Review article

The determinants of stunting: Can we regard the linear growth performance as a continuum of fetal development?

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The relationship between early post-natal growth and the possible links with intra-uterine development is emphasised in this review. In some Asian populations linear growth faltering starts very early after birth and the deficit is most marked in the first six months of life. Catch-up growth, later in life, is possible. Children in developing countries, however, will most often become short adults. The environment is not permissive for a catch-up growth. A conceptual model has been constructed and divided in two parts: intra-uterine factors and factors in the first year of life. Only those determinants which the author considered important for the link between fetal life and early post-natal linear growth are analysed.

Introduction

Linear growth retardation is perhaps the most prevalent worldwide nutritional problem. According to UNICEF1, 7.8% of the world's children are too thin and 42.2% are too short. South Asia is the worst affected area where 62.5% of the children below the age of five are too short.

The importance of short stature is to be found in the combination of its prevalence and the human suffering it represents. This suffering relates to the association of short stature and other outcomes such as pregnancy risk and work capacity, but even more so to the processes which lead to this phenomenon. Indeed short stature can be regarded as an indicator of the existence of events which affect linear growth and also morbidity and mortality.

The available evidence, on the determinants of stunting, indicates that stunting is an extremely complex and multi-causal phenomenon. The present review constructs a conceptual model which finds its legitimacy in the classical paradigm of experimental science: first construct a hypothesis, then derive from it a model which is the simplified representation of reality to be tested experimentally. In the present study, where determinants were found to be logical or where circumstantial evidence could substantiate their place in the model they where kept and serve as hypotheses to be tested further. The model is represented in Figures 1-3.

The main hypothesis put forward in the analysis is that the growth of children in the first year of life could, in part, be determined by fetal life experience.

A first evidence for this comes from a biologically-oriented mathematical model (ICP model) where the linear growth of children from birth to adulthood is modelled on the basis of three phases: Infancy, Childhood and Puberty[2]. For all three of the phases, a mathematical function describes the growth curves of children. These functions are additive, in the sense that the infancy function describes the growth of children up to the moment childhood growth starts, described by another function which is then added to the infancy curve.

The existence and shape of the infancy component of the ICP growth model is supported by the growth of children with growth hormone deficiency. They show a growth pattern for supine length close to the reference values given by the infancy function from birth up to the start of substitution therapy at about 2 years of age[3]. Infants with a late onset childhood component tend to continue growing according to the infancy growth component until the childhood growth phase starts[4-6].

If one extrapolates values for the mean infancy function, that is the values of attained height derived from the fitted curve on the observed values of infants, into fetal life, one observes that the extrapolated values are close to the mean values for cross-sectionally measured supine length of fetuses from about mid-gestation onwards[2].

Karlberg who studied different populations using his ICP model concludes that during the period preceding the age of onset of the childhood component, 83% of normal infants have a non-linear decelerating growth pattern, free from seasonal variation. For the majority of the infants in this phase growth seems very stable over time. We can add to this the information that the hormonal control of growth in the first months after birth is similar to the intra-uterine one. Indeed the resemblance in hormonal control between intra-uterine life and the first months of neonatal life are extraordinary. The childhood component of linear growth is triggered by the onset of growth hormone secretion.

Could it be possible that the infancy growth and fetal growth are very intricately interwoven, and form perhaps one continuum? How should we then interpret the observations that growth faltering start early?

Very few longitudinal studies have actually investigated when growth faltering starts. Cross sectional studies conclude that it indeed starts early, around two months and possibly earlier[7]. The possibility arises here that we are observing an artefact and that growth is sub-optimal from birth onwards and therefore determined by intra-uterine factors. This artefact might be the result of the observations being predominantly cross-sectional. If the average z-score of the studied population is below zero at 2 months, one decides that this is the period when growth faltering

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is first observed. But as Waterlow[8] and Golden[9] describe, it takes time to become stunted. The time is inversely proportionate to the magnitude of the growth deceleration when using z-scores. If we observe a difference at two months in z-score this would lead us to conclude that the process of stunting is already of a longer duration.

One supplementation study from Indonesia showed an effect on linear growth post natally when the mothers were supplemented during pregnancy. Supplements given to pregnant women resulted in an improved growth performance of their offspring in the first 3-6 months of life for those children whose mothers received a high energy supplement as compared to those who received a low energy supplement[10]. Although length at birth was comparable in the two groups, the high energy group maintained a high growth velocity in the first months. Children whose mothers had received a high energy supplement during pregnancy were still significantly taller at the age of five years. Length at birth was found to be associated with indicators of

