Undernutrition and Growth Restriction in Pregnancy

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Abstract
Newborn size is the result of intrauterine growth. Premature, low birthweight of <2,500 g, small for gestational age (SGA, <10th percentile), or intrauterine growth-restricted (IUGR) newborns may have similar weights. Serial fetal biometry (ultrasound), required for the diagnosis, timing and severity of intrauterine growth restriction in the individual infant, is still not common in epidemiological studies. SGA newborns have less lean body mass, but they particularly lack fat mass. The most important etiological determinants of intrauterine growth restriction in developed countries is cigarette smoking, while in developing countries it is usually longstanding food deprivation. Follow-up studies of SGA newborns consistently showed a positive association between birthweight and later lean body mass, whereas associations with adiposity were more variable. Most SGA infants had catch-up in length/height. Signs of the metabolic syndrome accompanied the catch-up in bodyweight and central adiposity. So far, no overarching model is available to explain how the epigenetic and hormonal tunings, which accompany intrauterine malnutrition from preconception through pregnancy, can program the regulatory systems of fundamental life processes. The theoretical concepts of a thrifty phenotype (Hales and Barker) and of a predictive adaptive response (Gluckman and Hanson) offer a comprehensive approach to understanding the empirical and experimental findings.

We owe it to Professor David Barker and his colleagues in Southampton for having called attention to the association between low birthweight and coronary death [1]. His pioneering ecological study in England und Wales showed a geographical relation for ischemic heart disease in 1968–1978 and infant mortality rates in 1921–1925. A follow-up study of men and women in Hertfordshire showed that those who had low birthweights had relatively high death rates from coronary heart disease in adult life [2, 3]. Another of
their studies pointed out that persons who were small at birth as a result of growth retardation rather than those born prematurely were at increased risk of coronary disease [4]. Similar trends were observed for cardiovascular disease risk factors [5]. Associations between birthweight and adult blood pressure were found in each social group and were independent of smoking, alcohol intake and obesity in adult life [3, 5]. To complete the signs of the metabolic syndrome, the prevalence of an impaired glucose tolerance and type 2 diabetes were inversely related to birthweight in a dose-response manner [6, 7]. These studies triggered an avalanche of publications worldwide, challenging and proving the Barker hypothesis of the ‘fetal origins of adult disease’.

Malnutrition in Utero – Intrauterine Growth Restriction, Definition and Diagnosis

A high proportion of premature infants do not grow properly in utero, particularly those delivered for medically indicated reasons [8]. Where gestational age is not known, as is common in developing countries, a low birthweight of <2,500 g has been used as an indicator for impaired fetal growth [9]. But even considering gestational age, newborns below the 10th percentile value of the corresponding population are defined as small for gestational age (SGA). Newborn size is only the result of intrauterine growth. Unless this is known, SGA according to a fixed (or ideal) growth standard is used as a proxy for intrauterine growth restriction (IUGR). But even these SGA newborns may be normally grown, and not pathologically small, and vice versa, a birthweight above this cutoff value may still be the result of IUGR. Customized antenatal growth charts take ‘physiological’ variables into account, such as fetal sex, height, parity, ethnic group, and pre-pregnancy weight of the mother [10]. Although we can argue over the sense of ‘normalizing’ the smallness of a newborn of an undernourished or smoking mother, customized, population-based birthweight standards improved the prediction of adverse perinatal outcomes better than non-adjusted standards [11–14]. But until now, customized birthweight standards have not been used to predict the long-term outcome of growth-retarded infants.

For over 20 years in utero analysis of fetal growth patterns has been possible by sonographic weight standards [15]. Even customized fetal weight percentiles are available, although they are less accurate than calculated intrauterine growth velocities [16]. A combination of serial fetal biometry and other biophysical measurements is used to determine the optimal time point for premature delivery of a growth-restricted fetus. Quantitative estimates of fetal body composition can currently be achieved using ultrasound tools [17]. Future studies will show if these methods are useful in predicting the long-term outcome.
SGA and IUGR, Prevalence Rates and Determinants

In the last 20–30 years an increase in the prevalence of premature births has been observed in wealthy countries [18–20]. A major part of this increase is associated with the birth of multiples after the use of assisted reproduction [18, 19, 21]. But around 25% of all preterm births in the USA were delivered for medical reasons, e.g. severe fetal growth restriction and fetal distress, the rest is spontaneous [20].

