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Multi-pronged strategy to combat vitamin D deficiency disorders in India

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Introduction

Vitamin D status has a profound effect on the growth and development of children and has major implications for adult bone health. Optimal calcium and vitamin D nutrition are essential for bone mineral health during childhood and adolescence, lead to adequate peak bone mass, and act as safeguards against osteoporosis and susceptibility to fractures among the elderly. In view of the above, industrialized countries have made it a routine practice to fortify milk and other food products with vitamin D. In contrast, food fortification with vitamin D was never considered in India, as it is situated between the latitudes of 8.4^0 and 37.6^{0}N, under the assumption that adequate sunlight needed for vitamin D synthesis in the skin is available throughout the year. However, literature over the last 15 years or so points to widespread prevalence of vitamin D deficiency with serum levels < 20 ng/ml across all ages and population groups-pregnant women, newborns, children and adolescents, young adults, and older men and women. The findings of a review of the global vitamin D status by the International Osteoporosis Foundation in 2009 underscores the fact that South Asia may be one of the worst affected regions in the world[1,2].

At present there is no consensus regarding the levels of serum 25(OH)D that would provide maximum health benefits to the general population. The Expert Committee convened by the Institute of Medicine - USA in 2011, reviewed the available literature on Calcium absorption, bone mineral density (BMD), rickets and osteomalacia. The Committee reported that a serum level of 30ng/ml bestowed no additional benefits on bone health as compared to a level of 20ng/ml (the level recommended by the Endocrine Society Task Force guidelines). In fact, the dose-response relationship between serum 25(OH)D and bone mineral parameters showed that 97.5% of the general population are assured of sound bone health with serum 25(OH)D levels of 20ng/ml[3]. Data from India indicate that the peak bone density of active healthy Indian men with adequate nutrition and no constraints to bone mineralization was comparable to that reported in white US men, with the mean serum levels of 25(OH)D ranging between 22.5 to 93.5 nmol/L[4].

Most studies in apparently healthy Asian Indians have revealed lower BMD and higher prevalence of osteoporosis than those reported in white Caucasians[5,6,7]. A recent large-scale study on healthy Indians above 50 years of age revealed a significantly higher prevalence of osteoporosis (35.1%, F-42.5%, M-24.8%) in comparison to US Caucasians (F-18%, M-6%), Europeans (F-21%, M-6%), Taiwanis (F-11.4%, M-1.6%) and SriLankans (F/M- 5.8%) but similar to the Chinese (F-50.1%, M-22.5%)[8].

The cause-effect association between deficiency of vitamin D and bone diseases such as childhood rickets and adult osteomalacia has been well-established. Recently, however, interest has been generated with regard to the possible association between vitamin D deficiency and extra-skeletal clinical manifestations which could have significant consequences to public health. A hypothesis emerged from observations in countries such as Australia that vitamin D deficiency is associated with an increased incidence of systemic diseases and/or mortality within these countries, the use of sun screen with a high protection factor for prevention of skin cancer led to low levels of vitamin D in the population[9]. The review of available epidemiological findings and those from experimental studies did strengthen the concept of possible association between low serum vitamin D levels and several extra-osseous diseases such as cancers, diabetes mellitus, autoimmune disorders and cardiovascular diseases. Systematic reviews of observational studies suggested the possibility that hypovitaminosis D increases the incidence of mortality from extra-osseous diseases; however, in many cases, the results were inconsistent or even conflicting.

It is important to remember that if confounding variables are not

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adequately controlled for, data from observational studies can lead to misinterpretation. For instance, body fat accumulation, sedentary lifestyle, skin color, and nutritional status, can simultaneously be, causes of vitamin D deficiency as well as risk factors for cancer, cardiovascular disease, diabetes, and low immunity; that is to say, the association between vitamin D deficiency and these non-communicable diseases may not be causal. There is also the possibility of a reverse bias; chronic diseases can result in the patient remaining at home, having low sun exposure, low physical activity, anorexia, and worsening of diet and nutritional status; all these will also lead to decreased levels of circulating 25(OH)D[3]. Currently, scientific evidence for a cause-effect association between low serum vitamin D and extra-skeletal disorders is not robust enough to draw firm conclusions[10].

Vitamin D deficiency disorders such as rickets and osteomalacia continue to exist in a significant proportion of the Indian population. Several reasons have been proposed to explain the high prevalence of vitamin D deficiency in Indians. These include:

- **Insufficient exposure to sunlight, especially in urban Indians:** Culturally, Indians avoid sunlight for fear of skin darkening or just because of the heat. This sun-fleeing behavior contrasts with the sun-seeking behaviour of Europeans or North Americans.

- **Clothing habits:** Traditionally, Indians, even when out in the sun, tend to keep their bodies well covered.

- **Skin pigmentation**: Melanin in the skin competes with 7-dehydrocholesterol for UV-B rays. Greater amounts of melanin in the skin reduces the efficiency of vitamin D synthesis. Pigmented skin requires a longer duration of sun exposure to synthesize equivalent amounts of vitamin D as compared to a white Caucasian skin. There are six types of skin based on degree of pigmentation and propensity to burn or tan. The lightest North European skin is classified as category I and African skin as category VI. Indians belong to skin categories IV and V.

- **Atmospheric pollution:** This may be playing a role in reducing the efficiency of vitamin D photosynthesis in Indian cities. The short UV-B wavelengths are scattered by atmospheric pollution. A high incidence of vitamin D deficiency rickets has been reported in toddlers living in areas of high atmospheric pollution in Delhi (latitude 28.35°N)[11].

