Maternal nutrition & low birth weight - what is really important?

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The prevalence of low birth weight (LBW) is higher in Asia than elsewhere, predominantly because of undernutrition of the mother prior to and during pregnancy. There are qualitative differences in dietary requirements during early and late pregnancy - micronutrients and proteins required in early pregnancy, and calories and other nutrients later. A paradigm shift from efforts to improve size at birth, to efforts to improve foetal growth and development might provide fresh insight into the problem. Micronutrient deficiencies during pregnancy have been shown to have serious implications on the developing foetus. Nearly half the pregnant women still suffer from varying degree of anaemia, with the highest prevalence in India, which also has the highest number of maternal deaths in the Asian region. Of specific concern is compliance with iron supplementation, cultural beliefs regarding diet in pregnancy, and the issue of nutrition supplementation and fortification. The coexistence of risk of LBW or intra uterine growth retardation (IUGR) associated with essential fatty acid docosahexaenoic acid (DHA) and vitamin B12 intake or status observed in the Indian sub-continent also requires further examination. There is a significant protective effect of higher maternal education (beyond high school). Optimal weight gain during pregnancy and a desirable foetal outcome may be a result of synergistic effects of improved food intake, food supplementation, improved micronutrient intake, education and the environment of the pregnant woman and her family.

Key words Education - energy - IUGR - low birth weight - maternal nutrition - micronutrients

Introduction

The period of intrauterine growth and development is one of the most vulnerable periods in the human life cycle. The weight of the infant at birth is a powerful predictor of infant growth and survival, and is dependent on maternal health and nutrition during pregnancy. Low birth weight (LBW) is defined as weighing less than 2,500 g at birth. In developing countries, including India, the majority of LBW infants because of intrauterine growth retardation (IUGR) are born small at term (> 37 wk of gestation) with only 6.7 per cent born prematurely. Low birth weight leads to an impaired growth of the infant with its attendant risks of a higher mortality rate, increased morbidity, impaired mental development, and the risk of chronic adult disease. Infants who weight 2,000-2,499 g at birth have a four-fold higher risk of neonatal death than those who weight 2,500-3,499 g. The more severe the growth restriction within the LBW category, the higher is the risk of death. LBW is a strong predictor for size in later life because IUGR infants seldom catch-up to normal size during childhood. Other important
causes could include maternal infections, low maternal nutrient intake, higher nutrient losses, and/or increased nutritional requirements during pregnancy. Maternal nutrition is an important factor from a public health point of view because it is modifiable and therefore susceptible to public health interventions. There is, therefore, an urgent need to determine ways and means to prevent LBW and its consequences. This paper reviews maternal nutritional and socio-economic factors and their role in low birth weight and IUGR.

