Prevention of Low Birthweight

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Abstract

Globally an estimated 20 million infants are born with low birthweight (LBW), of those over 18 million are born in developing countries. These LBW infants are at a disproportionately higher risk of mortality, morbidity, poor growth, impaired psychomotor and cognitive development as immediate outcomes, and are also disadvantaged as adults due to their greater susceptibility to type 2 diabetes, hypertension and coronary heart disease. Maternal malnutrition prior to and during pregnancy manifested by low bodyweight, short stature, inadequate energy intake during pregnancy and coexisting micronutrient deficiency are considered major determinants in developing countries where the burden is too high. LBW is a multifactorial outcome and its prevention requires a lifecycle approach and interventions must be continued for several generations. So far, most interventions are targeted during pregnancy primarily due to the increased nutritional demand and aggravations of already existing inadequacy in most women. Several individually successful interventions during pregnancy include balanced protein energy supplementation, several single micronutrients or more recently a mix of multiple micronutrients. Nutrition education has been successful in increasing the dietary intake of pregnant women but has had no effect on LBW. The challenge is to identify a community-specific intervention package. Current evidence supports intervention during pregnancy with increased dietary intakes including promotions of foods rich in micronutrients and micronutrient supplementation, preferably with a multiple micronutrient mix. Simultaneously a culturally appropriate educational component is required to address misconceptions about diet during pregnancy and childbirth including support for healthy pregnancy with promotion of antenatal and perinatal care services. While further research is needed to identify more efficacious interventions, an urgent public health priority would be to select and implement an optimal mix of interventions to avert the immediate adverse consequences of LBW and to prevent the impending epidemic of type 2 diabetes, hypertension and coronary heart disease which are negatively associated with LBW.
Introduction

Globally an estimated 20 million or 15.5% of babies are born with low birthweight (LBW) defined as less than 2,500 g at birth with wide variations over different geographic locations [1]. However, over 90% of all LBW infants are born in developing countries and nearly a half of the total global burden of LBW infants is distributed in South Central Asian countries. LBW infants represent a heterogeneous group of infants which may result from suboptimal fetal growth relative to gestational age, called intrauterine growth retardation (IUGR) or small-for-gestational age (SGA), or too early delivery, called preterm delivery (<37 week of gestation). In general, IUGR is the predominant type of LBW in populations in poorer settings where the prevalence of LBW is high, whereas preterm delivery predominates in settings where the prevalence of LBW is low as in developed countries [2]. The distinction between these two entities has important programmatic implications as the determinants are often different and so are the interventions.

LBW has enormous consequences for health and survival. Infants born with LBW are at an increased risk of mortality, morbidity, poor growth, impaired cognitive function, decreased motor and psychomotor development [3–7]. The mortality gradient increases several fold as birthweight decreases [8]. LBW also greatly increases the risk of infant death due to other causes, such as acute lower respiratory infection, pneumonia and diarrhea [9, 10]. Although very high birthweight also increases the risk of mortality and morbidity, such incidences in developing countries are low. Infants born LBW due to IUGR remain shorter and lighter as adults [11] and may also suffer immune incompetence as older children and as young adults compared to normal birthweight infants [12, 13].

The long-term negative consequences of LBW are associated with the risk of type 2 diabetes, hypertension, and cardiovascular diseases in later life [14–16]. The elevated risk of these disease outcomes is not just limited to LBW but ranges across the distribution of birthweights [17–19]. LBW has huge economic costs which are related to excess mortality, morbidity and productivity loss due to the disproportionately higher rate of stunting and cognitive deficits among those who born LBW [20].

Extensive review of studies from developed and developing countries identified determinants of LBW and population-attributable risk associated with each major determinant [21]. Subsequent studies also reported similar determinants [22–24]. In developing countries maternal nutritional factors that include low pre-pregnancy weight, short stature, low energy intake during pregnancy, or low gestational weight gain are the major determinants [21]. Teenage pregnancy and morbidity are also important risk factors for LBW. Cigarette smoking and alcohol consumption are important determinants but they are more important in developed countries. In some settings HIV status and malaria are also important determinants, particularly in African
countries where HIV and malaria coexist with maternal malnutrition [25–27]. Micronutrients play an important role in the growth and development of the fetus. In communities where LBW exists as a significant public health problem, widespread maternal malnutrition [28, 29] coexists with multiple micronutrient (MMN) deficiencies [30, 31]. This chapter briefly discusses some interventions deemed to be successful and which can be considered in the prevention of LBW, mainly in developing countries where the burden is too high.

