May 2002: (II)S2–S6

Multiple Micronutrient Supplementation in Pregnancy

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Nearly a third of full-term babies born in India are reported to be of low birth weight (less than 2.5 kg).[1,2] This figure has remained more or less stable over the last few decades in spite of striking declines in neonatal and infant mortality, giving the impression that India has not made much progress in improving the nutrition status of women.

However, the validity of the present estimates of low birth weight in the country as a whole needs to be carefully checked. This estimate is mostly derived from births taking place in government-owned public hospitals, which cater to the poorest sections of the population. This has become even more the case in recent years, with the opening of numerous nursing homes and private hospitals. Presently, most middle-class and affluent women (who together constitute two-thirds of the population) do not deliver in government hospitals. Therefore, the present estimate could be considered to better reflect the poorest segment of India's population. Even so, striking differences can be seen between different states of India. The incidence of low birth weights in Kerala, for example, is low compared with the central Hindi-speaking states of the country. The preliminary results of a study now being undertaken by the Nutrition Foundation of India show that incidence of low birth weight deliveries among the middle class is strikingly low—as low as 5.7%. Comparison of low birth weight incidence between different countries where the source of data may be different may not be valid. This is an area for further research.

Factors Contributing to Low Birth Weight

Low birth weight and poor pregnancy outcome are the result of multiple factors. Maternal prepregnancy weight and maternal weight gain during pregnancy are very important determinants. Poor antenatal care, anemia, heavy physical work until late in pregnancy, smoking, and poor diets are other important factors.

In most public health programs in India so far, the emphasis has been on infants and children. While lip service has often been paid to mothers, not much has been done to improve diets or antenatal care for pregnant women. Emphasis has been placed on growth monitoring in children, but there are no parallel efforts for assessing women's weight gains during pregnancy. This relative neglect of women during pregnancy now needs to be corrected.

Poor prepregnancy weights of mothers and poor nutrition status are a reflection of the poor status of girls during childhood and adolescence. Because little attention had been paid to the health and nutrition care of adolescent girls, many of them are anemic even at the time of conception. Under these circumstances, the current program of distributing iron and folate tablets during the last 100 days of pregnancy is hardly adequate to correct the prevalent anemia. Anemia in pregnancy, especially severe anemia, is an important determinant of poor pregnancy outcome. Only recently has the policy of relative neglect toward adolescent girls been recognized as shortsighted. The data obtained by the National Nutrition Monitoring Board (NNMB) at Hyderabad, India show that weights and heights of adolescent girls today are better than they were 15 years ago, a positive trend.[3] The recent proposals by the Planning Commission[4] and the Ministry of Health to intensify health care and antenatal care during adolescence, with focus on the treatment of severe anemia, should yield results within the next few years.

Diets, particularly those of pregnant women, are deficient in energy and, consequently, in several micronutrients. Energy intake ranges between 1200 and 1600 kcal in poor populations. Any proposal for correction of dietary deficiency in pregnant women should take note of this fact. Poor energy intake is a major factor, especially when coupled with women's high energy expenditures from having to perform heavy physical work till the last days of pregnancy. Under these circumstances, the logical approach toward correcting poor pregnancy outcome is to strive for all-around improvement in diets during pregnancy to ensure proper weight gain and better antenatal care.

Multiple Micronutrient Supplementation

In recent months, some international and bilateral groups have been proposing that health administrations of de-

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veloping countries of South Asia and Africa be persuaded to adopt a blunderbuss polypharmacy approach of daily distribution of a capsule containing a cocktail of about 15–17 micronutrients to all pregnant women and adolescent girls. This is being claimed as the instant public health solution to the problem of poor pregnancy outcome in these countries. A group of American and European experts that met in the United States in July reportedly decided as follows:

"A supplement containing 15 micronutrients at levels based on United States/Canada RDAs should be promoted for use on a daily basis as soon as the woman is known to be pregnant, and followed through for a minimum of 3 months postpartum and if possible throughout breastfeeding. The same supplement is also to be promoted on once or twice weekly basis to all nonpregnant, nonlactating women and adolescents."[5] According to the proposal this "cocktail" is to be encapsulated in Denmark and distributed by an international agency (fortunately not WHO and certainly not FAO) to 10 countries of South Asia (including India) and Africa. This proposal must indeed be music to the ears of the vitamin cartels! Strangely enough, no representative of any of the ten developing countries who were the intended "ostensible" beneficiaries of this approach, was ever invited to this meeting. Though we are now in the 21st century, 19th century mindsets apparently prevail in some quarters!

