Nutritional Supplementation and the Outcome of Pregnancy

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GUATEMALA STUDY

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The subject of this meeting is of great interest to us, because we find every day that we know very little about the effects of maternal nutrition on the outcome of pregnancy, although we have studied them for some time. I will be discussing these effects later, but first let me remind you that many people have been involved in our study and I am but a spokesman of the team.

Dr. Robert E. Klein, who is the Director of the Division of Human Development, is an experienced child psychologist. The previous directors of this project, or its antecedents, were Dr. Joaquín Cravioto and Dr. Cipriano Canosa. My closest colleagues at the Instituto de Nutrición de Centro América y Panamá (INCAP) are Dr. Charles Yarbrough, our statistician, and Dr. Guillermo Guzmán, field director, and above all, Dr. Aarón Lechtig, who has been responsible for the area we will be discussing, which is the prenatal period. Much of the methodology and most of the analyses have been done with Dr. Lechtig (Lechtig *et al*, in press, 1972a, b).

INCAP has a contract with the National Institute of Child Health and Human Development to elucidate the relationship between chronic malnutrition and mental development. Originally, the experimental design concentrated on children between the ages of weaning and 7 years, on the assumptions that the first years after weaning were the period of maximum malnutrition, and that stable estimates of mental development could be made by 7 years of age. Very quickly we discovered that we could not do this and that we would have to start investigations of intrauterine life.

There were three reasons for doing this:

1. Animal experiments and retrospective studies in children had revealed that the human intrauterine period was a period of great vulnerability for the central nervous system. Knowledge of fetal nutrition would therefore be necessary to fulfill the mandates of our study to clarify the effects of malnutrition on mental development.

2. Protein malnutrition in animals produces a syndrome of hyper-excitability and lack of purposiveness in behavior after the animals have been nutritionally rehabilitated. Similar behavior is known to be congenitally acquired in man, but on a nonnutritional basis. It might be expected that children with such behavioral charactistics would be at more risk of becoming malnourished since they would be less able to compete for food within the home, leading to an association between malnutrition and behavioral peculiarities. However, this association would not be caused by malnutrition. The identification of children at risk as those having these behavioral characteristics on a congenital, and not nutritional, basis is, therefore, important, and is a task that must be tackled at birth or before.

3. We had reason to suspect that intrauterine infection was prevalent in our study area.

When we started investigating the intrauterine period, we reviewed the literature for the effect of deficient nutrition (Lechtig *et al*, 1971). The evidence that severe caloric restriction influences birth weight is clear in the literature. That chronic protein or caloric malnutrition influences birth weight has been only associative in the literature so far; in populations where chronic malnutrition is evident, one also finds low birth weight. However, we have found in such populations that 60 percent of the children born have high *gamma* globulin $_{\gamma}$-^{M} (IgM) levels in the cord blood, which would indicate a very high rate of intrauterine infection, compared with, for instance,

the highest rates reported in the United States--4 percent for poor blacks in Alabama. This might be a cause for low birth weight; so the association between an inadequate diet and low birth weight may only be incidental, in that a poor diet is just one reflection of economic underdevelopment.

Some intervention studies employing supplement have been carried out in pregnant women. But there have been two difficulties: Either the studies lacked controls for self-selection biases or the subjects have been moved to new environments during the supplementation. After subjects had been moved, one could not be sure whether the effect on birth weight was due to the supplement or to other factors in the hospital environment in which the mothers were placed, such as a reduced probability of intrauterine infection.

On the other hand, there are a number of studies that show no effect of diet on birth weight, but if you look at these studies carefully, a few things are obvious. In a number of them, the investigator did not know how to measure diet. Since their methods were not adequate to measure real variations in the diets, it is not surprising that they did not show any variation in birth weight. Some studies had adequate measurements, but the variability or the dietary intake was over such a small range that they could not show a variation in birth weight. There is one study in which the extreme was very malnourished mothers, but with a very restricted range, and the report showed no variation in birthweight within this range. Most intervention studies have been carried out in mothers that appear to be optimally nourished. In this population, however, there may be about 10 percent that are suboptimally nourished. When the data are analyzed to determine the effect of supplement on birth weight, the benefit of the supplement to the small proportion of the total population is not evident, and the results of the study show no association between diet, supplementation, and birth weight.

We have tried to avoid these pitfalls. The pitfall we have not managed to avoid so far is that we have small numbers, and we will never have large numbers. We do get demonstrable differences, but that may be simply because we have bigger changes to show.

