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A REVIEW ON FACTORS CAUSING VITAMIN B12 DEFICIENCY IN PREGNANT WOMEN AND INFANTS

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Abstract: Cobalamin (Vitamin B12) deficiency affects people all over around the globe. People who are deficient in cobalamin possess a number of wellness issues. Preeclampsia, growth of the fetus restriction, premature delivery, infant neural tube irregularities symptoms of neurological disease, and miscarriage may all be related to cobalamin deficiency during pregnancy. Babies took care of by cobalamin-deficient mothers usually fail to develop properly and have digestive tract, hematologic, and neurological disorders. Despite the relatively low prevalence of vitamin B12 insufficiency, the illness should be identified due to its potential for catastrophic neurologic consequences. Neonatal reserves at birth and the amount in breast milk are two ways that infant B12 sufficiency is correlated with maternal levels. Even though vitamin B12 insufficiency in infants is uncommon, it should be identified because therapy can avert serious developmental delays and neurological consequences. For moms who are nursing their infants and who run the risk of developing a vitamin B12 deficiency, prevention involves adding supplements to their diet.

Index Terms - Cobalamin deficiency, Pregnancy, Infants, Diagnosis, Treatment.

I. INTRODUCTION

One of the important cobalamin also known as "cobalamin" cannot be made through their metabolism in individuals. It is the most massive and most complicated water-soluble compound known to mankind, containing cobalt, and can only be produced by specific microbes (Anwar et al., 2022a; Andres et al. 2016). It is essential for the generation of DNA, methylation, folate metabolism, RBCs production, neurological development, and functioning of the central nervous system, and also for regulating and fatty acids production. Also, it performs an important part in the generation of energy and also in the breakdown of proteins, phospholipids, and neurotransmitters (Anwar et al. 2022; Van Sande et al. 2013).

The methionine synthase process, which transforms homocysteine into methionine, uses cobalamin as a cofactor. Thus, a cobalamin E deficit might increase plasma concentrations of homocysteine, which in result increases the risk of cardiovascular illnesses. Additionally, methionine is required for the production of S-adenosylmethionine, an accessible methyl donor. Phospholipids, neurotransmitters, amines, DNA, RNA, and myelin basic protein all need to be methylated, and S-adenosylmethionine is a common methyl donor which is essential for above all . It has been established that reduced S-adenosylmethionine may influence methylation of the DNA, which may modify embryonic metabolic patterns and increase the risk of developing chronic medical conditions later in life. Methylmalonyl-CoA Mutase, an enzyme that catalyzes the transformation of methylmalonyl-CoA into succinyl-CoA in the mitochondria, requires cobalamin as a coenzyme. Therefore, a cobalamindeficit causes an increase in methylmalonyl CoA levels, which then promotes the production of methylmalonic acid (MMA), as a byproduct of the process. Deficiency incobalamin may affects on the cellular breakdown of carbohydrates and lipids (Siddiqua et al. 2014).The human body generates the cobalamin in three distinct forms: naturally, as hydroxycobalamin, 2.methylcobalamin (Me-Cbl) and 3.adenosylcobalamin (Ado-Cbl). (Smith and Coman 2014), Animal proteins which include beef, poultry, fish, eggs, dairy products, and fortified meals made

from plants are excellent sources of cobalamin but the human body is unable to generate it (Vashi et al. 2016; Vanderjagt et al. 2011).

An error in any one of the steps may give rise to cobalamin deficiency since cobalamin metabolism is a complicated, multistep mechanism. When ingested, cobalamin becomes attached to proteins and liberated by the hydrochloric acid in the stomach. By combining with haptochorrins, this free form of cobalamin has protection against chemical denaturation in the stomach. Glycoproteins called haptochorrins are produced by the stomach and salivary glands. As cobalamin has been bound in the stomach, the intrinsic substance released by the stomach supports in effective absorption in the ileum (Van Sande et al. 2013), where it is released ultimately ascobalamin (Sadasivan and Friedman 2012).

The liver acts as the biggest cobalamin storage location and transforms cobalamin into its most effective forms for utilization. the liver performs a number of functions and actively participates in metabolism.(AlMatroodi et al. 2020; Rahmani et al., 2020). A synthetically produced form of cobalamin known as cynacobalamin has been used for pharmaceutical and commercial purposes.

2. Cobolamin and metabolism

Cobalamin is essential for two biological functions. Me-Cbl acts as a cofactor for methionine synthase (MS; EC 2.1.1.13), that must be present for the synthesis of methyltetrahydrofolate to tetrahydrofolate and for the formation of methionine from homocysteine in the cytoplasm (Van Sande et al. 2013; Langan and Zawistoksi 2011; McCracken et al. 2006). Ado-Cbl is needed as a cofactor in the process in the second phase of the reaction for the enzyme known as methylmalonyl-CoA mutase (EC 5.4.99.2), which catalyzes the transformation of methylmalonyl CoA to succinyl CoA in mitochondria (Van Sande et al. 2013). Homocysteine and/or methylmalonate become produced in the serum as a result of a cobalamin deficiency (Smith and Coman 2014; Van Sande et al. 2013).

Methylmalonyl CoA is a common byproduct of the decomposition of cholesterol, odd chain fatty acids, and branched chain amino acids. Methylmalonyl CoA and its precursor metabolite, propionyl CoA, have higher concentrations as a result of the methylmalonyl CoA mutase's decreased activity. Acetyl CoA and oxaloacetic acid are usually compressed to produce citrate using using the enzyme citrate synthase. Propionyl CoA's becomes utilized inappropriately in the Krebs cycle. Whenever, oxaloacetate and propionyl CoA combined to produce MCA. As a result, MCA gets produced instead of the citrate required to complete the usual citric acid cycle (Takahashi-Iñiguez et al., 2012).

