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How maternal malnutrition affects linear growth and development in the offspring

Peggy C. Papathakis [a,*], Lauren N. Singh [b], Mark J. Manary [b]

[a] California Polytechnic State University, San Luis Obispo, USA
[b] Department of Pediatrics, Washington University School of Medicine, St. Louis, MO, USA

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A B S T R A C T

Maternal malnutrition is common in the developing world and has detrimental effects on both the mother and infant. Pre-pregnancy nutritional status and weight gain during pregnancy are positively related to fetal growth and development. Internationally, there is no agreement on the method of diagnosis or treatment of moderate or severe malnutrition during pregnancy. Establishing clear guidelines for diagnosis and treatment will be essential in elevating the problem. Possible anthropometric measurements used to detect and monitor maternal malnutrition include pre-pregnancy BMI, weight gain, and mid upper arm circumference. Food supplements have the potential to increase gestational weight gain and energy intake which are positively associated with fetal growth and development. Overall more studies are needed to conclude the impact of food/nutrient supplements on infant growth in undernourished pregnant women in developing countries. Currently, a study underway may provide much needed documentation of the benefits of treating malnutrition in pregnancy.

1. Malnutrition in pregnancy is a global health problem

Malnutrition during pregnancy is common in low-income women in the developing world due to inadequate dietary intake combined with increased nutrient requirements; the potential for complications for the mother and child in this at risk population is manifest in increased maternal and infant mortality (2000, Rush, 2000; Black et al., 2008; Lartey, 2008; Bloomfield, 2011) and the lifelong effects of fetal malnutrition (Barker, 2006; Victora et al., 2008). HIV infection, prevalent in some of these populations, exacerbates the risk of poor outcomes associated with malnutrition during pregnancy (Kupka et al., 2004; O'Brien et al., 2005; Mehta et al., 2010; Marazzi et al., 2011; Mehta et al., 2011).

Undernutrition during pregnancy results in maternal complications such as anemia, increased risk of life-threatening hemorrhage and hypertensive disorders of pregnancy such as pre-eclampsia (Wu et al., 2012). Hemorrhage and hypertension in pregnancy are the leading causes of maternal mortality worldwide (Firoz, Sanghvi et al.). Hemorrhage is associated with anemia and iron deficiency anemia while inadequate calcium intake is associated with the development of gestational hypertensive disorders (Buppasiri, Lumbiganon et al., Firoz, Sanghvi et al.). Infant complications from maternal undernutrition include intrauterine growth retardation (IUGR), low birth weight (LBW), pre-term delivery and birth defects such as neural tube defects (Wu et al., 2012). Additional complications include: poor cognition, academic performance, professional achievement and lower wages as adults (de Onis et al., 2012; Martorell and Zongrone, 2012). In addition, poor nutritional and socioeconomic status during pregnancy affects growth and development in subsequent generations (Martorell and Zongrone, 2012; Gigante et al., 2015).

Pre-pregnancy nutritional status and weight gain during pregnancy are positively related to fetal growth, development and birth weight. As early as 1975, observational studies of the Dutch Famine in 1944–45 identified a relationship between maternal undernutrition and fetal growth (Stein et al., 1978). Maternal undernutrition especially during the second and third trimester reduced birth weight and length (Stein et al., 2004). The first 1000 days, beginning at conception, are considered a critical time for prevention of childhood stunting, since growth failure begins in utero and continues until about two years of age (Victora et al., 2010).

Stunting, or poor linear growth, results primarily from inadequate nutrient availability and poverty that mainly affects low income countries. In a review of trends in stunting amongst pre-

* Corresponding author. Department of Food Science and Nutrition, California Polytechnic State University, San Luis Obispo, CA 93407-0258, USA.
E-mail address: ppapatha@calpoly.edu (P.C. Papathakis).

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school children worldwide, World Health Organization (WHO) estimated that there were 171 million children with stunting in 2010, with 97.6% of them living in developing countries. Although stunting has decreased globally from 39.7% of children under five years in 1990–26.7% in 2010, stunting in Africa has remained unchanged at 40% while it is decreasing in Asia and Latin America. Despite this general global decrease, stunting remains a significant public health concern with more than 132 million children estimated to be stunted in 2020 (de Onis et al., 2012).

The requirement for macro- and micronutrients increase during pregnancy; in many socioeconomically disadvantaged populations, nutrients from available foods are not sufficient to meet these increased needs. Foods consumed by pregnant women in developing countries are commonly low in micronutrients such as iron, zinc and vitamin A due to low intake of animal products (Ramakrishnan et al., 2012). Micronutrients needed inadequate amounts for fetal growth and development and prevention of IUGR include minerals phosphorus, potassium, iron and zinc; vitamins thiamin, riboflavin, niacin, folic acid and pantothenic acid (Wu et al., 2012), which are commonly deficient in undernourished populations. In their review of mechanisms for nutrient regulation during pregnancy, Wu et al. note that maternal undernutrition results in deficiencies of glucose, amino acids, fatty acids and micronutrients which lead to the metabolic changes including reduced placental growth, vascularity and function, oxidative stress, impaired cell signaling and regulation of protein synthesis causing fetal growth restriction (Wu et al., 2012).

