EUROPEAN JOURNAL OF BIOMEDICAL AND PHARMACEUTICAL SCIENCES
http://www.ejbps.com

ISSN 2349-8870
Volume: 7
Issue: 2
66-76
Year: 2020

A REVIEW ON THE ROLE OF VITAMINS IN CONGENITAL VENTRAL ABDOMINAL WALL DEFECTS; OMPHALOCELE AND GASTROSCHISIS

Mala Thakur[1]*, Ryanjit Singh Virk[2], Pritpal Singh Sangha[3], Alessia Genova[1], Komal Virk[4], Snehal Goud[5], Vaugn De Vera[5] and Pooja Shah[1]

[1]Xavier University School of Medicine, Woodbury, New York.
[2]University of California, Merced, California.
[3]Medical University of Lublin, Poland.
[4]San Francisco State University, San Francisco, California.
[5]Saint James School of Medicine, The Valley, Anguilla.

***Corresponding Author: Mala Thakur**
Xavier University School of Medicine, Woodbury, New York.

Article Received on 12/12/2019 **Article Revised on 01/01/2020** **Article Accepted on 22/01/2020**

ABSTRACT
Omphalocele and Gastroschisis are two of the rarest ventral abdominal wall defects which occur due to congenital malformations in utero. These defects fail to fuse the abdominal wall properly, which expose the abdominal organs such as the intestines, stomach, and liver outside the abdominal cavity. Omphalocele is the protrusion of the abdominal contents covered with peritoneum sac through the base of the umbilical cord.[1] It consists of Wharton's jelly in between both the amnion and peritoneum membrane. Meanwhile, Gastroschisis usually occurs to the right of the belly button and is the protrusion of the abdominal contents without the peritoneum sac covering.[1] Both of these birth defects can be detected prenatally by fetal ultrasonography as well as treated. Despite the technological advances in medicine, the explanation behind exactly why or how these defects occur are unclear. To examine the roles of different vitamins and their possible roles in the prevalence as well as manifestation of ventral abdominal wall defects, related studies were reviewed to find a possible explanation behind these malformations.

KEYWORDS: Omphalocele, Gastroschisis, Vitamins, Congenital, Abdominal Wall Defect.

I. BACKGROUND

Gastroschisis and omphalocele are congenital ventral abdominal wall defects which were first described as one entity in the 16th century. After several years of research Moore and Stokes in 1953 described it as two separate abdominal wall defects. Later in 1963 Duhamel described and emphasized their specific pathogenesis and clinical presentation. In recent years it has been identified that omphalocele is more common than gastroschisis. Omphaloceles have been shown to have an association with chromosome abnormality and other birth defects whereas, gastroschisis tends to be an isolated anomaly. Prognosis for infants with gastroschisis tends to be better than omphalocele. The survival rate for omphalocele is 50% to 60% with association to other chronic medical problems.[2] An omphalocele is a midline ventral abdominal wall defect with herniation of abdominal viscera into a membrane-covered sac consisting of an inner peritoneal layer and an outer layer of amnion, while omphalocele involves protruding of the organs out of the abdomen such as liver, intestines, spleen and in the ovaries. During the first early trimester, omphalocele is caused by failure of the physiological herniation to return back to the abdominal cavity. This occurs between 6 to 10 weeks.[3] Due to potential membrane rupture, diagnosis can be difficult to make. Depending upon the position of the defect, it has been categorized into epigastric, central and infraumbiical omphalocele, in which central is the most common form. Many different analysis and studies have shown a strong relation between central type of defect and abnormal karyotype of trisomy 18.[4] The distinctive point is the cord insertion site which is located in the umbilical sac in omphalocele. The estimated prevalence is from 1.0 to 3.8 per 10,000 live births. As compared to gastroschisis, the mothers age did not produce a significant risk factor for omphalocele. Of the other risk factors included were multiparity, pre-pregnancy overweight or obese. There was a marked association seen between infants born with lower birth weight and small for gestational age.[3] Gastroschisis is a ventral abdominal wall defect which causes an opening to the right of the umbilicus. The opening leads to the protrusion of abdominal organs such as intestines, liver and the other proximal organs outside of the body. The location of cord insertion site is paraumbilical in gastroschisis whereas the cord insertion site is present in the umbilical sac in omphalocele. Differentiating point from omphalocele is that there is an

absence of amniotic membrane in gastroschisis. Gastroschisis can identified using different diagnostic methods and blood test such as prenatal ultrasonography and maternal serum alpha fetoprotein level. Usually the alpha fetoprotein levels are elevated in Gastroschisis.[5] The prevalence of gastroschisis is increasing with reason being unknown. Certain risk factors have been associated with prevalence of gastroschisis such as mothers younger than 24 years of age, maternal race/ethnicity, while other risk factor include BMI less than 18 or underweight for mothers who gave birth to child with gastroschisis. There has been a strong correlation between the use and deficiencies of vitamins alongside the development of these ventral congenital defects.[6] The prevalence of gastroschisis on an average in united states ranges from 2.6 to 5.1 per 10, 000 live births. Research has shown there is an increasing birth prevalence with gastroschisis in both resource limited as well as resource rich environments.[2]

II. METHODS

The data presented here were gathered via Research Gate, PubMed, and Google Scholar to identify peer reviewed articles regarding vitamins and their impacts on congenital ventral abdomen defects.

III. EMBRYOLOGY OF OMPHALOCELE AND GASTROSCHISIS

During the 6th week of embryogenesis, the midgut herniates through the primitive umbilical ring on the ventral surface of the developing embryo. The herniation consists of three significate structures: the yolk sac (vitelline duct), connecting stalk, and allantois. All three structures are combined to form the primitive umbilical cord as the amnion, the innermost lining of the placenta that protects the amniotic cavity, expands. Meanwhile, allantois, which is an unfunctional structure, degenerates and forms the median umbilical ligament as the embryo becomes an adult. The umbilical cord consists of two umbilical arteries and one umbilical vein. The umbilical arteries carry deoxygenated blood from the fetus to the placenta while the umbilical vein carries oxygenated blood to the fetus from the placenta. Omphalocele occurs when the abdominal contents protrude through the umbilical ring covered by a translucent membrane sac. The physical inspection of the umbilicus in an omphalocele newborn infant would show a shiny, translucent peritoneum sac herniating through the base of the umbilical cord. Omphalocele is classified into large and small categories. The large omphalocele defect would consist of the stomach, intestines, and liver as to the small omphalocele, which would consist of only the intestines. Gastroschisis occurs when the abdominal intestines are exposed without any covering and are usually located to the right of the umbilical ring. This massive evisceration of the intestines is exposed to the amniotic fluid that causes the intestines to thicken and have adhesions due to the absence of peritoneal sac which protects it.

