We selected the following as examples of original contributions to Nutrition in Aging:

The Food and Drug Administration (http://www.cfsan.fda.gov) and USDA (http://www.nal.usda.gov) provide nutrition information, directly relevant to the public. At the USDA site, you will find topics such as food safety, nutrition labelling, food assistance programs, and even food and nutrition software and multimedia programs. The International Food Information Council (IFIC) has a home page (http://ificinfo.health.gov/IFICinfo.htm). Current food and nutrition issues or news can be viewed at the CNN Food and Health site (http://www.cnn.com/HEALTH/index.htm). There are newsletters, such as Food and Nutrition Digest (http://www.oznet.ksu.edu/dep/fruitnewsletter.html), which contain original material. FoodNet project at University of Minnesota (http://www.flic.umn.edu/foodnet/) is a collaborative effort by the Universities of Minnesota and Wisconsin Extension Services and the Nutrition Education and Training (NET) Programs of Minnesota and Wisconsin. The graphic design of the page is excellent and it provides useful links to sites in children's health.


The Florida Agricultural Information Retrieval System (FAIS) (http://hammock.ffas.ufl.edu/) of the Institute of Food and Agricultural Sciences, University of Florida has a search facility within the page. Documentation of plants, foods, flowers, etc. can be found from this site.

Consumer and Family Science (http://wwwcfs.cfr.purdue.edu/ fn.htm) of the Foods and Nutrition Department, Purdue University documents and conference workshop on food safety, nutrition, and volunteer management for staff and volunteers of food assistance organisations.

A few food and nutrition journals have made their way to the Internet. The Journal of Clinical Nutrition (http://www.fasae.org/jcn/jcn.htm) announces the abstracts from the latest issues and has links to other Web sites. The Journal of Food Science (http://www.ifsfpubl.com/journal.html) is another journal which has attempted to use the Internet to attract a wider readership. So far, there are “two” Internet journals of nutrition in the Web. There are several deals, such as Tony Holman, of Australia, who make available their professional and personal experiences in nutrition practice to the Internet community. His “Nutrition and the family physician - an Australian perspective” (http://nettaps.net.au/-helmut/nut_nut_disc.htm) discusses the great paradox in family physician-based nutrition at the present time.

American Cancer Society Nutrition page (http://www.ca. cancer.org/services/nutrition/) through its “Eat Right” program promotes a low fat, high fibre diet and encourages the consumption of nutritious vegetables and fruits that may prevent certain cancers.

(b) Food & Nutrition Web links

Web sites, dedicated to linking food and nutrition related web sites, provide convenient access to original nutrition information. These sites often index the links according to the nature of information provided by the source or designating site. For example, “MedWeb: Internet Medical Resources” has an index called “MedWeb: Medical Nutrition (http://medweb.medweb.nutrition.html) under which various sub-indices are used to group available information on the Net.

The following are some quality Web links sites:

The Virtual Nutrition Center, Martindale's Health Science Guide (http://www.sci.lib.edu/HSIG/Nutrition.html) is by far the most comprehensive nutrition link site. It provides international site linkages including almost all countries, non-food and non-multimedia programs.

World Wide Web Nutritional Links site (http://www.medlib.arizona.edu/nut www.htm) links to sites with quality content and non-profit motives.

Professor Geoff Skurray's Nutrition Information (http://www.hawkesbury.uws.edu.au/~geoff/) is an Australian site with food and nutrition groupings that are easily understood.

BURL: World Object Tree - Food and Drink (http://www.burl. iub.edu/BURL/Food.html) is a UK site and contains links to sites in Australia as well as international food and nutrition sites. Topics include Food Labelling, Educational Materials, Food and Nutrition Education in primary and secondary educational materials covering Food-borne illnesses and the Food Guide Pyramid.

WWW DJETETSICS (http://idiges.ie/~comdist/expnets.htm) is by dietitians from Ireland and contains AgriFAS, IFAS Resources, Food Science, Food Safety links and Nutrition and Health Links Worldwide with Guide References.

Applied Nutrition is a guide to applied and clinical nutrition resources on the Internet. It is a patient-oriented nutrition link site (http://netap.org.net/-helmut/nut_nut_disc.htm).

Nutrition Industry (http://www.medlib.arizona.edu/nut www.htm) includes a “single listing of every food and beverage related site on the World Wide Web and offers a directory of food industry professionals. Be warned that access to this site can be very slow at times.

Guide to nutrition resource on the Internet by Dr. Tony Holman (http://nutrition-net.org) is another site. A geographic version is also available at http://nettaps.net.au/-helmut/nut_nut_disc.htm. This page contains links to resources concerning food composition, food science and food safety.

Links (http://www.ag.arizona.edu/~foodnet/links.html) is the Iowa State University Dept of Food Science and Human Nutrition. You can submit your own entry to theencyclopedia.

Other Web Sites (http://www.education/other.htm) is a web site with links which may be of interest to food technologists and other food science professionals.

