Review

Vitamin B12: As Important to Pediatricians as to Geriatricians

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Review

Vitamin B12: As Important to Pediatricians as to Geriatricians

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Abstract: Vitamin B12 deficiency during infancy is not unusual in newly industrialized and developing countries however reports of vitamin B12 deficiency during infancy are uncommon in the industrialized areas of Western and Northern Europe, North America, Australia and New Zealand, and the majority of reported cases are in exclusively breastfed infants of mothers consuming vegetarian or vegan diets. Neonatal vitamin B12 status at birth is determined by mother's vitamin B12 status during pregnancy and vitamin B12 concentrations in breast milk are highly correlated with maternal vitamin B12 levels. Due to rapid brain and somatic growth, infant vitamin B12 stores can be quickly depleted if there is insufficient vitamin B12 in the breast milk. The most commonly described symptoms of deficiency during infancy are irritability, apathy, hypotonia, growth failure, refusal to wean from the breast or to eat complementary foods and developmental regression. Recent literature suggests vitamin B12 deficiency in breast-fed infants is much more common than previously recognized and given vitamin B12 plays an important role in the synthesis and methylation of DNA, the methylation of histones and other regulators of gene expression, and mitochondrial metabolism, even modest deficiency may be associated with subtle neurologic abnormalities and developmental delays.

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1. Introduction

Vitamin B12 is the largest and has the most complex structure of any vitamin and it is unique among vitamins in that it contains a cobalt ion. Vitamin B12 synthesis is comprised of more than 25 steps at a very large energy cost [1,2]. No multicellular organisms synthesize vitamin B12; vitamin B12 is exclusively synthesized by selected bacterial species. Some bacteria are vitamin B12 producers (e.g. *Klebsiella* and *Pseudomonas* spp), but most bacteria are vitamin B12 consumers and vitamin B12 availability modulates the intestinal microbiota [3].

In humans, vitamin B12 synthesis exclusively occurs in the colon, beyond the site of active and passive intestinal vitamin B12 absorption. Some mammals including many rodents resort to coprophagia as a means of assuring they are getting a sufficient supply of vitamin B12 [1,2]. Humans are entirely dependent on dietary sources of vitamin B12. Vitamin B12 is only present in foods of animal origin and some algae that harbor symbiotic vitamin B12 producing organisms. There are no naturally occurring bioactive forms of vitamin B12 in plants as plants do not synthesize B12 nor do they contain any vitamin B12 as they do not have any metabolic pathways that require it as a co-factor. The richest natural sources of dietary B12 are liver and kidney. It is also present in non-organ meat, dairy products, eggs and shellfish [1,3,4]. Although the vitamin B12 content of milk and eggs is not particularly high, milk, eggs and other dairy products are major contributors of vitamin B12 intakes in many parts of the world [4].

2. Functions of Vitamin B12

Vitamin B12 is the cofactor for two enzymes that are present in all mammals: cytosolic methionine synthase and mitochondrial l-methylmalonyl-coenzyme A mutase [1-3]. Methylmalonyl-CoA mutase coverts methylmalonyl-CoA to succinyl-CoA. Succinyl-CoA is a major intermediary of

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the tricarboxylic acid cyclic and thus vitamin B12 is required for the breakdown of certain branched chain amino acids and odd chain fatty acids. In the absence of adequate levels of B12, methylmalonic acid (MMA) levels rise. Vitamin B12 is required for the methionine synthase reaction converting homocysteine to methionine which is required for thymidine synthesis and thus essential for DNA replication and repair. The importance of these reactions extends beyond the production of methionine because methionine is also converted to S-adenosylmethionine (SAM) which is a methyl donor for a number of important compounds including but not limited to creatine, epinephrine, and sarcosine, DNA, histones and other regulators of gene expression. Vitamin B12 deficiency results in accumulation of homocysteine which induces cellular stress and apoptosis. In cell and animal models, vitamin B12 deficiency induces increased expression of protein phosphatase 2A, nerve growth factor and tumour necrosis factor, as well as decreasing expression of epidermal growth factor [1,2,5].