IV. DISCUSSION: MECHANISM OF ACTIONS IN THE ROLE OF VITAMINS

Vitamin A (Retinol)

Vitamin A, retinol, is a fat soluble vitamin and antioxidant which is essential for normal differential of epithelial cells into specialized tissues such as pancreatic cells and mucus-secreting cells. Retinoids like retinal and retinoic acid are present in animals and are available as retinyl esters. Liver, kidney, cream, butter, and egg yolk are all sources of retinoids. Beta carotene are present in plants as Carotenoids, specifically in yellow and dark green vegetables as well as in many fruits. Beta carotene are made up of two retinals and is considered a provitamin. In order for vitamin A to be absorbed by the human body, bile salts are required. Vitamin A is mainly stored in hepatic stellate cells (Ito cells) that play an important role in the body's homeostasis. These cells cause the formation of scar tissue when liver damage occurs.[7] Vitamin A deficiency can commonly cause blindness in developing countries. In the retina of the eye, rhodopsin is found which is made of retinal (active form of vitamin A) and opsin. When vitamin A levels are low, they cause a decrease in rhodopsin leading to night blindness.[8] Other manifestations of vitamin A deficiency are xerosis cutis, keratomalacia, xeropthalmia, and Bitot spots on conjunctiva.[9] Due to vitamin A being fat soluble, it is not as readily excreted compared to water soluble vitamins. Due to having this property, an excess of vitamin A is known to cause many toxic effects. Acute toxicity occurs within hours to days and most commonly presents with nausea, vomiting, vertigo, and blurred vision. Chronic toxicity can occur with persistent intake of vitamin A over years, and can present with alopecia, hepatic enlargement, and dry skin. The most critical toxic effect of excess vitamin A is pseudotumor cerebri, causing increased intracranial pressure, which can be fatal.[10] vitamin A deficient pregnant women have shown to have some correlation with congenital abdominal wall defects. The acne medication, Accutane (isotretinoin) is considered a teratogen, known to cause cleft palate and hydrocephalus.[11] For this reason, a negative pregnancy test is required before isotretinoin is prescribed. PAGOD (Pulmonary Artery, Gonadism, Omphalocele, Diaphragmatic anomalies) syndrome and vitamin A deficiency might be caused by similar gene mutations. Gavrilova studied retinol binding protein 4 (RBP4) in pregnant women, which is found in visceral endoderm prior to gastrulation. This is stimulated by retinoic acid 6 (STRA6), which can be found in the placenta during pregnancy. A mutation in STRA6 causes Matthew-Wood syndrome, which shows similarities in expression to PAGOD syndrome. However, in the test subject, no mutations were seen, suggesting that a vitamin A deficiency alone plays a role in PAGOD syndrome.[12]

Vitamin B1 (Thiamine)

Thiamine, also known as vitamin B1, is a nutrient naturally found in most foods and is vital for energy metabolism. Thiamine is an essential vitamin for the

human body due to it being a key component for the growth and development of cells as it serves as a cofactor for several enzymes involved in carbohydrate metabolism. The body does not produce endogenous thiamine therefore it must be ingested; it is typically found in whole-grains, meat and fish but can also be taken as a dietary supplement. When ingested, thiamine is absorbed by the duodenum and jejunum where it is converted to its active form of thiamine pyrophosphate through an active process.

After thiamine has been ingested, either through dietary consumption, or pharmacologically through a supplement, it is absorbed into the body through the small bowel by active and passive transport respectfully.[13] Active transport occurs through the nutritional doses and passive diffusion occurs through pharmacologically doses.[14] This is determined by the concentration of thiamine in the blood where it is then stored in the liver for 18 days. The two main pathological complications as a result of a deficient intake of thiamine are Beriberi or Wernicke-Korsakoff syndrome.[15] There are two different types of Beriberi, the two different types are wet Beriberi or dry Beriberi, with wet Beriberi affecting the cardiovascular system and dry Beriberi affecting the nervous system. Wet Beriberi, which is a more acute form, results in increased heart rate, edema, poor circulation, shortness of breath, and swelling of the lower legs which could ultimately lead to heart failure. However, with wet Beriberi, patients respond to treatment, which is the administration of thiamine, quickly. Dry Beriberi is characterized by the gradual degeneration of long nerves which results in a difficulty in walking, loss of feeling in the hands and/or feet, paralysis of the lower legs, loss of reflexes, speech difficulty and mental confusion. In response to treatment, patients with dry Beriberi respond more gradually to the administration of thiamine while in severe cases damage to nerve cells may be irreversible. In Wernicke-Korsakoff syndrome, the former is a result of thiamine pyrophosphate intake, which is the metabolically active form of vitamin B1. Beriberi causes peripheral neuropathy and cardiovascular impairment.[16] Wernicke-Korsakoff syndrome is actually a pair of two different conditions. Due to the lack of thiamine in the body, a person may develop Wernicke encephalopathy, causing damage to the thalamus and hypothalamus in the brain. As a result of this brain damage, the affected person will begin to suffer from Korsakoff psychosis.[17] There is no proven toxicity resulting from a high level of thiamine intake.[13] In relation to congenital abdominal abnormalities, a deficiency in thiamine could very well be a contribution due to its role in cell growth and development. Impaired cell growth may result in an inability to properly close the abdominal wall in the body of a fetus.

Vitamin B2 (Riboflavin)

Riboflavin (Vitamin B2) is a component of flavins: flavin adenine dinucleotide (FAD) and flavin mononucleotide (FMN). They are used as cofactors in various oxidation and reduction reactions; most importantly the succinate dehydrogenase reaction in the Citric Acid or TCA cycle and complex I and II in the electron transport chain (ETC) reactions which are required for cellular metabolism and release and utilization of stored energy by all aerobic organisms. Riboflavin plays a great role within the electron transport chain. Within the inner membrane of the mitochondria are complexes I–IV that consist of several different electron carriers. Complexes I and II contain flavoprotein reductases (dehydrogenases) and electron transferring flavoproteins.[18]

Food sources of riboflavin include plant and animal sources: organ meats, poultry, fish, and eggs. Dairy products, such as milk and cheese have the highest source of riboflavin. Plant sources, such as cereals, grain products, and breads provide nearly the entire dietary riboflavin intake of some developing countries. Green vegetables, such as broccoli, collard greens, and turnips, are also good sources of riboflavin.[18]

Riboflavin deficiency, also known as ariboflavinosis, can cause many different clinical signs and symptoms. Patients can develop a sore throat, cheilosis, angular stomatitis, glossitis with loss of filiform papillae and hypertrophy of fungiform papillae, seborrheic dermatitis of the face and ears, scrotal dermatitis, and dermatitis of the trunk and extremities.[19] Riboflavin over consumption orally from the diet or from multivitamin supplements rarely causes side effects or exhibits toxicity. Riboflavin that is not converted to FMN or FAD can exist as free riboflavin and be excreted by the kidney giving the yellow color of urine or gets secreted into extracellular fluids via the ABCG2 transporter.[18]

During the end of the middle trimester of pregnancy of inbred mice, many malformations are observed in the offspring. Among these malformations were skeletal, esophageal, and cranial malformations.[20] In Warkany's experiment with rats, malformations of soft tissues hardly occurred. But with addition of galactoflavin administration (riboflavin antagonism), malformations of the viscera were seen.[21]

Vitamin B3 (Niacin)

