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Vitamin B12: An Intergenerational Story

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Abstract

Vitamin B12 is a fascinating nutrient in that it is made by microbes but is essential for human metabolism. Humans can get it only from animal origin foods. Dietary deficiency rather than an absorption defect (Pernicious anemia, intrinsic factor defect) is the commonest cause of deficiency in the world, contributed by cultural and economic imperatives. Indians have a large prevalence of subclinical B12 deficiency due to vegetarianism. Birth cohort with long-term serial follow-up (Pune Maternal Nutrition Study) has helped reveal the life-course evolution of B12 deficiency: genetics, transplacental and lactational transfer from the mother, influence of family environment, rapid childhood and adolescent growth, and low consumption of milk all made a contribution. A novel association of low maternal B12 status was with fetal growth restriction and increased risk factors of diabetes in the baby. After demonstrating adequate absorption of small (2 µg) dose of vitamin B12, and a noticeable improvement of metabolic parameters in a pilot trial, we planned a supplementation trial in adolescents to improve outcomes in their babies (a primordial prevention called Pune Rural Intervention in the Young Adolescent). The results are awaited. The long-term effects in the babies born in the trial will contribute to a better understanding of the Developmental Origins of Health and Disease.

Vitamin B12 is arguably the most fascinating of the nutrients. It is synthesized only by prokaryotic microbes and thus contributed to the metabolism of the living from early days of life on earth [1]. Its synthesis is complex and involves around 30 steps. Not all microbes are equipped to synthesize it and some are dependent

Table 1. Pernicious anemia versus nutritional deficiency

Characteristics	Pernicious anaemia	Nutrient deficiency of Vitamin B12
Eetiology	Genetic/autoimmunity Lack of intrinsic factor Defective absorption	Low dietary intake of Vitamin-B12, absorption normal Vegans/vegetarians Low socioeconomic status
Associated conditions	Autoimmune disorders (skin, thyroid, etc.)	Other nutritional deficiencies (Iron, folate, etc.)
Severity	Usually severe and symptomatic (Anemia, neurological and cognitive)	Usually less severe and asymptomatic
Treatment	Injectable, sublingual or high dose oral B12	Small oral doses effective

on an external supply. Vitamin B12-producing bacteria symbiont in some of the algae are an additional source of the vitamin [2]. Animals eat bacteria and their products and store vitamin B12 in their tissues; it enters the human food cycle when products of animal origin are eaten by the humans. The common nutritional source of the vitamin for humans is thus meat, liver, eggs, fish, and milk. Those who do not eat animal origin foods (due to ethical, religious, cultural, and socioeconomic reasons) are thus at a high risk of becoming deficient. Long-term use of drugs like metformin (for type 2 diabetes) and proton pump inhibitors (for acid peptic disease) and *H. pylori* infection also contribute to vitamin B12 deficiency by interfering different aspects of B12 absorption or metabolism.

Conventional Wisdom: Pernicious Anemia versus Nutrient Deficiency (Table 1)

The textbook description of vitamin B12 deficiency is usually based on the findings in cases of Pernicious Anemia, which is a genetically driven autoimmune condition [3]. It involves immune damage to the gastric mucosal parietal cells that synthesize the intrinsic factor. Lack of intrinsic factor stops vitamin B12 absorption from the gut and results in severe B12 deficiency. In addition to the direct effects of vitamin B12 deficiency (megaloblastic erythropoiesis manifesting as macrocytic anemia and subacute combined degeneration affecting spinal cord and peripheral nerves, dementia, etc.), there may be manifestations of autoimmune damage to other organs: hypothyroidism, type 1 diabetes, vitiligo, and so on. In the absence of intrinsic factor mechanism, treatment involves parenteral injections or high-dose oral (relying on absorption of vitamin

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B12 by diffusion which is <1% of the dose) or sublingual (bypassing gastric-intestinal mechanisms) treatment. There is little information on lowest doses that are effective, and intuitively physicians consider large dose B12 treatment as safe.