3. Cobalamin deficiency

Cobalamin deficiency is a significant public health issue (Hvas and Nexo 2006), which is complicated condition (Hannibal et al. 2016). It can be driven due to nutritional deficiencies, inadequate absorption syndromes, drug-nutrient interactions, or genetic problems such hereditary metabolic diseases, autoimmune disorders conditions, as well as other gastrointestinal disorders (O'Leary and Samman 2010; Smith 2008) (Figure 1). A number of medications such as proton pump inhibitors (PPIs) like Lansoprazole (Prevacid), Omeprazole (Prilosec OTC), esomeprazole (Nexium), rabeprazole (Aciphex), and pantoprazole (Protonix), H2 Blocking drugs like famotidine (Pepcid AC) and Cimetidine (Tagamet); or certain diabetes medicines like metformin (Glucophage) trigger the cobalamin deficiency. People who strictly observe a diet free of animal products become cobalamin deficiency. The ability to absorb of cobalamin that depends on an individual’s digestive tract absorption is an essential factor for estimating the amount of cobalamin in their bodies. Because it correlates to an absence of an intrinsic component to bind with consumed cobalamin, pernicious anemia has been suggested to exist as the most prevalent fundamental reason for cobalamin deficiency. Additional factors which result in cobalamin deficiency include abdominal surgery, pancreatic insufficiency, infections with fish tapeworms, severe Cohn’s disease since these conditions can interfere with the absorption of cobalamin in ileum of small intestine. Aged people with disabilities, people who are vegetarians pregnant or nursing women, are particularly at the risk for a cobalamin deficiency.

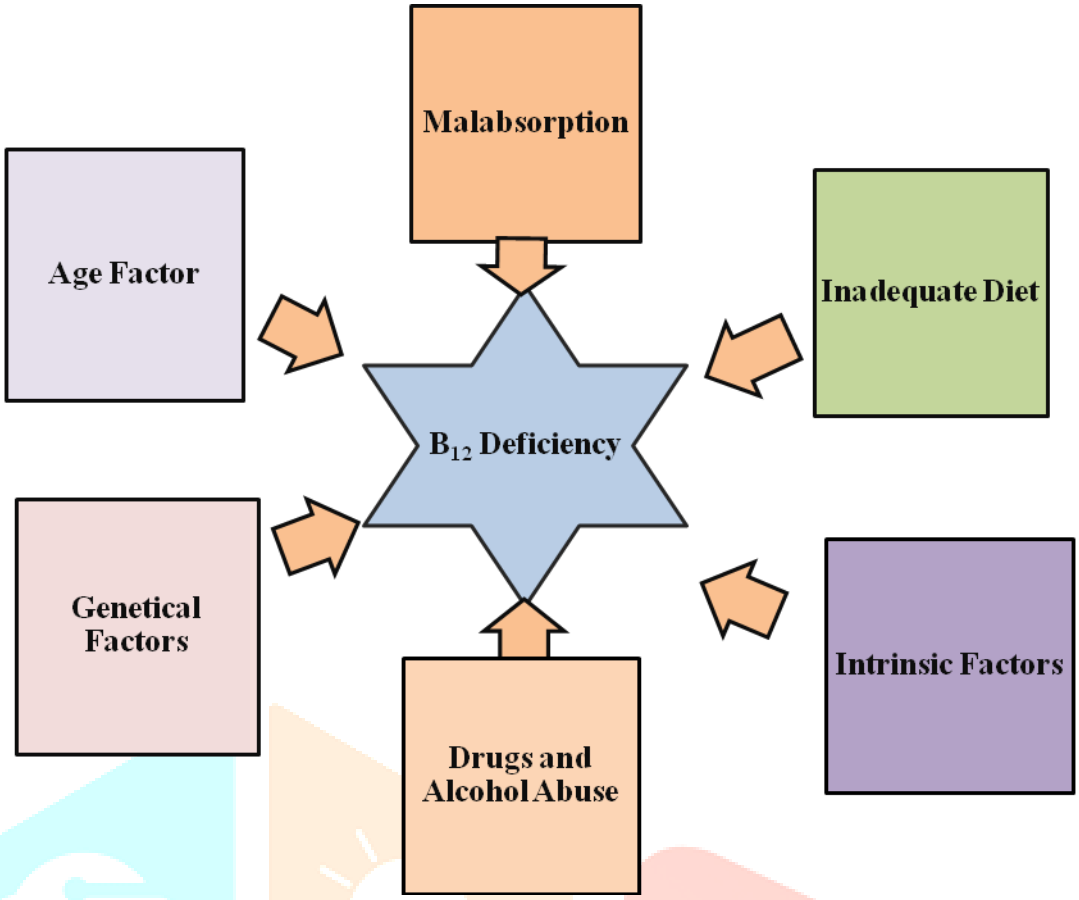

Figure 1- There are several causes of B12 deficiency in human body that leads to multiple noncommunicable complications.