Gestation represents 25% of the critical first 1000 days, thus it is a window of opportunity to optimize growth potential and prevent stunting by improving maternal nutritional status, both before and during pregnancy.

2. Evidence that mother's anthropometry and micronutrient status is associated with infant size and growth

Birth size is important for infant morbidity and mortality and for later adult health. Studies have identified indirect and direct effects of maternal age and height, genetic, demographic, socio-economic, behavioral and nutritional factors on birth size (Zhang et al., 2015). The US Institute of Medicine (IOM) established guidelines for weight gain during pregnancy based on pre-pregnancy BMI, as shown in Table 1, with the aim to optimize birth outcomes, including the prevention of LBW (Institute of Medicine (U.S.). Subcommittee on Nutritional Status and Weight Gain during Pregnancy. and Institute of Medicine (U.S.). Subcommittee on Dietary Intake and Nutrient Supplements during Pregnancy. 1990). WHO does not have recommendations on total weight gain or rate of weight gain at this time.

Currently there is no agreement on which anthropometric measurement method(s) should be used to detect, monitor and treat mild, moderate or severe undernutrition during pregnancy. Ideally an indicator would be simple to measure, valid and be universally applicable to pregnant women no matter the location or context.

Table 1
Institute of Medicine (IOM) weight gain recommendations in pregnancy.

Pre-pregnancy BMI (kg/m^2)	Total weight gain recommended (kg)	Gain/wk in 2nd and 3rd trimesters (g)
>18.5	12.7–18.2	450–590
18.5–24.5	11.4–15.9	365–420
25–29.9	6.8–11.4	227–320
>30.0 kg	5.0–9.1	180–270

Multiple micronutrient deficiencies are common in poor women in developing countries and contribute to LBW, IUGR and other adverse pregnancy outcomes. Several meta-analysis on the impact of multiple micronutrient supplementation on birth size have been conducted. Fall et al. looked at randomized control trials in 12 low income countries that mainly compared the standard of care, iron and folic acid supplementation, with one-times recommended dietary allowances (RDA) amounts of multiple micronutrient supplementation (Fall et al., 2009). They found that the multiple micronutrient supplementation was associated with improved birth weight of 22.4 g (95% CI 8.3–36.4) and a reduction in LBW risk (OR 0.89, 95% CI 0.81–0.97). Interestingly, the effect on birth weight (22.0–56.1 g) was stronger in women with a BMI higher than 20 kg/m^2 compared to mothers with BMI <20 kg/m^2 (Fall et al., 2009) which was also found in another study (Roberfroid et al., 2012). These authors suggested that although one-times RDA micronutrient supplement significantly reduces LBW, this amount of increased birth weight may not be sufficient to warrant this type of intervention and that better evidence of functional benefits are needed. Alternately, the amount of nutrients in the micronutrient supplement might not have been adequate in the undernourished women since the RDA is based on healthy populations rather than undernourished ones and that micronutrients might not have been fully utilized concurrent with inadequate energy intake (Roberfroid et al., 2012). In the meta-analysis by Ramakrishnan et al., 16 micronutrient randomized control trials were included to study the effect of micronutrient supplementation on pregnancy outcomes. It included one study of HIV-positive mothers and the content and dose of the micronutrient supplements varied; the control was usually iron and folic acid. In pooled analysis, they found overall a significant 14% reduced risk of LBW (95% CI, 0.81–0.91), similar to the Fall et al. meta-analysis. Birth weight in the multiple micronutrient groups was 53 g higher (95% CI. 41.6–63.7) than the control, (Ramakrishnan et al., 2012) which was nearly twice what Fall et al. found. In general, effects seemed strongest if the supplements contained 60 mg iron rather than 30 mg, but this was not statistically significant.

When prenatal food was fortified with multiple micronutrients in a study of 1296 pregnant women in Burkina Faso, Huybregts, et al. found an increase in birth weight (31 g) but this was not significantly more than the comparison group (Huybregts et al., 2009). The supplement provided 372 kcal, 14.7 g protein and one times RDA micronutrients and was compared to the control of one times RDA micronutrient supplement without macronutrients. Sixty to seventy percent of the enrolled women were anemic or vitamin deficient. After adjustment for gestational age at delivery, birth weight was not different between groups. In mothers who were underweight, however, birth weights increased by 111 g, but this was not statistically significant compared to the control group. Again, this may be the case of not enough nutrient support to have an impact.