Conclusions

In summary, the Internet has great potential for promoting collaborative efforts among members of the international nutrition community. Much of this work is a hypothesis; however, if it is supported by data from 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 held 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 these 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 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. Infants with a late onset childhood component tend to continue growing according to the infancy growth component until the childhood growth starts. 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.3

Karberg 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 growth promoting 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 community related and not the intra-uterine one. Indeed the resemblance in the 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 starts 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.1 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 post-natally 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 begins.
is first observed. But as Waterlow and Golden describe, it takes time to become stunted. The time is inversely proportional 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 postnatally 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. 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**

<table>
<thead>
<tr>
<th>Pre Natal Factors</th>
<th>Post Natal Factors</th>
</tr>
</thead>
<tbody>
<tr>
<td>Growth potential</td>
<td></td>
</tr>
<tr>
<td>Genetic inheritance</td>
<td></td>
</tr>
<tr>
<td>Maternal nutrition</td>
<td></td>
</tr>
<tr>
<td>Maternal environment</td>
<td></td>
</tr>
<tr>
<td>Maternal nutrition as a child</td>
<td></td>
</tr>
<tr>
<td>Maternal education</td>
<td></td>
</tr>
<tr>
<td>Maternal health</td>
<td></td>
</tr>
<tr>
<td>Maternal nutrition</td>
<td></td>
</tr>
<tr>
<td>Maternal education</td>
<td></td>
</tr>
<tr>
<td>Maternal health</td>
<td></td>
</tr>
<tr>
<td>Maternal nutrition</td>
<td></td>
</tr>
<tr>
<td>Maternal education</td>
<td></td>
</tr>
<tr>
<td>Maternal health</td>
<td></td>
</tr>
</tbody>
</table>

**Figure 2. Fetal nutrient availability**

<table>
<thead>
<tr>
<th>Fetal nutrient availability</th>
</tr>
</thead>
<tbody>
<tr>
<td>Fetal nutrient intake</td>
</tr>
<tr>
<td>Nutritional status</td>
</tr>
<tr>
<td>Maternal nutrition</td>
</tr>
<tr>
<td>Maternal environment</td>
</tr>
<tr>
<td>Maternal nutrition as a child</td>
</tr>
<tr>
<td>Maternal education</td>
</tr>
<tr>
<td>Maternal health</td>
</tr>
<tr>
<td>Maternal nutrition</td>
</tr>
<tr>
<td>Maternal education</td>
</tr>
<tr>
<td>Maternal health</td>
</tr>
</tbody>
</table>

**Figure 3. Postnatal factors**

<table>
<thead>
<tr>
<th>Postnatal Factors</th>
</tr>
</thead>
<tbody>
<tr>
<td>Infection</td>
</tr>
<tr>
<td>Psychosocial factors</td>
</tr>
<tr>
<td>Maternal nutrition</td>
</tr>
<tr>
<td>Social</td>
</tr>
<tr>
<td>Hormonal environment</td>
</tr>
<tr>
<td>Infant growth status</td>
</tr>
<tr>
<td>Childhood onset</td>
</tr>
</tbody>
</table>

**THE DETERMINANTS OF STUNTING**

<table>
<thead>
<tr>
<th>Factors</th>
</tr>
</thead>
<tbody>
<tr>
<td>Genetic inheritance</td>
</tr>
<tr>
<td>Maternal nutrition</td>
</tr>
<tr>
<td>Maternal education</td>
</tr>
<tr>
<td>Maternal health</td>
</tr>
<tr>
<td>Maternal nutrition</td>
</tr>
<tr>
<td>Maternal education</td>
</tr>
<tr>
<td>Maternal health</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Birth size</th>
</tr>
</thead>
</table>
| Birth size has been studied extensively as a determinant of further outcomes like morbidity, mortality and subsequent growth and development. 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 different but do not give conflicting results mainly because 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 often preferred; children are classified as stunted, wasted, normal, or stunted and wasted. Birth weight alone fails to diagnose intrauterine malnutrition. 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.

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. This would then cover the child's growth (disproportionate) and a group of children either stunted or wasted and (proportionate) growth retardation. This classification does not cover newborns who are stunted with a normal birth weight.

Miller and Hassenstein revisiting the diagnostic criteria for intrauterine 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 birth and low ponderal index (weight/birth) but relatively 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, i.e., a phase of cell replication, and another when predominantly becoming bigger and depositing fat, is towards the end of pregnancy. The first insult would predominantly affect linear growth, the second one predominantly the weight of the child. Hence the dichotomization 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.

The problem with most studies is that they start by dichotomizing the newborns first on a weight for age basis, to classify them as intrauterine growth retarded, and then for the growth retarded children as proportional and disproportional. 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 circumference. They catch up growth, both in length and in weight during the first three to six months. Their catch-up is, however, not complete with a deficit remaining at two years. Follow-up of the
In first observed. But as Waterlow and Golden describe, it takes time to become stunted. The time is inversely proportional 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 postnatally when the mothers were supplemented during pregnancy. Supplements given to pregnant women resulted in an improved growth performance of their offspring in the first 1-6 months of life for those children whose mothers received a high energy supplement as compared to those who received a low energy supplement. 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 social status in Karthen, where mothers with higher incomes and levels of education, tended to have longer children.

Based on this we have considered that early postnatal 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 dichotomization of postnatal versus prenatal 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. 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 is often preferred. Children are classified as stunted, wasted, normal, or stunted and wasted. Birth weight alone fails to diagnose intranatal malnutrition. Clinical diagnosis of malnourished infants at birth identify those children who later develop complications related to their malnutrition; 39% of malnourished newborns were diagnosed by using weight and an indicator alone.

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-gestation 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. Conversely, those proportionately growth-retarded infants who have symmetric growth reductions in weight, length, and head circumference. This would then cover the wasted children (disproportionate) and a group of children either stunted or wasted (proportionate growth retarded). This classification does not cover newborns who are stunted with a normal birth weight.

