricular system, brain, and spinal cord. NTDs can manifest as conditions such as spina bifida or fatal anomalies like anencephaly, characterized by the partial absence of the brain and skull, as well as the lack of key brain structures.

The proper development of the neural tube is influenced by a combination of genetic, nutritional, and environmental factors. Optimal maternal nutrition and the avoidance of teratogenic exposures play a crucial role in minimizing the risk of NTDs in the fetus.

Folic acid significantly reduces the risk of NTDs in women who supplement it during the preconception period, pregnancy, and breastfeeding. Folate deficiency disrupts DNA synthesis, methylation, and homocysteine regulation, all of which are essential for proper embryonic development. It supports cell division and differentiation, and its deficiency leads to improper neural tube closure.

Vitamin B12 is involved in DNA synthesis and methylation regulation, which affects the expression of genes essential for central nervous system development. A deficiency in vitamin B12 can lead to homocysteine accumulation, increasing oxidative stress and impairing neuroectodermal cell proliferation.

Choline serves as a precursor to phosphatidylcholine, a key component of cell membranes, and acetylcholine, a neurotransmitter essential for proper neuronal function.

Exposure to teratogenic substances, such as valproic acid, poses a significant risk of disrupting neurogenesis. Valproic acid, commonly used in epilepsy treatment, has well-documented teratogenic effects that increase the likelihood of NTDs, particularly when exposure occurs during the critical prenatal period.

B. Research questions:

The main research question of this dissertation is how selected nutritional and environmental factors lead to the development of neural tube defects. This study will also focus on folic acid and vitamin B12 supplementation in the prenatal period and the extent to which they eliminate the risk of neural tube defects.

C. Purpose and scope:

The work will include a review of the literature on the role of nutritional and environmental factors in the development of the neural tube, with particular emphasis on molecular mechanisms, teratogenicity of valproic acid, and interactions between key nutrients. The analysis will explore the influence of folic acid, vitamin B12, and choline on DNA methylation processes, homocysteine metabolism, and genome stability, highlighting their significance in neural tube development. Additionally, the study will examine the teratogenic effects of valproic acid, focusing on its impact on cell proliferation and the expression of genes responsible for proper neural tube closure. Furthermore, special attention will be given to the interactions between folic acid, vitamin B12, and choline, investigating how these nutrients influence each other and their collective effect on the risk of neural tube defects.

D. Structure of the essay:

Taking all the above aspects into account, this article will first analyze the proper development of the neural tube (Section 2), the consequences and defects resulting from its failed closure (Section 3), and the impact of both nutritional and environmental factors on its formation (Section 4). Finally, the text will include a summary in the Conclusion (Section 5)

2. Proper Development of the Neural Tube during Prenatal Period

Primary neurulation involves the process of neural tube closure and its transformation into the primitive brain and spinal cord up to the level of the lumbar segment.

A. Formation of the Neural Plate and Neural Tube

The notochord induces the thickening of the overlying ectoderm, leading to the formation of an elongated neural plate, which corresponds in length to the notochord.

- Around day 18, the neural plate undergoes invagination along its long axis, forming a central longitudinal neural groove with neural folds on each side.
- By the end of the third week, the neural folds approach each other and fuse, transforming the neural plate into the neural tube, the primordium of the brain vesicles and spinal cord.
- The neural tube soon separates from the superficial ectoderm, the free edges of which join together and differentiate into the epidermis.

The initiation of the fusion of the neural folds and the closure of the neural pores is driven by two main initiation sites of this process. The first site, α, is located in the area of the prosencephalon, while the second site, β, is located in the area of the forebrain. The fusion process starting at site α proceeds in both directions (cranial and caudal), while at site β, it proceeds only in one direction (cranial). [1]

- The anterior neural pore (cranial neuropore) closes around day 25; the posterior neural pore (caudal neuropore) closes two days later.
- Once the neural tube is closed, the brain begins to form.

B. Secondary Neurulation (around day 28–48)

- This process affects the sacral and coccygeal segments of the spinal cord.
- The ectodermal cells in the caudal part proliferate and form a structure known as the caudal neural eminence.
- This eminence undergoes cavitation, and the resulting cavities merge with the neural tube, extending its lumen caudally.