**Interventions for Prevention of LBW**

Success of public health interventions for the prevention of LBW depends on how well population-specific quantitatively important determinants are identified and targeted. Interventions with a life-cycle approach and targeting several generations are needed to alleviate this intergenerational effect. However, most of the interventions for LBW are targeted during pregnancy because the vulnerability of already existing dietary inadequacy is further aggravated during pregnancy. Major successful interventions which look at LBW as an outcome and have great relevance in developing countries include balanced protein energy supplementation, micronutrient supplementation (single or combination), and nutrition education.

**Food Supplementation and LBW**

Dietary deprivation during pregnancy has a negative effect on fetal growth. Studies on the Dutch Famine of 1944–1945 showed that, during the third trimester, pregnant women who were exposed to a severe energy-restricted diet delivered lighter babies than unexposed women [32]. This natural experiment provides strong justification for food supplementation during pregnancy in populations at risk of dietary inadequacy. A Cochrane Systematic Review of food supplementation trials during pregnancy concluded that only a balanced protein energy supplementation modestly increases birthweight and reduces the incidence of LBW [33]. The latest review of balanced protein energy supplementation trials included 6 trials which reported SGA as outcome and met the methodological criteria for the review (table 1). The trails represented populations from both developing (Taiwan, The Gambia, India and Columbia) and developed countries (Wales and USA). Although all the trials included were not similar in terms of timing and duration of supplementation, composition of the supplemental food, total energy content and allocation procedure, the homogeneity of effect with a lower relative risk for SGA was reported. All the trials, except the Gambian, obtained unity in the confidence interval for the relative risk due to the lack of adequate power. However, the pooled estimate showed a significant reduction (32%) in SGA in the intervention group. SGA infants
<table>
<thead>
<tr>
<th>Study</th>
<th>Population</th>
<th>Intervention</th>
<th>Treatment n/N1</th>
<th>Control n/N</th>
<th>Relative Risk (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Blackwell 1973</td>
<td>Taiwan</td>
<td>Supplemented: 40 g protein and 800 kcal/d plus vitamins and minerals Controls: vitamins and minerals</td>
<td>6/94</td>
<td>10/88</td>
<td>0.56 (0.21, 1.48)</td>
</tr>
<tr>
<td>Cessay 1997</td>
<td>The Gambia</td>
<td>Supplemented: 1,017 kcal energy, 22 g protein, 56 g fat, 47 mg calcium and 1.8 mg iron daily Controls: no supplement</td>
<td>69/620</td>
<td>94/553</td>
<td>0.65 (0.49, 0.87)</td>
</tr>
<tr>
<td>Elwood 1981</td>
<td>Wales</td>
<td>Supplemented: fat-free milk Controls: no supplement</td>
<td>27/591</td>
<td>27/562</td>
<td>0.88 (0.52, 1.50)</td>
</tr>
<tr>
<td>Girija 1984</td>
<td>India</td>
<td>Supplemented: 417 kcal energy and 30 g protein Controls: usual diet</td>
<td>0/10</td>
<td>5/10</td>
<td>0.09 (0.01, 1.45)</td>
</tr>
<tr>
<td>Mora 1978</td>
<td>Columbia</td>
<td>Supplemented: 865 kcal and 38.4 g protein Controls: usual diet</td>
<td>12/177</td>
<td>14/162</td>
<td>0.78 (0.37, 1.65)</td>
</tr>
<tr>
<td>Rush 1980</td>
<td>USA</td>
<td>Supplemented: 322 kcal energy and 6 g protein and vitamins/minerals Controls: vitamins/minerals only</td>
<td>30/265</td>
<td>43/264</td>
<td>0.70 (0.45, 1.07)</td>
</tr>
<tr>
<td>Total</td>
<td></td>
<td></td>
<td>1,757</td>
<td>1,639</td>
<td>0.68 (0.56, 0.84)</td>
</tr>
</tbody>
</table>