Low birthweight and IUGR are significant problems in developing countries. It was estimated that at least 13.7 million infants are born every year at term with a birthweight below 2,500 g, representing 11% of all newborns in developing countries, a rate that is 6 times higher than in developed countries [21, 22]. Of all newborns, not only of those born at term, 20.5 million were low birthweight. According to the 10th percentile of a sex-specific single-twin growth chart for Californian newborns, about 24% were IUGR, or approximately 30 million newborns per year. Nearly 75% were born in Asia, a smaller part in Africa and Latin America (table 1) [21]. The most important etiological determinants for IUGR in developing countries and the population-attributable risks in developed countries were calculated by Kramer et al. [23–25], and are listed in table 2. The major determinant in developed countries is cigarette smoking during pregnancy, but the main determinant in developing countries is a low energy intake (low pregnancy weight gain as a proxy) and

<table>
<thead>
<tr>
<th>Country</th>
<th>LBW (&lt;2,500 g), %</th>
<th>IUGR (&lt;10th percentile), %</th>
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</thead>
<tbody>
<tr>
<td>Argentina</td>
<td>6.3</td>
<td>9.7</td>
</tr>
<tr>
<td>China</td>
<td>4.2</td>
<td>9.4</td>
</tr>
<tr>
<td>Colombia</td>
<td>16.1</td>
<td>17.8</td>
</tr>
<tr>
<td>Cuba</td>
<td>8.1</td>
<td>14.7</td>
</tr>
<tr>
<td>Gambia</td>
<td>12.1</td>
<td>13.5</td>
</tr>
<tr>
<td>Guatemala</td>
<td>12.5</td>
<td>25.3</td>
</tr>
<tr>
<td>India (Pune)</td>
<td>28.2</td>
<td>54.2</td>
</tr>
<tr>
<td>Indonesia</td>
<td>10.5</td>
<td>19.8</td>
</tr>
<tr>
<td>Lesotho</td>
<td>10.3</td>
<td>13.0</td>
</tr>
<tr>
<td>Malati</td>
<td>11.6</td>
<td>26.1</td>
</tr>
<tr>
<td>Myanmar</td>
<td>17.8</td>
<td>30.4</td>
</tr>
<tr>
<td>Nigeria</td>
<td>12.4</td>
<td>22.2</td>
</tr>
<tr>
<td>Nepal, rural</td>
<td>14.3</td>
<td>36.3</td>
</tr>
<tr>
<td>Sri Lanka</td>
<td>18.4</td>
<td>34.0</td>
</tr>
<tr>
<td>Thailand</td>
<td>9.6</td>
<td>17.0</td>
</tr>
<tr>
<td>Vietnam</td>
<td>5.2</td>
<td>18.2</td>
</tr>
</tbody>
</table>
the poor nutritional status of the mother (low pre-pregnancy body mass index, BMI, and short stature as proxies). Usually, weight changes during the second and third trimester of pregnancy were considered the most important determinants of the birthweight of the newborn. But by using accurate measurements of pre-pregnancy weights rather than relying on reported weights, it could be shown that the weight change in first trimester of pregnancy more strongly influenced newborn size than the changes in the second and third trimester [26].

In order to identify the determinants of a birthweight below the 10th percentile (according to our own fixed growth standard), we analyzed the Berlin perinatal data of the years 1993–1999 (n = 169,000), independent of whether they occurred often or not (table 3). The most prominent determinant is a multiplet pregnancy, followed by hypertension. Although we have significant underreporting, cigarette smoking during pregnancy is an important determinant of IUGR and is closely related to a low social status. Other proxies for a low social status may be low gestational weight gain, short stature, binge drinking, and strenuous physical work, but also high weight gain and high pre-pregnancy BMI [22–24]. Being unmarried and having a short maternal educational period somewhat increased the risk for mild IUGR in Canadian newborns [25]. SGA clusters in families; the association is stronger for female than for male relatives, which can be attributed to environmental conditions, e.g. intrauterine ‘maternal constraint’ [27, 28]. But paternal as well as maternal height have been correlated with birth length, and to a lesser degree with birthweight, e.g. in Indian infants, which points to an involvement of fetal genes in the regulation of fetal growth, partly explaining ethnic differences [29, 30].

### Table 2. Determinants of intrauterine growth-restricted newborns (IUGR) in developing and developed countries, listed in decreasing order of importance

<table>
<thead>
<tr>
<th>Developed country</th>
<th>Developing country</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cigarette smoking</td>
<td>Low energy intake, low gestational</td>
</tr>
<tr>
<td>Low energy intake, low gestational weight gain</td>
<td>weight gain</td>
</tr>
<tr>
<td>Low pre-pregnancy BMI</td>
<td>Low pre-pregnancy BMI</td>
</tr>
<tr>
<td>Primiparity</td>
<td>Short stature</td>
</tr>
<tr>
<td>Low stature</td>
<td>Malaria</td>
</tr>
<tr>
<td>Pregnancy induced hypertension</td>
<td>Cigarette smoking</td>
</tr>
<tr>
<td>Nonwhite</td>
<td>Primiparity</td>
</tr>
<tr>
<td>Congenital anomalies</td>
<td>Pregnancy-induced hypertension</td>
</tr>
<tr>
<td>Other genetic factors</td>
<td>Congenital anomalies</td>
</tr>
<tr>
<td>Alcohol, drugs</td>
<td>Other genetic factors</td>
</tr>
</tbody>
</table>