- **Food habits and absence of food fortification**: Other than in fatty fish (widely consumed in Japan), very little vitamin D is available in the diet. Such fish are hardly consumed by Indians. Therefore, very little if any, vitamin D is available from dietary sources in India[12]. Unlike most Western countries, where milk, margarine, orange juice, and other commonly consumed food items are fortified with vitamin D, in India only hydrogenated fat and some vegetable oils are fortified with vitamin D. As a result, dietary intake of vitamin D is far below the RDA. The habitually low level of calcium intake in India further aggravates the problem.

Vitamin D status in adults

Several reports from across India in the last decade show a very high prevalence of hypovitaminosis D, ranging from 70% to 98% in adult Indians. In a series of studies from North India in cities including Delhi, Lucknow, and Srinagar, vitamin D deficiency has been shown to be very common. Winter levels of circulating 25(OH)D have been shown to be as low as 4–5 ng/mL in Delhi and Lucknow. Young adults, postmenopausal women, health professionals, and office workers have all been shown to be deficient in vitamin D. A recent study from Delhi in 1,346 Indians aged 50 years and above revealed vitamin D deficiency in 91.2% and vitamin D insufficiency in 6.8%, confirming the high prevalence of hypovitaminosis D[13].

Studies carried out in southern India on vitamin D status in rural and urban subjects residing in and around Tirupati in Andhra Pradesh also showed a wide prevalence of hypovitaminosis D despite adequate sunlight. Mean serum 25(OH)D levels were higher in South India as compared to the North, possibly because of a higher duration of cloud-free sunshine throughout the year (8-10 hours/day) in comparison to just 3.1 hours/day in the winters and 7 hours/day in summers in Delhi. Mean 25(OH)D levels in men in urban and rural areas were 18.54 ± 0.8 ng/mL and 23.73 ± 0.8 ng/mL, respectively. In women living in urban and rural areas, the 25(OH)D values were 15.5 ± 0.3 and 19 ± 0.8 ng/mL, respectively[14]. Thus, while vitamin D deficiency (serum 25(OH)D<20 ng/mL) is common across India, the mean levels are higher in Southern as compared to Northern India, better in rural than in urban regions, and better in summers than in winters.

Vitamin D status in pregnancy and lactation

Significant changes in maternal vitamin D and calcium metabolism occur during pregnancy to provide adequate calcium for foetal bone mineral accretion. Approximately, 25-30 gm of calcium is transferred to the foetal skeleton, most of it during the last trimester of pregnancy. Vitamin D deficiency in pregnant mothers results in foetal development taking place in a vitamin D-deficient environment. This is likely to have adverse effects in terms of foetal childhood bone development and innate immune function. Hypovitaminosis D and osteomalacia have been widely reported among pregnant South Asian women. However, till recently, most such studies were in Indians living in Europe. Vitamin D deficiency has also been noted in pregnant Muslim women in tropical countries. Here, the practice of wearing *purdah* (veil) could have played an important role. Data on vitamin D status in pregnant and lactating Indian women living in Delhi, Lucknow, and Mumbai reveal a very high prevalence of hypovitaminosis D (84– 93%)[15]. One study suggested that supplementation with vitamin D during pregnancy could result in better anthropometric indices in the newborns for up to 9 months of follow-up[16].

Vitamin D status in neonates and infants

Nutritional rickets due to vitamin D and/or calcium deficiency continues to exist as a major health problem in India. Studies from India have shown significant correlation of 25(OH)D levels between mother–infant pairs. Low vitamin D levels in mothers results in low vitamin D in cord blood and newborns. Exclusively breast fed infants continue to have low 25(OH)D levels. One study suggested that the risk of infants suffering from moderate to severe vitamin D deficiency was three to four times greater if their mothers had 25(OH)D levels below 10 ng/mL. It has also been shown that infants of mothers with hypovitaminosis D are at higher risk of hypocalcemic seizures[17,18].

A recent study in low-birth-weight, full-term infants re-evaluated the effect of weekly vitamin D supplementation upto 6 months on mortality, morbidity, and growth. It was observed that vitamin D supplementation resulted in a significant increase in SD scores for weight, length, and arm circumference and decreased the proportion of children with stunted growth[16].

Vitamin D status in Indian children

Approximately, 40-50% of total skeletal mass is accumulated during childhood and adolescence. Studies show that 60-80% of the variability in bone mass is due to genetic factors, with nutrition, lifestyle, physical activity, and hormonal factors accounting for the rest. If during this period, of childhood and adolescence, interventions to improve calcium and vitamin D status through non-pharmacologic strategies are adopted, the impact on peak bone mass will be maximal. Severe vitamin D deficiency, usually associated with 25(OH)D levels <5.0 ng/mL or <12.5 nmol/L, results in rickets and osteomalacia. However, these clinically overt cases of vitamin D deficiency represent only the tip of the iceberg of vitamin D insufficiency. A majority of children with biochemical hypovitaminosis D have adverse skeletal consequences secondary to raised parathyroid hormone (PTH), increased bone turnover, enhanced bone loss, and increased risk of fractures. In studies from India, severe hypovitaminosis D (<5 ng/mL or <12.5 nmol/L) was seen in 4-8.6% of the study population in summer months. In two studies, 37% and 29.9% of children, repectively, had serum 25(OH)D < 9 ng/mL. The mean serum concentrations of 25(OH)D reported in children and adolescents in urban North India were 11.8 $\pm$ 7.2 ng/mL and 13.84 $\pm$ 6.97 ng/mL, respectively. These were lower than the levels reported in children from South India. The mean 25(OH)D concentrations in urban (U) and rural (R) children from Andhra Pradesh were UB - 15.57 $\pm$ 1.21 vs RB - 17 $\pm$ 1.3 ug/ml and UG - 18.5 $\pm$ 1.6 vs RG - 19 $\pm$ 1.59 ug/mL, respectively for boys and girls. There was a significant correlation between serum 25(OH)D and estimated sun exposure ($r = 0.185$, $p = 0.001$) and percentage body surface area exposed ($r = 0.146$, $p = 0.004$) but not with socioeconomic status, suggesting that lifestyle-related factors contribute significantly to the vitamin D status of apparently healthy children[1]. The functional significance of low serum 25(OH)D levels in Indian children is reflected in their serum PTH values. As in adults, there is an inverse correlation between circulating 25(OH)D levels and PTH values. However, only 10.3–37.5% of subjects with vitamin D levels below 9ng/dL had high serum PTH concentrations. This could possibly be due to factors such as serum 1,25(OH)D levels, prolonged exposure to low vitamin D status, and dietary calcium intake.