1 n = Number of SGA infants; N = total number in the treatment/control.
Reproduced with permission from Kramer and Kakuma [33].
are the major contributor to the LBW burden in developing countries. Apart from the lower incidence of LBW (39% reduction), the Gambian study [34] reported several other beneficial outcomes including increased gestational weight gain, fetal growth, and a reduction in stillbirth and neonatal death. Birthweight benefit was greater in the hungry season than in the wet season (more food available), and supplementation benefited malnourished women more than well-nourished women.

A few supplementation trials not included in the Cochrane Review also reported LBW as an outcome. In Guatemala pregnant women were given either a high or a low calorie supplement. Those who received the high calorie supplement delivered heavier babies and had a lower rate of LBW infants [35]. Energy supplementation during pregnancy in Indonesia with high or low (465 or 52 kcal/day) energy found increased birthweight and a lower incidence of LBW in both groups [36]. A dose-response relationship between energy consumption and birthweight was also reported. The risk of LBW was modified by maternal pre-pregnancy weight, with those weighing more than 41 kg having less risk than those weighing less.

In a recent randomized food and micronutrient trial in Bangladesh in which pregnant women were either assigned to early (1st trimester) or usual (2nd trimester) food supplementation, and further randomly assigned to one of three micronutrient supplements (30 or 60 mg iron plus 400 folic acid or the UNICEF-recommended 15 micronutrient mix) during pregnancy. The results showed no significant difference in birthweight or the incidence of LBW between the food or micronutrient groups. No interaction between food and micronutrient supplementation on birthweight was reported [Arifeen and Persson, 2005, unpublished observation]. This study did not have a control group since all participants received both food and micronutrient supplements. However, the mean birthweight was higher and the incidence of LBW was lower relative to that reported earlier from the same population [37]. Other important food supplementation trials during pregnancy include high protein or isocaloric protein supplementation but none of those trials showed any beneficial effect on LBW. However, high protein supplementation in the relatively well-nourished population was reported to be harmful [38].

Despite strong theoretical plausibility that population groups at risk of dietary inadequacy should benefit from food supplementation during pregnancy, the effect on birthweight has been modest although the effect on LBW, particularly on SGA, has been stronger. Some inherent limitations of supplementation trials need to be carefully taken into consideration when interpreting the findings, including poor documentation of the adequacy of the usual diet and poor quantification of the real contribution of supplemental food to the pregnant woman’s diet. Other issues also deserve attention in interpreting the findings including compliance, substitutions of usual diet, ‘eating down’ during pregnancy (fear of large baby), sharing with other
family members, improper targeting, and above all choice of supplement and its cost. It is also critically important to evaluate whether supplementation resulted in net energy balance which is important for a positive birthweight outcome.

**Micronutrient Intervention and LBW**

Maternal micronutrient status during pregnancy plays an important role in fetal growth [39–42]. MMN deficiencies among women of childbearing age, particularly during pregnancy, are widespread in developing countries [30, 31, 43]. Anemia during early pregnancy is associated with poor fetal growth [44, 45]. Anemia mainly due to iron deficiency is highly prevalent in non-pregnant and pregnant women in developing countries [46–48]. In an Indian community two thirds of pregnant women were found to have zinc or iron deficiency and over half of the women had both zinc and iron deficiency coupled with inadequate intake of those nutrients [31]. This clustering of MMN deficiency and dietary inadequacy supports the contention that intervention with MMNs is more preferable to a single micronutrient. Often combined micronutrient intervention is more effective than when given individually. For example, intervention with both vitamin A and iron has been shown to be more effective in reducing anemia and improving vitamin A status than iron or vitamin A supplementation alone [49]. In 1999 UNICEF/WHO/UNU recommended a multi-micronutrient mix in developing countries for supplementing pregnant women who are supposedly suffering from MMN deficiencies [50]. This multi-micronutrient mix has been promoted since then with the aim of reducing the incidence of LBW as one of the major outcomes [51].