Vitamin B3, also known as niacin, is a water-soluble micronutrient that is converted by the body into the electron carrier nicotinamide adenine dinucleotide (NAD). NAD is utilized by hundreds of enzymes throughout the body to catalyze redox reactions. NAD is predominantly involved in the transfer of energy from carbohydrates, fats, and proteins to ATP which is the main form of energy utilized in metabolic processes.[22] As such, NAD is also involved in cellular communication, gene expressions, and genome integrity. Furthermore, increased intake of niacin-rich foods has also been associated with higher levels of apolipoprotein a1 and high-density lipoproteins. The proposed

mechanism for this process incorporates the finding that niacin selectively inhibits high density lipoprotein and apolipoprotein a1. As such, niacin also inhibits the high-density lipoprotein catabolism receptor.[23] Further studies have indicated that niacin amplifies the peroxisome proliferator-activated receptor-gamma in monocytes which activates the adenosine triphosphate transporter. This transporter transfers cellular cholesterol to high density lipoprotein molecules containing apolipoprotein a1. This is another mechanism by which niacin has been suggested to operate on high density lipoproteins. Given this, it is reasonable to assume that severe deficiencies in such a principal molecule will have drastic consequences. Researchers have shown that niacin deficiency can predispose cells to carcinogenesis. Specifically, following the ingestion of niacin and its subsequent transformation to the active NAD form, ADP-ribose polymers are generated as needed in response to incurred DNA damage. Therefore, the cells of individuals with suboptimal niacin concentrations are highly sensitive to carcinogen exposure due to their inability to produce ADP-ribose polymers.[24] The dietary sources of niacin, and by extension NAD, include fish, nuts, beef, legumes, and poultry.[22] As it relates to the congenital condition of gastroschisis, researchers have shown that a diet lacking niacin correlates to higher incidences of abdominal wall defects such as gastroschisis. In one such study, pregnant rats were provided with a vitamin B3 deficient diet with the niacinamide antimetabolite. During this study, researchers observed a high incidence of embryonic mortality as well as congenital defects such as gastroschisis.[25] Studies such as this make the importance of proper vitamin intake, particularly when pregnant, abundantly clear.

Vitamin B5 (Pantothenate)

Vitamins B5, also known as pantothenic acid, plays a crucial role in energy production.[26] The vitamin necessitates the break-down of fats and carbohydrate and therefore produces energy for the body. Vitamin B5 ensures healthy hair, skin, eyes, and liver. In living cells, this vitamin exists as a coenzyme A (CoA), which ensures that various chemical reactions take place in the body.[26] Coenzyme A synthesis takes place in the presence of vitamin B5.[26] The coenzyme is essential due to its actions in fatty acids synthesis. Furthermore, the conversion of food into fatty acids and cholesterol is initiated by coenzyme A. Finally, another role of this coenzyme is that it is needed by the liver when it comes to the metabolism of drugs.[26] It is through coenzyme A that the liver manages to metabolize some medications and toxins safely. Moreover, vitamin B5 helps in the maintenance of a healthy digestive system.[27] To achieve this, vitamin B5 ensures efficient uptake and use of the other types of vitamins by the body. For instance, vitamin B5 aids the body in the absorption and utilization of vitamin B2. The impact of this type of vitamin in the body is that it helps in the management of stress. Apparently, there is no evidence of vitamin B5 taking part in the management of stress, therefore it is the role of vitamin B2, which is absorbed in the body under vitamin B5 as the catalyst. Vitamin B5 serves as the skin moisturizer and therefore helps in the healing process of the skin.[27] Vitamin B5 has the ability of healing acne and has the capability of reducing the cases of acne on the human face when it is taken as a dietary supplement. Furthermore, vitamin B5 is essential in balancing cholesterol levels in the body.[27] The vitamins play an essential role in balancing blood cholesterol level, blood triglycerides, and fats. Absorbed vitamin B5 has to be first released from coenzyme A and acyl carrier protein (ACP). The process requires the action of peptidases and nucleosidases. The human intestine is exposed to two sources of vitamin B5 which are dietary and bacterial. Dietary vitamin B5 exists in the form of coenzyme A which is hydrolyzed to free vitamin B5 in the lumen of the intestine before its uptake. Free vitamin B5 is then taken to the absorptive cells through the sodium-dependent multivitamin transporter (SMVT), which is also responsible for the transportation of biotin and lipoate. Vitamin B5 is soluble in water (log P = − 1.69) and it is formed by pantothenate synthase, which catalyzes an ATP- dependent condensation reaction between β-alanine and pantoic acid. Vitamin B5 is known to be neutrally charged under low pH of between 2 to 3. Due to its instability, chemical decomposition takes place rapidly when it is in acidic and basic states and its degradation rate is always increased by heat. Many enzymes, around 70 of them needs CoA or ACP for their metabolic reaction to take place. For this reason, vitamin B5 is found necessary in the metabolism of carbohydrate, fats, and proteins and the citric acid cycle functioning. For the absorption of this vitamin to be effective, it has to be changed into free pantothenic acid.[29] CoA and ACP are then hydrolyzed into 4'-phosphopantetheine within the intestine lumen. Dephosphorylation of 4'-phosphopantetheine then takes place where it converted into pantetheine. The pantetheine is then hydrolyzed by pantetheinase to free pantothenic acid.[29] Lack of this vitamin is not common due to its availability in most of the foods.[30] It is therefore provided easily by any healthy diet. However, the groups of people under the risk of this vitamin include alcoholics, women undertaking oral contraceptives, the elderly, and people with various digestive disorders, which eventually affect the absorption of vitamin B5.

The deficiency of the acid was induced experimentally through co-administration of a pantothenic acid antagonist (omega-methylpantothenic acid). Participants present in this experiment complained of headaches, insomnia, intestinal disturbances, and tingling and numbness of their feet and hands.[30] These symptoms were, therefore, linked to perturbations in CoA and lipid metabolism. Vitamin B5 is considered water-soluble, and for this reason, it is not easy to have an excess of it in the body. The extra vitamin B5 is filtered by the organization and removed through the urinary tract.

Despite this fact, in case of high levels of this vitamin, some of the symptoms might be diarrhea and gastrointestinal distress.[30]

Pantothenic acid contained in B5 is beneficial to the body especially the muscles and hence it is boosts physical activity. Research findings of a study conducted by Rébeillé, et al. elaborates that the pantothenic acid makes wounds heal more quickly; therefore, healing to any damage done to the abdominal wall is facilitated by the B5 vitamin.[28] Individuals require more intake of B5 during stressful periods, and strenuous activities such as physical work and extreme athletics. However, congenitally, a deficiency of pantothenate may be a reason for abdominal wall defects because it is a precursor for synthesizing Coenzyme A. If Coenzyme A becomes deficient, then many other developmental delays may take place, possibly including congenital malformation of the fetal abdominal wall.

Vitamin B6 (Pyridoxine)

Pyridoxine (Vitamin B6) is an essential nutrient. In its active form of pyridoxal 5'-phosphate, it is a coenzyme in over 100 reactions involving amino acid, glucose, and lipid metabolism. It also is required for the synthesis of cystathionine, niacin, histamine, and several neurotransmitters (serotonin, epinephrine, norepinephrine, dopamine and GABA). Pyridoxine also plays a significant role in hemoglobin synthesis and function.