All cells in the body required cobalamin for functioning efficiently with regard to metabolism. Since many different systems of organs can be affected by a cobalamin deficiency, the condition has been linked to a wide range of clinical problems. Cobalamin deficiency cannot be identified in every person according to a single, characteristic clinical symbol because the signs of cobalamin deficiency are unclear and extremely diverse (Wong, 2015). The more serious cobalamin insufficient signs have been reported to have hematological and psychological symptoms. The signs and effects of cobalamin deficiency are extensive including peripheral neuropathy, demylanation and damage to the nerves, paraesthesia, numbness, impairment of memory, moodiness, psychosis, Alzheimer's disease, megaloblastic anemia, pancytopenia, glossitis, stomatitis, and mild jaundice (Langan and Zawistoski 2011). Cobalamin insufficient promotes important oxidative stress, which affects numerous macromolecules and parts of cells through oxidation. (Bito et al. 2017), In numerous conditions, protein glycation (Anwar et al. 2020) and oxidative stress (Rahmani et al. 2023) lead to major medical issues. When trying to fight against the oxidative stress carried on by the production of reactive oxygen species, the antioxidant enzyme superoxide dismutase (SOD) is essential (Younus and Anwar 2018; Khan et al. 2014; Anwar et al. 2014). Deficiency of cobalamin greatly reduces the activity of SOD (Bito et al. 2017), Megalobolastic anemia particularly is seen in a lack of both folate and cobalamin, can be caused by the interaction between folate and cobalamin (Stabler, 2013). Low folate and cobalamin utilization have been related to hyperhomocysteinemia and low blood levels of cobalamin and minerals in a study conducted on those suffering from type 2 Diabetes (Al-Maskari et al. 2012). General symptoms of cobalamin deficiency are included in figure 2.

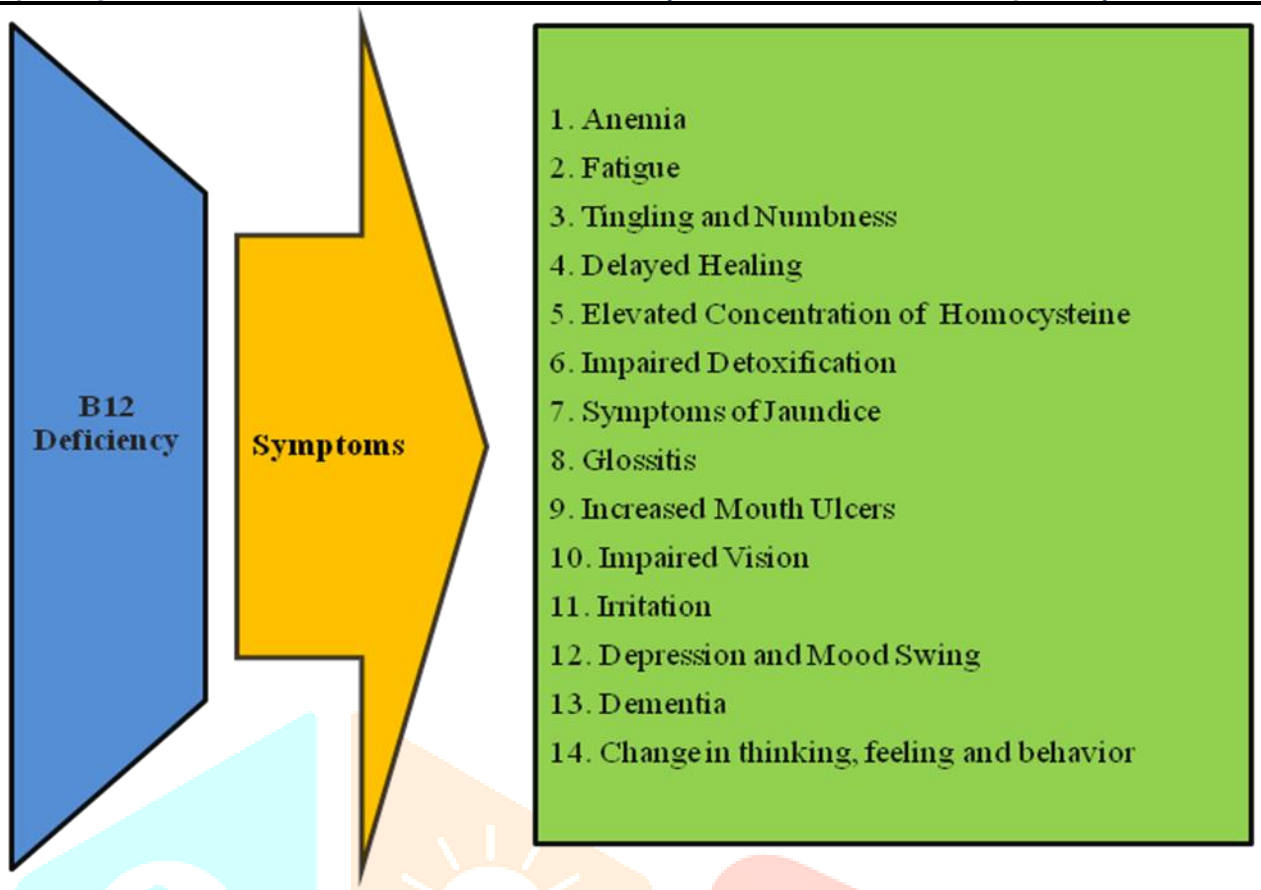

Figure 2- General symptoms of cobalamin deficiency. Various symptoms and signs of B12 deficiency are shown by human body after getting the cobalamin deficiency.

3.1. Stages of cobalamin deficiency

Nutritional deficiencies tend to occur in undernourished individuals or passionate vegans. Since cobalamin is widely stored within the body's liver, an actual insufficient usually requires years to become apparent. Megaloblastic, macrocytic iron deficiency either with or without neurological disorders identifies classic cobalamin deficiencies. There are a total of a total of four primary types of clinical indications of cobalamin deficiency: neuropsychiatric, hematologic, and digestive (GI), and dermatological. It is an extended process that occurs over many years and includes four stages (Pawlak et al., 2014).