3. Symptoms of Vitamin B12 Deficiency

Based on Osler's, Gardner's and Biermer's descriptions of a progressive pernicious anemia associated with macrocytosis and subacute degeneration of the spinal cord, many clinicians continue to associate vitamin B12 deficiency with macrocytic anemia and neurologic symptoms [6]. However given the crucial roles vitamin B12 plays in intermediary metabolism as well as DNA synthesis, repair and gene regulation, if our suspicion of vitamin B12 deficiency is based solely on the presence of macrocytic anemia and neurologic symptoms coupled with the fact that there may be a delay of between five and ten years between the onset of vitamin B12 deficiency and the appearance of clinical symptoms, we will miss a substantial number of vitamin B12 deficient individuals [6-8].

The manifestations of vitamin B12 deficiency are protean and extremely varied both in scope and severity and the absence of anemia and/or overt neurologic symptoms and signs does not exclude the diagnosis. In adults, common symptoms include fatigue, anorexia, altered sense of taste, atrophic glossitis (Hunter's glossitis), subtle personality changes, memory loss, emotional lability, sensory neuropathy and isolated macrocytosis and/or neutrophil hypersegmentation. More severe manifestations can include pancytopenia with or without recurrent infections, hemolytic anemia with accompanying jaundice, optic atrophy, and sclerosis of the spinal cord with all its consequences [5,7-9].

Symptoms of vitamin B12 deficiency in infants and young children are often non-specific and can include anemia, developmental delay or developmental regression, irritability, lethargy, feeding problems, and/or abnormal movements [5]. In infants, the average age at onset of symptoms is between three and four months and the average age at diagnosis is between seven months and a year. Anemia, growth failure and neurologic signs and symptoms are the most common presenting complaints however, a substantial number of infants present with difficulties weaning off the breast and introducing the bottle and/or introducing complementary foods as well as chronic or recurrent vomiting [10-12]. In a review of nearly 300 infants with vitamin B12 deficiency, the most prominent presenting signs and symptoms of vitamin B12 deficiency were growth failure, apathy/lethargy, anemia, developmental delay and hypotonia but refusal to eat solids and vomiting were quite common [13].

In Northern India, up to 2% of pediatric hospital admissions are due to "infant tremor syndrome" characterized by the tetrad of pallor, developmental delay/regression, skin hyperpigmention and scant scalp hair. Treatment with vitamin B12 typically results in prompt and dramatic symptomatic improvement. Nearly all of the reported cases occur in exclusively breast fed infants who refuse to wean from the breast or commence eating solid foods until they are treated with vitamin B12 [14].

The etiology of refusal to wean from the breast to the bottle and/or refusing to eat solids is unclear, but in adults, B12 deficiency is associated with a variety of oral manifestations including glossitis, glossodynia, recurrent oral ulcers, cheilitis, altered sense of taste, lingual paresthesia, and

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oral burning. In adults, the most common oral complaint is tongue pain [15] and so it may be that in infants who are vitamin B12 deficient, they refuse to transition off the breast because it hurts to eat.

4. Vitamin B12 Absorption

Dietary vitamin B12 is entirely derived from foods of animal origin and all dietary vitamin B12 is protein bound. Vitamin B12 dissociates from food proteins in the acidic environment of the stomach and once released, the free vitamin B12 binds to haptocorrin (previously called R protein) that is secreted in the saliva. To a much smaller extent, the free vitamin B12 binds to intrinsic factor (IF) which is produced by gastric parietal cells. Both haptocorrin (HC) and IF are resistant to gastric acid and pepsin however in the acidic stomach, HC is much more efficient at binding B12 than IF [5,6,16-19].