Figure 1. Linear growth retardation in the first year of life

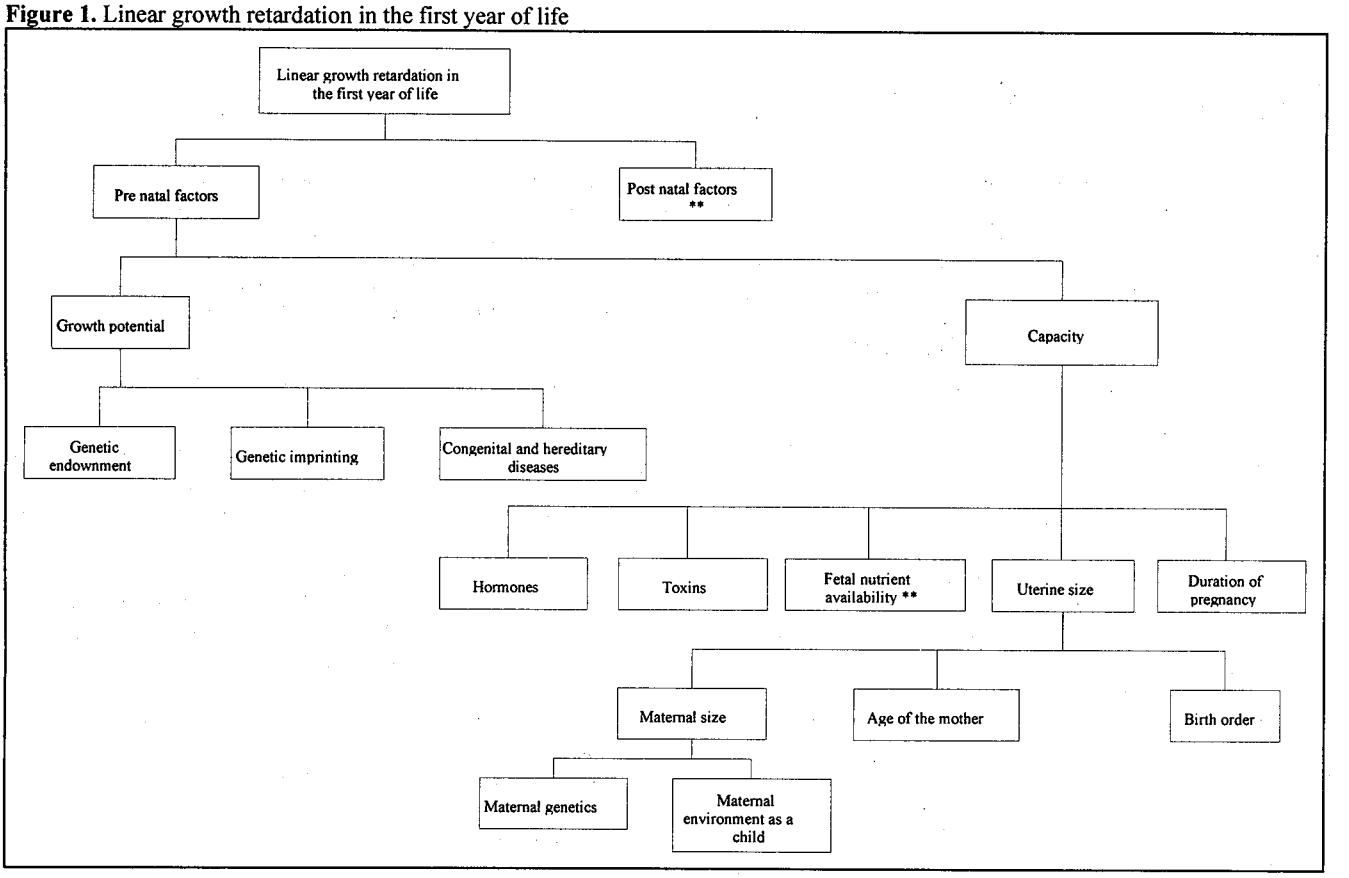


Figure 2. Fetal nutrient availability

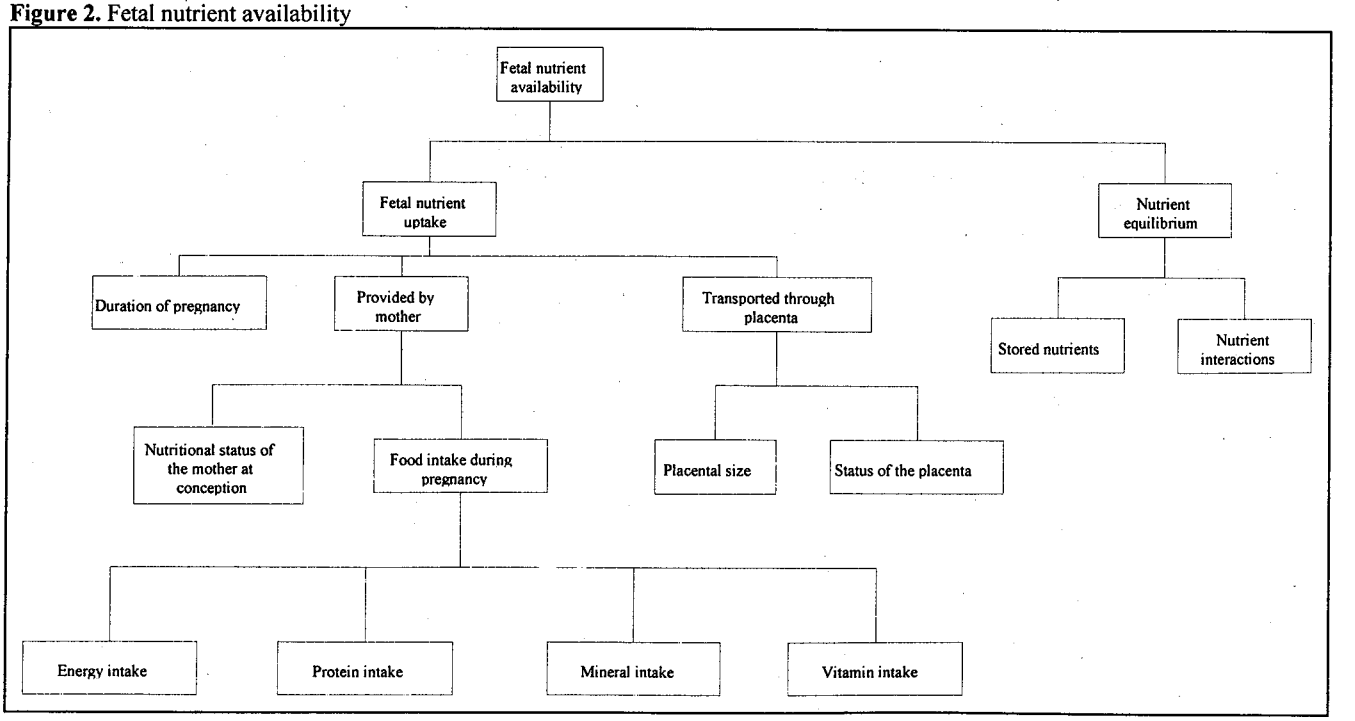
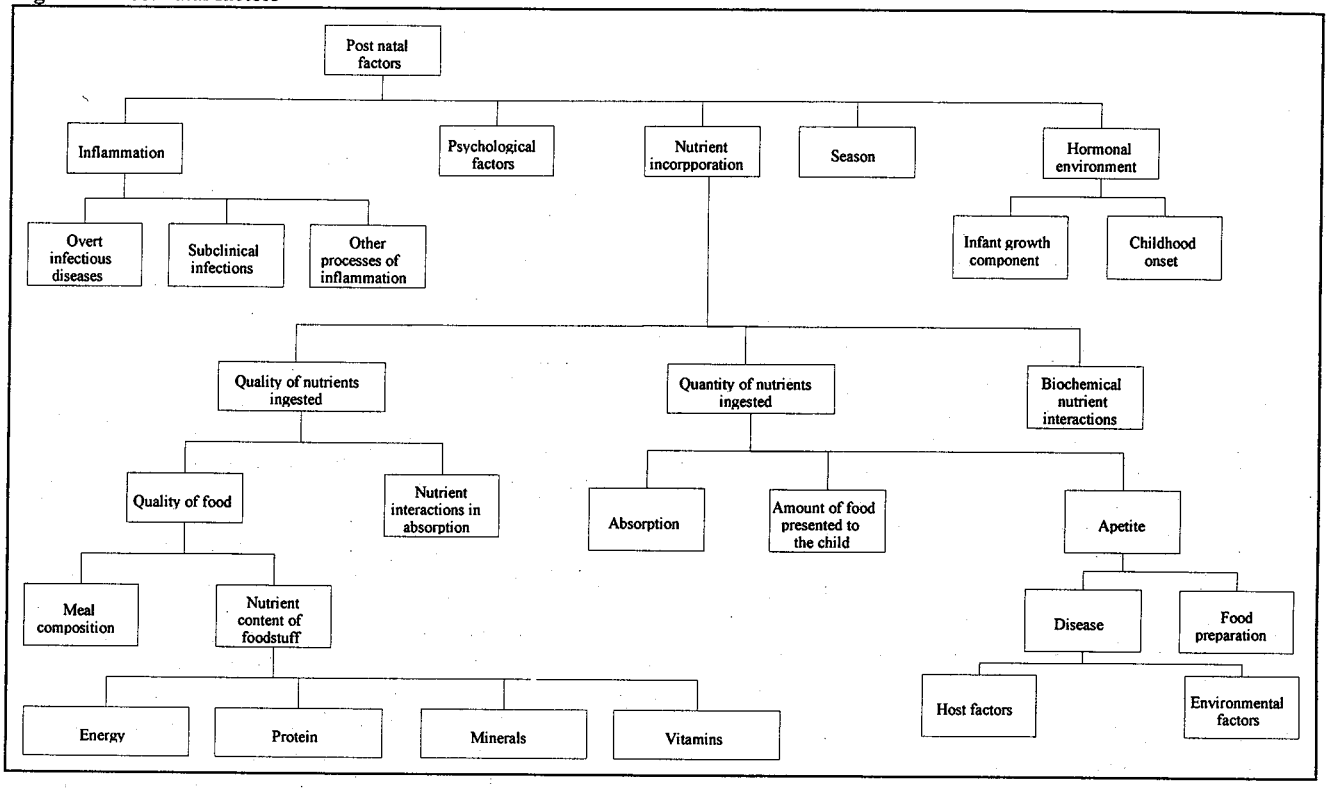


Figure 3. Post natal factors



social status in Karthoum, where mothers with higher incomes and levels of education, tended to have longer children[11].

Based on this we have considered that early post-natal growth can be influenced by prenatal factors, which not only determine birth size, but also exert their influence on linear growth in the first months of life. Growth in the first months of life may be a continuum with intra-uterine growth, particularly with its second half. Nevertheless, the dichotomisation of post natal versus pre natal factors may be kept in the model.

Birth size

Birth size has been studied extensively as a determinant of further outcomes like morbidity, mortality and subsequent growth and development[12-22]. In these studies it has mainly been birth weight, or more precisely weight for age, which has been taken as an indicator. The results of the studies are difficult to interpret and often give conflicting results mainly because weight for age is a very global indicator.

The use of weight for age as an indicator of nutritional status is limited and a classification based on height for age and weight for height[12,23] often preferred; children are classified as stunted, wasted, normal, or stunted and wasted. Birth weight alone fails to diagnose intrauterine malnutrition[24]. Clinical diagnosis of malnourished infants at birth better identifies those children who later develop complications related to their malnutrition; 39% of malnourished newborns were missed by using weight as an indicator alone[25].

Another problem with considering birth weight as a determinant is that it leads to a conceptual mix up between an indicator and a determinant. It could be that size at birth is a proxy indicator of a phenomenon rather than a real determinant, or that some of the determinants of birth-size, which are multiple, also affect linear growth whereas others not. Other literature is available on the subject and not included here.

To meet some of the deficiencies of using birth weight alone, a dichotomous classification of small-for-gestational age (SGA) newborns has been proposed. Low birth-weight infants are classified as disproportionately growth-retarded infants, who have a relatively normal length and head circumference for their gestational age but low weight, and proportionately intrauterine growth retarded infants who have symmetric growth reductions in weight, length, and head circumference[24,26]. This would then cover the wasted children (disproportionate) and a group of children either stunted or stunted and wasted (proportionate growth retarded). This classification does not cover newborns who are stunted with a normal birth weight.

Miller and Hassanein[27], revisiting the diagnostic criteria for intra uterine growth retardation, demonstrate the inadequacy of birth weight alone to evaluate fetal nutrition adequacy and give examples of infants with normal birth weights and variable high and low ponderal index (weight/ht^3) but respectively short and high normal stature. Most authors who propose a different approach from birth weight alone do so conceptually as if there are two different kinds of growth retardation; one more chronic starting early and affecting the fetus when still in a "growth" phase, ie; a phase of cell replication, and another when predominantly becoming bigger and depositing fat, ie towards the end of pregnancy. The first insult would predominantly affect linear growth, the second one predominantly the weight of the child. Hence the dichotomisation of proportionate and disproportionate intrauterine growth retarded infants would differentiate, respectively, the chronically malnourished infants from the acutely malnourished ones. Each type of intrauterine malnutrition may have a different outcome[20,22,24].

