THE RELATIONSHIP OF MATERNAL NUTRITION TO FETAL GROWTH AND OUTCOME

Arthur I Eidelman MD
Director, Department of Neonatology, Shaare Zedek Medical Center
Hebrew University School of Medicine, Jerusalem, Israel

Introduction

Maternal nutrition during pregnancy reflects both the increased metabolic requirements of the mother per se and the ever-growing nutritional demands of the developing fetus. The previously held concept that the fetus is a functionally obligate parasite who can develop in utero essentially independently of the mother's nutritional status has not been supported by recent studies, both animal and human. In fact, what exists is a complex interrelationship of maternal, placental and fetal metabolic processes. This chapter will discuss in detail these relationships and focus primarily on two questions: 1) to what extent can manipulation of the maternal diet during pregnancy effect fetal growth, development and ultimate outcome? and 2) can dietary supplementation effect an already established impairment of fetal growth?

The effect of the maternal nutritional status can be measured by five different parameters (Table 1). While each of these five parameters can be addressed as independent variables, it is clear that there is a complex interrelationship between these factors and that in the individual mother nutritional deficiencies or abnormalities can be expressed in any or combination of these endpoints.

Table 1
Impact of Maternal Nutrition Status During Pregnancy

- Maternal nutrition and maternal well being
- Maternal nutrition and pregnancy outcome
- Maternal nutrition and fetal growth
- Maternal nutrition and fetal development
- Maternal nutrition and adult diseases of the infant

Nutrition and Maternal Well Being During Pregnancy

Pregnancy makes major metabolic demands on the mother. The newly pregnant mother enters a hypermetabolic and anabolic state as compared to her prepregnancy condition. The normal pregnancy is characterized by a positive weight gain that reflects an increase in uterine, placental and mammary tissue, amniotic fluid and fat stores. Among the major challenges is the need for the mother to increase her circulating blood volume so as to provide the necessary perfusion of the ever-growing placenta. The expansion of blood volume takes place primarily in the second trimester and early part of the third trimester and reaches its peak at 32 weeks gestation with an increase of 45% above the pre pregnancy volume[1]. Additionally, the mother must also supply both the essential macro and micronutrient demands of the developing fetus as well as meeting her own metabolic requirements.

The major period, quantitatively, for fetal growth is in the third trimester, peaking at 32-34 weeks gestation. At times the macronutrient demands of the fetus exceed the capacity of the mother's intake. In those situations the mother must rely to a degree on the energy stores (primarily fat) that have been deposited in the second trimester. Abrams[2] studied weight gain by trimester in otherwise healthy non-obese women and noted that for each kilo of maternal weight gain in the 2nd trimester the fetus gained 33 grams above the mean, while a similar weight gain in the 3rd trimester resulted in only a 17 gram weight gain. These data emphasize the importance of weight gain in the second trimester and the need to allow the mother an unrestricted though balanced diet during this period.

Of interest are the studies of women suffering from severely inadequate nutrition (such as occurred in the Dutch winter famine of 1944-45[3] and the Leningrad siege during World War II[4]). The importance of the preconception period is clear from the observation that there was a 600 gram decrease in birth weight when the mothers conceived in an undernourished state and continued to be undernourished throughout the pregnancy, as in Leningrad. When the malnutrition was limited to the first trimester there was an increased incidence in early spontaneous abortions. Inadequate nutrition limited to the second trimester had relatively little effect on maternal health or fetal growth provided that there was adequate nutrition in the third trimester. Third trimester malnutrition however manifested a 10% reduction in average birth weight (less than 300 gram) and a 15% reduction in placental weight. These data relate primarily to the effect of acute near famine and have only partial relevance to the usual clinical situation in the developed world of adequate or marginal nutrition

The actual increased maternal nutritional requirements of the otherwise healthy pregnant mother as compared to her prepregnancy state are summarized in Table 2. These daily requirements calculate out to a need to ingest at least 2,300 kcal/day and 50-55 grams of protein a day. Contrary to previously held concepts, excess caloric intake will not lead to increased blood pressure though it might increase glucose intolerance in those mothers with a propensity for gestational diabetes. Table 3 summarizes in a different aspect the nutritional developments during pregnancy and expresses them as the total amount of nutrients that are incorporated by the mother and fetus during a normal pregnancy.

