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Future Challenges of Nutrition in Pregnancy and Lactation

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Introduction

We have recently moved from an era when malnutrition during pregnancy and lactation was widespread in many areas of the world, to a time when a general lack of food is becoming more uncommon. However, the quality of the food is still a problem and micronutrient deficiencies are very common, not only in developing countries but also in segments of the population in industrialized countries. Many programs are being launched to combat these micronutrient deficiencies, ranging from supplementation, fortification, food modification/diversification and altered food preparation methods to nutrition education. Progress to date has unfortunately been limited.

During the same time, there has been a dramatic increase in overweight, obesity and diabetes due to over-consumption of food and reduced energy output with more sedentary lifestyles. Although this trend started, and is far more abundant, in industrialized countries, this is now also happening in developing countries. Various strategies can be used to reduce obesity by decreasing food consumption, but this also puts demands on the nutritional quality of the food consumed. With a lower energy intake, the micronutrient content of the diet frequently becomes suboptimal; however, the micronutrient status of patients/populations that are recommended to consume less is very rarely considered or evaluated.

Thus, micronutrient deficiencies are likely to be a major challenge in the future, particularly in pregnant and lactating mothers and their infants. The magnitude of this challenge is attenuated by several findings of negative outcomes of both single and multiple micronutrient supplementation studies. It is highly likely that these adverse outcomes are due to interactions among micronutrients, both at the level of absorption and metabolically. It is also

possible that interactions between micronutrients and hormones in the pregnant or lactating woman can have adverse effects on the fetus and/or on the nursing infant. The challenge for us as nutrition scientists is therefore to improve our understanding of micronutrient interactions and find ways to eliminate or minimize them.

Anemia

Nutritional anemia is common during pregnancy and lactation in many populations. The anemia may be due to deficiencies of iron, vitamin A, folate or vitamin B_{12}. Whereas iron and vitamin A deficiencies result in microcytic anemia and folate/vitamin B_{12} deficiency in megaloblastic anemia, the type of anemia is rarely assessed in the field. Commonly anemia is assumed to be due to iron deficiency as this has historically been the case, and as the limited studies that have assessed iron stores by serum ferritin (or transferrin receptor) have documented a high prevalence of iron deficiency. However, when analyzing data from recent studies, there is not a high correlation between low serum ferritin values and low hemoglobin concentrations (unpublished observations). Thus, it is possible that there is both a high prevalence of iron deficiency, leading to some iron deficiency anemia, and a high prevalence of anemia due to other micronutrient deficiencies.

Anemia due to vitamin A deficiency was reported in Central America already in the 1970s when low serum retinol concentrations in children were found to be correlated to low hemoglobin, serum ferritin and transferrin saturation values [1]. These observations were made when iron intake was adequate; no correlation was found when iron intake was low. Subsequent clinical studies showed that the anemia induced by low vitamin A diets was refractory to treatment with medicinal iron and only when vitamin A status was restored did the subjects' hemoglobin values increase [2]. Studies in experimental animals subsequently showed that liver and spleen iron increases concomitantly with the decrease in serum iron and hemoglobin [3]. Radioisotope studies showed that the incorporation of ^{59}Fe into erythrocytes was significantly lower in vitamin A-deficient animals than in controls, but more ^{59}Fe was incorporated into the liver. Thus, it appears that the mechanism of interaction between vitamin A and iron is an impairment in the mobilization of iron from the liver and/or incorporation of iron into the red blood cell. Consequently, to optimize the outcome, it appears prudent to normalize vitamin A status of populations given additional iron. Studies on pregnant women in Indonesia [4] have shown that supplementation with both iron and vitamin A increases hemoglobin concentrations to a greater extent in anemic women than does iron supplementation alone (table 1).