Once in the duodenum, HC is quickly degraded by pancreatic peptidases releasing free vitamin B12 which very rapidly and avidly binds to IF which is resistant to degradation by pancreatic enzymes. The vitamin B12-IF complex travels through the jejunum and proximal ileum and in the distal half of the ileum the B12-IF factor complex is avidly absorbed via calcium dependent receptor mediated endocytosis [4,5,16-19]. This appears to be the rate limiting step of vitamin B12 absorption with an estimated maximum capacity of between 1.5 and 2.5 ug per meal. As a result, a substantial proportion of ingested vitamin B12 is lost in the stool complexed with IF [20,21].

In contrast to this highly regulated active transport process that evolved to absorb food associated vitamin B12, it is estimated about 1% of pharmacologic doses of crystalline B12 are absorbed in the absence of intrinsic factor via passive diffusion. It is unclear where in the small bowel this takes place, but numerous studies have demonstrated the effectiveness of pharmacologic doses of oral vitamin B12 in people lacking intrinsic factor due to autoimmune pernicious anemia [5,21-23].

Once inside the enterocyte, the vitamin B12-IF complex is transported into lysosomal vesicles where vitamin B12 is released and the IF degraded. The free vitamin B12 is then exported into the portal circulation by the ATP driven MDR1 protein [14,15]. Immediately after being secreted into the portal circulation, the free vitamin B12 binds to one of two vitamin B12 transport proteins: transcobalamin (TC) or haptocorrin (HC). Minimal if any vitamin B12 circulates unbound. 80 – 90% of circulating vitamin B12 is bound to HC and the remaining 10 – 20% is bound to TC [17,24].

TC is synthesized by numerous tissues including endothelial cells and ileal enterocytes and circulates largely in an unsaturated form [16,19,25]. It has the essential role of transporting vitamin B12 that has been absorbed to the remainder of the body. There are specific receptors for vitamin B12 bound to TC (holo transcobalamin or holo-TC) on the surface of all DNA synthesizing cells [6]. The importance of TC is exemplified by the rarity inborn errors of its synthesis. Affected infants are asymptomatic at birth, but within weeks, they develop severe B12 deficiency and if untreated they develop profound irreversible neurologic impairment [6,26].

In the kidney, holo-TC is filtered and then reabsorbed in the proximal tubule. It binds to megalin on proximal tubular cells and the complex undergoes receptor associated endocytosis [17.19]. Vitamin B12 accumulates in renal lysosomes suggesting the kidney may have a role in B12 storage [16,18]. This likely explains why after liver, kidney is the most concentrated source of B12 [6].

In humans, HC is present in a number of body fluids, including saliva, breastmilk and plasma. In addition to escorting vitamin B12 through the upper GI tract, HC binds a substantial amount of the vitamin in plasma and in breastmilk [27, 28]. From an evolutionary standpoint, HC is the youngest of the vitamin B12 binding proteins and it evolved as a duplication of the IF gene [27]. HC differs from IF and TC in its ability to bind not only vitamin B12, but also inactive forms of the vitamin produced by colonic microflora [6]. In contrast to TC, HC in blood is nearly fully saturated with both active vitamin B12 and inactive vitamin B12 analogs. Although it carries the majority of vitamin B12 in the circulation, hepatocytes are the only cells that have been identified with HC receptors and there is no evidence HC has any role in the uptake of vitamin B12 in cells other than hepatocytes, however, its role is still not entirely clear. One hypothesis is that its primary function is to transport potentially harmful analogs made by gut flora to the liver for excretion into bile [6].

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Human HC deficiency occurs, and while affected individuals have low circulating B12 levels, they are otherwise healthy [27]. Interestingly, the HC gene has been lost in a number of evolutionary lineages; it is present in most mammals, but not in mice or rat and is found in reptiles, but not in birds or amphibians [27].

5. How Much Vitamin B12 Do We Need?

There is no universally agreed upon way to assess B12 status [18]. The four things most commonly measured in blood are total vitamin B12 levels, holo-TC levels, HCY levels and MMA levels and each of these has its benefits and disadvantages. Moreover, there is a lack of consensus in choosing cut-off values for each of these markers. Methylmalonic acid (MMA) and homocysteine (HCY) levels are measures of vitamin B12 functional status as their levels rise in the face of B12 deficiency [6]. It is important to note that elevated levels of HCY and MMA are not entirely specific for vitamin B12 deficiency. Elevated HCY values can also be the consequence of folate or vitamin B6 deficiency, as well as impaired renal function, hypothyroidism, and certain medications [5,6] and MMA levels are elevated in people with impaired renal function [5,6]. As a result, many authors advocate measuring serum vitamin B12 levels plus MMA and/or HCY levels along with folate levels to assess vitamin B12 status [5,6,29,30].