Table 2
Increased Maternal Nutritional Requirements
Secondary to Pregnancy

- Calories: Additional 300 Kcal/day
- Protein: Additional 15 gram/day
- Calcium: Additional 250 milligram/day
- Iron: Additional 30 milligram/day
- Zinc: Additional 15-25 milligram/day
- Copper: Additional 2 milligram/day
- Folate: Additional 400 microgram/day

Table 3
Total Nutrition Accretion during Pregnancy by Mother and Fetus

- Protein: 925 grams
- Fat: 3,825 grams
- Calcium 20 grams
- Iron: 500 milligrams
- Zinc: 100 milligram

Maternal Nutrition and Pregnancy Outcome

Independent of the effect of maternal nutrition on fetal growth discussed below, malnutrition impacts in an undefined way on an increase in stillbirth and early neonatal deaths. Results of epidemiological observational studies on the relationship of maternal weight gain in pregnancy and prematurity rate have been conflicting[5]. Four studies[6,7,8,9] have noted a correlation of poor weight gain and increase in the prematurity rate while two other large studies could not document this association[10,11]. These confusing observations to some degree reflect basic methodological differences in the data collection and analysis. On the other hand, prospectively controlled supplementation studies[12,13] in populations wherein inadequate nutrition was a major feature noted a reduction in the incidence of still births and neonatal deaths, but no significant effect on length of gestation or prematurity rate. Similarly, after correcting for neonatal course, no long-term benefits in neurodevelopment[13] or IQ[14] could be documented in those infants whose mothers received nutritional supplementation during pregnancy. In fact, when supplementation was with a high protein diet not only was there no benefit, there was a non-significant increase in neonatal deaths[15].

Modern recommendations as to the desired weight gain during pregnancy thus relate both to the pre conception weight and the pregnancy period itself. For those mothers defined as underweight (Body Mass Index BMI <19.8) the recommended weight gain is 12.5-18 kilograms. For those mothers with a preconception normal weight (BMI 19.8-26) the weight gain should be 11.5-16 kilograms while in obese women (BMI >26) the recommended weight gain should be 7-11.5 kilograms[16].

Maternal Non-nutritional Factors and Fetal Growth

Fetal growth is influenced by a combination of genetic and intrauterine environmental factors independent of the supply of nutritional factors by the mother. Significant correlates to the rate of fetal growth have been noted in maternal height, maternal birth weight, maternal preconception weight and energy expenditure during pregnancy. It has been estimated that 40% of the birth weight variance relates to genetic factors while 60% relates to the uterine environment[17]. "Environmental" influence is evident from data from embryo transfer births where the birth weight correlated with the recipient's birth weight and not the donor's. Similarly, when comparing correlation of birth weight in half siblings, there is a significant correlation (r=0.58) with maternal half sibs (i.e. sharing the same uterus) and no correlation (r=0.1) with paternal half sibs[18]. The genetic influence is most obvious from the effect of the "Y" chromosome, as male infants weigh on the average 150-200 grams more than female infants[19].

Table 4
Placental Hormone Influence on Fetal Growth and Differentiation

- Chorionic gonadotropin
- Placental lactogen
- Chorionic cortocotropin
- ACTH
- Estrogen
- Progesterone
- Releasing Hormones e.g. TRH, SRIF. GnRh
- Beta-endorphin

Placental hormonal factors impact directly and indirectly on fetal growth and differentiation. These hormonal factors are listed in Table 4. The most important are chorionic gonadotropin and placental lactogen. Maternal disease processes that impair normal placental growth and metabolism (such as occurs in toxemia) can thus indirectly impact on fetal growth.