There is now increasing recognition that a large proportion of vitamin B12 deficiency in the world is not related to intrinsic factor defect but to smaller intake of dietary vitamin. Vitamin B12 is present only in animal origin foods and some algae that harbor symbiotic B12-producing microbes. Plants do not have vitamin B12 as they do not require it. Reasons for vegetarianism and veganism differ in different populations. In a country like India, it is based on religious and cultural traditions (Jain, Hindu, and Buddha religions support vegetarianism), and it owes its origin to Samrat Ashoka (500 BC) who preached "ahimsa" (non-violence) since he became Buddha's disciple. This suggests that vitamin B12 deficiency in these populations is multigenerational. In many parts of the world, poor socioeconomic conditions prevent purchase of animal origin foods and milk because they are expensive [4, 5].

Folate versus B12

It is also interesting to compare vitamin B12 and folate, the 2 vitamins with many actions in common because they both act on the same enzyme (methionine synthase which generates 1-C [methyl] groups which are crucial for multiple metabolic processes). Folate is of plant origin and, therefore, present in vegetarian foods. However, folate-rich vegetables and fruits can be expensive. Vitamin B12 has an additional influence on fatty acid and energy metabolism because it is also a co-factor for methyl-malonyl mutase enzyme which helps provide succinic acid and fatty acids for mitochondrial metabolism.

Folic Acid versus Folate

Naturally occurring folates are pteroyl polyglutamates, in reduced form and are damaged by cooking and exposure. On the other hand, the supplemental form folic acid is a synthetic monoglutamate in oxidized form that needs to be reduced in liver to active form. It is also heat stable, more bioavailable, and may circulate in free form in the absence of liver metabolism. Folic acid has a higher affinity for the folate receptor and could overstimulate the receptor or competitively inhibit natural folates from interacting with the receptor, with consequent ill effects.

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B12 Studies in India

Our interest in vitamin B12 started when we serendipitously investigated homocysteine metabolism in our diabetic patients and nondiabetic controls in early 1990 in collaboration with Dr. Helga Refsum who visited Pune as a Rotary exchange fellow! She helped us make the measurements, and it was a surprise to find that 40-year-old Indians had twice the concentrations compared to Europeans. Interestingly, the difference was explained by high prevalence of vitamin B12 deficiency rather than folate deficiency, supported by elevated MMA concentrations. There was considerable resistance to acceptance of these data, despite previous publications [6, 7]. We investigated vitamin B12 status in urban and rural men in Pune [8], which confirmed the high prevalence of vitamin B12 deficiency and its strong association with hyperhomocysteinemia. This study revealed an interesting association: vitamin B12 deficiency was twice as common in the urban middle-class men compared to the slum dwellers and the rural men. This difference could be partly explained by the higher prevalence of vegetarianism, better education and hygiene, and higher obesity in the middle class. These associations were understandable because ultimate source of vitamin B12 in nature is microbes.

Equipped with this knowledge and possible role of 1-C metabolism in fetal growth and development, we investigated vitamin B12 status in pregnant women in the Pune Maternal Nutrition Study. This is a preconception birth cohort to investigate the role of maternal nutrition in fetal growth and its life-course risk of noncommunicable diseases. The mothers were young, short, and thin (21 years, 1.52 m, 18.1 kg/m^2) and ate mostly vegetarian diet of 1,800 cals/day (72% calories carbohydrates), 45 g/day proteins. The babies born were 2.7 kg and thin (ponderal index 24.1 kg/m^3). Interestingly, when compared with English babies (3.5 kg, 27.5 kg/m^3), they had thicker skinfolds for a given body weight, thus revealing the "thin-fat" phenotype of Indian babies. The food items that were strongly related to baby's size were those rich in micronutrients (green leafy vegetables, fruits, and milk). Further investigations revealed that maternal circulating folate concentrations directly associated with neonatal size, while homocysteine concentrations were inversely related. There was little folate deficiency in these mothers. Two of 3 mothers had low vitamin B12, 1/3rd had high homocysteine and 9/10th high MMA concentrations. High homocysteine concentrations predicted small for age indicating that deranged 1-C metabolism is associated with growth disturbance [9, 10].