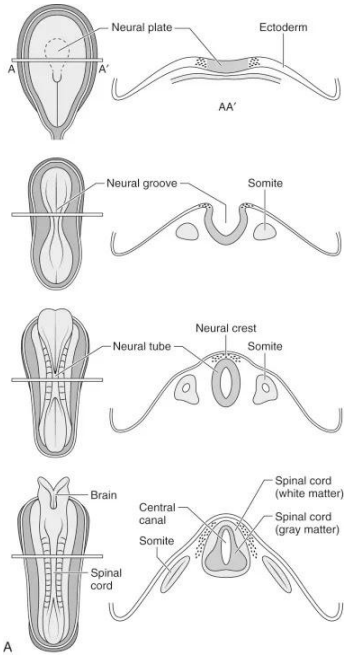

Figure 1. *Schematic depiction of the developing embryo* : external view *(left)* and corresponding cross-sectional view at about the middle of the future spinal cord.

3. Neural Tube Defects

Failure in the closure of the neuropores may lead to neural tube defects. Partial or complete failure of proper neural tube closure can result in several developmental defects, each characterized by a combination of abnormalities in the neural tissue, meninges, and adjacent bones and soft tissues. [2]

A. Defects Resulting from Failure of Anterior Neuropore Closure

An anomaly in the anterior end of the neural tube, leading to the absence of the brain and skull vault, is called anencephaly – the most severe defect resulting from failure of the anterior neuropore closure. It involves complete or partial absence of the brain, skull vault, and scalp. If present, the brain is rudimentary and often disorganized. Encephalocele (brain herniation) and hypoplasia of the prosencephalon may accompany this defect.

Structures of the posterior cranial fossa may be present to varying degrees. Anencephaly occurs at a frequency of approximately 1 in 1000 cases, with geographical, toxic, metabolic, rare chromosomal, and nutritional factors (e.g., folic acid deficiency) contributing to its occurrence.[3] Characteristic features of infants with anencephaly include a frog-like appearance, short neck, bulging eyes, and large tongue. About 12% of cases of anencephaly are associated with other structural abnormalities, including cleft lip, cleft palate, clubfoot, and omphalocele.[4] It can be diagnosed via ultrasound between the 12th and 13th week of pregnancy.[5]

Encephalocele is a defect in the central nervous tissue protruding through a skull defect. It may contain only the meninges (meningocele) or both the meninges and brain tissue (meningoencephalocele). It most commonly occurs in the suboccipital region or posterior cranial fossa. When it occurs at the front, brain tissue may be located in the sinuses. [3]

B. Defects Resulting from Failure of Posterior Neuropore Closure

Spina bifida is the most prevalent form of neural tube defect, occurring in 0.5 per 1000 pregnancies in Europe, including live births, pregnancy losses, and terminations. The number of affected individuals has not decreased significantly since the 1990s, despite the general recommendation for periconceptional folic acid supplementation. [6]

The most common defects affect the posterior end of the neural tube, which forms the spinal cord. These include asymptomatic bony defects (spina bifida occulta) and more severe forms of the defect, such as spina bifida, involving a flattened, disorganized section of the spinal cord, associated with an outpouching of the surrounding meninges. [3]

C. Types of Spina Bifida and Their Characteristics

Closed Spina Bifida (Spina Bifida Occulta)

Closed spina bifida is the mildest form of neural tube defect, resulting from incomplete fusion of the vertebral arches during fetal development. In this form, the spinal cord and meninges remain intact and are in their proper location. Skin abnormalities, such as a tuft of hair, small skin dimple, vascular stain, or lipoma, are often observed at the site of the defect. This condition usually does not cause significant clinical symptoms and is often detected incidentally during imaging studies of the spine. In rare cases, it may lead to neurological complaints, such as weakness in the lower limbs, back pain, or sensory disturbances.

Spina Bifida with Meningocele

This is a rare but more advanced form of neural tube defect. In this condition, the meninges protrude through a defect in the vertebral arches, forming a herniated sac on the surface of the child's back. Key features include:

- A hernial sac containing the meninges and cerebrospinal fluid
- Normal positioning and structure of the spinal cord
- Absence of significant neurological deficits (in most cases).

