

NUTRITION

Destiny's Child: Fetal Origin of Adult Disease

“Like mother, like daughter” and “the acorn doesn’t fall far from the tree” are adages that give us reason to expect an offspring to be much like their parents. However, statistics indicate a widening epidemic of obesity, heart disease and type II diabetes in children, many without family histories of these diseases. Interestingly, a concurrent pattern has begun to emerge. According to the National Center for Health Statistics, as many as 7.8% of the babies born in 2002 weighed less than 2,500 g and are considered to be low birthweight. This is the highest rate of low birthweight births in more than 30 years. These frightening patterns have caused researchers to investigate the relationship of how maternal diet influences the health outcomes of an offspring far into their adult years. Evidence has begun to confirm researchers’ suspicions that children are at risk for certain common diseases of adulthood due to biological programming resulting from poor maternal nutrition impacting fetal development during certain critical stages of gestation.

Historical data suggests that early nutritional deficits leave an everlasting impact on adult health. A Norwegian researcher, Forsdahl, in 1977 found a geographical correlation between coronary heart disease (CHD) mortality



between the years 1964-1967 and infant cohort mortality rates 70 years earlier (1896-1925). He sensed that “growing up in poverty led to permanent damage due to nutritional deficit that resulted in life-long vulnerability to affluent adult lifestyle and high fat intakes.” Research by David Barker and others has lent support to this theory. Using the 1911-1930 birth records from Hertfordshire England, Barker showed a higher death rate from CHD and stroke associated with newborns at the lowest birthweight and weight at one year, versus those newborns at the highest birthweight. This finding was replicated in an analysis of data from the Nurses’ Health Study of 70,297 nurses (Rich-Edwards JW et al. *BMJ*, 1997).¹ In this study, relative risk for nonfatal cardiovascular events was inversely related to birthweight.

After observing a relationship between poor maternal nutrition and disease in the adult offspring, Barker and colleagues developed the hypothesis known as the Fetal Origins of Adult Disease (FOAD) hypothesis. FOAD attempts to explain the association between small size at birth and later CVD. The hypothesis is based on the theory that the fetus, which is dependent on maternal nutrition, is forced to

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on the theory that the fetus, which is dependent on maternal nutrition, is forced to make metabolic adaptations when the nutrient supply is limited.

The Fetal Origins of Adult Disease hypothesis accounts for the offspring's increased risk of disease in adulthood by proposing that the adaptations made during critical stages of fetal development may be permanent and therefore "program" the individual for disease in later life. These permanent adaptations including reduced insulin sensitivity, pancreatic beta cell mass and number of nephrons in the kidney would not be advantageous in adulthood and therefore add to the disease risk profile of the offspring. Compounding these limitations is the additional stress of environmental challenges such as obesity and sedentary lifestyle. Thus the offspring's organs permanently adapted to undernutrition in the womb, are poorly suited to respond to the abundance and excesses of adult intake patterns, making them more susceptible to diseases such as metabolic syndrome.



**Fetal nutrient demand affects:
Fetal size and growth pattern**

**Maternoplacental nutrient supply controls:
Nutrient availability
Placental size and transfer capabilities**

**Fetal adaptations and development changes if demand is greater than maternoplacental supply:
Alterations in fetal body composition
Growth of specific organs
Alterations in fetal endocrine status
Fetal cardiovascular adaptations**

The Building

Many studies since Barker's initial findings have attempted to find a direct relation between maternal diet and the later health of their offspring. The strongest evidence for an association involves babies born at a low birthweight (LBW). Low birthweight is often defined as a weight at delivery of less than 2500 grams for an infant born at term (at least 37 weeks of gestation). These babies are at greater health risk during adulthood for elevated blood pressure and impaired glucose tolerance especially amongst thin, small for gestational age (SGA) babies. Current thinking is that once the fetus changes its metabolism to supply its preferred organs such as the brain with nutrients, other organs' development are permanently altered to handle an inadequate nutrient load. These organs then become programmed and unable to adjust to an environment that supplies an abundance of nutrients in later life. The altered metabolism during early development leads to the following adult disease states:

Blood Pressure and Cardiovascular Disease:

In 1990, Barker et al.² found that the highest blood pressures occurred in men and women who had been small babies with large maternal placentas (ponderal index = birthweight divided by length³). They postulated that the discrepancy between placental and fetal size can lead to circulatory adaptations in the fetus, altered arterial structure in the child and hypertension in the adult. The authors concluded, "Prevention of hypertension may depend on improving the nutrition and health of mothers". Moore et al. (J Hypertens.1999)³ showed that low birthweight was negatively associated with the offspring's systolic blood pressure at age 20 in both men and women. As would be expected, this relationship was enhanced with increased weight and weight for height. Their findings led them to consider poor infant growth and low birthweight as risk factors for the triad of disease states that are known as

the metabolic syndrome; type II diabetes, insulin resistance and high blood pressure. Besides elevated blood pressure, other cardiovascular risk factors such as total cholesterol levels show an inverse association with birthweight. Birthweight below 2,600 g was associated with a higher LDL cholesterol level and an elevated ratio of total cholesterol only in males. (Kuzawa and Adair 2003)⁴. Godfrey and Barker (Am J Clin Nutr 2006)⁵ found that males have higher requirements for growth and are more likely to have altered organ function if birthweight is interrupted thereby making males more vulnerable to coronary heart disease than females.

Obesity:

Adult obesity has been found to compound the risk of low birthweight. Vickers et al. (Am J Physiol Endocrinol Metab 2000)⁶ in laboratory studies of fetal programming found that adult obesity and hypertension in rats, found in pregnant rats were fed an undernutrition diet, were produced offspring that were significantly smaller than rats fed ad libitum. These UN offspring showed hyperphagia upon later weaning when supplied with postnatal hypercaloric intake. In addition, insulin resistance, metabolic abnormalities caused by fetal programming were found to include hyperinsulinemia, hyperleptinemia, hypertension and obesity. The researchers found a state of leptin resistance as well as insulin resistance in the offspring of undernourished mothers, which is responsible for the inappropriate catch-up growth and hyperphagia resulting from fetal programming.

In human research, lifestyle factors continue to influence health outcome. The greatest risk for CVD is found in men and women who were small at birth and became obese as adults. Accelerated child weight gain was associated with higher blood pressure in adults in a study by Eriksson et al. (BMJ 2000)⁷. This, confirmed by other studies, shows the effect of fetal programming on adult health.



Remembering the

In 1999, choline was identified as a required nutrient for human growth and recommended daily adequate intake amounts were established by the National Academy of

Sciences. An adequate intake for men was set as 550mg/day and for women 425mg/day. Choline has many functions within the body. One function important for infants is its role as a component of surfactant in the lung. A neonate without surfactant experiences respiratory distress syndrome frequently seen in premature infants. Choline is also a component of the cell membrane bilayer. With choline, the liver is able to package its lipoproteins and send them

into the blood stream. Without choline, the liver fills with fat and fatty liver results. Choline also plays a part in the synthesis of sphingomyelin, the insulating layer around nerve fibers that control nerve impulse transmission. All these functions are vitally important for normal development of the fetus and growing child however, probably the most interesting function of choline in the body is its importance in brain development.

In experimental studies with rats, those that received choline supplements in utero and as neonates showed superior visual spatial memory ability even through maturity and into old age. (Zeisel, *J Am Coll Nutr* 2000)¹¹. The change in memory function appears to be related to the permanent developmental changes in the hippocampus of the brain, which controls memory. During critical stages of fetal development, delivery of choline from the mother appears to influence the rate of birth and death of cells in the hippocampus of the brain. Thus, memory function in the

Blocks of Disease

Insulin resistance, high blood pressure, total cholesterol, and low birthweight. Children with an elevated ratio of LDL to HDL cholesterol (Am J Clin Nutr 2000)⁵ suggest that growth in utero and later on when nutrient intake is more restricted in females.

Children with high blood pressure, type II diabetes and insulin resistance to be greater in those who were born at a low birthweight. Frankel et al. (*Lancet* 1996)⁹ in a cohort study of 1258 men in South Wales, found an increased risk of coronary heart disease associated with low birthweight only in people with high BMI in adulthood. They concluded, "The risk of coronary heart disease seems to be defined by the combined effect of early life and later life exposures."