Maternal anthropometry and pregnancy outcome

The causes of low birth weight are complex and interdependent, but the anthropometry of the mother and her nutritional intake are thought to be among the most important. Pre-pregnancy weight, body mass index (BMI) and gestational weight gain all have strong, positive effects on foetal growth suggesting that energy balance is an important determinant of birth outcomes. The WHO collaborative study on maternal anthropometry and pregnancy outcomes, using data from 111,000 women from across the world reported that mothers in the lowest quartile of pre-pregnancy weight carried an elevated risk of IUGR and LBW of 2.55 (95% CI 2.3, 2.7) and 2.38 (95% CI 2.1, 2.5) respectively, compared to the upper quartile. Attained maternal weight at 20, 28 or 36 wk of gestation showed even higher odds ratios for IUGR of 2.77, 3.03 and 3.09 respectively when women were compared between quartiles of highest to lowest attained weight. This is possibly because it considers weight gain in pregnancy including that of the foetus. Women in the lowest quartile for both pre-pregnancy weight and weight gain during pregnancy were found to be at highest risk (up to week 20, OR 5.6; up to week 36, OR 5.6) of producing an IUGR infant. A study in India reported the odds ratio for LBW among Indian mothers to be three times more in severe chronically energy deficient (CED) low BMI groups when compared to normal BMI groups. A prospective pregnancy cohort study carried out in Bangalore, India, confirmed that a low maternal weight at baseline and poor weight gain in the second trimester to be important predictors of IUGR after controlling for potential confounding variables. Low maternal body weight had an association with higher risk of IUGR of marginal significance (AOR: 1.62; 95% CI: 0.83, 3.15; P=0.09). There was a very strong inverse association between weight gain per week during the second trimester and IUGR in both univariate and multivariate analyses. Compared with women in the highest quartile, the adjusted odds of IUGR was higher in women in the first quartile (AOR: 3.98; 95% CI: 1.83, 8.65), second quartile (AOR: 2.07; 95% CI: 0.94, 4.53) and third quartile (AOR: 1.32; 95% CI: 0.58, 3.03). Weight gain per week in the second trimester was <0.3 kg in 70 per cent of mothers who delivered IUGR babies. Lower weight gained in the third trimester was not associated with higher risk of IUGR. This study demonstrated that a low weight gain for even brief periods during pregnancy places the foetus at risk for IUGR. Abrams and Selvin also demonstrated that low maternal weight gain in the second trimester (<5.7 kg) was associated with decreased birth weights ranging from 48 to 248 g, depending on the pattern of weight gain in the other trimesters. Clearly improving maternal weight prior to conception and pregnancy weight gain are potential strategies to improve birth weight.

Effect of socio-economic status

Studies worldwide have examined the effect of socio-economic status (SES) indicators, including maternal education, on birth weight and IUGR. Maternal illiteracy and low SES have been shown to be major risk factors for IUGR. In the developing world, lacking proper health systems and resources, the level of maternal education may be of prime importance in the determination of health outcomes of mothers and their infants and children. In the Bangalore cohort study, a decreasing trend of IUGR was observed with an increase in maternal education, ranging from 46 per cent in women who had no schooling to 19 per cent in women who had a post-graduate education (T. Sarah, unpublished observations). In addition, the odds of IUGR for women with a high school education or below was 1.5 (95% CI: 1.04, 2.17) when compared to those with pre-university education, thereby underlining the importance of maternal education in determining a host of health-related behaviour/practices. It is important to understand that while achieving the universal primary education is laudable for India, promoting education to higher levels should be the ultimate goal. Factors relating to the care of women, environmental hygiene and sanitation, household food security, and poverty are all likely to operate simultaneously with a low level of maternal literacy in the aetiology of low birth weight and IUGR.

Macronutrient supplementation during pregnancy

An adequate nutrient supply to the foetus is an important area of research while investigating interventions to enhance birth weight. There is
controversy on whether dietary macro- and micro-nutrient supplementation in pregnancy can increase birth weight. A meta-analysis showed only modest increases in maternal weight gain and foetal growth following dietary supplementation13.

Evidence from systematic reviews of randomized controlled trials on the effectiveness of nutritional interventions aimed at reducing IUGR has demonstrated the beneficial effects of macronutrient (protein/energy) supplementation, with an overall odds ratio of 0.77 (95% CI 0.58, 1.01) for reducing IUGR14. Supplementation was associated with increases in maternal weight gain and mean birth weight, and a decrease in the number of LBW babies of borderline significance. A community based trial in rural Gambia showed that supplementing pregnant women with a high-energy groundnut snack significantly increased birth weight15. Supplementation significantly increased birth weight (by 136 g, P<0.001). Birth length was not affected. The effect of supplementation on birth weight was primarily achieved through a reduction in the number of babies who were “small for their dates,” rather than a reduction in prematurity, as gestational age was not affected. Over the whole year, supplementation reduced the prevalence of low birth weight from 17.0 to 11.1 per cent. However, data on the effects of maternal malnutrition on birth outcomes in 797 mothers in rural India found no relation between maternal energy and protein intake, but instead demonstrated a stronger relationship with dietary intake of micronutrient-rich foods16.