Miller and Hassan revisiting the diagnostic criteria for intrauterine 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 birth and low ponderal index (weight/birth) 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, i.e., a phase of cell replication, and another when predominantly becoming bigger and depositing fat, is towards the end of pregnancy. The first insult would predominantly affect linear growth, the second predominantly the weight of the child. Hence the dichotomization 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.

The problem with most studies is that they start by dichotomising using weight alone, and then for the growth retarded children as proportional and disproportional. They then split up, both in length and in weight during the first three to six months. 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. According to Falkner this is an oversimplification. Small for date infants, or small for gestational age neonates, are a heterogeneous group. Some children seem to catch up and others do not. Most of the asymptomatic 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 birth weight infants. The pattern in general 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 well nourished)

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 are smaller than correlations between weight and height which has been interpreted as a sign of independent growth. Birth weight has a better predictor for height and length than weight. The correlation between length at birth and height 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. Children born small for gestational age have a growth delay in the 2nd year of life. The deficit 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. Initially at the upper range of length follow their percentile for three months until they start to decelerate in growth.

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. Habiba concluded that genetic potential does influence the observed height differences in the attempts to define the best way to measure height and length at birth and to calculate the growth potential. By the time a child is one year old, a significant part of the genetic potential for height has been utilized. Studies of twins and first children are used as an adult size.

Genetic imprinting
Genetic imprinting is an epigenetic phenomenon, which switches genes off or on during the early stages of development. These switches can persist in childhood and adulthood. Golden notes that the expression of a monozygotic twin as an adult size 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 have zinc deficient offspring. The offspring of these immuno-defective mice are partially immuno-defective. It takes three generations to restore normality.

Variation in imprinting by specific epigenetic modification, and contributed by poor nutrition, provide an explanation for the above observations. Since oogenesis occurs in fetal life, the nutritional plane of the grandparent may influence the grandchild and be as important as the nutrition of the mother. If the mite and early in utero environment changes the pattern of epigenetic modification to alter the potential for future somatic development over several generations, it would provide an explanation for the close association between birth weight and height which in societies there were no racial differences in height. It also provides an explanation for the gradual secular trend in height which clearly transcribes 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 also was the second generation of offspring over exposed to famine, an effect was manifest in the offspring of women conceived during the famine. The timing of the intra uterine exposure to under nutrition appears in this study to be crucial.

Congenital and hereditary diseases
Short stature may typify congenital or hereditary disease. Although medically important and an indelible evidence of genetic involvement in stature, these diseases are less important for the study of stunting at a population level. Analysis and evaluation of growth patterns in the anatomy of stunting is not pursued further in this review.

Fetal nutrient availability
This determinate of stunting has been dichotomised as shown in Figure 2.

Food intake of the mother affects intrauterine development and growth, most factors of growth, energy and protein intake during pregnancy, weight gain during pregnancy, BMI pre-pregnancy and pre-pregnancy and socio-economic status.

Clinical supplementation studies in both developing countries and developed countries.

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 the period of famine weight decreased in maternal weight followed the decline in energy intake. Those, exposed in the third trimester suffered an average loss in postpartum weight of 5.1kg. Birth weight followed the same trend, the average birth weight of 3327g, in the cohort with the same third trimester exposure. In reverse, when normal rations were restored after liberalization, 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 decrease in maternal weight was less than 35% of pre pregnancy weight.

2) Epidemiological studies use mostly maternal weight gain, maternal body mass index (wht/ht), or postpartum maternal weight as indicators of maternal food intake during pregnancy. An inverse relation between maternal weight gain and birth weight also correlates with birth weight but its effect is in some studies accounted for by the concomitant increase in weight of the fetus.

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 supplementation enhanced fetal growth in mothers at nutritional risk, but failed to do so in the physically well nourished mothers.
   b) Gambian findings have similarities. Fetal growth was enhanced with historical controls women with normal intake and supplemented during the feeding season, when food was limited, and they had to work in the fields. However, when future mothers received a supplement during the dry season, the most 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 calorie supplement. In this particular group, body mass index of women in the community was marginally low, providing a background that weight of the mother was determined by her diet.
   d) In Chile, two groups of future mothers received supplementation during pregnancy. One was a milk powder supplement, and the other, a fortified milk-based supplement. This latter group had a higher intake of vitamins and mineral inakes 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 reached, but also
   i) studies describing similar increases in birth weight are those where mothers are nutritionally worse off. A period of very low food intake, 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 of young women at risk of delivering a small-for-dates baby who 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 of the infants in the zinc supplemented group was 3027g versus 2984g in the control group, 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 provoking evidence, but the group 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. Are the presently used indicators of birth weight, size and 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 how could determine length and subsequent growth.

These studies lead to the following conclusions: dietary restriction causes a decrease in birth weight whereas 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 Rona. The most brightly used indicator of birth weight is size, 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 how could determine length and subsequent growth.

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 underlying biological mechanisms. Sauer, analysing supplementation studies where pregnant women were given energy/protein, found conflict in putting cause or effect in length between energy intake, or mother’s birth weight and birth weight.

b) multiple regression analyses reveal a large proportion of the observed variance remains unexplained. In an observational study in Scortento, 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 Malawi showed 92% of the variance 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.

