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## Nutrition and Growth

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The objective of the decade is to move forward with emphasis on the role of the United Nations in promoting economic development and absolute poverty eradication today. The advances in science and technology of underdeveloped countries, Saharan Africa, are taking place rapidly, ushering in a new era. These changes will therefore, as well as many others, lead ahead to a more prosperous society. Both the United States and Santiago.

Among the major goals to generate employment opportunities about the world's population, individual health and family planning, disease prevention, education, shop, health care, etc., "Linear programming," two have learned from it was presented by speakers. The speakers learn and to identify the problems.

We thank

## Recent Advances in Nutrition and Intrauterine Growth

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Intrauterine growth retardation (IUGR) is a significant public health problem in many parts of the world and is associated with a range of adverse consequences, both short term and long term. The etiology of IUGR is complex and may vary by setting. Kramer (1), in his classic review over a decade ago, identified several causal genetic and environmental factors including smoking, nutrition, and infections such as malaria. A comprehensive set of articles reviewing the extent, causes, and consequences of IUGR was recently published as a supplement in the *European Journal of Clinical Nutrition*, based on presentations made at the International Dietary Energy Consultative Group (IDECG) Conference in 1996 (2,3). In this chapter, we will focus on recent advances that have been made in the last 3–4 years, especially on the role of nutrition. The first section provides an update on the extent and nature of the problem, including recent advances in the timing of IUGR, and it is followed by a brief discussion of the importance of nonnutritional factors such as malaria, hypertension, and smoking. The third section will focus primarily on the role of nutrition before and during pregnancy and will include recent evidence from experimental trials and programmatic interventions. The implications of the findings and future directions are discussed in the last section.

### THE EXTENT OF THE PROBLEM

#### Prevalence and Patterns of IUGR in Developing Countries

The true extent of fetal growth retardation has been difficult to estimate, and one of the major barriers has been inconsistencies in terminology (4). Smallness for gestational age (SGA), defined as below an established cutoff (e.g., the 10th centile of weight for known gestational age), is commonly used to denote fetal growth retardation and is therefore considered to be the appropriate indicator of IUGR. However, low birthweight, defined as <2,500 g at birth, is more widely used as a proxy for IUGR, but it fails to account for the effect of length of gestation. For example, in many

developed countries, more than half the low-birthweight infants are preterm (<37 weeks of gestation) and not necessarily growth retarded (5). In contrast, most low-birthweight infants in developing countries are born at term and are growth retarded. The latest United Nations Children's Fund (UNICEF) regional estimates for low birthweight are 33%, 20%, and 11% in South Asia, Sub-Saharan Africa, and Latin America, respectively (6). Recently, De Onis *et al.* (2) proposed the use of "term IUGR," namely, term infants (>37 weeks of gestation) who weigh below 2.5 kg, as a proxy for IUGR and estimated the overall rates of IUGR and term IUGR in developing countries to be 23.8% and 11%, respectively. As expected, the risks of being term IUGR were the highest in Asia, followed by Africa, Oceania, and Latin America.

In contrast to low birthweight, data on stunting at birth are limited. Data examining trends in IUGR are also limited. Steckel *et al.* (7), in a historical overview of IUGR, showed significant reductions in the prevalence of low birthweight in the last 100–150 years in developed countries. Although the data on the trends in the prevalence of stunting and underweight in young children in the last 25 years can be used to estimate changes in IUGR over time (8), there is a need to collect more reliable estimates, especially in developing countries, to assess progress in our efforts to address this public health problem.

### Reliability of Estimates

The reliability of estimates of the prevalence and pattern of IUGR in developing countries depends on various factors. Gestational age estimation is a considerable problem in many developing country settings, where many women may not recall the date of their last menstrual period or have access to early second trimester ultrasound. Likewise, the reliability of birthweight estimates depends on the quality of equipment and consistency in methods of taking weight measurements. Finally, although many of the estimates discussed in the previous section are based on national data, the extent to which these are representative is difficult to determine. In many regions of Africa, Asia, and Latin America, a large proportion of deliveries occurs in homes or small health clinics. Information regarding birthweight and gestational age is often not available from this setting, and its reliability, when available, may be questionable. This would likely result in an underestimation of the prevalence of IUGR in these regions, as lower-income higher-risk groups may be the least likely to be included in hospital- or urban-based datasets. The need to determine the extent to which data from developing countries are truly representative of the population has been identified previously (2) and continues to be a priority.

### Timing of IUGR

As well as considering what factors influence fetal growth, it is important to assess how the timing of certain insults during pregnancy may affect the growth of the fetus. There is much published evidence for the existence of two types of IUGR. At birth, the classification is typically made on the basis of Rohrer's ponderal index

[birthweight (g)/(birthweight)<sup>3</sup>]. The severity of IUGR is classified as mild (10–13) and possible early in gestation in proportionate IUGR, and as severe (14–16) and possible late in gestation in disproportionate IUGR. In the latter part of pregnancy, the fetus may be asymmetrical or disproportionate. Recently, attempts to assess nutritional status at birth, and length at birth, and women with low pre-pregnancy weight gain during pregnancy, weight at birth but underweight at a greater age, infants, and in this population. In a sample from the first trimester was associated with repeat ultrasound measurements of growth, the rate of growth was not between the second and third trimester growth (16). These findings suggest that IUGR, it may be useful. Further clarification of the timing of interventions, and nutritional ones, have

### ROLE OF NONNUTRITIONAL FACTORS

This section contains information that has been implicated in the etiology of IUGR. These are observational, and we will briefly discuss the results.

### Infection

Kramer (1) recognized the importance of birthweight in determining the magnitude of the effect. Due to the fact that women who have a higher density of blood films from the placenta at the time of delivery are primigravidae, with a higher parity, regardless of parity

[birthweight (g)/(birth length)<sup>3</sup> (cm<sup>3</sup>)]. Although the ponderal index is related to the severity of IUGR (9), it also appears to be related to the consequences of IUGR (10–13) and possibly to its etiology. It has been hypothesized that insults that begin early in gestation influence all aspects of fetal growth and result in symmetrical or proportionate IUGR (those with an adequate ponderal index), whereas insults occurring in the latter part of gestation influence primarily fetal weight gain and lead to asymmetrical or disproportionate IUGR (those with a low ponderal index) (5). Recently, attempts have been made to address this issue using measures of maternal nutritional status at different periods during pregnancy as predictors of birthweight, length at birth, and body proportionality. Neufeld *et al.* (14) found that among women with low prepregnant body mass index (BMI) from rural Malawi, a low rate of weight gain during the early/mid and late gestation was related to infant length and weight at birth but unrelated to infant ponderal index. In addition, women who gained weight at a greater rate during early to midpregnancy tended to have slightly longer infants, and in this population, longer infants tended to have lower ponderal indexes. In a sample from rural Guatemala, maternal nutritional status during the second trimester was associated with both birth length and birthweight (15). In a study using repeat ultrasound measures of tibia and femur length as proxies for fetal linear growth, the rate of maternal weight gain between the first and second trimesters, but not between the second and third trimesters, was related to the rate of fetal long-bone growth (16). These results suggest that, in terms of understanding the etiology of IUGR, it may be useful to consider weight and length at birth as separate outcomes. Further clarification of these relations could have important implications for the timing of interventions and may shed light on why some interventions, particularly nutritional ones, have not been effective at reducing IUGR.