Effect of vitamin B12 and folate

Recently, interest has turned to specific micronutrients as possible limiting factors for foetal growth. The effect of micronutrients in significantly decreasing the risk of low birth weight has also been demonstrated in randomized trials of multiple micronutrient supplementation of HIV-infected pregnant women in Tanzania17 and more recently in pregnant mothers in Nepal18. Data concerning the effects of maternal malnutrition on birth outcomes in rural India have been reported in a prospective study of 797 rural Indian mothers, where birth size was strongly associated with consumption, at week 28 of gestation, of green leafy vegetables (P<0.001) and fruits (P<0.01) even after adjustment for potentially confounding variables16. Erythrocyte folate at week 28 of gestation was also positively associated with birth weight (P<0.001) with no association between size at birth and maternal energy and protein intake.

Greater clarity on the determinants of IUGR would be obtained by the study of a more heterogeneous population, varied in their demographics, socio-economic status, access to food and variability of actual food intake, a situation likely to exist in urban women in developing countries. Data generated from the cohort of pregnant women in urban Bangalore, India, showed that women in the lowest tertile for serum vitamin B12 concentration during each of the three trimesters of pregnancy had significantly higher risk of delivering an IUGR baby (AOR, 5.98, 9.28 and 2.81 for trimesters 1- 3, respectively), when compared to women in the highest fertile19. An intriguing possibility is that of poor bioavailability of oral vitamin B12 intake. An earlier study reported negative correlations between birth weight and maternal vitamin B12 levels at delivery in smokers in a Western group of women19. An association between low serum and amniotic fluid concentrations of B12 and neural tube defects has also been reported20. It is now known that the prevalence of vitamin B12 deficiency is high in the Indian population, with metabolic evidence of deficiency in 75 per cent of young urban Indian men and women, in whom less than 5 per cent had both folate deficiency and anaemia21. It may be important to look into the potential role of vitamin B12 deficiency in elevating plasma homocysteine (Hcy) levels in pregnancy, and its implications for adverse pregnancy outcomes including low birth weight22. Methionine synthase is an enzyme which catalyzes the methylation of homocysteine to methionine using vitamin B12 as a cofactor and methylenetetrahydrofolate as a substrate22. Formation of methionine through this pathway represents an important component of the one-carbon metabolism for synthesis of phospholipids, proteins, myelin, catecholamines, DNA and RNA. A deficiency of either vitamin B12 and/or folic acid is likely to affect this pathway resulting in an elevation of plasma Hcy with a relatively low methionine level. Murphy et al24 have reported that mothers in the highest tHcy (total homocysteine) tertile at 8 wk of pregnancy had three times (OR: 3.26; 95% CI: 1.05, 10.13) and at labor had nearly four times (OR: 3.65; 95% CI: 1.15, 11.56) the odds of giving birth to a neonate in the lowest birth weight tertile. Additional studies are needed to elucidate the role of vitamin B12 together with homocysteine in the prevention of adverse outcomes, particularly IUGR.

Vitamin B12 concentration in the neonate (cord serum) was significantly higher than, but correlated to levels in the mother, at all trimesters of pregnancy25,26.
In general, both maternal and foetal vitamin B12 levels in Indians were lower than that reported in western subjects 25,26. This may be linked to their lower dietary vitamin B12 intake as has been suggested in ovo-lacto vegetarians and low-meat eaters. Cord serum vitamin B12 levels were linearly associated with birth weight, such that increasing cord levels were associated with increasing birth weight. An interesting association has also been observed between birth weight and cord serum B12 of term infants with a gestational age of 37-39 wk, but not in infants who were delivered at >40 wk gestation 26. It is known that as pregnancy extends post-term, the incidence of placental insufficiency and foetal postmaturity (dysmaturity) increases rapidly as a consequence of reduced respiratory and nutritive placental function 27. Postmaturity is correlated with an increased incidence of placental lesions, foetal hypoxia-asphyxia, intrauterine growth retardation, increased perinatal death, and neonatal morbidity. At the biochemical level, placental physiopathology in post term-post mature pregnancies is not well understood, however, it can be speculated that the relationship between blood nutrient levels and birth weight might be confounded by poor placental function in late term pregnancies.