Recent studies show that vitamin B_{12} deficiency may be far more common in developing countries than previously believed. Black et al. [5] found that anemia

Table 1. Supplementation of anemic pregnant women in Indonesia with vitamin A and iron

	Women without anemia	
	n	95% CI
Placebo (n = 62)	10 (16%)	7–29
Vitamin A (n = 63)	22 (35%)	22–48
Iron (n = 63)	43 (68%)	54–79
Vitamin A + Iron (n = 63)	61 (97%)	88–99

Adapted from Suharno et al. [4].

was prevalent in pregnant and lactating women in rural Mexico, and that only part of this anemia was due to iron deficiency. Low plasma vitamin B_{12} was common and increased from pregnancy through lactation. Vitamin B_{12} in plasma and breast milk was significantly lower in anemic women than in non-anemic women, and 62% of the breast milk samples were classified as deficient. A very low intake of meat products was found likely to be the cause of the vitamin B_{12} deficiency, but in a subsequent publication malabsorption was also suggested as a probable cause [6]. A study on Guatemalan women confirmed these results [7]. Plasma vitamin B_{12} was deficient or low in 47% of women at 3 months of lactation, and holotranscobalamin II concentrations were low in 32%, possibly indicating vitamin B_{12} malabsorption. Breast milk vitamin B_{12} was low in 31% of the women. The mean maternal dietary intake of vitamin B_{12} was significantly correlated ($r = 0.20$) with plasma vitamin B_{12} and was the main determinant in a linear regression model. The authors concluded that vitamin B_{12} deficiency is highly prevalent in this population, and suggested that the cause may be malabsorption, possibly exacerbated by a low dietary intake of vitamin B_{12}.

In an ongoing study in Bangladesh, we recently found that ~50% of pregnant women have deficient (<200 μg/l) and ~30% low (<300 μg/l) serum vitamin B_{12} concentrations (unpublished). The contribution of low serum vitamin B_{12} concentrations to the prevalence of anemia has not yet been assessed. With diets containing no or very little meat, these observations should not be too surprising; however, few studies to date have assessed vitamin B_{12} status during pregnancy and lactation. The consequences of vitamin B_{12} deficiency with or without anemia during pregnancy and lactation need to be assessed further.

Iron–Folate Interactions

Whereas anemia due to folate deficiency is likely to become increasingly rarer due to supplements given during pregnancy containing folate and to folate fortification of foods, it may be worthwhile to study the interaction between

iron deficiency and milk folate. Although iron deficiency also should become less prevalent with widespread intervention programs, it has been noted that many such programs have failed to effectively decrease iron deficiency. It has been shown in animal models that iron deficiency during pregnancy and lactation can result in low milk folate concentrations [8]. Rat pups being nursed by iron-deficient dams were found to be folate depleted by late infancy (day 17), even though the dams were fed twice the recommended levels of folate [9]. The folate status of pups born to control and folate-deficient dams was similar on day 2 of life, indicating that the accretion of folate during fetal life was not impaired. It was subsequently shown that milk folate was significantly reduced in iron-deficient dams on day 17 of lactation as compared to control dams. In addition, the milk of iron-deficient dams had a significantly reduced percentage of long-chain folylpolyglutamates, which may affect folate utilization by the pups [10]. Thus, low iron status impaired milk folate and offspring folate status in a rat model. There have been very few studies exploring this micronutrient interaction during pregnancy and lactation in human subjects.

Zinc–Vitamin A Interactions

Vitamin A deficiency is well recognized as one of the major nutritional deficiencies worldwide. Many programs have been launched to prevent or treat vitamin A deficiency during pregnancy and lactation, both by supplementation (capsules) and bolus injections, but results have been mixed. There is a strong possibility that the outcome of these interventions is dependent on the woman's underlying zinc status. Although previously less recognized than iron, vitamin A and iodine deficiencies, recent estimates suggest that suboptimal zinc status is just as prevalent [11]. It is, however, more difficult to accurately assess the zinc status of human populations, and the prevalence estimates are therefore more uncertain and based on intake data.

