The Journal of Nutrition
Supplement: Do We Need Preconception Nutrition Interventions to Improve Birth Outcomes beyond the Prevention of Neural Tube Defects? Current Knowledge and Future Directions

A Summary of Pathways or Mechanisms Linking Preconception Maternal Nutrition with Birth Outcomes[1–3]

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Abstract

Population, human, animal, tissue, and molecular studies show collectively and consistently that maternal nutrition in the pre- or periconception period influences fetal growth and development, which subsequently affects the individual's long-term health. It is known that nutrition during pregnancy is an important determinant of the offspring's growth and health. However, now there is evidence that the mother's nutritional status at conception also influences pregnancy outcome and long-term health. For example, the mother's nutritional status at conception influences the way energy is partitioned between maternal and fetal needs. Furthermore, placental development during the first weeks of gestation reflects maternal nutrition and establishes mechanisms for balancing maternal and fetal nutritional needs. Also, maternal nutritional signals at fertilization influence epigenetic remodeling of fetal genes. These findings all indicate that maternal parenting begins before conception. The following papers from a symposium on preconception nutrition presented at the 2015 Scientific Sessions and Annual Meeting of the ASN emphasize the importance of maternal nutrition at conception on the growth and long-term health of the child. *J Nutr* 2016;146(Suppl):1437S–44S.

Keywords: birth weight, gestational age, nutrition, preconception, pregnancy

Introduction

Evidence that the mother's nutritional health at conception influences the course and outcome of her pregnancy has been accumulating for decades. Undernourished women are more prone to have low-birth-weight (LBW[4]; <2.5 kg) babies. Providing better nutrition during pregnancy improves fetal growth, but some suboptimal outcomes potentially related to periconception nutrition, e.g., preterm birth and stunting, persist (1). The most well-known relation is the link between preconception folate status and the risk of neural tube defects (2). Studies done more recently show that placental development and function are influenced by maternal nutrition at conception (3, 4). Also, the influence of maternal nutrition on fetal genomic imprinting and programming at conception directly ties maternal periconception nutrition to the child's long-term health (5, 6). This review summarizes current knowledge and recent advances in our understanding of the role of preconception (i.e., before conception) and periconception (i.e., from before conception to early pregnancy) nutrition in optimizing pregnancy outcomes and the health and well-being of the next generation. It is important to keep in mind, however, that maternal nutrition before and during pregnancy does not encompass independent time periods, because changes in dietary habits after conception tend to be modest and reflect intakes before conception.

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[4] Abbreviations used: *GTL2-2*, Gene trap locus 2-2; IGF, insulin-like growth factor; IPI, interpregnancy interval; LBW, low birth weight; LMIC, low- or middle-income country; mTOR, mammalian target of rapamycin; WIC, Women, Infants, and Children.

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Preconception Nutrition and Pregnancy Outcomes: Early Evidence

In the 1800s, maternal food intake frequently was limited to restrict fetal growth and ease deliveries in women who had contracted pelvises because of poor nutrition during their childhood. The poor survival rate of those undergrown fetuses led to subsequent studies to identify maternal factors associated with poor fetal growth. Using data from >50,000 women delivering babies in Aberdeen, United Kingdom, between 1948 and 1964, Thomson et al. (7) evaluated the effects of 2 maternal factors, body size and social class, on fetal growth. In comparison with tall, heavy women, short, light women consistently had smaller babies. Over 55% of the women who were short (<152.4 cm) and weighed <100% of the standard weight for height gave birth to babies who weighed <25th percentile, whereas only 6.6% of the taller women (≥167.6 cm) weighing >120% of the standard weight for height had infants with weights <25th percentile. Maternal body size and length of gestation were the primary determinants of fetal growth; the influence of social class disappeared when birth weights were standardized for those 2 maternal factors.