This defect may be visible as a soft mass on the child's back. Surgical closure of the defect is required to prevent infection and neurological complications.

Spina Bifida with Myelomeningocele

This is the most severe form of spina bifida, characterized by the protrusion of the spinal cord and its nerve roots outside the spinal canal. These structures are contained within the hernial sac, which is not covered by skin, increasing the risk of infection and cerebrospinal fluid leakage. Major characteristics of this defect include:

- Presence of a hernial sac containing the spinal cord and/or nerve roots
- High association with hydrocephalus and Arnold-Chiari Type II malformation
- Possible co-occurrence with anencephaly or other central nervous system defects
- Significant neurological deficits, such as paralysis of the lower limbs, sensory loss, and incontinence.

Immediate surgical intervention is required to close the defect and protect the neural structures from further damage.

Myelocele

Myelocele is the most severe form of spina bifida, resulting from complete failure of the neural groove to close. In this defect, the spinal cord remains open and exposed on the surface of the body, with cerebrospinal fluid continuously leaking from it. This is one of the most severe forms of spina bifida, often leading to:

- Severe neurological damage
- Recurrent infections, such as meningitis
- Extreme motor and sensory dysfunction
- High risk of neonatal death.

Treatment is complex, involving both surgical closure of the defect and long-term rehabilitative care aimed at improving the patient's quality of life.

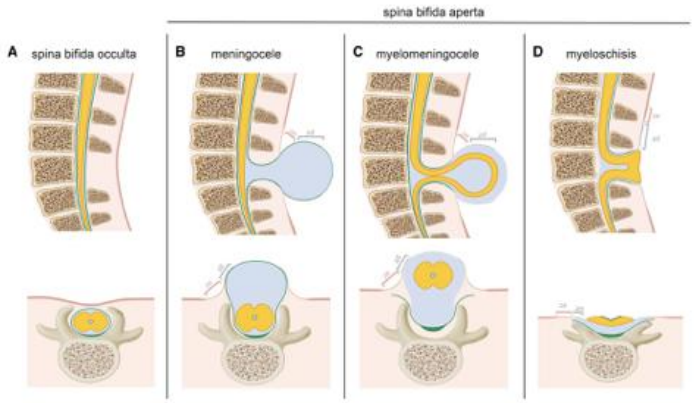

Figure 2. Types of spina bifida

Schematic drawing of SB subtypes. **(A)** Spina bifida occulta: longitudinal section on top, transversal section below. **(B)** Myelocele longitudinal section on top, transversal section below. **(C)** Myelomeningocele longitudinal section on top, transversal section below. **(D)** Myeloschisis longitudinal section on top, transversal section below. In the SBA phenotypes **(B–D)**, skin transition zones can be described as follows: below the skin defect, the spinal cord (yellow) can be identified. As the meninges and consequently the subarachnoid space is not closed, cerebrospinal fluid is leaking. Lateral to the lesion, the zona epithelioserosa (ze, gray) follows. This zone contains leptomeninges covered by a thin layer of squamous epithelium and hence forms a mixed tissue of epidermal and mesenchymal cells. In the zona dermatica (zd, pink), there is only a thin horn layer and dermal appendages like hair, sweat, and sebaceous glands (Essbach, 1961); this tissue then passes over to normal skin coverage that can have a thicker keratin layer or hypertrichosis lateral to the lesion. Other tissues are marked with the following colors: dura (green), subarachnoid space (light blue), and ependyma (dark blue). [6]