The problem with most studies is that they start by dichotomising the infants first on a weight for age basis, to classify them as intrauterine growth retarded, and then for the growth retarded children as proportional and dis-proportional.

When we look at the outcomes of intrauterine growth retarded infants (the small-for-dates) we find on the whole that they are smaller in length at birth with smaller head circumferences. They catch up growth, both in length and in weight during the first three two six months[16,17,19-22]. Their catch-up is, however, not complete with a deficit remaining at two years. Follow-up of the

children in one study showed that, even at the age of 19, the deficit remained[18]. According to Falkner this is an oversimplification[28]. Small for date infants, or small for gestational age neonates, are a heterogenous group. Some children seem to catch up and others do not. Most of the asymmetric SGA infants show a postnatal catch-up and grow well. A small proportion exhibit some catch-up but, at least by two years, do not reach the 5th centile.

Pre-term infants also show an intensive phase of catch-up growth which is sustained longer than for the small-for-dates so that by the age of three years they have caught up with normal controls[16,19]. The growth pattern of the small-for-dates is very heterogenous with a wide variety of growth velocities. Infants with a low ponderal index (wasted ones) do better after birth in terms of catch-up growth than the ones with a normal ponderal index (those who are most probably also short)[21].

In infants who are not growth retarded, ie children with a normal birth weight, further growth is not correlated with their birth weight. Correlations between birth size and subsequent growth velocities are near zero for weight and weight velocity and length and for length velocity[29]. When maternal weight is taken into account there are differences in long term weight gain. Low birth weight babies of low weight mothers grow at a slower rate than comparably low birth weight babies from high weight mothers[30]. One likely explanation is that the subsequent growth of the neonate reflects maternal body mass and the low weight infant born to the high weight mother is simply returned to a genetically programmed development course. This shifting of growth post natally has also been proposed as an explanation by other authors[31] who followed 90 children from a well-off background from birth. The correlation between length at birth and length at one and two years was very poor; however, by age one year the correlation to length at age two years is good for both girls and boys indicating that a proportion of the children shift. The shifting has two directions: upward and downward. Children born at the lower extremes start to cross growth percentile lines early after birth and achieve a stable growth percentile at the age of one year. Infants at the upper range of length follow their percentile for three months until they start to decelerate in growth[32].

Genetic endowment

Genetic endowment has an important influence on attained height and therefore on the way a child will grow in the first year of life. Habicht[33] concluded that genetic potential does influence the observed difference in attained height but that the accumulated deficit indicates that genetics play a lesser role than environment. This has been confirmed[8,31,32,34-38].

Rona[34] analysed studies of children's height, from a genetic view-point in two ways: one was to assess difference in growth between ethnic groups and the other to investigate anthropometric measurements of relatives sharing identical genes. The studies of ethnic groups have compared the same ethnic groups with shared genetic endowment, living in different environments and different ethnic groups living in similar environments. These provide evidence for the much more important influence of environment on adult stature.

Family studies which compare mono-zygotic and di-zygotic twins find correlations of height of the order of 0.93 by the age of three years for mono-zygotic siblings and 0.79 for dizygotic twins. In large samples of more than 500 pairs, most studies find parent - child correlations of 0.3-0.4 for attained height. However it is difficult to separate common environmental influences from genetic influence in theses studies. Adoptive parent-child correlations are 0.30, slightly lower than the 0.35 values quoted for parent-child relations. This suggests that common environment and behaviours play an important role.

We can conclude that genetics play an important role but have minor potential to influence growth compared with the environment[34].

Genetic imprinting

Genetic imprinting is an epigenomic phenomenon, which switches genes off or on during the early stages of development. These switches can persist in childhood and adulthood. Golden[9] notes that the smaller newborn of a monozygotic twin pair will end up as an adult of smaller size. Rats who, during their development receive a restricted diet, will, once they return to a normal diet, have larger offspring, it takes three generations for them to attain the size of the control group.

Mice on a zinc deficient diet demonstrate this "inheritable effect". The pups of mice, fed a zinc deficient diet during pregnancy become immuno-deficient. The offspring of these immuno-deficient mice are partially immuno-deficient. It takes three generations to restore normality.

Variation in imprinting by specific epigenomic modification, and contributed by poor nutrition, provides an explanation for the above observations. Since oogenesis occurs in fetal life, the nutritional plane of the grandparents may influence the grandchild and be as important as the nutrition of the mother. If the meiotic and early in utero environment changes the pattern of epigenomic modification to alter the potential for future somatic development over several generations, it would provide an explanation for the close association between height potential and familial height in societies were there are no racial differences in height. It also provides an explanation for the gradual secular trend in height which clearly transcends the genes in the germ line and yet is familial.

In The Netherlands a similar phenomenon was observed in relation to the Dutch winter hunger. Not only were the children born to mothers who suffered famine lighter at birth, but so also was the second generation of offspring. This "carry over" effect was manifest in the offspring of women conceived during the famine. The timing of the intra uterine exposure to undernutrition appears in this study to be crucial[39].

Congenital and hereditary diseases

Short stature may typify congenital or hereditary disease. Although medically important and as indirect evidence of genetic involvement in stature, these diseases are less important for the study of stunting at a population level. Analysis and enumeration of congenital and hereditary disease in the aetiology of stunting is not pursued further in this review.

Fetal nutrient availability

This determinant of stunting has been dichotomised as shown in Figure 2.

Food intake of the mother affects intrauterine development and growth, most frequently measured by birth weight. Available information comes from three distinct types of studies:

1) *Historical* ones where experimental starvation designs were imitated by natural calamities, such as the Dutch winter hunger of 1944-45 and the siege of Leningrad.
2) *Epidemiological* studies, involving large samples of the population, of the relationship between fetal growth and development with diet during pregnancy, weight gain during pregnancy, BMI pre-pregnancy and post-pregnancy and socio-economic status[40-44].
3) *Clinical supplementation* studies in both developing countries and developed countries[40,45-58].

To take these in turn

1) During the Dutch winter-hunger, a famine hit the west of Holland and lasted 27 weeks. Dietary restriction lasted for six months and was the result of a strict rationing of food to 750 Kcal and 28 g protein per day. After some delay a sharp decline in maternal weight followed the decline in energy intake. Those, exposed in the third trimester suffered an average loss in postpartum weight of 5.12kg. Birth weight followed in turn with a decline of 320g from an average birth weight of 3327g, in the cohort with the same third trimester exposure. In reverse, when normal rations were restored upon liberation of Holland, the same sequence held for women in the third trimester; recovery of 5.7kg in postpartum maternal weight was followed in birth weight of 380g to a mean of 3387g. Adverse effects on birth weight were not noted when the daily energy intake remained above 1500 Kcal.
2) Epidemiological studies use mostly maternal weight gain, maternal body mass index (wt/ht^2), or postpartum maternal weight as indicators of maternal food intake during pregnancy. Maternal weight correlates with birth weight; height also correlates with birth weight but its effect is in some studies accounted for by the concomitant increase in weight[44].
3) Supplementation studies can be divided into three categories: those where there has been a positive effect on birth weight, no effect or effect only in certain circumstances. Some examples follow:
    a) *At Sorrento, Birmingham*[47,48], supplementation enhanced fetal growth in mothers at nutritional risk, but had no effect, or possibly adverse effects, in the adequately nourished.
    b) *Gambian* findings[52] have similarities. Fetal growth was enhanced compared with historical controls when mothers received a supplement during the rainy season, when food was limited, and they had to work in the fields. However, when future mothers received a supplemented during the dry season, the more affluent season, growth was not enhanced. Indeed, it was even slightly below the controls.
    c) In *Indonesia* an increase in birth weight was observed in the mothers who received a high energy supplement. In this particular group, body mass index of women in the community was marginally low, indicating chronic energy deficiency.
    d) In *Chile*[55], two groups of future mothers received supplements during pregnancy. One was a milk powder supplement, and the other, a fortified milk-based supplement. This latter group had vitamin and mineral intakes which were considerably higher for vitamins A, C, D, E, niacin, pyridoxine, folic acid, iron, magnesium, zinc, copper and iodine. In this study there was a large increase in birth weight in the supplemented groups. Compared to other studies, where increases are noted of 30-70g in birth weight, this study found increases of 258g and 335g. The larger increase was noted in the mothers who received the vitamin and mineral supplement. Not only was the order of magnitude of the birth weight increase in this study remarkable, but also
        i) studies describing similar increases in birth weight are those where mothers are nutritionally worse off [48] or in a period of very low food intake[52], whereas in this particular study the average weight for height percentage was 90% and
        ii) the larger increase occurred in the group receiving the mineral and vitamin supplement.