Adapted from Kramer et al. [22, 23].
Prevention of IUGR by Reducing the Risk

Although fetal nutrition is not directly dependent on maternal nutrition – the maternal metabolic and endocrine status, uterine blood flow, placental transport and metabolism, and the metabolic and endocrine status of the fetus are translating and modulating the dietary effect – mean birth weights were higher by about 20–30 g, if mothers received calorie or balanced protein/calorie supplements [31, 32]. There is a tradeoff in nutrient partitioning between the mother and the fetus, evidently with the goal of sustaining maternal fertility: Malnourished women in Guatemala taking a nutritional supplement gained weight from one delivery to the next consecutive delivery (reproductive cycle), but their second (study) infant tended to weigh less than their previously born infant [33]. In contrast, just marginally nourished women lost weight during their reproductive cycle, and their second infant tended to weigh more at birth than the first born. In rural Gambia, a high energy supplement, consumed by chronically undernourished women from mid-pregnancy (in the presence of birth attendants), reduced the risk for low birthweight babies, and increased the mean birthweight significantly by an average of 201 g

### Table 3. Risk factors for a birthweight <10th percentile (according to a local growth for gestational age fixed standard) in Berlin newborns, utilizing perinatal data of 1993–1999 (n = 169,000)

<table>
<thead>
<tr>
<th>Risk factor</th>
<th>OR</th>
<th>95% CI</th>
</tr>
</thead>
<tbody>
<tr>
<td>Multiplet delivery</td>
<td>6.67</td>
<td>6.27–7.11</td>
</tr>
<tr>
<td>Hypertension in pregnancy (chronic or acute)</td>
<td>2.90</td>
<td>2.64–3.18</td>
</tr>
<tr>
<td>Smoking in pregnancy</td>
<td>2.31</td>
<td>2.22–2.39</td>
</tr>
<tr>
<td>Mother's height ≤ 160 cm</td>
<td>1.86</td>
<td>1.79–1.93</td>
</tr>
<tr>
<td>Firstborn infant</td>
<td>1.83</td>
<td>1.76–1.89</td>
</tr>
<tr>
<td>Pregnancy weight gain</td>
<td></td>
<td></td>
</tr>
<tr>
<td>&lt;250 g/week</td>
<td>1.71</td>
<td>1.64–1.77</td>
</tr>
<tr>
<td>≥400 g/week</td>
<td>0.61</td>
<td>0.59–0.64</td>
</tr>
<tr>
<td>Female infant</td>
<td>1.70</td>
<td>1.65–1.76</td>
</tr>
<tr>
<td>Pre-pregnancy BMI</td>
<td></td>
<td></td>
</tr>
<tr>
<td>&lt;20</td>
<td>1.67</td>
<td>1.65–1.78</td>
</tr>
<tr>
<td>&gt;30</td>
<td>0.51</td>
<td>0.47–0.55</td>
</tr>
<tr>
<td>Malformation</td>
<td>1.60</td>
<td>1.44–1.78</td>
</tr>
<tr>
<td>Mother's age</td>
<td></td>
<td></td>
</tr>
<tr>
<td>&lt;20 years</td>
<td>0.95</td>
<td>0.89–1.03</td>
</tr>
<tr>
<td>&gt;30 years</td>
<td>1.10</td>
<td>1.07–1.14</td>
</tr>
<tr>
<td>German</td>
<td>1.04</td>
<td>1.00–1.08</td>
</tr>
<tr>
<td>Diabetes in pregnancy</td>
<td>0.64</td>
<td>0.56–0.73</td>
</tr>
<tr>
<td>Constant</td>
<td>0.03</td>
<td></td>
</tr>
</tbody>
</table>

Logistic regression, adjusting for all other variables.
in the hungry season, and by 136 g in the harvest season [34]. But high protein supplements may increase the risk of IUGR [32]. In stunted populations with a long history of scarce food resources nutrient supplementation of the pregnant mother has to be carefully balanced. A more prudent approach is to improve the growth and nutrition of females as early as possible.

In most studies micronutrient supplements to combat deficiencies (‘hidden hunger’) in pregnant women have not shown striking effects on the prevalence of IUGR. But maternal iodine supplements in deficient areas significantly increased the mean birthweight by 157 g [35]. Multiple micronutrient supplementation beginning in mid-pregnancy in Nepal, compared to routine iron and folic acid supplements, resulted in a significant increase in birthweights by 77 g, and a fall in the proportion of low birthweights by 25% [36]. Multi-nutrient supplementation of anemic women in Guinea-Bissau increased birthweights by 218 g and decreased the risk of low birthweight [37]. Birthweights in women who gave up smoking in pregnancy were significantly higher by 292 g compared to continuing smokers [38].