The typical Western diet provides between 4 and 6 ug of vitamin B12 daily of which between 1 and 5 ug is absorbed [17,19]. In the United States it is recommended adults ingest at least 2.4 ug/d. The recommended intakes for pregnant women and lactating are a bit higher at 2.6 ug/d and 2.8 ug/d respectively. The recommended intakes for children vary from 0.4 ug/d for 0 – 6 month olds to 1.8 lg/d for 9 – 13 year olds [31]. The European Food Safety Authority, recommends a daily intake of 4.0 μg of vitamin B12 for adults, and requirements are higher during pregnancy and lactation [4].

It is important to note that recommended daily intakes do not take into account the bioavailability of vitamin B12 from various foods which varies widely. The bioavailability of vitamin B12 from cow's milk is better than from a number of other animal food sources and there are some data suggesting vitamin B12 in cow's milk may be more bioavailable than vitamin B12 in human milk [32]. It also is important to recognize that most of the studies used to generate the recommended daily allowances of vitamin B12 as well as a number of other nutrients are decades old, were comprised of small numbers and the guidelines were focused on preventing symptoms of severe deficiency as opposed to subclinical deficiency. For vitamin B12 this may be particularly problematic as absolute vitamin B12 levels do not always correlate with the functional measures of vitamin B12 status and moreover, we have come to learn that mild or subclinical deficiency is much more common than previously recognized [4,6,8].

In healthy young and middle aged adults, plasma concentrations of the functional markers of vitamin B12 status, MMA and HCY tend to level off at daily intakes between 4 and 10 μg per day and so daily intakes between 4 and 10 μg are probably adequate for the prevention of subclinical deficiency and its long term consequences [17].

6. Causes of Vitamin B12 Deficiency

Worldwide, vitamin B12 deficiency is quite common, particularly in developing nations where individuals have low intakes of animal products. In portions of Africa, Asia and Latin America, between 10 and 20% of people have vitamin B12 levels below 150 which are clearly in the deficient range, and in some locales half or more of the population have low or marginal vitamin B12 levels. While the number of vitamin B12 deficient people is lower in Europe, North America, Australia and New Zealand, the numbers are still quite substantial [4,7].

In the developing world, the most common cause of vitamin B12 deficiency is inadequate intake as a result of general undernutrition or malnutrition coupled with the lack of intake of foods of animal origin. In contrast, in industrialized nations the most common causes of vitamin B12 deficiency are

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lack of intake due to elective adherence to a vegetarian or vegan diet or malabsorption of vitamin B12 as a result immune mediated pernicious anemia [5-7,33].

Hermann and colleagues assessed markers of vitamin B12 status in 144 healthy Dutch and German adults by measuring holo-TC, MMA, and homocysteine levels. 79 of these people were omnivores, 53 were lacto-ovo-vegetarians, and 12 were vegans. None of these people had low folate levels which can cause elevated serum homocysteine levels. Of the three groups, vegans had the lowest vitamin B-12 status. Low holo-TC levels were found in 11% of omnivores, 77% of lacto-ovo-vegetarians, and 92% of vegans and elevated MMA levels were found in 5% of omnivores, 68% of lacto-ovo-vegetarians, and 83% of vegans [34].