Strategies to overcome vitamin D deficiency in India

In view of the high prevalence of chronic vitamin D deficiency, low bone mineral density, high prevalence of osteoporosis and the projection that 50% of all osteoporotic hip fractures in the world by the year 2050, will occur in Asia[19], suitable interventions are urgently needed to combat the major public health problem of vitamin D deficiency. A multi-pronged approach with advocacy for regular sun exposure, consumption of foods rich in vitamin D, daily or monthly intake of vitamin D supplements and food fortification strategies would be ideal. Indian diets contain only minimal amounts of vitamin D, as most Indians are vegetarians and no Indian foods are fortified with vitamin D. The intake of vitamin D in Indian school children (using US Department of Agriculture Provisional Tables on vitamin D content of foods) was only 60-110 IU/day[12,20].

Solar ultraviolet irradiation of the skin is the main source of endogenous vitamin D synthesis. About 90% of vitamin D is produced in the skin through the ultraviolet light (290-310nm UV-B) activation of its precursor molecule, 7 dehydrocholesterol present in the epidermis of the skin. The main factors that determine the amount of vitamin D synthesis in the skin are the quantity and quality of UV-B radiation reaching the earth's surface; this, in turn, is related to the solar zenith angle, latitude, season, atmospheric pollution and ozone layer. Poor exposure to sunlight due to life style changes is an important contributing factor to vitamin D deficiency. But there is a need to have information with regard to the best time of the day for sun exposure and the percentage body surface area (BSA) exposure required for adequate daily synthesis of vitamin D for darker skinned Indians. Our recent study on the effect of sun exposure on vitamin D synthesis showed that the maximum UV– B radiation reaching the earth's surface was in summer followed by autumn and winter and the peak radiation was recorded between 11AM-1PM throughout the year across India[21]. A similar observation was reported by Harinaryanan et al who showed that the maximum conversion of 7-dehydrocholersterol to pre-vitamin D3 was maximal between 11AM and 2 PM[22]. Children exposed for 4 weeks in summer with 30% BSA exposure showed a significantly greater rise in serum 25(OH) D than those with 15% BSA exposure; there was no synthesis in extreme winter months. The results of this study showed that, despite exposure to sunlight for one month with 30% BSA exposure between 11AM-2PM, the subjects did not achieve normal serum 25(OH)D levels of 20ng/ml[23]. Therefore, a strategy that relies solely on advocating greater exposure to sunlight is unlikely to be effective enough. Supplementation with 60,000 IU of vitamin D per month for 6-12 months in children and adults has been effective in achieving serum 25(OH)D of 20 ng/ml; studies are under way to explore the adequacy of daily intake of vitamin D in Indians[24,25].

A systemic review[26] evaluating several randomized intervention studies with vitamin D fortification in community-dwelling adults shows that 14 of the 15 studies revealed significant effects of fortified food on serum 25(OH)D concentrations. Our two recent studies evaluating the impact of vitamin D-fortified milk supplement on vitamin D status of healthy school children aged 10-14 years have shown this to be a safe and effective strategy[27,28]. As food fortification strategies have consistently been shown to have significant beneficial effects on serum 25(OH)D, many countries have opted for mandatory or voluntary food fortification with vitamin D[26,29]. While dairy products are the foods that are most often fortified with vitamin D, non-dairy foods are also being fortified. The Food Safety and Standards Authority of India has issued a draft notification on 6th December 2016 calling for fortification of toned, double toned and skimmed milk with 550 IU of ergocalciferol/cholecalciferol per litre of milk.

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Food Fortification to Combat Micronutrient Deficiencies in India

Prema Ramachandran

Micronutrient deficiencies - referred to as hidden hunger - are the most common type of nutritional deficiencies in India, as indeed they are globally. It is estimated that over 2 billion persons in the world, including a majority of the 1.3 billion Indians, are deficient in one or more micronutrients. India was quick to recognise that iodine-deficiency goitre, vitamin A-deficiency blindness and iron- and folic acid-deficiency anaemia were major public health problems. The country embarked on intervention programmes utilising all the three major modes of combating micronutrient deficiencies: dietary diversification, food fortification and nutrient supplementation. Nutrition education aimed at improving dietary diversification and intake of vegetables rich in micronutrient content was an important component of all nutrition interventions. The National Goitre Control Programme utilised fortification of salt with iodine to combat iodine deficiency disorders. Massive-dose vitamin A supplementation to under-five children was the strategy for combating blindness due to vitamin A-deficiency. The National Anaemia Prophylaxis Programme envisaged supplementation of iron and folic acid to pregnant women and preschool children for reducing the prevalence of anaemia.