**Iron status and pregnancy**

Iron deficiency is the most commonly recognized nutritional deficiency in both the developed and the developing world. It is estimated that < 50 per cent of women do not have adequate iron stores for pregnancy. Requirements for absorbed iron increase during pregnancy from 0.8 mg/day in the first trimester to 7.5 mg/day in the third trimester. Average requirement during the entire gestation is approximately 4.4 mg/day. An adequate iron balance during pregnancy implies body iron reserves of >500 mg at conception. The physiologic iron requirements in the second half of gestation cannot be fulfilled solely through dietary iron 28. Iron deficiency anaemia has been shown to be associated with low birth weight and preterm delivery 29,30. Data from Shanghai suggested that the effect of maternal anaemia on preterm delivery was the most detectable during the 1st trimester, before maternal plasma volume expanded 31.

The mechanisms that operate by which poor iron status may affect birth weight and preterm births remains poorly understood. A few tested hypotheses are (i) poor iron status may affect immune function adversely and thus increase the host susceptibility to genital tract infections, (ii) iron deficiency may increase the stress hormones norepinephrine and cortisol, (iii) low haemoglobin concentrations may cause chronic hypoxia, which can activate the body’s stress response and thus increase circulating levels of corticotrophin-releasing hormone, and (iv) iron deficiency may increase oxidative stress of the placenta 32. Randomized trials of iron prophylaxis during pregnancy have demonstrated positive effects on reducing low haemoglobin and haematocrit, and increasing serum ferritin, serum iron and other measures, including bone marrow iron 33.

A placebo-controlled study from Nepal with a high prevalence of iron deficiency demonstrated that a supplement of 60 mg of ferrous iron and 0.4 mg of folic acid daily from 11 wk gestation significantly increased the birth weight 34. A placebo-controlled study from Cleveland demonstrated that 30 mg of ferrous iron daily in pregnancy, started before 20 wk of gestation, gave a significantly higher birth weight compared with the placebo group 35. The results of these studies suggest that to obtain a maximum effect on birth weight, iron supplements should be started in early pregnancy 29,34,35. However, evidence is insufficient to prove that iron deficiency plays a causal role in poor pregnancy outcome 36. The debate concerning prophylactic iron supplementation to pregnant women is still controversial and there exists no consensus on this important issue.