Maternal Nutrition and Fetal Growth and Development

The nutritional requirements of the fetus can be divided into the macronutrients; protein, fat and CHO; and the mineral and vitamin micronutrients. The macronutrients provide for the fetus' basic energy needs, maintenance and growth (anabolic tissue production). For comparison, the fetus' energy needs are compared with those of a preterm infant of equivalent post conceptional age (Figure 5). The first trimester and the major part of the second trimester reflect, in the classification of Winnick, the phase of cellular hyperplasia (phase 1: cellular hyperplasia, phase 2: hyperplasia plus a degree of cellular hypertrophy, phase 3: cellular hypertrophy). The third trimester is primarily one of growth that reflects cellular hypertrophy. Table 6 details the daily net gain in the third trimester (26th-40th week of gestation). This is compared to the increments of the first trimester of less than 5 gram per day weight gain and a protein incorporation of a few hundred milligrams per day. Thus, if the mother does not provide adequate macronutrient substrate during the first and second phase there is uniform decrease in the number of cells and cell size leading to symmetric intrauterine growth retardation. Inadequate nutrition in the third phase, especially in the last two months of the pregnancy, will lead to a non uniform decrease in cell size and only minimal decrease in cell numbers. This situation leads to the clinical entity called asymmetric intrauterine growth retardation. Of interest is the observation that low maternal levels of the non-caloric micronutrients zinc[20] and folic acid[21] have also been correlated with intrauterine growth retardation.

Table 5
Fetal and Preterm Infant Energy Needs (Gestational Age 32 weeks)
(kcal/kg/day)

Component	Fetus	Preterm Infant
Baseline expenditure	50	50
Activity (> baseline)	0	15
Cold stress	0	10
S.D.A.	8	8
Fecal Loss	0	12
Growth	40	25
Total	95-100	120

Table 6
Daily Fetal Increments

Gest Age (wk)	Wgt (gr)	Prot (gr)	Lipid (gr)	Ca (mg)
24-25	11.4	1.25	0.5	61
29-30	23.1	2.76	2.6	138
34-35	31.4	4.23	4.4	258
39-40	17.1	2.50	5.0	302

Thus fetal energy needs, especially those of the third trimester, can be met by the mother by either increasing her nutrient intake, decreasing her own energy expenditures, increasing her utilization of maternal fat stores or down regulating maternal lipid synthesis and storage.

The results of observational studies of human mothers with poor nutrition have varied between the outcomes in populations from undeveloped or developing societies and those from developed industrialized countries. In general, mothers in developing countries suffer from a degree of chronic malnutrition and have lower preconception birth weight[12]. This in and of itself leads to lower infant birth weight. When coupled with a pattern of high energy expenditure typical of the chronically malnourished woman in undeveloped countries, birth weight is on the average 300-400 grams less and incidence of low birth weight is nearly twice as common as for infants born to well nourished women in developed countries. In contrast, observational studies in populations from developed countries have resulted in inconsistent findings and essentially have not documented any correlation between maternal macro nutrient state and birth weight[22]. Only in the extreme of an outright famine situation such as that which occurred in Amsterdam[3] and Leningrad[4] was there documented decrease in birth weight, and then only in mothers who were starved before conception and throughout the pregnancy or primarily in the third trimester. These differences in the studies can best be explained by assuming that the association of maternal weight gain with neonatal birth weight is a reflection of a common mechanism or condition, i.e., that maternal weight gain per se does not impact directly on fetal weight gain. Poor weight gain may only be a marker of maternal pathology. Thus, the lack of any correlation of birth weight with a variance of maternal macro nutrient intake is not surprising.