A review of the situation four decades later has shown that the country is nearing the goal of universal household access to iodized salt. Keratomalacia caused by severe vitamin A deficiency had been eliminated over two decades ago. The prevalence rates of night blindness and Bitot spots are low except in pockets, but subclinical biochemical vitamin A deficiency is reported to be common. Although, there has been some decline in its prevalence and severity, anaemia and its adverse health consequences continue to be major public health problems in the country. Over the years more micronutrient deficiencies with adverse health consequences have been identified, such as those of vitamin D and vitamin B 12.

Experience in implementing the supplementation programmes for combating vitamin A deficiency and anaemia in the last four decades showed that it is difficult to achieve and sustain near-universal coverage. The success of the Iodine Deficiency Disorders (IDD) control programme through mandatory iodine fortification of salt has given an impetus to efforts to use a similar strategy to combat widespread micronutrient deficiencies such as iron deficiency anaemia. The intake of micronutrients in populations consuming fortified food shifts towards the right (Figure 1) without any dietary modification. With fortification of appropriate food stuff, it is possible to achieve sustained improvement in intakes of micronutrients and reduction in micronutrient deficiencies at the population level. Rapid improvements in the technology of fortification, and improved packaging, transport and marketing have made food fortification a viable, sustainable, effective and inexpensive strategy to combat widespread micronutrient deficiencies. The current status of food fortification in the country is briefly reviewed in this manuscript.

FIGURE 1 GAP BETWEEN CURRENT INTAKE AND ADEQUATE INTAKE

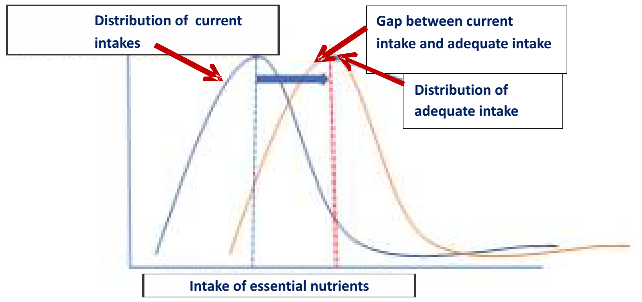
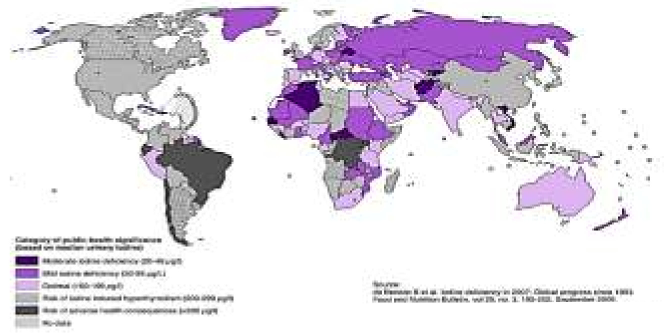


FIGURE 2 PREVALENCE OF IDD 1993-2006



Iodine deficiency disorders

Iodine deficiency disorders (IDD) are caused by deficiency of iodine in water, soil and foodstuffs; they affect all socio-economic groups living in defined geographic areas. Iodine deficiency results in a wide range of disorders depending upon the time of exposure, and the severity and duration of deficiency. Endemic cretinism due to intrauterine exposure to maternal iodine deficiency is the most severe form; varying grades of brain damage, intellectual disability, psychomotor defects, hearing and speech impairment are the other manifestations of intrauterine exposure to iodine deficiency. Iodine deficiency is a major cause of preventable mental retardation and brain damage in children. Higher infertility, abortion and still-birth rates have been reported in women with iodine deficiency. Goitre and hypothyriodism are seen in all age groups.

Iodine deficiency disorders are global public health problems. In the early 1920s, Switzerland and the U.S.A initiated salt iodization programmes to combat endemic goitre. Steep reduction in the prevalence of goitre as well as other manifestations of iodine deficiency was reported in the next decade, and universal fortification of salt was globally accepted as the appropriate strategy for combating IDD. The prevalence of IDD in India is relatively low (Figure 2). Initially it was thought to be a major problem only in the sub-Himalayan areas. Successful demonstration of the efficacy of iodised salt in reducing goitre in the Kagra valley in India's 'goitre belt' led to the initiation of the National Goitre Control Programme (NGCP) in 1962. Initially, the programme aimed at providing iodized salt to the population living in the well-recognized sub-Himalayan goitre belt. However, availability of salt was erratic, and a majority of the households continued to use the cheaper non-iodized salt. As a result, reduction in IDD under the programme conditions was not substantial.

In the 1980s the data from DGHS/ICMR surveys indicated that IDD is a problem that is not confined to the sub-Himalayan regions, and that there are pockets of iodine deficiency in all the States. In August 1992, the NGCP was renamed as the National Iodine Deficiency Disorders Control Programme (NIDDCP), bringing into its ambit the control of the entire spectrum of IDD. It was decided to iodize all the edible salt for human consumption in the country. The goal of the NIDDCP was to ensure universal household access to iodized salt and reduction in prevalence of IDD to below 10% in goitre endemic districts of the country. Adequate production of iodized salt in the country is an essential pre-requisite for improving household access to iodised salt. Production of iodised salt was less than 2,00,000 metric tonnes (MT) per year in the 1980s; by the 1990s, the installed capacity was scaled up to over 10 million MT per year. India's production could meet not only its own needs (5- 6 million MT) but also the requirements of the landlocked non-salt producing neighbouring countries . Another concern was the cost of transport of iodised salt from the coastal salt-producing states to other states (especially the distant northern and north eastern states). Appropriate steps were taken by the Railways to test salt for iodisation, subsidise the cost of rail transport for sending iodised salt from salt producing states to other states and to accord priority to transport of iodised salt.

