

# PREVENTING LOW BIRTHWEIGHT

**T**he prevalence of low birthweight (LBW) is higher in Asia than elsewhere<sup>10</sup>, predominantly because of undernutrition of the mother before pregnancy, exacerbated by undernutrition during pregnancy. About 60% of women in South Asia and 40% in South-East Asia are underweight (<45 kg), 40% of them are thin, with body mass index (BMI) <18.5, and more than 15% are stunted (<145 cm)<sup>11</sup>. Being of low weight at birth has a profoundly adverse effect on the health and development of the neonate. It is a risk factor for stunting, which starts *in utero* and becomes worse if the diet or health status is inadequate during postnatal development. LBW is probably the main reason why over 50% of the children in South Asia are underweight<sup>12</sup>. The adverse consequences of LBW continue to be manifested during childhood, and are passed on to the next generation when women, who have been chronically undernourished in their past, become pregnant. LBW and subsequent stunting are caused by undernutrition and other health problems, rather than by racial or ethnic differences. Improvements in maternal nutrition and health can increase birthweight, survival and growth of the child, and subsequent size and function (including health, productivity and mental performance) in adult life.

Drawing on much recent work<sup>13</sup>, the prevalence, consequences and causes of LBW, and the efficacy of nutrition interventions aimed at preventing LBW are reviewed here. The main focus is on interventions during pregnancy, but approaches to improving adolescent nutrition status are also reviewed. Micronutrient interventions are evaluated from the perspective of their effect on birthweight, rather than on micronutrient deficiency, which is addressed later. Recommendations are made about the nature, timing and targeting of nutrition interventions to improve pregnancy outcome. Many non-nutrition or indirect interventions, such as immunization and sanitation, have significant nutrition effects<sup>9</sup> but these are beyond the scope of this review.

## Definitions and Indicators

Numerous terms have been used to describe infants who are born smaller than is desirable. Many of these are confusing, overlapping, and of limited practical value in developing countries. The focus here is on the most practical and commonly applied terms. LBW is defined as weighing less than 2,500 g at birth. It is one of the most common statistics because it requires a single measurement, weight at birth, and no information about gestational age. There are two main causes of LBW: being born small for gestational age, or being born prematurely. In developing countries, the majority of LBW infants are small but are not born prematurely. Nevertheless, 6.7% of LBW infants are born preterm in developing countries<sup>14</sup>.

To deal with the influence of prematurity, a World Health Organization (WHO) Expert Committee proposed the term "IUGR-LBW" ("Intrauterine Growth Retardation – Low Birthweight")<sup>15, 16</sup>. This refers to infants born at term (>37 weeks of gestation) with LBW (<2,500 g). It replaces the older term "small-for-gestational-age" (SGA). It is often difficult or impossible to assess gestational age accurately. For example, using ultrasound rather than the reported date of the last menstrual period (LMP) lowers the estimated prevalence of SGA by about 30 to 50% in developed countries<sup>17, 18</sup>. In Asia, LBW (including preterm infants) estimates are only slightly higher than IUGR-LBW estimates (Table 1).

This means that, for practical purposes, LBW is a valid indicator of the prevalence of IUGR. A regression equation, developed using data from 60 countries where both LBW and gestational age data were recorded<sup>10</sup>, can be used to convert LBW to IUGR-LBW. An important caveat is that both the LBW and IUGR-LBW definitions exclude infants who weigh more than 2,500 g at birth, but less than the 3,300-3,500 g birthweight of well nourished infants in developing countries. Many of these "smaller than normal" infants are likely to have been IUGR and will probably suffer adverse functional consequences of their suboptimal weight. The IUGR-LBW category also

**TABLE 1: Incidence (%) of low birthweight (LBW) and LBW with intrauterine growth retardation (IUGR-LBW) in some Asian countries**

Country, location	Year	LBW (%)	IUGR-LBW (%)
People's Republic of China, 6 subdistricts of Shanghai	1981-1982	4.2	3.4
India, Pune	1990	28.2	24.8
Indonesia, Bogor area	1983	10.5	8.0
Myanmar, rural and urban	1981-1982	17.8	12.7
Nepal, rural	1990	14.3	11.8
Nepal, urban	1990	22.3	18.2
Sri Lanka, rural	1990	18.4	15.8
Thailand, rural and urban	1979-80	9.6	6.9
Viet Nam, Hanoi + 1 rural district	1982-1984	5.2	4.2

Source: Modified from de Onis M, Blossner M, Villar J (1998) Levels and patterns of intrauterine growth retardation in developing countries. *European Journal of Clinical Nutrition* 52: S5-S15.

excludes preterm infants who were IUGR. For these reasons, the IUGR-LBW category substantially underestimates the true magnitude of intrauterine growth retardation. Defining IUGR as a birthweight below the 10<sup>th</sup> percentile of the international 'birthweight for gestational age' curve<sup>16</sup>, has given, on average, incidences that are 14.5% higher than when the IUGR-LBW definition is used<sup>10</sup>.

### Wasting or Stunting *in utero*

The foetus undergoes its maximum increase in length at 20-30 weeks of gestation, and in weight during the third trimester<sup>19</sup>. Therefore, the timing of undernutrition *in utero* has different effects on weight and length. Stunted (also called symmetrically or proportionately growth-retarded) infants have a normal ponderal index (PI) (defined as weight/length<sup>3</sup>) but their weight, length, head and abdominal circumferences are below the 10<sup>th</sup> percentile of reference values. Wasted (asymmetrically or disproportionately growth retarded) infants have a relatively normal length and head circumference, but their body weights and PIs are low due to a lack of fat, and sometimes of lean tissue. Wasting is thought to result from undernutrition that occurs late in pregnancy, when fat deposition is most rapid. Only 1% of foetal body weight is fat at 26 weeks compared to 12% at 38 weeks. However, stunting may reflect undernutrition throughout pregnancy<sup>14</sup>. The postnatal development and function of wasted newborns is distinctly different from those who are stunted.

### Prevalence of Intrauterine Growth Retardation (IUGR)

In developing countries, IUGR has been estimated to affect between 14 and 20 million infants per year<sup>10</sup>, or as many as 30 million<sup>11</sup>. Fourteen million is equivalent to 11% of all births in developing countries<sup>10</sup>. The higher estimates may be closer to reality because most birthweight data are obtained from clinics and, in developing countries, babies born at home are more likely to have LBW. Nevertheless, these estimates provide a useful basis from which to target attention and to allocate resources.

Rates of IUGR-LBW can be categorized as percentages of all births, as follows: low (<5%), moderate (5-10%), high (10-15%) and very high (>15%). For LBW and IUGR-LBW respectively, the highest incidences are found in South Central Asia (28%, 33%). The average prevalence is 11% of births in all developing countries, and about 21% in South-East Asia<sup>10</sup> (Table 2). At the national level, the highest incidences for LBW and IUGR-LBW respectively are: Bangladesh (50%, 39%), India (28%, 21%) and Pakistan (25%, 18%). For other Asian countries, the corresponding data are: Sri Lanka (19%, 13%); Cambodia (18%, 12%); Viet Nam and the Philippines (11%, 6%); Indonesia and Malaysia (8%, 4%); Thailand (8%, 3%), and the People's Republic of China (PRC) (6%, 2%)<sup>10</sup>.

**TABLE 2: Estimated incidence (%) and expected numbers of low birthweight (LBW) and LBW with intrauterine growth retarded (IUGR-LBW) infants in developing countries in 2000**

	Incidence (%) (<2,500 g) <sup>b</sup>	LBW Expected No. (thousands) <sup>c</sup>	Incidence (%) (<2,500 g; <sup>3</sup> 37 weeks)	IUGR-LBW Expected No. (thousands) <sup>c</sup>
<i>Africa</i> <sup>a</sup>	n.a.	n.a.	n.a.	n.a.
Eastern	n.a.	n.a.	n.a.	n.a.
Middle	21.3	853	14.9	597
Northern	n.a.	n.a.	n.a.	n.a.
Southern	n.a.	n.a.	n.a.	n.a.
Western	17.2	1,451	11.4	962
<i>Asia</i> <sup>d</sup>	<b>18.0</b>	<b>13,774</b>	<b>12.3</b>	<b>9,344</b>
Eastern <sup>e</sup>	5.8	1,250	1.9	409
South Central	28.3	10,917	20.9	8,062
South Eastern	10.3	1,190	5.6	647
Western	8.3	417	4.5	226
<i>Oceania</i> <sup>e</sup>	<b>15.0</b>	<b>29.2</b>	<b>9.8</b>	<b>19</b>
Melanesia	15.4	29	9.9	19
Micronesia	n.a.	n.a.	n.a.	n.a.
Polynesia	4.0	0.2	0.2	0.03
<b>All developing countries</b>	<b>16.4</b>	<b>17,436</b>	<b>11.0</b>	<b>11,677</b>

<sup>a</sup> The nomenclature of subregions follows that of the United Nations

<sup>b</sup> Source: de Onis M, Blossner M., Villar J (1998) Levels and patterns of intrauterine growth retardation in developing countries. *European Journal of Clinical Nutrition* 52: S5-S15.