In another study, 53 healthy omnivores were randomized to a controlled vegan diet or a meat-rich diet for four weeks. Vitamin B12 status was assessed by total serum vitamin B12, holo-TC and MMA levels. All measures of B12 status were comparable in the two groups at the onset of the study. After four weeks, B12 and holoTC levels were unchanged in the people eating the meat rich diet, whereas levels significantly declined in the people eating the vegan diet. MMA levels remained unchanged in the meat eaters, and trended upwards in the people eating the vegan diet but this didn't reach statistical significance. Given these people were eating an omnivorous diet before the study, and had normal markers of B12 status, they were B12 replete at the onset of the study, and so a month of suboptimal B12 intake on the vegan diet did not result in vitamin B12 deficiency [35].

Both vegans and vegetarians are unlikely to achieve the recommended dietary allowances of vitamin B12, since as previously stated plant derived foods have no, or only trace amounts of vitamin B12. Some vitamin B12 may be provided by plants contaminated with vitamin B12-producing bacteria through fertilization with manure, since feces are a good source of vitamin B12 [36]. In largely vegetarian populations with lower standards of hygiene, poorer people tend to have higher vitamin B12 levels than the urban middle-class. In one large study from India, 81% of urban middle-class men had vitamin B12 levels below 150 as compared to 51% of slum residents. The authors proposed this difference was due to the slum dwellers ingesting more microbial vitamin B12 from contaminated food and water [37].

After inadequate intake, the second most common cause of vitamin B12 deficiency is inadequate absorption. Inadequate vitamin B12 absorption can be due to autoimmune pernicious anemia during which gastric parietal cells are destroyed resulting in lack of production of IF [5,6,18,38].

Other causes of vitamin B12 malabsorption can include gastrectomy, gastric bypass, atrophic gastritis associated with chronic H. pylori infection or chronic therapy with proton inhibitor drugs all of which can diminish the release of vitamin B12 from foodstuffs due to inadequate gastric acid and/or pepsin [5,6,16,38]. In people treated chronically with proton pump inhibitors, genetic polymorphisms that diminish microsomal cytochrome P450 catabolism of omeprazole are associated with lower vitamin B12 levels [39]. Patients with pancreatic insufficiency may malabsorb vitamin B12 because the vitamin is not released from haptocorrin due to lack of pancreatic peptidases. Ileal resection/short bowel syndrome/villous atrophy can cause deficiency due to impaired absorption of the B12-IF complex. Patients suffering from small bowel bacterial overgrowth can develop deficiency as a result of impaired absorption of the B12-IF complex and/or excessive bacterial metabolism of ingested vitamin B12 [4,5,18]. Metformin therapy induces malabsorption of vitamin B12 via inhibition of calcium dependent binding of the IF-Cbl complex to cubam receptors in the ileum. This effect can be reversed by increasing calcium intake. [40,41].

There are congenital causes of B12 deficiency but they are all rare. IF deficiency caused by mutations in the gene coding for intrinsic factor typically presents by age five with symptoms and signs typical of adult onset pernicious anemia. Immerslund-Grasbeck disease is caused by mutations in the genes that code CUBN or AMN which are parts of the B12-IF receptor/transporter. Symptoms are highly heterogenous and affected individuals also often experience proteinuria. Transcobalamin deficiency typically presents very early in infancy with growth failure, megaloblastic anemia, pancytopenia, vomiting, diarrhea, recurrent infections, hypotonia, global developmental delay

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[42,43]. There are also a number of very rare congenital abnormalities of B12 metabolism and utilization but these are all very rare [43].

7. Why Do Infants Develop Vitamin B12 Deficiency?

While vitamin B12 deficiency during infancy is not unusual in newly industrialized and developing countries [44], reports of vitamin B12 deficiency during infancy are uncommon in the industrialized areas of Western and Northern Europe, North America, Australia and New Zealand where nearly all of the reported cases are in exclusively breastfed infants of mothers consuming vegetarian or vegan diets and/or suffering from unrecognized pernicious anemia [10,13]. The apparent susceptibility of breast fed infants to becoming vitamin B12 deficient suggests at least some of these infants might start out with diminished vitamin B12 stores raising questions about maternal transport to the fetus during pregnancy.