Microenvironments
The effects of minerals and vitamins on linear growth have mainly been studied in adults 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 micronutrients, 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 reviewed with
children in one study showed that, even at the age of 19, the deficit remained\textsuperscript{a}. According to Falkner this is an oversimplification\textsuperscript{a}. Small for date infants, or small for gestational age neonates, are a heterogeneous group. Some children seem to catch up and others do not. Most of the asymptomatic SGA infants show a postnatal catch-up and grow well. A small proportion exhibit some catch-up but, at best, 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 weight. However, weight velocity and length for length velocity are very heterogeneous 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 not wasted). In infants who are not growth retarded, i.e., children with a normal birth weight, further growth is not correlated with their birth weight. Correlations between birth size and subsequent growth in weight and weight velocity and length and for length velocity\textsuperscript{7} 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 of high weight mothers\textsuperscript{8}. One likely explanation is that the subsequent growth of the neonate reflects maternal body mass and the low weight infant bears the highest risk of being relatively short genetically programmed development course. This shifting of growth postnatally has also been proposed as an explanation for other adverse outcomes such as prematurity who are born to mothers with a low birth weight. The correlation between length at birth and length at one and two years was very poor; however, by age one the correlation to length at age two years is good for both girls and boys. This could be explained by a shift in the developmental trajectory. The shifting has two directions: upward and downward. Children born at the lower extremes start to cross growth percentiles lines early after birth and achieve a stable growth percentile at the age of one year. Indeed, at the upper range of length follow their percentile for three months until they start to decelerate in growth\textsuperscript{9}.

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\textsuperscript{a} concluded that genetic potential does influence the observed differences in the attainment of the mean. The accumulated deficit indicates that genetics play a lesser role than environment. This has been confirmed\textsuperscript{10,11}.

Rona\textsuperscript{12} analyzed studies of children's height, from a genetic viewpoint 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 over genetic factors.

Fetal nutrition availability

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

Food intake of the mother affects intrauterine development and growth, most often it is linked with growth in the first year of life. 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 famine 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\textsuperscript{8,9}.

3) Clinical supplementation studies in both developing countries and developed countries\textsuperscript{10,11,12}.

To take these in turn

1) During the Dutch winter-famine, 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 the reduction of the calorie intake to an average birth weight followed the decline in energy intake. Those exposed in the third trimester suffered an average loss in postpartum weight of 5.1kg. Birth weight followed the growth velocity of 230g 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, there was no rebound to the growth velocity of those born in the third trimester; recovery of 57g in postpartum maternal weight was followed in birth weight of 380g to a mean of 338g. Adverse effects on birth weight were not noted when the exposure to the famine occurred during the second trimester of pregnancy.

2) Epidemiological studies use mostly maternal weight gain, maternal body mass index (wht’r), or postpartum maternal weight as indicators of maternal food intake during pregnancy. Decreases in maternal weight gain during pregnancy also correlates with birth weight but its effect is in some studies accounted for by the concomitant increase in weight during pregnancy.

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 future work:

a) At Sorrento, Birmingham\textsuperscript{14}, supplementation enhanced fetal growth in mothers at nutritional risk, but did not change the possibility adverse effects, in the adequately nourished.

b) Gambian findings\textsuperscript{15} have similarities. Fetal growth was enhanced compared with historical controls when mothers received a supplement during the second trimester of pregnancy, when food was limited, and they had to work in the fields. However, when future mothers received a supplement during the third trimester, the more affluent season, growth was not enhanced. Indeed, it was even slightly below the controls.

c) In Indonesia\textsuperscript{16} an increase in birth weight was observed in the mothers who received a high rice supplement. In this particular group, body mass index of women in the community was marginally low, and it enhanced both weight and height. Improvement was noted that weight of the infant increased by 250g 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\textsuperscript{18}.

4) Minor supplementation studies in the same range of supplementation were, as expected, in the group of children who received iron and folic acid, and a small increase in birth weight, sex of the offspring, parity and skinfold thickness during pregnancy could only explain 30% of the variance in birth weight growth and weight birth and weight\textsuperscript{19}.

a) provide little information on cause or underlying mechanisms. Maternal birth, state of nutrition, age of the mother, parity are all found to be correlated with birth weight, but provide little or no information on the underlying mechanisms Sauer, analysing supplementation studies where pregnant women were given energy/protein, found conflict in putting cause and effect between energy intake, or mother's weight and birth weight, i.e., 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 by Rona\textsuperscript{12} noted that weight of the infant at birth had an effect on the growth of the infant 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 growth and weight birth and weight\textsuperscript{20}.

b) Minor supplementation studies in the same range of supplementation were, as expected, in the group of children who received iron and folic acid, and a small increase in birth weight, sex of the offspring, parity and skinfold thickness during pregnancy could only explain 30% of the variance in birth weight growth and weight birth and weight\textsuperscript{21}.

Micronutrients

The effects of minerals and vitamins on linear growth have mainly been studied in adults 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 micronutrients, 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 reversed with
Zn treatment. Zinc deficiency is associated with metabolic disturbances of a variety of enzymes, growth retardation, and infections. Children with severe, malnourished anemia and infections excreted lower levels of Haemoglobin (Hb), plasma fructose and vitamin A levels.

In Bangladesh, children with malnutrition and infections excreted lower levels of Haemoglobin (Hb), plasma fructose and vitamin A levels.

In contrast, zinc deficiency in anemic children of Bangladesh excreted lower levels of Haemoglobin (Hb), plasma fructose and vitamin A levels.

Zinc supplementation significantly increased the levels of Haemoglobin (Hb), plasma fructose and vitamin A levels.