**Body Composition of Small and Growth-Restricted Infants, Tracking**

In the human fetus lipid is deposited quite rapidly during the last trimester of pregnancy [39]. Premature infants therefore especially lack adipose tissue. The body composition of SGA newborns is different from appropriately grown (AGA) and from large for gestational age (LGA) newborns of similar gestational age, as could be shown recently by dual-energy X-ray absorptiometry (DXA) measurements (table 4) [40]. While lean body mass (LBM) is lower by 22% in SGA, and 20% higher in LGA compared to AGA newborns, there is 51% less fat mass in SGA, and 128% more fat mass in LGA newborns. In the malnourished fetus preferential blood flow to the brain and heart may deprive other organs from oxygen and nutrients. In growth restricted newborns the volumes of liver and kidney are more decreased than the body as a whole [41]. Maternal smoking in pregnancy selectively reduces LBM but not fat mass [42]. Although being born 800 g lighter at birth, Indian newborns have similar sub-scapular skinfold thicknesses as British newborns, but for each ponderal index unit the skinfold value is higher, a phenomenon described as the thin-fat Indian baby [43].

European children born short (rather than light) for gestational age had a 6- to 7-fold increased risk of adult short stature; about 10–14% remained short [44, 45]. When adjusted to mid-parental height (target height) small for gestational length children remained 4–5 cm shorter [45]. But former premature AGA children in the Netherlands attained normal height at 10 years of age [46]. The strongest predictor of stunting in malnourished African infants was small birth size [47].
Those of the European SGA children who as adults remained short had a slightly increased risk of being overweight [48, 49]. Former SGA infants of the cross-sectional survey NHANES III in the USA continued to remain lighter and LGA infants heavier through early childhood, but the discrepancies in weight up to 4 years were primarily attributable to differences in muscularity (LBM) and only to a limited extend to fatness [50]. In a sample of British 7-year-old children and adolescents LBM but not fat mass was associated with the birthweight z score [51]. Older Englishmen (in a small study) who had a birthweight below the 25 percentile compared to those above the 75 percentile had significantly less LBM [52]. They were not different in fat mass (assessed by DXA) but differed slightly in favor of a more central fat distribution. The birthweights of 9- to 10-year-old children of the large ALSPAC study in Bristol were positively associated with both LBM, but also with fat mass (DXA determination) [53]. In these children, weight and length at birth did not predict central adiposity. A similar, but smaller study in Spanish adolescents found an association between birthweight and LBM (as well as bone mass), but not with fat mass, and only a marginal (not significant) association with truncal adiposity [54]. These follow-up studies have consistently shown a positive association between birthweight and LBM, whereas associations with adiposity were more variable.

**Catch-Up Growth in Length/Height and Weight**

Catch-up growth in length/height was observed in European SGA infants, most of it occurring in the first 12 months of life, birth length and mid-parental height being significantly related to its magnitude [55–57]. Consequent to

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**Table 4.** Body composition of small for gestational age (SGA), appropriate for gestational age (AGA), and large for gestational age (LGA) German and Swiss newborns, measured by dual-energy X-ray absorptiometry [40]

<table>
<thead>
<tr>
<th></th>
<th>SGA (n = 26)</th>
<th>AGA (n = 118)</th>
<th>LGA (n = 15)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Gestational age, weeks</td>
<td>38.2 ± 2.7</td>
<td>38.3 ± 3.0</td>
<td>39.1 ± 1.8</td>
</tr>
<tr>
<td>Age at study, days</td>
<td>5.0 ± 2.4</td>
<td>4 ± 2.2</td>
<td>4.7 ± 2.1</td>
</tr>
<tr>
<td>Birthweight (BW), g</td>
<td>2,320 ± 660</td>
<td>3,150 ± 680</td>
<td>4,430 ± 630</td>
</tr>
<tr>
<td>Birth length, cm</td>
<td>46.1 ± 4.8</td>
<td>49.7 ± 3.5</td>
<td>52.3 ± 2.5</td>
</tr>
<tr>
<td>BMI</td>
<td>10.4 ± 1.4</td>
<td>12.2 ± 1.5</td>
<td>15.0 ± 1.7</td>
</tr>
<tr>
<td>Fat mass, g</td>
<td>210 ± 100</td>
<td>430 ± 190</td>
<td>980 ± 510</td>
</tr>
<tr>
<td>(% of BW)</td>
<td>(8.6 ± 3.1)</td>
<td>(13.1 ± 4.3)</td>
<td>(22.2 ± 8.2)</td>
</tr>
<tr>
<td>Lean body mass, g</td>
<td>2,080 ± 520</td>
<td>2,650 ± 520</td>
<td>3,170 ± 360</td>
</tr>
<tr>
<td>Bone mineral content, g</td>
<td>39.2 ± 16.0</td>
<td>54.5 ± 15.8</td>
<td>81.1 ± 16.7</td>
</tr>
</tbody>
</table>
catch-up weight gain in the first two years, SGA infants in a recent study in Barcelona showed a dramatic transition towards central adiposity [58]. Infants of maternal smokers, who were small at birth, showed complete catch-up growth during the first 12 months; likewise the infants of primiparous women, who overshoot other infants and were significantly heavier and longer at one year [59]. Maternal smoking was a significant risk factor for overweight and obesity in 3- to 7-year-old children (BMI and skinfold thickness), especially when mothers smoked in early pregnancy, when they had a higher catch-up gain in the first year, and when being bottle-fed [60–63]. Interestingly, in the Dutch famine study, obesity in women was more prevalent if their mothers had suffered from famine in early gestation [64]. Weight in former extremely low birthweight infants (25% SGA) declined up to three years, only thereafter they started to catch-up [65]. In the small Indian children, greater weight gains in late infancy and adolescence were associated with increased adult, especially central adiposity [66].