Subsequent animal studies have shown that the overall effects of poor maternal nutrition varied with the stage of tissue cellular growth when nutritional inadequacies occurred (7). If the dietary restriction occurred during the entire period of hyperplastic growth, or the increase in cell number, the effects were permanent. However, if the restriction was imposed later when the cell number had been established and it was then growing in size, the consequences could be reversed by improved nutrition. These studies clearly demonstrated that the long-term effects of nutrient deficiencies were related directly to the timing of the insult. Data from the Dutch famine (8) also demonstrated the importance of timing of the nutritional deficiency on the outcome in the human offspring. A period of acute starvation (400–800 kcal/d) occurred for 6 mo in the West Netherlands during the winter of 1944–1945. Consequently, some women conceived during the siege, whereas others were in early or late pregnancy (9). Subsequent analysis of those data show that exposure to acute starvation in the periconception period lowered scores on the mental component of a quality-of-life questionnaire and increased scores on a depression survey in the offspring as adults (10). The primary mental effects were schizophrenia and antisocial personalities (11). Later studies suggested that those outcomes were linked to differences in the methylation of the insulin-like growth factor (*IGF*) 2 gene (12). An increased risk of cardiovascular disease was also reported in persons conceived during the Dutch famine (13). If the onset of acute starvation occurred in the first trimester, preterm births, stillbirths, and deaths in the first week of life increased; obesity was also more common in the survivors later in life. If acute starvation was not initiated until in the third trimester, birth weight was lowered and mortality increased during the first 3 mo of life (8). Certainly, the degree of undernutrition during the Dutch famine was more severe than that encountered by women with limited access to food today. Yet, the findings demonstrate clearly that the timing of nutritional deficits during pregnancy is a major determinant of the consequences and that inadequacies at the time of conception influence the long-term health of the child.

Another "natural experiment" conducted in the 1980s showed that the mother's periconception nutrition influenced pregnancy outcomes. At that time, the state of California altered fiscal support for the Women, Infants, and Children (WIC) program because of a financial crisis (14). Postpartum WIC supplementation was cut, but implementation of the cut was staggered. Consequently, some women continued to receive WIC supplements for 5–7 mo postpartum, whereas others only received supplements for 2 mo. This situation provided an opportunity to compare the effects of longer and short postpartum WIC supplementation on birth outcomes in the next pregnancy. The results clearly showed that longer postpartum supplementation improved fetal growth in the next pregnancy; birth weight increased by 131 g, birth length increased by 0.3 cm, and the incidence of LBW (≤2500 g) babies declined. Those mothers with longer interpregnancy supplementation also had higher hemoglobin concentrations when they registered for prenatal care at the onset of their next pregnancy. These population studies, and others not reviewed here, show that maternal nutritional status at conception influences the growth and long-term health of the child.

Periconception Nutrition Intervention Trials: Past and Ongoing

More recently, scientists have begun randomized controlled trials to study the effect of undernutrition on pregnancy outcomes. Multiple micronutrient deficiencies are common in women in lower-income countries. In 2001, Rao et al. (15) reported that the birth weight of infants born to poor Indian mothers was related to the intake of micronutrient-rich foods, rather than energy and protein intake. Birth size was associated with the reported intake of milk, leafy green vegetables, and fruits at midpregnancy. Subsequently, these investigators studied the effect of consuming a micronutrient-rich snack before conception and throughout pregnancy on birth weight (16). The micronutrient-rich snack was made from leafy green vegetables, fruit, and milk, and was compared with a low-micronutrient snack made from potatoes and onions. Snack consumption was initiated before conception and continued to delivery. The increase in birth weight (26 g) did not differ between the groups ($P = 0.22$). Maternal BMI and length of prepregnancy supplementation influenced the response to the micronutrient-rich snack. Women with a BMI (in kg/m^2) >21.8 who took the snack for >90 d preconception gave birth to babies weighing 113 g more ($P < 0.001$) than control women with similar body size and length of snack consumption. This difference was not seen in women with a low (<18.6) or midrange (18.6–21.8) BMI. These data showed that the impact of preconception nutrition on subsequent pregnancy outcomes is influenced by the mother's weight status. This finding agrees with earlier studies conducted in the Gambia and Guatemala (17–19), which are discussed later in this review. Additional data from the study in Mumbai, which are part of this symposium, showed that the incidence of gestational diabetes was significantly lower in women receiving the micronutrient-rich snack than in women receiving the control snack (20).

The findings from another trial comparing the effects of micronutrient supplements given before conception on birth outcomes and maternal and infant micronutrient status were also part of this symposium (21). Three treatments, folate only, iron plus folate, and multiple micronutrient supplements, were provided weekly for ≥12 wk before conception. After testing positive for pregnancy, all of the women were given iron and folate daily until delivery. Preconception micronutrient supplementation did not alter fetal growth (22), but other outcomes are still under study.