Research on experimental animals clearly shows that a low zinc status impairs the vitamin A status. Rats fed zinc-deficient diets had significantly lower serum retinol concentrations than control rats, whereas liver retinol was increased [12]. The reduction in serum retinol coincided with a reduction in serum retinol-binding protein (RBP), the major carrier of retinol in serum [13]. The reduction in RBP was considerably larger than in other serum proteins, which usually occurs in zinc-deficient animals. Using a much more moderate level of zinc deficiency in a non-human primate model, Baly et al. [14] were able to show that a reduction in plasma zinc in marginally zinc-deficient pregnant monkeys was accompanied by a reduction in serum retinol and RBP concentrations. Thus, maternal zinc deficiency during pregnancy causes an impairment in circulating vitamin A levels, which appears to be due to a reduction in serum RBP. This may impair the transport of vitamin A to the fetus, and subsequently, the transport of vitamin A into milk. These observations

may explain why provision of vitamin A to pregnant and lactating women is sometimes successful and in other populations is less effective. Christian et al. [15] showed that zinc potentiated the effect of vitamin A in restoring night vision among night-blind women, but this only occurred in women with low initial serum zinc concentrations. Further studies on vitamin A supplementation of human populations with different zinc status or provided zinc are clearly needed.

Zinc–Copper Interactions

Whereas it is well known that high intakes of zinc or copper can competitively inhibit the absorption of each other, much less is known about interactions between these micronutrients when the intake or status is low. We recently found that rats fed a marginal zinc diet during pregnancy and lactation had normal tissue and milk zinc concentrations, but higher plasma ceruloplasmin activity, and higher milk copper and ceruloplasmin activity [16]. The mammary gland copper transporters Ctr1, Atp7A and Atp7B were all upregulated during zinc deficiency, most likely explaining the higher mammary gland and milk copper concentrations in these animals. Immunostaining demonstrated that the localization of Ctr1 and Atp7A within the mammary gland epithelial cell was altered, which has previously been shown to affect their function. Thus, a marginal zinc-deficient diet could alter copper metabolism in the lactating mother and increase milk copper concentrations, which usually are unaffected by copper intake [17]. These increased milk copper concentrations may have deleterious effects on the offspring, as small intestine copper concentrations were increased, but plasma copper decreased. It is possible that excess copper intake from milk during early life may have an adverse effect on the copper status of the newborn.

Another recent study in Honduras suggested that a similar situation may occur in lactating women [18]. We found that lactating Honduran women had significantly lower plasma zinc concentrations than Swedish women, possibly due to the low zinc intake and/or high intake of factors limiting zinc absorption (e.g. phytate). Honduran mothers also had significantly higher (+33%) milk copper concentrations than Swedish women. Thus, it is possible that marginal zinc nutrition during pregnancy and lactation affects milk copper and that increased milk copper may have adverse effects on breast-fed infants. Further studies are needed to explore this in human populations.

Zinc–Prolactin Interactions

Prolactin is the primary hormone regulating milk protein synthesis and maintaining lactation, and some physiological conditions, such as dieting and malnutrition, have been shown to affect plasma prolactin concentrations in

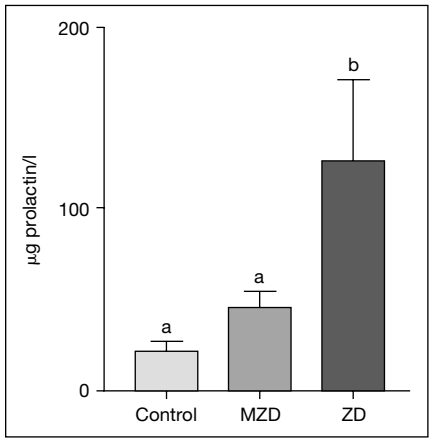

Fig. 1. Plasma prolactin concentrations in rats fed control (25 mg Zn/kg), marginally zinc-deficient (MZD; 10 mg/kg) or zinc-deficient (ZD; 7 mg/kg) diets throughout pregnancy and lactation day 11 (means ± SD). Different letters denote significant differences at $p < 0.05$. Adapted from Chowanadisai et al. [22].

lactating women. McCrory et al. [19] have shown that plasma prolactin concentrations are higher in lactating women who are dieting. In addition, Lunn et al. [20] have shown that plasma prolactin concentrations are higher in lactating Gambian women with poor nutrition, and decrease when they are given dietary supplements to increase their energy intake. Zinc deficiency has been associated with hyperprolactinemia in men [21]; however, the effects of zinc deficiency in women during pregnancy and lactation are largely unknown. It is, of course, quite possible that women who are voluntarily restricting their food intake (i.e., dieting), as well as women with poor nutritional status living in rural settings have suboptimal zinc status.