Pyridoxine can be found in many different foods in its free and bound forms. Some foods that contain pyridoxine in large amounts are breakfast cereals, meats such as pork, beef, and turkey, and fruits and vegetables; specifically, bananas, chickpeas, and potatoes.[31]

A diet deficient in pyridoxine can cause many different signs and symptoms. The most common are hyperirritability, convulsions, peripheral neuropathy (inducible by isoniazid), and sideroblastic anemia.

Patients taking isoniazid are co-administered vitamin B6 to prevent peripheral neuropathy. This is caused by 2 mechanisms: the first is that isoniazid directly inactivates pyridoxine species. The second, it inhibits pyridoxine phosphokinase, preventing the conversion to the active form of pyridoxal 5' phosphate which is necessary and acts as a coenzyme in many reactions.

In acute isoniazid toxicity, convulsions/seizures are very common. This is due to the fact that pyridoxine is necessary for the production of gamma-aminobutyric acid (GABA) which is an inhibitory neurotransmitter. Without this inhibition, brain activity will demonstrate over excitability resulting in convulsions/seizures.[31] Sideroblastic anemia is another common side effect of pyridoxine deficiency. This causes the disruption of heme synthesis within the mitochondria of erythroblasts, where the rate-limiting step involving the enzyme Amino levulinate synthase requires Vitamin B6 as a cofactor to convert glycine + succinyl-CoA into Aminolaevulinic acid.[32] Without the cofactor, ringed sideroblasts are seen in bone marrow and basophilic stippling of red blood cells (RBCs) are seen under microscopy of peripheral blood smears.

Pyridoxine deficiency has exhibited many defects that can occur congenitally. When pyridoxine deficient diets and co-administration of 4-deoxypyridoxine (Vitamin B6 antagonist) were given to pregnant rats, the results showed that fetuses were much smaller in size and were anemic. Major malformations such as omphalocele, cleft palate, micrognathia, and splenic hypoplasia were seen in these fetuses as well.[33]

Vitamin B7 (Biotin)

Biotin (Vitamin B7) is a water-soluble vitamin which is involved in many metabolic processes. Biotin acts as a cofactor which is responsible for the transfer of carbon dioxide in reactions important in fatty acid synthesis, branched-chain amino acid catabolism, and gluconeogenesis.[34] All enzymatic activity involving carboxylases require biotin as a cofactor. Fatty acid synthesis occurs via the rate-limiting enzyme Acetyl-CoA carboxylase (ACC) where Acetyl-CoA is converted to malonyl-CoA in the cell cytoplasm. Biotin is also a cofactor for propionyl-CoA carboxylase which converts branched chain amino acids (valine, isoleucine, methionine, and threonine) into methylmalonyl-CoA which enters the TCA cycle via succinyl-CoA. Lastly, biotin acts as a cofactor with pyruvate carboxylase which can convert pyruvate to oxaloacetate in the mitochondria in order to replenish the TCA cycle or can further be used in gluconeogenesis.[35] Biotin is extensively produced by intestinal bacteria for the most part. Biotin in food is known to be in a protein-bound form, also known as biocytin. Biotinidase is an enzyme that cleaves biocytin and makes biotin which can be used by carboxylase enzymes.[36] Biotin is not destroyed by cooking foods that contain it. Some food sources that are rich in biotin are cooked chicken liver, beef/pork liver, salmon, and eggs.[37] Biotin deficiency is relatively rare, however, avidin, which is present in raw egg whites, binds to biotin causing it to denature and become inactivated. In humans, the most common observed symptoms of B7 deficiency is dermatitis, glossitis, and alopecia.[38] Maternal biotin deficiency has been proven to cause multiple congenital malformations in mice. In Watanabe's study, adding avidin to pregnant mice's' diets reveals fetuses that exhibit micrognathia, cleft palate, and micromelia.[39]

Vitamin B9 (Folic Acid)

Vitamin B9 is also known as folic acid.[28] This type of vitamin is not naturally found in food; instead, it is added to supplements and other processed food like bread. Folic acid is known to have an impact in tube defect prevention.[28] Low levels of vitamin B9 during the early pregnancy weeks has been seen as the cause of tube

defects in infants. Some of these defects include brain malfunctioning and spinal cord defects. The finding was arrived at since children born of women supplemented with folic acid in the early weeks of their pregnancy were born with lower rates of these defects.[28] Folate has been found to play a role in cancer prevention.[28] Lung, pancreas, gut, and breast cancers can be prevented from high folate intake. Vitamin B9 has been found to take part in cancer prevention as it plays a role in gene expression. In terms of gene expression, vitamin B9 is said to be in control when the genes are turned off or on. Low levels of vitamin B9 is seen to hamper this process and for this reason, the chances of a person contracting these types of cancer will be high.[28] Unstable and the type of DNA which can be easily broken is another cause of cancer; the reason for such type of DNA is insufficient folate in the body. Folate helps in Homocysteine reduction.[29] Homocysteine is an inflammatory molecule which leads to the formation of heart diseases. Vitamin B9 is required in the break-down of homocysteine into methionine. Folate is required in large quantities so as to speed up this process which will ensure that the levels of homocysteine are significantly reduced in the body. Herrmann, & Obeid (2011) shows that daily uptake of folic acid supplements reduces the levels of homocysteine in the body by 25%.[29] Folic acid is first reduced into the cofactors dihydrofolate (DHF) by enzyme dihydrofolate reductase (DHFR).[29] The vitamin is synthesized by the action of bacteria from the substrate para-amino-benzoic acid (PABA). After being manufactured, it is transported to cells of a mammal. Sulfonamides compete with PABA as enzyme dihydrofolate synthase substrate. Both sulfonamides, trimethoprim, ormetoprim, and pyrimethamine are bacteriostatic; therefore, they inhibit the actions of dihydrofolate reductase for the synthesis of purine and pyrimidine nucleotide.[29] At a different point within the metabolic process, they are also seen to inhibit the synthesis of folic acid. Still, the action in which the synthesis of vitamin B9 is inhibited is different from the sulfonamides. Dihydropteroate synthase is not found within the cell of a mammal.[29] Within the mammalian cell, pyrimethamine and trimethoprim are always active against the parasite's dihydrofolate reductase as compared to the mammalian enzyme. Post absorptive reduction of folic acid into tetrahydrofolate (THF) takes place for activation of its metabolism. Through this reaction, folic acid is incorporated into body folate pools. The reaction is a two-step, the first of the process is the folic acid conversion into dihydrofolate, and it is usually gradual. As DHFR activity is always low in humans, the utilization of folic acid from supplements and other types of fortified foods is considered unfavorable.[29] After the reaction, folic acid functions in the body in the form of tetrahydrofolic acid.[29] The acid functions within the body as the methyl-transfer agent, which transports single carbon units in various metabolic reactions. It is through this action that folic acid is enabled to serve as catalyzed in the synthesis of thymidine, a deoxyribonucleic acid agent.[29] It is through this action that the role of this vitamin can be traced within the various body reactions. Vitamin B9 is necessary for the production of new red blood cells.[30] The lack of this vitamin, therefore, leads to folic acid deficiency anemia as the red blood cells are required to transport oxygen to the other body organs. Insufficiency in red blood cells leads to anemia, which is a condition that makes the body weak and tired. For pregnant women, folic acid anemia can cause defects like spina bifida to the unborn child. It is recommended that people who have a deficiency of vitamin B9 should take supplements to increase the level of this acid in the body and thereby eliminate the risk of becoming anemic. Sufficient folic acid in the body has also been seen to reduce the risk of colon cancer and other heart diseases. When taken in large amounts, folic acid can correct the megaloblastic anemia.[30] It has also been noted that high amounts of vitamin B9 can "mask" the deficiency of vitamin B12 until the neurological impacts associated with it becomes irreversible.[30] High amounts of this acid in the body have also been linked to the accelerated progression of preneoplastic lesions bringing about colorectal and other types of cancers in the body of people.[30] Excessive folic acid exceeding the ability of the body to convert them into THF causes unmetabolized folic acid.[30] Such type of folic acid has been linked to the reduction of the number of killer cells and also their functioning. Therefore, this has adverse effects on the immune system. Moreover, cognitive impairment among adults is linked to the availability of unmetabolized folic acids in their bodies.