A recent systematic review of the literature on the effect of micronutrients on fetal growth concluded that there was no significant effect of prenatal micronutrient supplementation on fetal growth [52]. However, the authors recognized the paucity of evidence from well-designed, adequately powered, randomized trials on the efficacy of a single micronutrient on birthweight or LBW as the outcome. Among single micronutrient supplementation trials only calcium and magnesium supplementation during pregnancy has been found to reduce LBW in selected population groups [52]. Iron supplementation with or without folic acid during pregnancy has been shown to improve iron status and reduce anemia, but no effect on birthweight or LBW has been reported [53]. One recent study in the United States reported that iron supplementation during pregnancy in iron-replete non-anemic women improved birthweight and reduced the incidence of LBW [54].

Results of MMN supplementation on birthweight and the incidence of LBW have been mixed. Some studies showed no additional benefits on birthweight or LBW over traditional iron folic acid supplementation and some reported the superior efficacy of MMN. However, more recent studies have consistently shown the superior efficacy of MMN supplementations over traditional iron folic acid in reducing the incidence of LBW (table 2).
A randomized trial in Nepal showed no additional benefit from prenatal MMN when compared to traditional iron and folic acid supplementation, although both groups had a lower incidence of LBW (MMN vs. iron and folic acid: 14 vs. 16% reduction) as compared to a placebo group who received vitamin A only [55]. Similar results were reported from a semi-urban community in Mexico [56]. One study in Zimbabwe reported a statistically nonsignificant decrease in LBW associated with MMN supplementation [57]. However, a more recent report from Nepal showed that prenatal MMN supplementation was associated with a 25% lower incidence of LBW than traditional iron folic acid supplementation [58]. Noticeably, the positive effect of MMN shown in Nepal selectively worked on heavier (normal BMI) women and female infants, which underscores the importance of pre-pregnant nutrition of women. In a randomized trial in Niger reported a 14% fall in LBW associated with MMN supplementation when compared with iron and folic acid supplementation [10]. The effect of MMN was even stronger in women who had a longer

<table>
<thead>
<tr>
<th>Study</th>
<th>Population</th>
<th>Intervention</th>
<th>Relative risk (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Christian et al. [55], 2003</td>
<td>Nepal</td>
<td>Vitamin A FA FA + I FA, I, Zn MMN</td>
<td>1.00 1.00 (0.88–1.15) 0.84 (0.72–0.99) 0.96 (0.83–1.11) 0.86 (0.74–0.99)</td>
</tr>
<tr>
<td>Ramakrishnan et al. [56], 2003</td>
<td>Mexico</td>
<td>I MMN</td>
<td>1.00 0.98 (0.55–1.74)</td>
</tr>
<tr>
<td>Friis et al. [57], 2004</td>
<td>Zimbabwe</td>
<td>I + FA MMN</td>
<td>1.00 0.84 (0.59–1.18)</td>
</tr>
<tr>
<td>Osrin et al. [58], 2005</td>
<td>Nepal</td>
<td>I + FA MMN</td>
<td>1.00 0.69 (0.52–0.93)</td>
</tr>
<tr>
<td>Zagré et al. [10], 2007</td>
<td>Niger</td>
<td>FA + I MMN Supplementation &gt;150 days FA + I MMN</td>
<td>8.4±8.9 7.2±5.9 6.7±10.4 3.8±6.1</td>
</tr>
<tr>
<td>Gupta et al. [59], 2007</td>
<td>India</td>
<td>FA + I MMN (29 vitamins and minerals)</td>
<td>1.00 0.30 (0.13–0.71)</td>
</tr>
<tr>
<td>Shankar et al. [60], 2008</td>
<td>Indonesia</td>
<td>FA+I MMN</td>
<td>1.00 0.86 (0.73–1.01)</td>
</tr>
</tbody>
</table>

I = Iron; FA = folic acid; Zn = zinc; MMN = multiple micronutrients.
duration (150 days or longer) of supplementation. The effect on LBW was also stronger among women whose pre-pregnancy nutritional status was poorer. MMN supplementation in malnourished pregnant women in India has been shown to be associated with a 70% reduction in the LBW incidence as compared to iron folic acid supplementation [59]. In Indonesia MMN supplementation during pregnancy was reported to be associated with a 14% lower risk of delivering a LBW infant than for those who received iron and folic [60]. The effect was stronger for MMN in women who were anemic on enrollment. One earlier study in Tanzania showed that HIV-infected pregnant women who were supplemented with multivitamins had a 44% lower risk of delivering a LBW infant than those who received a placebo [61]. Dietary intervention with micronutrient-rich foods has also been shown to increase birthweight and reduce LBW in a poor Indian community [62].