Three other preconception nutrition intervention trials are ongoing. Hambidge et al. (23) at the University of Colorado are comparing the effect of a lipid-based micronutrient supplement given for ≥3 mo preconception with a supplement during the last 2 trimesters of pregnancy or no supplementation. The study is being conducted in 4 countries: Guatemala, India, Pakistan, and the Democratic Republic of the Congo. Birth length is the primary outcome, because birth length, in contrast with birth weight, is determined primarily early in fetal life (23). A second study, led by Tu Ngu (24), is underway in a rural area of northern Vietnam. In that study, primigravid women are divided into 3 groups, with 1 group receiving a small, nutrient-dense meal rich in iron, zinc, vitamin A, vitamin B-12, and folate from the time of marriage to delivery; a second group receiving the same nutrient-dense meal from 16 wk gestation to term; and the third group receiving nutrition counseling. The primary outcomes are birth weight and length and the incidence of preterm birth. The combined results from these periconception nutrition intervention studies, along with data from published studies, will provide new information regarding the impact of the quality of the mother's diet at conception on the health of the newborn.

Maternal-Fetal Competition for Nutrition

Access to sufficient, high-quality food is a key determinant of a woman's nutritional status at conception. A systematic review of 45 articles showed that preconception and periconception intake of vitamin and mineral supplements was associated with a reduced risk of preterm deliveries and having an LBW or small-for-gestational-age baby (1). In addition to the availability of quality foods, 2 other factors indirectly influence a woman's nutritional status at conception. Those factors are the age of the woman and the length of time between pregnancies. Young mothers are more likely to have LBW or preterm infants (25). A meta-analysis of maternal age and LBW showed that very young mothers (≤14 y) were 82% more likely to have an LBW baby than were an older reference group (25). The data also showed that as maternal age increased, the risk of LBW and very LBW declined. Low maternal age also increased the risk of preterm birth (<37 wk gestation) by 68% and very preterm birth (≤32–34 wk gestation) by 87% (25).

Maternal–fetal competition for nutrients is thought to be the primary reason why infants of adolescent mothers are smaller, even though these young mothers tend to gain more weight (26). Leptin surges in the third trimester may prevent maternal fat breakdown and increase the use of glucose for maternal growth, which does not cease during pregnancy, making less energy available for the fetus. Also, the smaller placenta generally seen in young mothers may reflect a competition for nutrients that limits placental growth in early gestation, leading to less nutrient transfer to the fetus (25).

It is important to note that most of these studies of early maternal age and pregnancy outcome were done in high- or middle-income countries (25). Approximately 16 million girls between 15 and 19 y of age become pregnant each year; 95% are from low- or middle-income countries (LMICs). Girls in LMICs presumably are more likely to be undernourished, and the negative effects of age on pregnancy outcomes may be even greater than that reported above. Using data from Gambian women, Allal et al. (27) estimated the optimal mean age for the first birth that would maximize reproductive success, as measured by infant survival. Their model integrated the interaction between maternal growth and infant survival, i.e., when a girl would stop allocating energy to her growth and start shifting nutrients primarily to reproductive needs. The model predicted a median age of 18 y for the first birth in this Gambian population. Thus, educational programs in LMICs that support delaying pregnancies until after 18 y of age may be one of the most effective ways to improve pregnancy outcomes and overall infant health (28).

The length of the interpregnancy interval (IPI), i.e., from birth to conception, also influences maternal nutritional status at conception. If the time between pregnancies is insufficient to replete the mother's nutritional reserves, she will enter pregnancy with a maternal depletion syndrome that limits fetal growth and development (29). The length and intensity of breastfeeding, which often is not well documented, is a component of the IPI. In many cases in which the IPI is less than 6 or 7 mo in women in LMICs, the women were breastfeeding at conception and during early pregnancy. A meta-analysis of the length of the IPI and pregnancy outcomes showed that a short interval (less than 6 or 7 mo) increased very preterm births of <32 wk by 58%, late preterm births (<37 wks) by 41%, stillbirths by 35%, and LBWs by 44% (30). Multiple factors could contribute to the increased risk of poor pregnancy outcomes with short IPIs. Some possibilities include lower red blood cell and serum folate concentrations that occur for several weeks postpartum (31), an elevated inflammatory state postpregnancy, and the duration, frequency, and intensity of lactation (30). Furthermore, short IPIs tend to be associated with lower socioeconomic status and access to prenatal care, which also are associated with poor pregnancy outcomes.