The findings may explain the small increases in birth weight after energy and protein supplementation, in that other factors such as minerals and vitamins limit the increase in birth weight. Evidence for an effect of mineral supplementation itself comes from a study[59] where women at risk of delivering a small-for-dates baby were assigned to a zinc supplement or a placebo group. The zinc supplemented group required less medical intervention in terms of induction of labour and Caesarean section for fetal distress. Birth weight was higher in the supplemented group (3060g vs 2780g), but the difference was not significant, probably due to the small numbers in the supplemented (n=13) and control (n=16) group. Figures on length at birth are not provided, but the ponderal index which was smaller in the supplemented group, 0.02 vs 0.23, combined with the higher birth weight lets us suppose that the newborns in the supplemented group were longer.

As mentioned previously, the most frequently used indicator of birth size, is weight. Very little information is available on length at birth and the subsequent growth of newborns, thus, in the following analysis birth weight and factors determining it, or associated with it are considered, as a proxy to understand what could determine length and subsequent growth.

These studies lead to the following conclusions: dietary restriction causes a decrease in birth weight while supplementation studies show less than the desired effect; on average the birth weight increases by 50g. High density protein supplements are consistently associated with decreased mean birth weight, as concluded by Rush[60].

Studies of the determinants of birth weight, although they find different strengths of association or correlation, or are in conflict have at least the following in common:

a) they provide little information on cause or underlying mechanisms. Maternal stature, birth order, age of the mother, parity are all found to be correlated with birth weight, but provide little information on the possible explanatory mechanisms. Susser, analysing supplementation studies where pregnant women were given energy/protein, found conflict in putative causal links between energy intake, or mother's weight and birth weight[53].
b) multiple regression analyses reveal a large proportion of the observed variance remains unexplained. In an observational study in Sorrento, Birmingham, 78% of the variance was unexplained; comparison of two groups of women ten years apart improved the results, but still left 47% unexplained. A similar study in Kenya, found that weight of the mother at three months pregnancy, her height, her weight gain during pregnancy, sex of the offspring, parity and skinfold thickness during pregnancy could only explain 30% of the variance in birth weight[40].

Micronutrients

The effects of minerals and vitamins on linear growth have mainly been studied in infants and children. Very little is available on the effect of vitamin and mineral status during pregnancy and linear growth in the first year of life. (The question is which micronutrient, if there is need of an effect, can affect linear growth?)

Minerals

The following minerals have been proposed as necessary for optimal linear growth: calcium, phosphorous, sulphate, magnesium, iron, iodine, zinc, copper. The elements reviewed here are zinc, iron, copper and iodine.

Zinc

Zinc deficiency in children depresses growth, appetite, skeletal maturation and gonadal development, which can be reserved with

Zn treatment. Zinc deficiency is associated with metabolic disturbances of a wide range of hormones, cytokines, and enzymes involved in growth and bone development. Zn deficiency affects the immune system, the structure of the skin and intestinal mucosa, wound healing and dark adaptation[61]. Children with severe malnutrition show clinical signs and immunological deficits which are correctable by zinc[62]. How zinc affects bone growth and maturation is not clear.

There have been a number of observations which suggest that Zn deprivation may be implicated in human growth retardation. Adolescent nutritional dwarfism in Middle-Eastern countries, characterised by poor growth and delayed sexual maturity, has been related to Zn deficiency in association with deficiencies of other nutrients. In addition, poor Zn status. as suggested by low Zn levels in blood or hair, has been described in growth retarded Chinese, Mexican, Thai and Papua New Guinean children[61,63].

Supplementation studies show more mixed results. Over-all boys respond more or only to a zinc supplement. Comparison of the different studies is difficult due to the heterogeneity of subjects, dosages and duration of the supplements given. Despite this, the accumulating evidence suggests that Zn supplementation can increase the height and weight gains of certain groups, particularly infants and adolescent boys, in both developing and developed countries[61].

The results of zinc supplementation are more dramatic for children, male and female, recovering from severe malnutrition. In Jamaica, children who received a zinc supplement increase their lean body mass and total body water at the expense of adipose tissue[64]. Marasmic children in Chile responded to zinc supplementation, given for 90 days, by increasing their weight-for-length but not their length-for-age[65]. Schlessinger et al observed that a zinc-fortified formula improved linear growth of Chilean infants (average age 7 months) recovering from marasmus, compared to a non-fortified formula containing standard amounts of zinc (and other nutrients). The difference was not much over a period of 105 days, but the supplemented male infants had an earlier growth spurt. Immune response was also better in the supplemented group, although there was no effect on the number or duration of infectious episodes, suggesting that the beneficial effect on growth was not explained by lower morbidity.

How zinc affects linear growth is not clear. Zinc is a potent appetite regulator. It is also necessary for the mobilisation of vitamin A, affecting the synthesis of apo-retinol, and its metabolism at the periphery where it affects retinal dehydrogenase activity, decreasing the conversion of retinol to retinal. Zinc is also an essential element in protein synthesis, as part of DNA and RNA performance.

Iron

Evidence of the effect of Iron on linear growth is rather scant and the results of the few supplementation studies either do not report linear growth effects or give conflicting results[63]. These mixed results might be explained in part by the difficulty of detecting significant growth differences in the relatively short periods during which iron supplements were given. Most probably linear growth only responds to iron treatment if the child is initially anaemic. Two studies from Indonesia[66,67] confirm this effect of supplementation in anaemic children on linear growth. In both studies, anaemic children were thinner and shorter before the supplementation and they considerably improved their weight and height after supplementation. Whether this effect is directly related to iron or mediated by another mechanism is not clear. Anaemic adults increase their food intake after treatment, but, in one study where food intake was measured, no increase in food intake was noted. Less morbid episodes could be an explanation. Treated children showed significantly less morbid episodes as measured by fever, respiratory infections and diarrhoea[67].

In Bangladesh, children with low height-for-age indices showed lower levels of haemoglobin, (Hb), serum copper and serum vitamin A levels[68].

Iron plays a role in the maintenance of a normal immunity and myeloperoxidase activity of the lymphocytes is decreased in anaemic subjects. The relationship of iron to morbidity could be explained by a reversal of depressed immunity in these studies .

Iron also has roles as a co-enzyme. Thus it is involved in a wide range of cellular functions from the cellular respiratory chain and ATP generation, to amino acid metabolism and hydroxylation of steroids. Iron supplementation in anaemic and iron deficient non-anaemic female workers has a beneficial effect on energy expenditure and work activity[69]. Supplemented workers have lower heart rate and total energy expenditure. The change in production efficiency after treatment is significantly correlated with the change in Hb values, but not with the change in heart rate at work. It is concluded that the improvement in production efficiency is not explained directly by the decrease in mean heart rate at work. A possible explanation is that the specific activities of iron containing enzymes in the mitochondrial electron transport system and related muscular efficiency increase with improved iron status. A direct effect of iron through cellular metabolism is likely.

Information of these kinds on the effects of supplementation in iron deficient, as opposed to anaemic children is not available.

Copper

Children recovering from severe malnutrition have low copper stores and benefit from copper supplementation especially if on high energy, low copper diets[39]. Supplementing copper was found to have a beneficial effect on weight gain and weight-for-length in 11 children recovering from malnutrition. Only those children with initially low serum copper and ceruloplasmin were found to benefit. Energy intake was also higher after supplementation. Length increase was greater, but not significantly so, perhaps because the period of study was short and the number of subjects small. In Zaire, children who failed to respond to treatment for malnutrition where found to increase their weight and length growth after having received a copper supplement[70].

Iodine

Iodine deficiency, when severe, causes stunting. It is a classical sign of the severe deficiency state. Marginal deficiency is also associated with short stature[71]. It is even possible that iodine deficiency during fetal life has a persistent effect on later growth. In a region of Ecuador with severe iodine deficiency, interventions with iodinated oil failed to change children's growth. On the other hand, if women are given iodinated oil prior to conception, the birth weight of their infants is increased[63].

Vitamin A

Vitamin A has been known to be required for growth since its discovery in 1913[72]. Deceleration in weight gain is one of the earliest, most predictable events after acute withdrawal of vitamin A from the diet of young animals, attributable to losses in efficiency in food, and specifically, protein utilisation. Prolonged deficiency exhausts circulating and hepatic levels of vitamin A causing cessation of growth and subsequent weight loss, accompanied by reductions in body fat and deranged protein metabolism. Resupplementation with vitamin A restores normal growth[73].

The relationship between vitamin A and linear growth has been demonstrated in several cross-sectional and longitudinal studies. Children with clinical signs of vitamin A deficiency are,

in most studies, found to be more stunted than children without signs[74-79]. There is also a relationship between vitamin A status and wasting. In Malawi, however, no association was found between vitamin A status and either stunting or wasting[80].