2.1. Pre-pregnancy BMI

The pre-pregnancy BMI measurement is a reflection of maternal nutritional status while gestational weight gain is the aggregate change of mother's, child's and placental mass in the physiologic state of pregnancy. Ay et al. followed 8451 pregnant women in the Netherlands and measured fetal growth in relation to maternal anthropometry (Ay et al., 2009). They found an increased effect of BMI on fetal weight in the second half of pregnancy and the largest effects on fetal weight were near the end of pregnancy. The fetal growth rate difference between the lowest quintile BMI and the highest was 4.49 g/wk (95% CI: 3.48–5.29). Pre-pregnancy BMI was associated with birth weight difference (−88 g, 95% CI-120,-57)

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when comparing lowest to reference quintile (Ay et al., 2009). In a study of 2670 pregnant primarily white women, pre-pregnancy BMI was independently associated with birth weight, with lean women having a 51% higher risk of delivering an infant with LBW compared to the referent group (BMI 19.8–20.6 kg/m^2) after adjustment for confounders (Frederick et al., 2008). Several others have found a similar relationship between low maternal BMI and risk of LBW (Merchant et al., 1999). In the meta-analysis completed by WHO, a pre-pregnancy BMI of 18.4–21.0 kg/m^2 had an odds ratio of 2.3 (95% CI 1.7–3.1) for LBW compared to 1.5 (95% CI 1.3–1.8) for women with a pre-pregnancy BMI in a higher range of 21.0–26.7 kg/m^2 (WHO, 1995). Similar odds were found for the risk of IUGR (1.8, 95% CI 1.4–2.6 and 1.5 95%CI 1.3–1.7, respectively) (WHO, 1995).

A limitation of using pre-pregnancy BMI is that women commonly are not aware of their pre-pregnant weight in a developing country context, and typically first present for medical care well into the second trimester.

2.2. Weight gain during pregnancy

The WHO Collaborative study generally found that a weekly weight gain between 50 and 300 g in the second or third trimester increased the odds of having an infant with LBW by 1.6–1.7 respectively (WHO, 1995). Those women who gained 35–360 g in their 7th to 9th month had an OR of having an infant with LBW of 1.7 (95% CI 1.2–2.4) and OR for IUGR of 2.2 (95% CI 1.7–2.9) (WHO, 1995). Ververs et al. suggest that a weekly weight gain of <300 g indicates an increased risk for LBW but at least two measures must be taken to determine an average weekly weight gain (Ververs et al., 2013).

In Frederick's study noted above, women who gained less than 15.9 kg total during pregnancy had a 2 times increased risk of delivering an infant with LBW compared to those who gained ≥15.9 kg. Lean women (pre-pregnancy BMI <19.8 kg/m^2) who gained less than 15.9 kg had an even higher risk of delivering an infant with LBW (RR 2.97, 95% CI 1.63–5.43) after adjusting for confounders (Frederick et al., 2008). Ververs review found, however that a gestational weight gain of 11.5–12.5 kg had a RR of 1.85 (95% CI 1.1–1.99) for LBW outcome (Ververs et al., 2013). Several others have found a similar relationship between low weight gain during pregnancy and having a higher risk of LBW, and especially so in mothers with low pre-pregnancy BMI and low gestational weight gain (WHO, 1995; Merchant et al., 1999; Zhang et al., 2015). In the Ay et al. study, an interaction was noted in that the highest risk for low birth weight was found in mothers with low pre-pregnancy BMI combined with low gestational weight gain (OR 6.8, 95% CI 2.7,17.5) (Ay et al., 2009).

While there is no agreement for optimal weight gain during the course of pregnancy, it is clear that an average weight gain of less than 300 g/week in the second and third trimesters in women who were reasonably well-nourished prior to pregnancy reduces fetal growth and that fetal growth is optimized at a weight gain rate of approximately 360–450 g/week in such women, consistent with the IOM guidelines.

2.3. BMI during third trimester

In the Médicines Sans Frontiéres review of use of maternal anthropometric measurements to identify undernourished pregnant women, they found that BMI of <18.5 to <20.5 kg/m^2 in the third trimester was associated with an 1.9 to 7.6 increased risk of LBW, and that a BMI of 22.8–24.6 kg/m^2 at that stage was protective against LBW (Ververs et al., 2013). The WHO review had similar findings for the third trimester (WHO, 1995). In addition, the WHO review found that a BMI of 17.7–20.7 kg/m^2 at 20 weeks of gestation was associated with an OR for LBW of 2.0 (95% CI 1.4–3.1) and for IUGR 1.8 (95% CI 1.3–2.5) with the odds of LBW reduced with increasing BMI at this stage. At 28 weeks, a BMI <22 was associated with an OR for LBW of 1.5–2.0.

More study is needed before BMI can be used as a robust measure to determine when intervention is needed, but it is clear that low BMI (<18.5 kg/m^2) during pregnancy is associated with smaller infant size and it is likely that a BMI of 20–22 kg/m^2 in the last two trimesters respectively is also associated with reduced fetal growth.