In the 1960s–1980s, a number of food supplementation trials were conducted in pregnant women in settings in which the mother's nutritional status was poor. The findings from these studies showed that the interaction between maternal and fetal nutrition is very complex and varies with the degree of maternal undernutrition. For example, Lawrence et al. (32) found that underweight Gambian women reduced, rather than increased, their basal metabolic rate during the first trimester, presumably to conserve energy for fetal development. These investigators subsequently showed that Gambian women essentially sustained their prepregnancy level of energy expenditure throughout gestation by reducing the energy cost for both basal metabolism and work (19). This is in sharp contrast with well-nourished women, who increase their basal and total energy metabolism in early pregnancy, which then continues to rise until term (33). Although the Gambian women gave birth to infants who weighed less than infants born to Western women, the reduced energy demand for synthesizing the tissue of a smaller fetus does not account for the degree to which the basal energy expenditure declined. Instead, underweight women appear to have a greater capacity to enhance the flexibility with which they use their limited energy supply. This is seen more clearly in animal studies (34).

Another study in Guatemala at about the same time was, to our knowledge, one of the most comprehensive investigations of the relation between maternal nutrition and pregnancy outcomes ever undertaken (35). It involved all women of childbearing age in 4 villages in a long-term prospective study to see what effects maternal nutrition had on the physical growth and mental development of their offspring. Dietary supplements were supplied to all pregnant women in the villages. However, the women were free to determine how much of the supplement they consumed (36). Two different supplements were distributed in the 4 villages. Two villages received a high-protein, high-energy supplement called "Atole," which provided 163 kcal and 11 g protein/serving, and the other 2 were given a no-protein, low-energy (59 kcal/serving) supplement called "Fresco."

Supplement consumption was recorded for all pregnant and lactating women, as well as the children. On average, the supplements increased total energy intake by 26,820 kcal during the entire course of pregnancy. Because supplement consumption was voluntary, there was a wide range of intake. The investigators, therefore, divided the women into low and high supplement groups; 20,000 kcal throughout pregnancy was chosen as the dividing line. When the women were divided that way, there was a difference of 34,000 kcal throughout pregnancy between the mean supplemental intake of the high and low groups. Birth weight differed significantly between the low and high consumers of the supplement (18). The rate of LBW was roughly 50% lower when the mothers consumed ≥20,000 supplemental kcal throughout pregnancy and the placentas from those mothers were ~11% heavier. There was no effect of consuming supplemental calories with or without protein.

Further analysis of the data from this study showed that consuming high amounts of the energy supplement had a greater effect on birth weight if the mother entered pregnancy with low energy stores, as measured by a lower skinfold thickness, than if she had a high skinfold thickness (**Figure 1**A) (37). This increase in birth weight occurred as the result of a small amount of weight loss in the mothers (Figure 1B). In the mothers in the highest quartile of energy stores, measured by skinfold thickness at conception, the effect on birth weight is relatively small, and more energy is transferred to maternal weight gain. It appears, therefore, that reproduction is sustained in women in poor nutrition by preferentially transferring energy into fetal growth. The opposite occurs in women entering pregnancy in better status; they gain weight while limiting fetal growth. These results suggest that the fetus is only (if ever) a "perfect parasite" when the mother's nutritional status is at a low level.

The relation between maternal nutritional status, energy intake, and fetal growth differs, however, when the mothers are divided by a longer-term measure of maternal undernutrition, i.e., knee breadth (37). In mothers in the lowest quartile for knee breadth, a high intake of supplemental energy did not increase fetal growth, but they gained some weight themselves (Figure 1C and D). Conversely, in women in the highest quartile for knee breadth, a high energy intake increased birth weight and maternal weight gain.

These data show that the relation between maternal current and longer-term preconception nutrition and fetal growth is complex. Mothers entering pregnancy with both long-term and current good nutrition use supplemental energy to increase birth weight and their own weight. However, supplementing women who have long-term undernutrition does not increase birth weight, although it modestly increases maternal weight. These data suggest that energy partitioning and metabolic efficiency is altered to sustain maternal function while supporting fetal growth to the extent possible when the energy supply is limited.

Preconception Nutrition, Placental Function, and Developmental Programming

For years it was thought that genes and adult lifestyle factors were the primary determinants of metabolic diseases, e.g., type 2 diabetes and cardiovascular disease. However, Barker's observation