In a longitudinal prospective study in Indonesia, 4000 children were followed for a period of three months[81]. Children with signs of xerophthalmia were found to grow less in weight and height, which extrapolated over one year would amount to 0.2-1.7cm less growth in length. After supplementation, children showed a catch up in weight but not in length. Girls were more affected than boys which, according to the authors, could be explained by girls having more severe signs of xerophthalmia. Another supplementation study in Indonesia[73] found vitamin A supplementation to improve child growth, but only in males and only in weight. Since the supplements only raised retinol levels for 2-3 months before returning to baseline values the authors proposed that the supplement raised the retinol values insufficiently to sustain a catch-up growth in length. This might explain why fortification of monosodium glutamate with vitamin A showed a strong and consistent advantage in linear growth among programme children at every age[82,83]. Another possible explanation, not researched by these studies, is the possible role other micronutrient deficiencies may have on the effect of vitamin A supplementation.

Interactions of micronutrients

Failure to study the effect of iron and vitamin A on growth is partly related to the difficulty of isolating observations to one nutrient, because a variety of nutrients interact to carry out biological functions.

Hodges et al reviewed the conclusions of eight studies by the US Interdepartmental Committee for National Defence on non-pregnant and non-lactating women in developing countries where iron intake was more than 14mg per day. There was no relation between haemoglobin and iron intake, but a strong correlation between serum vitamin A and haemoglobin. A positive correlation between retinol in serum and haemoglobin in the blood of children in Ethiopia and in pregnant women in Indonesia has been demonstrated[84].

Iron deficiency is more easily corrected when there is no vitamin A deficiency. Studies have demonstrated a higher efficiency of the treatment of anaemia when vitamin A is added to the treatment, even in the absence of clinical vitamin A deficiency[84-86]. An explanation is not available for the observed relationship from human studies. Prolonged vitamin A deficiency in animals negatively affects haematopoiesis with a gradual replacement of the bone marrow by fibrous and fat tissue. The iron absorption increases in vitamin A deficient animals and at the same time haemosiderosis of the spleen and the liver can be demonstrated. The phenomena reverse after vitamin A supplementation[86].

In the late 1970s, several workers tried to elucidate the relationships between vitamin A and iron. In an experiment involving a vitamin A deficient group of otherwise healthy volunteers, an association between iron metabolism and hypovitaminosis A was established. The experimental group developed anaemia refractory to medicinal iron but responsive to vitamin A. In Central America vitamin A fortification of sugar without an increase of iron in the diet had a positive impact on iron metabolism[87]. The authors observed that after six months of a vitamin A fortification, indices of iron status improved. Because the levels of total iron binding capacity (TIBC) increased and the levels of ferritin decreased, it seems that, after fortification, there was an increase in the availability of serum iron by depletion of the iron stores for haematopoiesis. After two years of vitamin A fortification an overall significant improvement of all the iron nutritional indices was observed; serum iron, percent saturation, and ferritin had increased significantly and TIBC had decreased. A plausible explanation for this phenomenon is that vitamin A enhances both haematopoiesis and the availability of serum iron by depleting the iron stores. This may trigger the improvement of dietary iron absorption and as a consequence might lead, after two years of fortification, to elevated levels of ferritin and a decrease of TIBC levels as may be expected in normal iron metabolism[87]. These findings were confirmed first in a cross-sectional study[88] and later in a supplementation study in Thailand[89] where a single dose of vitamin A was found to improve iron status. The difference in serum retinol and serum retinol binding protein which increased between the control and the supplemented group where not significant anymore four months after intervention. These findings support the thesis of studies in Latin America where a single dose supplement did not affect linear growth but fortification, which provides vitamin A for longer periods, did.

The above mentioned studies support the hypothesis that the interaction between iron and vitamin A has three modes of action: 1) lack of vitamin A immobilises iron stored in the reticuloendothelial system; 2) the initial depletion of iron stores, and consequently increased utilisation after vitamin A supplementation, triggers the dietary absorption of iron and leads to the observed higher levels of ferritin after four months; 3) the association between vitamin A stores and infections leads to a decreased morbidity in children who receive a supplement, and this in turn positively affects iron utilisation. Zinc is also known to interact with vitamin A. Zinc deficiency decreases levels of serum albumin, pre-albumin and transferrin. Pre albumin levels increase rapidly with a zinc supplementation of 10-15 days[90]. This effect is probably mediated through the effect of zinc on protein synthesis, most noticeable in the effect of zinc deficiency on the synthesis of retinol binding protein[91]. Here zinc deficiency is found to be necessary for normal mobilisation of vitamin A from the liver and maintenance of normal serum levels. A study from India involving malnourished children supports this concept. These children showed a significant increase of plasma Vitamin A and retinol binding protein in response to zinc supplementation. In a study in Thailand, no adverse effect on retinol binding protein or serum retinol was noted when zinc was added to vitamin A supplementation as compared to children who received vitamin A alone[92]. In this study, however, it was not clear whether the children were significantly zinc deficient or to what degree.

Gestational age

This is discussed in the birth size paragraph.

Uterine size

As with other determinants of stunting, the influence of the fetal environment on birth outcome has been studied predominantly by using birth weight as an outcome. Some studies have, however, demonstrated that the fetal environment does have an effect on length. A classical experiment addressing this question is the one of Walton and Hammond[93] in which offspring of matings between Shire and Shetland ponies were studied. There is approximately a fourfold difference in weight between the Shire and Shetland mares. The reciprocal crosses, achieved by artificial insemination provided embryos of substantial different genotype in uteri of different sizes. The hybrid foals born to Shetland mares were comparable in size to pure-bred Shetland while foals born to Shire mothers were considerably larger, approaching but not equalling the weight of pure bred Shires. Both types of foals had normal proportions. Similar results have been obtained in cattle and in sheep[94].

Roberts[35] in a synthetic article cites an example where 38% of the variance in individual birth-weights among surviving infants

can be attributed to heredity. However this 38%, is made up of only 16% from fetal heredity factors other than sex, 2% from fetal sex, and 20% from maternal hereditary constitution. The greater part of the variance, the remaining 62%, was attributable to environmental causes, of which 18% derived from the mother's general health and nutrition, 6% from her health during each particular pregnancy, 7% from her parity, and 1% from her age, the remaining 30% being attributable to unknown intra-uterine influences. In the same article mention is made of a study of Morton who analysed massive data from Japan. Account was taken of the effects of maternal age, parity, the sex of each child, and the number of pregnancies intervening between each pair of siblings. At birth, like-sexed twins, with a high degree of common heredity were not more alike than full siblings or even half-siblings from the same mother. By contrast, the half-siblings with the same father were notably unalike. The effect of consanguinity was negligible, indicating no detectable effect of recessive genes. The mothers phenotype seems to be a principle determinant of the size of the newborn child.

Similar studies have been done by Tanner, who found that the correlation between length at birth and adult height is very low, about 0.3. By six months it rises to 0.5 and by one year to 0.7; by two years a stable prepubertal level of nearly 0.8 is reached[95].

In the first part of fetal development, the weight gain of the fetus merely reflects cell growth. A period of linear peak growth velocity can be assumed later on, but the gestational age at which this occurs is still somewhat uncertain with estimates for 16 weeks of gestation[28]. After this, linear growth velocity decreases and continues to do so well into the postnatal period[28]. According to the same author, fetal growth slows down at 34-36 weeks owing to space constraints. Twins slow down considerably earlier when their combined weight is approaching that of a 36-week singleton fetus.

A problem in the construction of a causal model is the question of a primary operational focus. Should we put height of the mother as a determinant of uterine size? Do we have any indication that taller women have more space to accommodate a bigger uterus and so allow for taller children. Is that the mechanisms by which maternal height effects it influence?

We reflect a similarities on birth order. Why are first born children lighter? Does the uterus have to go through an adaptation process by which it is smaller in the first pregnancy and becomes bigger afterwards? Is this a stretching phenomenon?

How does the age of the mother affect the size of the offspring? Younger women are not full grown and have lesser space for the uterus. Is this the explanation? Age of the mother may determine uterine size and fetal outcome.

Placental size

Falkner[28] quotes the Louisville Longitudinal Study of Twins which provides evidence of a strong correlation between placental weight and birth weight. In monozygous twins, who are phenotypically similar, differences in birth weight and in postnatal growth may be determined by placental weight. The concentrations of several biochemical and nutritional substances are the same in the placental segments belonging to each twin, but, because of the difference in placental weights, the absolute amounts are different.

The hormonal environment

Post natal growth depends on four main hormonal regulating mechanisms: a) Growth hormone via somatomedin, b) thyroid hormone, c) cortisol and d) sex hormones during adolescence .

Insulin has a more permissive role in post natal growth[96]. The fetus in contrast depends less on growth hormone and thyroid hormone for its growth and more on insulin and tissue growth factors.

Maternal growth hormone does not cross the placental barrier, making the fetus entirely dependant on its own hormone homeostasis for growth.