**Effect of essential fatty acids**

Docosahexaenoic acid (DHA; 22:6n-3) and arachidonic acid (AA; 20:4n-6) are essential long chain polyunsaturated fatty acids (LCPUFA) of the n-3 and n-6 families that are important structural constituents of the highly specialized membrane lipids of the brain and the human central nervous system, critical for normal growth and development. DHA is particularly found in the membranes of neuronal synapses and in the outer segments of retinal rods and cones where it constitutes 50 per cent of the total PUFA 37,38. During pregnancy, accretion of maternal and foetal tissues occurs and consequently the LCPUFA requirements are high. The developing human foetus accumulates as much as 400 mg DHA per week during the last trimester 39, most of which is incorporated into the structural lipids of the developing brain 40,42. Because the foetus depends primarily on placental transfer of these fatty acids, it is important that maternal LCPUFA status and supply is adequate to meet foetal requirements 43. In the early 1990s, positive associations between maternal fish intake and birth weight were found during pregnancy in Danish
fish eating communities\textsuperscript{34,45}. In the same population, Olsen and Secher\textsuperscript{46} more recently demonstrated a strong negative association of fish intake with the risk of both low birth weight and preterm delivery. Populations that consume largely cereal based diets with little or no seafood such as in India, depend on the consumption of plant sources of essential fatty acids (EFA), \(\alpha\)-linolenic acid (ALA; 18:3n-3) and linoleic acid (LA;18:2n-6) and their endogenous conversion to DHA and AA, respectively. However, there is evidence to suggest that there may be an inefficient conversion of ALA and LA to their respective LC PUFAs and that both ALA and LA compete for the same desaturation and elongation enzymes for conversion to DHA and AA\textsuperscript{47,48}. Recent data also suggest that the absolute amounts of ALA and LA in the diet determine ALA conversion in the body\textsuperscript{49}, and not their ratio, as previously believed\textsuperscript{50}. Consequently, the adequate consumption of food sources rich in both n-3 and n-6 fatty acids may be important to maintain their status in the pregnant mother. In Bangalore, south India, overall intakes of fish and of DHA and AA were very low\textsuperscript{51}. Median fish intakes were about 5-10 times lower than those reported in Danish pregnant women\textsuperscript{46}. Consequently, long chain n-3 fatty acid intakes were also proportionally lower (by 100 fold or more) than in the diets of western pregnant women. Muthayya et al\textsuperscript{51} also found increases of between 100 and 200 g in birth weight between the lowest and highest fish/DHA intake groups. Women who did not eat fish during the 3rd trimester had a significantly higher risk of LBW (OR: 2.49, \(P=0.019\)). Similarly, low EPA intake during the 3rd trimester had an association with a higher risk of LBW (OR: 2.75, \(P=0.011\)). Low maternal intakes of fatty acids that are critical for foetal growth and development are a matter of concern in this population. This underlines the need for further investigation of the potential of marine foods and/or n-3 PUFA in improving foetal growth in India, where low birth weight affects nearly 30 per cent of the infants. DHA and AA concentrations are increased in the foetal circulation because of preferential transfer by the placenta from the mother to the foetus\textsuperscript{52}. The foetus is also able to synthesize DHA from its fatty acid precursor; however, this ability (measured soon after birth) may be impaired in IUGR infants\textsuperscript{53}. The mechanism of action of DHA in improving foetal growth may be linked to its effect on endothelium\textsuperscript{54}. DHA increases flow mediated vasodilation in young adults\textsuperscript{55}, and improves membrane receptor activity probably through improvements in membrane fluidity\textsuperscript{56}. Therefore, it is possible that these fatty acids may increase foetal growth rate by increasing placental blood flow through the ratio of biologically active prostacyclins to thromboxanes and reduced blood viscosity\textsuperscript{57}.

**Body composition of the neonate**

In Indian infants, increasing birth weight must be evaluated with regard to their body composition at birth, since they are thought to have a similar amount of fat (assessed by one or two skinfold thickness) as western children have, even though their body weight is lower\textsuperscript{58,59}, leading to their characterization as “thin-fat”. This relatively greater adiposity of Indian children is of interest in view of the possible effects of foetal programming that could occur in later life. Follow up studies of Indian children have suggested that skinfold thickness track into early childhood\textsuperscript{60}. The adiposity of infants in relation to their body weight, given the “thin-fat” phenotype, and its tracking into later life, is important to characterize when considering initiatives to reduce LBW, since increasing birth weight could be associated with a greater degree of adiposity. The implicit association that can be derived is that of increased body fat at birth, tracking into adulthood depending on environmental constraints. Increasing birth weight in such babies might also imply that the accumulation of fat may be disproportionately more as birth weight increases. This is not unlikely, as adult Indian populations have been shown to have a higher per cent body fat for a given BMI, than western populations\textsuperscript{61,62}, and it is worth assessing if a similar steeper slope in the adiposity-birth weight relationship is present in Indian babies. This is possible if one considers the use of surrogates of adiposity such as the relationship between the measured skinfolds or arm fat index (AFI), and body weight. The relationship between skinfold and birth weight in Bangalore babies\textsuperscript{63} can be compared with earlier studies in the UK, in Southampton, and in India, in Pune and Mysore\textsuperscript{59,60}.