When these children were followed-up, they maintained their thin-fat phenotype in relation to English babies into childhood [9]. We found that high maternal folate status during pregnancy predicted higher adiposity and higher insulin resistance in the children at 6 years of age (Fig. 1). Insulin resistance was the high-

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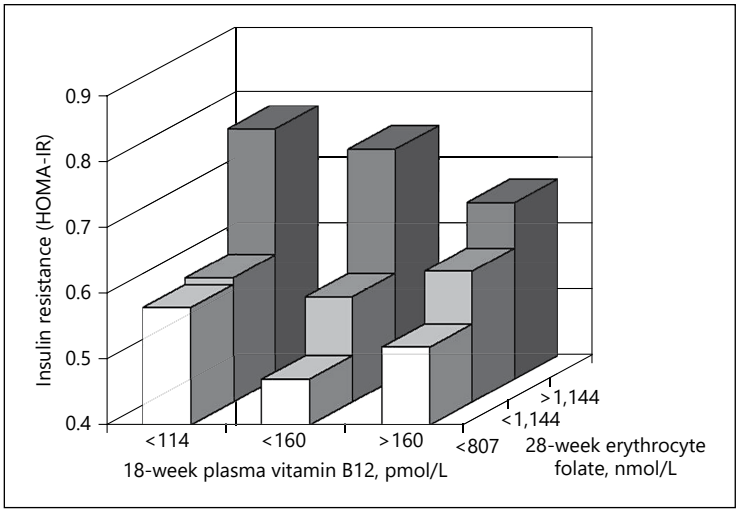

Fig. 1. HOMA-IR in the children in relation to maternal vitamin B12 (18 weeks) and red cell folate levels (28 weeks). Low maternal vitamin B12 (18 weeks) and high erythrocyte folate (28 weeks) predict high insulin resistance in the child at 6 years of age. Combined with the finding of higher adiposity in the children of mothers with high folate status suggests that maternal imbalance between these 2 vitamins during pregnancy may increase the risk of diabetes in the offspring. HOMA-IR, homeostasis model assessment of insulin resistance.

est in children of mothers who had low B12 but high folate status in pregnancy. Thus, an imbalance between vitamin B12 and folate status and the associated deranged 1-C metabolism appear to influence fetal growth, body composition, and future risk of diabetes ("programming") [10]. The high rates of vitamin B12 deficiency in this population favor a public health approach to improve the nutritional deficiency and influence intergenerational health in the population. Our further research therefore, included a formal test of vitamin B12 absorption and a pilot intervention with vitamin B12 to understand the size of the effect.

Vitamin B12 has the most amazing absorption and transport pathway, unmatched by any other nutrient (Fig. 2) [11]. In addition to that obtained from contaminant bacteria in water and food, dietary vitamin B12 is entirely from animal origin foods that is protein bound. This is dissociated from the protein in the stomach by the action of hydrochloric acid and binds to haptocorrin secreted in the saliva. This complex is further dissociated by the pancreatic and intestinal digestion, and the liberated vitamin B12 combines with intrinsic factor secreted by the parietal cells lining the stomach. This complex travels through the small intestine to the terminal ileum that has receptors for intrinsic factor (cubam) and is internalized in the enterocytes. It is transported across the intestinal wall by complex mechanisms and delivered to the transporting proteins in the circulation (haptocorrin and transcobalamin). The complex of vitamin B12