Vitamin B12 is concentrated by the placenta; fetal vitamin B12 blood levels are two to three times those of mother's. Maternal holo-TC is actively transported across the placenta via receptor-mediated endocytosis. Maternal HCY and MMA levels rise during the latter half of pregnancy suggesting maternal vitamin B12 depletion and the increases in HCY and MMA are significantly lower in women taking B12 supplements [45].

Neonatal vitamin B12 status at birth is largely determined by mother's vitamin B12 status during pregnancy. During each trimester, fetal vitamin B12 levels correlate with maternal vitamin B12 status and maternal homocysteine levels during the second and third trimesters are inversely associated with neurocognitive outcomes at 30 months of age [10]**.** Maternal vitamin B12 deficiency during pregnancy has been associated with an increased risk of maternal obesity, maternal insulin resistance and gestational diabetes, pre-eclampsia, neural tube defects, intrauterine growth restriction, low birth weight and preterm delivery [45-47].

Vitamin B12 insufficiency during pregnancy is common even in non-vegetarian populations [48,49]. Five percent of Canadian women of childbearing age are vitamin B12 deficient and 20% have marginal stores [50]. Moreover, at least 5% of women of childbearing age suffer from autoimmune thyroid disease [51], and up to a third of these women ultimately develop autoimmune pernicious anemia, most of whom are asymptomatic [52,53].

Virtually all of the vitamin B12 in breast milk is bound to HC; human milk contains roughly 100 times more HC than plasma [28]. Vitamin B12 concentrations in breast milk vary widely and are highly correlated with maternal serum vitamin B12 levels; concentrations are diminished in the breast milk of mothers with deficient or marginal vitamin B12 status. Vitamin B12 concentrations in breast milk are highest early in infancy and then gradually decline peaking at approximately 12 weeks gestation and dropping by half by 24 weeks [4,15,28,45]. In contrast, all commercially prepared infant formulas are enriched with B12, and higher levels of vitamin B12 and lower levels of HCY and MMA are seen in formula-fed infants than in breastfed infants.

While there remains some debate as to how to define vitamin B12 deficiency in infants, the emerging consensus in the literature defines it as a total vitamin B12 level of less than 148 and/or a plasma MMA of > 0.3 and/or a plasma HCY level of > 6.5 [54-56].

Ljungblad and colleagues examined the prevalence of vitamin B12 deficiency in 250 healthy Norwegian infants at between four and 6 months of age. 97% of the mothers did not have any dietary restrictions or precautions and only one mother was vegan. Roughly 10% of the mothers received supplemental vitamin B12 during their pregnancy, 13 took high dose oral vitamin B12 and eight were given vitamin B12 injections. None of their infants had low vitamin B12 levels or high HCY levels shortly after birth. At 20 $\pm$ 5 weeks of age all of the infants had normal folate levels, 46% had HCY levels > 8 umol/L, 19% had HCY levels > 10 umol/L, 4% had vitamin B12 levels < 150 pmol/L and 24% had vitamin B12 levels < 200 or HCY levels >10. Exclusive breast-feeding was the only predictor of an infant having a HCY umol/L > 8 with an odds ratio of 2.93. The authors noted significant associations between elevated HCY levels and infant tremors, excessive infant sleep, and scores on the fine motor subscale of the Ages and Stages Questionnaire [57].

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In an analysis of 5000 serum samples from the Norwegian newborn screening program, when vitamin B12 deficiency was defined as the combination of HCY >10 and vitamin B12 level < 200, approximately five percent of all infants were vitamin B12 deficient. These are very conservative criteria for newborn vitamin B12 deficiency and almost certainly underestimate the true prevalence [58].

In another study, 107 healthy term infants were randomized to receive a 400 ug IM injection of vitamin B12 or no injection at six weeks of age. The control and intervention groups were well matched. 72% of the infants in the control group were exclusively breast-fed as compared to 89% in the group who got vitamin B12. Baseline folate, vitamin B12, HCY and MMA levels were the same in the two groups. As would be expected, at four months, the supplemented infants had significantly higher vitamin B12 levels than did the controls. The group that got vitamin B12 had a substantial reduction in median plasma HCY from 7.46 to 4.57 whereas levels did not change in the controls remaining above 6.5, and MMA levels fell from 0.58 to 0.20 in the treated group, while levels did not change in the control group remaining above 0.3. At four months of age, 35 of the 53 control infants had plasma HCY levels above 6.5 which is the 97th percentile whereas none of the supplemented infants did [56].