### ROLE OF NONNUTRITIONAL FACTORS IN THE ETIOLOGY OF IUGR

This section contains a brief review of the role of nonnutritional factors that have been implicated in the etiology of IUGR. The majority of the studies presented here are observational, ecological, or studies conducted in animal models. In each section, we will briefly discuss the implications of the study design for the interpretation of the results.

#### Infection

Kramer (1) recognized malarial infection as one of the established causes of low birthweight in developing countries and identified the need to determine the magnitude of the effect. During pregnancy, women are more susceptible to malaria and tend to have a higher density of parasitemia than nonpregnant women (17,18). With use of blood films from the maternal side of the placenta, *Plasmodium falciparum* infection at the time of delivery was associated with a reduction in birthweight of 130 g in primigravidas, with no effect in multigravidas (19). Others have found similar effects regardless of parity (20). There is some evidence that subsequent pregnancies are

protected by immunity to the organism acquired during the first pregnancy (18). Whether immunity does reduce the risk of IUGR associated with malarial infection in multigravida women needs to be confirmed. Malaria is also a cause of maternal anaemia in many developing countries, which in turn may be related to poor intrauterine growth and low birthweight because of preterm delivery. The use of effective malaria prophylaxis (mefloquine, 750-mg dose plus a weekly dose of 250 mg) has been shown to reduce the prevalence of IUGR in a nonblind, random-assignment controlled trial (compared with no treatment or treatment with chloroquine) (20). The prevention of malaria with strategies such as insecticide-impregnated bed nets should be further investigated as a means of reducing IUGR in malaria-endemic regions (19,21).

In a recent review of the literature, it was concluded that urinary tract infections during pregnancy are associated with low birthweight resulting from preterm delivery but not with IUGR (22). Although the evidence for the relation between sexually transmitted diseases and pregnancy outcome is weak, mainly because of limitations in study design, the importance of this relation has been stressed owing to the high prevalence of sexually transmitted diseases in some developing country populations (23). *Chlamydia trachomatis* (24) and syphilis (25) detected at the beginning of pregnancy or at delivery were not associated with birthweight or the prevalence of IUGR. Others have reported evidence that *C. trachomatis* infection may be associated with low birthweight resulting from preterm delivery (26).

In an attempt to find viable options in regions where the cost of individual detection and treatment is prohibitive, a randomized double-blind placebo-controlled trial of the administration of a single dose of the antimicrobial drug cefotaxime/pivoxil (a derivative of ceftriaxime) was conducted in a population of high-risk women from Kenya (23). The treatment was associated with higher mean birthweight (153 g;  $p = 0.01$ ) and a trend toward a lower risk of low birthweight (4% vs. 9.2%;  $p = 0.08$ ) in the treatment group. Although not specific to any one organism, this type of intervention may shed some light on the relation between sexually transmitted diseases and fetal growth. Various studies have reported an association between human immunodeficiency virus (HIV) infection and birthweight (27,28). Adequate control of confounding, particularly HIV infection and nutritional status during pregnancy, may eliminate the relation between HIV infection and fetal growth (29,30). Few studies have examined the significance of the interaction between nutrition and infection in the etiology of IUGR.

## Hypertension

There is considerable evidence of a relation between pregnancy-induced hypertension (PIH) and an increased risk of IUGR, particularly when pre-eclampsia occurs and if PIH is accompanied by proteinuria (31). There is some inconsistency in the findings for less severe PIH. These inconsistencies have been attributed to (a) lack of control for confounding factors such as parity, smoking, and multiple gestation, (b) lack of consistency in the definition of hypertension during pregnancy (chronic hypertension, gestational hypertension, pre-eclampsia, eclampsia) and of the outcome

variables (low birthweight due to length of gestation and/or fetal growth), and (c) inadequate sample sizes (32,33). Calcium deficiency may be an important factor in the development of PIH. In a recent meta-analysis of controlled trials, calcium supplementation during pregnancy was shown to result in a twofold reduction in the incidence of hypertension and pre-eclampsia, but only among women at high risk of PIH or with low dietary intakes of calcium or both (34). The extent to which PIH contributes to IUGR in developing countries needs to be established, as does the role that calcium may play in alleviating this problem.

### Environment

There is strong evidence of a causal link between exposure to cigarette smoke during pregnancy and poor fetal growth. Increased carboxyhemoglobin from carbon monoxide and nicotine and reduced placental blood flow resulting in low fetal tissue oxygenation appear to be the principal mechanisms responsible for restricted fetal growth in smoking mothers (35). On the basis of several well-designed studies, an effect size in the range of 100–450 g has been reported (1,31,36,37) as well as a dose-response relation between the number of cigarettes smoked and birthweight reduction (36). Reductions are also reported in infant length, head circumference, and various other anthropometric measures (36,37). The infants of women who smoked at the beginning of pregnancy but ceased to smoke during the first trimester have birthweights similar to the infants of nonsmoking women, supporting the evidence for a causal relation between smoking and IUGR.

Exposure to environmental tobacco smoke has also been associated with reduced birthweight and IUGR. Reported effect size ranges from 25 to 200 g (37,38), with an increase in risk of IUGR between two- and fourfold (32). In the meta-analysis published by Kramer (1), cigarette smoking was not considered to be a major contributor to fetal growth retardation in developing countries owing to the low prevalence of maternal smoking. However, this may no longer be true in some settings, and, more importantly, the possibility of retarded fetal growth caused by exposure to environmental tobacco smoke, both at home and in the workplace, in a developing country setting needs to be investigated.

Both carbon monoxide and particulates have been found in high concentrations in the homes where biomass fuels are burned in open fires for cooking, and women who use open fires have been found to have raised levels of carboxyhemoglobin (39). It is difficult to establish whether birthweight is influenced by indoor air pollution in observational studies, owing to the high correlation between socioeconomic status and other predictors of IUGR and the type of stove used (40). The possibility that smoke from the burning of biofuels for cooking in rural areas of developing countries influences birthweight needs to be investigated using methods that can establish causality.

Reports of a relation between outdoor air pollution and fetal growth are typically based on ecological studies from which it is difficult to infer causality. A negative association between total suspended particulates, sulfur dioxide, and birthweight or risk of low birthweight has repeatedly been reported (41–43). In one study controlling for

confounding on an individual basis, a dose-response effect was found between both particulates and sulfur dioxide and risk of low birthweight (42). Studies that replicate previous findings in different regions and databases, distinguish effect on fetal growth *versus* duration of pregnancy, provide adequate control for confounding, and describe a biologically reasonable mechanism would provide strong evidence for the existence of a causal relation between outdoor air pollution and fetal growth.

Various ecological studies have been conducted to evaluate the association between exposure to herbicides and the risk of IUGR. An increased risk of IUGR (relative risk 1.8; 95% confidence interval 1.3-2.7) was found in 13 communities served by a herbicide-contaminated water source in rural Iowa in comparison with communities with noncontaminated water (44). The relation persisted after control for several confounding factors at the community level. Similar results were found in a study of the influence of exposure to wood preservatives on fetal growth (45). These results have all the same limitations related to study design that are discussed above. Owing to the high prevalence of use of herbicides in rural communities, these results should be confirmed in studies with more rigorous design.