4. The impact of both nutritional and environmental factors on its formation

A. The Importance of Folate Metabolism in Neural Tube Development

One of the functions of folic acid is to prevent neural tube defects in the fetus. Fetal development is a process in which, due to intense cell division, the production of DNA acids increases, thereby raising the demand for folates.[7] Numerous scientific studies have shown that folic acid supplementation during pregnancy and before conception can reduce the risk of certain congenital developmental defects in newborns. The biologically active form of folates in the body is tetrahydrofolic acid. Its polyglutamyl derivatives act as coenzymes in many biochemical processes occurring in the body. Their main role is to provide one-carbon groups to various compounds involved in cell division (nucleic acid synthesis), protein synthesis, amino acid transformations (the interconversion of serine and glycine), histidine catabolism to glutamic acid, and the conversion of homocysteine to methionine.[8] Folate is essential for the formation of the myelin sheath around nerve fibers. Moreover, it reduces the risk of congenital defects related to improper neural tube closure. [7]

Folate Content in Food

Folate is present in both plant and animal products, mainly in the form of reduced folate derivatives (tetrahydrofolate and dihydrofolate). The richest sources include raw or briefly cooked leafy green vegetables, such as broccoli, Brussels sprouts, spinach, kale, asparagus, and lettuce. Large amounts of folate are also found in legumes (peas, soybeans, beans) – 150-200 μg/100 g. Yeasts, whole grains, and wheat germ are also rich sources. Other valuable sources include vegetables and fruits rich in vitamin C and β-carotene, such as parsley, kale, bell peppers, kiwi, raspberries, and oranges. Nuts provide 66 μg/100 g (walnuts) to 110 μg/100 g (peanuts). Among animal products, the richest sources of folates are organ meats, especially liver (200-580 μg/100 g). Processed meats and milk contain small amounts (about 5 μg/100 g), while fermented dairy beverages, such as buttermilk and yogurt, contain 7-10 μg/100 g of folate synthesized by lactic acid bacteria. Hard cheeses contain 10-40 μg/100 g, cottage cheese about 30 μg/100 g, and soft ripened cheeses (brie, camembert) – 60-100 μg/100 g. Eggs provide 65 μg/100 g, mainly in the yolk. Of fish, the richest source of folates is salmon (26 μg/100 g). [9,10,11]

Folate belongs to the group of water-soluble vitamins. Folic acid is a synthetic form of folates that is more stable than naturally occurring folates in food. [12] The dominant and most active form of folates in blood serum is L-5-methyltetrahydrofolate (5-methyl THF), which is transported into cells. This compound can be directly incorporated into the cell's metabolic cycle, while the most important compound in the folate cycle is 5,10-methylenetetrahydrofolate (5,10-methyl THF) [12, 13]. Folate metabolism is responsible for maintaining appropriate methionine and homocysteine levels within the cell, as well as normal S-adenosylmethionine (SAM) levels, which is a methyl group donor in DNA methylation reactions. [14] The unimpeded functioning of folate metabolic pathways is crucial for the processes of cell proliferation and differentiation, which are essential for normal fetal growth and development, particularly during organogenesis. The main task of biochemical pathways involving folates is to provide one-carbon groups (-CH3) in enzymatic reactions occurring in the biosynthesis of purines and pyrimidines, amino acid transformations (serine and glycine interconversion), biomolecule methylation (including DNA), the conversion of homocysteine to methionine, and homocysteine to cysteine (transsulfuration reaction), as well as the catabolism of histidine to glutamic acid. Folate deficiency can lead to the accumulation of homocysteine, which is toxic to cells and may disrupt neural tube closure. Folates actively participate in protein biosynthesis, membrane lipid metabolism, the myelin sheath of nerve fibers, and drug metabolism.[13] Deficiency in folates and insufficient utilization in these metabolic processes may be caused by genetic polymorphisms in genes encoding proteins and enzymes directly involved in their transport and metabolic pathways [7].

A series of enzymes, including methylenetetrahydrofolate reductase (MTHFR), are responsible for folate metabolism. Mutations in the MTHFR gene can lead to reduced enzyme activity, resulting in decreased ability to convert folates into their active form. Individuals with specific variants of these genes may have elevated homocysteine levels, which increases the risk of neural tube defects (NTDs). In such individuals, supplementation with methylated folates, such as L-5-methyltetrahydrofolate (5-MTHF), which is more readily absorbed by the body, is recommended. Genes encoding individual enzymes and non-enzymatic proteins are considered candidate genes that shape the individual risk of NTDs [7].