Diabetes:

Another abnormality related to FOAD whose incidence is well established, is the development of diabetes in the adult offspring of undernourished mothers. Phipps et al. (*Diabetologia* 1993)⁹ recruited 140 men and 126 women age 50 who were born in Preston, England between 1935 and 1943 for whom record of birth size was recorded. Subjects that were found to have abnormal glucose tolerance or type II diabetes at age 50 had a lower birthweight, a smaller head circumference and were thinner at birth. The researchers suggest that the association reflects the long term effects of reduced growth of the endocrine pancreas and other tissues in utero, as a consequence of maternal undernutrition.

In an effort to establish a relationship between size at birth and type II diabetes, Lithell et al. (*BMJ* 1996)¹⁰ observed the incidence of glucose intolerance amongst a cohort of 2322 men born during 1920-4 in Uppsala, Sweden. Results indicated an association between reduced fetal growth and an increased risk of diabetes. This association was especially strong when the infant was thin at birth. The combination of thinness at birth and overweight in adult life was associated with higher insulin concentrations at 1 hour after intravenous glucose, suggesting an effect on insulin resistance rather than impairment in beta cell function. They consider control of obesity in adult life to be especially effective in reducing the risk of noninsulin dependent diabetes in those who were thin at birth.

Limitations and Caveats:

The FOAD hypothesis assumes that both animals and humans are able to adapt to malnutrition by altering hormone production or sensitivity to hormones as an evolutionary advantage designed to protect the highest priority fetal organs and preserve the continuity of the species. Barker suggests that disproportion in body length relative to head size is a way that the fetus is able to redistribute oxygenated blood away from the body to preserve brain function.

In the past, researchers have attempted to definitively determine the mechanisms responsible for the alterations and increased disease risk associated with poor fetal growth. Low birthweight and small for gestational age, common measures of fetal growth, have been shown to misrepresent a fetus that was undernourished during a critical stage in development yet due to genetic disposition (ie, having large parents), meets the standard for normal birthweight or size. In this case, CHD risk factors would not be attributed to fetal undernourishment, yet they may exhibit the triad of disease states in adulthood. Similarly, not all low birthweight or SGA infants may be the result of fetal undernourishment, making the use of data sets from large population studies difficult to interpret.

Other research has shown that the incidence of cardiovascular disease is independent of length of gestation, indicating that fetal growth restriction rather than premature birth to be a better indication of future disease risk. More detailed measurements of body size at birth including placental weight, abdominal circumference and maternal nutritional intake records are needed to allow better understanding of the adaptations that a fetus made to preserve its vital organs. In lieu of prevention, predicting which babies may have experienced arrested fetal development can go a long way in preparing for and possibly avoiding the risk of cardiovascular disease in adulthood.

Next Generation

offspring is dependant on the maternal supply of choline.

It has been known for some time that all pregnant mammals concentrate choline in their amniotic fluid. In fact, the choline concentration in human amniotic fluid is ten times greater than maternal blood levels. Because transport of choline through the placenta from mother to the fetus depletes maternal choline stores adequate maternal intake of choline is of critical importance. An adequate intake of choline during pregnancy has been established to be 450mg and 550mg during lactation.

Folate and choline are perfect examples of nutrients that alter development when in short supply during specific stages of fetal development. Those changes have been shown to profoundly affect the health of the offspring throughout its life making adequate maternal intake essential.



CHOLINE CONTENT OF COMMON FOODS

Food	Choline concentration/ 100 gram of food
Beef liver, pan fried	418.22 mg
Egg	251.00 mg
Wheat germ, toasted	152.08 mg
Chicken, roasted w skin	65.83 mg
Milk, 2%	16.40 mg
Salmon	65.45 mg
Spinach, raw	22.08 mg

Source: Zeisel et al. *Am Soc for Nutr Sci* 2003

Good Nutrition Holds the Key

According to the American Dietetic Association (*J Am Diet Assoc* 2002) the key components of a health promoting lifestyle during pregnancy include "appropriate weight gain; consumption of a variety of foods in accordance with the USDA Food Guide Pyramid; appropriate and timely vitamin and mineral supplementation; avoidance of alcohol, tobacco and other harmful substances and safe food handling." The ADA position paper goes on

to explain that impaired intrauterine growth and development can program the fetus for cardiovascular, metabolic or endocrine disease, and type 2 diabetes.