Trials of prenatal MMN supplementations are not exactly comparable in supplement composition, timing of allocation, and total duration of supplementation; however, homogeneity of the effect on LBW findings is noticeable. From a programmatic point of view increasing micronutrient intake is a greater challenge than simply increasing the overall dietary intake. Most of the dietary intake of micronutrients depends on the contribution from animal sources, which is relatively low in the diet of pregnant women in developing countries [63].
Nutrition Education and LBW

Cultural rules relating to food proscription and prescription during pregnancy and lactation have been described in many populations, and approaches that have been used to successfully promote diet and nutritional status have some important common elements [64]. Apart from food availability, dietary intakes during pregnancy are guided by other cultural beliefs, food taboos and behavior, and relate to birth outcomes. Often nutrition knowledge of diet during pregnancy is guided by misconception and folk beliefs [65]. Women in developing countries even reduce food intake during pregnancy, commonly known as 'eating down', to avoid having a large baby [66].

Although it is expected that increased energy intake should have a positive effect on pregnancy weight gain and birthweight, review of nutrition education intervention trials concluded that educational intervention is successful in improving the dietary intake of pregnancy women, reducing the risk of fetal and neonatal death, but has no effect on LBW [33]. However, nutrition education has been shown to reduce the incidence of premature deliveries, one of the major causes of LBW [67]. Nutrition education may also potentiate the effect of other interventions in lowering the risk of LBW [68]. The efficacy of nutrition education in reducing LBW needs to be evaluated with respect to its content, cultural appropriateness and social acceptance, and above all its effect on dietary intake and net energy balance.

Intervention for LBW and ‘Large Baby’ Issue

Interventions for increasing birthweight have been criticized for increasing the risk of possible cephalopelvic disproportion and therefore obstructed labor [69] which is dangerous for women in developing countries where most deliveries take place at home and emergency obstetric care is rarely available. Increased birthweight is often accompanied by an increase in head circumference. However, data from different studies show that a very small increase (less than a third of a centimeter) in head circumference occurs due to supplementation, which is unlikely to cause such a problem [34]. Supplementation in a malnourished population is also of concern as it might contribute to increased adiposity in the offspring, a risk factor for insulin resistance [70, 71]. This issue of food supplementation on body composition needs further research in different settings.

Conclusions

This chapter focuses mainly on successful interventions that have potential in the prevention of LBW in developing countries. Interventions for LBW should be considered in a much broader perspective than just considering its
immediate consequences. LBW is determined by multiple precipitating factors and lowering the incidence is obviously a formidable challenge particularly for resource-constrained developing countries. Improved dietary intake and micronutrient status before and during pregnancy are critically important in the prevention of LBW. Benefit from a single intervention seems to be small and unlikely to reduce the LBW burden effectively. This suggests that a population-specific optimal mix of interventions needs to be identified and implemented. However available evidence is sufficient to support a package of interventions that promotes increased dietary energy intake including micronutrients and culturally appropriate nutrition education that can remove misconceptions related to dietary intake during pregnancy and enhance mobilization of household resources to support healthy pregnancy. It is well documented that LBW is perpetuated through intergenerational effects, and therefore is strong justification for sustained effective interventions to improve maternal health and nutritional status for several generations. Thus household food security and intra-household food distribution issues with special emphasis on the diet of pregnant women require attention. Culturally appropriate nutrition education tools need to be developed, packaged and delivered to address the misconceptions related to diet, pregnancy and childbirth. While IUGR seem to respond well to intervention, preterm delivery is more complex and resilient to intervention and will require further research on the mechanistic aspects of this problem for identifying effective interventions. Prevention of LBW is an urgent public health priority not only for averting immediate adverse outcomes but also for preventing the impending global epidemic of diabetes, hypertension and cardiovascular diseases, which are negatively associated with size at birth.

