Long-term health consequences of poor nutrition during pregnancy

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The long-term effects of poor prenatal nutrition are becoming a matter of increasing concern throughout the world. While the consequences of inadequate caloric and/or vitamin intake during pregnancy have been well characterized, in recent years it has become clear that serious long-term adverse effects may also result from gestational nutrient imbalance, even when total caloric intake is more than sufficient to meet the demands of pregnancy. Excessive fat, carbohydrate or protein intake may permanently alter the homeostatic mechanisms in the fetus, predisposing the offspring of affected pregnancies to serious chronic diseases, including cardiovascular disease, diabetes and cancer. This review summarizes the growing literature on this subject, with particular emphasis on the lasting health-related effects of macronutrient imbalance on fetal development.

Nutrition has a critical role in overall health status. Both under- and over-nutrition may seriously impact on long term health status and life expectancy. Well publicized studies over the last 50 years have clearly demonstrated links between obesity and many of the most serious chronic human diseases, including diabetes, cardiovascular disease and cancer ¹.

What is less well-known is the fact that prenatal malnutrition can have lasting effects on the children from affected pregnancies. Most of the research to date has focused on micronutrients, such as vitamins and minerals, which have been widely recognized to play a critical role in fetal health outcome ^{2,3}. A less well-defined, but equally important, area of study is the influence of the macronutrient status in the mother. Carbohydrates, lipids and proteins are necessary for energy requirements and need to be maintained in a proper balance for optimal health and growth. During pregnancy, maternal energy requirements are substantially increased, exacerbating the consequences of an unhealthy or inadequate diet in the mother.

While the idea that inadequate macronutrient status during pregnancy might impair fetal development seems almost self-evident given the metabolic demands of pregnancy, there is a growing body of evidence to indicate that *excessive* macronutrient intake can also have serious long-term health consequences. Currently, the North American diet tends toward excessive fat and carbohydrates, resulting in macronutrient overindulgence. The incidence of diseases associated with overeating is on the rise ^{4,5}. The direct

effects can be seen in the current generation; negative consequences on the offspring of these individuals are only now becoming apparent. In other regions of the world the opposite situation exists, in which people are unable to obtain adequate nutrition, particularly protein. Surprisingly, the effects of inadequate nutrition frequently mirror the effects of overeating, suggesting potential common underlying mechanisms of response to abnormal dietary conditions.

The goal of this article is to summarize the available information on the long-term health consequences of inadequate prenatal nutrition and to link this information to potential underlying mechanisms in pregnancy. The mechanisms involved in fetal metabolic programming will be briefly described, leading into consideration of the consequences of abnormal macronutrient intake on specific organ systems. Finally, we consider the potential long-term public health impact of inadequate prenatal nutritional care, within the context of ongoing efforts to improve maternal nutritional status.

THE CONCEPT OF “FETAL PROGRAMMING”

The first evidence for long-term effects of malnutrition in pregnancy came from studies performed on human populations exposed to famine. A particularly well-studied epidemiological example is the Dutch Hunger Winter. From 1944 to 1945, residents in the Netherlands were subjected to a period of food rationing, where caloric intake fell as low as

400-800 calories per day (typical caloric intake is approximately 2000 calories per day⁶.) Follow-up studies done on people born during that time found that the affected individuals had impaired glucose tolerance, a greater incidence of coronary heart disease and elevated blood pressure⁶. The potential links between overall nutritional status and long term health have been expanded over the years. Essentially, malnutrition *in utero* is viewed as causing the fetus to undergo structural and functional changes that result in an increased risk for disease and physiological impairment in adulthood⁷. How this occurs remains the subject of considerable debate, but a number of clues have emerged from studies in experimental animals. In rodents, insufficient levels of protein are associated with an increase in age-related disorders and thereby a decrease in lifespan⁸. At birth, many of these animals are born smaller than their control counterparts but postnatally they exhibit a period of catch-up growth that has a faster rate of weight gain than the controls⁹. This predisposes the offspring to overeating, causing obesity that presages subsequent disorders¹⁰. The fetus, in effect, is programmed to adapt to the kind of diet that it “expects” after birth, adapting metabolic and hormonal regulatory processes to be compatible with that particular diet¹¹. This results in a constellation of disorders (collectively termed the “metabolic syndrome”) when the postnatal diet exceeds energy requirements. Consequences of disrupting metabolic processes during development include cardiovascular dysfunction, hypertension and obesity¹¹, as well as effects on the urogenital¹² and central nervous systems¹³. Because of the links between hormonal and nutritional status and long-term cancer risk, prenatal dietary abnormalities may cascade into increased cancer incidence. The long-term consequences of fetal malnutrition also appear to be system-dependent: some systems can overcome prenatal nutritional stress, while others appear to be irreversibly programmed¹⁴. It is not yet known what mechanisms are responsible for the programming of some functions, leaving others to remain malleable after birth¹⁴.