### Sociodemographic and Genetic Factors

Various sociodemographic characteristics have been associated with fetal growth. Female infants and firstborns tend to have lower birthweights and higher rates of IUGR, without associated negative consequences (4). There is also a tendency for birthweight to increase with increasing parity, and studies have reported increases of 100-200 g in birthweight in each subsequent pregnancy (46). At higher parities (five or more), birthweight may then begin to decrease again. Adolescent pregnancy is associated with lower average birthweight and higher rates of IUGR, particularly if the mother has not yet ceased to grow (47). In developed countries, adolescent pregnancy may be further complicated by a high prevalence of other risk factors for IUGR, such as low maternal weight before pregnancy and low weight gain (48). Similar conditions may exist in developing countries, and one strategy to reduce the prevalence of IUGR may be to delay the first pregnancy. Both short and long birth intervals have been associated with a higher incidence of IUGR (49,50). The length of the "ideal" interval, however, appears to vary by population and may be highly associated with socioeconomic and cultural factors such as length of lactation, diet, and maternal work demands, among others. It has been observed that women of low socioeconomic status tend to have a higher prevalence of IUGR babies. The extent to which this relation is mediated by various maternal factors including health and diet has been clearly shown (51). The role of women's status in the etiology of IUGR, especially in settings such as South Asia where gender bias is common, has also been suggested but remains to be demonstrated (52).

In a classic study of siblings and twins published in 1955, Morton (53) concluded that the resemblance in birthweight between siblings is attributable mainly to the similarity of the intrauterine environment in subsequent pregnancies. Polani (54) estimated that the fetal genotype in humans accounts for approximately 15% of the

variation in birthweight. In Scandinavia, Morton (53) found a correlation between infant birthweight and birthweight at birth ( $r = 0.117, p < 0.05$ ). Birthweight was also higher in women who had a previous pregnancy (4), and it is difficult to distinguish the effects of environmental stresses from genetic factors.

### RECENT ADVANCES IN IUGR

Kramer (1) concluded that the majority of IUGR cases are accounted for by maternal factors. However, most studies are cross-sectional, and the influence of anthropometric factors on pregnancy outcome has not been fully established. Although there have been many studies, the role of maternal factors on the role of IUGR remains unclear. On evidence from epidemiologic and genetic studies, the role of maternal factors in IUGR is still unclear.

### Preconception

Maternal prepregnancy weight has been studied in many studies, such as BML, and has been found to be a predictive indicator of IUGR. A study of over 1000 women in a collaborative study concluded that low prepregnancy weight was a risk factor for IUGR. A study of 19 women with IUGR in severe form concluded that low prepregnancy weight was a risk factor for IUGR. A study of 19 women with IUGR in severe form concluded that low prepregnancy weight was a risk factor for IUGR. A study of 19 women with IUGR in severe form concluded that low prepregnancy weight was a risk factor for IUGR.

The interrelationship between prepregnancy weight and pregnancy outcome is still unclear. The woman's status in the etiology of IUGR, especially in settings such as South Asia where gender bias is common, has also been suggested but remains to be demonstrated (52).



variation in birthweight. In a recent study of successive births conducted in Scandinavia, Magnus *et al.* (55) found a significant correlation between mother and infant birthweight ( $r = 0.205$ ,  $p < 0.001$ ) as well as father and infant birthweight ( $r = 0.117$ ,  $p < 0.001$ ), suggesting an influence of genetics on fetal growth. Maternal birthweight was also the lowest for the group of infants who were born to women who had a previous SGA birth. It should be noted that in developing countries, the many environmental influences on fetal growth are likely to obscure genetic effects (4), and it is difficult to rule out similarity of environment stresses including nutritional stresses between generations or the influence of intergenerational effects.

## RECENT ADVANCES IN UNDERSTANDING THE ROLE OF NUTRITION IN IUGR

Kramer (1) concluded that maternal nutritional factors both before and during pregnancy accounted for >50% of low birthweight in many developing countries. However, most of the evidence was based on the prepregnancy nutritional status using anthropometric criteria and the adequacy of energy and protein intakes during pregnancy. Although IUGR remains a significant public health problem, advances have been made in our understanding of the role of nutrition in its etiology: for example, the role of micronutrients and intergenerational effects. Here, we will focus on the role of nutrition before and during pregnancy, the discussion based primarily on evidence from research studies. Then, we will examine the evidence from programmatic interventions.

### Preconceptional Nutritional Status

Maternal prepregnant size is a well-known determinant of birth size. The most widely studied indicators are height, weight, mid-upper arm circumference, and indexes such as BMI. Prepregnancy weight has been shown in several studies to be a sensitive indicator of the risk of delivering an IUGR infant. Based on a large meta-analysis of over 100,000 women in 25 population groups from all over the world, the WHO collaborative study on maternal anthropometry and pregnancy outcomes (56) concluded that *low prepregnancy weight* was the best single indicator of an increased risk of IUGR (odds ratio 2.55). Maternal height, prepregnant BMI, and mid-upper arm circumference were less predictive, with odds ratios ranging between 1.7 and 1.9. Short maternal height, however, has been associated with an increased risk of IUGR in several populations, and cutoff points between 140 and 150 cm have been proposed for screening. It is also the best simple indicator for the risk of obstetric complications. Finally, a recent study has proposed calf circumference as a useful indicator predictive of the risk of delivering an IUGR infant (57).

The interrelation between preconceptional nutritional status and weight gain during pregnancy is also important. In East Java, Kusin *et al.* (58) found that the lower the woman's prepregnant BMI, the more weight she was likely to gain during pregnancy. However, prepregnant nutritional status remained the major determining

predictor of low birthweight. The optimal anthropometric indicators for both risk detection and intervention targeting are prepregnancy weight (odds ratio 2.55) and attained weight at midpregnancy, that is, at 20 weeks (odds ratio 2.77), and their value is significantly enhanced if they are combined (56,59). The WHO collaborative study concluded that low prepregnancy weight with consistently low relative weight gain, which is common in many developing country settings, results in a fivefold increased risk of delivering a growth-retarded infant. Only if a woman gained at least 10.5 kg during pregnancy could she expect, on average, to deliver an infant weighing  $>3$  kg, regardless of where her prepregnancy weights fell between the range of 44–54 kg. This, however, may not be feasible in many of these settings, where weight gains range between 5 and 9 kg, and point to the need to give at least equal importance to preconceptional nutritional status and to weight gain during pregnancy.

### Interventions to Improve Preconceptional Nutritional Status

Few interventions have been carried out to improve women's preconceptional nutritional status. The key questions are when to intervene and how. Delaying the age at first pregnancy is a practical and effective intervention that will ensure that a woman has enough time to reach her optimal body size with adequate nutrient stores before conception. Ensuring women's access to good nutrition in terms of quantity and quality of food intake is important and often a challenge in settings where food availability is limited or women are marginalized. The promotion of low-cost fortified foods and multivitamin/mineral supplements for all women of reproductive age has been proposed as a strategy to improve micronutrient status (60). The role of micronutrients is further discussed below. Counseling newlywed couples on the importance of nutrition is another approach being tested in Bangladesh International Center for Diarrheal Disease Research, Bangladesh [ICDDR], personal communication—G. Fuchs).