Using the equation derived in the Bangalore study between subscapular skinfold and birth weight in the whole group, we could predict the mean subscapular or triceps skinfold for the reported mean birth weight in those studies. In the UK study, the predicted and measured mean subscapular skinfolds were identical. In contrast, for the birth weights reported in Pune\textsuperscript{59} and Mysore\textsuperscript{60}, the measured subscapular and triceps skinfolds were about 0.4-0.5 mm higher than the predicted value. The reason for this discrepancy is not clear; it is unlikely to be methodological as all sites reported good measurement practices, and all excluded mothers with gestational diabetes mellitus. It is also
pertinent to consider that the difference in the skinfold value between all these reports is about 10-15 per cent, which might simply be accounted for by measurement error (inter- and intra-measurer errors can approach 1 to 1.5 mm in adults and could be greater in the more hydrated tissue of infants).

**Effect of daily physical activity**

An important additional effect on birth weight could be daily physical activity which is an important and variable factor in the antenatal period, since women have variable physical activities at work outside the house and with domestic household chores. The importance of this is highlighted in studies which have demonstrated that manual physical activity during pregnancy is associated with small for gestation age (SGA) babies and lower birth weights and pregnancy weight gain, particularly when energy intake is sub-optimal. Similarly, strenuous physical work during pregnancy has also been associated with increased rates of abortion and premature delivery. Increased household chores have been related to preterm birth, while the evidence for leisure time physical activity suggests that participation in moderate to vigorous activity throughout pregnancy may enhance birth weight, with more severe physical activity regimens resulting in the opposite effect. In India, studies have demonstrated an inverse relationship between daily physical activity and birth weight in a cohort of rural women, the majority of whom had high levels of physical activity related to agricultural and domestic activities. In developing countries like India, women are responsible for a wide range of household work and childcare duties, as well as work outside the home. These women are also the women at highest risk for a poor birth outcome.

Physical activity can be assessed through an integrated index such as physical activity level (PAL), assessed through the administration of a physical activity recall questionnaire, or, through the assessment of the time spent in, and the intensity of, different activities in the domains of work, domestic chores, transport, leisure and sleep. The relationship between physical activity and birth weight might be expected to operate through the maternal weight either at the first trimester, or in terms of gestational weight gain, since these variables are associated with birth weight. In this framework, relationships might be expected between physical activity and maternal weight or gestational weight gain; in sequence, these anthropometric variables might have a subsequent relationship with birth weight, and finally, a direct relationship between maternal physical activity and birth weight might also be demonstrated. If this latter relationship was adjusted for maternal weight, it suggests that maternal physical activity has a direct association with birth weight, independent of its effects on maternal weight gain. South Indian women who had moderate/heavy physical activity in the 1st trimester of pregnancy had a significantly higher odds of giving birth to lower birth weight babies as compared to women who had sedentary physical activity (unpublished findings). This was also in agreement with a study in Ethiopia in which women were compared between categories of hard and light work during pregnancy.

A few studies have shown association of work in the third trimester and preterm births and low birth weight. In one study, a 150-400 g decrease in birth weight occurred in women who continued to work outside the home during the third trimester compared with those who remained at home during pregnancy. A similar decrease of 181 g in birth weight for babies of women who worked in a heavy mode outside the home during the third trimester was observed by us. Reports from Africa show that hard physical work by women during pregnancy can retard foetal growth and increase foetal/neonatal mortality. Indeed, the detrimental effect of third trimester work upon birth weight has been reported to be exacerbated if pregnant women worked in a standing position, were hypertensive, were poorly nourished, or had other young children at home.

In summary, there appear to be several maternal nutritional variables that seem to be operating in association with low birth weight and IUGR in developing country women during pregnancy. While socio-economic status is one such, and may indeed be an issue that underpins many of the other aetiological factors, it also seems that maternal weight gain is important, in addition to specific nutrients such as vitamin B12, folate and essential fatty acids, particularly n-3 LCPUFA. The analysis of the clustering of these risk factors in specific socio-economic or home circumstances, or in specific cultural behaviours, or in food intake patterns is of interest, as such analyses may provide the way forward for effective and sustainable prevention strategies.

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