We have investigated the effects of maternal zinc deficiency during pregnancy and lactation on zinc metabolism, prolactin and lactation performance in rats [22]. We used two levels of zinc deficiency, both of which may occur in human populations; these were achieved by feeding the rats either a marginally or a moderately zinc-deficient diet. Many previous studies in rodent models have used a more severe zinc deficiency, which is unlikely to occur in human populations, except in subjects with the inborn error of zinc metabolism, acrodermatitis enteropathica. We found that plasma prolactin was increased 2-fold in rats fed the marginal zinc diet, and 6-fold in those fed the moderately zinc-deficient diet (fig. 1). Several components of the prolactin regulatory pathway in the pituitary gland were altered and prolactin receptors were significantly lower in the zinc-deficient animals. Milk intake was significantly lower in pups from rats fed both the marginal and moderately zinc-deficient diets. These findings suggest that marginal zinc status during

pregnancy and lactation may compromise milk production despite increased prolactin levels. Thus, the effects of suboptimal zinc status in lactating women on prolactin metabolism and infant breast milk intake should be investigated. In addition, as hyperprolactinemia is known to be associated with decreased bone mineral density and increased risk for osteopenia [23], the consequences for the decrease in bone density occurring during lactation should be explored.

Iron–Zinc Interactions

When it was recognized that suboptimal zinc nutrition may be common in large segments of the population, particularly during pregnancy, various strategies to prevent zinc deficiency were considered. Since zinc is stable in water solution and non-toxic, oral supplements would be one possible avenue. However, in areas where zinc deficiency may be expected, iron deficiency is frequently common, and iron supplements are frequently given. Therefore, Solomons and Jacob [24] evaluated the effect of oral iron on zinc absorption by giving zinc and ferrous sulfate to human subjects in different molar ratios. They found that iron lowered zinc uptake as measured by the increase in plasma zinc at a molar ratio of 2:1. This obviously could be a concern if iron and zinc were to be given together. However, very large amounts of iron and zinc were given because of the method used (plasma area-under-the-curve) and it is conceivable that these two elements would only compete with each other when given in water solution and possibly not when food is present. This was investigated by Sandström et al. [25] who studied zinc absorption at physiological intakes using radioisotopes. When excess iron was added (25:1 ratio), zinc absorption from a water solution was inhibited significantly, whereas no effect was observed when they were given in a meal. As the inhibitory effect was abolished when histidine (chelator of zinc) was added, it was believed that when iron and zinc are chelated to their 'normal' ligands, resulting from digestion of foods, they will be absorbed via different pathways and no interaction would occur. A study by Rossander-Hulthén et al. [26] showed that similar results were obtained for iron absorption in humans when excess zinc was added, i.e. an inhibitory effect of zinc on iron absorption was found when they were given in water solution, whereas no effect was seen if they were given with a meal. These studies strongly suggested that iron and zinc may interact when given as supplements, but that this would not occur when they are given as food fortificants.

Two recent studies on iron and zinc supplementation of Indonesian infants [27, 28] show that antagonistic interactions between iron and zinc do in fact occur when they are given as supplements (drops). In a study by Dijkhuizen et al. [27] infants were given iron alone (10 mg/day), zinc alone (10 mg/day), both elements together (10 + 10 mg/day) or placebo from 4 to 10 months of age. Supplementation significantly reduced the prevalence of anemia, iron

Table 2. Effect of iron (10 mg/day), zinc (10 mg/day), iron + zinc (10 + 10 mg/day) or placebo on iron status and plasma zinc in Indonesian infants supplemented from 6 to 12 months of age

	Fe group	Zn group	Fe + Zn group	Placebo group	p value
Hemoglobin, g/l	119 ± 15[a,b]	116 ± 15	115 ± 14	13 ± 16	0.012
Serum ferritin, μg/l	46 ± 2[a,b]	13 ± 4	32 ± 3[a]	13 ± 4	0.001
Serum zinc, μmol/l	8.8 ± 1.2[a]	11.6 ± 1.4	10.8 ± 1.3[a]	9.1 ± 1.3	0.001