Nutrient needs can be and should be addressed through a varied diet that includes food sources such as milk and dairy products, whole grains, fruit and vegetables, eggs, meat, fish and poultry. It is surprising that although between 19% and 38% of pregnancies occur in women

who are overweight at the time of conception; nutrient intakes are frequently below the levels recommended for women age 20 to 49 years. One must not assume that weight assures an adequate intake.

Specifically, Minimum daily servings from the Food Guide Pyramid (American Dietetic Association, *J Am Diet Assoc* 2002) during pregnancy are as follows:

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Group	Serving Size	Servings/Day
Grains, breads, cereal, rice and pasta	1 slice bread, 1/2 cup cooked rice, pasta or bulgur, couscous, barley or oats. 1 tortilla, 1/2 bun, bagel. 1 small muffin or biscuit. 1 pancake, or 2 cups popcorn	9
Vegetable	1 cup green leafy raw vegetable, 1/2 cup vegetable such as bok choy, broccoli, corn, collard greens, snow peas, tomatoes, pumpkin, bamboo shoots, carrots or 3/4 cup vegetable juice	4
Fruit	1 medium sized fruit, 1/2 cup berries, cooked or canned fruit or 3/4 cup fruit juice	3
Milk, yogurt, cheese	1 cup milk or yogurt, 1-2 ounces of 1/2 cheese, 1 1/2 cup cottage cheese, 1 cup soy milk or buttermilk	2-3
Meat, eggs, poultry, fish, beans and nuts	2-3 ounces of cooked meat, fish or poultry, (1 ounce=1 egg, 1/2 cup tofu, cooked dried beans, 2 Tbs. peanut butter, 1/3 cup nuts	2 (totaling 6 ounces daily)

It is now becoming clearer that maternal nutritional status affects fetal growth and thereby risks programming the offspring for increased risk of heart disease, diabetes and obesity. Nutrient

and oxygen supply appear to be the dominant factors that determine the developmental success of the fetus. It is well established that fetal development occurs in critical stages and any

interference with the supply of nutrients or oxygen during the different stages can permanently affect fetal organ development.

Q: What if the mom's diet was poor in the beginning, will the fetus compensate later? At what stage is good nutrition most essential?

a: From animal studies, it is known that fetal undernutrition in early gestation produces small but normally proportioned offspring however; undernutrition in late gestation can have a major impact on body proportions without affecting birthweight. Proportionally small babies are at increased risk of high blood pressure when they reach adulthood but do not seem to develop coronary heart disease. In humans however, early gestational exposure to famine is associated with higher LDL/HDL cholesterol concentrations and higher BMI in women. In contrast, individuals who were disproportionately short at birth seem to have a greater risk of coronary heart disease and abnormal function of systems related to the liver. Evidence of this was seen in men and women whose mothers were subjected to the Dutch famine (1944-1945) during the last trimester of pregnancy and later developed impaired glucose tolerance, insulin resistance and increased incidence of Type 2 diabetes in adult life (Fall 2003, *Indian Pediatrics*).¹²

Animal studies also have shown that undernutrition over many generations has a cumulative effect on reproductive performance. When rats were fed a protein deficient diet over 12 generations it resulted in progressively greater fetal growth retardation over the generations which took 3 generations to reverse with a normal diet (Stewart, *Br J Nutr* 1980).¹³ In humans, Godfrey and Barker (*Am J Clin Nutr* 2000)⁵ found that low birthweight mothers tended to have thin infants with a low ponderal index at birth. It is believed that thin babies who were born with a small placenta (low ponderal index) are at an increased risk of insulin resistance syndrome and coronary heart disease as a result of fetal undernutrition in the last stages of pregnancy. They theorize that maternoplacental supply of nutrients is unable to satisfy fetal nutrient demand in low birthweight mothers. Other studies have shown neonatal size to be strongly associated with maternal BMI, height and birthweight. This association may be related to both genetic and environmental factors but is more likely related to the nutritional status of the female throughout her life as well as during pregnancy.