2.4. Weight for gestational age

In the Médicines Sans Frontiéres review, the authors found that generally a maternal weight between 43.5 and 50 kg was associated with LBW, but there is no clear evidence how to use maternal weight to assess the need for intervention as pregnancy progresses (Ververs et al., 2013). A limitation is that most women do not know their last menstrual period, so establishing trimester is difficult. For example a weight of <50 kg at 28 weeks is associated with an OR for LBW of 2.7 while a weight of 57–68 kg reduces the odds to 2.0 (WHO, 1995).

More study is needed before a weight alone can be used as a cut point to determine risk, but it is clear that low maternal weight is associated with smaller infant size.

2.5. Mid upper arm circumference

Mid upper arm circumference (MUAC) is often used in screening for malnutrition in all populations, but there is no agreement on cut-offs for moderate or severe malnutrition for adults or during pregnancy. It general, MUAC is considered a good indicator of lean mass and a smaller measurement is consistent with low lean muscle mass and/or loss of subcutaneous fat. In settings where anthropometric measurements to assess undernutrition are limited, use of MUAC is simple in that only one measurement is needed for screening and follow-up. Low maternal MUAC has been consistently associated with LBW infants, but studies varied in inclusion criteria from 21.5 to 29 cm. Low MUAC has also been associated with IUGR and preterm delivery (Tang et al., 2013).

In a study of 913 HIV-infected mothers in Malawi, there was a positive association between maternal MUAC and birth weight; for each 1 cm increase in MUAC there was a 31.8 g increase in birth weight. Those with higher MUACs had a reduced OR for LBW (0.85, 95% CI 0.77–0.94) (Ramlal et al., 2012).

In a prospective study of 1066 Argentinian women, Lopez, et al. found that on average the MUAC increased by 1.7 cm (95% CI, 1.5–1.8) between 16 and 36 weeks of gestation, with the largest increase (1.1 cm) occurring between 13 and 28 weeks (Lopez et al., 2011). Women who gave birth to infants weighing >3000 g had mothers with MUACS on average, almost 2 cm greater throughout pregnancy than women who delivered infants with LBW (Lopez et al., 2011). Others have noted somewhat similar findings in that MUACs remain relatively stable or increase slightly throughout pregnancy, with the increase is mainly in the second and third trimesters (Tang et al., 2013).

In the WHO review and meta-analysis, mothers with MUAC between 21 and 24 cm had an increased risk of infants with LBW (OR 1.9 95% CI 1.7–2.2) and IUGR (OR 1.5, 95% CI 1.3–1.8) (WHO, 1995). Complicating the issue is that women with a MUAC of <26 cm during pregnancy were also at a similar risk (WHO, 1995). Ververs et al. suggest using a cut point of <23 cm in a humanitarian relief context in order to prevent LBW pregnancy outcome (Ververs et al., 2013) while Lopez suggests that for prevention of LBW, MUAC

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cut-offs at 6-, 28-, and 36 weeks of 24.5, 25.5 and 26.5 cm, respectively are protective of low maternal BMI (Lopez et al., 2011). The cut points that most studies have used to detect undernutrition are generally below these.

In summary, low maternal BMI is associated with low fetal growth, resulting in LBW and IUGR; maternal BMI more strongly affects fetal growth in the second half of pregnancy (Ay et al., 2009).

3. Summary of evidence that food changes mother's anthropometry

Food supplements during pregnancy may ameliorate malnutrition in the mother as well as improve infant birth outcomes (Allen et al., 2009). Studies have shown that both gestational weight gain and energy intake are strongly and positively associated with fetal growth and development (Kramer and Kakuma, 2003). These associations may be even stronger in undernourished women such as those with low pre-pregnancy weight-for-height. Worldwide there are numerous examples of food supplementation programs targeting malnourished mothers; however, the effectiveness of these supplementation programs varies. Interventions have included supplements of iron, folate, multiple micronutrients, calcium, and balanced energy and protein but of these few have been tested on a large scale (Bhutta et al., 2008).