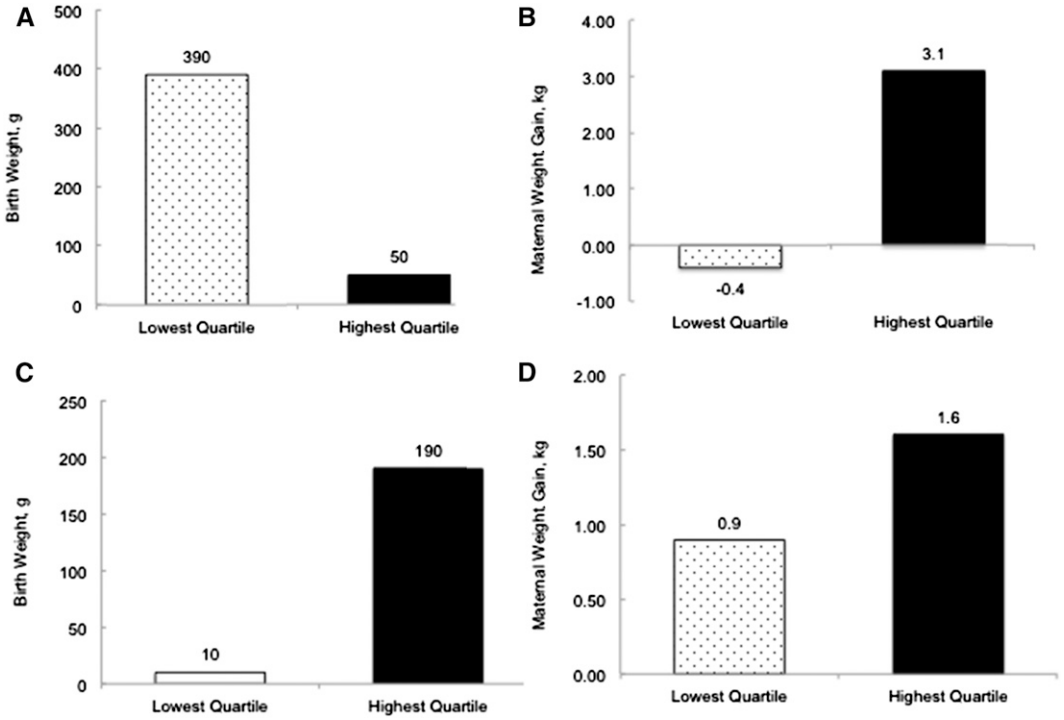

FIGURE 1 An energy supplement during pregnancy affects infant and maternal outcomes differently in women experiencing current (A and B) or long-term (C and D) nutritional deficits. Women in the lowest quartile of skinfold thickness (A), an indicator of current nutritional status, have a greater increase in birth weight than those in the highest quartile when exposed to a higher amount of an energy supplement. An opposite relation is shown for maternal weight gain (B), suggesting that the supplemental energy is used for fetal growth at the expense of maternal gain. Knee breadth, which is determined by bone growth early in the mother's life, is an indicator of long-term maternal nutrition. A high intake of supplemental energy had a small effect on birth weight in mothers in the lowest quartile for knee breadth (C) who gained less weight (D), suggesting that mothers with long-term undernutrition are less responsive to energy supplementation during pregnancy. This was exploratory work, so the authors used $P < 0.20$ as the criterion for significance in analysis of these 2-way interactions. All differences in each panel meet this criterion for statistical significance. Adapted from reference 37 with permission.

that an adverse intrauterine environment enhances subsequent metabolic diseases shifted thinking dramatically about the origins of adult disease (38). It is now known that the genetic material from the oocyte and sperm at conception shape the future development and the health trajectory of the offspring (39). During progression from conception through the blastocyst stages, the preimplantation embryo is extremely vulnerable to its nutritional, biochemical, and physical environment. The oviductal fluid surrounding the embryo provides nutritional, metabolic, and inflammatory markers that reflects the mother's outside world (39). In this way, the mother and the embryo jointly create a developmental trajectory that reflects the mother's external environment. If the resulting phenotype poorly matches the environment after birth, or if these early adaptations constrain the ability to adapt to latter environment challenges, the health of the offspring is at risk (39).

Maternal diet at conception is a major determinant of embryonic development (40). For example, reducing maternal dietary protein for the first 3 d of embryogenesis retards blastocyst cellular development; this change persists throughout implantation and thereby influences placental development and nutrient transfer capacity (41). Maternal inflammation, which may be an indirect marker of maternal nutrition, also influences the offspring's phenotype as an adult (36). For example, the exposure of mice to bacterial LPS on day 1 of pregnancy induced increased body fat in the pups and a reduced cytokine response to an LPS challenge as adults (42). Thus, maternal health at conception appears to alter the immune function of the child. In a way, the developmental impact of maternal and paternal health on the developmental trajectory of the fetus and ultimately the child's lifetime health shows that parenting begins before conception (39). These data strongly advocate initiating nutritional programs to improve maternal nutrition and health before conception.