The role of growth hormone in fetal growth has been studied in different species by depriving the fetus of its pituitary gland in utero. Normal fetal growth is possible when growth hormone is lacking or is markedly reduced. GH-dependant growth is not observed until well after birth; in humans at six months. The hypothesis that growth hormone is not an important determinant of fetal or neonatal growth has been advanced by Karlberg[2,5] who based his ICP model for growth on this concept. Growth hormone dependence becomes noticeable with the onset of the childhood component of growth in this model. Intrauterine hormonal homeostasis seems to go beyond intrauterine life.

Thyroid hormones are also not transferred from the mother to the fetus and the fetus is dependant on its own thyroid gland for thyroid hormone production. Human newborns suffering from congenital hypothyroidism, or radiothyroidectomised in utero by radioactive iodine given inadvisedly to the mother, have a normal size and weight at birth[96]. Thus thyroid hormones appear to have little effect on fetal growth in most species, but they are essential for normal neural and osseous maturation[97].

Insulin

The concept that insulin might be an important hormone for fetal growth arose primarily from clinical observations with insulin excess or insulin deficiency. The infants of diabetic mothers are larger (on average 500g) and somewhat longer (on average 1.5cm) than control infants[98], though most of the overweight is due to lipid deposition. Since the excessive growth becomes obvious after the 28th week[99], at a time where the fetal pancreas becomes sensitive to glucose[100], it has been suggested that maternal hyperglycaemia is attended by fetal hyperglycaemia which, in turn, stimulates insulin secretion by the fetal pancreas and induces macrosomia. In contrast, newborns with pancreatic agenesis have profound intrauterine growth retardation associated with deficient adipose tissue and a decease in muscle mass[101]. Infants with transient neonatal diabetes also have a defect in insulin secretion which is associated with a low birth weight[102]. These infants have reduced adipose tissue and reduced muscle mass which undergoes rapid development with postnatal insulin treatment. The birth size of infants born with marked fetal hypoinsulinemia suggests that the human fetus can reach the size of a 30 to 32 week gestation fetus independent of insulin. The evidence suggests that insulin not only has a permissive role but also a regulatory role in fetal growth[96].

The insulin like growth factors.

The term somatomedin (SM) and insulin-like growth factors(IGF) are synonymous. Somatomedin A and C are analogous to IGF-I. IGF-II is equivalent to multiplication stimulating activity (MSA), discovered in the rat. The IGFs share a large structural homology with proinsulin.

IGFs do not cross the placenta and the IGF-I and the IGF-II found in fetal plasma in various species are produced by fetal tissues. Although in postnatal life the liver is the main producer of IGF-I, during fetal life most tissues produce the same including liver, heart, kidneys and skin[103]. Lung and intestine have the highest concentration, liver the lowest. The concentrations in these tissues are far in excess of amounts that can be accounted for by contamination from the blood.

On the basis of these findings the classical concept that IGFs act as endocrine factors has been progressively abandoned in favour of the concept of paracrine or autocrine function. The

concentrations of IGFs in fetal plasma probably do not reflect the functional situation. Most of the IGFs are bound to a carrier protein; total IGF concentration does not reflect the hormone available to react with the receptors. Fetal hormonal regulation differs from post natal life in the relative role of growth hormone, which becomes apparent about 6 months postnatally with a more autocrine and paracrine character of regulation[96,97,104]

IGF-I production is not controlled by GH. Fetal decapitation, hypophysectomy, or electrocoagulation of the hypothalamus of the lamb or rat abolishes GH from the fetal circulation but has no effect on circulating somatomedin or IGF-I levels. Moreover, GH fails to stimulate IGF secretion by the rat fetus. or by cultured rat fibroblasts. In addition, human anencephalic infants have normal somatomedin levels in cord blood (reviewed in vol 18 p29). Insulin concentrations affect IGF concentration. In situations where insulin levels are low, IGF-I tends to be decreased whereas IGF-II remains normal. Conversely, in situations of hyperinsulinaemia, IGF-I levels are increased. IGF-II levels are unaffected.

Human placental lactogen (HPL) is a peptide secreted by the placental trophoblast. HPL is secreted into the maternal and the fetal circulations. HPL secreted in the maternal circulation stimulates the mobilisation of metabolites and increases nutrient delivery to the fetus, by acting as an insulin antagonist. Indirect evidence suggests that it also stimulates maternal IGF-I secretion. HPL in the fetal circulation stimulates IGF-I production. Based on the above findings, the following working hypothesis has been proposed[104]: fetal cellular growth is dependant on nutrient delivery (eg, glucose, amino acids, and fatty acids). The uptake of nutrients by the fetal cells is stimulated by insulin. Fetal insulin secretion is stimulated by amino acids up to 28 weeks of gestation and by amino acids and glucose thereafter. Cellular anabolism progresses to replication under the influence of growth factors. Growth factor synthesis and release are stimulated not only by intracellular events such as delivery of fuel, which is augmented by insulin, but also by HPL, which may be acting on many fetal tissues in a manner analogous to GH acting on the hepatocyte postnatally. Finally, there is a long loop in which insulin reinforces the anabolic process by stimulating HPL secretion.

Conclusions

There is a very intricate relationship between mother and child which lasts beyond the birth of the child. The nutritional status of the mother and her energy and protein intake during pregnancy play an important role, but they explain only part of the observed growth outcomes of the child. This could be due to the fact that the timing of the insult is important and in most studies not taken into consideration and because of the role micronutrients are likely to play.

The role of micronutrients is difficult to interpret when interaction between different elements at the biochemical level is concerned. For some minerals the link between endowment at birth in these elements and the subsequent growth of the child are clear. The iron status and vitamin A status of the newborn are determined by gestational age and the reserves the mother had. Food diversity is particularly a determinant of the intake of micronutrients. This could then perhaps explain why growth faltering is found to start earlier in rural populations as compared to urban ones. The most likely candidates to possibly affect linear growth of children are vitamin A, zinc and iron, two of which belong to the most important micronutrient deficiencies worldwide.

Perhaps it is time for a research reorientation more towards the study of the relationship between fetal growth and early postnatal linear growth. So far research has concentrated predominantly on the relationship between macro-nutrients and birth outcome, this mostly expressed as birth weight. But linear growth of children, particularly early after birth could also be an indicator of what one could consider the "hidden hunger". The nutritional status, more particularly the micro-nutrient homeostasis of women at the time of conception, might have important repercussions for young children.

A review on the determinants of stunting. Can we regard the linear growth performance a continuum of fetal development?

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發育障礙決定因素的評論：能否把線性成長的特性視作胎兒發育的連續？

摘要

這是一篇評論文章。作者特別強調出生後的早期成長和子宮內發育的可能關係。這可從一些亞洲人群在出生後不久其線性生長就開始緩慢得到証實。這種現象在出生後頭 6 個月內最爲明顯。本來在以後的歲月內，趕上生長是可能的，但由於環境不允許，因此在發展中國家的兒童，成年時往往較矮。本文評論了概念模型的建立，並把它分成兩部份：子宮內因素和產後頭一年因素。作者僅分析了胎兒和產後線性生長之間的關係，並考慮這些決定因素是重要的。

References

1. Child malnutrition. Progress toward the world summit for children goal. New York: UNICEF, 1993.
2. Karlberg J. A biologically-oriented mathematical model (ICP) for human growth. Acta Pediatr Scand 1989; Suppl. 350: 70-94.
3. Karlberg J, Albertsson-Wikland K. Infancy growth pattern related to growth hormone deficiency. Acta Pediatr Scand 1988; 77: 385-391.