References

Prevention of Low Birthweight


Alam

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Discussion

Dr. Kalhan: I have two questions. The outcome measures we are looking at, birthweight, head circumference, for example, are complex functions of a very large number of factors which may be related to a single micronutrient or to an array of micronutrients. Therefore are we realistic when we say that supplementing with zinc alone will solve the problem of head circumference, for example? I always have problems with these data that supplementation assumes that the society has a state of insufficiency. My second question is, when the meta-analyses were done, were these studies assuming that there is a state of insufficiency or do they correct for the state of sufficiency versus insufficiency? Assuming that the mother has an adequate caloric intake, the question that arises is whether supplementing another 300 kcal of energy is going to resolve the problem? My intuitive feeling is that if I give 300 kcal in a Western society, that is already eating plenty, it is probably not going to have any effect.
**Dr. Alam:** May I answer your second question first? The literature on food supplementation does not contain any information on the adequacy of a woman's usual diet, and therefore whether a 300-kcal/day supplementation would be sufficient to resolve the problem is hard to say. It has been observed that high protein supplementation in healthy women can even have a negative effect on birthweight. Of course while doing meta-analyses the authors set some criteria and they cannot go back. If the information regarding adequacy is not provided by the authors of the individual publications, then it is impossible to find, and most of the publications lack that information. But from the food balance, food distribution or food consumption data, population groups in which the low birthweight (LBW) burden is high have diets which are inadequate in both macro- and micronutrients. Regarding your first question whether a single micronutrient or single supplement could be effective in reducing the incidence of LBW: as you rightly mentioned it is a very complex issue. Evidence in the literature shows that an inadequacy of certain micronutrients coexists or is associated with a high prevalence of LBW and supplementation of women during pregnancy is often targeted to deal with micronutrient deficiency. LBW is a multifactorial outcome and just a single or multiple micronutrient intervention is not the full solution to the problem; probably a comprehensive package of interventions is required to reduce the burden.

**Dr. Sesikaran:** With iron and folic acid supplementation, most of the studies have shown benefit, haven't they?

**Dr. Alam:** Prenatal iron and folic acid supplementation has so far not been shown to influence birthweight and LBW, although they have other maternal benefits like improved iron status in iron-deficient women and a reduced incidence of anemia. However, one very recent study in the United States reported that iron supplementation in iron-replete non-anemic women improved birthweight and reduced the incidence of LBW [1].

**Dr. De Curtis:** I would like to know if in the studies in developing countries were carried out using regional neonatal growth charts or charts from developed countries? In Italy, for example, we have seen that there is a difference in birthweights between Italian newborns and those of families coming from developing countries. Moreover we have seen that in the last decades there has been a change in the percentage of SGA infants. I would like to underline that IUGR and SGA are not the same thing. An SGA newborn is an infant with a birthweight below the 10th percentile, while an IUGR baby is an infant who presents growth restriction during pregnancy which is detectable only with prenatal ultrasound. Therefore, I think that in developing countries it is perhaps better and easier to speak only of SGA.

**Dr. Alam:** I accept your comment. We reviewed studies which looked at LBW as the outcome. We didn't take into account whether the LBW infants were SGA or appropriately grown. A normal birthweight infant may also be SGA. Use of a regional growth chart is a debated issue.

**Dr. Rahman:** You have shown us the positive effect of using these micronutrients in combination during pregnancy to prevent LBW. Would you like to tell us which period of gestation is best to give those micronutrients, what amount should be given, and for how long?

**Dr. Alam:** It is quite difficult to comment on the appropriate timing, choice of combination of micronutrients, dose, and duration to have maximum benefits. Kramer's [2] meta-analysis showed that maternal nutrition before entering pregnancy is a major determinant of LBW. So in my view, a lifecycle approach is more important than targeting a narrow window during pregnancy with any combination of supplementation. The current pregnancy should not be neglected because a better outcome is needed to ensure a heavier and healthier baby, and this should continue to ensure healthier
babies in the next generation. The target of supplementation should not be making babies too big but ensuring optimal growth and development.