The Effect of Nutritional Supplementation during Pregnancy

Isocaloric balanced protein supplementation (i.e. substitution of protein for an equal quantity of non-protein nutrients while maintaining the same caloric intake) has been studied in three different trials involving 996 mothers. There was no effect on mean gestational age or incidence of preterm infants. However there was a decrease in maternal weight gain and mean birth weight and an increased risk for small for gestational age births (less than 10% percentile for given gestational age)[23]. High protein nutritional supplementation itself (added calories solely from protein with the protein providing over 25% of the caloric intake) was studied in two trials involving over 1000 mothers. While there was a small increase in maternal weight gain there was no evidence of any benefit to the fetus. In fact the mean birth weight was less in the supplemented pregnancies. In one study there was a non-significant increased risk in neonatal death. Thus, it is clear that supplementation with protein alone has no benefit and may in fact be deleterious to the fetus and newborn[15].

Balanced protein energy supplementation (increase in both calories and protein) has been extensively studied in 13 prospective randomized controlled trials. Kramer[24] performed a meta-analysis of these studies. In all the studies the protein content did not provide more than 25% of the ingested calories. The majority of these studies involved populations with documented or suspected nutritional deficiency or marginal diets. This ranged from studies on rural Gambian women suffering from “chronically marginal nutrition”[12], to poor primaparous women from rural East Java[25], to low income Black women in Harlem[26], to Scottish women at high risk for low birth weight infants because of low maternal height and/or weight or poor weight gain in the 2nd trimester[27]. In only 3 studies[27-29] were well nourished women on normal diets studied. In all these studies there were major methodological problems ranging from issues of randomization, compliance with supplement, different quantity and caloric value of supplement, unknown substitution of control diet and lack of power of individual studies.

Despite all these methodological limitations a definite pattern of results exists. Supplementing the baseline diet with additional calories and protein leads to an increase in maternal weight of 17 gram per week and a minimal increase in mean birth weight of 25 gram. The most striking result was a decrease in the number of small for gestational age (SGA) infants, an Odds Ratio of 0.64 (CI 0.53-0.73). In addition there was a significant decrease in the number of still births and neonatal deaths with lower perinatal mortality in the supplemented group[12]. In the study where the supplement to undernourished women in Gambia exceeded 1000kcal per day, the most dramatic effect occurred during the non-harvest hungry season. Supplemented mothers in this group had infants with an increase in mean birth weight of 201 grams, a decreased odds ratio for low birth weight (<2,5000 gram) of 0.61 (CI 0.47-0.79), and a decreased perinatal mortality rate odds ratio of 0.47, (CI 0.23-0.99). Of interest was the observation that there was no effect of supplementation on the length of gestation or the prematurity rate (Table 7).

Table 7
Effect of protein/energy supplementation: (*Adapted from Ceesay*)[12]

	Control gp	Supplement gp	Odds Ratio (CI)	p
	Number (%)	**LBW Infants**		
Harvest period	96/605 (15.9)	63/589 (10.7)	0.64 (0.45-0.90)	<0.01
Hungry period	80/432 (18.5)	49/421 (11.6)	0.58 (0.39-0.86)	<0.01
All year	176/1037 (17)	112/1010 (11.1)	0.61 (0.47-0.79)	<0.01
	Number (%)	**of Deaths**		
Stillbirths	24/1021 (2.3)	11/1061 (1)	0.47 (0.23-0.99)	<0.05
Perinatal deaths	60/1021 (5.9)	32/1061 (2.4)	0.54 (0.35-0.85)	<0.01

No long term effect of these protein energy supplements was noted as to Bayley scores at age 1 year[26] or subsequent IQ (Stanford and Binet at 5 year), though it should be pointed out that follow up studies were only performed in 2 of the studies reviewed[14,26].

The relatively minimal, if any, correlation of maternal nutrition and pregnancy outcome in a population living in the industrialized developed world was confirmed by Matthews[22], who studied English women. Placental and birth weight was unrelated to intake of any macronutrient. After adjusting for many variables including maternal height and smoking, the only micronutrient that correlated with birth weight was first trimester vitamin C levels. When this result is coupled with previous reports that maternal levels of zinc and folate correlated with birth weight, the importance of micronutrients becomes more apparent.