3.1.1. Stage 1: Decreased levels of cobalamin in the blood.

The typical values are approximately 118 and 701 picomoles per litre (pmol/L) or 160 and 950 picograms per milliliter (pg/mL). A cobalamin deficiency is usually determined by values which are lesser then 160 pg/mL (118 pmol/L). Individuals who are affected by such insufficiency are probably going to display signs either now or later. Cobalamin values below 100 pg/mL (74 pmol/L) in people over 65 can lead to signs (https://www.webmd.com/a-to-z-guides/vitamin-b12-test). Methylmalonic acid concentrations in bloodstreams must be investigated regularly to verify an inadequacy. Whenever it's elevated, there is an actual cobalamin deficit. A tingling or numbness in the hands and feet, vulnerability, and diminished equilibrium may all occur from decreased cobalamin level. A number of additional circumstances are possible during the examination (Vashi et al. 2016).

1. Recurrent delirium or unexpected acute confusion
2. Alzheimer's disease, an impairment of mental abilities
3. Metabolic causes of Alzheimer
4. Disorders of the the nerves, such as nerve damage in the peripheral regions.

3.1.2. Stage 2: Low concentration of cobalamin in the cell and metabolic abnormalities.

Whenever the human body fails to obtain or assimilate sufficient of the mineral cobalamin that it requires for functioning effectively via the foods that you ingest, cobalamin insufficiency develops. A necessary mineral called cobalamin contributes in the synthesis of red blood cells as well as DNA in the body. If unattended, a deficiency of cobalamin might result in physical in nature neurological and psychiatric problems. The symptoms that follow are possible basic indications of cobalamin deficiency: excessive tiredness or vulnerability, Feeling unwell, vomiting, or suffering bowel movements, failing to feel as hungry as common, Decline of weight, possessing yellow skin, an inflamed tongue, or discomfort in your

mouth (Wolffenbuttel et al. 2019). Various indicators include tingling or feeling numb in the hands and feet, eye sight complications, and mood swings. In addition, the victims could face difficulty in communicating, impaired moving difficulty in understanding the facts and usually get stuck frequently. It's likely that the neurological disorders caused by a deficiency of cobalamin are unable to be healed. A low level of cobalamin may result in psychological effects including anxiety, depressive disorders, and an alteration in the manner that you feel and act (Serin et al. 2019).

3.1.3. Stage 3- Increased levels of homocysteine and MMA and decreased DNA synthesis resulting in neuropsychiatric symptoms.

Elevated blood MMA and homocysteine levels are initial diagnostic signs of cobalamin insufficiency and may occur in spite of a condition of typical serum cobalamin levels. After obtaining medication for cobalamin deficiencies blood levels of MMA or homocysteine may be maintained into normal (Lee et al. 2019). Amplification of these two indicators divides people who are considered as cobalamin-deficient from those individuals with folate-deficiency (Vashi et al. 2016; Lee et al. 2019).

Whenever bloodstream cobalamin levels are insufficient (350 pg/mL) and the both MMA and homocysteinemia have elevated levels, or if MMA increases without diminished volume or kidney-related medical conditions, or if homocysteinemia is exceptionally high without folate deficiency, cobalamin deficiency is considered. Elevated levels of homocysteine are also associated with MMA. Cobalamin insufficiency can basically be considered out when these two indicators are within the normal range. Megaloblastic anemia, a blood disorder which occurs on due to the absorbing of folate cofactors in the form of of 5-methyltetrahydrofolate (5-methylTHF) and associated suppression of de novo thymidylate (dTMP) generation, may be caused by severe cobalamin insufficiency (Acharya et al. 2008).

Cobalamin works in the cell's cytosol to methylate homocysteine to methionine, regenerating THF from 5-methyl THF. Tetrahydrofolic acid (THF) is essential for de novodTMP produce in the cell nucleus, and in cobalamin deficit deficient DNA-thymine synthesis seems to be caused by a diminished process for converting N5-methyltetrahydrofolic acid to THF. A cobalamin coenzyme, most likely methylcobalamin, is required for the N5-methyl THF-homocysteine methyltransferase to act as catalyst for the synthesis of N5-methyl THF (Briani et al. 2013). In accordance with all of the above, methyl-cobalamin appeared to be the most effective variant of cobalamin for repairing inappropriate DNA-thymine biosynthesis in cobalamin-deficient marrow cells. This was determined using the Deoxyuridine's capability to avoid DNA form incorporating tritiated thymidine acted as an indicator for such. Whereas methyl-cobalamin effectively corrected the issue with the DNA production (Halczuk et al. 2023).

3.1.4. Stage 4: Macrocytic anemia

A disorder of the blood called macrocytic anemia develops whenever the bone marrow produces disproportionately larger blood cells called red blood cells. Although macrocytic anemia is not considered a hazardous sickness, it may have severe implications for your physical well-being when you fail to treat it. Two types of the most common macrocytic anemia are given below.

3.1.4.1. Megaloblastic macrocytic anemia

It usually occurs when individuals fail to consume sufficient amounts of folate or cobalamin. The marrow in your bones is unable to generate properly functioning red blood cells which can carry oxygen throughout your entire organism without these substances being present (Hariz and Bhattacharya 2023).