The experimental design to investigate the effects of nutrition on mental development requires working with Spanish-speaking populations in rural villages in Guatemala. I mention this because INCAP is well known for its studies in Indian populations. Only half of Guatemala is Indian; the other half is Ladino of Hispanic culture. Because of psychological testing, we work with Spanish-speaking populations in four villages, two of which receive a supplement containing 91 calories and 6.4 g of protein/100 ml plus vitamins and minerals. The other two villages, until recently, received a supplement surrogate.

The surrogate (a prepared drink) was nonnutritional except for 33 calories/100 ml. We have recently added fluoride and vitamins to the surrogate. I will explain why later.

The total sample consists of 262 mothers. With such small numbers, there is a risk that maternal characteristics that affect birth weight, but are not related to nutrient intake during pregnancy, appear by chance more frequently within one of the groups than would be the case if we had larger numbers. Larger numbers would ensure greater stability in sampling variation. We adopted the strategy of first identifying all characteristics that might influence birth weight and are not related to nutrition during pregnancy. We then corrected each birth weight for these characteristics.

The characteristics that do not reflect nutritional status of the mother during pregnancy but do affect birth weight are the mother's age, number of previous pregnancies, previous births, maternal height, and maternal weight in the first trimester. The sex of the child also affected the birth weight.

In order to correct for nonnutritional characteristics related to birth weight, we chose to correct all the birth weights for the height of the mother, the parity of the child, and the sex of the child. With respect to the number of previous births, the effect is more or less linear, until higher parities (eight or more) are reached. When we corrected all the birth weights for the mother's height, the parity, and the baby's sex, we found that until one reached parity 8, interval had no effect. After parity 8, the birth weights differed, the amount depending on the length of the spacing since the previous pregnancy.

We found that above parity 8 and for birth intervals of less than 18 months, the children were smaller than at intervals greater than 18 months. This is possibly an indication of a nutritional effect in the recuperation of the mother from previous pregnancy.

Another factor probably related to nutrition is weight gain during pregnancy, which, of all the variables investigated, is the one most strongly associated with birth weight. Of course, the height of the mother reflects her childhood nutrition, but our concern is restricted to nutrition during pregnancy.

Now, we turn to the dietary intake of these mothers. Vitamin A intake was found to be very inadequate. Regardless of whether it is a 24-hour recall, or a 72-hour recall, or a whole week of measuring, we always find that most of the people have less than 40 percent of the recommended allowance of vitamin A.

However, when we look at the variability of these dietary methods, we find that the coefficient of variation of the vitamin A estimates is about 250 percent. This imprecision just does not allow individual classification.

Furthermore, when we did a biochemical survey of children and of lactating mothers, we found that vitamin A was never in a deficient range.

Therefore, we decided that vitamin A is not a nutrient with which we could deal, and we now give adequate amounts of vitamin A to both the control group and the supplemented group. Essentially the same considerations hold for riboflavin and iron. Our study is, therefore, investigating only protein and calorie nutritional status. For protein, the coefficient of variation of estimate by dietary surveys is 20 percent; for calories, about 10 percent. This is small, compared with the coefficient of variation for these nutrients in the population itself.

The association between calories and proteins in pregnant mothers--this does not hold for children--has a correlation coefficient of 0.8. But with a coefficient of variation of 20 percent in proteins; the highest correlation coefficient that you could possibly get is 0.8. This means that there is no easy way to separate the ingestion of proteins from the ingestion of calories in the diets of these women. I am going to talk about caloric intake, but it could just as easily be an effect of protein as an effect of calories. At the end of the discussion, I will give some indication of which may in fact be limiting.

We now get practically all women within the first month or so of pregnancy, but at the beginning of the study we did not. Some women came in early and some came in late, and we thought that there could be a selective factor associated with the diets--that women who cooperated were more intelligent and would have better diets than those who did not. We looked at the intakes, noting whether they were related to the number of surveys these women had during the pregnancy. The number of surveys made no difference in the diet. Our fears of self-selection bias were thus unwarranted as far as

home diets are concerned. Now we have increased the interval between surveys to 3 months over the whole of pregnancy, because the variability of these two nutrients, proteins and calories, is low enough to make three estimates suffice.

During the first trimester, nutrient intake is less than during the next two trimesters. So, in all the results reported here, we have taken the mean of the second and third trimesters and have not included the information from the first trimester.

We studied variation of birth weight with caloric intake, as estimated by the dietary surveys, and at very low levels the birth weight is less than at slightly higher levels.

Factors other than diet, such as the infections we talked about, may vary with caloric intake. It may be that these other factors affecting birth weight are associated with diet but are not parts of a cause-and-effect relationship. The only way to be sure that this is not the case is to do an intervention study in which you supplement the people in such a way that selection for a supplemented person is the same as selection for a control person.