Adapted from Lind et al. [28].
[a]Significantly different from placebo.
[b]Significantly different from Fe + Zn group.

deficiency anemia and zinc deficiency. Iron supplementation did not negatively affect plasma zinc concentrations, and zinc supplementation did not increase the prevalence of anemia. However, iron supplementation combined with zinc was less effective than iron supplementation alone in reducing the prevalence of anemia (20 vs. 38% reduction) and in increasing hemoglobin and plasma ferritin concentrations. There were no differences in growth among the groups, and the growth of all groups was insufficient to maintain their z scores for height-for-age and weight-for-height, showing that overcoming these micronutrient deficiencies is not sufficient to improve growth performance in these infants.

In the study by Lind et al. [28], the infants received the same treatments, but from 6 to 12 months of age. After supplementation, the iron group had higher hemoglobin and serum ferritin than did the iron + zinc group, indicating an effect of zinc on iron absorption (table 2). The zinc group had higher serum zinc than did the placebo group, whereas this was not the case for the iron and iron + zinc groups, suggesting an effect of iron on zinc absorption. Thus, supplementation with iron + zinc was less efficacious than were single supplements in improving iron and zinc status, with evidence of a negative interaction between iron and zinc when the combined supplement was given. In this study, significant effects on growth were observed.

It may be very important to evaluate the outcome of a nutritional intervention in relation to initial nutrient status. In our study in Sweden and Honduras [29], we found a negative effect of iron supplementation on length gain in Swedish infants, but not in Honduran infants, and believed that this was a consequence of the difference in iron status in the two populations. However, when the Honduran infants were divided into iron-sufficient and iron-depleted infants at the initiation of the supplementation, a negative effect on length gain was found for the iron-replete, but not the iron-deficient infants. We speculate that this may be due to excessive absorption of iron in the iron-replete infants, as we have shown that there is no homeostatic regulation

of iron absorption in young infants [30]. Similar evaluations need to be done in interventions during pregnancy and lactation.

A study on pregnant Peruvian women showed that when iron was given alone (60 mg daily) or together with zinc (15 mg daily) there was no difference in hemoglobin or serum ferritin concentrations during pregnancy or in cord blood [31]. Indicators of zinc status did not differ between the 2 treatment groups but were significantly lower than in the placebo group, suggesting that iron supplementation affected the zinc status of the mother and her infant negatively. Zinc absorption studies using stable isotopes showed a negative effect on zinc absorption, most likely explaining the effect on zinc status [32].

Conclusions

A major challenge for us as nutritionists will be to better understand the mechanisms underlying interactions among and between micronutrients and hormones. Such knowledge is necessary to interpret results from intervention studies and to delineate reasons why some studies find adverse outcomes or no effect of multi-micronutrient supplementation [33]. Without this knowledge it will be difficult or impossible to design strategies for eliminating micronutrient deficiencies and improve pregnancy and lactation outcome, both for women and their infants.

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Discussion

Dr. Uauy: I think Dr. Lönnerdal has definitely challenged us all to look more carefully at what we do. One question I would like to ask though: is this at all levels or is this when you go for the big hit like 60 mg iron or 50 mg zinc, is this general? Obviously it is

a generalized phenomenon but to the degree we see here where there are adverse effects because I think that the more you push it the more likelihood the impact. Every time we eat we see this interaction, so probably has to go beyond traditional intakes into more or less pharmacological uses to start to see more of this. Should this make us re-address especially when supplements such as pills. The phenomenon is fully different when the supplements are spread over the day or spread through a meal with a fortified food? So not only is it a dose but also the time in which the dose is delivered and I think the higher the dose and the shorter the time, the more likely you are to have adverse effects. Perhaps I am just being philosophical when I say this, but I am saying this because the problem is not only in the results presented here, but is a more general phenomenon. In fact I think when we start to look at this problem in more detail a lot of the supplements, the more hesitant we should be in using them. Unless there is very severe deficiency, and Would you prefer foods, would you prefer fortified foods when needed? Should we use supplements only under very extreme deficiency for given periods and for given situations? I think the evidence should provided support this view.