**Catch-Up Growth and the Metabolic Syndrome**

A follow-up study of Chilean SGA and AGA infants from 48 h of life to 3 years showed that, according to the catch-up in weight and BMI, a marked transition occurred from lower pre-feed insulin and increased insulin sensitivity at birth to insulin resistance at 3 years [67]. In the thin-fat Indian newborns already at birth glucose and insulin concentrations were higher [68].

Concomitant with their catch-up growth and the transition towards central adiposity, the SGA infants of a study in Barcelona developed increasing insulin resistance between 2 and 4 years of age [58]. A large follow-up study of young adults in France who had been SGA and AGA newborns of 32–42 gestational weeks showed that the mean waist to hip ratio was significantly higher in the SGA group [69]. The SGA group had significantly increased triglyceride, lower HDL-cholesterol, increased plasma fasting and 120min after-load glucose concentrations, and an increased insulin resistance index. While catch-up in height was not significantly related to any of the parameters of the metabolic syndrome, catch-up in BMI was inversely related to BMI at birth, i.e. thinness at birth.

In a systematic review of 80 studies, blood pressure was shown to increase with decreasing size and head circumference at birth, while accelerated postnatal catch-up growth increased blood pressure [70]. An early alteration in the hypothalamic-pituitary-adrenal axis as a mediator of elevated blood pressure has repeatedly been studied in many settings. In children urinary glucocorticoid metabolite excretion was higher in those who had been light or heavy at birth [71]. This U-shaped relation persisted after adjustment for sex and current weight. In 20-year-old South Africans plasma cortisol levels in the morning and after low dose ACTH stimulation were higher in former SGA
newborns [72]. In adults from three populations the cortisol concentration fell with increasing birthweight [73].

A meta-analysis of 14 studies involving 132,180 persons found a U-shaped relation between birthweight and later risk of type 2 diabetes [74]. The risk of small newborns (<2,500 g) compared to newborns of normal weight (2,500–4,000 g) was increased by OR = 1.47 (95% CI 1.26–1.72), a value slightly higher than that for a birthweight over 4,000 g.

The Thrifty Phenotype

In 1962 the geneticist Neel [75] invented the concept of the thrifty genotype to characterize the inherited ability of subjects to store energy in times of food surplus in order to survive in times of shortage. The term thrifty phenotype was proposed by Hales and Barker [76] to describe the metabolic adaptation of a malnourished fetus that allows him to survive in a deprived environment. Gluckman and Hanson [77] elaborated the concept of the predictive adaptive response, a metabolic tradeoff to permit immediate survival even facing long-term costs. They reflected ‘that the risk of disease is increased when the actual postnatal environment does not match that predicted prenatally’ [78]. Prentice [79] regrets that we still do not have a definite plausible overarching biological mechanism through which empirical findings and these hypothetical models can be explained. But a wealth of empirical data, and an exponentially growing number of experimental studies, are filling the hypothetical framework.

Potential Mechanisms

The factors governing placental development have a major impact on the etiology of IUGR and later outcome [80, 81]. An epigenetic modification of the allele of a gene, i.e. ‘genomic imprinting’, plays a central role in the control of the fetal demand and the placental supply of nutrients to the fetus from the peri-conceptional period and the earliest stage of the fetoplacental development [82, 83]. Generally, paternally derived imprinted genes enhance placental and fetal growth, while maternal imprinted genes suppress growth [83]. For example, glucose transporters can be upregulated (programmed) by hyperglycemia in the first trimester leading to accelerated fetal growth in late gestation [84]. Hypoxia can decrease expression of system A in the trophoblast, a transporter of neutral amino acids [85].

Hormones, such as insulin, insulin-like growth factors (IGFs), thyroxine and the glucocorticoids, play a central role in regulating fetal growth and development [86]. The glucocorticoids are key regulators of organ development and maturation [81]. They act directly on genes and indirectly through changes in the bioavailability of hormones [85]. Some of the endocrine
changes induced by glucocorticoids in utero are transient while others persist after glucocorticoid levels have returned to normal values [85]. In the long-term they can permanently reset endocrine systems, such as the somatotropic and hypothalamic-pituitary-adrenal axis.

The IGFs-1 and 2 are expressed in fetal tissues from the earliest stage of pre-implantation to the phase before birth [86]. IGF-2 supports embryonic growth and IGF-1 is important in later gestation. Peri-conceptional nutrient restriction decreases IGF levels in mid-gestation, probably by an epigenetic mechanism [87]. Glucocorticoids affect the expression of both IGF genes [85]. Growth hormone has relatively little effect on the fetal IGF axis [86]. At birth a shift from IGF-2 to IGF-1 predominance occurs, and IGF-1 production becomes growth hormone-dependent to induce postnatal growth.