The importance of early childhood nutrition in predicting adult size and the role of intergenerational effects in perpetuating IUGR are other recent topics of investigation. Although weight can change during the course of one's lifetime, it is closely related to stature, and women normally complete growth in stature by early adulthood. Recent work has shown that most of the growth retardation in many developing countries occurs during the intrauterine period and early childhood. The prevalence of stunting at birth has been reported to be 51% in Malawi (14) and 25% in Guatemala (61). Nearly one-third of young children are stunted worldwide (height for age  $<2$  SD of reference median), and catchup growth appears unlikely in many developing country settings (62,63). The results from the longitudinal follow-up studies in Guatemala, in which subjects received food supplementation during pregnancy or early childhood, show that whereas growth rates during early childhood were much lower, from 3 to 18 years they were similar to those of Mexican Americans in the USA, who have a common ancestry (62). Overall, adult heights are much lower in this population, but those who were stunted in early childhood were significantly shorter and lighter and had reduced muscle mass compared with those who were not (64).

Little is known about whether these deficits can be made up during later childhood or adolescence. Some studies have shown that micronutrient interventions such as iron and multivitamin/mineral supplements can improve micronutrient status and weight gain during adolescence, but we do not know if these are long-term benefits. Finally, there is evidence of intergenerational effects on birthweight and length, and these are almost twice as great in poor environments as in developed countries (65), where most of the studies have been carried out to date. These intergenerational effects probably reflect both genetic and environmental influences across generations, and the importance of environmental influences may be greater in poor settings. A strong correlation between child nutritional status and low birthweight rates over a span of 10–20 years has also been reported, using trend data available at the national level (66), supporting the need to invest in maternal and child health and nutrition over two to three generations.

### Nutrition During Pregnancy

The findings from recent supplementation studies—primarily intervention trials that have examined the role of single nutrients first, followed by multiple nutrients including food supplements and multivitamin/mineral supplements—will be reviewed in this section. Most of the studies were identified using database searches and secondary references from published studies and review articles. Before the results are presented, some important methodological issues need to be considered. The most important is study design. Although observational studies provide valuable insights and may infer causal relations, the double-blind randomized placebo-controlled intervention trial (RCT) is considered the design of choice. The other major concern is adequate sample size. Many studies in the past have failed to detect significant differences between groups owing to lack of statistical power (67). A sample of at least 200/group would be required to detect a difference of about 100 g, which is considered biologically relevant, assuming a significance level of  $p = 0.05$ , 80% power, and SD of 450 g. The sample sizes are even larger if the desired outcome is a reduction in the prevalence of IUGR. A sample size of 200/group will be adequate to detect only a large effect, for example, a 50% reduction, from 20% to 10%, in Guatemala. More subjects will be required if the prevalence of IUGR is lower (68).

### Macronutrients

Inadequate intakes of specific macronutrients such as protein were considered a major cause of IUGR in the early 1970s and 1980s, and many trials were conducted, with inconclusive results. A systematic review of some of these trials that provided isocaloric protein supplements (*i.e.*, >25% of the energy came from protein) found no beneficial effects (69). Some studies have also examined the importance of essential fatty acids, also with inconclusive results for IUGR (31). Studies that have increased energy intakes during pregnancy typically increased intakes of several macronutrients and some micronutrients at the same time and are described in the

section on multiple micronutrients below. The role of calcium, a macromineral, is discussed along with minerals.

### Micronutrients

Two recent reviews have examined the role of micronutrients in IUGR (2,67). Herein, therefore, we will focus on the main findings from these reviews and on new advances. A summary of the experimental trials that have examined the role of micronutrients on birthweight is given in Table 1. A more detailed description of the earlier studies is available in a review by Ramakrishnan *et al.* (67).

#### Water-Soluble Vitamins (B Complex, C, Folate)

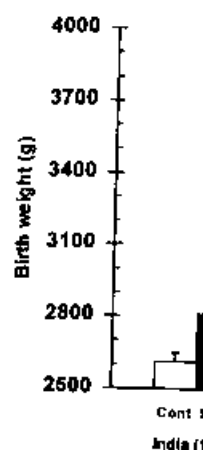
Several prospective studies, mainly from developed countries, have reported a positive association between folate and birthweight. For example, Scholl *et al.* (70) found that both low dietary intakes of folate ( $<240 \mu\text{g/day}$ ) and lower concentrations of serum folate measured at 28 weeks of pregnancy were associated with a twofold increased risk of preterm delivery and term low birthweight, even after controlling for several maternal characteristics. The results of six experimental trials are shown in Fig. 1. An early experimental study conducted in India reported increased birthweight using a design that compared iron with iron/folate supplementation (71). The dropout rates were high, leaving in question the validity of the findings. In an RCT conducted in Denmark, the infants in the folic acid group were 12.7% heavier than those in the control group ( $p < 0.01$ ) (72). In contrast, three studies also conducted in developed countries showed no benefits of folic acid supplements on fetal growth (73–75). Whereas the benefit of folic acid in reducing the risk for neural tube defects is well established (76), the effect of folic acid on fetal growth is less clear, and there is a need for well-designed experimental trials in settings where folic acid deficiency and IUGR are more common.

Although animal studies and a few observational studies suggest a potential role for vitamin C and some of the B complex vitamins such as thiamine and riboflavin, in both fetal growth and length of gestation, very little work has been done to date (67).

TABLE 1. Vitamins, minerals, and birthweight

Vitamin	Experimental trials (n)		Mineral	Experimental trials (n)	
	Total	Positive effects*		Total	Positive effects*
Vitamin A	4	—	Iron	4	—
Folic acid	6	3	Zinc	12	5
Vitamin B <sub>1</sub>	—	—	Calcium	7	3
Vitamin B <sub>6</sub>	1	—	Copper	1	—
Vitamin B <sub>12</sub>	—	—	Iodine	5	3
Vitamin C	—	—	Magnesium	4	2
Vitamin D	2	—	Manganese	2	1
Vitamin E	—	—	Selenium	—	—

\* $p < 0.05$ .



#### Fat-Soluble Vitamins

Vitamin A deficiency is common in many developing countries. High doses of vitamin A have been associated with fetal abnormalities, including stillbirths, containing less than 1000 g, in deficient populations. In some studies and a few prospective studies, vitamin A status and birthweight were associated. A recent RCT conducted in India found that pregnant women who received vitamin A during pregnancy and allantoic fluid levels of vitamin A only, multivitamin, or placebo. All groups had similar birthweight at late supplements and birthweight was similar compared with the control. Differences in the prevalence of these findings.

The birthweight of infants which significant reduction in the interval 0.37–0.84 kg (79), will definitely reduce IUGR. Preliminary findings suggest that these findings are yet to be confirmed. Less is known in the

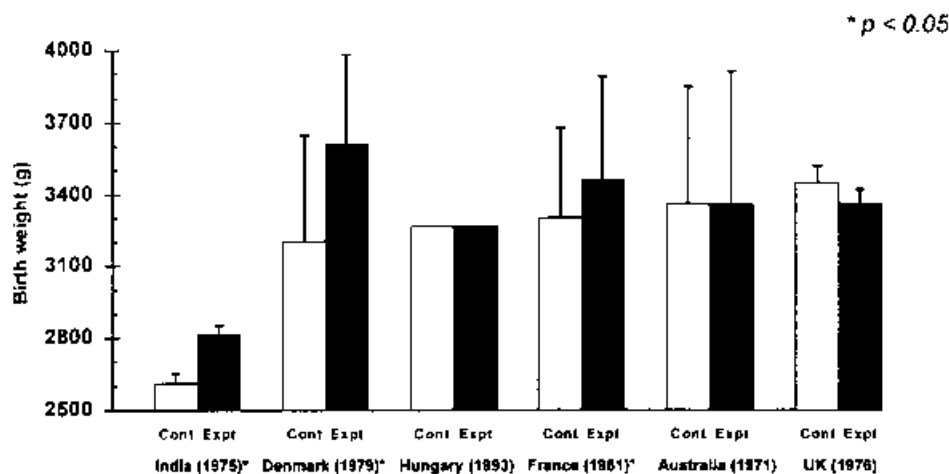


FIG. 1. Experimental trials with folic acid.