4. Karlberg J, Jalil F, Lindblad S. Longitudinal analysis of infantile growth in an urban area of Lahore, Pakistan. Acta Pediatr Scand 1988;77:392-401.
5. Karlberg J, Engström I, Karlberg P, Fryer JG. Analysis of linear growth using a mathematical model I. From birth to three years. Acta Pediatr Scand 1987;76:478-488.
6. Karlberg J, Henter J, Tassin E. Longitudinal analysis of infantile growth in children with coeliac disease. Acta Pediatr Scand 1988;77:516-524.
7. Waterlow JC. Causes and mechanisms of linear growth retardation (stunting). Eur J Clin Nutr 1994;48 (Suppl.1): S1-S4.
8. Waterlow JC. Reflections on stunting. Int Child Health 1991; 2 No.2: 25-35.
9. Golden MHN. Is complete catch-up possible for stunted malnourished children? Eur J Clin Nutr 1994; 48 (Suppl.1): S58-S71.
10. Kusin JA, Sri Kardjati, Houtkooper JM, Renqvist UH. Energy supplementation during pregnancy and postnatal growth. Lancet 1992; 340: 623-626.
11. Harrison GA, Brush G, Zumrawi FY. Interrelations between growth, weaning and disease experience in Khartoum infants. Eur J Clin Nutr 1992; 46: 273-278.
12. Gueri M, Gurney JM, Jutsum P. The Gomez classification. Time for a change? Bull WHO 1980; 58: 773-777.
13. Stewart AL, Reynolds EOR, Lipscomb AP. Outcome of very low birthweight: survey of world literature. Lancet 1981; 1038-1041.
14. Brimblecombe FS, Ashford JR, Fryer JG. Significance of low birth weight in perinatal mortality. Brit J prev soc Med 1968; 22: 27-35.
15. Mavalankar DV, Gray RH, Trivedi CR. Risk Factors for preterm and term low birthweight in Ahmedabad India. Int J Epidemiol 1992; 21: 263-272.
16. Cruise MO. A longitudinal study of the growth of low birth weight infants. I. Velocity and distance growth, birth to 3 years. Pediatr 1973; 51: 620-628.
17. Westwood M, Kramer MS, Munz D, Lovett JM, Watters GV. Growth and development of full-term non asphyxiated small-for-gestational-age newborns: follow-up through adolescence. Pediatr 1983; 71: 376-382.
18. Fitzhardinge PM, Stevens EM. The small for date infant. I. Later growth patterns. Pediatr 1972; 49: 671-681.
19. Martell M, Falkner F, Bertolini LB, et al. Early postnatal growth evaluation in full-term, preterm and small for dates infants. E Hum Dev 1978; 1/4: 313-323.
20. Georgieff MK, Sasanow SR, Mammel MC, Pereira GR. Mid-arm circumference/head circumference ratios for identification of symptomatic LGA, SGA, and SGA newborn infants. J Pediatr 1986; 109: 316-321.
21. Tenovuo A, Kero P, Piekkala P, Korvenranta H, Sillanpää M, Erkkola R. Growth of 519 small from gestational age infants during the first two years of life. Acta Pediatr Scand 1987; 76: 636-646.
22. Kramer MS, McLean FH, Olivier M, Willis DM, Usher RH. Body proportionality and head and length 'sparing' in growth retarded neonates: a critical reappraisal. Pediatr 1989; 84: 717-723.
23. Waterlow JC. Note on the assessment and classification of protein-energy malnutrition in children. Lancet 1973; 2: 87-89.
24. Miller HC, Jekel JF. Malnutrition and growth retardation in newborn infants. Pediatr 1989; 83: 443-444.
25. Hill RM, Verniaud WM, Deter RL, et al. The effect of intrauterine malnutrition on the term infant. A 14 year progressive study. Acta Pediatr Scand 1984; 73: 482-487.
26. Kramer MS, Olivier M, McLean FH, Dougherty GE, Willis DM, Usher RH. Determinants of fetal growth and body proportion. Pediatr 1990; 86: 18-26.
27. Miller HC, Hassanein K. Diagnosis of impaired fetal growth in newborn infants. Pediatr 1971; 48: 511-522.
28. Falkner F, Holzgreve W, Schloo RH. Prenatal influences on postnatal growth: overview and pointers for needed research. Eur J Clin Nutr 1994; 48 (Suppl.1): S15-S24.
29. Pomerance HH, Krall JM. The relationship of birth size to the rate of growth in infancy and childhood. Am J Clin Nutr 1984; 39: 95-99.
30. Garn SM, LaVelle M. Interaction between maternal size and birth size and subsequent weight gain. Am J Clin Nutr 1984; 40: 1120-1121.
31. Davies DP. The importance of genetic influences on growth in early childhood with particular reference to children of Asiatic origin. In: Waterlow JC, ed. Linear growth retardation in less developed countries. Nestle Nutrition Workshop Series. Vol.14. New York: Raven Press, 1988: 75-90.
32. Smith DW, Truog W, Rogers JE, Reizer LJ, Skinner AL, McCann JJ. Shifting linear growth during infancy: illustration of genetic factors in growth from fetal life through infancy. J Pediatr 1976; 89: 225-230.
33. Habicht JP, Martorell R, Yarbrough C, Malina RM, Klein RE. Height and weight standards for preschool children. How relevant are ethnic differences in growth potential? Lancet 1974; 611-614.
34. Rona RJ. Genetic and environmental factors in the control of growth in childhood. Br Med Bull 1981; 37: 265-272.
35. Roberts DF. Genetics of growth. Br Med Bull 1981; 37: 139-246.
36. Marshall WA. Geographical and ethnic variations in human growth. Br Med Bull 1981; 37: 273-279.
37. Tanner JM. Population differences in body size, shape, and growth rate. A 1976 view. Arch Dis Childh 1976; 51: 1-2.
38. Martorell R, Mendoza F, Castillo R. Poverty and stature in children. In: Waterlow JC, ed. Linear growth retardation in less developed countries. Nestle Nutrition Workshop Series. Vol.14. New York: Raven Press, 1988: 57-73.
39. Castillo-Duran C, Uauy R. Copper deficiency impairs growth of infants recovering from malnutrition. Am J Clin Nutr 1988; 47: 710-714.
40. Kusin JA, Jansen AJ. Maternal nutrition and birthweight: selective review and some results of observations in Machakos, Kenya. Ann Trop Paediatr 1986; 6: 3-9.
41. Robyn C, Keita MS, Meuris S. Intrauterine growth retardation in Africa. In: Senterre J, ed. Intrauterine growth retardation. Nestle Nutrition Workshop Series. Vol 18. new York: Raven Press, 1989: 165-181.
42. Wharton B. Causes of low birthweight in developing countries. In: Senterre J, ed. Intrauterine growth retardation. Nestle Nutrition Workshop series. Vol 18. New York: Raven Press, 1989: 143-155.
43. de Nobrega FJ, Lopez FA, Segre CAM. Anthropometry in Brazilian newborn infants: Studies of association with some maternal factors. In: Senterre J, ed. Intrauterine growth retardation. Nestlé Nutrition Workshop Series. Vol 18. New York: Raven Press, 1989: 157-164.
44. Bhargava V, Chatterjee M, Prakash A, Bhatia B, Mishra A. Fetal growth variations. I. Influence of maternal size and nutrition on identification of fetal growth retardation. Ind Pediatr 1983; 20: 549-559.
45. Rush D, Stein Z, Susser M. A randomized controlled trial of prenatal nutritional supplementation in New York city. Pediatr 1980;65:683-697.
46. Osofsky HJ. Relationship between prenatal medical and nutritional measures, pregnancy outcome and early infant development in an urban poverty setting. Am J Obstet Gynecol 1975; 682-690.
47. Viegas OAC, Scott PD, Cole TJ, Eaton P, Needham PE, Wharton BA. Dietary protein energy supplementation of pregnant Asian mothers at Sorrento, Birmingham. I. Unselective during second and third trimester. Br Med J 1982; 285: 589-592.
48. Viegas OAC, Scott PD, Cole TJ, Eaton P, Needham PE, Wharton BA. Dietary protein energy supplementation of pregnant Asian mothers in Sorrento, Birmingham. II. Selection during the third trimester only. Br Med J 1982; 285: 592-595.
49. McDonald EC, Pollit E, Mueller W, Hsuek AM, Sherwin R. the Bacon-Chow study: maternal nutritional supplementation and birth weight of offspring. Am J Clin Nutr 1981; 34: 2133
50. Lechtig A, Habicht JP, Delgado H, Klein RE, Yarbrough C, Martorell R. Effect of food supplementation on birth weight. Pediatr 1975; 508-520.
51. Mora JO, de Paredes P, Wagner M, et al. Nutritional supplementation and outcome of pregnancy. I. Birthweight. Am J Clin Nutr 1979; 32: 455-462.
52. Prentice AM, Whitehead RG, Watkinson M, Lamb WH, Cole TJ. Prenatal dietary supplementation of African women and birthweight. Lancet 1983; i: 489-492.
53. Susser M. Maternal weight gain, infant birth weight, and diet: causal sequences. Am J Clin Nutr 1991; 53: 1384-1396.
54. Suescun J, Mora JO. Food supplements during pregnancy. In: Senterre J, ed. Intrauterine growth retardation. Nestle Nutrition Workshop Series Volume 18. New York: Raven Press, 1989: 223-241.
55. Mardonnes-Santander F, Rosso P, Stekel A, et al. Effect of a milk-based food supplement on maternal nutritional status and fetal growth in underweight Chilean women. Am J Clin Nutr 1988; 47: 413-419.
56. Adair LS, Pollit E. Outcome of maternal nutritional supplementation: a comprehensive review of the Bacon-Chow study. Am J Clin Nutr 1985;41 :948-978.
57. Moser-Veillon PB, Reynolds RD. A longitudinal study of pyridoxine and zinc supplementation of lactating women. Am J Clin Nutr 1990; 52: 135-141.
58. Sri Kardjati, Kusin JA, Schofield WM, de With C. Energy supplementation in the last trimester of pregnancy in East Java, Indonesia: effect on maternal anthropometry. Am J Clin Nutr 1990; 52: 987-994.
59. Simmer K, Lort-Phillips L, James C, Thompson RPH. A double-blind trial of zinc supplementation in pregnancy. Eur J Clin Nutr 1991; 45: 139-144.