Environmental factors, such as insufficient folate levels in the body, are one of the leading causes of neural tube defects. This deficiency may be linked to medications that interfere with folate absorption and metabolism. These drugs include dihydrofolate reductase inhibitors (e.g., methotrexate, sulfasalazine, trimethoprim) and antiepileptic drugs (valproic acid, carbamazepine) [15,16,17].

The recommended daily intake of folates is 400 μg for adults and 600 μg for pregnant women [18]. A healthy human body stores 5-10 mg of folic acid, about half of which is stored in the liver. If folates are completely absent from the diet, these stores are depleted within 3-4 months [9,10].

A study conducted in Poland showed that pregnant women consumed folic acid at 53% of the recommended levels. This is concerning, as pregnancy is a period in a woman's life when proper folic acid intake is particularly important. Adequate folate levels in the diet prevent neural tube defects and reduce the risk of miscarriage, as well as other congenital defects, such as heart defects, limb abnormalities, or craniofacial deformities.[12] Charkiewicz et al. assessed the dietary habits of women after a spontaneous miscarriage. It was found that the folate content in their daily food rations covered only 35% of the recommended amount for pregnant women. [7]

In 1991, a multicenter, randomized study (Medical Research Council Vitamin Study) was conducted with 1817 women who had previously given birth to a child with an NTD. The study showed that folic acid supplementation 4 weeks before conception and during the first 12 weeks of pregnancy, at a dose of 4 mg, reduced the risk of NTDs by 72%. The authors concluded that the intake of other vitamins (A, D, B1, B2, B6, C, and nicotinamide) did not prevent further neural tube defects in families. The results of this groundbreaking work became the basis for implementing primary prevention programs for neural tube defects with folic acid in many countries, including Poland. Subsequent epidemiological studies have also shown that periconceptional folic acid supplementation reduces the incidence of NTDs in newborns. In American researchers' work, it was proven that supplementing the diet with 0.4 mg or higher folic acid, at least 3 times a week, 3 months before conception and during the first 12 weeks of pregnancy, reduced the risk of a recurrence of neural tube defects in the next child [adjusted odds ratio (AOR) = 0.42; 95% confidence interval (CI) = 0.19-0.94]. Using lower doses of folic acid during the periconceptional period or consuming foods rich in folates also statistically significantly reduced the incidence of this defect in the studied group of women [19].

Inadequate folate nutrition during pregnancy increases the frequency of miscarriages and pregnancy complications, as well as reduces the newborn’s birth weight. A serious consequence of insufficient folate intake during pregnancy is neural tube defects in the fetus. The crucial moment for the formation of the neural tube, from which the brain and spinal cord later develop, occurs during the first two months of fetal life. [7]

B. Valproic acid as an environmental factor influencing neural tube development during the prenatal period

Valproic acid, which for many years has been a first-line treatment, including for generalized seizures, has proven to be the most teratogenic drug among the classic antiepileptic drugs (AEDs).[20,21] This drug is known for its high efficacy in preventing seizures and its wide range of indications. In the case of idiopathic generalized epilepsy or juvenile myoclonic epilepsy, it is often the most effective treatment.[22] VALPROIC ACID - is available in the form of free acid, its sodium salt, and a mixture of free acid and sodium salt in a 1:1 ratio under the name DIWALPROEX. DIWALPROEX is absorbed more slowly and causes fewer adverse effects on the central nervous system and gastrointestinal tract. WALPROMIDE is a prodrug that releases valproic acid, also used in bipolar disorder.[23]

The mechanism of action of these compounds includes inhibition of T-type calcium channels and voltage-gated sodium channels, increased activity of glutamate decarboxylase (an enzyme involved in GABA synthesis), as well as inhibition of enzymes that break down GABA. [23] Despite the high risk of malformations in the fetus, valproate is used in women of childbearing age. The risk of MCM (major congenital malformations) in the fetus is 6.2-17.4%. [24,25] The use of valproate in the first trimester of pregnancy has been associated with the occurrence of characteristic congenital defects, including spina bifida and neural tube defects. [26]

The mechanisms by which valproic acid leads to neural tube closure defects involve several key biological processes: [14]

Inhibition of histone deacetylases (HDACs):
VPA acts as an inhibitor of histone deacetylases, enzymes responsible for removing acetyl groups from histones. Acetylation of histones leads to chromatin relaxation, allowing gene transcription. Inhibition of HDAC by VPA results in histone hyperacetylation, which may lead to abnormal expression of genes critical for nervous system development. These changes can disrupt the differentiation and proliferation of neuroectodermal cells, negatively affecting neural tube closure.