We will, however, examine this proposal for multiple micronutrient supplementation purely on its *scientific merits*. There have been some excellent reviews on this subject in recent years that have been noted.[6,7]

Points for Consideration

The following points need careful attention in this regard.

Poor pregnancy outcome is the result of *multiple* factors and cannot be corrected by a narrow pharmaceutical shortcut. It calls for overall improvement in antenatal care and dietary diversification. This task cannot be evaded. There are no magic bullets.

Diets of pregnant women in poor income groups are deficient not only in micronutrients but in *energy* as well. What women require is *food* of good nutritive value, not just a capsule of some selected synthetic nutrients. Besides the vitamins that are envisaged to be provided by the capsules, foods provide a whole range of bioactive phytochemicals (so called non-nutrients). Many more such non-nutrients in food are likely to be discovered in the future. The famous ATBC study in Finland[8] has shown that, while fruits and green leafy vegetables protect against epithelial cancers, a combination of alpha-tocopherol and beta-carotene was found to actually aggravate the development of epithelial cancer.

At present, there is a lack of clear knowledge and information of baseline micronutrient status or even of suitable outcome indices in poor Indian populations to whom these interventions are proposed to be targeted. What precisely are the micronutrient deficiencies in Indian women that have a bearing on their poor pregnancy outcome? If there are any specific micronutrient deficiencies responsible for poor pregnancy outcome, are these deficiencies such that they cannot be combated through dietary improvement, using locally available, inexpensive foods? We presently have no answers to these questions.

The assumption that the micronutrient requirements of populations in developing countries, like India, are identical to those of the United States or Canada may be totally unwarranted. The suggested composition of the recommended multiple micronutrient supplement, based on the United States/Canadian RDA, is likely to be substantially in excess of the requirements of populations in developing countries, even though there may be individuals in the population who are depleted in a number of micronutrients. Since it is intended that the supplement be taken on a daily basis, a significant proportion of pregnant women will end up with intakes that are substantially in excess of their individual requirements. There is evidence that micronutrients (e.g., vitamin A and zinc) given in high doses during pregnancy may be harmful to either the mother or the developing fetus.

Staple diets in developing countries are different from those in the United States and Canada, and micronutrient requirements could be totally different as well. Calcium requirements, for example, are shown to be higher in populations subsisting on diets high in animal proteins compared with those who consume low–vegetable protein diets. Several decades ago, Najjar and Holt suggested that some essential micronutrients can be synthesized in the large gut. Their suggestion was dismissed by later investigators who failed to find evidence of such synthesis in subjects subsisting on usual Western diets. It is high time that this whole question be reinvestigated in populations subsisting on predominantly cereal-based diets. It is now known that a substantial proportion of carbohydrates ingested as cereals reach the large gut where they undergo fermentation and produce short-chain fatty acids, like butyric acid, which are beneficial to the integrity of the colonic epithelium. Najjar and Holt's observation may still prove to be right in predominantly cereal-eating populations. However, this line of thinking may be no more then speculation at this stage. Even if this possibility is ruled out, the need for proper re-examination of micronutrient requirements in populations of developing countries on different staple diets should not be ignored. The supplementation levels currently being recommended on the basis of American

RDAs may be largely inapplicable to populations in developing countries.

Increasing micronutrient intakes to high levels will bring about changes in cellular metabolism. Supplementing micronutrients at levels much higher than the habitual intake levels for just a short period and subsequent abrupt reversion to earlier, lower levels, could prove counterproductive and harmful. In the Harvard Study on HIV-infected pregnant women in Africa, it was claimed that multiple micronutrient supplementation brought about significant increase in infant birth weight. It would be wrong to extrapolate the result of a study on HIV-infected mothers to noninfected pregnant women. It is also not known what happened to those poor pregnant women in the Harvard study after the supplementation finally ceased. One wonders whether the short period of high multiple micronutrient supplementation followed by sudden cessation hastened their end!