<sup>c</sup> Total live births for 2000 are based on the UN (1998) World Population Prospects. New York: United Nations.

<sup>d</sup> Excludes Japan.

<sup>e</sup> Excludes Australia and New Zealand.

n.a. = not applicable because the coverage of live births was < 80%.

## Consequences of Low Birthweight

### Increased Mortality and Morbidity

Whether a newborn infant is stunted or wasted has an important influence on its future development. For example, stunted infants have a higher neonatal mortality than those who are wasted, and also contribute most to poor child survival and development. Wasted infants demonstrate more postpartum weight catch-up<sup>20, 21</sup>, whereas stunted infants tend not to catch up to the reference growth norms.

Infants who weigh 2,000-2,499 g at birth have a four-fold higher risk of neonatal death than those who weigh 2,500-2,999 g, and a ten-fold higher risk than those weighing 3,000 - 3,499 g<sup>22</sup>. The more severe the growth restriction within the LBW category, the higher the risk of death. For example, weighing more than 2,500 g but less than 3,000 g at birth, also carries a greater risk for neonatal mortality and morbidity. This is especially true for infants with a low PI<sup>23</sup>. For a given birthweight, being born small because of preterm

delivery is a stronger risk factor for perinatal mortality than if the smallness is due to growth restriction<sup>22</sup>. Being born preterm, as well as having LBW carries the strongest risk of mortality<sup>10</sup>. IUGR and LBW infants are more susceptible to hypoglycaemia and to birth asphyxia. In a substantial number of studies they suffered more diarrhoea and pneumonia for a few months after birth<sup>22</sup>, explaining in part why LBW is also a risk factor for postneonatal death.

In the few studies from which data are available during the first weeks of life, wasted, LBW newborns experienced more morbidity<sup>21, 23, 24</sup> whereas stunted newborns were more likely to die during this time<sup>25, 26</sup>. This may reflect the greater capacity for the LBW infant to catch up in weight and immune function. The impaired immunocompetence of stunted infants is more likely to persist. In a retrospective study in The Gambia<sup>27</sup>, being born during and up to two months after the so-called "hungry season" was a strong predictor of mortality after age 15 years. Being born in the hungry season was also associated with about a four-fold greater risk of dying between the ages of 15 and 45 years, and a ten-fold greater risk of

dying between the ages of 35 and 45 years. The deaths were mostly related to infections, or to childbirth in women, and were probably caused by the effects of undernutrition *in utero* on development of the immune system.

### Greater Risk of Stunting

Weight at birth is a strong predictor for size in later life because most IUGR infants do not catch-up to normal size during childhood. In Asian countries, such as Bangladesh, the PRC, India, Pakistan, the Philippines and Sri Lanka, the incidence of LBW predicts the prevalence of underweight during preschool and subsequent years<sup>5</sup>.

A review of 12 studies that provided data on the subsequent growth of IUGR infants (preterm infants excluded) revealed that they underwent partial catch-up growth during their first two years of life<sup>28</sup>. After age 2 years, there was little further catch-up and the IUGR infants remained stunted during the rest of their childhood, adolescence and adult life. At 17 to 19 years of age, males and females who were born IUGR-LBW were about 5 cm shorter and weighed 5 kg less than those who were not born IUGR-LBW. Importantly, the magnitude of these differences is similar in developed and developing countries. This suggests that, as a general rule, later undernutrition does not magnify the impact of IUGR. Controlling for maternal height did reduce the influence of birthweight on size at 17-19 years, but birthweight remained a significant predictor. Low maternal height is in itself a reflection of prior undernutrition. Menarche and maturation are probably not delayed by being born IUGR<sup>29</sup>.

From a Guatemala longitudinal study<sup>28</sup>, data are available on a subset of children followed from birth to adolescence. Although the length Z-scores of the IUGR infants tended to catch up somewhat by 3 years of age, the absolute increments in length were the same for children born IUGR, both with birthweights 2,500 – 3,000 g and 3,000 – 3,500 g. In other words, IUGR children actually grew the same amount during the first 3 years of life as those with a heavier birthweight. The apparent catch-up in Z-scores is an artefact, due to the splayed distribution of these scores: smaller children improved their Z-scores more per unit growth<sup>28</sup>. The above-mentioned studies illustrate that the size and nutritional status of pregnant women are more important than postnatal factors as determinants of the growth of their children in later life.

### Poor Neurodevelopmental Outcomes

LBW infants are more likely to experience developmental deficits. Undernutrition that affects

head circumference before 26 weeks of pregnancy has a greater impact on neurologic function than does undernutrition later in pregnancy<sup>30</sup>. The adverse effects of early childhood undernutrition on behaviour and cognitive development may not be fully redressed, even with better diet and care later. In the USA, from a collaborative study on births between 1959 and 1965, the mean IQ scores at four years of age for each birthweight group were: 737-2,000 g, 94; 2,000-2,500 g, 101; and 2,500-3,000 g, 103. A study of the association between IUGR and cognitive development and behaviour in the first six years of life<sup>31</sup> concluded that deficits in performance of the IUGR group began to appear between 1 and 2 years of age. These deficits were larger in high risk subgroups; e.g., those who were born smallest, or when IUGR occurred early in pregnancy. The size of the difference was less at 4 to 7 years of age. However, it is unclear whether IUGR followed by good postnatal nutrition has a measurable effect on cognitive or behavioural development in adolescence, because of dilution by many socio-environmental influences on development<sup>32</sup>.

### Reduced Strength and Work Capacity

In the Guatemala longitudinal study<sup>28</sup>, males and females at an average of 15 years of age, who were born IUGR, performed significantly more poorly on tests of strength, compared to those born weighing at least 2,500 g<sup>28, 33</sup>. Specifically, they could apply approximately 2 to 3 kg less force to a hand grip dynamometer. The lower work capacity of adults who were IUGR babies is mostly attributable to their lower fat-free mass. IUGR has a serious adverse impact on later work productivity and income generating potential.

### Increased Risk of Chronic Disease

The consequences of LBW probably continue throughout life<sup>1</sup>. The risk of diseases such as hypertension, coronary heart disease, stroke and noninsulin dependent diabetes (together called "syndrome X"), are associated with size, wasting and stunting at birth<sup>34, 35</sup>. The association between adult disease risk and birthweight is seen across the range of birthweights, not just LBW. In developing countries, there is evidence that mortality from infections during early adulthood is higher in individuals who were malnourished *in utero*<sup>27</sup>. IUGR may cause individuals to be programmed differently, as a result of their adaptations to adverse *in utero* environments: the concept of 'foetal programming'<sup>1, 36</sup>. This hypothesis has been challenged<sup>37, 38</sup>. The magnitude of effects of intrauterine and early childhood growth retardation

on future disease risks has been recently reviewed<sup>1</sup>. Further work comparing such effects with those of other lifestyle factors is needed.

## Causes of Intrauterine Growth Retardation

Undernutrition is the major determinant of IUGR in developing countries. It has been estimated<sup>39</sup> that about 50% of all IUGR in rural areas of developing countries is attributable to small maternal size at conception (low weight and short stature), and low gestational weight gain. Other important causes include malaria in endemic areas<sup>40</sup> and maternal infections that can cause loss of appetite, higher nutrient losses or requirements, abnormal placental blood flow or structure, or foetal infections<sup>41</sup>.

In developed countries, where maternal undernutrition is relatively uncommon, the majority of LBW is caused by premature delivery. Cigarette smoking during pregnancy is the most important factor causing IUGR, followed by low gestational weight gain and low BMI at conception<sup>42</sup>. There is increasing evidence that deficiencies of some micronutrients, such as folic acid, increase the risk of preterm delivery.

## Prenatal Food Supplementation

Many nutrition interventions have been tested for their ability to improve birthweight and other aspects of pregnancy outcome. However, most of these trials had serious limitations: e.g., lack of a control group; failure to randomize treatments; large number of drop-outs; distribution to other household members of foods intended for the pregnant woman; small sample size; or the inappropriate nature of an intervention.

This summary of the efficacy of interventions to improve pregnancy outcome uses the Cochrane Library's Pregnancy and Childbirth Database 2001. Other reviewers have used a similar approach<sup>43</sup>. Cochrane-based systematic reviews are frequently updated, meta-analyses of intervention trials that meet certain criteria, including: random controlled design, prevention of systematic errors, good execution of the intervention; and adequate assessment of outcomes. The design and limitations of each trial are considered and discussed, and may influence the conclusions. Databases on randomized clinical trials have the advantage that they combine data across studies. It has been estimated that a sample size of at least 200 women per group is needed to detect an intervention-induced increase in birthweight of 100 g<sup>44</sup>. Many individual trials do not come close to having an adequate sample size. Combining studies from

different locations also makes the results more generalizable, especially where the outcome is susceptible to nonintervention influences, and where the effect of the intervention is relatively small. This is indeed the case for birthweight and other measures of pregnancy outcome. The results of meta-analyses need to be interpreted with caution, however, keeping in mind that most of the trials have usually been conducted in developed countries, where there is a low prevalence of undernutrition, and that the results may not translate easily into policy decisions.