***Fat-Soluble Vitamins (A, D, E, and K)***

Vitamin A deficiency is one of the big three micronutrient deficiencies and is common in many developing countries, but concerns about the teratogenic effects of excess vitamin A have meant that very few studies have been done during pregnancy. High doses of vitamin A during early pregnancy have been shown to increase the risk of fetal abnormalities (77), especially during early pregnancy. However, supplements containing less than five times the recommended daily allowance, especially in deficient populations, are unlikely to have any adverse effects. Several cross-sectional studies and a few prospective studies have suggested an association between poor vitamin A status and IUGR, but these inferences are limited by their study design (67). A recent RCT conducted in Tanzania failed to detect any benefits of vitamin A (78). Pregnant women who were HIV positive were recruited between 12 and 27 weeks of pregnancy and allocated to receive daily supplements containing either vitamin A only, multivitamins including vitamin A, multivitamins excluding vitamin A, or placebo. All groups (approximately 200 women each) also received routine iron/folate supplements and were followed until delivery. Although the prevalence of low birthweight was slightly lower among those who received only vitamin A (14.5%) compared with the placebo group (17%), there were no statistically significant differences in the prevalence of low birthweight or mean birthweight. The generalizability of these findings remains to be verified.

The birthweight results from the Nepal Nutrition Intervention Project, Sarlahi, in which significant reductions in maternal mortality (odds ratio 0.56, 95% confidence interval 0.37–0.84) with vitamin A supplements during pregnancy were reported (79), will definitely provide more insight into the role of vitamin A in preventing IUGR. Preliminary findings suggest that there may be no impact on birthweight, but these findings are yet to be published (K. P. West, personal communication). Even less is known in the case of the other fat-soluble vitamins, although some studies

suggest a potential role for vitamins D and E in fetal growth and on duration of pregnancy.

### Calcium

Several intervention trials that provide 1–2 g of calcium have been carried out, mostly in developed countries, but few have examined the impact on IUGR. In a recent review of six trials, Bucher *et al.* (80) estimated that the odds ratios for preterm delivery and IUGR were 0.69 (0.48–1.01) and 0.77 (0.51–1.16), indicating no benefit of calcium supplementation (80). However, most of these studies were conducted among populations in which calcium intakes were not low and therefore women were less likely to respond. A recent trial of calcium supplementation in India (81) found, in addition to a reduction in the incidence of pre-eclampsia, a significant increase of about 100 g in the birthweight of infants born to nulliparous women who received 2 g of calcium daily from 20 weeks of gestation ( $2,731 \pm 278$  g) compared with the placebo group ( $2,626 \pm 309$  g). This may reflect the lower incidence of pre-eclampsia. Although there were no significant differences in the prevalence of low birthweight, these findings are important and need to be replicated in similar settings.

### Iron

Iron deficiency anemia is one of the most common nutritional problems, especially among pregnant women in developing countries. In response to this, many national programs recommend or provide routine iron supplementation for all pregnant women. Nonetheless, very few intervention trials have examined the impact of improving iron status on birth outcomes, including IUGR. This may be explained in part by the ethical difficulties in conducting such studies in settings where routine prenatal care includes iron supplementation. Several observational studies have suggested an association between anemia and low birthweight (67). The best evidence comes from a more recent well-designed prospective study by Scholl *et al.* (82), in which iron deficiency anemia during early pregnancy was predictive of lower birthweights even after controlling for several confounding factors. This study was carried out among high-risk adolescent African-American women in Camden, NJ, USA. Similar relations can be expected in developing countries where iron deficiency anemia and IUGR are common. In one of the few placebo-controlled intervention trials, Preziosi *et al.* (83) showed a possible relation between iron status and IUGR in Nigeria. The infants born to women who began daily iron supplements (100 mg) from 28 weeks of pregnancy were 30 g heavier and 0.7 cm longer at birth. The differences in birthweight were not statistically significant, probably because of the small sample size and lack of statistical power.

### Iodine

Iodine is an essential component of the two thyroid hormones thyroxine ( $T_4$ ) and triiodothyronine ( $T_3$ ), which are critical for normal growth and development, starting from conception to about 2 years of age. Although mean values were not significantly

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Birth weight (g)

different, Pretell *et al.* (84) reported a consistent tendency for lower birthweight, length, and head circumference among children born to iodine-deficient mothers than to mothers treated with iodized oil. This study was carried out in the context of an iodination program. No biological tests examining thyroid function were available from the study.

The most detailed studies of iodized oil given during pregnancy have been conducted in Zaire, Algeria, and Malawi in areas of severe iodine deficiency, where endemic goiter and cretinism have been reported (67). In a double-blind RCT conducted in Zaire (85), pregnant women ( $n = 983$ ) were recruited at their first prenatal clinic visit and were allocated to receive either iodized oil (1 ml of 1 M Lipiodol; treated group) or placebo (control group). Although the increase in mean birthweight was not statistically significant for the group overall, birthweight was greater ( $p < 0.05$ ) in the children born to the subset of mothers who were iodine deficient at baseline (urinary iodine  $< 5 \mu\text{g/dl}$ ). The mean birthweights were  $2,634 \pm 52 \text{ g}$  ( $n = 112$ ) and  $2,837 \pm 55 \text{ g}$  ( $n = 98$ ) for the neonates born to mothers who received the placebo and iodized oil, respectively. Although these findings appear to indicate a relation between iodine deficiency and IUGR, there are also studies from India and Bhutan that have failed to detect any improvement in birthweight with iodine supplements (67). There is a need for further well-controlled studies.

### Zinc

Zinc is the most widely studied micronutrient. Over 40 animal and observational studies that have been conducted over the years suggest an important role for zinc in the etiology of IUGR (86). The findings from experimental trials ( $n = 12$ ), however, are mixed (Fig. 2). Most of these trials were carried out in developed countries in

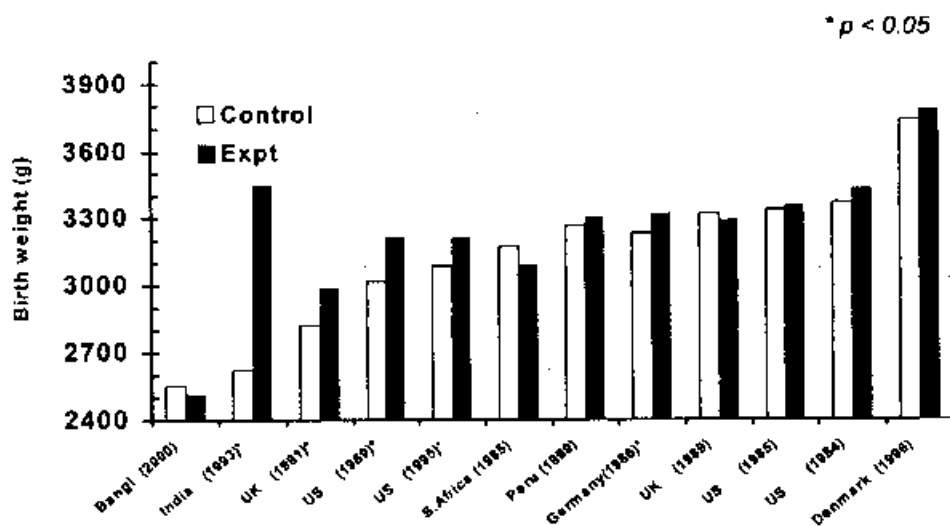


FIG. 2. Experimental trials with zinc.