The following studies in Table 2 provide evidence that supplementation can change a mother's anthropometry positively and thus improve fetal growth. One study carried out in Chile with 1135 underweight pregnant women tested the effectiveness of a fortified milk product versus a powdered milk product. The products had similar energy intakes but the fortified product had greater amounts of vitamins and minerals. All women were less than 20 weeks pregnant when they started the milk supplements. Women who received a fortified milk product had greater weight gain (12.3 vs 11.3 kg, $p < 0.05$) than women receiving a powdered milk supplement (Mardones-Santander et al., 1988). In a study that took place in rural Gambia, 1460 chronically undernourished pregnant women received a food supplement from 20 weeks gestation to delivery, the control groups received the same supplement after delivery. The supplement was biscuits that contained roasted groundnuts, rice flour, sugar, and groundnut oil, and they provided a maximum possible daily intake (two biscuits) of 4250 kJ energy, 22 g protein, 56 g fat, 47 mg calcium, and 1.8 mg iron. Supplementation increased weight gain in pregnancy particularly during the nutritionally debilitating hungry season (June to October). Weight gain increased by 201 g ($P < 0.001$) in the hungry season, by 94 g ($P < 0.01$) in the harvest season (November to May), and by 136 g ($P < 0.001$) over the whole year (Ceesay et al., 1997). Another study with 340 Colombian women at risk for malnutrition received a food supplementation starting at the third trimester of pregnancy. The intervention included dry skim milk, enriched bread, vegetable oil, and vitamins. Compared to the control group who did not receive any type of supplementation, weight gain of mothers pregnant with males was significantly higher. The difference between those supplemented 13 weeks or more and the controls amounted to 140 g week (Mora et al., 1979). In a smaller study done with 69 pregnant teenagers in Nigeria both an increased height and weight gain during pregnancy occurred when given a folic acid and iron supplement. The participants were anywhere between 8 and 24 weeks pregnant when supplementation started. A significantly greater proportion of girls who were supplemented grew by 2.9 cm during pregnancy; there was a significant correlation between increase in height and mean weekly weight gain and, although not statistically significant, the mean weight gain was 366 g (SD 155) in the supplemented group and 297 g (SD 157) g in the non-supplemented group. (Fleming et al., 1985).

All of the studies above demonstrate how a supplementation intervention improved mother's anthropometry, even if it was only a modest effect. Other studies have shown that supplementation did not improve gestational weight gain and there is still some controversy about the likely effectiveness of dietary supplementation (Ceesay et al., 1997; Kramer and Kakuma, 2003). Lack of effectiveness is seen when food supplementation was not targeted to women who were undernourished, arguing against a blanket feeding strategy (Ceesay et al. 1997). There is a need for larger clinical trials to be done that test the effectiveness of supplements in malnourished women. The findings of these studies will facilitate developing effective interventions for pregnant malnourished women and thus improve birth outcomes.

4. Summary of evidence that food/nutrients change newborn length

Adequate micronutrient status before and during pregnancy is important in determining fetal growth, health and survival. Micronutrients may lead to improved birth outcomes in several ways – by supporting and enhancing both maternal nutritional status and immunological function; they may lead to reduced maternal morbidity (Fawzi et al., 2007). Providing supplemental iron and folic acid are a standard of care during pregnancy in many developing countries. Prenatal multiple micronutrient supplements are regularly used during pregnancy in developed countries although their effect has not been adequately studied in any setting

Table 2
Studies on the effect of dietary supplement during pregnancy on maternal anthropometry.

Study	Subjects/Participants	Intervention	Findings
(Mardones-Santander et al., 1988)	n = 1135 women ≤20 weeks pregnant.	National powdered milk vs. Vita-Noval (fortified powdered milk)	Treatment produced a greater gestational weight gain
(Ceesay et al., 1997)	n = 1746 live births from chronically undernourished Gambian women (BMI at enrollment 20.7–21.3); RCT	Two groups: Daily nutritional biscuit (1015 kcal, 22 g protein, 56 g fat, 47 mg calcium, 1.8 mg iron) administered around 20 weeks until delivery or IFA during pregnancy and biscuit taken 20 weeks after delivery (control).	Treatment group had a weight gain increase in the hungry season
(Mora et al., 1979)	n = 340 Columbian women at risk for malnutrition starting in 3rd trimester	food supplement with dry skim milk, enriched bread, vegetable oil, and vitamins vs health care	Treatment group had higher weight gain only in mothers pregnant with males; those supplemented 13 weeks or more had increase in weekly weight gain.
(Fleming et al., 1985)	n = 69 pregnant Nigerian teenagers	five treatment groups-placebo, antimalarials only, antimalarials and iron, antimalarials folic acid, and antimalarials, iron and folic acid.	The effect of supplementation of either iron, folic acid had resulted in mean maternal height increase.

(Fawzi et al., 2007). Relatively recently, multiple micronutrient supplementation trials during pregnancy to determine potential benefit on maternal and infant health outcomes have been conducted in developing countries, where women are more likely to be undernourished. This review is mainly considering the impact of maternal nutrition on newborn length, but comments on other fetal growth effects are noted in Tables 3 and 4.