After implantation of the blastocyst during the first 3 d after conception, placental formation begins, and the general placental structure is formed within ~3 wk. Maternal nutritional, metabolic, and inflammatory signals carried by the blastocyst influence placental development and the subsequent interchange of nutrients, hormones, and immune factors between the mother and fetus. The placenta senses perturbations in the maternal compartment, such as reduced blood flow or altered nutrient and/or hormone concentrations and modifies the fetal nutrient supply (43). For example, decreases in circulating concentrations of IGF-I, leptin, and insulin, and increases in maternal serum adiponectin concentrations, reflect nutrient restriction in the mother; consequently, the activity of amino acid transporters in the trophoblast, which are responsible for transferring amino acids to the fetus, are reduced (**Figure 2**) (44). A reduced supply of oxygen (e.g., at high altitudes) or blood flow has the same effect as reduced nutrition (44). Alternatively, increases in IGF-I, leptin, and insulin and decreases in maternal serum adiponectin reflect maternal overnutrition (i.e., obesity and diabetes) and an oversupply of amino acids to the fetus. An array of nutrient-sensing signaling agents within the placental trophoblast cells integrate placental metabolism to alterations in the maternal nutrient supply (45). Mammalian target of rapamycin (mTOR) is a primary placental nutrient-sensing signaling agent. It is sensitive to the availability of free FAs, amino acids, glucose, ATP, and oxygen from the mother, and it functions as a placental nutrient sensor to balance fetal demand with the ability of the mother to support the pregnancy (46, 47). It is likely that this integrated placental nutrient sensing system evolved initially to link fetal growth to the mother's nutrient environment. When the nutrient supply is low, the placenta balances the maternal nutrient supply with fetal needs so that the mother will have an undergrown baby who, in most instances, will survive and be able to reproduce. It is likely that these regulatory loops also function in the reverse direction with the overnutrition that exists today.

Recently, the effect of periconception multiple-micronutrient supplementation on placental function was studied rural Gambian women (48). A total of 376 women met the inclusion criteria and were randomly assigned to a multiple micronutrient supplement or a placebo. The women had been menstruating regularly within the previous 3 mo. Taking a multiple micronutrient supplement during early pregnancy lowered uterine artery vascular resistance indexes, but the effect size was small (~0.25 SD) and of no clinical significance. The data show, therefore, that periconception nutritional supplementation in early pregnancy can alter placental vascular function, but it is unclear whether the changes play a meaningful role in altering fetal growth.

Although the placenta functions as a nutrient sensor and balances the maternal–fetal nutrient exchange through hormonal signals, molecular mechanisms also play a role in the process of integrating maternal–fetal nutrition. A dynamic phase of epigenetic remodeling begins at fertilization based on environmental signals, and it is completed just before implantation (39). Two mechanisms mediating epigenetic effects are DNA methylation of cytosine residues and histone modifications (acetylation and methylation) (49). DNA methylation is catalyzed by DNA methyltransferases, with *S*-adenosylmethionine as the methyl donor. Vitamins involved in one-carbon unit metabolism (i.e., folate, vitamin B-12, and vitamin B-6) regulate *S*-adenosylmethionine availability. Ultimately, gene methylation influences the expression of the gene, with hypermethylation repressing expression or silencing the genes. Mouse studies show that DNA methylation may be altered by periconception nutritional interventions, such as folate supplementation, and thereby change the phenotype of the offspring (50). For example, dietary supplementation of pregnant agouti mice with folic acid, cobalamin, choline, and betaine shifted the coat color of the litter from predominantly yellow to brown. This color shift was accompanied by hypermethylation of several dinucleotides. Data from the Dutch Famine Study showed that dramatic shifts in the maternal diet that occurred caused long-term epigenetic and phenotypic changes in the offspring (50). The gene methylation pattern of the offspring of mothers exposed to the famine during pregnancy differed from their nonexposed siblings. The methylation changes were seen predominantly in individuals exposed to the famine during early rather than late gestation, suggesting that preconception maternal nutrition is sensitive to gene methylation. Another recent study of rural Gambian women showed that seasonal dietary differences influenced plasma concentrations of key methyl donor substrates at the time of conception that subsequently predicted increases/decreases in DNA gene methylation in genes located in the newborn's lymphocytes and hair follicles (5). Furthermore, pre- and periconception micronutrient supplementation of Gambian women reduced the methylation of 2 specific genes, *IGF2R* in girls and Gene trap locus 2-2 (*GTL2-2*) in boys (51). To our knowledge, this is the first randomized controlled trial demonstrating that periconception nutrition alters offspring methylation of imprinted genes. These findings lay the groundwork for an emerging field of periconception nutritional interventions to reduce the risk of chronic disease later in life.