populations with mean birthweights of  $>3$  kg. In many, both groups received a daily multivitamin/mineral supplement containing several micronutrients, the only difference being the presence of zinc in the experimental group. Contrary to expectations, the results of the two most recently completed studies that were carried out in populations with inadequate zinc intakes in Peru (87) and Bangladesh (88) are not encouraging. Both studies were large RCTs in which the treatment group received zinc along with routine iron/folate supplements, whereas the control group received only iron/folate supplements. The prevalence of IUGR was extremely high (75%) in Bangladesh, whereas it was not a major problem in Peru, where the mean birthweight was over 3.0 kg. The reasons for a lack of response may vary in these two contrasting settings. The positive results found in an earlier RCT that was carried out among high-risk young African-American women in the USA who had lower serum zinc concentrations (89) suggest that only a subgroup of women with low serum zinc values may benefit from zinc supplementation during pregnancy. Using the same study population in Alabama, USA, Tamura *et al.* (90) recently reported that zinc status was not associated with birthweight among subjects who were excluded from the original trial, that is, with serum zinc level of  $>10.5$   $\mu\text{g/dl}$ . These findings suggest a selective response to zinc supplementation and that more work is needed to identify the appropriate indicators of response.

### Multiple Nutrients

#### Food Supplements

Several intervention trials were carried out in both developed and developing countries during the late 1970s and 1980s to determine whether increasing food intake during pregnancy, especially energy and protein, would improve birth size and thereby reduce the prevalence of IUGR. Most of these studies used balanced protein and energy supplements (*i.e.*, protein did not account for  $>25\%$  of the total energy content) and were often fortified with several micronutrients. Several reviews and meta-analyses of these trials have been published to date (1,31,91,92), and until recently, most of them concluded that the evidence supporting the role of increasing energy and protein intakes in reducing IUGR was weak. It should be noted, however, that some of the earlier large trials that had shown positive results, such as the ones conducted in Guatemala (93) and Gambia (94), were excluded from these reviews and meta-analyses owing to design limitations. For example, in Guatemala, the treatment was allocated at village level, and there were only four villages (two per treatment). The conclusions in the latest systematic review of clinical trials in the Cochrane database on balanced protein/energy supplementation during pregnancy (92) have changed, primarily because of the inclusion of the significant results of a large RCT that was carried out in Gambia (95). Kramer (92) concluded that "supplementation was associated with modest increases in maternal weight gain and fetal growth as indicated by a small but significant increase in birthweight; smaller non-significant increases in birth length and birth head circumference; and a reduction in the incidence of SGA births." Fourteen trials were included in this review; some of



the larger ones were from Taiwan (96), New York (97), Wales (98), Bogota (99), East Java (100), and Gambia (95). The weighted relative risks for SGA and preterm births were 0.68 (95% confidence interval 0.56–0.82) and 0.80 (0.6–1.08), respectively. Kramer also concluded that the observed effects did not vary by the preconceptional nutritional status, which may be open for debate owing to the large confidence intervals. Similarly, the results from the Dutch Famine Study (101), which was a natural experiment, cannot be overlooked.

### *Multivitamin/Mineral Supplements*

The potential role of multinutrient supplements in reducing the prevalence of IUGR is a recent but not entirely new development in the field of nutrition. Increased awareness of the interrelations between nutrients at the point of absorption and utilization, combined with the increased risk of multiple nutrient deficiencies due to inadequate intakes and poor dietary quality in many developing country settings, have led to a significant interest in promoting multivitamin/mineral supplements for pregnant women, women of reproductive age, and young children. Despite the increasing momentum in promoting the use of these supplements by several international agencies (60), few have examined whether multivitamin/mineral supplements can reduce IUGR. In an early study from Sweden (102), the prevalence of low birthweight was significantly reduced among women who regularly consumed iron or multivitamin/mineral supplements. A few recent studies provide interesting evidence. Scholl *et al.* (103), in a large, prospective, well-controlled trial, reported that the risk of preterm delivery (<33 weeks) and of low birthweight was reduced by at least half among pregnant women who regularly consumed multivitamin/mineral supplements compared with those who did not, after controlling for several known confounding factors. The protective effect of the supplements was greater if started earlier (first *versus* second trimester) and was greatest for very low birthweight. However, most of the effect was due to a reduction in prematurity and not IUGR. Approximately 60% of the low-birthweight infants were born preterm, which is very different from the situation in developing countries, where most of the low-birthweight infants are term IUGR (5). In another recent retrospective case-control study, Shaw *et al.* (104) found that women who consumed multivitamin supplements containing folic acid during the periconceptional period (4 months) were 62% less likely to deliver a preterm baby (odds ratio 0.38, 95% confidence interval 0.16–0.88) than those who did not consume supplements. There were no differences in the prevalence of low birthweight. Finally, Fawzi *et al.* (78), in a large RCT carried out among HIV-positive women ( $n = 1,067$ ) in Tanzania, reported that multivitamin supplementation resulted in improved immune status and a significant reduction in the risk of fetal death, low birthweight (44%), severe preterm birth (39%), and fetal growth retardation (43%). The prevalence of low birthweight was only about 9% in the two groups that received multivitamins with or without vitamin A compared with 14.5% and 17.2%, respectively, in the groups that received vitamin A with iron/folate or iron/folate only. Mean birthweight was 120 g greater among those who received multivitamin

supplements than in those who received standard treatment, that is, iron/folate supplements. It is noteworthy that none of the groups received zinc, which might have provided additional benefits.

Without doubt, we need to see if these results can be generalized to all pregnant women living in other settings. Such a study is underway in Cuernavaca, Mexico, in collaboration with Emory University and the Instituto Nacional de Salud Publica in Cuernavaca, Mexico, with financial support from the Thrasher Research Fund, UNICEF, and CONACyT, Mexico. This study is a randomized, double-blind, controlled trial in which women are recruited at between 8 and 13 weeks of gestation and assigned to receive daily, under supervision, either a multivitamin/mineral supplement containing 1–2 recommended daily allowances of several vitamins and minerals or only 60 mg of iron, which is the standard supplement. Data collection is almost completed, and preliminary results are expected to be available soon.

In summary, the evidence from the single-nutrient studies suggests that vitamin A, folic acid, iodine, iron, and zinc may all play a role in the etiology of IUGR. Although it could be difficult to justify more experimental trials from an ethical standpoint, owing to the other known effects of these micronutrients, more can be done in programmatic settings as well as for the other water-soluble vitamins, namely, the B complex vitamins and vitamin C, about which less is known. In the case of multiple micronutrients, although there are very few experimental trials looking at specific combinations of nutrients, recent data suggest that there may be benefits from multivitamin/mineral supplements.