Q: How can arrested fetal development be detected if birthweight and gestational age aren't accurate predictors?

a: Ponderal index and placental size may only be an indirect measurement of maternal ability to transfer nutrients to the fetus however, it is strongly associated with fetal size at birth. In sheep, ewes that were poorly nourished around the time of conception, and then given adequate nutrition early in pregnancy were found to have large placentas. However, ewes that were well nourished around the time of conception and received adequate nutrients during early pregnancy, developed smaller placentas (Godfrey and Barker, *Am J Clin Nutr* 2000).⁵

Q: What effect do specific nutrients have on fetal development?

a: In an observational study of 538 women who delivered at term, those who had high carbohydrate intakes during early pregnancy and low intakes of dairy protein in late pregnancy had smaller placentas and thin offspring. These effects were independent of mother's height, BMI, social class and smoking status. The researchers concluded that, "high carbohydrate intake in early pregnancy suppresses placental growth, especially if combined with a low dairy protein intake late in pregnancy. Such an effect could have long term consequences for the offspring's risk of cardiovascular disease" (Godfrey et al. *BMJ* 1996).¹⁴ Similarly, a cohort study of 40-year-old men and women in England found that women, who had reported animal protein intakes of less than 50 grams/day with a high carbohydrate intake, had a greater incidence of high blood pressure in their adult offspring. Interestingly, women who reported animal protein intakes of greater than 50 grams/day and a low maternal carbohydrate intake were also found to have offspring with high blood pressure. This indicates that correct balance and adequate intake of all nutrients are needed to foster a healthy offspring.

review articles

Maternal weight plays an important role in pregnancy from the success of conception to full fetal growth through enhanced lactational performance. Children of

obese women are at a greater risk of hypertension, gestational diabetes, macrosomia, low Apgar scores and childhood obesity. Hickey (Am J Clin Nutr

2000)15 found that only 30-40% of women actually gain weight within the recommended ranges for pregnancy. The guidelines for prenatal weight gain are:

Body Mass Index (BMI)	Recommended weight gain	Weight gain/ week after 12 weeks
Body Mass Index (BMI) <19.8	12.5 to 18 kg (28-40 lbs)	0.5 kg (~1 lb)
BMI of 19.8 to 26.0	11.5 to 16 kg (25-35 lbs)	0.4 kg
BMI > 26.0 to 29.0	7 to 11.5 kg (15-25 lbs)	0.3 kg
BMI > 29.0	At least 7.0 kg (15 lb)	
Other: Twin pregnancy	15.9-20.4 kg (34-45 lb)	0.7 kg
Triplet pregnancy	Overall gain of 22.7 kg (50 lbs)	0.7 kg

It is important to remember that regardless of mother's prepregnancy weight, low weight gain in either the second or third trimester will increase the risk of fetal growth retardation. Higher weight gains and greater postpartum weight retention are most frequently seen when pregnant teenagers are still growing compared to teens who have completed their own growth. Multiparous teens are also at greater risk for delivering low birthweight offspring. Therefore, adequate weight gain should be encouraged with efforts made toward weight control after delivery.

National intake surveys show that of the many nutrients established by the Institute of Medicine to be essential for pregnant women, several nutrients have been found to be commonly in

short supply in a pregnant women's diet including folate, iron, vitamin B6, vitamin E, magnesium, zinc and calcium.

Specific nutrient requirements can be addressed by adding the following foods to the pre-pregnant woman's or maternal meals or snacks:

Protein: extra 1 cup lowfat milk, 1 egg, or 1 ounce cheese

Calcium: 1/2 cup turnip greens, 1/2 cup yogurt, 1/2 cup tofu or fortified orange juice

Iron: 3/4 cup prune juice, 1 egg yolk, 1 cup fortified cereal, 3 ounces of meat

Folate: 1/2 cup spinach, 1/2 cup split pea soup, 3/4 cup orange juice, 1/2 avocado

Vitamin B6: 1 ounce almonds, 1/2 cup black beans, 2 Tbs. peanut butter

Vitamin E: vegetable oils, seeds and nuts, whole

grains and 2 Tbs. peanut butter

Magnesium: 1/2 spinach, 1 ounce pecans, 1/2 cup whole wheat pasta

Zinc: 3 ounces of meat, 1/2 cup tofu, 1 egg, 1/4 cup wheat germ, 3 ounces crab

Choline: 1 egg, 3 ounces chicken liver, 1/4 cup of wheat germ, 2 strips bacon

In summary:

Women of childbearing years should maintain good nutritional status by eating a varied nutrient dense diet throughout their lives to prevent disease and improve the chances of a healthy pregnancy outcome. Children who were lean at birth should avoid rapid weight gain during childhood and adolescence and adults should avoid obesity which can increase their risk of cardiovascular disease.



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