B9 vitamin contains folic acids. The folic acids contained in this vitamin plays a huge role in reducing damage to the abdominal wall. It is recommended that it should be taken in large quantities around conception. There exists a relationship between abdominal wall defects with the folate metabolic enzyme gene methylenetetrahydrofolate reductase (MTHFR). A study conducted with births between 1998 and 2005 in New York illustrated the association of single nucleotide polymorphisms (SNPs), which is essential in folate, vitamin B12, and chlorine metabolism.[6] In all studies, variation in transcobalamin receptor gene (*TCblR*), rs2232775 (Q8R), and the *MTHFR* gene, rs1801131 (1298A>C) were all linked to abdominal wall defects.[41]

Vitamin B12 (Cobalamin)

Cobalamin (vitamin B12) is a water-soluble vitamin that is a cofactor in DNA synthesis (specifically purines and thymidine), fatty acid and amino acid metabolism. Its most important role is during the synthesis of myelin.[41] Vitamin B12 is essential for the conversion of methylmalonyl-CoA to Succinyl-CoA during metabolism of odd-chained fatty acids and branched-chain amino acids. It is also needed in the conversion of homocysteine to methionine which requires vitamin B12 and folate (Vitamin B9). In normal physiology, vitamin B12 binds with Intrinsic Factor (IF), which is released

from parietal cells of the stomach, and facilitates the absorption of vitamin B12 at the terminal ileum.[42]

The main source of vitamin B12 in the diet is from animal sources. Meats, fish, and dairy products are rich in vitamin B12. Specifically, cooked clams and beef liver have the highest amount of vitamin B12.[43] Vitamin B12 is not generally present in plant foods, but food manufacturers have fortified breakfast cereals, soy products and energy drinks/bars with vitamin B12 catered to vegetarians.[44]

A very large reserve pool is stored primarily in the liver. The reserve pool can last several years. Deficiencies can be caused by malabsorption, lack of IF, absence of the terminal ileum, or insufficient intake. Macrocytic, megaloblastic anemia can be seen on peripheral blood smears. Paresthesia and subacute combined degeneration (degeneration of dorsal columns, lateral corticospinal tracts, and spinocerebellar tracts) can also result from a deficiency.[42] A prolonged deficiency can cause irreversible nerve damage. Pernicious anemia is common in the elderly who have a history of gastritis or have anti-parietal cell antibodies. In children with vitamin B12 deficiency, developmental delay and hypotonia can also be present.[45] Folate supplementation can mask the hematologic symptoms of vitamin B12, however, the neurologic symptoms will still be present. Since both folate and vitamin B12 are involved in the some of the same metabolic pathways, the congenital abnormalities are similar. Folic acid administration during pregnancy can reduce the chances of the offspring having neural tube defects. In Mills' study, an association between folate-related genes and omphalocele was significant. Having the variant methylenetetrahydrofolate reductase (MTHFR) polymorphism showed an increased risk for having an omphalocele in the fetus. A reduction in the enzymatic activity of MTHFR caused the increased risk, which concludes that giving a multivitamin with folic acid can prevent a congenital abdominal wall defect in-utero.[46]

Vitamin C

Vitamin C, also known as L-ascorbic acid, is an important physiological antioxidant and is involved in the biosynthesis of certain proteins and neurotransmitters.[47] Specifically, vitamin C is key in the formation of collagen through enzymatic transfer of hydroxyl groups proline and lysine residues. This transfer leads to the arrangement of procollagen chains and sugar moieties are added to these monomeric chains via the enzyme glycosyltransferase.[48] Following this, the chains undergo spontaneous self-assembly into helical trimers which are trimmed by proteinases resulting in the generation of the collagen triple helix. Collagen is then secreted by smooth muscle cells into the arteries and is recognized as the main structural protein in connective tissue. As such, a lack of vitamin C leads to insufficient production of stable collagen yielding fragile blood vessels.[48] Historically, vitamin C deficiency, also known as scurvy, was a common ailment afflicting poorly nourished sailors. These sailors were noted to exhibit symptoms such as anemia, poor wound healing, myalgia, and petechiae or bleeding under the skin. In 1753 James Lind discovered that vitamin C rich foods such as potatoes, broccoli, strawberries, kiwi, and cantaloupe were an effective remedy for this particular malady.[48] Conversely, as with any substance, excessive consumption of vitamin C can lead to adverse effects. For example, excess ascorbic acid has an osmotic effect on the intestines causing an increase in peristalsis which may cause the consumer to experience diarrhea and abdominal cramps. Additionally, exorbitant vitamin C ingestion has been linked to the formation of stone in the urinary tract. Researchers have hypothesized that this may be due to the increased conversion of ascorbic acid to oxalate in certain individuals. This rapid conversion results in hyperoxaluria, or excessive urinary excretion of oxalate, increasing the likelihood of stone formation.[49] As explained previously, gastroschisis is a congenital defect in which a newborn's intestines are found outside of the body. Studies have shown that adequate nutrition prior to and following conception is paramount in the reduction gastroschisis. As it pertains to vitamin C, a longitudinal population-based study involving 694 gastroschisis cases and 6157 controls demonstrated that a greater than 25% reduction in risk was present in mothers that had a diet consisting of higher vitamin C ingestion.[50] This is important because it illustrates the significance of proper vitamin C consumption as it relates to congenital gastroschisis.

Vitamin D

Vitamin D is a nutrient found in certain foods and is vital to maintain strong bones. Vitamin D is typically observed in salmon, tuna, egg yolks, and can also be obtained from sunlight. The mechanism of action involved in the body's utilization of vitamin D includes the transcription factor vitamin D receptor.[51] This particular transcription factor contains two zinc fingers that bind to vitamin D response elements after which, coregulatory complexes are recruited to the activation site. The heterodimer VDR/RXR is the primary active transcriptional unit during this process. Physiologically, vitamin D is first metabolized to 25 hydroxyvitamin D and then to 1,25-dihydroxyvitamin D. 1,25-dihydroxyvitamin D is the ligand for the vitamin D receptor and is catabolized by CYP24A1.[51] As it pertains to vitamin D insufficiency, a lack of vitamin D most notably leads to disease states such as osteomalacia and rickets. Additionally, inadequate vitamin D consumption in children has been shown to cause growth retardation and, in the elderly, a marked increase in the risk of falling and sustaining a fracture. Researchers have also identified through cross-sectional observation and laboratory studies that reduced vitamin D concentrations can lead to reduced insulin sensitivity and, as a result, diabetes.[52] As it pertains to gastroschisis, studies have shown that vitamin D intake is imperative for children who have survived this disease due to their risk of poor

childhood growth. That is, children that have been successfully treated for gastroschisis are noted to have poor bone growth. Researchers found that these children had a distinctly lower BMI at age 11 which is indicative of poor adult bone mass density.[53] Thus, the consumption of calcium and vitamin D is exceedingly important for proper development, particularly in children affected by gastroschisis.