Dr. Agarwal: We published two national studies, one in the Indian Journal of Medical Research [3] and one in Indian Pediatrics [4]. There are two programs in India, one of which is integrated in the child development services. Two centers were chosen, in Hyderabad and Varanasi, to evaluate the impact of supplementation to pregnant women, and the final observations were analyzed on more than 6,000 deliveries in Varanasi. The women selected were deprived and of lower socioeconomic status. Food supplementation showed two things: women gain a mean of 100 g weight and the birthweight gain was about 65 g. This worked very well. The second program is a controlled national anemia program. We also evaluated this program which was run at 5–6 centers in the country to see what the impact was. Iron folate supplementation worked, birthweight increased, maternal iron stores increased as assessed by ferritin, and C-reactive protein was reduced. We came to the conclusion that instead of 60 mg we should raise the supplement to 100 mg. So the Indian national iron prophylaxis tablet contains 100 mg iron and 400 µg folate. All this work has been reported in the Indian Journal of Pediatrics and the Indian Journal of Medical Research. In 2003 and 2004 I surveyed maternal nutrition and anemia in 7 states of this country. To summarize in Himachal Pradesh the results were tremendously good, and what I learned from there is that a doctor will examine a pregnant women 3 times during pregnancy and delivery will be conducted by the doctor. Maternal mortality is lowest in Himachal Pradesh, there is no severe anemia, the anemia prevalence is low, and the LBW incidence in the Indian subcontinent is lowest in Himachal Pradesh. So the achievement is that during antenatal care, we only gave folate iron and it worked. A little more can be found on the internet about studies in the poor countries like ours.

Dr. Alam: Thank you for sharing this information. I used mostly a high-quality review level and some literature that was not included in those reviews. We should carefully look into these Indian experiences and evaluate the findings.

Dr. Christian: The meta-analysis that you showed on balanced protein energy supplementation, you said that it did not include the Gambia CC trial but in fact it does, the trial by Ceesay et al. [5], and it was highly weighted. Can you talk a little bit about the MINIMat trial from Bangladesh, and the lack of impact of food supplementation that you saw in that study? Given the high rates of LBW in that population and we know those women also had low BMIs and stunting, etc., why did you not see any benefit of food supplementation?

Dr. Alam: I accept your first comment, but the meta-analysis did not include the West Kiang trial which is what I meant. I will try to answer to your second question about the MINIMat [6] as I am also a part of the investigating team. Unfortunately we haven’t been able to publish the work yet. As you know, it was not intended as a supplementation trial because the government program was distributing food, the equivalent of 600 kcal made of rice powder, pulse powder and a little bit of molasses mixed together. It was distributed through community nutrition centers to malnourished pregnant women (BMI <18.5). What the ICDDLB study did was to modify the government program a little bit. Some publications have shown that normally malnourished women cannot respond quickly to supplementation because they have a lot of deficit to replete, and maternal–fetal transfer only occurs when the maternal need has been satisfied. Pregnant women were identified by pregnancy testing in the community (<8 weeks gestation) and were invited to the clinic where pregnancy was further confirmed by ultrasound. Then they were randomly allocated to food supplementation early (1st trimester) or usual (2nd trimester), and further randomly assigned to iron (60 or 30 mg) and folic acid (400 mg) or the UNICEF recommended multiple micronutrients mix [7]. As all women received both food and micronutrient supplements, we
did not have a true control group. In fact, there is evidence that women who attended the supplementation center shared this with their young children who loved the food more than the mothers actually did. We did not find any difference in energy intake as measured by repeated 24-hour dietary recall between supplemented and non-supplemented subjects. So it means that even though they attended the clinic or received the supplement, it did not affect the amount of energy in the total diet of the women; so it is obvious that the effect might not be there. On the other hand, we looked at the correlation between energy intake and birthweight where we found a positive correlation; it could be interpreted that the increased energy intake had a positive effect, although supplementation failed to show that. With respect to the multiple micronutrient and iron issue: as you did the first analysis from Nepal you know the results better than I, and we did not expect very much difference from that. Neither food supplementation nor micronutrient supplementation was associated with birthweight or the incidence of LBW.