3.1.4.2. Non-megaloblastic macrocytic anemia

If you suffer from medical problems that impede the ability of your system for utilizing vitamins and minerals, you could suffer from this type of macrocytic anemia. Previously published articles have suggested several clinical conditions linked with non-megaloblastic macrocytic anemia (Nagao and Hirokawa 2017).

a. Myelodysplastic syndrome

When something went improper with the bone marrow in your body, it stops producing blood cells that are healthy, leading to this group of illnesses.

b. Alcoholism

Consuming liquor to an excessive extent could prevent the human body form absorbing cobalamin.

c. Hypothyroidism

This medical condition may be associated with macrocytic anemia and alters how the thyroid gland performs.

3.2. Neurological manifestations of cobalamin deficiency

Neurological symptoms, Hematological, gastrointestinal, and mental health disorders are indicative of cobalamin insufficiency. Myelopathy, neurological disorders, Alzheimer's disease, and neuropsychiatric conditions are just some of the neuropsychiatric symptoms generally associated with cobalamin deficiencies. Optic nerve deterioration is an unusual phenomenon. Although it is a rare cause of myelopathy, SACD (Sub-acute combined cord degeneration) is one of the most prominent medical symptoms of cobalamin insufficiency (Briani et al. 2013).

In addition to clinical features such as spastic paraparesis, extensor plantar response dysfunction, and insufficient positional and vibratory sensitivity, the stocking-type neuropathy and absence of ankle jerks in this patient are consistent with SACD. Epidermal growth factor (EGF) and tumor necrosis factor (TNF) excess production and reduced synthesis of both of these neuroprotective agents have been suggested to be the causes of the neuropathological lesions. Neuropsychiatric symptoms, which may develop in people without hematological symptoms or low normal cobalamin levels, include impairment of memory, behavioral modifications, psychosis, mood swings, and uncommon delirium or coma. However, neither anemia nor similar psychological symptoms were observed in this individual. Cerebellar ataxia, leuko-encephalopathy, orthostatic tremors, myoclonus, ophthalmoplegia, catatonia, vocal cord paralysis, a distribution of motor and sensory abnormalities resembling syringomyelia, and dysfunction of the autonomic nervous system are uncommon neurological signs of the illness (Ralapanawa et al. 2015).

4. Cobalamin deficiency in pregnant women

Pregnant women are more probable to suffer from cobalamin deficits due to the mainly entirely vegetarian dietary pattern, a poor background, overpopulation, generally ignorance towards dietary intake, and inadequate services provided by the government (Ramirez-Velez et al. 2016). From the placenta to the developing baby, this nutritional supplement is continuously transmitted. Since the developing baby is unable to produce cobalamin, it has to depend on maternal cobalamin for its metabolic functions (Van Sande et al. 2013). Because of this, cobalamin insufficiency is common during pregnancy (Chandyo et al. 2017).

The serum cobalamin concentration decreases gradually during pregnancy, beginning in the early stages of pregnancy and staying, and it reaches the lowest level at the end of 32 weeks of pregnancy as the consequence of blood loss, hormonal fluctuations, changes in the level of cobalamin binding proteins, and placental transportation of cobalamin to the developing baby. Cobalamin has been scientifically shown to be essential in preventing repetitive miscarriages. According to studies conducted by scientists, between 12 and 15 percent of all clinically observable pregnancies terminate in spontaneous miscarriages, and fifteen to twenty percent of women in the overall population have recurrent pregnancy loss. Low levels of cobalamin insufficiency and high homocysteine concentration are the primary causes of previous unsuccessful pregnancies in thirty-three percent of women. Low levels of cobalamin have been identified to represent a usual cause of termination of pregnancy, with a prevalence of approximately 38.4% (Chandyo et al. 2017).

5. Clinical manifestations of cobalamin deficiency in pregnant women

For healthy cell division, sufficient placental activity, and pregnancy, an appropriate amount of coblamine is essential. The chance for multiple issues during pregnancy increases by maternal coblamine deficiency (Garima et al. 2016; Chandyo et al. 2017). The primary symptoms of a coblamine deficiency involve an increased rate of fertility problems, unwanted abortions, premature deliveries, and premature or underweight offspring (Scolamiero et al. 2014). Insufficient amounts of coblamin or a deficiency of cobalamin induce improper ovulation, a high homocysteine level, and improper placentation, each of which increases the possibility of miscarriage (Sawant 2015).

Since the embryo and placenta depend upon the mother cobalamin level for the development of cells and replication, a cobalamin deficiency can result anomalies in developing neural tubes, growth retardation in the uterus, preeclampsia, early pregnancy termination, and premature delivery (Vanderjagt et al. 2011). There is actually an important association between folate and cobalamin and the preliminary stages of embryogenesis (Garima et al. 2016),

Overweight or obese adults and resistance to insulin have a strong correlation with low levels of cobalamin during pregnancy (Ramirez-Velez et al. 2016). It was recently confirmed that maternal cobalamin adequate supply is essential for embryonic development and neurological development, as well as for the well-being of mothers and their unborn children. Preterm delivery, impairment of intrauterine growth, congenital cardiac disorders, neural tube disorders (NTDs), and impaired cardio-metabolic health in the offspring are all related to low maternal cobalamin level. Infant cobalamin level is greatly affected by the maternal cobalamin level.