Dr. Lönnerdal: You have brought up several very good points. First, it is certainly a matter of dose level. On the other hand I am a little bit skeptical of trying to kind of titrate the dose throughout the day. I don't think it is going to take care of the problem. I have heard people saying that if you give 5 mg iron to children instead of 10 mg, it is possible that you can then lessen the effect. On the other hand there have been studies before saying that they most likely wouldn't benefit from 10 mg. Perhaps they should have 10 mg iron in the morning, 10 mg zinc in the evening, or 10 mg iron on Monday and 10 mg zinc on Tuesday and so on. I think alternative approaches need to be tried and the dose effect in itself would really take too much time and effort. We have an idea where we should be but we have to think along new lines of doing this. When it comes to fortification of course you are right; if we give lower levels and spread it out in the diet the interactions will either disappear or be minimized. In Peru we have fortified the flour which is used and that can be done at central milling facilities. But as you are well aware, in Indonesia there are very few central facilities and what food should be fortified there? I can understand many agencies: if there is definitely a high prevalence of micronutrient deficiencies you have to go in and do something, and the quickest intervention is to do supplementation. On the other hand that is also the one that brings in risks, certainly benefits, but also at the same time risks.

Dr. Di Renzo: A very challenging presentation, but I was a little bit disappointed because you didn't discuss the fourth and probably the most important deficiency micronutrient, which is iodine. There are recent data saying that it is the major micronutrient deficiency in the world [1], and it accounts for the most mental retardation occurrence in the world as well. You just mentioned a little about some antagonism between iodine and some other components. Can you speculate a little bit more? What do you think can be done about iodine deficiency?

Dr. Lönnerdal: I don't have any personal experience with iodine and that is why I stayed away from it. Iodine deficiency is certainly common but I don't think that the prevalence is as high as some of the other micronutrient deficiencies. I think there is much more iron deficiency than iodine deficiency, but that doesn't mean we should ignore iodine deficiency. It is much more geographically confined than iron deficiency. Iron deficiency is spread over all the continents; iodine deficiency is a little bit more geographically localized. We have intervention strategies for iodine and I have seen very little problems with them. The problem with the other micronutrient deficiencies is that we have solutions but when we go in and use them they don't work. When the iodine solutions that we have are being used properly, they will work. There are very recent studies from Switzerland, from Zimmermann et al. [2], showing that you actually have a synergistic effect between iron deficiency and iodine deficiency, and if you give iodine to children or women who have an underlying iron deficiency, the effect

on prevention of goiter will be less efficient. But to what extent that occurs, I don't know, I don't have any personal experience with that.

Dr. Pencharz: The issue that I was reminded of, if I heard you correctly about that Zanzibar study, was a study a number of years ago in which rats were infected with salmonella. It was shown if the rats had a normal iron status a certain number died; if they were mildly iron-deficient a lot more died, and if they were very severely iron-deficient they were protected. So in other words the microorganism needs iron as well as the host and if you then gave iron to the mildly deficient they all died. So in other words giving iron to a mildly deficient host who is also infected with an organism that needs iron puts him at risk. I wonder whether the Zanzibar study was related to having microorganisms that were iron-dependent which put them at increased risk?

Dr. Lönnerdal: A very good point, they have not analyzed that. I talked to the investigators and they are now looking into that. Unfortunately I don't think they will have any classification of the pathogens present. They have controlled for malaria of course, but not for the pathogens. In fact there are quite a few microorganisms that really have this obligatory need for iron and my personal feeling is that the consequences on infection and infectious morbidity in this case may not be a direct iron effect. I would be much more inclined, and this has been showed by many other investigators [3], that zinc status would be impaired and with impaired zinc status, immune function is being impaired. Many of these facets that Dr. Moore talked about are zinc-dependent processes, and in that case I think it may be more the capacity to fight infection than the presence of the pathogen.

Dr. Yin: I am very interested in your study because in China micronutrient deficiencies are very common in pregnant and lactating women. Also there are so many micronutrient supplements on the market. What is the best ratio for iron and zinc in supplements for pregnant and lactating women?