Induction of oxidative stress:
Exposure to VPA may increase the production of reactive oxygen species (ROS) in cells. Excessive ROS leads to oxidative stress, which can damage proteins, lipids, and DNA. In the context of embryonic development, oxidative stress can induce apoptosis in neuroectodermal cells, disrupting neural tube closure and contributing to developmental defects.

Disruption of folic acid metabolism:
One of the proposed theories is folic acid deficiency, essential for proper neural tube development. This deficiency may result from the antagonistic action of valproic acid against folic acid. [26] VPA can interfere with folic acid metabolism, which is crucial for nucleotide synthesis and DNA methylation. A deficiency of active forms of folic acid leads to disturbances in DNA synthesis and methylation processes, which can result in abnormal development of embryonic cells and neural tube defects.

Disruption of signaling pathways:
VPA affects key signaling pathways such as Wnt and BMP, which play a significant role in neurulation. Disruption of these pathways can lead to improper migration and differentiation of nerve cells, ultimately resulting in neural tube defects. [27]

C. Vitamin B12 as an essential nutrient responsible for proper neural tube development:

Deficiencies of this vitamin can be an important factor in increasing the risk of neural tube defects (NTDs) in the fetus. It is estimated that the frequency of NTDs in the case of vitamin B12 deficiency may increase by up to five times. [28]

Water-soluble vitamin B12 is necessary for DNA and RNA synthesis, myelin and acetylcholine production, as well as erythrocyte maturation. Moreover, the optimal intake of this vitamin ensures proper homocysteine levels. Vitamin B12, like folic acid, donates methyl groups. [29]

The term vitamin B12 refers to a group of compounds called cobalamins, which contain a cobalt ion in their structure. The cobalt ion can be bound to a methyl, 5'-deoxyadenosyl, hydroxyl, or cyanide group. Hydroxocobalamin and cyanocobalamin are converted in the body into methylcobalamin and 5'-deoxyadenosylcobalamin, which actively participate in endogenous metabolism. In food, primarily hydroxy-, methyl-, and 5'-deoxyadenosylcobalamin are present, and their sources include animal products such as meat, fish, milk, and eggs. Methylcobalamin is a cofactor for methionine synthase, involved in the conversion of homocysteine to methionine. In the case of methylcobalamin deficiency, a functional folate deficiency occurs. After oral administration, methylcobalamin levels rise in the serum within 15 minutes and remain elevated for the next 24 hours. Notably, methylcobalamin is the active form of vitamin B12. [30,31]

During pregnancy, vitamin B12, along with folic acid and vitamin B6, participates in DNA synthesis and its methylation during fetal development. This substance ensures proper folate cycle functioning, which is crucial for the rapid cell division of the fetus and placenta. The fetus utilizes vitamin B12 for numerous biochemical reactions, but it cannot synthesize it. During pregnancy, a decrease in serum vitamin B12 levels is observed due to hemodilution, hormonal changes, fluctuations in binding protein levels, and, to a large extent, increased transport to the fetus. [29]

Vitamin B12, as a cofactor for methionine synthesis, affects the incorporation of folates into the cellular pool and the proper transfer of one-carbon groups for DNA synthesis or methylation processes. DNA synthesis is a critical process during embryonic development. However, other triggering factors that induce developmental changes, such as gene expression differentiation, are partially controlled by methylation reactions. Disruptions at the level of these processes may underlie the development of NTDs related to vitamin B12 deficiency. [28]

D. Metabolism and role of choline:

In recent years, there has been increasing attention on the need to increase choline intake in the diet of pregnant women. This is due to several important factors. Primarily, choline is an essential nutrient for proper fetal development, as well as for the functioning of the placenta and the mother's liver. Significant amounts of choline are transferred to the baby through the placenta during pregnancy, and after birth, it is provided through breast milk.