Vitamin E (Tocopherol)

Vitamin E is an antioxidant that exists in multiple chemical forms with alpha tocopherol being the most important for humans. As an antioxidant, this particular vitamin is utilized by the body to protect cells against the damaging effects of free radicals that accumulate as byproducts of fat oxidation.[54] Specifically, vitamin E donates a hydrogen atom to the lipid peroxyl radical preventing it from propagating the lipid peroxidation chain reaction. As such, vitamin E becomes oxidized to the alpha tocopheroxyl radical which reacts with a separate peroxyl radical inhibiting the formation of reactive oxygen species.[55] Additionally, vitamin E has been shown to inhibit cyclooxygenase activity. Cyclooxygenases are a group of enzymes that participate in the body's immune response through the promotion of inflammation and fever. Cyclooxygenases are bifunctional enzymes that utilize heme as a cofactor. As such, hydroperoxide activators bind to heme producing a protein radical that oxidizes arachidonic acid. Following this, a peroxyl radical is formed which forms prostaglandin G2.[56] The peroxidase activity found in cyclooxygenase permits the reduction of the hydroperoxy group of prostaglandins G2 resulting in the generation of prostaglandin H2. Prostaglandin H2 is a precursor for prostaglandin which is a well-known inflammatory immunomodulator. During this process, the heme radical is reformed allowing the reaction to continue in a cycle. Vitamin E, as well as other antioxidants, are able to inhibit this process through the elimination of certain important intermediates. Vitamin E in particular prevents cyclooxygenase activation by directly reducing hydroperoxide levels.[56] As it pertains to vitamin E deficiency, studies have demonstrated that inadequate vitamin E consumption is correlated with a decreased red blood cell survival rate. Researchers have hypothesized that a lack of vitamin E may allow for the accumulation of lipid peroxides which bind sulfhydryl groups found in red blood cell membranes; this binding shortens the red blood cell's lifespan and may result in the development of anemia.[57] Despite this, excessive vitamin E consumption has been linked to adverse physiological effects. These effects include the reduction of antibody production which at first glance may indicate a functional paradox due to vitamins E's aforementioned role as an immunomodulator, however, this is not the case because of vitamin E's ability to act as a prooxidant as well as an antioxidant depending on its redox potential, environment, and concentration.[58] The role of vitamin E as it relates to congenital abdominal wall defects has been researched and found to be minor. That is, studies in animals have shown that high vitamin E intake leads to fetal protection from the damaging effects of ethanol as well as maternal diabetes. This protection aids proper fetal cerebral and body development. In studies on humans, increased vitamin E intake was not found to correlate with the occurrence of congenital abdominal wall defects such as gastroschisis and omphalocele.[59]

Vitamin K

Vitamin K functions as a cofactor for vitamin K carboxylase which is required for the synthesis of hemostatic proteins as well as proteins involved in bone metabolism. Vitamin K is typically found in leafy green vegetables such as spinach and broccoli. Gamma-glutamyl carboxylase in conjunction with vitamin K catalyze the carboxylation of glutamic acid to gamma-carboxyglutamic acid which is commonly found in clotting factors.[60] Physiologically, the body stores a minimal amount of vitamin K which would be quickly exhausted if it were not for the vitamin K-epoxide cycle. The vitamin K-epoxide cycle essentially allows the body to reuse and recycle vitamin K eliminating the need to consume and store vast amounts of this fat-soluble micronutrient. The cycle commences with the reduced form of vitamin K, vitamin K hydroquinone, which donates a pair of electrons to gamma-glutamyl carboxylase. Gamma-glutamyl carboxylase selectively carboxylates glutamic acid in vitamin K dependent proteins. The result of this reaction is the generation of the oxidized form of vitamin K, vitamin K epoxide.[61] This form of vitamin K is converted back to vitamin K hydroquinone in two steps through the use of two enzymes. First, vitamin K epoxide is converted to vitamin K via the enzyme vitamin K-epoxide reductase. Following this, vitamin K is transformed to vitamin K hydroquinone through an unknown reductase enzyme that may be dependent on NADH.[62] As it relates to the mechanism by which vitamin K is able to coagulate blood, a coagulation cascade is imperative. A coagulation cascade includes several protein factors such as factor II, VII, IX, and X. Additionally, protein Z promotes factor II's association of phospholipids within cell membranes. Proteins C and S function as anticoagulants and promote balance to this process through feedback mechanisms. This is important due to increased and unrestrained clotting amplifying the risk of arterial clots or deep vein thrombosis.[63] In addition to the role of vitamin K in clotting, vitamin K is also vital in bone growth and maturation. Specifically, vitamin K gamma-carboxylation is necessary in osteocalcin, a protein synthesized by osteoblasts. Osteocalcin synthesis is regulated by vitamin D, however, the calcium-binding capacity exhibited by the protein is dependent on vitamin K gamma-carboxylation of three glutamic acid residues.[64] Predictably, a deficiency in vitamin K leads to ineffective clotting of the blood. As such, individuals that have an insufficient amount of vitamin K may experience excessive nosebleeds, bruising, blood in their urine, heavy menstrual bleeding, and black stools

indicating gastrointestinal bleeding.[63] As it pertains to the occurrence of gastroschisis, vitamin K is widely implemented prior to surgical closure of the abdominal wall. Intramuscular injection of vitamin K preceding surgery was done in order to prevent hemorrhagic disease in newborns, particularly those affected with gastroschisis or omphalocele.[65]

V. CONCLUSION

Researchers continue to explore the mysterious pathogenesis behind omphalocele and gastroschisis. Vitamin deficiency can lead to congenital defects and can possibly be the reasoning behind gastroschisis and omphalocele. Thus, as mentioned above, vitamins play a significant role in the embryonic development and possibly in the rare occurrence of the ventral abdominal wall defect. Incorporating vitamins into the diet, especially in an expectant mother only imposes benefits for the developing fetus. The recommended daily allowances of vitamins should be noted before consumption to prevent toxicity. However, furthermore studies between the correlation of vitamins and genetics need to be applied to omphalocele and gastroschisis in order to understand an accurate presentation behind the pathogenesis and the prevention to the congenital defect.