Zinc supplementation increased the levels of Haemoglobin (Hb), plasma fructose and vitamin A levels.

Zinc supplementation significantly increased the levels of Haemoglobin (Hb), plasma fructose and vitamin A levels.

Zinc supplementation significantly increased the levels of Haemoglobin (Hb), plasma fructose and vitamin A levels.

Zinc supplementation significantly increased the levels of Haemoglobin (Hb), plasma fructose and vitamin A levels.

Zinc supplementation significantly increased the levels of Haemoglobin (Hb), plasma fructose and vitamin A levels.

Zinc supplementation significantly increased the levels of Haemoglobin (Hb), plasma fructose and vitamin A levels.

Zinc supplementation significantly increased the levels of Haemoglobin (Hb), plasma fructose and vitamin A levels.

Zinc supplementation significantly increased the levels of Haemoglobin (Hb), plasma fructose and vitamin A levels.

Zinc supplementation significantly increased the levels of Haemoglobin (Hb), plasma fructose and vitamin A levels.

Zinc supplementation significantly increased the levels of Haemoglobin (Hb), plasma fructose and vitamin A levels.

Zinc supplementation significantly increased the levels of Haemoglobin (Hb), plasma fructose and vitamin A levels.

Zinc supplementation significantly increased the levels of Haemoglobin (Hb), plasma fructose and vitamin A levels.

Zinc supplementation significantly increased the levels of Haemoglobin (Hb), plasma fructose and vitamin A levels.

Zinc supplementation significantly increased the levels of Haemoglobin (Hb), plasma fructose and vitamin A levels.

Zinc supplementation significantly increased the levels of Haemoglobin (Hb), plasma fructose and vitamin A levels.

Zinc supplementation significantly increased the levels of Haemoglobin (Hb), plasma fructose and vitamin A levels.

Zinc supplementation significantly increased the levels of Haemoglobin (Hb), plasma fructose and vitamin A levels.

Zinc supplementation significantly increased the levels of Haemoglobin (Hb), plasma fructose and vitamin A levels.

Zinc supplementation significantly increased the levels of Haemoglobin (Hb), plasma fructose and vitamin A levels.

Zinc supplementation significantly increased the levels of Haemoglobin (Hb), plasma fructose and vitamin A levels.

Zinc supplementation significantly increased the levels of Haemoglobin (Hb), plasma fructose and vitamin A levels.

Zinc supplementation significantly increased the levels of Haemoglobin (Hb), plasma fructose and vitamin A levels.

Zinc supplementation significantly increased the levels of Haemoglobin (Hb), plasma fructose and vitamin A levels.

Zinc supplementation significantly increased the levels of Haemoglobin (Hb), plasma fructose and vitamin A levels.

Zinc supplementation significantly increased the levels of Haemoglobin (Hb), plasma fructose and vitamin A levels.

Zinc supplementation significantly increased the levels of Haemoglobin (Hb), plasma fructose and vitamin A levels.

Zinc supplementation significantly increased the levels of Haemoglobin (Hb), plasma fructose and vitamin A levels.

Zinc supplementation significantly increased the levels of Haemoglobin (Hb), plasma fructose and vitamin A levels.

Zinc supplementation significantly increased the levels of Haemoglobin (Hb), plasma fructose and vitamin A levels.

Zinc supplementation significantly increased the levels of Haemoglobin (Hb), plasma fructose and vitamin A levels.

Zinc supplementation significantly increased the levels of Haemoglobin (Hb), plasma fructose and vitamin A levels.

Zinc supplementation significantly increased the levels of Haemoglobin (Hb), plasma fructose and vitamin A levels.

Zinc supplementation significantly increased the levels of Haemoglobin (Hb), plasma fructose and vitamin A levels.

Zinc supplementation significantly increased the levels of Haemoglobin (Hb), plasma fructose and vitamin A levels.

Zinc supplementation significantly increased the levels of Haemoglobin (Hb), plasma fructose and vitamin A levels.

Zinc supplementation significantly increased the levels of Haemoglobin (Hb), plasma fructose and vitamin A levels.

Zinc supplementation significantly increased the levels of Haemoglobin (Hb), plasma fructose and vitamin A levels.

Zinc supplementation significantly increased the levels of Haemoglobin (Hb), plasma fructose and vitamin A levels.

Zinc supplementation significantly increased the levels of Haemoglobin (Hb), plasma fructose and vitamin A levels.

Zinc supplementation significantly increased the levels of Haemoglobin (Hb), plasma fructose and vitamin A levels.

Zinc supplementation significantly increased the levels of Haemoglobin (Hb), plasma fructose and vitamin A levels.

Zinc supplementation significantly increased the levels of Haemoglobin (Hb), plasma fructose and vitamin A levels.

Zinc supplementation significantly increased the levels of Haemoglobin (Hb), plasma fructose and vitamin A levels.

Zinc supplementation significantly increased the levels of Haemoglobin (Hb), plasma fructose and vitamin A levels.

Zinc supplementation significantly increased the levels of Haemoglobin (Hb), plasma fructose and vitamin A levels.

Zinc supplementation significantly increased the levels of Haemoglobin (Hb), plasma fructose and vitamin A levels.

Zinc supplementation significantly increased the levels of Haemoglobin (Hb), plasma fructose and vitamin A levels.

Zinc supplementation significantly increased the levels of Haemoglobin (Hb), plasma fructose and vitamin A levels.