*Dr. Ganapathy:* Just on iron and zinc, the micronutrient issue. There is an interaction between zinc and copper and zinc and iron. I think we should know about this as zinc can give rise to hypochromic microcytic anemia by blocking copper, and zinc can also prevent the absorption of iron. So it requires a very optimal ratio of iron to zinc if you want both of them to get into your system.

*Dr. Kikafunda:* You correctly said that the birthweight should, if possible, be kept around the median. That is good. However, although the lower limit of 2,500 g is strictly observed, I believe we should also set an upper limit and observe it. I fear that tomorrow somebody is going to come up with the theory that these bigger babies will have problems in the future. Especially in urban areas, the rate of cesarean births has greatly increased in recent times. I am not saying that cesarean births are the result of large babies, but I am sure that it is one of the factors.

*Dr. Alam:* Thank you very much for raising this issue that we should also look at the right side of the distribution; having too many big babies can cause not only perinatal problems, but may also cause some adverse health outcomes. Barker [8] and subsequent studies [9] have shown that there is a linear trend of a decreased risk of diabetes, cardiovascular disease and other health outcomes. But recent publications on diabetes show that there is a relationship between birthweight and type 2 diabetes, but the safer range is between 3,000 and 4,000 g [10], and an increased risk is associated with birthweight beyond that limit. So too a large baby is obviously an issue.

*Dr. Prentice:* I wonder if I could make a little comment here; I think there is a great deal of misunderstanding. Dr. Alam has just described the shape of the curve for birthweight and diabetes. If we look at the shape of the curve for birthweight versus neonatal mortality, which obviously would include a lot of those obstetric difficulties, then in fact if we set for any individual community at unity for a birthweight of 3,000–3,500 g then the odds of neonatal mortality continue to decrease as birthweight increases. As you go to 3,500–4,000 g it goes down to about 0.6; from 4,000 to 4,500 g it goes down to about 0.5, and you have to go up to very high birthweights before you start to see an increase in those neonatal mortality rates. Furthermore as Dr. Alam pointed out, the trials so far have shown no significant effect overall in the Cochrane analysis of increased head circumference. Perhaps head circumference is not the key measure, you may need to measure the chest circumference as well, but even in our trial where we have shown a significant increase, the increase was 0.3 cm, i.e. a diameter increase of 1 mm which I find difficult to imagine that that is going to increase any problems of CPD. And finally the thing we should concentrate on is that with any intervention trial we are trying not to promote abnormal growth, we are trying to prevent LBW.
Dr. Polberger: I have a question about chorioamnionitis or placental inflammation which seems to be an emerging cause of LBW and preterm birth. Is this a worldwide problem?

Dr. Alam: Chorioamnionitis or placental insufficiency may cause preterm delivery, which has not been well investigated.

Dr. Polberger: I mean chorioamnionitis or inflammation.

Dr. Alam: Yes, it is a cause of prematurity. There are a lot of publications showing that bacterial vaginosis or even asymptomatic urinary tract infection can increase the risk of preterm delivery. But treatment of these conditions does not have any effect on preterm delivery. Also in the MINIMat trial in Bangladesh, a randomized trial with metronidazole for those who had asymptomatic bacterial vaginosis and those who were symptomatic or syndromically classified as having bacterial vaginosis did not make any difference in preterm delivery.

Dr. Sesikaran: I think many of these studies have not taken the placental factors which could influence LBW into consideration. We have done a study where we compared the medical termination of pregnancy in terms of mothers who are underweight compared with mothers who are normal weight, and we looked at the placenta. A lot of factors seem to play a role in causing placental insufficiency: villous density, the number of blood vessels per villi, and the number of syncytial strokes, and several factors take place in underweight mothers in trying to improve the placental circulation to the baby. So in many supplementation studies we are probably not succeeding. No one has really looked and seen whether there are any other factors which could interfere with the full benefit of the supplementation, but rather blamed the supplementation that it did not work. So your point is very well taken and it needs to be looked into as far as placental function is concerned.

References