REFERENCES

1. Zahouani T, Mendez MD. Omphalocele. [Updated 2019 Mar 2]. In: StatPearls [Internet]. Treasure Island (FL): StatPearls Publishing; 2019 Jan-. Available from: https://www.ncbi.nlm.nih.gov/books/NBK519010/
2. Omphalocele and gastroschisis: An 18-year review study *Pei-Jen Hwang, MD, and Boris G. Kousseff, MD.* Giant Omphalocele in an Adolescent Boy Tanveer Akhtar, Anand Alladi, and O. S. Siddappa.
3. A report on omphalocele and associated congenital deformity with intrauterine death: Need for early diagnosis.
4. Review of Management and Outcomes. The long term physical consequences of gastroschisis☆ Emma L. Harris[ab], Corrado Minutillo[b,c],□ , Susannah Hart[d], Teresa M. Warner[a], Madhur Ravikumara[c], Elizabeth A. Nathan[e], Jan E. Dickinson[d].
5. Vitam Horm, 2007; 75: 131-59. Vitamin A-storing cells (stellate cells). Senoo H[1], Kojima N, Sato M.
6. Department of Cell Biology and Histology, Akita University School of Medicine 1-1-1 Hondo, Akita 010-8543, Japan.
7. Rahi J S, Sripathi S, Gilbert C E, Foster A (1995). "Childhood blindness due to VAD in India: regional variations". *Archives of Disease in Childhood*, 72(4): 330–333. doi:10.1136/adc.72.4.330
8. Optometry, 2006 Mar; 77(3): 124-33. Xerophthalmia secondary to alcohol-induced malnutrition. Roncone DP, Roholt Vision Institute, Boardman, Ohio 44512, USA. davidproncone@hotmail.com
9. VITAMIN A INTOXICATION AS A CAUSE OF PSEUDOTUMOR CEREBRI George Morrice Jr., M.D.; William H. Havener, M.D.; Frederick Kapetansky, M.D. Columbus, Ohio, Department of Ophthalmology, University Hospital. *JAMA*, 1960; 173(16): 1802-1805. doi:10.1001/jama.1960.03020340020005
10. Acta Neuropathological, September 1985; 65(3–4): 335–337| Isotretinoin teratogenicityL. A. Hansen, G. S. Pearl
11. Gavrilova R, Babovic N, Lteif A, Eidem B, Kirmani S, Olson T, Babovic-Vuksanovic D. 2009. Vitamin A deficiency in an infant with PAGOD syndrome. Am J Med Genet Part A, 149A: 2241–2247.
12. Mills, J.L., Carter, T.C., Kay, D.M. *et al.* Folate and vitamin B12-related genes and risk for omphalocele. *Hum Genet*, 2012; 131: 739–746. doi:10.1007/s00439-011-1117-3 https://link.springer.com/article/10.1007/s00439-011-1117-3#citeas
13. National Institute of Health. (2019, July 9). Office of Dietary Supplements - Thiamin. Retrieved December 29, 2019, from https://ods.od.nih.gov/factsheets/Thiamin-HealthProfessional/. https://ods.od.nih.gov/factsheets/Thiamin-HealthProfessional/
14. Nguyen-Khoa, D.-T., Busschots, G. V., & Vallee, P. A. (2019, November 10). Beriberi (Thiamine Deficiency). Retrieved December 29, 2019, from https://emedicine.medscape.com/article/116930-overview. https://emedicine.medscape.com/article/116930-overview
15. The Editors of Encyclopaedia Britannica. (2018, June 27). Beriberi. Retrieved December 29, 2019, from https://www.britannica.com/science/beriberi. https://www.britannica.com/science/beriberi
16. Penn State Hershey Medical Center. (2018, February 27). Wernicke-Korsakoff syndrome. Retrieved December 29, 2019, fromhttp://pennstatehershey.adam.com/content.aspx?productid=117&pid=1&gid=000771. http://pennstatehershey.adam.com/content.aspx?productid=117&pid=1&gid=000771
17. Riboflavin John T Pinto, Janos Zempleni Author Notes Advances in Nutrition, September 2016; 7(5): 973–975, https://doi.org/10.3945/an.116.012716 Published: 07 September 2016).
18. Lane, M., Aifrey, C. P., Jr., Mengel, C.E., Doherty, M. A., and Doherty, J: The rapid induction of human riboflavin deficiency with galactoflavin. J. Clin. Invest, 1964; 43: 357.
19. Problems in Applying Teratologic Observations in Animals to Man Josef Warkany, Pediatrics, May 1974; 53(5): 820.
20. CONGENITAL MALFORMATIONS INDUCED BY RIBOFLAVIN DEFICIENCY IN STRAINS OF INBRED MICE: Harold Kalter, Pediatrics, January 1959; 23(1): 222-230.