4.1. Micronutrient supplementation and birth length

The impact of maternal nutrition supplements on birth length is key with respect to achieving the newly launched Sustainable Development Goals by the United Nations. The following studies in Table 3 represent the mixed evidence that micronutrient supplementation improve fetal growth. Of the six multiple micronutrient supplementation trials identified that included information on birth length, one found no effect on birth length (Christian et al., 2003); of the five remaining studies, all showed an increase in birth length, but only two of these were significant (Gupta et al., 2007; Roberfroid et al., 2012) and one additional study was significant only in females (Friis et al., 2004) when compared to the control of iron and folic acid. The size of the effect on mean birth length ranged from a trend of 0.2 cm increase ($p > 0.05$) to a significant increase of 0.43–0.8 cm ($p < 0.05$). The effect size in mean birth weight was 42–69 g. It is difficult to compare the studies, however since the doses and timing of the supplements differ, as do the nutritional status of the women at enrollment. Interestingly, Kaestrel, et al. compared birth weights of mothers receiving either iron with folic acid, one or two times the RDA for 15 micronutrients (UNIMMAP). They found that the mean birth weight was 53 g (95% CI, 19–125) higher in the one times RDA and almost double that (95 g, 95% CI, 25–166) in the two times RDA group (Kaestel et al., 2005), suggesting that multiple micronutrient supplementation in undernourished groups with one times RDA may not be enough to optimize fetal growth. There is some speculation that the supplements increase gestation by several days and this accounts for the increase in birth measurements.

A meta-analysis of randomized controlled trials providing various doses of vitamin D supplementation for varying periods of time found birth length increased significantly, as did birth weight (Perez-Lopez et al., 2015). Although the effect was small, the authors suggest that vitamin D supplementation may indirectly affect fetal cell mass and growth, function and skeletal metabolism. The authors report other studies that showed shorter birth length in infants from vitamins D deficient mothers. In comparison, the UNIMMAP supplement contains 15 micronutrients at one times the RDA concentrations including 200 IU vitamin D. The authors suggest that a dose of 600 IU may be more appropriate in the developing world context where few women consume the RDA (Perez-Lopez et al., 2015).

Finally, Osendarp, et al. looked at whether zinc supplementation during the second and third trimesters among poor urban pregnant women in Bangladesh affected fetal growth (Osendarp et al., 2000). Supplementation of zinc alone had no impact on birth measurements.

4.2. Protein and energy supplementation and birth length

Most trials of protein and energy supplementation in pregnancy report on birth weight as the primary outcome, rather than linear growth. A recent meta-analysis looked at nutritional advice and protein/energy supplements and their effect on birth outcomes (Ota et al., 2015). While the analysis of 16 trials found that nutritional advice and supplements tended to improve birth weight with lower rates of small for gestational age and pre-term delivery, unfortunately it did not include birth length as an outcome. An older meta-analysis looked at nutritional advice and protein/energy supplements to increase maternal weight gain and fetal growth (Kramer and Kakuma, 2003). The 20 trials identified found that increased energy and protein intake increased as did gestational weight gain, but had no impact on fetal growth and birth length (Kramer and Kakuma, 2003).

Seven studies on balanced protein (<25% of energy), two from meta-analysis (Imdad and Bhutta, 2012; Stevens et al., 2015) contributed information on birth length for this review. The Stevens et al. meta-analysis of seven trials of balanced protein-energy

Table 3
Effect of maternal micronutrient intervention on birth length.

Study	Subjects/Participants	Intervention	Findings
(Christian et al., 2003)	n = 4926 pregnant women in Nepal; MUAC at enrollment of 21.8–22.0 cm; RCT	Daily supplements of folic acid, folic acid-iron, folic acid-iron-zinc, multiple micronutrients; all given with vitamin A or vitamin A alone (control). Women were enrolled before pregnancy, but intervention started at 11 weeks. Intervention stopped at 12 weeks after birth.	Folic acid-iron and multiple micronutrient supplementation had no effect on birth length. Folic acid group showed a **decrease** in birth length of −0.32 (95% CI: −0.58 to −0.05).
(Friis et al., 2004)	n = 1669 pregnant women (enrolled at 22–35 weeks of gestation) 30% HIV-infected; RCT	Two groups: daily multiple micronutrient (MMN: 15 micronutrients, 1- times RDA) or placebo. Supplementation from enrollment to delivery. Both groups received iron and folic acid.	MMN group had a non-significant increase in birth length. Marginally significant interaction between MMN and infant sex for birth length. For girls only, MMN increased gestational duration with an **increase** in birth length for girls only. Larger effect in HIV-infected
(Gupta et al., 2007)	n = 200 pregnant women with BMI <18.5 and/or a hemoglobin lof 7–9 g/dL; enrolled at 24–32 weeks of gestation; RCT	Two groups: daily multiple micronutrient supplementation until delivery (mean 55 days) or placebo (mean 52 days)52 days. Both groups received iron and folic acid.	Micronutrient group had a significant increase in birth length. MUAC increased and LBW was lower by 70% in the micronutrient group
(Fawzi et al., 2007)	n = 8468 pregnant women; enrolled between 12 and 27 weeks; negative for HIV and adequately nourished (BMI); RCT	Two groups: daily multivitamins (2× RDA for many micronutrients but 6–10× for vitamin C and B vitamins. Vitamin A and zinc not included) or placebo. Both groups received iron and folic acid.	Micronutrient group had a non-significant increase in birth length; significant increase in birth wt and gestational age; 18% decrease in LBW; 23% reduction in SGA
(Zeng et al., 2008)	n = 5828 socio-economically disadvantaged women who became pregnant; RCT	Villages were randomized for intervention into 3 groups: daily folic acid (control), iron with folic acid, or multiple micronutrients with 1-times RDA of 15 vitamins and minerals.	in comparison to folic acid alone, birth length significantly increased in iron-folic acid group; in the multiple micronutrient group, there was a non-significant increase in birth length. In the micronutrient group, mean birth weight increased