The hypothalamic neuropeptides that regulate energy intake and expenditure in adult life are already present in the fetal brain, e.g. neuropeptide Y has been found to be present from 21 weeks of gestation in the human hypothalamus, and at this stage there are already projections between the nucleus arcuatus and the paraventricular nuclei [88]. Nutritional or hormonal exposures during fetal or early neonatal life may be important in the subsequent development of the appetite-regulatory system, e.g. by prenatal nutritional deficiency and postnatal abundance [89]. The development of appetite control in a growth-retarded infant is supported by breastfeeding, which helps to establish the regulation of food intake in a critical period. Feeding regimens in premature infants have to balance the requirements for catch-up growth and normal development, while avoiding the hazards of overfeeding [90, 91]. The most promising approach in the prevention of adult diseases induced by disadvantageous environments in fetal and early life is to increase the personal and social resources, especially of females, including optimal nutrition, physical activity, no tobacco, no alcohol, no drugs as the basis for a bright future.

References


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Discussion

Dr. Ogra: Thank you Dr. Bergmann for a very elegant presentation. What is the definition of a small for gestational age or low birthweight infant in the developing and the developed world? Is it based on the total cellular mass, the DNA content in the first trimester, or does it relate to total bodyweight as a function of body fat?

Dr. R. Bergmann: What I understood from the data of Yajnik et al. [1] is that the body composition of Indian newborns was different from that of European newborns. Although they had a lower birthweight, the percentage of fat mass was higher and muscle mass lower. Even at birth they already had insulin resistance while, according to the European data, this seems to develop over the first year [2]. In the Dutch famine study, the offspring of mothers who experienced starvation during the first part of pregnancy had a higher prevalence of obesity [3]. My hypothesis is that they were programmed for small size in the first part, and had catch-up growth during the second part of pregnancy. Dr. Barker may have another explanation.

Dr. Ogra: How relevant is it to the eventual normal functioning of the human host? If the infants start with very low birthweight and continue to have a lower birthweight in Brunei as compared to English children, for example, they will remain smaller than the British children. Yet these are probably normal children. Are there any data to suggest otherwise?

Dr. R. Bergmann: You might be right. This opinion is supported by the observation that long resident high altitude populations exhibit less altitude-associated IUGR and pre- and postnatal mortality than people who have lived there for shorter periods, e.g. as in a study in Tibet [4]. When people are turning into a modern society, challenges occur that they are not designed for. So they must be careful while establishing this new way of life.

Dr. Ogra: Because malaria is very ubiquitous in many of these countries, how extensively have the low birthweight babies been screened in the first trimester for congenital infections other than malaria? Congenital infections such as cytomegalovirus or herpes simplex or some perinatal bacterial infections may also affect growth.

Dr. R. Bergmann: The main risk factors for permanent stunting are malnutrition and infections, which Dr. Hanson will deal with in his presentation.

Dr. Walker: Much of the work that has been done and a lot of the work that you reviewed suggest that it is a vicious cycle. Once you start down the road of IUGR or small for gestational age, it is propagated from generation to generation. Has anyone looked at this in reverse? As nutrition starts to improve, do the changes that occur during pregnancy as an adaptation to intrauterine starvation modify, and the infants become larger, and again later their offspring become larger? Has that been looked at?

Dr. R. Bergmann: I presented the results of the analysis by Kramer and Kakuma [5]. Balanced protein-energy supplements in pregnancy increased birthweights significantly, but the increase was rather low. We are not sure how much is due to a low compliance of pregnant women. In the studies in the Gambia this was taken care of: birthweight increased by 201 g during the hungry season [6]. I don’t think it is good to force supplements on pregnant women who are not adapted to a high intake.
Dr. Prentice: It is very complex as you stated. Just as a matter of information, we are following up the offspring from those trials now. Unfortunately they are not really old enough; they are still in their adolescence at the moment so it will take time. Also the Guatemalan supplementation studies are being followed up by Dr. Martorell and others. This kind of data will come out in due course.

Dr. R. Bergmann: Analysis of the data from the INCAP study in Guatemala showed that malnourished women gained weight if they received supplements over a reproductive cycle, but their second-born infant weighed less [7]. Marginally nourished women lost weight during the reproductive cycle, but their second-born infant weighed more than their first-born, and supplements reduced their own weight loss. There seems to be a delicate partitioning of the share in energy between mother and fetus in order to maintain reproductive success.