21. Penberthy WT, Kirkland JB. Niacin. In: Erdman JW, Macdonald IA, Zeisel SH, eds. Present Knowledge in Nutrition, 10th ed. Washington, DC: Wiley-Blackwell, 2012: 293-306.
22. Kamanna, V. S., & Kashyap, M. L. (n.d.). Mechanism of Action of Niacin. https://doi.org/10.1016/j.amjcard.2008.02.029
23. Jacobson, E. L. (2013). Niacin deficiency and cancer in women., *5724*(1993). https://doi.org/10.1080/07315724.1993.10718330
24. Kamanna, V. S., & Kashyap, M. L. (n.d.). Mechanism of Action of Niacin. https://doi.org/10.1016/j.amjcard.2008.02.029
25. Herrmann, W., & Obeid, R. (Eds.). (2011). *Vitamins in the prevention of human diseases*. Walter de Gruyter.
26. Schellack, G., Harirari, P., & Schellack, N. (2016). B-complex vitamin deficiency and supplementation. *SA Pharmaceutical Journal*, *83*(4): 14-19.
27. Rébeillé, F., Ravanel, S., Marquet, A., Mendel, R. R., Smith, A. G., & Warren, M. J. (2007). Roles of vitamins B5, B8, B9, B12 and molybdenum cofactor at the cellular and organismal levels. *Natural product reports*, *24*(5): 949-962.
28. Sheppard, S. K., Didelot, X., Meric, G., Torralbo, A., Jolley, K. A., Kelly, D. J., ... & Falush, D. (2013). Genome-wide association study identifies vitamin B5 biosynthesis as a host specificity factor in Campylobacter. *Proceedings of the .national academy of sciences*, *110*(29): 11923-11927.
29. Neuhouser, M. L., Nijhout, H. F., Gregory, J. F., Reed, M. C., James, S. J., Liu, A., ... & Ulrich, C. M. (2011). Mathematical modelling predicts the effect of folate deficiency and excess on cancer-related biomarkers. *Cancer Epidemiology and Prevention Biomarkers*, *20*(9): 1912-191.
30. "Vitamin B_6". Micronutrient Information Center, Linus Pauling Institute, Oregon State University, Corvallis, OR. May 2014.
31. https://www.ncbi.nlm.nih.gov/books/NBK531488/, Isoniazid Toxicity Madhuri Badrinath; Savio John. Treasure Island (FL): StatPearls Publishing; 2019 Jan-.
32. Sylvia S. Bottomley (1991) Sideroblastic Anemia, Hospital Practice, 26sup3: 37-40. DOI: 10.1080/21548331.1991.11704283
33. Teratogenicity of Vitamin B_6 Deficiency: Omphalocele, Skeletal and Neural Defects, and Splenic Hypoplasia, Starkey D. Davis, Thomas Nelson, Thomas H. Shepard, *Science*, 25 Sep 1970; 169(3952): 1329-1330, DOI: 10.1126/science.169.3952.1329
34. "Biotin – Fact Sheet for Health Professionals". Office of Dietary Supplements, US National Institutes of Health. 8 December 2017.
35. "Biotin". Micronutrient Information Center, Linus Pauling Institute, Oregon State University, Corvallis, OR. 21 October 2015.
36. Gropper SS, Smith JL, Groff JL (2005). *Advanced nutrition and human metabolism*. Belmont. ISBN 0-534-55986-7.
37. Staggs CG, Sealey WM, McCabe BJ, Teague AM, Mock DM (December 2004). "Determination of the biotin content of select foods using accurate and sensitive HPLC/avidin binding". *Journal of Food Composition and Analysis*, 17(6): 767-776. doi:10.1016/j.jfca.2003.09.015. PMC 1450323. PMI D 16648879.
38. D Balnave - The American journal of clinical nutrition 30: September 1977; 1408-1413.
39. Teratogenic effects of avidin-induced biotin deficiency in mice, Dr. Toshiaki Watanabe, Akira Endo, Experimental Teratology, August 1984; 30(1): 91-94.
40. Kastenberg, Z. J. & Dutta, S. (2013). Ventral abdominal wall defects. *Neo Reviews*, *14*(8): e402-e411.
41. "Vitamin B_{12}". Micronutrient Information Center, Linus Pauling Institute, Oregon State University, Corvallis, OR. 4 June 2015.
42. Vitamin B12 deficiency. ROBERT C. OH, CPT, MC, USA, U.S., Army Health Clinic, Darmstadt, Germany, DAVID L. BROWN, MAJ, MC, USA, Madigan Army Medical Center, Fort Lewis, Washington, *Am Fam Physician*, 2003 Mar 1; 67(5): 979-986.
43. "Foods highest in vitamin B_{12} (based on levels per 100-gram serving)". *Nutrition Data*. Condé Nast, USDA National Nutrient Database, release SR-21. 2014.
44. Subar AF, Krebs-Smith SM, Cook A, Kahle LL. Dietary sources of nutrients among US adults, 1989 to 1991. J Am Diet Assoc., 1998; 98: 537-47.
45. Long-term neurologic consequences of nutritional vitamin B_{12} deficiency in infants, MBBS, FRACPStephen M.Graham[ab] FRACPOtto M.Arvela[ab] FRACPGraham A.Wise[ab] Prince of Wales Children's Hospital, Randwick, Australia Wollongong Hospital, Wollongong, Australia DOI: https://doi.org/10.1016/S0022-3476(05)81897-9
46. Folate-related genes and omphalocele, American Journal of Medical Genetics, Volume 136A, Issue 1 James L. Mills Charlotte M. Druschel Faith Pangilinan Kenneth Pass Christopher Cox Rebecca R. Seltzer Mary R. Conley Lawrence C. Brody First published: 03 June 2005 https://doi.org/10.1002/ajmg.a.30772
47. Yi Li, Herb E. Schellhorn, New Developments and Novel Therapeutic Perspectives for Vitamin C, *The Journal of Nutrition*, October 2007; 137(10): 2171–2184.
48. Libby, P., & Aikawa, M. (n.d.). Vitamin C, Collagen, and Cracks in the Plaque, 1396–1398. https://doi.org/10.1161/01.CIR.0000012513.58079.
49. Hathcock, J. (1982). *Nutritional Toxicology* (Volume 1). Ames: Elsevier.

https://doi.org/https://doi.org/10.1016/B978-0-12-332601-0.X5001-3

50. Feldkamp, M. L., Carmichael, S. L., Shaw, G. M., Panichello, J. D., Moore, C. A., & Botto, L. D. (2011). Maternal nutrition and gastroschisis : findings from the National Birth Defects Prevention Study. *YMOB*, *204*(5): 404.e1-404.e10. https://doi.org/10.1016/j.ajog.2010.12.053
51. Holick, M. F., & Chen, T. C. (2008). Vitamin D deficiency : a worldwide problem with health, *87:* 1080–1086.
52. Tai, K., S, M. B. B., Need, A. G., Ph, D., Horowitz, M., Ph, D., … Ph, D. (2008). Vitamin D, glucose, insulin, and insulin sensitivity, *24*: 279–285. https://doi.org/10.1016/j.nut.2007.11.006
53. Harris, E. L., Minutillo, C., Hart, S., Warner, T. M., Ravikumara, M., Nathan, E. A., & Dickinson, J. E. (2014). The long term physical consequences of gastroschisis ☆. *Journal of Pediatric Surgery*, *49*(10): 1466–1470. https://doi.org/10.1016/j.jpedsurg.2014.03.008
54. Traber MG. Vitamin E. In: Shils ME, Shike M, Ross AC, Caballero B, Cousins R, eds. Modern Nutrition in Health and Disease. 10th ed. Baltimore, MD: Lippincott Williams & Wilkins, 2006; 396-411.
55. Frei, B., & Ph, D. (1994). Reactive Oxygen Species and Antioxidant Vitamins : Mechanisms of Action, *97:* 5–13.
56. Sera, M. (2000). Dietary vitamin E and T cell-mediated function in the elderly : e ectiveness and mechanism of action, *18*.
57. Oski, F. A., & Barness, A. (1967). Vitamin E deficiency.: A previously unrecognized cause of hemolytic anemia in the premature infant, *70*(2): 211–220.
58. Friedman, A., Bartov, I. D. O., & Sklan, D. (1998). Humoral Immune Response Impairment Following Excess Vitamin E Nutrition in the Chick and Turkey, 956–962.
59. Boskovic, R., Gargaun, L., Oren, D., Djulus, J., & Koren, G. (2005). Pregnancy outcome following high doses of Vitamin E supplementation, *20:* 85–88. https://doi.org/10.1016/j.reprotox.2005.01.003
60. Ferland G. Vitamin K. In: Erdman Jr. JW, Macdonald IA, Zeisel SH, eds. Present Knowledge in Nutrition. 10th ed. Ames: Wiley-Blackwell, 2012: 230-247.
61. Rishavy MA, Hallgren KW, Wilson LA, Usubalieva A, Runge KW, Berkner KL. The vitamin K oxidoreductase is a multimer that efficiently reduces vitamin K epoxide to hydroquinone to allow vitamin K-dependent protein carboxylation. J Biol Chem., 2013; 288(44): 31556-31566.
62. Tie JK, Jin DY, Straight DL, Stafford DW. Functional study of the vitamin K cycle in mammalian cells. Blood, 2011; 117(10): 2967-2974.
63. Olson RE. Vitamin K. In: Shils M, Olson JA, Shike M, Ross AC, eds. Modern Nutrition in Health and Disease. 9th ed. Baltimore: Lippincott Williams & Wilkins, 1999: 363-380.
64. Gundberg CM, Lian JB, Booth SL. Vitamin K-dependent carboxylation of osteocalcin: friend or foe? Adv Nutr., 2012; 3(2): 149-157.
65. Mcnamara, W. F., Hartin, C. W., Escobar, M. A., & Lee, Y. (2011). Outcome Differences Between Gastroschisis Repair Methods. *Journal of Surgical Research*, *165*(1): 19–24. https://doi.org/10.1016/j.jss.2010.05.054