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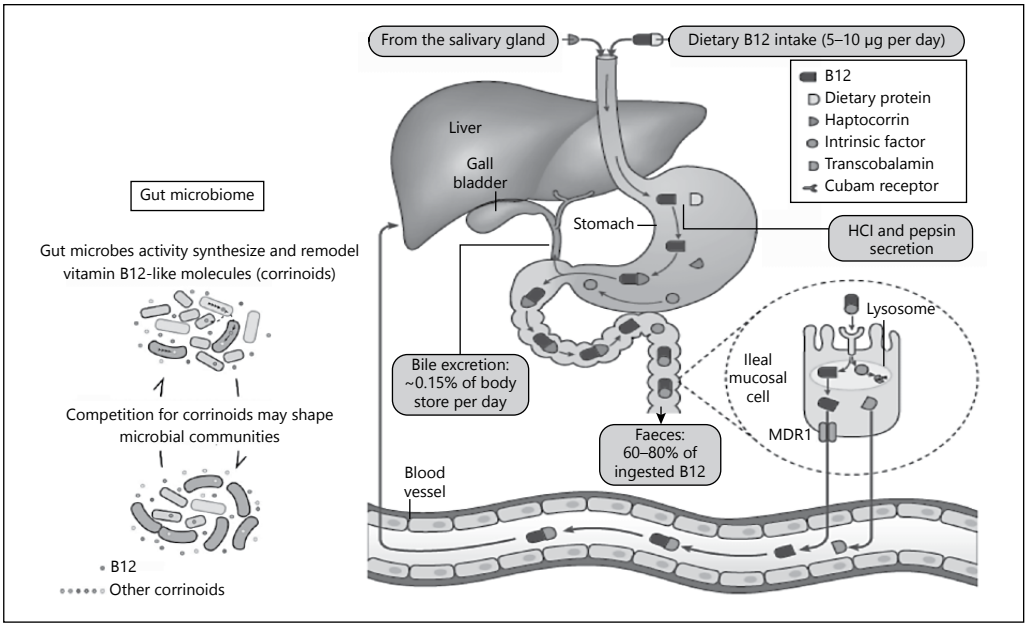

Fig. 2. Vitamin-B12 absorption. Vitamin B12 (B12) is mainly derived from animal sources. Following intake, it is released from its food carrier proteins by proteolysis in the acidic environment of the stomach, where it binds to haptocorrin. Haptocorrin is produced by the salivary glands and protects B12 from acid degradation. Degradation of haptocorrin and the pH change in the duodenum favour B12 binding to gastric intrinsic factor, which is produced by gastric parietal cells. The intrinsic factor-B12 complex binds to the cubam receptor (consisting of cubilin and amnionless). This receptor mediates the uptake of the intrinsic factor-B12 complex in the enterocytes of the distal ileum via receptor-mediated endocytosis. After lysosomal release, B12 exits via the basolateral membrane of the enterocyte, facilitated by multidrug resistance protein 1 (MDR1), and binds to transcobalamin, the blood carrier of B12 that is responsible for cellular delivery of B12. The majority of B12 is stored in the liver; some B12 is excreted in bile and undergoes enterohepatic circulation. A new consideration in the process is the role of the microbiome in B12 status of the humans. Microbes can both produce and utilize B12, and the composition of microbiome in the gut may influence host B12 status.

and transcobalamin II is called holo-transcobalamin and is the active form of circulating B12 that is taken up by receptors on the nucleated cells of the body. The complex with haptocorrin forms –70% of the circulating vitamin and is delivered to the liver where it is stored. Given the involvement of so many proteins (carriers) in the pathway of vitamin B12 absorption and transport, we would expect an association between the vitamin B12 status and genetics of the proteins that are involved. We performed a GWAS of vitamin B12 deficiency in our population and mostly found similar genetic associations as in the Europeans [12]. The genes involved in absorption pathway (TCN1, Cubilin, multidrug resistance protein 1, fucosyl transferase 2 [FUT2], and 6 [FUT6]) and transport

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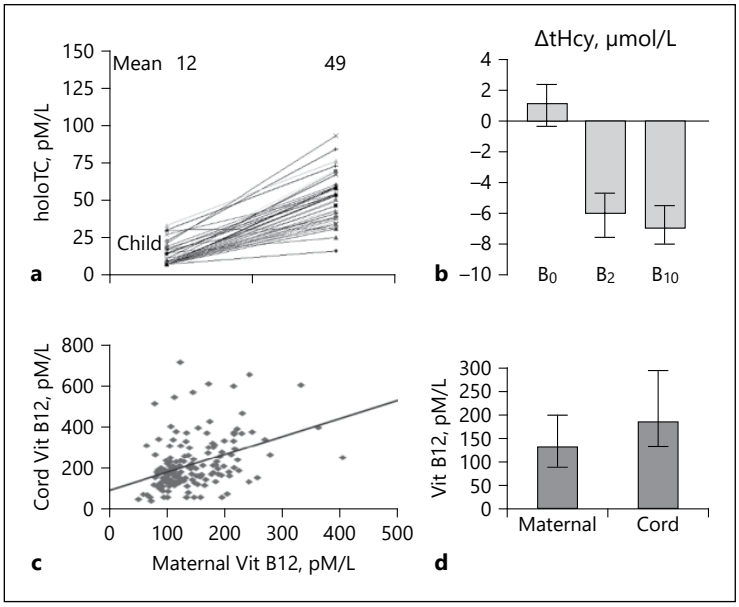