As I mentioned before, we distribute a supplement and record the amount of supplement ingested in two experimental villages, and we do exactly the same with a supplement surrogate in the two control villages. There are no differences between the mothers in the control and those in the experimental villages with respect to home caloric intake per day, days of disease per month, or maternal height. There is a significant difference in parity, but when we analyze the data, both including and excluding mothers with high parity, we find it makes no difference in the outcome.

Within each of the four villages in our study there are people who attend and people who do not attend the central feeding centers. We have examined the data on the supplemented mothers at various numbers of liters of intake throughout pregnancy. For mothers who drank less than 10 liters, there were no significant increases in birth weight, compared with those who drank no supplement. For mothers who drank more than 30 liters, there were significant increases in birth weight (Figure 1). On the other hand, for those mothers who drank 30 liters of the surrogate, equivalent in calories to less than 12 liters of supplement, there was no effect on birth weight.

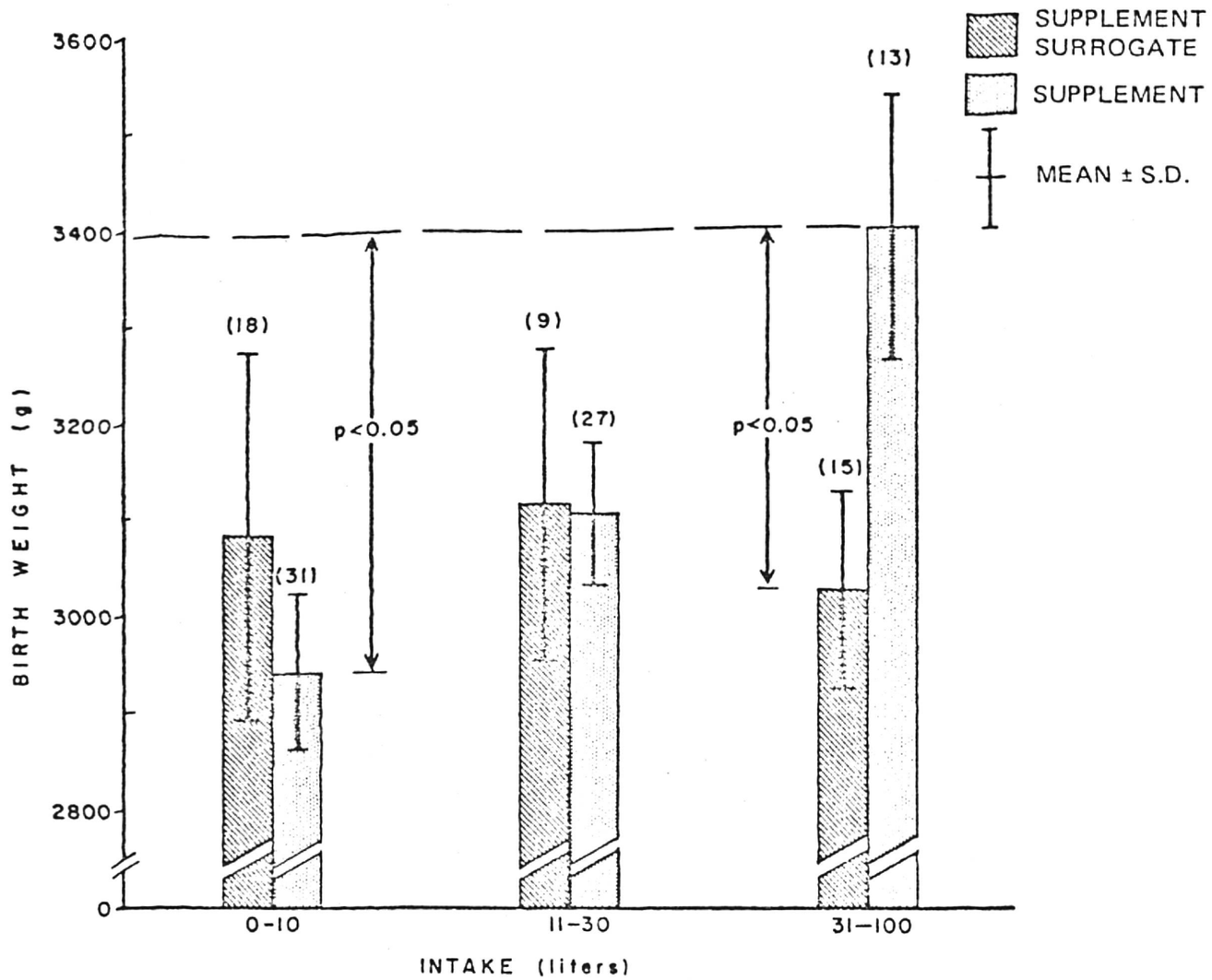

FIGURE 1 Birth-weight in relation to intake of supplement and of supplement surrogate. The surrogate is a no-protein, low-calorie prepared drink.
Source:

Based on Figure (IN-71-342) which appeared in "Lechtig, A., Habicht, J-P, de León, E., and Guzmán, G.: Influencia de la nutrición materna sobre el crecimiento fetal en poblaciones rurales de Guatemala. II Suplementación alimentaria." *Archivos Latinoamericanos de Nutrición*, 1972, XXII, (1) 117-181

The problem remains that this is not a double-blind study and we are not sure that we do not have differential selection factors working in these villages. The first factor to consider would be the differential appeal for the drinks, the supplement, and the surrogate. We never say that one supplement is nutritional and one is not. The appeal to people to come to the centers is not made on a nutritional basis. We have implemented a common appeal by incorporating fluoride into both the supplement and the surrogate, because we have a very high incidence of caries in these villages and a very low fluoride content in the water. Thus, we say to both groups that the pregnant and lactating women and the children should come to prevent dental caries in the children. As I said earlier, we also add all the other nutrients that we cannot measure in the home diets and that might be limiting in the home diets.

The second factor to consider would be measures of self-selection. These control and experimental villages were chosen to be as closely matched as possible, in size, demographic composition, occupation of the inhabitants, and so on. They are very small villages. The general feeling of anthropologists and other people was that they were homogeneous and, therefore, one did not have to worry about any sort of selection factor that would be related to socioeconomic differences. On the other hand, some anthropologists said that in every community there is heterogeneity and it is just a matter of measuring enough things to find it.

We measured 800 items, such as the number of machetes (bush knives) in the house and the number of rooms in the house. In fact, two measures, each composed of a group of related items, turn out to be related (correlations of ± 0.3) to both physical growth and mental development. One was an index showing how good and how big the house was. The other appraised parents'

concern about the education of their children. Did one take the child aside and say "Now you get dressed like this," or did one just let the child learn by watching? We found that both of these are related to the subjects' attendance at the supplementation centers, but they are related in exactly the same fashion in the control villages and in the supplemented villages. On these bases, we feel that high and low supplement consumers are comparable, respectively, with high and low surrogate consumers and that the birth-weight differences presented in Figure 1 are causally related to nutrition during pregnancy.

The final question is "Is it calories or is it proteins that are limiting in the maternal home diets?" From all that I have said up to now, there is no way of knowing. Fortunately, some people like the surrogate so much that they drink a tremendous amount of it; thus we can look at a wide range of calorie ingestion. We found that both those mothers who drink 27,000 calories of supplement and those who drink an isocaloric amount of the surrogate have a significant increase in the birth weight of their children. Those who drink the surrogate have somewhat smaller babies, though not significantly so. This would indicate that calories have an effect that is independent of the effect of protein.

With this evidence I think one can accept as fact what we have suspected all along: Chronic maternal calorie-protein malnutrition during pregnancy does reduce the birth weight, and appropriate supplementation can increase the birth weight substantially. The effects shown here are in the order of 10 percent (Figure 1). The next vital question is whether this increase in the quantity of the baby has any effect on the present and future quality of the baby. To answer this question, we are collecting data on the babies' vitality at birth and their psychological and physical development through 7 years of age.

REFERENCES

Lechtig, A., J. P. Habicht, G. Guzmán, and E. M. Girón (In press). Influencia de las caracteristicas maternas sobre el crecimiento fetal en poblaciones rurales de Guatemala. Arch. Latinoamer. Nutr.

Lechtig, A., G. Arroyave, J. P. Habicht, and M. Behar. 1971. Nutricion materna y crecimiento fetal. Arch. Latinoamer. Nutr. 21:505-530.

Lechtig, A., J. P. Habicht, E. de León, G. Guzmán, and M. Flores. 1972a. Influencia de la nutrición materna sobre el crecimiento fetal en poblaciones rurales de Guatemala. I. Aspectos dietéticos. Arch. Latinoamer. Nutr. 22:101-115.

Lechtig, A., J. P. Habicht, E. de León, and G. Guzmán. 1972b. Influencia de la nutrición materna sobre el crecimiento fetal en poblaciones rurales de Guatemala. II. Suplementación alimentaria. Arch. Latinoamer. Nutr. 22:117-131.