RDAs are usually estimated in healthy, infection-free populations. It is known that some micronutrients are preferentially lost in the presence of infections, for example, vitamin A in respiratory infections and riboflavin in many infections associated with negative nitrogen balance. So in real-life situations in poor communities, the micronutrient requirements could be totally different.

Complex interactions between micronutrients (such as between zinc and copper, iron and zinc, and vitamin C and zinc) are known and are likely to be evident at higher doses. The specific nutrient-nutrient interactions in this mixture are unknown, especially in undernourished populations.

The implications suggested by the proposal appear to be that pregnant women in poor developing countries are unlikely to overcome their dietary deficiencies through improved food intake using locally available foods, and therefore they have to depend on imported tablets and pills. This is clearly an unjustified and defeatist approach that will prove to be unsustainable in the long run and is not conducive to the promotion of self-reliance.

There is currently no evidence based on well-conducted randomized clinical trials in developing countries that justify the use of multiple micronutrient supplementation on grounds of efficacy, compliance, and clearly defined explicit outcome measures. There is no convincing evidence drawn from randomized clinical trials to intervene on a programmatic or pilot basis with respect to multiple micronutrients in pregnancy. Under the circumstances, any pilot study of the nature proposed by the group at the U.S. meeting, would raise ethical issues and commit governments to unnecessary expenditure on interventions that are not based on reliable scientific evidence. The proposal as it stands, will no doubt save vitamin cartels from the need for expensive experimental studies and clinical trials. It would, however, be wrong to use pregnant women of poor countries as human guinea pigs for their benefit.

All this is not to say that there are no micronutrient deficiencies involved in poor pregnancy outcome. In all probability there are. But the way to overcome these deficiencies is not to resort to a fishing expedition—a hit-or-miss, blunderbuss, polypharmacy approach involving a few micronutrients that may be necessary, quite a few that may not be, and a few that may even be harmful. It is also possible that the proposed composition does not include quite a few other micronutrients, phytochemicals, and antioxidants that may, in fact, be useful.

For this reason, this proposal for multiple micronutrient supplementation, as it now stands, is *unscientific*, *unethical*, and *unsustainable*.

Under the circumstances, it is not surprising that the Indian Council of Medical Research (ICMR) Expert Group Committee meeting held on January 15–16, 2000 under the chairmanship of the Director General of ICMR came to the following unanimous conclusions:

Prerequisites for Multiple Micronutrient Supplementation

Adequate data needed on:

- magnitude of deficiency—clinical and biochemical;
- associated functional decompensation;
- therapeutic trials demonstrating reversal of functional, clinical, and biochemical change—experimental and clinical data on interactions of more than one nutrient.

In India, these prerequisites for initiation of multiple micronutrient supplementation have not been fulfilled. Multiple micronutrient supplementation trials cannot be initiated.

We are deeply appreciative of the contributions the pharmaceutical industry is making toward advancement of medical science, combating diseases, and national development. We also recognize that some major public health programs, such as those addressing goiter and iron deficiency anemia, require the use of supplements. There is vast legitimate scope for contributions from the pharmaceutical industry toward health promotion in developing countries. What we are emphasizing here, however, is that the specific multiple micronutrients responsible for poor pregnancy outcome must first be scientifically established, and the *level* at which the supplementation has to be carried out to correct these deficiencies must be carefully identified. The micronutrient deficiencies identified as requiring correction should be those whose correction cannot be achieved through dietary diversification using locally available foods.