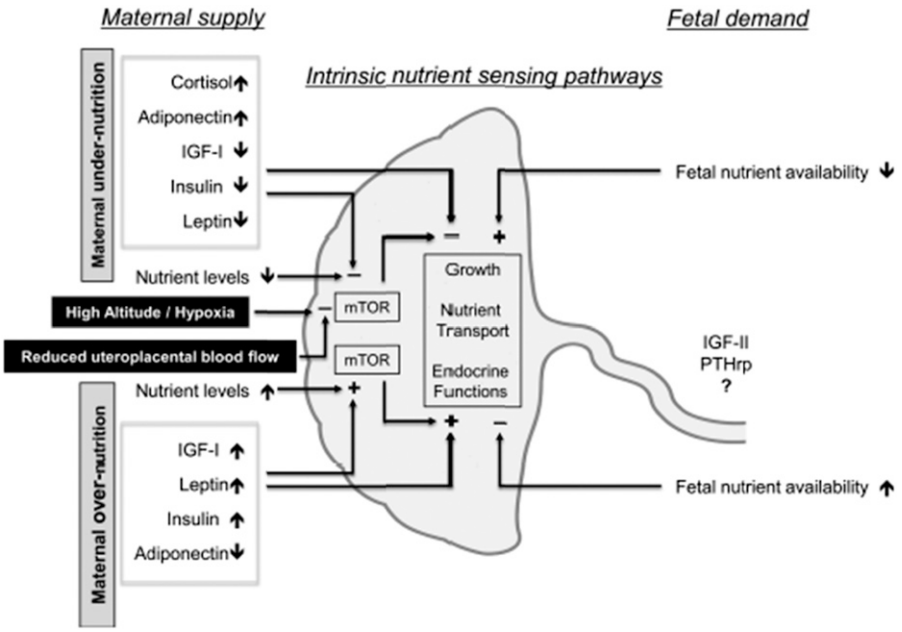

FIGURE 2 Placental nutrient sensing. The placenta integrates maternal and fetal nutritional signals with information from intrinsic nutrient sensors, such as mTOR signaling. This process balances fetal demand with the ability of the mother to support pregnancy. Thus, the placenta plays a critical role in sensing the mother's nutrition at conception and throughout pregnancy, and then modulates resource allocation. IGF, insulin-like growth factor; mTOR, mammalian target of rapamycin; PTHrp, parathyroid hormone–related peptide. Reproduced from reference 41 with permission.

Maternal nutrition during the periconception period also influences fertility. An imbalance between pro-oxidants (iron and copper) and antioxidants (vitamin C, vitamin E, zinc, and glutathione) has been linked to infertility (52). Insufficient intakes of the B vitamins (folate and vitamins B-6 and B-12) are also important because of their role in homocysteine metabolism. A low intake of these vitamins may cause hyperhomocysteinemia, which has been associated with in vitro fertilization failures (53). Adherence to Mediterranean diets, which tend to be high in folate, by couples undergoing in vitro fertilization treatments increased the probability of pregnancy by ~40%. Thus, preconception nutrition plays a role in fertility, as well as placental and early fetal development.

Next Steps

Population, human, animal, tissue, and molecular studies show collectively and consistently that maternal nutrition in the pre- and periconception period influences fetal growth and development, which subsequently affects the long-term health of the offspring. As discussed earlier, it is known that maternal characteristics, i.e., height, fat stores, nutritional status, and age, influence a woman's response to pregnancy (**Figure 3**). Nutritional interventions supplying food, such as that provided by the WIC program in the United States, or the provision of special nutrient-rich foods, as is currently being studied in 2 ongoing randomized controlled trials (23, 24) is one solution. In this