## Beneficial Nutrition Interventions

In a Cochrane analysis, maternal supplements that provided balanced protein and energy were the only intervention that improved birthweight<sup>45</sup>. These balanced supplements were defined as foods that provided less than 25% of their energy content as protein. No minimum protein content was defined. Fourteen such trials were subjected to analysis. Supplementation was associated with modest increases in maternal weight gain, a small but significant increase in birthweight, and smaller, nonsignificant increases in birth length and head circumference. SGA prevalence was reported in seven of the trials: from Bogota, Colombia; East Java, Indonesia; Harlem, New York City, USA; India; Taipei, China; Thailand; and Wales, U.K. Overall the supplements decreased the prevalence of SGA babies, although this was of borderline significance<sup>45</sup>. Overall there was a 32% reduction in risk of SGA, a 21 g per week higher maternal weight gain and a 32 g increase in birthweight. A significant reduction in stillbirths and neonatal deaths was found in three of the four trials in which it was assessed.

Among these studies, three were carried out in Asia, two of which had very small sample sizes. In India, 20 women of low socioeconomic status were given 417 kcal and 30 g protein daily in the form of 50 g sesame cake, 40 g of *jaggery* (raw sugar) and 10 g oil<sup>46</sup>. There was no intervention in the control group. Birthweights were not significantly different. The means were 2,939 g in the experimental group and 2,676 g in the control group. The SGA prevalence was 0/10 in the experimental group, compared to 5/10 in controls. No data were presented on food intake, so the supplement may have partially substituted for the usual diet rather than adding to it. Reported energy intakes were higher before supplementation. A study in Thailand was also small, involving 43 healthy women at a mean of 28 weeks gestation<sup>47</sup>. They were fed one of two different supplements that each provided an additional 350 kcal and 13 g protein per day as typical foods. The control group received no

intervention. Again there was no information on dietary substitution, but mean birthweight was significantly higher in the supplemented women (3,096 g compared to 2,853 g in the controls). The prevalence of SGA was 0/28 in the intervention group compared to 2/15 in the unsupplemented group.

An Indonesian study of 747 clearly undernourished women in East Java, found no significant effect of a supplement on birthweight (2,908 g and 2,948 g in the experimental and control groups respectively) or SGA<sup>48</sup>. The mean birthweights were 2,908 g in the experimental group and 3,948 g in the control group. Women in the experimental group were provided with a supplement containing 465 kcal and 7.1 g protein per day, and those in the control group received 52 kcal and 6.2 g protein per day. The intervention started at 26-28 weeks gestation. In the experimental group, 29/258 infants were SGA, compared to 24/252 in the control group. Again substitution of usual foods by the supplement, and its distribution to other household members, were not assessed. Also, the study was carried out during a period when there was a remarkable improvement in birthweight in East Java, which might have affected the ability of the intervention group to respond, as well as the status of the control group<sup>49</sup>.

The Cochrane meta-analysis included the most recent trial in The Gambia<sup>50</sup>. This has caused a resurgence of interest in the benefits of supplementing pregnant women with energy and protein. This trial provides a valuable example of an effective intervention. It was a study of 1,460 different women, with 2,047 births in 28 rural villages. There is no doubt that the women were chronically undernourished, especially during the hungry season when weight loss averaged 3-6 kg due to scarcity of food and heavy energy demands for agricultural work. At recruitment, their average weight was 53 kg and their BMI 21.0. From mid-pregnancy, the women were provided with locally prepared biscuits made from groundnuts, rice flour, sugar, and groundnut oil. These biscuits provided 1,017 kcal, 22 g protein, 56 g fat, 47 mg calcium and 1.8 mg iron per day. Project staff observed their consumption. Control villages were not supplemented. The supplements produced remarkable improvements in pregnancy outcome: average birthweight increased by 136 g; LBW decreased by 39%; and head circumference increased, on average, by 3.1 mm. Length was not affected, nor was gestational age. In the hungry season, the differences were even greater: 201 g for birthweight; 3.9 mm for head circumference; 0.41 cm (significant) for length; and LBW 42% lower. Importantly, a similar seasonal difference was found in an earlier study where supplementation averaged only 430 kcal/day<sup>51</sup>.

The more recent trial 50 recorded 40 neonatal (days 1-28) deaths in the control group compared to 25 in the intervention group, but no difference in deaths during the remainder of the first year of life. This is the same community for which being born in the hungry season carries a major excess of premature adult mortality<sup>27</sup>.

Why was this study able to show such a large impact of supplementation? Contributing factors probably included the following: the mothers were undernourished and in energy deficit prior to supplementation; the supplement was high in energy and contained a substantial amount of protein; the biscuits were actually consumed by the mothers; and the sample size was large. Interestingly the supplements did not provide much in the way of micronutrients. The women were given routine iron-folate supplements but not multiple micronutrients. It is remarkable that supplementation here did not start until 20-24 weeks of gestation and the women came for their biscuits only on an average of 82 days. Starting sooner might have had an even greater impact. The biscuits were culturally acceptable and produced locally, providing a sustainable method of supplementation.

### **Nonbeneficial Nutrition Interventions**

It does not appear to be useful to replace dietary energy with supplements that contain more protein. In a Cochrane meta-analysis, three trials were considered in which some of women's usual dietary energy had been "isocalorically" replaced with a balanced (<25% energy as protein) protein-energy supplement. Two of these trials were conducted in Birmingham, England, on 153 and 130 women of Asian descent<sup>52,53</sup>. In the first of these<sup>52</sup>, the supplement provided 273 kcal/day, of which 11% was protein, and both the supplement and the placebo contained vitamins and minerals. In the second<sup>53</sup>, the supplement provided 425 kcal/day, 10% as protein, and again both groups were given vitamins and minerals. In both studies, the controls received the same amount of energy but no supplemental protein. The third trial, in Chile, involved 683 low income women, prior to 20 weeks of gestation, who had a low weight-for-height at their first prenatal visit<sup>54</sup>. They were given a high protein (22% of energy), milk-based supplement. The controls had an isocaloric supplement that contained 12% kcal as protein and even more vitamins and minerals than the high protein group. The meta-analysis of these three trials included 966 women, most of whom were from the Chilean study. When protein intake was increased, without raising energy intake, there were trends to lower maternal weight gain and lower birthweight, and a higher risk of SGA births.

There was no effect on gestational age or incidence of preterm birth.

Maternal supplementation with high protein supplements (>25% of the energy content) may affect pregnancy outcome adversely in well nourished populations. Two trials were identified for a Cochrane meta-analysis. In the district of Harlem in New York City, 1,051 women entered a study before 30 weeks of gestation and were provided with a supplement containing 470 kcal and 40 g protein per day, vitamins, and minerals<sup>55</sup>. The control group received a supplement containing 322 kcal and 6g protein per day, plus vitamins and minerals. The second study was based on 25 Indian women of low socioeconomic status in Hyderabad, India. They were employed in manual labour and had low protein and energy intakes at 36 weeks of gestation. The trial provided hospitalization, a hospital diet and a supplement containing 350 kcal/day, 35 g protein, iron and vitamins<sup>56</sup>. The control group received the same treatments except that their supplement did not contain protein. The meta-analysis of the two studies reflected mostly the results of the much larger Harlem trial. The protein supplement resulted in a small, nonsignificantly higher weight gain, a higher (but again nonsignificant) increase in neonatal death in the Harlem group, and no greater foetal growth. There were no differences in infant growth or mental or motor development assessed by the Bayley scale one year later.

## Optimizing Interventions

When designing the most effective nutrition interventions for pregnant women, it is important to know: i) who would benefit most; ii) the stage of pregnancy when the supplement would be most effective; and iii) the optimal nutrient composition of supplemental food. There is limited information available from the literature on all three of these questions, but some general guidelines can be drawn.

### Targeting Supplements to Undernourished Women

A Cochrane meta-analysis<sup>45</sup> concluded that the increment in birthweight due to supplementation was no larger in those women who were undernourished prior to or during pregnancy. However, the group defined as being “undernourished” included women in New York City, and short or thin women in Aberdeen, Scotland. The “well nourished” group included women with marginal diets in Taipei, China who normally consumed 40g protein or less per day. Contrary to the conclusion of the meta-analysis, there is some evidence across individual studies to suggest

that the most undernourished women may benefit most from supplementation, as discussed in the following sections. Discussion of this evidence requires being able to identify women at greatest risk of IUGR. The best predictors are as follows.

### Best Predictors for Women at Greatest Risk of IUGR

#### *Prepregnancy Weight*

The WHO Collaborative Study on Maternal Anthropometry and Pregnancy Outcomes data<sup>15</sup>, collected between 1959 and 1989, on 111,000 women in 25 populations across the world, show that being in the lowest quartile of prepregnancy weight carries an elevated risk of IUGR of 2.5, compared to the upper quartile. A preconception weight of 40 kg (assuming average height is 150 cm) has been proposed as a useful cut-off for predicting IUGR risk in developing countries. This would include more than 50% of women in western India<sup>57</sup> and almost none in the USA. Clearly improving maternal weight prior to conception is a potential strategy to improve birthweight.