These requirements have to be satisfied before any pilot trials with multiple micronutrient supplements are

Table 1. An Illustrative (Not Exhaustive) List of Commonly Available Micronutrient-rich Foods

Food Groups	Common Indian Foods Rich in Micronutrients
Vegetables	Rape leaves, cauliflower greens, amaranth, curry leaves, garden cress, drumstick (leaves), fenugreek leaves, beet greens, spinach, betel leaves, parsley, turnip greens, parslane, mint, carrots, lotus stem, tapioca chips, colocasia, radish, sweet potato, yam
Condiments & Spices	Poppy, cumin, coriander, oregano, green chilies (fresh/dry), turmeric, ginger, fenugreek, pepper, garlic, mango powder
Nuts & Oilseeds	Coconut (deoiled/dry/milk), groundnut, cashew nut, pistachio nut, gingelly seeds, garden cress seeds, safflower seeds, mustard seeds, niger seed
Fruits	Indian gooseberry, watermelon, custard apple, wood apple, tomato, guava, mango, pineapple, orange, papaya, grapes, banana, bael, pomegranate

attempted. A blunderbuss polypharmacy approach in the absence of such data will amount to exploitation of poor communities and will be putting an unnecessary strain on the already stretched resources of the health systems of poor countries. The fair name of the pharmaceutical industry should not be allowed to be sullied by overzealous promotion of pharmaceutical solutions to basic public health programs of poor countries. *Supplements* should not be promoted as *substitutes* for food.

The Challenge

India is no barren desert. It is a country that can rightly be proud of its vast biodiversity. The challenge before Indian scientists is to investigate how best to use the vast array of micronutrient-rich foods available right at their own doorsteps in judicious combinations to combat micronutrient deficiencies. Diseases like beriberi and pellagra, which were once rampant in India, have now disappeared as public health problems. This was not brought about through supplementation of thiamin or niacin, but through socioeconomic development and dietary diversification. Classical kwashiorkor was not overcome through the distribution of fish protein concentrates that were vigorously advocated by the Bureaus of Commercial Fisheries of powerful countries. Keratomalacia was eliminated as a pubic health problem in spite of the failure of the massive dose vitamin A prophylaxis program initiated by the National Institute of Nutrition in India more than 25 years ago. As one who has had a ringside view of the changing nutrition scene for more than 50 years now, I can testify to these developments.

Plant foods are often low cost, could provide several nutrients, and are in plentiful supply in the country (Table 1). Traditionally, many of these foods have been widely used in various combinations during pregnancy, lactation, and other specific situations. Unfortunately, in recent years these inexpensive foods and food combinations have been largely dismissed as folklore. It is time that we return to take a good look at our traditional heritage to see how the micronutrient-rich foods available within our country can be combined in judicious combinations and used appropriately. Women of poor communities who are largely unskilled could be at the forefront of such a program, because the technology needed would not be sophisticated and expensive.

Agricultural scientists in India are currently engaged in ambitious programs augmenting the production of pulses and green leafy vegetables, which are rich sources of micronutrients. The programs had suffered relative neglect in the days of the Green Revolution, but these mistakes are now being corrected. Health scientists should join hands with agricultural food scientists in promoting the production and consumption of pulses and green leafy vegetables to achieve an improvement in the quality of habitual diets in poor households. Emphasis should be on food-based, rather than drug-based, solutions. Food resources available within the country should be put to maximal use instead of resorting to commercial pharmaceutical shortcuts.

Concluding Comments

A meaningful agenda for research on micronutrients in pregnant Indian women must include the following:

- assessing present micronutrient status of Indian women;
- investigating the effect of pregnancy on micronutrient status, and the relationship of micronutrient deficiency to actual pregnancy outcome and low birth weight (this information is at present extremely scant);
- defining micronutrient requirements in pregnancy;
- using modern analytical procedures to update information on micronutrient, bioactive phytochemical, and antioxidant content of locally available, low-cost foods and identifying optimal ways of using these foods singly or in combination for combating micronutrient malnutrition.

There is a vast potential for Indo-U.S. cooperation with the research agenda proposed above. Such meaningful cooperation could prove far more rewarding for nutritional uplifting of poor populations, and would

make far greater contributions toward the advancement of nutrition science than would be the case if the cooperation were limited to the distribution of an arbitrary list of multivitamin tablets at arbitrary levels.

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