Fig. 3. Aspects of vitamin B12 metabolism in Indian children. **a** The rise in plasma holo-transcobalamin concentrations after 3 doses of 2 μg of vitamin B12 in children, suggestive of good absorption of oral low dose vitamin B12. **b** The substantial fall in plasma homocysteine concentrations in rural Indians after 1-year treatment with 2 and 10 μg/day. There was no significant difference in the 2 doses. **c** The direct association between maternal and cord blood B12 concentrations. **d** Stresses the point that cord blood concentrations are higher than those in the mother, suggesting active transport and storage.

pathway (TCN II) were associated. The strongest association worldwide is with a set of genes called FUT that are involved in posttranslational modification of proteins (fucosylation), which is an important requirement for "secretory" status and has been implicated in the gut-microbe interaction, which has substantial implications for the function of microbes in the intestinal wall. We found a novel SNP in FUT2 gene, and its specific role in B12 deficiency in Indians will be of interest. It will also be of interest to see if genetics will help tease out the role of maternal B12 deficiency in fetal programming of body composition and other systems that might increase future risk of diabetes.

We tested vitamin B12 absorption using the Danish protocol (Cobasorb) [13] (Fig. 3a). This involves 3 doses of oral vitamin B12 6 h apart and measuring circulating holo-TC concentration before and after. We used 10 μg tablet (as per protocol) as well as 2 μg and demonstrated that both doses were absorbed very satisfactorily. We then performed a 1-year pilot trial to test 0, 2, and 10 μg per day of vitamin B12 along with 0 or 200 μg per day of folic acid in a factorial design in 100 families (children and parents) [14] (Fig. 3b). The results showed that

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the B12 status improved after supplementation, 85% of the effect at 1 year was seen within 4 months. There was a 5 mmol/L decrease in circulating tHcy concentrations. Folic acid by itself had very little effect, and at these doses, we did not observe any side effects of either vitamin.

Daily requirements of vitamin B12 are around 2 μg, the ICMR in 2009 had suggested a value of 1 μg [15] (Narasinga Rao [15] 2010) which is lower than the NIH recommendation of 2.4 μg [16] (O'leary and Samman [16] 2010). We made a pragmatic decision to use 2 μg/day, avoiding larger doses because there could be metabolic adaptations in this population due to multigenerational nutrient deficiency and, therefore, protect against possible detrimental effects. Also, large doses would be unsustainable in public health because of the cost.

Our data from other studies showed a significant direct correlation between maternal and cord blood concentrations of vitamin B12, folate, and homocysteine [17] (Fig. 3c). The cord blood concentrations were higher than the maternal concentrations, indicating active transplacental transport and storage in the fetus (Fig. 3d). Interestingly, maternal vitamin B12 concentrations in pregnancy were still a significant determinant of child's B12 concentrations at 2 years [18, 19] and even 6 years of age. In addition, continued breast feeding at 2 years of age predicted lower and consumption of animal milk (cow or buffalo) a higher B12 status. These findings provided further support to improving maternal B12 status before, during and after pregnancy to benefit the child for its growth and development in utero as well as infancy. Equipped with all these results, we planned a vitamin B12 trial in adolescents in the Pune cohort to improve their nutrient status from before marriage and pregnancy with a view to improve the fetal growth and reduce the programming of future diabetes [20]. This would be a very substantial undertaking of time, effort, and money and involved cooperation from the participants. The final support for our decision came from the analysis (Mendelian Randomization) [9] of the maternal homocysteine-neonatal size association using maternal MTHFR C677T polymorphism as the genetic marker. The maternal T allele (rs1801133) was associated with elevated homocysteine levels and lower offspring birth weight (61 g, $p = 0.019$).