#### *Attained Maternal Weight at 20, 28 or 36 Weeks of Gestation*

Maternal weight during gestation predicts IUGR risk slightly better than prepregnancy weight because it considers weight gain in pregnancy, including the foetus. Comparing women in the lowest quartile of attained weight to those in the highest quartile, the odds ratios for IUGR are 2.7, 3.0 and 3.1 at 20, 28 and 36 weeks of gestation respectively. Including short (below average) maternal height increased the odds ratio to about 3.5, whereas including below-average prepregnancy weight increased the odds ratio to closer to 4.0.

### Additional, Less Useful Predictors of Women at Greatest Risk of IUGR

#### *Low Maternal Body Mass Index (BMI)*

Body Mass index (BMI) is defined as weight (in kg) divided by height (in m) squared. Maternal BMI is more a reflection of fatness than of lean tissue mass and, of course, correlates strongly with weight. It is certainly true that there is an interaction between maternal BMI at conception, weight gain during pregnancy and birthweight. It is also clear that women with a low BMI and who do not gain adequate weight, are at greatest risk of delivering a LBW infant<sup>58</sup>.

Likewise, pregnancy weight gain has a stronger beneficial effect on foetal growth in initially thinner women than in those who are fatter. In the WHO Collaborative Study<sup>15</sup>, mothers with a BMI in the lowest quartile were about twice as likely to produce an IUGR infant compared to those in the upper quartile. Thus, low maternal BMI was a poorer predictor of IUGR than either maternal prepregnancy weight or attained weight.

Another limitation of BMI as an indicator of IUGR risk is that fatness influences physiological adaptations to energy available during pregnancy. The thinnest women gain most weight during pregnancy and the fattest gain least. In fact, recommended pregnancy weight gains in the USA<sup>58</sup> and Europe are inversely proportional to BMI at conception. In East Java, Indonesia<sup>59</sup>, Pakistan<sup>60</sup>, Taipei, China<sup>61</sup> and rural Mexico<sup>62</sup>, the highest pregnancy weight gains occurred in the thinnest women. For example, in the Pakistan study, women weighing <45 kg postpartum gained 4.5 kg during one reproductive cycle. Those weighing 45-56 kg lost 0.6 kg, and those >56 kg gained 0.6 kg<sup>60</sup>. In the Mexico study, total pregnancy weight gain was strongly negatively related to preconception BMI, skinfolds, and percent body fat (correlation about -0.5), and thinner women also spontaneously consumed more energy during pregnancy<sup>62</sup>. Conversely, for women with a high BMI (>27) at conception, birthweight is practically independent of pregnancy weight gain<sup>58</sup>.

These interactions between prepregnancy BMI and gestational weight gain can be explained by the fact that the resting metabolic rate of fatter women is increased dramatically during pregnancy, thereby consuming more energy and leading to a generally lower weight gain<sup>63</sup>. In contrast, the metabolic rate of thin women may even fall in early pregnancy<sup>64</sup>. Their overall energy cost of pregnancy is much lower, and their pregnancy weight gain may be substantially more than that of fatter women.

These physiological responses to maternal BMI probably involve the hormone leptin. Serum leptin concentrations are strongly correlated with maternal BMI prior to pregnancy and in the second trimester<sup>65</sup>. Higher leptin is normally associated with a higher metabolic rate. In contrast, thinner women become more efficient at utilizing dietary energy for weight gain during pregnancy. This is especially true if their energy intake is low; an intervention with a protein-energy supplement in The Gambia did benefit birthweight, but some of the supplemental energy was expended in increased metabolism<sup>64</sup>.

Based on these considerations it does not seem useful to choose low BMI as the indicator of IUGR risk, compared to low prepregnancy weight or

attained weight. It appears to be low lean tissue mass, rather than low fat mass, that predicts IUGR.

### *Pregnancy Weight Gain*

The WHO Collaborative Study<sup>15</sup> found that women in the lowest quartile of both low prepregnancy weight, and pregnancy weight gain (to week 20, odds ratio 5.6; or to week 36, odds ratio 5.6) were at highest risk of producing an IUGR infant.

Pregnancy weight gains of women in Asia tend to be low. It has been estimated<sup>12</sup> that most women in South Asia gain little more than 5 kg rather than the 10-15 kg gain by women in developed countries. However, there are certain limitations to using weight gain as the only predictor of IUGR risk. Two measures are required. Weight gain is inversely related to BMI so, as discussed above, it will be higher in thinner women as long as the energy-sparing adaptations associated with low fat mass can buffer any concurrent low energy intakes. To complicate the picture further, it has been hypothesized that the degree of maternal undernutrition may affect the response to supplementation<sup>66</sup>. Supplementation of moderately malnourished women produces an increase in birthweight but has little impact on maternal weight gain. However, when seriously malnourished women are supplemented they cannot 'afford' to direct the energy to the foetus and therefore such supplementation improves maternal weight gain more than birthweight<sup>60, 67</sup>. This needs to be tested in more studies.

Clearly, energy intakes are so low for many women that the adaptive mechanisms described above cannot prevent low pregnancy weight gain. It has been estimated that women in developing countries who weigh 44-55 kg would deliver an infant with birthweight >3 kg if they gained 10.5 kg during pregnancy<sup>15</sup>. This would be a much higher weight gain than the 5-9 kg range that usually occurs.

### *Maternal Height*

Maternal height, although it contributes to total maternal mass, has less value than weight or BMI for predicting IUGR<sup>15</sup>. Low height is a good indicator of obstetric complications such as obstructed labour and need for assisted delivery<sup>15</sup>. It is therefore useful to refer short women to appropriate childbirth facilities.

### *Timing of Supplementation*

Some 20 years ago, the favoured hypothesis was that timing maternal supplementation during the third trimester of pregnancy would be most likely to increase birthweight<sup>14</sup>. The rationale was that foetal fat deposition was fastest during this stage of

pregnancy. In earlier trimesters, when maternal fat is increasing fastest, supplementation would be more likely to benefit maternal weight gain. This hypothesis was supported by analysis of pregnancy outcomes in the Dutch famine towards the end of World War II. Women who were in their third trimester during the famine produced babies with the lowest birthweights<sup>68</sup>. In The Gambia, the prevalence of LBW increases the most if the third trimester occurs during the hungry season<sup>51</sup>. The trial of supplementation during pregnancy in Taipei, China found as much improvement in birthweight with supplements given during the third trimester as when given before and throughout pregnancy<sup>69</sup>.

Subsequent research contradicts this hypothesis, however, and suggests that nutrition interventions earlier in pregnancy will have the strongest effect on birthweight. In the longitudinal Guatemala intervention study, the amount of fat gained in early pregnancy was the strongest positive predictor of birthweight. A recent analysis of this study revealed that, after adjustment for six potentially confounding factors, each kg of maternal weight gain in the second and third trimesters led to significant increases in birthweight, of 62 g and 26 g respectively<sup>70</sup>. This association between higher maternal weight gain in the second trimester and birthweight was independent of initial maternal size. An even stronger association was seen between gain in maternal thigh fat in mid-pregnancy and birthweight. Mid-pregnancy maternal weight gain and increments in thigh skinfolds were significantly associated with the newborn's length, weight and head circumference and were more strongly predictive of birthweight and other newborn outcomes than were maternal measures in late pregnancy. Similarly, low income teenagers in the USA were almost twice as likely to produce an IUGR infant if they gained inadequate amounts of weight in the first half of pregnancy, regardless of whether their weight gain caught up by the end of pregnancy<sup>71</sup>.

It is important to remember that birthweight is clearly not the only important outcome affected by the timing of supplements given to pregnant women. For example, evidence from The Gambia suggests that undernutrition in mid-pregnancy may impair development of the immune system, because infants born two to three months after the hungry season were later seen to have a higher rate of adult morbidity<sup>27</sup>.

### Duration of Supplementation

In the Guatemala intervention study, women who were supplemented during one pregnancy, then during lactation and the subsequent pregnancy, produced heavier infants in their second pregnancy

than those who were unsupplemented in their prior pregnancy. In fact, in these short (average height, 151 cm) women, mean birthweight was increased by this continued supplementation to 3,290g, compared to 2,944g in unsupplemented women<sup>72</sup>. These results imply that it is possible to compensate, during her reproductive years, for at least some of the adverse effects of a woman's previous undernutrition. Supplementation of the undernourished mother, before she becomes pregnant, can be expected to improve the outcome of a subsequent pregnancy.

## Micronutrient Supplementation During Pregnancy

Until the late 1990s, little attention was paid to the micronutrient status of pregnant women, except for the constant concern about the high prevalence of maternal iron deficiency. The energy and protein supplements provided in intervention studies often contained some micronutrients but generally failed to include adequate amounts of all important minerals and vitamins. Evidence is beginning to accumulate that the vitamin and mineral status of pregnant women can have major effects on pregnancy outcome. A meta-analysis of the impact of micronutrient supplements in 19 randomized controlled trials<sup>43</sup> concluded that only folic acid reduced the incidence of term LBW. However, only six of the trials were done in regions of the world where micronutrient deficiencies were expected to be a problem. The following evidence supports the importance of micronutrient supplements for pregnant women.