6. Clinical manifestations of cobalamin deficiency in breastfeed infants and children

Preliminary indications of cobalamin deficiency include nausea, frustration, and unwillingness to consume food, vulnerability, and fail to develop properly (Smith and Coman 2014; Langan and Zawistoski 2011; Vanderjagt et al. 2011). Insufficient level of cobalamin in baby may have a long time permanent adverse impacts on young people's intellectual and neurological growth (Jeruszka-Bielak et al. 2017). Infants fed breast milk and their mothers are cobalamin insufficient level are more probable to suffer from major problems related to the hematopoietic (megaloblastic anemia), neurological (hypotonia, lack of voluntary coordination of muscle movements, and developmental retardation), and gastrointestinal tract inflammatory problems (Ramirez-Velez et al. 2016),

Developmental regression, abnormal eye movements, frustration, headaches, a slight shaking movement, and convulsions are additional prominent neonatal symptoms of neurological disorders (Smith and Coman 2014). According to investigations, the neurological side effects of cobalamin deficiency in newborns may be due to delayed thickening or degeneration of nerves, a change in the S-adenosylmethionine-S-adenosylhomocysteine ratio (SAM/SAH), and a disparity among neurotrophic and neurotoxin cytokines (Vanderjagt et al. 2011). According to previous investigations by Guerra-Shinohara and colleagues, a cobalamin lacking in newborns induces methylation responses to become defective (Vanderjagt et al. 2011). Older children with cobalamin deficiency has been reported to show paraesthesia, ataxia, unusual movements, glossitis, alterations in personality, and unusual the pigmentation around the dorsum of the fingers and toes and in the maxillae, arms, and medial thighs (Smith and Coman 2014).

7. Factors affecting the level of cobalamin

7.1. Zero intake of animal products

Since cobalamin can only be found primarily in animal-based food items like fish, seafood, meat, chickens, and milk products individuals who skip out on these kinds of foods run an increased risk of being insufficient in it. This is especially essential to women who are pregnant because the fetus needed appropriate cobalamin for the brain's growth and a deficit may result in for a long time neurological problems (Obeid et al. 2019).

7.2. Lack of intrinsic factors

Since the intrinsic factor, which is essential for cobalamin absorption, has been eliminated due to the autoimmune illnesses pernicious anemia, the cobalamin is unable to be assimilated. Different kinds of anemia and neurological impairment might develop from cobalamin insufficiency. Even using a high-dose cobalamin supplementation will not be beneficial since there is not enough intrinsic factor for the body to take it (Wang et al. 2018).

7.3. Inadequate stomach acid or medications that cause decreased stomach acid.

Allopathic medicine-based treatment has been shown to be highly effective, yet it has also been noted to have serious side effects (Almatroodi et al., 2020). An inadequate acid in the stomach is a significantly more prevalent cause of cobalamin deficiency, particularly among people over 65. This is due to stomach acid must be present for the elimination of cobalamin from their meals. Approximately, 10 and 30 percent of people older than 50 reportedly show complications linked with consumption of cobalamin obtained from their meals. For illnesses like gastro-esophageal reflux disease (GERD) or peptic ulcer disease (PUD), individuals who continuously use drugs like proton-pump inhibitors, H2-blocking medications, or different antacids that regulate stomach acid may suffer problems consuming cobalamin from their meals. A healthcare practitioner must keep an attentive eye on any individual utilizing these medicines for a long period of time who may also be susceptible for cobalamin insufficiency for other causes (Mohan et al. 2018).

7.4. Intestinal surgeries or digestive disorders that cause malabsorption

Surgery which impacts the ileum, wherever cobalamin gets into the bloodstream, or the gastrointestinal tract, wherever intrinsic factor synthesized, could increase the probability of a deficit status. The probability of insufficiency further rises through particular diseases, for example Crohn's illness and celiac disease, both of that may have an adverse effect on the gastrointestinal tract (Shaw et al., 1989).

7.5. Medications interfering with absorption.

As it can inhibit adsorption, continuous administration of the type 2 diabetes medicine metformin has been significantly correlated with cobalamin insufficiency and diminished folic acid levels and that can raise levels of homocysteine and elevate cardiovascular susceptibility (Owen et al. 2021). The influence on cobalamin concentrations can also be correlated with the use of drugs such as proton pump inhibitors and histamine receptor blockers medications are administered for controlling acid production in the stomach (Miller, 2018).

8. Diagnosis and functional biomarkers of cobalamin deficiency

Treatment of cobalamin deficiency depends significantly on early identification. There presently exists no "gold standard" for correctly recognizing someone with a cobalamin deficiency in their body (Wong, 2015). A complete count of blood cells and a serum cobalamin level can be utilized for establishing a preliminary medical diagnosis for a suspicious individual (Hannibal et al. 2016; Vashi et al. 2016). This analysis has errors yet, because several types of preclinical disorders can cause levels to seem mistakenly normal (Langan et al. 2011). Indeed, serious functioning deficiencies can occur in the context of normal amounts of cobalamin, and low levels in the blood of cobalamin might not reflect a deficiency. In accordance with the World Health Organization, serum cobalamin levels < 148 pmol/L show insufficiency (Allen 2009-Sir Project), yet cobalamin level of total serum by themselves are not an accurate measure of cobalamin level (Hannibal et al. 2016).

No investigations have yet been documented which indicate the most effective cutoff value for the pregnant woman's blood levels immediately before conceiving, during the pregnancy, and while the practice of breastfeeding (Van Sande et al. 2013). A gradual physiological decrease occurs in the bloodstream concentration of the cobalamin during a straightforward pregnancy (Ramirez-Velez et al. 2016). In addition, this decrease establishes into cobalamin insufficiency as the pregnancy progresses (Van Sande et al., 2013). Direct indicators like total cobalamin and holotranscobalamin, along with functional indicators including methylmalonic acid (MMA) or total homocysteine, may be employed for assessing the biochemical cobalamin level in an individual. Serum HCY and MMA levels which are increased have been reported to be considered extremely sensitive to indicators of cobalamin deficiency (Schroder et al. 2016; Wong 2015; Langan et al. 2011).