60. Rush D. Nutrition in pregnancy. Proceedings of the tenth study group of the Royal College of Obstetricians and Gynaecologists. London 1983; 233-241.
61. Prentice A, Bates CJ. Adequacy of dietary mineral supply for human bone growth and mineralisation. Eur J Clin Nutr 1994; 48 (Suppl.1): S161 -S177.
62. Golden MHN. The role of individual nutrient deficiencies in growth retardation of children as exemplified by zinc and protein. In: Waterlow JC, ed. Linear growth retardation in less developed countries. Nestle Nutrition Workshop Series. Vol.14. New York: Raven Press, 1988: 143-163.
63. Allen LH. Nutritional influences on linear growth: a review. Eur J Clin Nutr 1994; 48 (Suppl.1): S75-S89.
64. Golden MHN, Golden BE. Effect of zinc supplementation on the dietary intake, rate of weight gain, and energy cost of tissue deposition in children recovering from severe malnutrition. Am J Clin Nutr 1981;34: 900-908.
65. Castillo-Duran C, Heresi G, Fisberg M, Uauy R. Controlled trial of zinc supplementation during recovery from malnutrition: effects on growth an immune function. Am J Clin Nutr 1995; 45: 602-608.
66. Chwang L, Soemantri AG, Pollit E. Iron supplementation and physical growth of rural Indonesian children. Am J Clin Nutr 1988; 47: 496-501.
67. Angeles IT, Schultink WJ, Matulessi P, Gross R, Sastroamidjojo S. Decreased rate of stunting among anemic Indonesian preschool children through iron supplementation. Am J Clin Nutr 1993; 58: 339-342.
68. Ahmed F, Barua S, Mohiduzzaman M, Shaheen N, Bhuyan MAH. Interactions between growth and nutrient status in school-age children of urban Bangladesh. Am J Clin Nutr 1993; 58: 334-338.
69. Li R, Chen X, Yan H, Deurenberg P, Garby L, Hautvast JGAJ. Functional consequences of iron supplementation in iron deficient female cotton mill workers in Beijing, China. Am J Clin Nutr 1994; 59: 908-913.
70. Goyens P, Brasseur D. Cuivre et malnutrition proteino-energetique. In: Ingenblek Y and Hennart P, eds. Alimentation et nutrition dans les pays en developpement. 4es Journees Internationales du GERM. Karthala, Paris. 1991, 562-573.
71. Neumann CG, Harrison GG. Onset and evolution of stunting in infants and children. Examples from the Human Nutrition Collaborative Research Support Program. Kenya and Egypt studies. Eur J Clin Nutr 1994; 48 (Suppl.1): S90-S102.
72. McCollum EV, Davis M. The essential factors in the diet during growth. J Biol Chem 1915; 23: 231 -254.
73. West KP, Djunaedi E, Pandji A, et al. Vitamin A supplementation and growth: a randomized community trial. Am J Clin Nutr 1988; 48: 1257-1263.
74. Chase HP, Hambidge KM, Barnett SE, Houts-Jacobs MJ, Lenz K, Gillespie J. Low vitamin A and zinc concentrations in Mexican-American migrant children with growth retardation. Am J Clin Nutr 1980; 33: 2346-2349.
75. Mele L, West KPJ, Kusdiono, et al. Nutritional and household risk factors for xerophthalmia in Aceh, Indonesia: a case-control study. Am J Clin Nutr 1991; 53: 1460- 1465.
76. Ganguly C, Mukherjee KL, Phil D. Relationship between maternal serum Vitamin A and Vitamin A status of the corresponding fetuses. J Trop Pediatr 1986; 32: 287-289.
77. Dricot d'Ans C, Dricot J, Diniz AS, Mariath JGR, Santos LMP. Geographic distribution of xerophthalmia in the state of Paraiba, northeast Brazil. Ecology of Food and Nutrition 1988; 22: 131-138.
78. Santos LMP, Dricot JM, Asciutti L, Dricot-d'Ans C. Xerophthalmia in the state of Paraiba, northeast of Brazil: clinical findings. Am J Clin Nutr 1983; 38: 139-144.
79. Brink EW, Perera DA, Broske SP, et al. Vitamin A status of children in Sri Lanka. Am J Clin Nutr 1979; 32: 84-91.
80. Tielsch JM, West KPJ, Katz J, et al. Prevalence and severity of xerophthalmia in southern Malawi. Am J Epidemiol 1986; 124(4): 561-568.
81. Tarwotjo I, Katz J, West KPJ, Tielsch JM, Sommer A. Xerophthalmia and growth in preschool Indonesian children. Am J Clin Nutr 1992; 55: 1142-1146.
82. Muhilal, Murdiana A, Azis I, Saidin S, Basuni Jahari A, Karyadi D. Vitamin A-fortified monosodium glutamate and vitamin a status: a controlled field trial. Am J Clin Nutr 1988; 48: 1265-1270.
83. Muhilal, Permeisih D, Idjradinata YR, Muherdiyantiningish, Karyadi D. Vitamin a-fortified monosodium glutamate and health, growth, and survival of children: a controlled field trial. Am J Clin Nutr 1988; 48: 1271-1276.
84. Suharno D, West CE, Muhilal., Karyadi D, Hautvast JGAJ. Supplementation with vitamin A and iron for nutritional anaemia in pregnant women in West Java, Indonesia. Lancet 1993; 342: 1325-1328.
85. Mejia LA, Chew F. Hematological effect of supplementing anemic children with vitamin A alone and in combination with iron. Am J Clin Nutr 1988; 48: 595-600.
86. Hodges RE, Sauberlich HE, Canham JE, et al. Hematopoietic studies in vitamin A deficiency. Am J Clin Nutr 1978; 31: 876-885.
87. Mejia LA, Arroyave G. The effect of vitamin A fortification of sugar on iron metabolism in preschool children in Guatemala. Am J Clin Nutr 1982; 36: 87-93.
88. Bloem MW, Wedel M, Egger RJ, Speek AJ, Schrijver J, Saowakontha S. Iron metabolism and vitamin A deficiency in children in Northeast Thailand. Am J Clin Nutr. 1989; 50: 332-338.
89. Bloem MW, Wedel M, Agtmaal EJ, Speek AJ, Saowakontha S, Schreurs WHP. Vitamin A intervention: short-term effects of a single, oral, massive dose on iron metabolism. Am J Clin Nutr 1990; 51: 76-79.
90. Bates J, McClain CJ. The effect of severe zinc deficiency on serum levels of albumin, transferrin, and prealbumin in man. Am J Clin Nutr 1981; 34: 1655-1660.
91. Smith JR JC, McDaniel EG, Fan FF, Halsted JA. Zinc: A trace element essential in Vitamin A metabolism. Science 1973; 181: 954-955.
92. Udomkesmalee E, Dhanamitta S, Sirisinha S, et al. Effect of vitamin A and zinc supplementation on the nutriture of children in Northeast Thailand. Am J Clin Nutr 1992; 56: 50-57.
93. Walton A, Hammond J. The maternal effects on growth and conformation in Shire horse-Shetland pony crosses. Proc R Soc Biol 1938; 125: 311-324.
94. Snow MHL. Growth and its control in early mammalian development. Br Med Bull 1981;37: 221 -226.
95. Tanner JM. Catch-up growth in man. Br Med Bull 1981; 37: 223-238.
96. Girard J. Hormonal regulation of fetal growth. In: Senterre J, ed. Intrauterine growth retardation. Nestlé Nutrition Workshop Series. Volume 18. New York: Raven Press, 1989: 23-37.
97. Rappaport R. Endocrine control of growth. In: Waterlow JC, ed. Linear growth retardation in less developed countries. Nestlé Nutrition Workshop Series. Vol.14. New York: Raven Press, 1993: 109-126.
98. Osler M, Pedersen J. The body composition of newborn infants of diabetic mothers. Pediatr 1960; 26: 985-992.
99. Cardell BS. The infants of diabetic mothers: a morphology study. J Obstet Gynaecol Br Commonw 1953; 60: 834-853.
100. Milner RDG, Hill DJ. Fetal growth control: the role of insulin and related peptides. Clin Endocrinol 1984; 21: 415-433.
101. Hill DE. Effects of insulin on fetal growth. Sem Perinatol 1978; 2: 319-328.
102. Hill DE. Fetal effects of insulin. Obstet Gynaecol Ann 1982; 11: 133-149.
103. D'Ercole AJ, Hill DJ, Strain AJ, Underwood LE. Tissue and plasma somatomedin C/insulin)like growth factor I (SM-IGF-I) concentrations in human fetus during the first half of gestation. Pediatr Res 1986; 20: 253-255.
104. Milner RDG. Determinants of growth in utero. In: Waterlow JC, ed. Linear growth retardation in less developed countries. Nestle Nutrition Workshop Series. Vol.14. New York: Raven Press, 1988: 91-108.