One of the interesting considerations in our research is the life-course trajectory of vitamin B12 deficiency in Indians and the possible contributions of various determinants. We have a unique opportunity to make such observations from the prospective birth cohorts in Pune (PMNS and the IAEA-B12 cohorts). The PMNS cohort was set up between 1993 and 1996 by enrolling the parents (F0), studying the pregnancies in F0 mothers, and serially following the F1 children as well as the parents for last 25 years. Interestingly, the F2 generation is now being born (many in the Pune Rural Intervention in the Young Adolescent trial), so we will be able to continue our intergenerational life-course story into the 3rd generation. In this ar-

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ticle, we will discuss only broad observations because much of these data are being prepared for publication. On the other hand, the IAEA-B12 cohort has provided crucial information on maternal–offspring nutritional associations in early life.

In both the PMNS and the IAEA-B12 cohorts, we found a progressive fall in the circulating levels of B12 in the mother with advancing pregnancy. This has been described before and ascribed to fall in levels of haptocorrin that carries majority of the vitamin in circulation; levels of holo-TC remain fairly constant across gestation. There is a concomitant fall in circulating levels of homocysteine and albumin, suggesting a contribution of volume expansion and dilution of vascular compartment to the fall in the levels of different metabolites. Mother is the only source of vitamin B12 for the baby, and falling levels would also reflect active transfer across the placenta. Mother's vitamin B12 levels increased after delivery and then remained fairly constant in later years, as did in fathers. On the other hand, vitamin B12 concentrations progressively fell in the children (F1 generation) from childhood to early adulthood, accompanied by a progressive increase in homocysteine concentrations and the volume (MCV) of the red blood cells. Children have higher prevalence of vitamin B12 deficiency and hyperhomocysteinemia in late adolescence compared to their parents. The vitamin B12 status of the child is influenced by its genetics, maternal transfer during pregnancy and lactation, family environment (diet, hygiene, etc.), and growth during childhood and adolescence in addition to child's own dietary intake (especially of milk). This analysis helps to view vitamin B12 status in the "rainbow" framework in epidemiology, which highlights the interaction between individual's biology and "environmental" influences from family, community, and national and international ecosystems (Fig. 4). Religion, culture, and sociopolitical factors influence the phenotype through such ecosystems. Our model also resonates with the Developmental Origins of Health and Disease concept of evolution of health and disease in a life-course framework, with possible intergenerational and early life windows of opportunity for influencing outcomes (Fig. 5). On this background, it is obvious that cross-sectional associations, usually in the adults, will necessarily miss capturing the windows of opportunity for prevention.

Based on the findings in our various studies, we launched the Pune Rural Intervention in the Young Adolescent trial in 2012 under an Indo-UK research collaboration [21]. It involves the adolescent participants of the PMNS, starting at 17 years of age. We excluded those with very low vitamin B12 levels (<100 pM) in this placebo-controlled trial for ethical imperative and treated them with vitamin B12. The remaining participants were randomized to 2 μg B12/day as a capsule, with or without multi-micronutrients and the third arm is a placebo. All groups receive iron and folic acid tablets as per Government of India stan-

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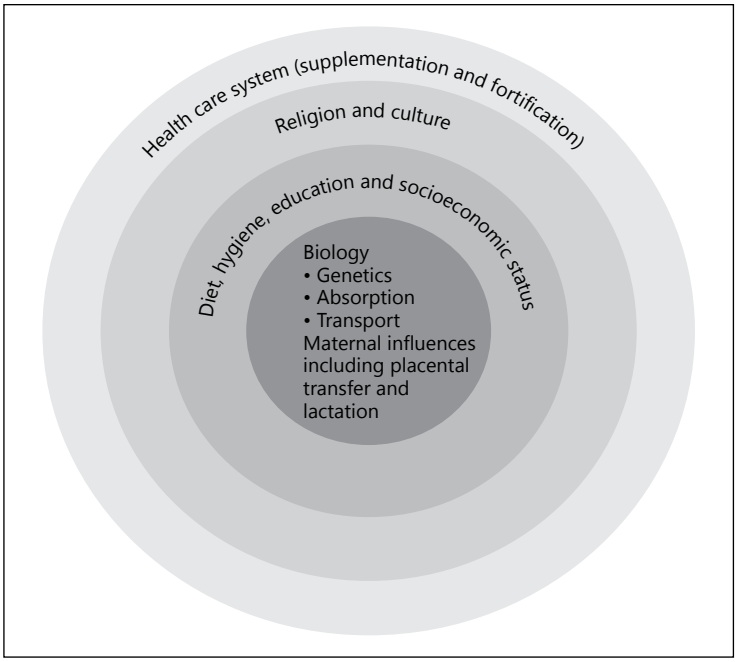