An innovative method was recently utilized for screening pregnant women for cobalamin deficiency in just one test via determining the concentration of MCA that appeared to possess the best capability. It is highly recommended to use both combination of one direct and one functional indicator due to issues with sensibility and selectivity of individual tests (Jeruszka-Bielak et al. 2017).

9. Utility and limitations of biomarkers of cobalamin deficiency

Up to four biomarkers, including two direct (total cobalamin and holotranscobalamin, formerly known as holoTC) and two functional (homocysteine and methylmalonic acid, more commonly known as MMA) indicators, have been employed for assessing the cobalamin level in a particular person. For a very long time, a typical clinical test has consisted of a determination of blood total cobalamin. Cobalamin insufficiency is frequently characterized as cobalamin values less than 148 pmol/L, but this may differ among laboratories (Jarquin Campos et al. 2020). The microbiological technique has been demonstrated to have a high efficacy for evaluating clinical cobalamin insufficiency for this purpose. As a way to measure the general public's cobalamin levels in the United States, the National Health and Nutrition Examination Survey chose to employ the combination of serum total cobalamin and MMA. In addition, methods have been developed for recognizing cobalamin insufficiency like the "Fedosov's Wellness Score," an integrated cobalamin index which applies two, three, or four cobalamin biomarkers collectively and take aging and folate level into consideration (Sakyi et al. 2021). Considering the limits of particular tests, professionals in this field nowadays recommend applying a multiple biomarker for accurately identifying cobalamin insufficiency including the most recent development of techniques that determine insufficient status using combinations involving a number of biomarkers.

10. Prevention and treatment of cobalamin deficiency

The liver is a vital organ that serves a variety of purposes. It also plays a significant function in metabolism. (Al Matroodi et al. 2020; Rahmani et al. 2020)A lack of cobalamin exerts an unfavorable effect on the national GDP and economic growth in along with negative pregnancy results, slowed neurological and intellectual development, and increased probability of morbidity and mortality in children. (Ramirez-Velez et al. 2016).

A number of investigations have shown that both time and the extent have a helpful association with long-term advantages. Treatment strategies always concentrate on the fundamental problems.Because the extent and time frame of the insufficiency have always been associated with long-term effects, medical treatment with essential drugs and supplements needs to start immediately as soon as feasible to overcome the negative effects of cobalamin deficiency. It may be potentially challenging to determine how to treat a person whose physical manifestations and laboratory testing report are in conflict (Hvas and Naxo 2006).

The researches shows that the medication for individuals suffering from critical cobalamin deficiency indications should be required according to the results obtained from laboratory tests (Solomon 2005). A standard adult woman's Estimated Average Requirement (EAR) is 0.2 g/day, as reported by a WHO investigation. Considering nourishments never get 100% metabolized, an expecting mother's EAR is advised to be 2.2 g/day and her recommended dietary allowance (RNI) is 2.6 g/day. Since they release 0.4 g/day into their breast milk, breastfeeding women have EAR of 2.4 g/day and RNI of 2.8 g/day (Van Sande et al. 2013).

For the medical treatment of cobalamin deficiency, both preliminary and continual, multiple recommendations are put forward. Choosing the dosage, administration method, and kind of cobalamin that needs to be employed and also the requirement of continuous surveillance are essential for the formulation of an effective cobalamin treatment strategy. There are multiple types of cobalamin that may be utilized, including cyano, hydroxyl, and methylcobalamin (Hvas and Naxo 2006). Even though intramuscular cobalamin injections are still among the most common ways of curing cobalamin deficiency, innovative ways to cobalamin delivery, including oral and nasal, are currently being investigated (Lane and Rojas-Fernandez 2002). In the UK, current medical practice recommends employing injectable hydroxocobalamin to treat cobalamin deficiency. To help to overcome deficiencies in cobalamin metabolism, hydroxycobalamin is suggested over cyanocobalamin since it has greater absorption, is more readily available to the cells, and does not require decyanation. The suggested first medication for individuals having neurological problems is 1000 g of hydroxycobalamin delivered through the muscle at least three times per week for two weeks. Patients with this condition subsequently get 1000 g of hydroxycobalamin injected intramuscularly every three months as continuing treatment. In order to cure a cobalamin deficiencies accompanied symptoms of neurological dysfunction, 1000 mg of hydroxycobalamin should be administered intramuscularly on an as-needed basis unless no further reduction in symptoms is seen (Devalia et al. 2014).

The rate of recuperation depends on the extent to which serious and persistent the neurological impairments. Measuring the efficacy of the medication is important, and the amount of medication taken must be modified according to variations in the concentrations of plasma homocysteine, the urine MMA, and red blood cell indices (Smith and Coman 2014).

High dosage oral cobalamin medication is becoming more common because of its capacity to cure cobalamin deficiency with the same efficacy as injections into the muscles. In accordance to investigations involving radioactively tagged oral cobalamin, both individuals in good health as well as individuals with serious anemia may passively consume 0.5% to 4% of oral cobalamin. In combination with systemic medical treatment, taking an oral dose every day of 2000 mg caused a considerable decrease in methylmalonic acid levels, an important rise in cobalamin levels, and a restoration of a normal cobalamin level (Hvas and Naxo 2006).

A different study evaluating oral and intramuscular cobalamin (1000 g dosages, daily for 10 days, then weekly for 4 weeks, and finally monthly afterwards) demonstrated that following 90 days, the two groups' cobalamin status had identical improvements. It is essential to remain in mind that while oral cobalamin may deal with small nutritional deficiencies, reintroducing animal foods on by itself is insufficient (Chan et al. 2016).