### Supplementation with Single Micronutrients

#### *Iron*

The prevalence of anaemia in pregnancy is high, especially in poor regions of the world. Therefore, it is difficult, for ethical reasons, to find placebo-controlled trials of iron supplementation in pregnant women. A meta-analysis of the Cochrane database found that iron supplementation significantly reduced the prevalence of haemoglobin (Hb) concentrations below 100 or 105 g/l in late pregnancy<sup>73</sup> but did not affect any other outcomes. Most investigators have looked for associations between maternal Hb and birth outcomes. Several studies have reported an association between low maternal Hb in early pregnancy and increased risk of preterm delivery<sup>74, 75, 76</sup>. In a study of 829 women from Shanghai, the PRC<sup>77</sup>, rates of LBW and preterm delivery, but not of IUGR, were higher when maternal Hb concentrations were low (anaemia) or high (poor plasma volume expansion), especially

in early pregnancy. This pattern has been observed in other studies. The fact that associations are strongest between preterm delivery and maternal Hb concentrations in early pregnancy may result from the variability in Hb concentration introduced by haemodilution later in pregnancy. In the few randomized, controlled intervention trials where birthweight was measured, three (two in Europe and one in Niger) found no effect and one (in The Gambia, using a folic acid control) found birthweight to be increased whereas gestational age was unaffected<sup>78</sup>. Thus, evidence for an effect of iron supplements on preterm delivery and birthweight is still weak, due to a lack of randomized controlled trials<sup>79, 80</sup>.

### **Folic Acid**

Folic acid is commonly a constituent of iron supplements provided to pregnant women. More data on its prevalence are urgently needed, but there is presently little evidence that folate deficiency is common<sup>79</sup>. This vitamin is present in large amounts in leaves and legumes. A meta-analysis using the Cochrane database concluded that folate supplements increased serum and red cell folate, reduced the prevalence of low Hb concentrations in late pregnancy (odds ratio, 0.61), and possibly increased birthweight<sup>81</sup>. However, a trial in Myanmar and Thailand found no additional improvement in Hb when folic acid was added to iron supplements<sup>82</sup>.

In trials in developed countries, and in the PRC<sup>83</sup>, folic acid taken prior to conception and during the first six weeks of pregnancy does afford some protection against the occurrence and recurrence of neural tube defects. In the PRC, 400 µg/day folic acid supplements reduced the occurrence of neural tube defects by up to 80%<sup>83</sup>. Folic acid supplements are effective for the substantial number of women who require more folate because their metabolism of this or of related metabolites is different<sup>84</sup>. Periconceptional folic acid supplementation effectively reduced neural tube defects, even in the populations in the USA where the diets of healthy individuals contain relatively substantial amounts of the vitamin. This led to the recent policy of mandatory fortification of wheat flour with folic acid in the USA.

The metabolic cause of neural tube defects is not yet understood but probably involves abnormalities in enzymes that are affected by this vitamin. Women who have given birth to a previous baby with neural tube defects are at much higher risk of this problem recurring in a second pregnancy and should be counselled to take folic acid supplements prior to conception. In general, however, unless such women are identified before they conceive or in the first few

weeks after their last menstrual period, providing folic acid in pregnancy is too late to prevent neural tube defects.

At present the most convincing evidence for supplementing women with folic acid later in pregnancy is that it might prevent some cases of preterm delivery and lower the risk of other birth defects. Low serum or red blood cell folate, and subsequently elevated plasma total homocysteine concentrations, are often associated with other pregnancy complications. In low income, mostly African-American women in the USA, those with low folate intakes and low serum folate concentrations at the end of the second trimester had twice the risk of preterm delivery, when potential confounding factors were controlled in the analysis<sup>85</sup>. An analysis of randomized, controlled clinical trials found that folate supplements reduced the risk of antepartum haemorrhage and Caesarean section (one trial each)<sup>86</sup>. A large, retrospective Norwegian study<sup>87</sup> showed that women in the upper vs. lowest quartile of plasma homocysteine concentrations (and presumably more folate deficient) had increased risks as follows: pre-eclampsia, 32% higher risk; preterm delivery, 38% higher risk; and preterm delivery, 101% higher risk.

### **Zinc**

There has long been interest in the potential for zinc supplements to improve birthweight and pregnancy outcome, because of the important role of zinc in cell division, immunocompetence, and hormone metabolism. Evidence for the efficacy of zinc supplements has, however, been very mixed. Cochrane meta-analyses found no effects of zinc supplementation on labour outcomes or on maternal or foetal mortality or morbidity<sup>88</sup>. A review of 10 zinc supplementation trials conducted up to 1996 showed that birthweight was higher in the supplemented group in four out of 10 trials<sup>44</sup>. Preterm delivery was reduced by zinc in three of the trials, of which two were the same as those showing an improvement in birthweight.

All of these trials were in developed countries except for the Republic of South Africa and India, and most had methodological flaws. The Indian trial, in which 45 mg zinc per day was provided to 168 women, found an improvement in birthweight and less preterm delivery but there was no placebo group<sup>89</sup>. One of the larger trials, that found zinc to be effective, enrolled women in the USA who had below average plasma zinc concentrations, in order to target those with poorer zinc status<sup>90</sup>. In Peru, a well-designed, recent trial using 1,295 women with poor zinc intakes, provided per day 60 mg iron and 250 µg folic acid,

with and without 15 mg zinc, starting at 10 to 24 weeks of gestation. Gestational age was assessed with ultrasound and other techniques. There was no impact of the zinc on gestational age, birthweight or length, or any other anthropometric measure<sup>91</sup>. It is not clear how many of these Peruvian women were zinc deficient, but their status would have been marginal at best. Similar results were found in a randomized, placebo-controlled trial on 559 women in the slums of Dhaka, Bangladesh<sup>92</sup>. The supplements were started relatively early, between 12 and 16 weeks of gestation, and provided 30 mg zinc per day. The investigators speculated that the low maternal energy intakes and deficiencies of other micronutrients might have overwhelmed any benefits of zinc. The evidence indicates that supplementing undernourished pregnant women with zinc alone is unlikely to lower the prevalence of LBW.

### *Vitamin A*

In rural Nepal, women who became night blind near the end of pregnancy had two to three times more urinary tract infections, diarrhoea and dysentery, eating problems, pre-eclampsia and eclampsia, and anaemia<sup>93</sup>. Vitamin A or beta-carotene supplementation reduced perinatal mortality by 44% in a group of more than 2,000 Nepali women<sup>94</sup>. The supplements (7000 µg retinol equivalents, RE) as retinyl palmitate or beta-carotene) were provided weekly prior to conception, throughout pregnancy and into lactation. However, there was no effect on IUGR. Additional studies are needed to show whether these results can be replicated in other situations, and whether supplemental retinol or beta-carotene would be equally effective if started later in pregnancy, when women more typically enter prenatal care. Due to the toxicity of retinol to embryos, pregnant women should be given no more than about 3,000 µg retinol per day.

### *Calcium*

Calcium supplementation during pregnancy reduces the risk of hypertension, pre-eclampsia and eclampsia, and lowers the blood pressure of the neonate<sup>95</sup>. A Cochrane meta-analysis of randomized controlled clinical trials showed that this effect was strongest in women with lower calcium intakes (<900 mg per day), and that preterm delivery was reduced in women at high risk of developing hypertension. In India, calcium supplementation of women with low calcium intakes substantially reduced the risk of hypertension and eclampsia<sup>96</sup>. It seems that daily supplementation with 1–2 mg calcium is required to produce this response, but this might be worthwhile

attempting in regions where pregnancy-induced hypertension and eclampsia are major causes of maternal mortality.

### *Iodine*

Maternal iodine deficiency during pregnancy causes cretinism in the neonate, with permanent adverse effects on subsequent growth, general development and cognitive function. A Cochrane meta-analysis examined the effects of maternal iodine supplementation during pregnancy, using three acceptably controlled trials involving 1,551 women<sup>97</sup>. In the two trials conducted in areas with severe iodine deficiency, the Democratic Republic (DR) of Congo (formerly Zaïre) and Papua New Guinea, iodized oil injection produced a significant (about 30%) reduction in deaths during infancy and early childhood<sup>98,99</sup>. The DR Congo trial showed that the injection was effective even when given in mid-pregnancy. Based on this meta-analysis, it was concluded that additional placebo-controlled trials to test the benefits of iodine supplementation on pregnancy outcome are no longer ethically justifiable. More information on iodine interventions is provided below.