Although the pregnant woman's body can synthesize choline through increased gene expression under the influence of rising estrogen levels, its primary source remains the diet. Unfortunately, studies show that even in highly developed countries, the choline intake of pregnant women is often insufficient. Therefore, the demand for this nutrient seems higher than the current nutritional standards indicate. [32,33]

During pregnancy, the need for choline significantly increases. It is actively transported across the placenta (with 14 times higher concentration in fetal tissues compared to maternal blood). At the same time, choline production by the PEMT gene is an important pathway for incorporating DHA (docosahexaenoic acid) into phosphatidylcholine, which may increase the supply of this nutrient to the developing brain tissues of the child. [29]

Shaw et al. demonstrated a relationship between low serum choline levels in the mother's blood and an increased risk of neural tube defects in the fetus, regardless of adequate folate levels. [34]

Choline plays a key role in the proper development of the fetus, influencing many biological processes. Choline phospholipids, such as phosphatidylcholine and sphingomyelin, are essential for the biogenesis of cell membranes, myelination of nerve fibers, cell division, tissue growth, and lipid transport. Furthermore, choline is a precursor to acetylcholine – a neurotransmitter crucial for brain development, neurogenesis, and synapse formation. It is worth noting that acetylcholine is largely synthesized and stored in the placenta, where it serves as a signaling molecule, influencing the differentiation and proliferation of cells. [33,35,36]

Choline metabolism is closely related to the B-vitamin and methionine cycles. These pathways intersect at the point of homocysteine methylation and methionine synthesis. After oxidation to betaine, choline can be a methyl group donor for this reaction. Alternatively, the donor of methyl groups necessary for methionine synthesis can be 5-methyltetrahydrofolate in a pathway dependent on the presence of vitamin B12. Therefore, dietary requirements for choline, folates, and methionine are interrelated. Moreover, the risk of choline deficiency increases in cases of insufficient folate or methionine intake. [32,37]

	PRECONCEPTION PERIOD	PREGNANCY	LACTATION
OBJECTIVE	Saturation of the body to reduce the risk of neural tube defects and other disorders	Normal cell division, methylation, lowering homocysteine in mother and fetus	Normal methylation, lowering homocysteine in mother
FOLATES	**400 ug 5-MTHFR + 400 ug folic acid**	**800 ug 5-MTHF**	**800 ug 5-MTHF**
EPIGENETICS	**Choline + metylocobalamin (B12) + pirydoxal phosphate (B6)**		

Figure 3. Own table inspired by the article Experts' Position of the Polish Society of Gynecologists and Obstetricians on folate supplementation and conditions of use of additional choline supplementation and vitamins B6 and B12 in the preconception period, pregnancy and postpartum period

Conclusion

Proper development of the neural tube during the prenatal period is crucial for the formation of the nervous system, and the process of neurulation plays a fundamental role in the formation of the brain and spinal cord. Improper closure of the neuropores can lead to severe defects such as anencephaly or spina bifida. Early prenatal diagnosis, including ultrasonography, is essential in detecting defects and planning interventions.
Folic acid supplementation, essential in metabolism, nucleotide synthesis, and DNA methylation, reduces the risk of neural tube defects. Despite recommendations for its use, cases of defects still occur, suggesting a need for further research into their mechanisms and prevention. Folate deficiency, especially in women of reproductive age, can lead to congenital defects. Proper supplementation, as well as monitoring drug therapy, including alternative treatment methods, are essential. Vitamin B12, supporting methylation processes, is also crucial in preventing neural tube defects and should be included in prevention efforts. Ensuring adequate intake of folate and vitamin B12, along with health education, is key in preventing these defects and improving the health of future generations. Additionally, an important factor disrupting folate metabolism is certain medications,

such as valproic acid, which can lead to improper closure of the neural tube through epigenetic mechanisms and oxidative stress. Therefore, it is important to monitor drug therapy in women of reproductive age and consider alternative treatment methods when using teratogenic substances.

List of Figures

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