Dr. Prentice: This field has started to use a phrase, perhaps it originated from Dr. Barker, about 'harmonious growth', a concept that I believe is very important. What we were trying to do with our supplementation program in the Gambia was to prevent fetal growth retardation. Some of these studies are done in periods when there is actually no really good evidence for fetal growth retardation, and what they are trying to do there is to promote fetal overgrowth. So it is very important indeed for us to be looking at the size of the baby in relation to the size of the mother. Just a few moments ago you mentioned the customized growth charts by Gardosi et al. [8] and the babies who have very low perinatal mortality in spite of being born very small: they are appropriate, they harmoniously grown. So it comes back to what Dr. Barker was saying yesterday, how do we get out of this cycle? We have small mothers, and in fact if they have small babies it is actually probably totally appropriate. But we want to get them out of that cycle somehow, and can they be gotten out in one generation by prenatal supplementation? We don't know. First of all it is difficult to do. You very generously cited our studies in which we had the biggest effect, but most of the studies have had a much smaller effect. So it is hard to do and then we question whether it is the right thing to do anyway.

Dr. Barker: One point about harmonious growth might be that a small mother has a small baby; now that might be harmonious or it might not be, it depends how the baby grew. If the baby started on a slow growth trajectory and held to it, which is broadly what happens in China, then what is delivered at birth is a miniature human being. That is very different from the trajectory of growth in Asia, which is broadly a more rapid initial trajectory of growth which is not sustainable in late gestation. The end product is a baby of the same size as the Chinese baby, but the body composition and the long-term consequences are profoundly different. So small mothers may have small babies because the baby senses very early on that he is just going to grow slowly or they may have small babies because they can't sustain a more rapid growth trajectory. That is one of the great mysteries out there. What is it in very early gestation that sets the fetal growth trajectory because it is an extremely important trajectory whatever it is. If it is not sustained then there are adverse consequences, and at birth the babies are disproportionate rather than the Chinese baby who is simply a proportionate miniature human being. My second comment, and I don't know how secure the factual basis for this is, but I was told recently that Pygmies are starting to get taller now. Geneticists have long held that Pygmies have a genetic basis. In the Cameroun the Pygmies are now getting taller and it may be that for Pygmies it will take many generations to escape from what was once an adaptation to profound undernutrition. We just don't know, but the literature certainly talks of many generations before you can put this right.

Dr. R. Bergmann: I have another comment regarding Dr. Prentice's proposal: customized growth charts also adapt for factors that are either not important or should
not be cleared away, e.g. the father’s weight or the mother’s BMI or even smoking during pregnancy. The father’s weight does not matter much regarding fetal growth, but the mother’s BMI and smoking are risk factors and not neutral determinants of newborn weight.

**Dr. Haschke:** My question is related to DHA and its influence on BMI at 21 months of age. At the Nestlé Research Center data have recently shown in a mouse model that just supplementing the animal during pregnancy with DHA results in a lower, different body composition of the offspring. This means that the offspring of the mice who received DHA had a lower body fat content and higher muscle mass, which could correspond with your findings. Were those infants whose mothers were supplemented with DHA during late pregnancy exclusively breastfed, and was there a difference in breastfeeding between the two groups? If yes, this could be attributed to the duration of breastfeeding. You showed that the body composition of breastfed infants differs at 21 months of age; what could be the cause of this?

**Dr. R. Bergmann:** The children we observed were all breastfed; 80% of them exclusively for 3 months. We used mixed models to adjust for influential variables [9]. We did not expect these results; they were a surprise. The findings are supported by animal experiments, e.g. bodyweight and adipocyte size of the rat pups whose mothers received an n-3 diet were higher than with a n-6/n-3 diet [10]. This could be a biological explanation for the change observed. Dr. Makrides might know more about this. We did not measure the body composition on these children, we just relied on anthropometric data as a proxy.

**Dr. Malka:** Smoking combined with caffeine is negatively associated with birthweight, and pregnant smokers require more micronutrients. I also want to mention environment which can have an adverse influence in later life. A low socioeconomic status and poverty and the psychosocial consequences associated with low social class are very important.

**Dr. R. Bergmann:** Yes, in our analysis cigarette smoking explained more of this reduction in birthweight than social class [11]. Smoking mothers may also have a poor diet which we could not control for.

**Dr. K. Bergmann:** There is some discussion about why IUGR and, on the contrary, macrosomia might similarly lead to increasing the incidence of type 2 diabetes and all its consequences. We speculate that IUGR produces small muscle mass which is tracked over a long time. This muscle mass is not only small, but at the same time it is programmed to somehow have impaired glucose uptake. If under affluent conditions body mass is then added, this preferably would be fat. The relation between fat mass and muscle mass is exceeded more easily if the muscle mass is low, and this produces metabolic syndrome even with lower total BMI status. The macrosomic infant has a high muscle mass plus a high fat mass and this is what is called the adiposo-gigantic type of an obese person who, because both muscle mass and fat mass are very high, produces the same phenotype of metabolic syndrome.

**Dr. Hanson:** With regard to IUGR, it certainly is a complex condition. One thing we found is that there is a significant reduction in the placenta of the mRNA for IL-10, an immunosuppressive and anti-inflammatory cytokine. We found this in Swedish pregnancies, but especially in Pakistan where IUGR is, as in many other similar countries, a very common condition [12]. This may well indicate that somewhere along the line inflammation is a mechanism involved.