### **Supplementation with Multiple Micronutrients**

There is considerable interest at present in moving towards the use of multiple micronutrient supplements. In developing countries, where diets are of poor quality and infections and parasites impair the absorption or increase losses of several nutrients, and where women are repeatedly depleted by pregnancy and lactation, it is usual for individuals to be deficient in several nutrients simultaneously. HIV-infected individuals may also have low serum concentrations of several vitamins and minerals<sup>100</sup>. When HIV-positive, pregnant women in Tanzania were given multiple micronutrients, compared to a placebo, this reduced LBW by 44%, births before 34 weeks of gestation by 39% and IUGR by 43%<sup>101</sup>. In low income women in the USA, multiple micronutrient supplements in the first two trimesters of pregnancy halved the risk of preterm delivery, although this was not a randomized controlled trial<sup>102</sup>. Additional trials of the benefits of multiple micronutrients for pregnancy outcome are ongoing in Bangladesh, Mexico, and Tanzania. The results of these studies will be important in decisions over whether or not to adopt a multiple micronutrient supplementation strategy for pregnant women in developing countries. Some concerns have been raised about this approach in India<sup>103</sup>. An important

consideration is that improving maternal micronutrient stores during pregnancy will increase the concentration of many of these nutrients in breastmilk, and prevent maternal depletion during lactation. The nutrients that should receive greatest priority are thiamine, riboflavin, vitamins B<sub>6</sub> and B<sub>12</sub>, vitamin A, iodine and selenium. These nutrients have been termed "Priority I" for the lactating woman, because: a) maternal status and intake affects their concentration in breastmilk; b) low intakes from breastmilk can have adverse effects on the infant; c) the concentration of these nutrients in breastmilk can be readily improved by increasing maternal intake; and d) for most of them, foetal storage is relatively low and the infant is particularly dependent on an adequate supply in breastmilk<sup>104</sup>.

## Non-Nutritional Interventions During Pregnancy

A comprehensive review of 24 non-nutritional pregnancy interventions found that only two improved birthweight<sup>105</sup>. These were smoking cessation, which improved birthweight and lowered term LBW by about 20%, and antimalarial prophylaxis. Data from 11 trials, on more than 3,000 women in endemic areas for malaria, showed the strongest effect of antimalarials on primagravidae, where birthweight increased by 112 g<sup>106</sup>.

It is inappropriate to conclude that non-nutritional interventions are not effective for reducing LBW. Very few trials have been attempted in malnourished populations and indeed few logical interventions have been tested in randomized, controlled trials. On a group or population basis, such interventions will make a difference only if they improve adverse factors or behaviour that affect a substantial proportion of the population [population-attributable risk (PAR)], and that cause a substantial increase in the relative risk (RR) of an adverse outcome (such as IUGR)<sup>42</sup>. This explains in part why smoking and antimalarial prophylaxis are effective interventions.

There has been some research on whether prolonged standing or strenuous work is associated with IUGR. Many studies found no association, although some did; e.g.<sup>107,108,109</sup>. In a large analysis of 7,722 pregnancies in the USA, work outside the home by pregnant women in the third trimester was associated with birthweights 150 to 400 g lower and more placental infarcts, compared to women who remained at home<sup>108</sup>. Working had the strongest negative association with foetal growth in mothers who were underweight at conception, had low pregnancy weight gain, and whose work required standing. Low placental blood flow was offered as an

explanation. In Asian countries, large numbers of women work very hard during pregnancy. This makes their energy requirements harder to meet and increases the risk of energy deficit and IUGR. Advice to protect the pregnant woman from excessive activity, especially during late pregnancy, should be tested for its effects on birthweight<sup>110</sup>.

## Adolescent Nutrition

### Adolescent Growth

During adolescence, growth in height accelerates, driven by hormonal changes, and is faster than at any other time in the individual's postnatal life, except in the first year<sup>111</sup>. More than 20% of total growth in stature and up to 50% of adult bone mass are achieved during adolescence<sup>112</sup>. Nutrient requirements are significantly increased above those in the childhood years.

Among girls, the "growth spurt" or peak growth velocity occurs normally about 12-18 months before menarche (onset of menstruation), at some time between 10 to 14 years. Growth in stature continues, however, for up to 7 years after menarche. Maximal adult height in women may thus be attained as early as 16 years or, particularly for populations with high rates of undernutrition, as late as 23 years<sup>113</sup>. Moreover, for several more years after growth in height is complete, the pelvic bones are still growing. This is a process that is crucial for reducing the risk of obstructed labour<sup>114</sup>. The development of the birth canal is not fully completed until about 2-3 years after growth on height has ceased<sup>115</sup>, whereas peak bone mass is not achieved until the age of 25 years<sup>116</sup>.

Better nourished girls have higher premenarcheal growth velocities and reach menarche earlier than undernourished girls. The latter grow more slowly but for longer, because menarche is delayed. In India<sup>117</sup>, both peak weight and height velocities were delayed by 18 months for children who were stunted at age 10 years. Ultimately, these two factors tend to balance out and total height achieved during adolescence (not necessarily attained adult height) may be similar for well nourished and undernourished adolescents<sup>118,119</sup>. The adult height finally attained may still differ as a result of pre-existing childhood stunting. The delay in menarche is thought to be partly related to low iron stores in childhood<sup>120</sup>.

### Adolescent Pregnancy

For nutrition, the important aspect of the abovementioned findings is that underweight, adolescent girls are growing for longer, and thus may not finish growing before their first pregnancy. In

India, for example, up to 67% girls were classified as being at obstetric risk (by weight and height criteria) in their 15th year as compared to about 20% in their 19th year<sup>121</sup>. In a report on 242 adolescent pregnancies (10-18 years) from Gorakhpur in Uttar Pradesh, India<sup>122</sup>, LBW and prematurity rates were 67% and 33%, respectively. The corresponding figures for mothers below 17 years of age were 83% and 33%, respectively.

Viewing these statistics against data on the age of marriage in India, the potential for severe maternal undernutrition and heightened LBW risk becomes clear. In six large, north Indian states, the mean age of marriage of rural girls was 13.8 years, and their age of conception 15.3 years<sup>123</sup>. In general, at least 25% of adolescent girls in the developing world have had their first child by age 19 and a great many more shortly thereafter<sup>124</sup>. In many countries, the proportion of unmarried adolescents becoming pregnant is at an all-time high<sup>125</sup>.

Research has shown that adolescents who are still growing are likely to give birth to a smaller baby than mature women of the same nutrition status<sup>126, 127</sup>. This is probably due to competition for nutrients between the growing adolescent and the growing foetus<sup>120, 128</sup> and poorer placental function<sup>129</sup> which in turn increases the risk of LBW and neonatal mortality<sup>130</sup>. In addition, concurrent pregnancy and growth have a particularly detrimental effect on micronutrient status of adolescent girls, after controlling for energy intake and other confounding effects<sup>128</sup>. Calcium status is a particular concern, because the bones of adolescents require calcium for growth at a time when foetal needs for bone growth are also high.

Adolescent pregnancies also confer a higher risk of maternal and infant mortality and preterm delivery. As with other women, these risks are further elevated in adolescents when birth care is inadequate. In India, it was found that children born to teenage mothers were 40% more likely to die in their first year than those born to women in their twenties<sup>131</sup>. Among five countries in Asia the corresponding figure was 50%<sup>132</sup>. In Bangladesh, maternal mortality ratios for 15 to 19-year-olds have been found to be twice as high as those for 20 to 24-year-olds<sup>133</sup>. The younger the adolescent, the greater the risk. In Jamaica and Nigeria, for example, women under 15 years were up to eight times more likely to die around the time of delivery than those in the 15-19 years age group<sup>133</sup>. Risks are further heightened by the fact that pregnant, adolescent girls are less likely to use antenatal and obstetric services.

There are fewer studies and less consensus on the risks of lactation to adolescents<sup>134</sup>, although there is suggestive evidence of a greater weight loss during lactation<sup>135</sup> and poorer breastmilk production<sup>136</sup> among

adolescents, as compared to adult women. It has been suggested<sup>137</sup> that there is a higher loss of bone minerals among lactating adolescents, though these findings have been challenged<sup>138</sup>.

With respect to attained adult height (or capacity to achieve genetic potential for size), a very strong association was found in India with under-five height status and to a lesser degree with weight status in the school-age group (5-10 years)<sup>117</sup>. Stunting in early childhood is thus likely to persist into adulthood; as corroborated by studies of the International Center for Research on Women (ICRW)<sup>139</sup> (see below).

### Adolescent Nutritional Status

Adolescent anthropometry at specific chronological ages varies significantly worldwide<sup>119</sup>. Many of the differences are attributable to variations in timing of the growth spurt. There is a dearth of detailed work on the specific cut-offs, predictive values and PARs of adolescent anthropometric indices<sup>127</sup>. Moreover, there are no reference data that are widely applicable to pregnant adolescents.

The most notable set of studies to date on adolescent nutritional status were carried out by the ICRW. Male and female prevalence of stunting, thinness and anaemia among adolescents were compared as part of a multicountry study<sup>139</sup>. Their findings, summarized here, are revealing. The prevalence of stunting or short stature (% below the 5th percentile National Center for Health Statistics/World Health Organization height-for-age reference) was between 27 and 65% in nine of the 11 studies. The stunting process occurs in early childhood, when rapid growth is supposed to occur. These children were stunted as they came into adolescence and their height-for-age did not improve across the eight years of adolescence. Gender differences were neither common, nor consistent where they did exist. Among eight studies, only two (Benin and Cameroon) showed worse male stunting, and only one (India) showed worse female stunting.

Thinness (percentage below the 5th percentile NCHS/WHO BMI-for-age) was highly prevalent (23-53%) in only three of the eight studies and, surprisingly, boys appeared to have at least twice the prevalence of girls in seven of the studies. BMI, unlike height, improved during adolescence for all girls, whatever their initial nutrition status at 10 years, but only among boys with low BMI at 10 years. This "improvement" may, however, be an artefact of late maturation, delaying the growth spurt in these developing-country adolescents as compared to the USA reference population. Moreover, the greater prevalence of thinness among boys suggests they were

more delayed, relative to their reference data, than girls were relative to theirs. This interpretation is supported by the observation that the linear growth of boys, unlike that of girls, had not stopped by age 19 years.