Zinc supplementation significantly increased the levels of Haemoglobin (Hb), plasma fructose and vitamin A levels.

Zinc supplementation significantly increased the levels of Haemoglobin (Hb), plasma fructose and vitamin A levels.

Zinc supplementation significantly increased the levels of Haemoglobin (Hb), plasma fructose and vitamin A levels.

Zinc supplementation significantly increased the levels of Haemoglobin (Hb), plasma fructose and vitamin A levels.

Zinc supplementation significantly increased the levels of Haemoglobin (Hb), plasma fructose and vitamin A levels.

Zinc supplementation significantly increased the levels of Haemoglobin (Hb), plasma fructose and vitamin A levels.

Zinc supplementation significantly increased the levels of Haemoglobin (Hb), plasma fructose and vitamin A levels.

Zinc supplementation significantly increased the levels of Haemoglobin (Hb), plasma fructose and vitamin A levels.

Zinc supplementation significantly increased the levels of Haemoglobin (Hb), plasma fructose and vitamin A levels.

Zinc supplementation significantly increased the levels of Haemoglobin (Hb), plasma fructose and vitamin A levels.

Zinc supplementation significantly increased the levels of Haemoglobin (Hb), plasma fructose and vitamin A levels.

Zinc supplementation significantly increased the levels of Haemoglobin (Hb), plasma fructose and vitamin A levels.

Zinc supplementation significantly increased the levels of Haemoglobin (Hb), plasma fructose and vitamin A levels.

Zinc supplementation significantly increased the levels of Haemoglobin (Hb), plasma fructose and vitamin A levels.

Zinc supplementation significantly increased the levels of Haemoglobin (Hb), plasma fructose and vitamin A levels.

Zinc supplementation significantly increased the levels of Haemoglobin (Hb), plasma fructose and vitamin A levels.

Zinc supplementation significantly increased the levels of Haemoglobin (Hb), plasma fructose and vitamin A levels.

Zinc supplementation significantly increased the levels of Haemoglobin (Hb), plasma fructose and vitamin A levels.

Zinc supplementation significantly increased the levels of Haemoglobin (Hb), plasma fructose and vitamin A levels.

Zinc supplementation significantly increased the levels of Haemoglobin (Hb), plasma fructose and vitamin A levels.

Zinc supplementation significantly increased the levels of Haemoglobin (Hb), plasma fructose and vitamin A levels.

Zinc supplementation significantly increased the levels of Haemoglobin (Hb), plasma fructose and vitamin A levels.

Zinc supplementation significantly increased the levels of Haemoglobin (Hb), plasma fructose and vitamin A levels.

Zinc supplementation significantly increased the levels of Haemoglobin (Hb), plasma fructose and vitamin A levels.

Zinc supplementation significantly increased the levels of Haemoglobin (Hb), plasma fructose and vitamin A levels.

Zinc supplementation significantly increased the levels of Haemoglobin (Hb), plasma fructose and vitamin A levels.

Zinc supplementation significantly increased the levels of Haemoglobin (Hb), plasma fructose and vitamin A levels.

Zinc supplementation significantly increased the levels of Haemoglobin (Hb), plasma fructose and vitamin A levels.

Zinc supplementation significantly increased the levels of Haemoglobin (Hb), plasma fructose and vitamin A levels.
Treated children showed significantly less morbidity episodes as measured by respiratory infections and diarrhoea. In Bangladesh, changes in pulmonary function indices showed lower levels of hemoglobin (Hb), serum copper and serum vitamin A levels. Children with preserved 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 and copper deficiency in children with mixed infections. Overall boys respond more or only to a zinc supplement. Comparison of the different studies is difficult due to the heterogeneity of subjects, duration and the doses of the supplements given. Despite this, the accumulating evidence suggests that zinc supplementation can increase the height and weight gain of certain groups, particularly infants and adolescent boys, in both developing and developed countries.

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. Marasmic children in Chile responded to zinc supplementation, given for 90 days, by increasing their weight-for-length but not their length-for-age. Schleisinger et al. observed that a zinc-fortified formula improved linear growth of Chilean children (average age 7 months) recovering from marasmus. They gained weight and length from the moment they recovered from marasmus. Only those children initiated with low zinc are caught up in the catch-up period after the zinc benefit. Energy intake was also higher after supplementation. Length increase was greater, but not significantly so, perhaps due to the relatively low weight gain associated with the small zinc. In Zaire, children who failed to respond to treatment for malnutrition where found to increase their weight and length after having received a copper supplement.

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. An explanation is not available for the observed relationship from human studies. Prolonged vitamin A deficiency in females negatively affects hair, with a gradual replacement of the base of body hair by fine and fat tissue. The iron absorption increases in vitamin A deficient animals and at the same time haemopoiesis of the spleen and the liver can be demonstrated. The phenomena reverse after vitamin A supplementation.