The data from NFHS-2 (1998-99) showed that in most northern states more than 80% of the households were using iodised salt; but in coastal states like Tamil Nadu, Andhra Pradesh, Kerala, and Gujarat, the percentage of households consuming iodised salt is much lower. The population in states in the erstwhile goitre belt, familiar with the severe adverse consequences of IDD, hastened to access iodised salt once it was made available. Unlike salt transported by rail, salt transported by road was not subjected to checks regarding iodisation. As a result, cheaper non-iodised salt was transported by road and sold in coastal states. The populations who had not experienced the adverse consequences of IDD purchased and used the non-iodised salt. Efforts were intensified, through all modes of communication, to improve the awareness of adverse consequence of IDD and importance of using iodised salt in the coastal states.

Having ensured adequate production and economically viable transport, the Government of India advised all the states to ensure mandatory iodisation of salt meant for human consumption. A majority of the states introduced a ban on the sale of non-iodised salt. In the year 2000, the ban on the sale of non-iodised salt was

FIGURE 3 TIME TRENDS IN HOUSEHOLD ACCESS TO IODISED SALT (NFHS 2-4)

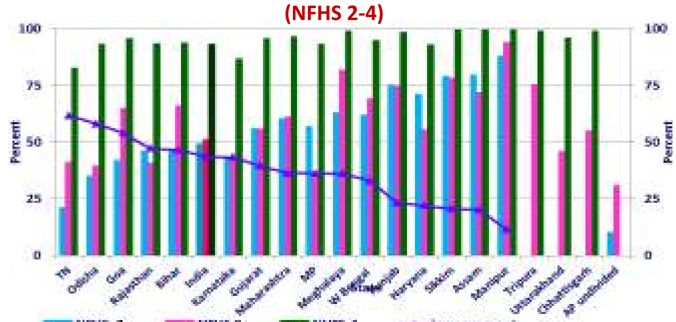
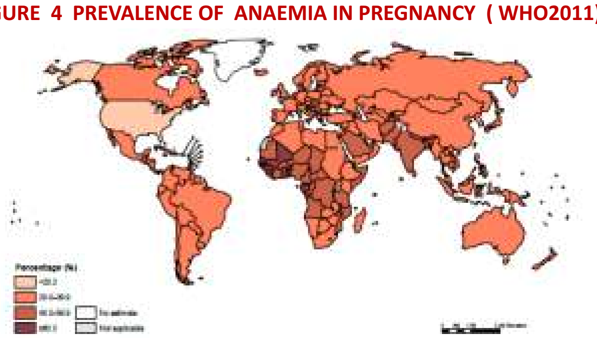


FIGURE 4 PREVALENCE OF ANAEMIA IN PREGNANCY (WHO2011)



lifted. Surveys conducted after the ban was lifted showed that there was a reduction in households using iodized salt. The Tenth Five Year Plan emphasised that “It is essential to ensure that only iodised salt is made available for human consumption in order to enable the children of the 21st century to attain their full intellectual potential and take their rightful place in a knowledge based-society”[1]. The Tenth Five Year Plan set the goal of universal access to iodised salt and reduction in the prevalence of IDD to less than 10% by 2012.

Recognising the potential adverse health consequences of reduction in iodised salt use, Government of India reinstated the ban in 2005. Since then there has been a sustained, steady increase in the percentage of households using iodised salt Figure 3[2,3,4] . Data from NFHS-4 indicate that, currently, over 90% of the households in the country use iodised salt. This has demonstrated that, once the production, distribution, and sale processes have been streamlined and awareness has been generated, it is possible to increase household use of iodised salt by nearly 50% within a decade, and raises the hope that the country will be able to scale up access to and use of iron-fortified iodised salt to combat both IDD and anaemia .

Iron fortification to combat iron deficiency anaemia

Iron is an important micronutrient needed for the synthesis of haemoglobin and myoglobin which deliver oxygen to the tissues .It is a constituent of cytochrome involved in cellular respiration. Vegetables, especially green leafy vegetables, are the richest source of iron in a vegetarian diet; legumes, pulses and millets also contain iron. Animal foods contain haem iron which is readily absorbed. The estimated average intake of iron from Indian diets ranges from 10-15 mg per day. This intake is not much lower than the iron intake in developed countries. But the bioavailability of iron from phytate and fibre-rich Indian diets is only 5-8%, whereas bioavailability of haem iron from animal food is over 40 %. Poor bioavailability of iron from Indian diets is the major factor responsible for anaemia in India. Globally and in India, iron deficiency is the most common micronutrient deficiency and is the major cause of anaemia; but not all nutritional anaemia is due to iron deficiency alone. Folate deficiency is the other common deficiency associated with anaemia. In India, during the last two decades there have been reports of reduction in folate deficiency and increase in vitamin B12 deficiency. Iron deficiency results in microcytic hypochromic anaemia. Combined iron and folate and/ or vitamin B12 deficiency results in dimorphic anaemia. India is among the countries with the highest prevalence of anaemia in the world (Figure 4). A majority of Indians, across the entire spectrum of age, sex, education and economic status, are iron-deficient and anaemic. In India, anaemia begins right from infancy and childhood, increases in severity during adolescence in girls, is present well before pregnancy, and gets aggravated during pregnancy. Prevalence of anaemia is high not only among undernourished persons but also in normal and over-nourished individuals. Over the last four decades, there has been some increase in the vegetable intake and some reduction in the prevalence (Figures 5 and 6)[5,6,7] and severity of anaemia (Figures 7 and 8)[5,6,7] and some of the adverse consequences associated with it .