Anaemia was the greatest nutrition problem and was highly prevalent (32-55%) in four of six studies in which it was assessed. There was no gender difference in three of four studies in which it could be assessed. In the fourth study (Ecuador), more boys were anaemic than girls. Prior to the ICRW study, little research had been done on anaemia during adolescence, although its mean prevalence among adolescent girls in developing countries had been estimated at 27%<sup>140</sup>. Adolescent girls lose more iron through menstruation, but adolescent boys may need more per kg weight gained, because they build up relatively more muscle. The surprising gender difference in thinness may be because anaemia constrains the weight gain of boys more than that of girls. As adolescent growth slows, however, the iron status of boys improves; whereas that of girls tends to worsen, with more serious future consequences.

Adequate nutrition during adolescence implies adequacy of dietary intake and/or body stores of both macro- and micronutrients, with respect to the activity level of the individual. Dietary studies in adolescents have shown serious shortfalls in intakes. Among 13-15 year old girls in Haryana, India, for example, mean intakes of energy, protein, iron, riboflavin, niacin and vitamin A were all well below recommended intakes<sup>141</sup>. The widespread cultural constraints on the freedom of postmenarcheal girls to leave their home may limit their access to seasonal fruit, commercially-prepared foods, or other significant sources of dietary diversity<sup>142</sup>, while gender discrimination in intra-household food allocation may also limit their intake. Few studies have attempted to relate adolescent micronutrient status to LBW risk. With regard to activity level, adolescent girls are often already employed in full-time labour carrying out high intensity tasks. It is at this time that they begin to be given more responsibility for the multiple tasks culturally defined as female.

### Can Adolescents Catch-Up Incomplete Childhood Growth?

The question whether adolescents catch up incomplete childhood growth caused by undernutrition was studied by various authors; e.g. <sup>143,144</sup>. Four studies were carried out on undernourished children from poor families who were adopted, by age five, into middle-class families<sup>145</sup>. These adoptees did catch up lost

growth to some extent but not completely, even under optimal conditions. Such partial catch-up reflects the accelerated growth rates in adolescence and can also involve a longer period of fast adolescent growth when biological maturation is delayed because of previous undernutrition.

A study was made on the effects of adoption of poor Indian infants (81% LBW) into wealthy Swedish families soon after birth<sup>146</sup>. There was marked catch-up growth in childhood: mean stunting prevalence dropped from 62% to 20% after two years. However, the individual height and weight differences among these children at birth persisted into childhood. The mean adult height attained (154 cm) by the adopted Indian girls was just 1 cm greater than the mean height of poor adult women living in India, and significantly less than that for more affluent women in India (159 cm). Girls who were stunted when adopted in infancy, were also significantly shorter in adulthood than their peers who were not stunted at the time of adoption. The improved early childhood growth in these adopted girls hastened menarche considerably and shortened the period of rapid premenarcheal growth. This has been summarized thus: "what was gained in the swing (accelerated growth in childhood) was more than lost in the roundabout (shortening of overall duration of growth due to earlier onset of puberty)" <sup>147</sup>. Note, however, that only 8% of these adopted girls attained heights of less than 145 cm, with risks of obstetric complication, as compared to over 15% of women throughout Asia<sup>148</sup> and 12-25% of women in India<sup>149</sup>.

In addition to these studies of adoptees, there have been longitudinal studies (without interventions). In three out of four such studies<sup>143,150,151</sup> there was partial catch-up. The fourth<sup>144</sup> failed to show any catch-up. A cross-sectional study of a Kenyan population, living in adverse circumstances, found partial catch-up growth during adolescence, without a specific intervention<sup>118</sup>. The catch-up was due largely to delayed maturation.

Overall, there remains little evidence that growth retardation suffered in early childhood can be significantly caught up in adolescence. There are no known studies to determine whether growth-retarded children respond, with catch-up growth during adolescence to nutrition and health interventions<sup>127</sup>. When maturation is delayed in children who are malnourished on entering adolescence, the delay is usually for less than two years<sup>117</sup>, possibly not enough to compensate significantly for lost growth in childhood. Stunted children are more likely than nonstunted children to become stunted adults, while they remain in the same environment which gave rise to the stunting. Growth failure in early childhood manifested by stunting, may therefore be irreversible to a large extent<sup>145</sup>. Moreover, even if adolescent catch-

up growth could be stimulated by an intervention and stunting thereby reduced, this would not necessarily also rectify all the problems of earlier undernutrition, for which stunting is merely a marker. For example, a reduction in stunting would probably reduce obstetric risk due to small maternal size, but would not necessarily reverse the effects of early childhood stunting on cognitive function. This has been shown in a recent study in the Philippines<sup>152</sup>. Some catch-up growth was achieved between the ages of 2.0 and 8.5 years, among children who were up to two years of age, but their cognitive deficits persisted<sup>152</sup>. Early childhood stunting and its functional correlates can be addressed together only if the environment in which the young child grows is improved at that time; i.e., within the first two years of life<sup>145</sup>.

In a study of the reproductive lives of girls born during the Dutch famine and with adequate growth during childhood, it was shown that they gave birth to a higher proportion of IUGR babies than other Dutch cohorts<sup>153,154</sup>. IUGR may produce some prenatal insults to the foetal reproductive system that damages future reproduction, manifesting itself a generation later. In India, early childhood stunting among young girls was correlated significantly with the birthweights and mortality risk of their infants<sup>155</sup>.

In a Guatemalan study on adult women, whose nutrition status had been measured at three years of age, nearly 67% of severely stunted and 34% of moderately stunted three-year-old girls became stunted adult women<sup>156</sup>. Moreover, the prevalence of LBW was nearly doubled in infants of women who had suffered severe stunting ( $< -3$  Z-scores) at three years of age, compared to those who were not stunted ( $> -2$  Z-scores) at the same age. Women who had experienced greater growth retardation during childhood also had smaller body frames as adults, and were thus at greater risk of obstructed labour.

Examination of national anthropometric data, showed a strong correlation between prevalence of underweight in children under five years of age in the 1970s and the prevalence of underweight in adult women in the 1980s<sup>148</sup>. Furthermore, there were strong associations between underweight in adult women and LBW (1980), and between LBW (1988) and under-five child underweight (1990). These correlations are again broadly indicative of the tendency for smallness to be perpetuated across generations. Small girls do seem likely to become small women who have small babies. McCarrison may have been right, over 50 years ago when he said: "The satisfaction of nutritional needs in pregnancy begins with the antenatal lives of the mothers of our race" (quoted<sup>157</sup>).

## Intervening in Adolescence

Of the main factors found to be related to LBW risk, three - namely, the height and weight of the woman at the time of conception and her iron status and intake - would suggest the potential for improvement during adolescence. Let us examine feasible options.

### Improving Dietary Intake

There is very limited evidence for partial catch-up during the adolescent growth spurt (see above) and studies have yet to be undertaken to find out whether intervening would promote additional catch-up. It has been suggested that three important questions be asked before a food intervention (the most common) is considered<sup>139</sup>. First, how much height could be gained? The only study that comes close to answering this<sup>158</sup> showed that growth hormones were elevated in premenarcheal participants of a food intervention (i.e., there was the potential for faster growth). Height changes were not measured.

Second, is menarche hastened and, if so, what are the implications? If a food intervention succeeds only in hastening menarche and thus reducing the period of fastest growth (e.g.<sup>145,146</sup>), it may not increase height by much. If this possibility is avoided, by delaying the intervention until after menarche, can further pelvic growth be achieved in this later period of slower growth? A study in India has suggested not<sup>117</sup>: dietary intake after menarche was not associated with adolescent growth. Even if greater attained heights were possible with either of these two options, would this benefit the woman or future child?

Third, how much fat is gained simultaneously? Raising attained height, through a food intervention, would also increase body weight, including fat stores<sup>139</sup>. This would be advantageous to the thin and stunted adolescent, but might lead to overweight among girls who, though stunted, are not thin during adolescence. The ICRW studies<sup>139</sup> together suggest the need for caution here because, by age 18-19 years, few girls were thin, as assessed by BMI-for-age.

Existing knowledge therefore suggests that height gain during adolescence might not be feasible as a nutrition objective. In 1993, an International Dietary Energy Consultative Group (IDECG) workshop on the causes and mechanisms of linear growth retardation concluded that there was: "no evidence that intervention at the time of puberty has any special effect on linear growth and in any case it would not be justifiable to delay intervention until such a late stage. The time for intervention is early childhood, when growth is first becoming retarded"<sup>159</sup>.

Nevertheless, there are important potential benefits other than linear growth, from improving dietary intake. These include weight gain among thin adolescent girls, and improved micronutrient (particularly iron and folate) status, to improve their wellbeing in the present as well as their nutrition status during any subsequent pregnancy.