In the late 1970s, several workers tried to elucidate the relationship between iron and vitamin A. The idea of involving a vitamin A deficient group of otherwise healthy volunteers, an association between iron metabolism and hypervitaminosis A was established. The experimental group defined a linear, approximately linear relationship between iron loss to the vitamin A. In Central America vitamin A fortification of sugar was done without an increase in iron, on the other hand, a deficiency involving a vitamin A deficient group of otherwise healthy volunteers, an association between iron metabolism and hypervitaminosis A was established. The experimental group defined the association of iron to vitamin A as linear, approximately linear relationship between iron loss to the vitamin A. In Central America vitamin A fortification of sugar was done without an increase in iron, on the other hand, a deficiency involving a vitamin A deficient group of otherwise healthy volunteers, an association between iron metabolism and hypervitaminosis A was established. The experimental group defined the association of iron to vitamin A as linear, approximately linear relationship between iron loss to the vitamin A. In Central America vitamin A fortification of sugar was done without an increase in iron, on the other hand, a deficiency involving a vitamin A deficient group of otherwise healthy volunteers, an association between iron metabolism and hypervitaminosis A was established.
can be attributed to heredity. However this 38% is made up of only 16% from fetal growth factors other than sex, 2% from maternal nutrition, 5% from maternal heredity. The greater part of the variation, the remaining 62%, is 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 preceding living siblings of 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 unlike. The effect of consanguinity was negligible, indicating no detectable effect of recessive genes. The mothers phenotype seems to be a principal determinant of the size of the newborns.

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 prepuberal level of nearly 0.8 is reached.

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. After this, linear growth velocity decreases and continues to do so at a nearly constant rate. 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 or her nutritional status first? We have no indication that taller women have more space to accommodate a bigger uterus and so allow for taller children. Is that the mechanism by which maternal weight 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 thereafter?

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. Age of the mother may determine uterine size and fetal outcome.

Placental size

Falkner 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 indistinguishable, the birth weight in intrauterine growths 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 differences 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 somatotropin, b) thyroid hormone, c) cortisol and d) sex hormones during adolescence.

Has a more post natal growth. The fetus in contrast less depends 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 dependent 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-dependent 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 growth has been advanced by Karsh in 1970 who based his IGF model for growth on this concept. Growth hormone dependence becomes noticeable with the onset of the childhood component of growth in this model. Intrauterine homeostatic mechanisms are then thought to be able to compensate.

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

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 50% larger) at birth than controls, though most of the overgrowth is due to lipid deposition. Since the excessive growth becomes obvious only after the neonatal period has passed, the fetus is sensitive to glucose. It has been suggested that maternal hyperglycaemia is attended by fetal hyperglycaemia which, in turn, stimulates insulin secretion by the fetus. This results in macroglossia. In contrast, newborns with pancreatic agenesis have profound intrauterine growth retardation associated with deficient adipose tissue and a decrease in muscle mass Infants with transient neonatal diabetes also have a defect in insulin secretion which is associated with a low birth weight. These infants have reduced adipose tissue and reduced muscle mass which underlies development. For example, infants born with marked fetal hypoglycaemia 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.

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-1. IGF-2 is equivalent to somatomedin activity (MSA), discovered in the rat. The IGFs share a large structural homology with proinsulin.

IGFs do not cross the placenta and the IGF-1 and the IGF-2 found in fetal blood in various species have their own receptors. Although in postnatal life the liver is the main producer of IGF-1, during fetal life most tissues produce the same including kidney and skin. Long and de Jost have the highest concentration, liver the lowest. The concentrations in different 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 IGRs act as endocrine factors has been progressively abandoned in favor 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.

IGF-1 production is not controlled by GH. Fetal decapitation, hypothyreosis, or electrocution of the hypothalamus of the lamb or rat abolishes GH from the fetal circulation but has no effect on circulating somatomedins or IGF-1 levels. Moreover, GH fails to stimulate IGF secretion by the rat fetu, or by cultured rat fibroblasts. In addition, human amniotic fluids 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-1 tends to be decreased whereas IGF-2 remains normal. Conversely, in situations of hyperinsulinaemia, IGF-2 levels are increased. IGF-2 levels are high in plasma of normal children.

Human placental lactogen (HPL) is a peptide secreted by the placental trophoblast. HPL is secreted into the maternal and fetal circulations. HPL secreted in the maternal circulation stimulates the mobilization of metabolites and increases nutrient delivery to the fetus, by acting as an insulin antagonist. Indirect evidence suggests that it also stimulates maternal IGF-3 secretion. IGF-3 is found in the fetal circulation stimulating IGF-1 production. Based on the above findings, the following working hypothesis has been proposed. Fetal cellular growth is dependant on nutrient delivery (eg, glucose, amino acids, and fatty acids). The uptake of nutrients by the fetal cells is limited by insulin secretion. Intrauterine growth 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 inhibits the anabolic process by stimulating HPL secretion.

Conclusions

There is a very intricate relationship between mother and child which last beyond the birth of the child. The nutritional status of the mother and her energy and protein intake during pregnancy play an important role in the growth of both the child and the mother. The growth and development of the child is due to the fact that the timing of the insult is important and in most cases it is not taken into consideration because of the role microenvironmental factors are likely to play.

The role of micronutrients is difficult to interpret when interaction between different elements at the biochemical level is considered. For some minerals the link between endowment in birth and in these elements and the subsequent growth of the child are clear. The iron status and vitamin A status of the newborn are improved 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 failure 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 postnatal linear growth. So far research has concentrated predominantly on the relationship between macro-nutrients and the birth outcome, this mostly expressed as birth weight. But linear growth of children, particularly early after birth could also be the 28th week of gestation and a new 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? Kolsker, Patrick


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

這是一篇論文。作者特別強調出生後的早期成長和宮內發育的可能關係。試從一些亞洲人群的研究後，表達出關於線性成長的彈性得到證實。這種現象在出生後 6 個月內最為明顯。本來在以後的歲月內，難以生長是可能的，但由於環境不允許，因此在發展中國家的兒童、成年時往往較短。本文論述了概念模型的建立，並把分成兩部份：子宮內因素和胎兒後一階段。作者更估計胎兒和產後線性成長的共同因素，並考慮這些決定因素的重要性。

References


can be attributed to heredity. However this 38% is made up of only 16% from fetal hereditary factors other than sex, 2% from fetal sex, and 20% from maternal hereditary constitution. The greater part of the variation, 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- or-sterile 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 previous siblings of each pair of twins. At birth, like-sexed twins, with a high degree of common heredity were no more alike than full siblings or even half siblings from the same mother. By contrast, the half-siblings with the same father were notably unlike. 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.