### Evidence from Programmatic Settings

Routine antenatal care is recommended as part of primary health care throughout the world. It typically includes several visits to a health care provider for monitoring the adequacy of weight gain, identification and appropriate management of high-risk pregnancies (hypertension, diabetes, infections), and often provision of iron supplements and nutritional counseling. Epidemiological and observational studies tend to show that women who receive antenatal care have lower maternal and perinatal mortality and better pregnancy outcomes. These studies also suggest that there is an association between the number of prenatal visits or the gestational age at the initiation of care and the pregnancy outcome, after controlling for confounding factors such as the length of gestation (105). A systematic review of controlled trials among low-risk pregnancies (four from developed countries and two from developing countries) showed that a moderate reduction in the number of antenatal visits to a minimum of four, with increased emphasis on the content, could be implemented without any adverse biological perinatal outcomes (106), and a large WHO multicountry randomized trial is underway in four countries (Cuba, Argentina, Thailand, and Saudi Arabia) to test a new model of antenatal care (107).

There is a dearth of evidence on the impact of nutrition interventions in the context of programs that show reductions in IUGR. This is surprising in light of the fact that considerable resources are currently being invested in conducting

supplementation. Women, Infants, and Children (WIC) is a large program of food assistance for low-income women who are at high risk of poor pregnancy outcomes. The program is associated with higher birthweight (108). However, the impact of the program on IUGR is uncertain. It is unclear if the program is associated with a need to be cared for in the neonatal intensive care unit.

India's Integrated Child Development Services (ICDS) program, which provides supplementary feeding to children under 6 years of age, is one of the largest in the world. It is a government program that provides supplementary feeding to children under 6 years of age. The program is associated with higher birthweight (109). However, the impact of the program on IUGR is uncertain. It is unclear if the program is associated with a need to be cared for in the neonatal intensive care unit.

Since 1997, the World Bank has been supporting the success of the T. A. Rivera-Dorantes program in Indonesia. The program is a large-scale supplementary feeding program that provides supplementary feeding to children under 6 years of age. The program is associated with higher birthweight (110). However, the impact of the program on IUGR is uncertain. It is unclear if the program is associated with a need to be cared for in the neonatal intensive care unit.

Several factors may act as barriers to the choice of food. The choice of food may influence the outcome of pregnancy. Food intake during pregnancy is an important determinant of fetal growth. The choice of food may influence the outcome of pregnancy. Food intake during pregnancy is an important determinant of fetal growth.

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supplementation programs for pregnant women in different parts of the world. The Women, Infants, and Children (WIC) program in the United States is an example of a large program in a developed country, which provides nutritional counseling and food assistance to pregnant women who are from poor socioeconomic conditions or who are at high risk of poor pregnancy outcomes. Regular participation in the WIC program is associated with improved birth outcomes, including a reduction in low birthweight (108). However, these impacts are not seen when the reasons for participation are controlled for. Factors associated with participation in these programs need to be carefully examined if we want to reduce the incidence of IUGR.

India's Integrated Child Development Services scheme, with over 100 million participants, is one of the largest supplementary feeding programs for pregnant and lactating women and young children. A national evaluation of the Integrated Child Development Services program reported that only 26% of eligible women participated in the supplementary feeding intervention. This is in contrast to 52% participation for supplementary nutrition provided for young children in the same program. The investigators concluded that the failure to reach pregnant women was one of the major weaknesses of the program (109). Similarly, although the Tamil Nadu Integrated Nutrition Project has been very successful in reducing childhood malnutrition, the coverage of some services for pregnant and lactating women has been inadequate. Only 50% of eligible pregnant and lactating mothers were enrolled in supplementation, and some of the problems identified were the inconvenience of the times at which supplementary feeding was offered, deficiencies in the selection of beneficiaries, and cultural factors against participation (110,111). More recently, the World Bank has supported the Bangladesh Integrated Nutrition Project (based on the success of the Tamil Nadu Integrated Nutrition Project), which targets locally prepared on-site supplementary feeding to pregnant women with a BMI of  $<18.5 \text{ kg/m}^2$ . Although preliminary results suggest reductions in low birthweight, the effectiveness of this approach remains to be evaluated in a rigorous way. Regular consumption of iron/folate tablets alone was associated with an increase in birthweight of 172 g in a program in Indonesia (112).

Since 1997, the government of Mexico has also begun to provide micronutrient-fortified food supplements to pregnant women from low socioeconomic backgrounds. Unlike the other programs, this one is not linked with the provision of antenatal care (J. A. Rivera-Dommarco, personal communication). The program includes a package of benefits including a nutritional supplement. An evaluation of the impact of the nutrition component is currently underway. Finally, although there are few national programs that provide nutrition supplements besides iron in Africa, several nongovernmental agencies such as CARE (Catholic Relief Services) do provide food supplements in selected communities, and these may be targeted to pregnant women.

Several factors such as poverty, women's status, and cultural beliefs and practices may act as barriers to successful programs. Poverty acts to limit access to care as well as the choice of foods and the amounts available to pregnant women. Women's status may influence pregnancy weight gain through the family's response to her pregnancy. Food intake may also be constrained by physical discomfort, particularly in

small women consuming a low-energy/density diet because of gastric compression by the fetus and placenta. A third factor—the phenomenon of so-called “eating down”—may exacerbate the vulnerable condition of pregnant women. Eating down refers to deliberate efforts to restrict food consumption in pregnant women to reduce the size of the fetus and the risk of delivery complications. Brems and Berg (113) reviewed evidence from around the world and found that many women restrict the intake of foods that they believed would contribute to a large baby and thus to a difficult delivery. It should be noted, however, that there is no scientific evidence to support this fear. The increase in head circumference after nutritional supplementation is very small (about 1 mm) despite an increase in birthweight and is unlikely to increase the risk of cephalopelvic disproportion and related obstetric complications (92). Although several studies have documented cultural practices that might influence food intake during pregnancy, no study to date has quantified effects on dietary intakes and the relation to birth outcomes. Few have developed and evaluated appropriate behavioral strategies that could be used to counter such fears and improve birth outcomes (114). There is an urgent need to develop and test an appropriate package of interventions that use behavior change approaches to improve the quality and quantity of food intake during pregnancy.

## CONCLUSIONS

Based on the evidence from research studies on the etiology of IUGR, the following themes emerge:

- Timing of insult to fetal growth may occur even earlier than originally recognized, that is, in early pregnancy.
- Single-nutrient interventions may be inadequate to reduce IUGR.
- Multiple approaches may be more effective and need to be evaluated rigorously in different settings, for example, the provision of fortified food supplements combined with control of infections such as malaria and other high-risk conditions.

The lack of evidence from programmatic settings is a major limitation. Well-designed program evaluations that examine the effectiveness of intervention strategies such as balanced protein/energy, iron/folate, and multivitamin/mineral supplements during pregnancy are needed to justify investments in maternal and child nutrition to policymakers and funding agencies. Innovative approaches that focus on improving maternal nutritional status before pregnancy need to be pursued as well, especially as most women do not begin antenatal care before 20 weeks of gestation in most settings.