It is difficult to produce, procure, cook and consume the large quantities of rather tasteless micronutrient rich vegetables needed to meet the RDA (ranging from 17 mg in men and over 25 mg in children) to improve the haemoglobin status of Indians. It is impossible to meet the RDA of 38 mg in pregnant women through dietary diversification alone. Taking this into account, scientists in the National Institute of Nutrition (NIN) have developed the technology for fortification of salt with iron and iodine (DFS) at the level of 1mg/g of salt. DFS represents the most feasible, economical and sustainable method of increasing iron intake by an average of 10mg/day (without any major dietary change) and reduce the prevalence of iron deficiency. The technology for iron fortification of iodised salt, developed by NIN, has been transferred to the industry. Currently, two technologies for producing DFS have been approved by FSSAI. The cost of iron-fortified iodised salt (DFS) is higher by Rs 2-3/kg as compared to iodised salt. The cost differential may come down with increased volume of production. Once production picks up, DFS will become readily accessible.

Salt is used by all segments of the population and it is unlikely that excessive amounts would be consumed by any individual. The per-person consumption of DFS salt can never cross the Tolerable Upper Limit (TUL) for iron. There is, therefore, no risk of side effects of excessive iron from the consumption of fortified salt alone. Centralised production and pre-existing programmes for fortification of salt with iodine offer a very ready platform to launch iron-fortified iodised salt. Once the production, distribution and sale of DFS have been scaled up, it might be possible to make iron-fortified iodised salt for human consumption mandatory, achieve sustained, population-wide increase in the intake of iodine and iron, and combat IDD and anaemia. In view of the widespread nature of iron deficiency, there has been advocacy for fortifying multiple foodstuffs with iron. Given that folic acid and vitamin B12 deficiencies also contribute to anaemia, there have been efforts to fortify rice and *atta* with iron, folate and vitamin B12. The FSSAI has recommended standards for rice and *atta* fortification with iron, folate and vitamin B12. The advantages and disadvantages, as well as the impact of using rice fortified with iron, folate and vitamin B12, and of *atta* fortified using Na iron EDTA, folate and vitamin B12, both at *atta chakki* level and at an industry-scale level, are being investigated.

Globally, there is a growing recognition of the potential adverse health consequences of excessive intake of some micronutrients and/or imbalance of intake of inter-related micronutrients (eg folic acid and vitamin B12) by segments of the population consuming a variety of food stuffs fortified with multiple micronutrients. The RDA for iron in Indians is high (17 mg /day in men 38 mg/day in pregnant women). The tolerable upper limit of iron has been estimated to be 40 mg/day (Figure 9). If multiple food items are fortified with iron, some segments of the population may consume more than one food fortified with iron. Under these circumstances, it is possible that TUL may be exceeded and the population may experience gastro-intestinal side effects. Experience with IFA supplementation shows that minor gastrointestinal side-effects are

FIGURE 5 TIME TRENDS IN PREVALENCE OF ANEMIA IN PREGNANT WOMEN (DLHS 2 & AHS)

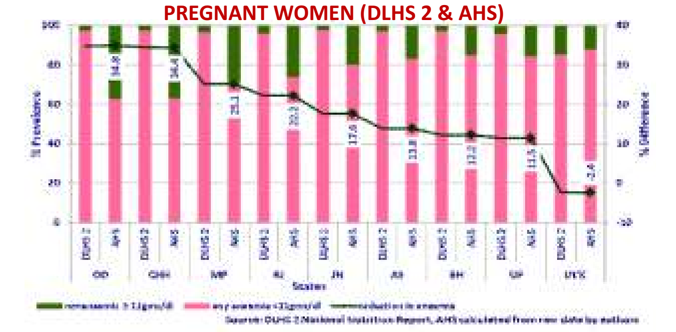
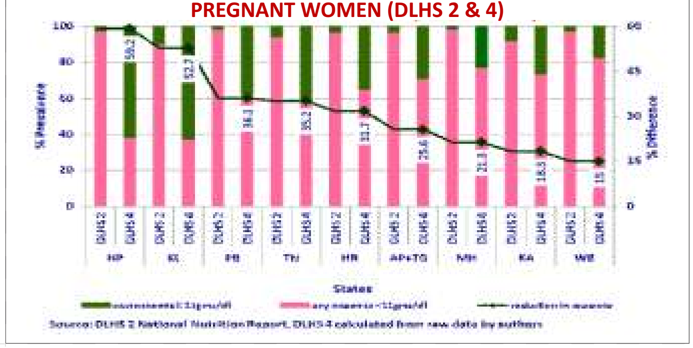


FIGURE 6 TIME TRENDS IN PREVALENCE OF ANEMIA IN PREGNANT WOMEN (DLHS 2 & 4)



initially seen in 10-20% of persons who received iron supplements. These minor but unpleasant side effects do make the population averse to taking the supplements; a similar situation can arise with the use of multiple food stuffs fortified with iron. Taking all these aspects into consideration, it is preferable to concentrate the efforts on scaling up production of iron fortification of iodised salt, achieve universal access to DFS, improve iron intake, and achieve the SDG target of 50% reduction in prevalence of anaemia in women .

Folic acid fortification

Folate is a water-soluble vitamin that is present both in vegetables and animal food. Folic acid, the stable synthetic form of folate, is used in food fortification and supplementation programmes. Many critical cellular pathways including those for DNA, RNA and protein methylation are dependent on folate as the one carbon source. In Indian diets, vegetables are the major source of folate. Low vegetable intake has been thought to be the major factor responsible for the poor folate status in Indians. Available limited data suggest that cooking losses in dietary folate could be about 30%; but bioavailability of folate is high (over 40%). Folate deficiency often coexists with iron deficiency and the combined deficiency results in dimorphic anaemia.