Table 4
Effect of maternal macronutrient intervention on birth length.

Study	Subjects/Participants	Methods	Findings
(Huybergts et al., 2009)	n = 1296 pregnant women in Burkina Faso (Mean MUAC 25.9, 12% of women had BMI <18.5); RCT	Two groups: fortified food supplement (FFS) with MMN (372 kcal, 14.7 g protein) or control (MMN).	Compared with MMN, the FFS group had a significant increase in birth length. There was a significant larger increase in birth length in mothers with BMI <18.5 and in anemic mothers. No significant effect on birth weight
(Adu-Afarwuah et al., 2015)	n = 1320 women in Ghana who enrolled ≤20 weeks pregnant and were adequately nourished (BMI average = 24.8): RCT	Three groups: IFA, MMN or LNS (118 kcal, 2.6 g protein, 10 g fat) with same MMN contents as MMN group.	No significant difference in birth length between groups; primiparous and younger mothers had significant higher birth lengths in the LNS group compared to the IFA and MMN group. No significant difference between groups in birth weight.
(Toe et al., 2015)	n = 1296 pregnant women in Gambia (BMI 20.8–21 at enrollment); RCT	Two groups: LNS with MMNs (72 g, 372 kcal, 14.7 g protein).) or MMN only (control).	No significant effect on birth length. LNS resulted in a significant increase in birth length compared to the MMN alone. Seasonal affect noted.
(Ceesay et al., 1997)	n = 1746 live births from chronically undernourished Gambian women (BMI at enrollment 20.7–21.3); RCT	Two groups: Daily nutritional biscuit (1015 kcal, 22 g protein, 56 g fat, 47 mg calcium, 1.8 mg iron) administered around 20 weeks until delivery or IFA during pregnancy and biscuit taken 20 weeks after delivery (control).	A non-significant increase in birth length was found in the treatment group. Seasonal affect noted.
(Chong et al., 2015)	n = 835 pregnant women from Singapore; GUSTO (Growing up in Singapore Towards Healthy Outcomes)	Observational cohort study that used maternal dietary assessment at 26–28 weeks of gestation which included 24-h recall and 3-day food diary.	Higher maternal carbohydrate or fat intake with lower protein was associated with higher birth length in male infants, Significantly lower birth length in younger mothers or with low BMI (<18.5), higher birth length for higher educated and higher income.

supplements, three of which contained multiple micronutrients, found a non-significant increase in mean birth length of 0.23 cm (SE 1.38, $p = 0.1$) with an increase in birth weight of 203 gm (SE 88.0, $p = 0.021$). In the Imdad et al. meta-analysis, seven studies contributed information; they found a significant increase in mean birth length of 0.16 cm (95% CI, 0.02, 0.31 cm). Fifteen studies contributed to the birth weight meta-analysis which identified a significantly higher birth weight of 73.8 gm (95% CI, 30.4, 117.15 gm). The impact was higher in the mothers who were undernourished ((Imdad and Bhutta, 2012; Stevens et al., 2015).

The following studies in Table 4 provide representative and mixed findings that macronutrient supplementation can improve fetal growth. Of four intervention trials, balanced protein supplementation generally increased birth length, but only two identified a significant increase (0.16–0.46 cm) (Huybregts et al., 2009; Imdad and Bhutta, 2012). Sub group analysis, however, identified significant increase in birth length in certain groups: mothers with low BMI (Huybregts et al., 2009), in mothers with anemia (Huybregts et al., 2009), in primaparous mothers (Huybregts et al., 2009; Adu-Afarwuah et al., 2015) and in younger mothers (Adu-Afarwuah et al., 2015). Toe et al. noted that their LNS supplement had a significant seasonal effect – infants of supplemented women in their second half of pregnancy during the rainy season benefitting the most from the supplement (Toe et al., 2015). The authors suggest that energy supplementation during the rainy/lean season (September to December) in sub-Sahara may be more effective in affecting linear growth. Ceesay et al. also noted a seasonal effect of their balanced protein supplement on birth length, although it was not significant (Ceesay et al., 1997). There was a seasonal effect of the supplement on birth weight as well, especially in the hungry season defined as June to October (Ceesay et al., 1997).