Similar studies have been done by Tanner, who found that the correlation between length at birth and adult height is very, 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.

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, but the gestational age at which this occurs is still somewhat uncertain with estimates for 16 weeks of gestation. After this, linear growth velocity decreases and becomes a non-linear period depending on 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 the primary focus and have any indication that taller women have more space to accommodate a bigger uterus and so allow for taller children. Is that the mechanism by which maternal weight effects it influence?

We reflect on a similarities at 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 thereafter?

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. Age of the mother may determine uterine size and fetal outcome.

Placental size

Falkner quotes the Louisville Longitudinal Study of Twins which provides evidence of a strong correlation between placental weight and birth weight. In monzygotic twins, who are phenotypically the same, birth weight and intrapair 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

Postnatal growth depends on four main hormonal regulating mechanisms: a) Growth hormone via somatotropin, b) thyroid hormone, c) cortisol and d) sex hormones during adolescence. Insulin has a major role in postnatal growth. The fetus in contrast less depend 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 dependent on its own hormone homeostasis to survive.

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 while growth hormone is lacking or is markedly reduced. GH-dependent growth is not observed until well after birth; in humans at six months. The hypothesis that growth hormone is not an important determinant of neonatal growth has been advanced by Karlsberg who based his IGF 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 is to go beyond beyond intratrophic life.

Thyroid hormones are also transferred from the mother to the fetus and is dependent on its own thyroid gland for thyroid hormone production. Human newborns suffering from congenital hypothyroidism, or radiothyrodeiodenectomised in utero by radioactive iodine given inadvisably to the mother, have a normal size and weight at birth. Thus thyroid hormones appear to have little effect on fetal growth in most species, but they are essential for normal neural and osseous maturation.

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 are more likely to survive. Fetal growth is less than control infants, though most of the overweight is due to lipid deposition. Since the excessive growth becomes obvious only after birth, where the fatty tissues become more sensitive to glucose, it has been suggested that maternal hyperglycaemia is attended by fetal hyperglycaemia which, in turn, may stimulate the fetal secretion of peptide hormones such as somatomammotrophic hormone. In contrast, newborns with pancreatic agenesis have profound intratrophic growth retardation associated with deficient adipose tissue and a decrease in muscle mass. Infants with transient neonatal diabetes also have a deficit in insulin secretion which is associated with a low birth weight. These infants have reduced adipose tissue and reduced muscle mass which undergoes hypoplasia. Insulin is essential for placental function. Insulin is essential for placental function. The evidence suggests that insulin not only has a permissive role but also a regulatory role in fetal growth.

The insulin like growth factors.

The term somatomedins (SM) and insulin-like growth factors(IGF) are synonymous. Somatomedin A and C are analogous to IGF-1, IGF-II is equivalent to the mitogenic stimulating activity (MSA), discovered in the rat. The IGFs share a large structural homology with proinsulin.

IGFs do not cross the placenta and the IGFs and the IGF-II found in fetal blood are present in various species and even in tissues. Although in placental life the liver is the main producer of IGF-I, during fetal life most tissues produce the same including liver, kidneys and skin. 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 IGF-II act as endocrine factors has been progressively abandoned in favor 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 postnatal life in the relative role of growth hormone, which becomes apparent about 6 months postnatally with a more autocrine and paracrine character of regulation.

IGF-I production is not controlled by GH. Fetal decapitation, hypophysectomy, or ectopic hypophysis of the lamb or rat abolishes GH from the fetal circulation but has no effect on circulating somatomedins 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 trophotroph. HPL is secreted into the maternal and the fetal circulations. HPL secreted in the maternal circulation stimulates the mobilization 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. Fetal cellular growth is dependant on nutrient delivery (i.e. glucose, amino acids, and fatty acids). The uptake of nutrients by the fetal cells by insulin secretion is stimulated by amino acids up to 28 weeks of gestation and by amino acids and glucose thereafter. Cellular anabolic progress 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 in the development of the birth 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 in birth in these elements and the subsequent growth of the child are clear. The iron status and vitamin A status of the newborn are not determined by gestational age and the reserves the mother had. Food diversity is particularly a determinant of the infant micronutrients. This could then perhaps explain why growth faltering is first seen at earlier 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.

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

Kolsteren, Patrick


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？

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？

這是一篇評論文章。作者特別強調出生後的早期成長和宮內發育的可能關係。此論著從一些亞洲人群在出生後不久線性成長就開始緩慢得到證實。這種現象在出生後6個月內最為顯著。本文報告在以後的歲月內，赶上成長是可能的，但由於環境不允許，因此在發展中國家的兒童，成年時往往較低。本文論述了概念模型的建立，並把它分成兩部份：宮內因素和產後因素。作者分別分析了胎兒和產後線性成長之間的關係，並考慮這些決定因素的重要性。

References