A number of genetic polymorphisms affecting folate metabolism have been shown to be associated with an increased risk of neural tube defects (NTDs). A randomised control trial carried out by the Medical Research Council, UK, on the effectiveness of peri-conceptional folic acid supplementation for prevention of the recurrence of NTDs in the subsequent pregnancy, showed that the administration of high doses of folic acid (4 mg daily) resulted in a 79% reduction in recurrence of NTDs in the subsequent pregnancy[8]. Since then, several studies using varying doses of folic acid supplementation have confirmed these findings. Studies on peri-conceptional supplementation with folic acid (400µg daily) for prevention of NTDs in women who have had no previous history delivering infants with NTDs, showed that there was some reduction in NTDs in this group also, but that the magnitude of reduction was lower[9]. Based on these data, programmes for peri-conceptional folic acid supplementation (400µg daily) for primary prevention or prevention of recurrence of NTDs were initiated in several countries. The compliance rate with peri-conceptional folic acid supplementation and the number of NTDs averted due to the supplementation programme were relatively low. In view of this, some countries (e.g., USA, Canada, South Africa) initiated mandatory fortification of wheat flour with folic acid in different doses. Studies in the US have shown that, subsequent to the implementation of mandatory fortification of wheat flour with folic acid, there has been a 19 to 32% reduction in the incidence of NTDs[10]. Data from other countries have shown similar trends, suggesting that mandatory folic acid fortification of wheat does prevent some, but not all, NTDs.

Mandatory folic acid fortification of wheat to prevent NTDs exposes the entire population in the country to additional folic acid intake; in persons whose intake was sufficient, this may result in excessive folic acid intake. Initially, it was assumed that the excess of folic acid would be excreted in the urine and is, therefore, unlikely to lead to any adverse health consequences. Ongoing monitoring of the mandatory folic acid fortification programme has brought to light some potential adverse health consequences such as masking of vitamin B12-deficiency anaemia and delaying the diagnosis of vitamin B12 deficiency. Some studies have suggested that folic acid supplementation may enhance the development and progression of already existing, undiagnosed premalignant and malignant lesions or increase the risk of cardiovascular diseases. Currently, the data is insufficient to draw conclusions about the increase in risk of adverse health consequences in the general population exposed to mandatory folic acid fortification of wheat flour for prevention of NTDs. In India, *atta* and rice fortification with iron, folic acid and vitamin B12 is being tried; this multiple micronutrient fortification is aimed at improving the dietary intake of these three nutrients and thereby reducing anaemia. This programme is, therefore, not comparable to the ongoing mandatory folic acid fortification for prevention of NTDs in some developed countries. The FSSAI has prescribed standards for voluntary fortification of *atta* and rice with iron, folic acid and vitamin B12. Ongoing studies in India will show the feasibility, efficacy and cost effectiveness of these fortifications in reducing anaemia. As both folic acid and vitamin B12 are being used in the programme in India, the masking of vitamin B12-deficiency anaemia is not a concern

Fortification with Vitamins A and D

Vitamin A is a fat-soluble vitamin essential for maintaining normal growth, regulating cellular proliferation and differentiation, controlling development, and maintaining visual and reproductive functions. Diet surveys have shown that the intake of Vitamin A is significantly lower than the recommended dietary allowance in young children, adolescent girls and pregnant women in India. In spite of the fact that there has not been any significant improvement in the dietary intake of vitamin A, and although coverage under Massive Dose Vitamin A supplementation programme has been low, there has been a decline in clinical vitamin A deficiency in under-five children in the country. This could perhaps be due to better access to health care resulting in reduction in severity and duration of childhood morbidity due to infections and consequent reduction in loss of vitamin A during infection. However, biochemical deficiency of vitamin A continues to be common.

Vitamin D, which is essential for bone health across all age groups, is also a fat soluble vitamin. Vitamin D is manufactured in the skin, and this is the major source of vitamin D. In the last four decades, rickets, osteomalacia and other severe clinical manifestations of vitamin D deficiency have not been widely reported; this led to the belief that in sunny India vitamin D deficiency is unlikely. However, with the development of vitamin D assays, it became obvious that biochemical deficiency of vitamin D is widespread in the population across all age and economic groups. In view of the high prevalence of

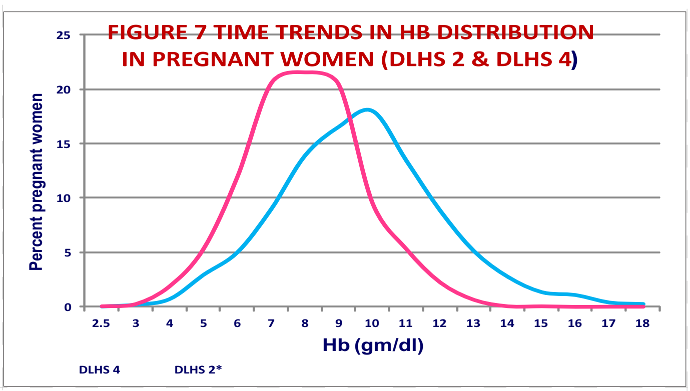


FIGURE 7 TIME TRENDS IN HB DISTRIBUTION IN PREGNANT WOMEN (DLHS 2 & DLHS 4)