High protein supplementation (>25% of energy) increased the risk of having an infant with small for gestational age in one study (Rush et al., 1980). In their observational study, Chong et al. looked at whether maternal macronutrient intake during pregnancy had an effect on birth size in a multi-ethnic Asian population (Chong et al., 2015). Overall, they found no effect by macronutrient in linear growth. In male infants, however, lower protein intake along with either higher carbohydrate or fat intake was associated with longer birth length.

Limitations of the studies are that standard criteria to identify undernourished pregnant women are not used, micronutrient content and concentration of micronutrients differ, and the supplements are initiated at different times during pregnancy and for varying time periods. When considering only the balanced protein products, some contained multiple micronutrients as well as macronutrients, but the supplements were also of varying energy and protein content, making comparisons across studies difficult. In the review by Imdad and Bhutta, they consider that balanced protein supplements with multiple vitamins and minerals have the potential for the strongest influence on birth length compared to multiple micronutrients alone (Imdad and Bhutta, 2012). Overall there have been an inadequate number of studies to conclude the impact of balanced protein supplements on infant and child growth in undernourished pregnant women in low income countries (Stevens et al., 2015).

5. Future prospects

The benefits of treating moderate malnutrition during pregnancy remain largely undocumented.

5.1. Mamachiponde study

The Mamachiponde study in Malawi is a large comprehensive, targeted, food supplementation trial executed by this paper's authors to test the hypothesis that providing either fortified corn soy flour plus a multiple micronutrient tablet (UNIMMAP) or a fortified paste-based supplementary food designed to replete the nutrient deficits during pregnancy will result in improved maternal nutritional recovery rates and higher infant birth weights and lengths. It is a randomized, controlled clinical trial of 3 supplementary foods in 1800 moderately malnourished Malawian women who are pregnant. Moderate acute malnutrition (MAM) is defined by mid-upper arm circumference (MUAC) of less than or equal to 23.0 cm and equal to or above 20.6 cm among attendees at antenatal clinics, where about 20% of the women are HIV infected. Subjects will receive one of 3 food rations: 1) a ready-to-use supplementary food formulated to deliver about 200% of the RDA of most micronutrients in pregnancy, 2) fortified corn soy blend (also known as CSB+ or supercereal) with a multiple micronutrient tablet (UNIMMAP) chosen to deliver about 200% of the RDA of most micronutrients for pregnancy or 3), the standard of care which is CSB+ with supplementary iron and folic acid tablets (CSB+), delivering between 0 and 350% of the RDA. Subjects will receive the supplementary food until they recover from MAM (as defined by a MUAC equal to or above 23.1 cm on two consecutive visits) or deliver. The outcome of the pregnancy and maternal nutritional status will be followed until 3 months after delivery. The primary outcomes are MAM recovery rate, birth weight and birth length. Secondary outcomes include duration and adherence of MAM treatment (assessed by a questionnaire); maternal changes in MUAC, mid upper arm muscle area, and skin fold thickness; infant linear and ponderal growth; gestational age as measured by fundal height and infant survival at 3 months of age. Subgroup analyses for HIV+ and HIV− women will be conducted. It is anticipated that such a study will document the benefits of treating moderate malnutrition in pregnancy with modern evidence-based medicine, so that international agencies and national nutrition programs can make the most appropriate choices as they strive to reach the Millennium Development Goals.

5.2. Future research

Much is known about the consequences of LBW, IUGR and stunting but much less is known about how to ameliorate or prevent these by improving maternal nutritional status and access the food and supplements given the complex individual, community and societal changes and support that will be required.

In order to better design nutritional supplementation more information on the following is necessary, in addition to what food/composition to use, when to initiate it and for how long, and to whom:

To intervene in the appropriate target population, determining the most appropriate cut-point for use of MUAC, BMI, gestational weight gain, weight or other measures is required to diagnose malnutrition during pregnancy considering both maternal and fetal outcomes.

To determine the optimal energy content of the intervention, knowledge of energy expenditure during pregnancy, especially in rural settings, is required. More study on the length of intervention is important. The studies reviewed provided treatment throughout pregnancy, mainly enrolling either at the second or third trimesters, which might be cost-prohibitive for many health agencies, compared with treatment only until mothers recover from malnutrition. Since it is likely that malnourished mothers will share their intervention food with their families, more insight into how minimizing sharing be accomplished, and in a cost-effective manner is needed.

To determine the optimal micronutrient content, knowledge of likely inadequate nutrient intake is needed in order to determine how much needs to be provided of select micronutrients in order for the mother to become replete during pregnancy. To measure micronutrient status and change is expensive and not all regions have access to equipment to measure this makes this a challenge.

Even though the food intervention may have had a small impact on birth measures, longer term follow-up is important to determine if the intervention had an impact on health, infections and cognition during the first five years of life.

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