**Dr. Walker:** Coming back to DHA, there are some mixed views about DHA supplementation during the pregnancy. There are people who feel that DHA is very helpful in preventing prematurity and other things. As I understood, DHA supplementation caused an initial increase in body size and then it fell off with ongoing supplementation. Is that right?
**Dr. R. Bergmann:** We stopped the supplementation of lactating mothers at 3 months. The BMI increased in these breastfed infants (which is typical for breastfeeding) of both DHA-supplemented and not supplemented mothers, but a little bit more (though not significantly) in the DHA group.

**Dr. Walker:** To me that implies that over the latter part of gestation BMI was falling off with DHA supplementation, or did I misinterpret that? What is the mechanism; what is the evidence to support that mechanism?

**Dr. R. Bergmann:** The mechanism, as I understood it, is that n-3 PUFAs have an antiadipogenic effect [13].

**Dr. Walker:** How does that occur? What is the mechanism by which those fats alter the maturation of adipocytes?

**Dr. Makrides:** I am not sure that the mechanisms are well sorted out; there is a lot of work going on in the area. Some other work that might be relevant was done quite some time ago [14, 15]. It was shown that muscle tissue that is higher in the long chain n-3 fatty acids has a better glucose response and is less insulin-resistant. Lean muscle tissue with a higher composition of the long chain fatty acids, specifically of the n-6 variety, also react quite differently to muscle tissue with membranes that are more saturated. We are undertaking a large scale randomized trial involving 2,500 women to test n-3 fatty acid supplementation in pregnancy; this is being funded by the National Health and Medical Research Council in Australia. Although the study is focused on neurodevelopmental outcomes, from what I have heard this meeting it signifies that we should also look at the metabolic side. We are in the process of putting together a rationale for doing this and the new data that seem to be coming out signify that we should really be planning that into the long-term.

**Dr. Walker:** Has anybody actually taken pre-adipocytes? Has anybody incubated pre-adipocytes with different types of fat and looked at its conversion? My understanding is that fatty acids change membrane composition, they incorporate themselves, and long chain fatty acids have a different effect and saturate in other forms. I had no idea that they actually had an effect on maturation itself.

**Dr. R. Bergmann:** Yes, and the hypothesis is that the increase in adiposity, this epidemic in the United States, is caused by the consumption of too much peanut butter and vegetable oils in the USA, while the consumption of n-3 PUFAs has not increased over the last decades. This has changed the fatty acid composition of breast milk as well [13].

**Dr. Prentice:** My understanding of this is that Dr. Ailhaud and his team have shown that some of the long chain PUFAs, in particular their derivatives PGE2, are the ancestral ligands for PPARɣ, and so that is one proposed mechanism. The question I want to ask is a bit of a challenge. I am concerned that we keep propagating what I think is a myth; namely that IUGR babies end up being obese. Really the only evidence that is persuasive is the data of Ravelli et al. [3] on 19-year-olds; their data [16] on 50-year-olds is really not persuasive. There is one small subgroup which shows a tiny significant 7% increase in BMI which, if you adjust for multiple testing, disappears completely. I am persuaded much more by what Dr. K. Bergmann described, that they are likely to have a low muscle mass. But I really think we have got to stop propagating this myth that low birthweight babies become obese. The meta-analysis by Oken and Gillman [17] shows quite the reverse: it is the big babies that become obese, not the small ones.

**Dr. R. Bergmann:** I agree. We should be cautious and warn our colleagues here that they should not introduce our way of life into their countries too fast, because it may not be appropriate for their populations.

**Dr. Maldonado:** My question relates to what Dr. Ogra was talking about regarding inflammation. A few years ago, there was a large study of about 2,000 HIV-infected
pregnant women in Malawi, Tanzania and Zambia looking at the effect of subclinical chorioamnionitis on HIV transmission. In that study the women were randomized to normal prenatal care versus antibiotic treatment for presumed chorioamnionitis in 28 and 32 weeks of gestation. There was no effect on HIV transmission but there was an effect on decreasing IUGR, small for gestational age babies as well as decreasing sepsis in newborns which would be expected. It is very unclear to me what the definition of subclinical chorioamnionitis was. Are you aware studies of this nature where antibiotic treatment of potential not clinically recognized inflammatory states can influence the outcome of pregnancy?

Dr. R. Bergmann: In developed countries, besides unknown causes, the main etiological determinant for premature birth is infection of the genitourinary tract, often chronic such as bacterial vaginosis [18]. Twenty percent of premature babies in the USA are delivered prematurely due to maternal or fetal indications, e.g. severe growth restriction, and 30% due to premature rupture of the membranes, often as a consequence of chorioamnionitis [19]. Part of this growth restriction could be avoided by antibiotic treatment.

Dr. Maldonado: Do you believe that might have an effect on longer term outcomes beside just reversal of IUGR? I imagine that hasn't been looked in a longitudinal fashion.

Dr. R. Bergmann: I don't know of any study.

References