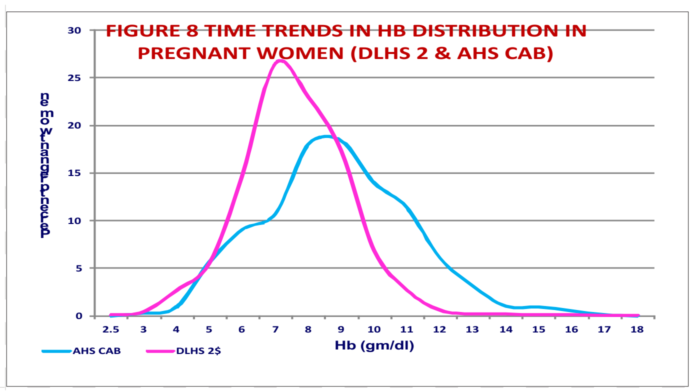
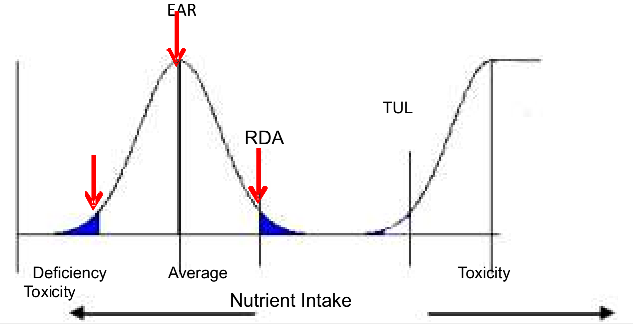


FIGURE 8 TIME TRENDS IN HB DISTRIBUTION IN PREGNANT WOMEN (DLHS 2 & AHS CAB)

FIGURE 9 RELATIONSHIP BETWEEN DEFICIENCY, EAR, RDA, AND TUL IN MICRONUTRIENT INTAKE



biochemical vitamin A and D deficiency across all segments of the population, attempts are being made to explore the feasibility, sustainability and efficacy of fortification of foods with vitamins A and D.

Fortification of oil with vitamins A and D

Fortification of vanaspati with vitamin A has been mandatory in India since 1953. Given the global data on the adverse health consequences of using hydrogenated fat, it is likely that the manufacture of vanaspati will be progressively phased out. Vegetable oils can readily be fortified with vitamins A and D. It is estimated that the current consumption of oil is about 20-30g / person / day. Fortification of edible oils and fats with vitamins A and D is a simple and easy process. The FSSAI has notified the standards for fortifying vegetable oils with vitamins A and D. Fortified oil can provide 25%-30% of the recommended dietary allowances of vitamins A and D. In Gujarat, oil fortification with vitamins A and D has been mandatory since 2006. Currently, several medium and large scale oil producers are voluntarily fortifying edible oil with vitamins A and D. It is estimated that about 1.5 MMT of edible oil is fortified with vitamins A and D and is reaching about 200 million consumers.

Fortification of milk with vitamins A and D

Over the last four decades there has been progressive increase in milk production and consumption in India. Currently, the per-capita production of milk is about 300 ml/day; production is projected to increase to more than 350 ml/day by 2020. About 20% of the total milk produced is processed in the organised sector. Milk is a rich source not only of high quality protein but also of calcium and fat-soluble vitamins A and D. Vitamins A and D are lost when milk fat is removed during processing for production of toned, double toned and skimmed milk. This loss needs to be replenished through vitamins D and A fortification of milk. The standards for fortification of toned, double toned and skimmed milk with vitamins A and D have been notified by the FSSAI. The process of milk fortification is simple and could be undertaken in all milk processing units. Some of the large-scale milk producers have voluntarily started fortification of toned, double-toned and skimmed milk with these vitamins.

Summary and conclusion

Micronutrient deficiencies especially iodine, iron, folate, vitamin B12, vitamins A and D are major public health problems in India . With fortification of appropriate food stuffs, it is possible to achieve sustained improvement in intakes of these micronutrients and reduction in micronutrient deficiencies at population level. India's efforts to ensure universal household use of salt fortified with iodine has made enormous strides in the last decade; currently, over 90% of households use iodised salt.

Globally and in India, iron deficiency is the most common micronutrient deficiency and is the major cause of anaemia. DFS represents the most feasible, economical and sustainable method of increasing iron intake by an average of 10mg/day (without any major dietary change) and reduce the prevalence of iron deficiency. The FSSAI has set the standards and has approved two technologies for DFS manufacture. Centralised production and pre-existing programmes for fortification of salt with iodine offer a very ready platform to launch iron-fortified iodised salt and raises the hope that the country will be able to scale up access to and use of iron-fortified iodised salt to combat both IDD and anaemia and achieve the SDG target of 50% reduction in prevalence of anaemia in women.

Currently, there are ongoing studies to explore feasibility and efficacy of *atta* and rice fortified with iron, folic acid and vitamin B12 to combat anaemia. Voluntary fortification of vegetable oils with vitamins A and D is underway. Vitamins A and D are lost when milk fat is removed during processing for production of toned, double toned and skimmed milk. Voluntary replenishment fortification of toned, double toned and skimmed milk with vitamins D and A is being taken up by some major milk producers.

Food fortification does represent a sustainable method of increasing intake of selected micronutrients. However, fortification of multiple food stuffs with multiple micronutrients is not advisable because of the potential adverse health consequences of excessive intake of some micronutrients and/or imbalance of intake of inter-related micronutrients (eg folic acid and vitamin B12) by segments of the population consuming a variety of food stuffs fortified with multiple micronutrients.

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FOUNDATION NEWS

- Dr Prema Ramachandran was an invited speaker in the Second David Barker Memorial Symposium on 18th February 2017, at Pune and made a presentation on "Nutrition Transition in India".

- Dr Prema Ramachandran participated in the ICMR Task Force Meeting on Anaemia on 13th February 2017.

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