Fig. 4. Rainbow concept in the Epidemiology of vitamin B12 deficiency. Important factors that affect the demand and supply of vitamin B12 (B12) at the individual and population levels and throughout the patient's lifetime are highlighted. It is striking that the mother exerts a triple influence on the B12 status of the offspring: genetics, intrauterine and lactational B12 transfer, and postnatal family environment (socioeconomic status, hygiene, diet, religion, and culture). The father exerts a double influence: genetic and family environment. A female child will continue to propagate the direct maternal influences into the next generation. The suspected role of epigenetics in all 3 processes awaits elucidation. The nutritional status of the population and, therefore, the public health measures to improve it depend on the socioeconomic factors, religious and cultural practices, and the public health policies of the local, national, and international regulatory systems. Although targeting the B12 deficiency at an individual level is needed, more widespread interventions targeting the population are needed to influence prevalence of B12 deficiency in the population.

dards of practice. The ultimate outcome will be the diabetes risk in the children, but an interim outcome is the birth size and cord blood concentrations of vitamin B12 and multi-OMICs (DNA methylation, transcriptome, metabolome, proteome) in the cord blood. In addition, there will be a microbiome study of serial samples collected in the mothers and the children. The trial is ongoing, and due to socio-economic development and educational aspirations of the rural young, the rate of marriages is lower than predicted. Thus, at the end of 5 years of intervention, we stopped the trial in boys (only 21 marriages, 7 deliveries) but continued in the girls (over 150 marriages, 130 deliveries, 100 more expected in next few years). Even though we are blinded to the intervention groups,

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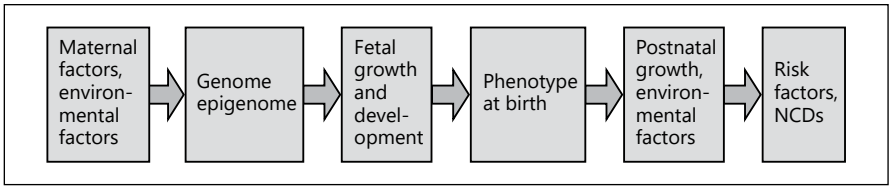

Fig. 5. Developmental Origins of Health and Disease describes the life-time evolution of health and disease susceptibility in an individual. On the background of the inherited "fixed" DNA sequence, chemical modifications in the genome regulate gene expression and therefore the phenotype of the individual. The most critical windows are in early life but continue to operate throughout the life (life-course model), manifesting in health and disease susceptibility.

we already have interesting observations on intergenerational changes in this rural population that is transitioning rapidly due to social and economic development. There is an increase in the height, BMI, and glucose and lipid concentrations of the pregnant daughters (F1 generation) compared to those in their mothers (F0), and their babies (F2) are bigger than their own size at birth.

Finally, we must discuss the exciting possibility that a part of vitamin B12 status of humans may be linked to the microbiome. Most of the thinking in this area is influenced by investigations of the gut (stool) microbiome. Only some microbes can synthesize vitamin B12 but not all of them [2]. Those who cannot, depend on external supply. Although classical thinking envisages bacterial colonization only in the distal colon, there is evidence for the presence of bacteria throughout the tract. A definite association of vitamin B12 deficiency is with *Helicobacter pylori* infection in the stomach [22]. This may be due to chronic gastritis that affects the production of acid and intrinsic factor. Stool microbiome studies have mostly shown an association between over population of vitamin B12 requiring bacteria rather than a paucity of B12-producing bacteria [2]. Some probiotics have caused a small increase in vitamin B12 status. Further studies are needed to expand the microbiome story for vitamin B12 nutrition, including intergenerational transfer from the mother to the baby. It will be important to study these issues in Indians who have a different microbiome compared to Europeans.

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Disclosure Statement

The author declares no conflicts of interest in relation to this article.

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