The long term biologic price of being small for gestational age and growth retarded has been discussed by Barker[31], who has hypothesized that intrauterine events “set” the metabolic activity of the organism with long term consequences (Table 8). In particular, the phenomenon of increased type II diabetes (adult onset) in infants born small for gestation age, emphasizes the concept that there are fetal and neonatal origins of adult disease. It is postulated that inadequate intrauterine nutrition leads not only to poor growth but also to a degree of down regulation of metabolic processes that in turn cannot tolerate the long term postnatal loads, especially of carbohydrates.

Table 8
Low Birth Weight and Adult Disease (*Barker hypothesis*)

Low Birth Weight is Associated with:

- Increased coronary heart disease
- Increased hypertension
- Increased type II diabetes
- Increased fibrinogen and cholesterol levels
- Increased polycystic ovarian syndrome

The effect of marine oil supplementation during pregnancy has recently undergone extensive study. Uncontrolled epidemiological observational studies[32] from the Faroe Islands suggested that birth weight was increased in mothers who subsisted on a marine diet. The proposed mechanism for this observation was the observation that marine oil supplements prolong gestation thus reducing the incidence of preterm infants and secondarily increasing the mean birth weight of the population. In addition it was postulated that marine oil diets rich in long chain polyunsaturated fatty acids improve placental blood supply by affecting the throboxane/prostacyclin ratio.

In an attempt to determine whether these observations were valid, a series of prospective randomized trials of marine oil supplement was performed[33]. Four prophylactic trials involving mothers with previous preterm deliveries or intrauterine growth retarded infants with and without associated pregnancy induced hypertension were studied. Table 9 details the findings. The major result from the marine oil supplementation was a significant reduction in preterm deliveries. However, there was no effect, independent of length of gestation, on birth weight, incidence of intrauterine growth retardation or pregnancy induced hypertension. Of interest was the fact that the effect of reducing the preterm delivery rate occurred only in singleton births and not with twins.

Table 9
Effect (%) of Marine Oil Supplement (*Adapted from Olson*)

Study	n	Fish Oil	Olive Oil	Odds Ratio	p
Preterm recurrence	228	23/108 (21.3)	40/120 (33.3)	0.54 (0.3-0.98)	<0.05*
IUGR recurrence	263	43.131 (32.8)	37/132 (28)	1.6 (0.74-2.12)	<0.42
PIH recurrence	350	55/167 (32.9)	61/183 (33.3)	0.98 (0.63-1.53)	<1.0

IUGR = Intrauterine Growth retardation
PIH= Pregnancy Induced Hypertension
** = significant*

Gulmezoglu[34] recently reviewed the issue of maternal nutrient supplement for suspected impaired fetal growth. Three controlled studies involving a total of 121 mothers were analyzed. Nutrient supplements included carnitine, amino acids and glucose infusions. All these studies had major methodological limitations and it was therefore concluded that the trials were inadequate and preclude any conclusion. What is clearly needed is a properly designed prospective large randomized trial to evaluate if there is any nutritional supplement that can reverse an already established pattern of intrauterine growth retardation.

Summary and Conclusion

Reviewing the above data one can come to the following conclusions:

1. In developed industrialized countries differences in macro nutrient nutritional intake in otherwise adequately nourished mothers has little effect on birth weight.
2. As such, routine nutritional supplementation for mothers is unwarranted and not recommended.
3. Protein supplementation leading to a diet where protein supplies over 25% of the calories may well be detrimental to the fetus.
4. There is no evidence to date that any nutritional supplementation will reverse established intrauterine growth retardation.
5. In chronically undernourished mothers, especially in undeveloped or developing countries, balanced protein/energy supplementation may be warranted. Supplementation should begin pre-conceptually and is most important in the second trimester.
6. In mothers at risk for growth retarded infants decreasing the maternal energy expenditure may be more beneficial than any dietary manipulation.
7. Greater attention should be paid to micronutrient intake, especially in the first trimester, including folate, zinc, iron and vitamin C.

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