79 or 75% of 105 infants less than eight months of age referred to the Pediatric Outpatient Clinic in Bergen, Norway due to feeding difficulties, subtle neurologic symptoms, and/or mild delays in motor development had biochemical evidence of vitamin B12 deficiency. These 79 infants were randomized to get a single 400 ug shot of vitamin B12 or a placebo injection and they were reassessed one month later. There were no significant differences in clinical characteristics between the treatment and placebo groups at enrollment. The mean age at enrollment was four months, and mother's vitamin B12 level was the single best predictor of the infant's vitamin B12 status. As expected, as compared to the infants who got the placebo injection, the infants who got vitamin B12 injections had significant increases in their serum vitamin B12 levels, and their HCY and MMA levels fell significantly whereas none of these changed in the placebo group. At inclusion, 19% of infants scored below the 10th percentile on the Alberta Infants Motor Scale (AIMS), and 71% scored below the 50th percentile. As compared to the infants treated with placebo, the infants who received a vitamin B12 injection demonstrated significantly greater improvement in motor functioning and feeding difficulties and frequency of regurgitation over the month [59].

In a prospective study of 80 healthy infants with birthweights between 2000 and 3000 g, infants were assessed at six weeks, four months and six months. In each case, infant B12 status at 6 months of age was strongly associated with the duration of exclusive breast-feeding; that is the longer they were exclusively breast fed, the lower their vitamin B12 levels were and the higher their HCY and MMA levels were. The researchers assessed developmental status using the AIMS and the Ages and Stages Questionnaire (ASQ). Formula fed infants had significantly higher median AIMS scores than breastfed infants and in the breastfed group two thirds of infants scored below the 50th percentile and 21% below the 10th percentile. The higher the level of MMA or HCY, the smaller the change in AIMS scores over time and as such, the duration of exclusive breastfeeding was a significant negative predictor of positive changes of AIMS scores. At 6 months, 45% of these infants had plasma HCY levels above the 98th percentile of 6.5. 32 infants were elevated HCY levels were randomized to get a single vitamin B12 injection or a sham injection. As expected, changes in vitamin B12, HCY and MMA levels from inclusion to follow-up were significantly greater in the treatment group than the placebo group. AIMS and ASQ gross motor scores increased in both groups over the next month however, the increases for both scores were significantly higher for the group that got a vitamin B12 injection than in the placebo group [60].

Together, these studies strongly suggest there is a link between prolonged exclusive breast feeding and vitamin B12 deficiency in healthy infants challenging many current breastfeeding recommendations as exclusively breastfed infants appear to be more likely to develop subclinical vitamin B12 deficiency which may affect their development as well as other long-term health outcomes.

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8. Conclusions

Vitamin B12 deficiency in infants is much more common than many people realize, particularly in exclusively breast-fed infants. Clinicians should think about the possibility of vitamin B12 deficiency in any breast-fed infant/young child with poor growth and/or neurologic symptoms, developmental delay, or feeding difficulties such as apathy, lethargy or irritability, motor delays or unusual movements or refusal to transition to the bottle or eat complementary foods particularly if the mother is a vegetarian or vegan and/or she suffers from hypothyroidism.

Given the potential impact of even mild vitamin B12 insufficiency on infant growth and development and the lack of evidence of any toxic effects of vitamin B12 supplementation/therapy, it seems reasonable to encourage all pregnant women to take vitamin B12 supplements particularly if they consume a vegan or vegetarian diet, and/or suffer from hypothyroidism. It also seems reasonable to supplement all breast fed infants with vitamin B12 and perhaps formula fed infants who are being treated chronically with proton pump inhibitors.

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