Dr. Lönnerdal: We really don't know too much about that because the studies are too few. This is something that Dr. Uauy also brought up, and we need to look at. The other thing which may be considered, and again I am not marketing any supplement whatsoever, but in this case perhaps the interaction between iron and zinc can be minimized by adding some amino acids, as long as we are not creating an imbalanced supply of amino acids. That may be something that could also be tried. Perhaps Dr. Pencharz has some ideas. But I think we need to look a little bit more widely than just giving the micronutrients alone.

Dr. Pencharz: I don't have any particular ideas, but you got me thinking about what you said and what Dr. Uauy said. My colleague Dr. Zlotkin is using sprinkles. He is supplying a variety of micronutrients by sprinkling them on food, so it would be more nicely distributed, which is sort of Dr. Uauy's idea. Perhaps that is the way we should be going.

Dr. Lönnerdal: Thank you for bringing that up. I think Dr. Zlotkin has a very good idea and he has certainly been participating in these efforts. What he is suggesting is kind of an intermediate; it is food fortification with supplementation levels of micronutrients. The problem here is that we don't have a whole lot of data. In his first study in Ghana there seemed to be an effect of iron on zinc when zinc was added [4]. I still think we need to wait, but it is certainly a good idea to add micronutrients to food. We need to look at some of the studies that he is doing now in several locations all over the world, a very ambitious approach. It is a fascinating idea, it may well work, but he may have been overly ambitious with regard to the levels used. I think that he can actually go down a little bit in levels, which he is also trying now, and still achieve very positive results.

Dr. Ballèvre: I would like to raise another area of interest which is the bioactive proteins of the milk. Can you report any studies which have shown a beneficial effect

of maternal nutrition during pregnancy or lactation on the composition of colostrum or milk?

Dr. Lönnerdal: When it comes to bioactive proteins in the milk?

Dr. Ballèvre: In particular for colostrum and immuno active proteins.

Dr. Lönnerdal: There are very few studies that have shown that. It seems as though the mother is quite capable of self-regulating milk protein synthesis and that nutritional status doesn't have a lot of effect. There are some indications in the Gambia that some of the active proteins would be compromised with poor maternal nutrition [5], but many studies have not found that. I think also that the studies that have looked at these bioactive proteins have looked at very few proteins, and there are many of them. It needs to be done in a much broader context and we also need to find out or get better evidence of how bioactive these are in infants, because they are certainly bioactive in vitro in our laboratories. But we have had a very little direct evidence of efficacy because again we have had no supply on purified proteins. That was a side consequence of this study in which we were expressing recombinant human milk proteins. But not until we have a kilogram of these purified breast milk proteins, can we add them and see if they would have this bioactivity in the context of a non-breast milk matrix.

Dr. Uauy: With regard to hyperprolactinemia associated with zinc deficiency, have you observed any functional effects of hyperprolactinemia in terms of milk volume and milk fat composition, which would be expected, or is this something that is unrelated or you have not evaluated because prolactin plays a role in milk volume and milk fat?

Dr. Lönnerdal: Milk volume was reduced in this case. Milk fat was normal but we haven't looked at the fatty acid composition of the milk, which may be worthwhile doing. Right now we are far more interested in the long-term consequences and will follow these pups longer. For both the mothers and the rat pups this has long-lasting consequences, similar to what we are doing with IGF-I and insulin resistance.

Dr. Butte: There is also the development of different fortified drinks, perhaps somewhere in between the supplement and the actual food fortification. Do you have any experience with these various drinks fortified with multiple nutrients at once? Could you also comment on the efforts to supplement with calcium and maybe with B_{12}?

Dr. Lönnerdal: I don't have any experience with B_{12}. I don't think that it is prone to interact at the absorption level. We have done some studies on B_{12}-binding protein in breast milk in infants, but it is not that population you are talking about. Calcium may be a concern for iron; if it is given in a liquid there is an interaction between them, if it is given in a food there is not an interaction between them. There is an adaptive response with time, but we don't know to what extent it is occurring. It depends a little bit on what the drink is made of. If it is a straight juice in which there aren't a lot of proteins and so on, you may expect more interactions than you would if it is a milk shake or something like that or somewhere in between. But I don't have any experience with that. Normally when we look at infant formula, the protein there would usually take care of most of these interactions that you would see happen in water solutions.

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