11. Discussion

This review highlights the requirement for cobalamin throughout the pregnancy, unfavorable results of pregnancy, both the immediate and long-term impacts of cobalamin insufficiency on the development of babies, and also the recognition and treatment of cobalamin insufficiency. The demand for cobalamin increases all around breastfeeding and during pregnancy, and during the course of pregnancy the requirement has become so high that it simply cannot be met by meals alone (Siddiqua et al. 2014). In order to protect the well-being of both the woman who gives birth and the unborn child, it is important that we protect women who are in their reproductive years from suffering from cobalamin insufficiency. Low mother cobalamin status can contribute to a number of problems with youngsters (Jeruszka-Bielak et al. 2017). Low concentrations of cobalamin as well as its transportation protein TC II in the spinal fluid of an infant could represent a probable root of neurological problems like infantile tremor syndrome in 4–11 month-old newborns. Cobalamin inadequate levels of young children and newborns have been identified as being associated with maternal deficiency (Garima et al. 2016).

The effects of low mother cobalamin level on the physical wellness and psychological growth of daughters and sons are established. To avoid the adverse impacts of reduced maternal cobalamin level on the growth along with growth of the developing baby, it is recommended that mothers initiate getting pregnant with adequate cobalamin level (Van Sande et al. 2013).

Insufficient consumption of cobalamin and its inadequate absorption as result of serious digestive problems can result in inadequacy Cobalamin insufficiency has been suggested to be the cause of unexplained anemia, neuropsychological signs and symptoms, and/or digestive symptoms such as tender tongues, an eating disorder, and diarrhoea. Cobalamin deficiency is frequently identified by examinations of the levels of the metabolic indicators MMA and they along with blood cobalamin concentrations. In accordance to numerous investigations, cobalamin correlated with transcobalamin, also known as holoTC, may act as a warning sign of cobalamin insufficient supply. Identifying whether holoTC may be employed individually or in combination with other cobalamin biomarkers persists to be essential. Identifying the reason of cobalamin insufficiency is essential after a diagnosis, because there are a number of techniques that may be performed to determine the performance of the wall of the stomach to inquire in the lack of an essential component. Since there is an important possibility of multiple effects, include long-term neurodevelopmental anomalies it is essential to start supplemental medication immediately as possible after the announcement of the diagnosis. Individuals with sufficient ingestion but cobalamin deficient might be suggested to consume a daily vitamin pill providing at least 6 g of cobalamin. A technique for organizing the means of administration, dose, and type of cobalamin that is utilized is necessary for the medical treatment of people with a permanent reason for cobalamin shortages, who should require lifetime treatment that includes a pharmacological dose of cobalamin. Intramuscular injection is the most common way of treatment cobalamin deficiencies, although oral and intranasal routes of administration are additionally researched. Cobalamin may be administered orally, and the oral treatment's mechanism depends on the theory that most cobalamin enters the body via the digestive tract by through passive absorption (Andres et al. 2016).

Methylcobolamin may prevent RNA and incoming NTP from attaching, according to Narayanan and Nair. Therefore, the COVID-19-nsp12 enzyme's RNA-dependent RNA polymerase activity may be inhibited by Methylcobolamin. Therefore, inhibition of this enzyme can result in lower viral titres and decreased morbidity of the disease. It has been proposed that methylcobalamin's capacity to inhibit the nsp12 protein (Narayan and Nair, 2020). It has been shown that there is a striking resemblance between the symptoms of COVID-19 and those of B12 deficiency (Anwar et al., 2022a). Consequently, B12 might be connected to these individuals' poor health. Individuals with low socioeconomic status and compromised immune systems may be more vulnerable to COVID-19. Moreover, the elderly, those with underlying medical issues, expectant mothers, newborns, and people living in long-term care institutions are especially vulnerable to the coronavirus. Reduced immunity is one of the primary causes of the illness in these individuals. B12 has been found to have a significant impact on cellular immunity, particularly in regard to CD8+ and natural killer cells. Moreover, B12 is an immunomodulator of cellular immunity. Dehghani-Samani et al. (2020) and Munteanu et al. (2024) have suggested that B12 facilitates the immune system's proper functioning. To the best of our knowledge, no published prospective study has shown how taking cobalamin can reduce the likelihood of congenital anomalies such as neural tube defects in infants. Research must be done to determine how effective cobalamin supplementation is in this situation.

12. Conclusion

Plant-based medicines and their byproducts have long been used to treat a variety of human ailments. They are typically reasonably priced and safe. Meals from animals can be included in a nutrient-dense diet to cure a cobalamin deficiency. Low levels of cobalamin have been associated with several issues. Cobalamin deficiency can occur occasionally in the elderly, meat-averse, autoimmune, gastrointestinal, and pregnant populations; however, because the symptoms are usually mild, it frequently remains undiagnosed. The main health issue that pregnant women face is an insufficient supply of cobalamin, which is essential for healthy cell division and placental function. Reproductive women are more prone to cobalamin deficits because of their custom of eating vegetarianism and general care for dietary practices. Cobalamin deficiency is one of the main causes of unexplained recurrent miscarriages. As a result, it is crucial to tell a potential mother about the negative consequences of low maternal cobalamin levels on pregnancy and offspring. Further prospective research was also necessary to establish the best cobalamin delivery method, dosage, and outcomes for all expectant and nursing moms.

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All authors declare that they have no conflicts of interest.

Ethical approval
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