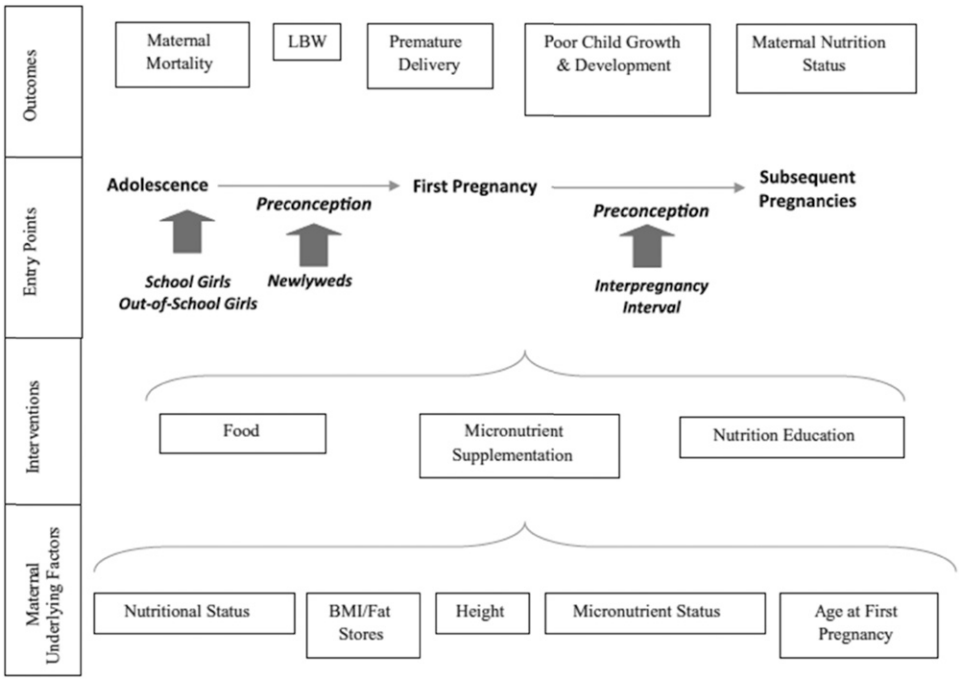

FIGURE 3 Conceptual framework of stages of pregnancy potentially affected by nutrients. Various aspects of maternal underlying nutrition and nutritional interventions influence the growth and development of girls and their future pregnancy outcomes. LBW, low birth weight. Reproduced from reference 1 with permission.

symposium, 2 other interventions were discussed—a nutrient-rich snack provided to Indian women (16), and a micronutrient supplement intervention (22). Nutrition education is another option. To date, little effort has been focused on providing nutritional advice to women before conception. For years, women planning pregnancies have been advised to take folate supplements to reduce the risk of neural tube defects. However, compliance with this recommendation is <20% (54). During the last decade, many have advocated preconception care and counseling to improve pregnancy outcomes in women with pre-existing health issues, e.g., diabetes. Surveys of women show that they would welcome preconception advice (55). When such a program was offered in Australia, it reduced the incidence of preterm birth and hypertensive disorders of pregnancy, and tended to reduce gestational diabetes, large-for-gestational-age babies, and fetal anomalies (56), showing that preconception nutritional advice can improve pregnancy outcomes. Entry points for women before conception include adolescent girls in and out of school, newlyweds, and health check-ups during the IPI (Figure 3).

To be effective, preconception interventions need to be culturally appropriate and focused on the at-risk nutrients in the target population. The needs of women in LMICs will differ from those in moderate- to high-income countries. Provision of nutrient-rich foods or supplements may be necessary in LMICs, whereas nutrition education counseling may suffice in populations in which the goal is to shift food purchases and consumption to more nutrient-rich foods.

Research needs to be linked to preconception programs to better define the most effective interventions for different populations. Some questions that need to be answered include the following:

- What is the minimum amount of time to deliver an intervention for it to be effective?
- Are the needs of primiparous women different from those of multiparous women?
- How do the needs of young growing mothers differ from those of mature women?
- Which delivery systems work best: supplements, fortified foods, or increased access to nutrient-rich, local foods?
- What nutrients need to be provided: a few critical vitamins and minerals, a supply of all essential micronutrients, or essential micronutrients along with energy?

In addition to developing criteria for clinical programs and policies, it is essential to continue research of the underlying mechanisms linking periconception nutrition with early placental and embryo development. The mechanisms discussed in this paper come primarily from underfed experimental animals. Research is needed to understand the effects of maternal overnutrition on early development and pregnancy outcomes in humans.

As reviewed in this paper, alterations in the early life environment may increase the risk of obesity and other metabolic disorders later in life. It appears that these outcomes reflect the epigenetic modifications resulting from earlier nutritional states. The mechanisms underlying this link between early environmental experiences or insults and subsequent health are relatively unclear. A better understanding of the epigenetic basis for developmental programming and how these effects may be transferred across generations is essential for designing interventions to prevent obesity and metabolic disease.

In sum, the time has arrived to begin parenting before conception by providing women with nutritional guidance to prepare for conception. One of the first steps is to identify the dietary patterns and nutrient intake amounts associated with good outcomes. The results reported in this symposium publication begin that process.

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