Adolescents have special needs and face particular challenges during pregnancy. Behaviour and culture, in addition to the nutrition and biological factors, influence the outcomes of adolescent pregnancies. In many cultures, adolescent girls are responsible for the majority of household duties, including caring for younger siblings, carrying water, and preparing meals for the family, among whom they are the last to eat. During pregnancy, these responsibilities become an even greater burden on the still growing adolescent girl, who may not be able to consume enough food to meet her energy needs. Pregnant adolescents may be less likely to admit they are pregnant and thereby may deny themselves proper nutrition and food. They may also delay seeking antenatal care for various reasons: lack of money; lack of power to make decisions regarding personal health; and poor treatment from health providers who are not sensitized to provide the particular care that pregnant adolescents require<sup>160</sup>.

There may be, however, particular opportunities for improving the nutrition status of adolescents. Their dietary practices may be more flexible than those of adults; and they may have fewer cultural constraints or restrictive taboos. School enrolment of female adolescents is usually higher than antenatal care coverage, facilitating coverage of supplementation schemes.

Promotion of a balanced diet during adolescence need not wait for the results of a longitudinal study. However, there would be value in investigating the effectiveness of food supplementation in raising prepregnant nutrition status among thin and stunted adolescent girls. Significant gains in height are unlikely, but it would be useful to know whether any significant gains in weight are achievable, among thin girls of low BMI-for-age, and by what means. Micronutrient status also could be investigated as an outcome. An example of a useful research design might be a longitudinal study to investigate the growth of three groups of adolescent girls: a) no intervention; b) food intervention; and c) food intervention, plus iron and folic acid supplementation and/or multivitamin-mineral supplementation.

### **Improving Iron and Folate Status**

The one clear area for likely benefits of a nutrition intervention is improving iron and folic acid status.

This improves current nutrition status, as well as increasing iron stores for girls who may soon become pregnant. Borderline iron stores before conception are the main cause of iron deficiency anaemia during pregnancy<sup>120</sup>. Given the difficulty of identifying early pregnancy, it might be too late to prevent neural tube defects if folic acid supplementation is delayed until pregnancy is known.

Most efforts have focused on controlling anaemia in pregnant women who can be reached through the health system. There is also a need for a more *preventive* approach: raising the iron stores of women before they become pregnant. The iron requirement of adolescent girls is: *“very difficult, if not impossible to satisfy even with good quality, iron-fortified diets”*<sup>161</sup>. Weekly supplementation of iron deficient non-pregnant women in California, USA, with 60 mg iron + 250 µg of folic acid for 7 months (30 tablets) was effective for controlling iron deficiency anaemia and improving iron status. The positive effect of iron supplements, especially if given daily<sup>162</sup> on iron stores is relatively temporary (about 6 to 12 months) so supplementation is best continued up to the time of conception and throughout pregnancy<sup>163</sup>.

A preventive, life cycle approach needs to be community-based, using different avenues for reaching different groups, including adolescent girls. New approaches should be monitored, evaluated and documented so that others can learn from success. Schools, health clinics, youth clubs and the media are all avenues through which such interventions can be promoted. Boys should be involved as well as girls, given the high rates of anaemia found in the multicountry ICRW study<sup>139</sup>.

### **Delaying First Pregnancy**

The first pregnancy should be delayed at least until adolescent growth has finished. Approaches might include: incentives to delay marriage until after 19 years of age; incentives for girls to stay in school; and disincentives to early sexual activity for boys and girls below 18 years of age. Article 1 of the Convention on the Rights of the Child<sup>164</sup>, defines under 18-year-olds as “children”, and should be used for vigorous advocacy on this issue.

However, a study of 19 countries, in which there has been at least a half-year rise in the average age of women at marriage, shows that there was no parallel increase in the time elapsed between marriage and first birth<sup>165</sup>. Urgency to marry and have children early is related to the precariousness of the status of girls rather than to fertility goals. The links between poverty and early childbearing in developing countries have been largely neglected, both in research and policy-making.

Laws and regulations should facilitate the availability of contraceptives to adolescents, and their use. Health agencies need to ensure access to confidential reproductive and sexual health information and services, protected by law. Information-education-communication (IEC) approaches for adolescents should be designed by adolescents, so as to be made more relevant. Peer motivation should be used to reinforce messages.

At a more basic level, the empowerment of women through sustained raising of their social, economic and educational status, would result in more value being placed on women's productive and social roles in society as opposed to reproductive roles. Improved education status, through staying in school, would also increase receptivity to family planning programmes. In India, approaches to raising the status of adolescent girls are being explored within the Integrated Child Development Services (ICDS) programme. These approaches involve vocational training, as well as direct nutrition support, and education geared to delaying marriage, but they have not yet been evaluated.

In summary, the most successful interventions will be those that provide a package of care to address the social and behavioural challenges faced by pregnant adolescents, in addition to providing nutrition education and antenatal care<sup>166</sup>. In developing countries, however, interventions must address the special needs of pregnant adolescents while developing long term strategies that focus on improving the nutrition status of girls during childhood, delaying marriage and first pregnancy, keeping girls in school, and empowering women.

## Summary and Conclusions

Asia has a higher prevalence of low birthweight (LBW, <2500 g) than any other continent, ranging from well over 30% in South Central Asia and Bangladesh. Much lower rates, <10%, are seen in the PRC, Thailand, the Philippines and Malaysia. The prevalence of LBW is strongly associated with the relative undernutrition of mothers in the region; about 60% of women in South Asia and 40% in South-East Asia are underweight (<45 kg). LBW is probably the main reason why over 50% of the children in Asia are underweight. It also increases the risk of other health and developmental problems. Interventions to reduce the prevalence of LBW should therefore receive very high priority.

The conclusions that can be drawn from randomized, controlled efficacy trials include the following.

- Only supplements that provided more energy caused a significant improvement in birthweight. Although the protein in these supplements provided up to 25% of the energy, the results of at least one study suggest that supplements containing no protein can increase birthweight. In that study, the supplement did contain some micronutrients, the intake of which covaried with energy intake. In populations where protein intake is adequate, providing high protein supplements (>25% of energy) to pregnant women may even increase neonatal death rates.
- Maternal supplementation can also increase maternal weight gain, infant head circumference and, when there is a serious energy shortage, the length of the newborn infant.
- The magnitude of the expected benefit from maternal supplementation in Asia remains to be determined but is expected to be considerable. The largest, well designed trial was conducted in The Gambia. From mid-pregnancy, locally produced biscuits providing 1017 kcal and 22 g protein per day reduced LBW prevalence by 39%, and increased birthweight by 136 g. In the season when maternal energy intake was most inadequate supplementation reduced LBW by 42% and increased birthweight by 201 g. The infant mortality rate fell by about 40%. Women in The Gambia are generally heavier (53 kg on average at enrollment) than those in many parts of Asia. This may provide some protection against LBW, but they may be more seriously energy deficient during the hungry season.
- For undernourished women, or those who have a low body weight (<40 kg), these improvements in pregnancy outcome could be obtained by encouraging them to consume more of their normal diet where possible, and/or providing appropriate energy-containing supplements. The supplements should ideally be formulated from local foods. Clearly any supplements should be consumed by the mother and not by other family members.
- Where the normal diet is particularly low in protein, or as is often the case, low in micronutrients, it is important to ensure that these nutrients are also provided as supplements.
- If targeting is desired, women with the lowest weight (at conception through early pregnancy) and/or lowest energy intakes may be most likely to benefit. Targeting interventions based on maternal BMI, skinfold thickness or height is unlikely to be more useful than targeting based on weight.

- There are conflicting data on whether supplementation during the second trimester vs. third trimester is most effective for improving birthweight. However, it is clear that supplementation during either trimester can reduce the prevalence of low birthweight. In The Gambia, supplementation did not start until 20-24 weeks of gestation and the biscuits were consumed for only 82 days on average. The total amount of energy provided by supplements during pregnancy is likely to be the most important factor, so that supplementation for the longest possible time becomes more critical where the amount of daily energy provided by supplements is lower.
- Young maternal age at conception is an additional risk factor for poor pregnancy outcome so that it is also important to target interventions to those who are still growing.
- Continued supplementation of the mother during her subsequent lactation and pregnancy may cause an even greater improvement in the birthweight of her next child.
- Whenever possible attention should be paid to improving the quality as well as the quantity of food consumed during pregnancy. There is little evidence from randomized controlled trials that supplementation with individual nutrients (including iron, zinc, folic acid, vitamin A and calcium) can improve birthweight, unless this is through a reduction in preterm delivery. However, supplementation of underprivileged pregnant women with micronutrients is certainly extremely important and can lead to substantial reductions in maternal anaemia, may reduce maternal mortality, birth defects and preterm delivery, and improve breastmilk quality and infant nutrient stores. Trials are ongoing to test the efficacy of providing supplements containing balanced amounts of multiple rather than single micronutrients.
- In areas of endemic iodine deficiency, adequate maternal iodine status is critical for the prevention of neonatal deaths, low birthweight and abnormal cognitive and physical development of the infant.
- Non-nutritional interventions that can improve pregnancy outcome include reducing energy expenditure in physical work, increasing age at conception, malarial prophylaxis and cessation of cigarette smoking.