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## DISCUSS

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## DISCUSSION

*Dr. Bhan:* Our search for new or better approaches to reducing low birthweight stems from the fact that whatever we did in the past didn't seem to produce results. If you look at all the large programs, not only is there an issue of participation, but we never really achieved substantial improvements in energy intake. These programs did achieve a reduction in severe malnutrition, but they never had an impact on moderate malnutrition. If you look at all the food supplementation trials that were done in Asia in children, you see the same thing: a shift of energy intakes up from the bottom level, but never approaching optimal. What we really need to address is the changes that are required to get people to consume food in sufficient amounts if it is available. I think that unless the illiteracy rate and other social conditions change, then no matter what we do, we are not going to achieve the levels of intake that are necessary to optimize growth. Take a clue from the infant or child supplementation trials of individual micronutrients: Even 16 micronutrients combined give only a 0.5-cm increase in length and a small increase in weight, which is marginally better than with zinc alone or with any other single micronutrient. If that has any implications for pregnancy, then it would appear to me that to expect even those 16 micronutrients to produce the large increment in growth needed to reduce low birthweight substantially is not realistic. For me, the general message seems to be that the prevention of childhood undernutrition and INTRAUTERINE growth failure is about achieving substantially increased intakes of energy and protein, and what determines that appears to be more social than anything else.

*Dr. Ramakrishnan:* I think the Gambia trial (1) shows the need for a targeted approach. The food supplements given in that trial produced a dramatic reduction in low birthweight, but the effect was mostly in the hungry season. In general, the worse off you are, the more impact such a program will have. We do need to think about targeting as well as about applying broad-based approaches that affect the whole population. And maybe we are being impatient: We want magic bullets. IUGR is perhaps an outcome that will not be reduced overnight, and we need to be persistent.

*Dr. Räihä:* I would like to call your attention to the uterine circulation as a cause of IUGR and premature birth. It is well known that during normal pregnancy, both the maternal blood volume and the cardiac volume increase, as in an athlete who is training. There have been several reports showing that in some pregnant women, the heart volume and blood volume do not increase normally during pregnancy. This can be studied by ultrasound. In Finland, there was a trial some years ago where women were screened during pregnancy, and those in whom the heart volume did not increase were rested during the last trimester. By doing this, it was possible to decrease the rate of IUGR, premature birth, and perinatal mortality substantially. Of course, the supply of nutrients to the infant may be affected if the circulation is poor.

*Dr. Ramakrishnan:* There are other studies that have looked at the role of maternal workload and IUGR (2). We are looking at situations in which women have high workloads, do not get any rest, eat inadequately, and have high exposure to infections. That's the reason why I said that we should not confine ourselves to looking at nutrition.

*Dr. Uauy:* I think unless you approach nutrition within the context of maternal care, control of infection, workload, and other stresses, we are going to see marginal effects. What are you doing in your study in Mexico?

*Dr. Ramakrishnan:* In the Mexico study, we are looking primarily at multivitamin/mineral supplements *versus* iron, and we are collecting data on dietary intakes, but we are not looking at maternal workload.

*Dr. Masood:* With respect to the different types of IUGR, are you investigating factors responsible for proportionate and disproportionate growth retardation?

*Dr. Ramakrishnan:* In most developing countries, we find symmetric IUGR because the deprivation is chronic, but very few studies have made an attempt to classify cases in this way. Some of them do not even assess gestational age, let alone the prevalence of IUGR—I often have no other information than mean birthweight! It would be interesting to investigate this from a research point of view, but in general, and from the point of view of interventional programs, developing countries are usually dealing with symmetric IUGR.

*Dr. Gibson:* As far as I recall, the plasma zinc levels of women in Bangladesh and Peru were not particularly low at the beginning of the trial, whereas in the trial in the USA, they recruited women on the basis that they had plasma zinc below the median. Maybe one of the reasons why they did not see an effect in Bangladesh and Peru was because the zinc status of the women was not as suboptimal as they had envisaged at the beginning.

*Dr. Ramakrishnan:* You are absolutely right, which is why the verdict is still out. Indeed, someone might say, looking at these studies, that zinc does not have an effect. But we do know that zinc intakes are poor in both those populations and the bioavailability is low. The mechanism whereby zinc may influence birthweight is not yet fully understood.

*Dr. Guesry:* To follow up on Dr. Gibson's comment, Henri Dirren in our research center has conducted a study in Ecuador in an area where the intake of zinc is very low, giving zinc supplementation during the last 6 months of pregnancy (to be published). There was an increase in plasma zinc but no effect on the birthweight of the baby.

*Dr. Gibson:* Do you think it is possible that the zinc supplementation was not started early enough in that particular study? There's evidence that we should even be starting before conception if we want to see the maximum impact.

*Dr. Guesry:* Well, in that case, maybe we should add zinc to contraceptive pills! When you stop your pill, you have had your zinc.

*Dr. Frongillo:* Recent work by Anna Winkvist at Umeå University in Sweden and some colleagues at Cornell has shown that the outcome of interventions to increase birthweight is complicated (3). Depending on the initial weight of the mother, there may be benefit for birthweight, for the mother, or neither, or both. With this in mind, previous studies may not have been able to show the effects that might have occurred. This has important implications for how we design new programs and the evaluation of those programs.

*Dr. Barros:* We saw a clear effect on prevention of IUGR in our Santiago study, in which multivitamin and multimineral supplements were given (7). There were indications that greater water retention linked to plasma volume expansion was the mechanism. We then studied a similar group of women, looking at changes in body composition and water retention during pregnancy. We found in a multiple regression analysis that total body water explained much of the effect on fetal growth. I support Dr. Rivera-Dommarco's micronutrient approach in Mexico. We need to get beyond the classic protein/energy issue; we need a better quality of food, as many of us are pointing out in our Chilean programs.

*Dr. Ramakrishnan:* But if we are dealing with countries like India where energy intake is highly limiting, we don't know whether just providing multivitamin and mineral supplements will be adequate. We need to consider where we are working and the magnitude of the problem. Fortified food supplements may be the way to go. Clearly the provision of adequate antenatal care and other supportive interventions needs to be taken care of as well.

*Dr. Youssef:* We are currently conducting a study in Egypt on zinc levels in women who just have delivered and have started breast-feeding. We believe, after taking random samples, that plasma zinc does not reflect the true zinc status in these women. We came to the conclusion that the best way of determining whether they were deficient or not was to analyze samples of hair and nails. When supplements are given to women with low zinc in hair and nails, they have an effect.

*Dr. Ramakrishnan:* I think we all know the problems with zinc assessment. In the Mexico study, we are also looking at a variety of indicators—we are looking at breast milk levels and we are following up the children as well for morbidity, growth, and psychosocial development.

*Dr. Adair:* I think it might also be useful to start looking at some of the stress hormone pathways, as cortisol production can be increased in response to undernutrition and other types of stress during pregnancy. There are a couple of interesting lines of research: the animal models of metabolic programming that show stress pathways and also stress responses to infrequent meals. There has been a tendency to look at total food consumption but not at meal patterns, and irregular meals may be a problem for women in many places where there is severe food shortage. They may go for long periods without eating anything. Long overnight fasts have been shown to increase corticotropin-releasing hormone levels, which in turn has been associated with preterm birth and restricted fetal growth. This may be a very important new area of investigation to complement some of the studies on nutrition.

*Dr. Ramakrishnan:* I agree. This aspect has not been studied adequately.

*Dr. Cassorla:* How do you address the issue of compliance in your Mexican study? This is likely to be a huge problem in such populations.

*Dr. Ramakrishnan:* We use DOT—direct observed therapy—where village-level workers distribute the supplement on a daily basis and observe the women consume it.

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