One other important consideration in evaluating the effects of prenatal nutrition is that the effects may be highly dependent on when during the pregnancy the metabolic problem occurred. The concept that there are “critical” periods during development in which an abnormal nutrition may have particularly severe effects echoes observations in endocrinology that have shown that the effects of hormone imbalance are likewise highly dependent on the stage of development at which the imbalance occurred¹⁵. As we will see, this may be more than coincidental because many of the lasting effects of prenatal malnutrition may at least partially be based on alterations in endocrine homeostasis. The potential hormonal link is emphasized by studies indicating that long-term effects of prenatal malnutrition may be highly sex dependent. Abnormal protein intake in rat pregnancy, for example, affects blood pressure, food efficiency and body

weight of the offspring in adulthood in a sex-dependent manner¹⁶⁻¹⁸.

MACRONUTRIENT TRANSFER TO THE FETUS: THE ROLE OF THE PLACENTA

In order for the fetus to maintain adequate growth and development, nutrients must reach the uterine environment, commencing before implantation of the embryo. During the first trimester, the placenta has not yet established a strong connection between fetal and maternal circulations, so nutrients are provided by the endometrium and placenta¹⁹. Once the placenta has been established, it acts as the link between the mother and the fetus. The basic structure of the human placenta at birth consists of maternal capillaries, the intervillous space, microvillous membrane (MVM), the syncytiotrophoblast, the basal membrane (BM), the cytotrophoblast, and fetal capillaries¹⁹. The placenta acts as a barrier through which passage of macronutrients is highly regulated, primarily by specific transporter proteins. There are many similarities in the transport of the three major macronutrients, each of which affect the fetal environment accordingly.

Glucose has been one of the most studied macronutrients in relation to fetal development because it is the primary energy source for the fetus. There are six main transporters for glucose (GLUT1 - GLUT6)¹⁹. GLUT1 is the major transporter in the placenta and exists on both the MVM and BM. There is significantly higher expression of GLUT1 on the MVM than on the BM, and it has been widely accepted that the BM acts as the rate-limiting step for glucose transfer from mother to fetus²⁰⁻²². GLUT1 transporter proteins demonstrate saturation kinetics, which assist in the regulation of glucose transfer.²³ However, the fetus can obtain glucose from both maternal circulation and the placenta via breakdown of glycogen precursors^{23, 24}. Thus, both the amount of GLUT1 and the placental concentration of glucose regulate the amount of glucose actually reaching the fetus. Placental glycogen concentrations are highest in early gestation and decrease until term²⁴. Similarly, the concentration of GLUT1 transporters in the placenta decreases over gestation. This could be due to both the immaturity of the placental link during early gestation, as well as increased fetal glucose production towards the end of gestation. Although the overall number of transporters increases to provide for the growing energy needs of the fetus, their absolute concentration declines due to the increased size of the placenta²³. Hence, while the fetus is most dependent on the mother for glucose in early gestation, if the mother experiences hyperglycemia, the fetus will be exposed to this increase in blood glucose concentration throughout gestation.

Amino acid (AA) concentrations are higher in the fetus compared to the mother, an indication of their vital role in

fetal development^{22, 23}. AAs are utilized as sources for carbon and nitrogen, inter-conversion to other amino acids, as well sources of metabolic energy for the placenta or fetus²⁵. While the placenta itself metabolizes and utilizes amino acids²⁶, there are three fundamental steps of AA transfer across a placenta into the fetus: uptake from the maternal circulation across the MVM, transport through the trophoblast cytoplasm, and transport out of the trophoblast across the BM into fetal circulation²⁵. Most AA transport is energy-dependent, the AA being taken into the placenta by transporters, concentrated and then released into the fetal circulation²³. Although AA transporters are highly stereospecific in that L-amino acids are transported more easily than D-amino acids, they also have overlapping specificity, allowing several different AAs to be transported simultaneously²⁶. System A is the most researched and well-understood AA transporter. It is a sodium-dependent, neutral AA transporter, and is found on both the MVM and BM^{22, 23, 25, 26}. Some AAs are not transported from the mother at all, including the anionic AAs, glutamate and aspartate^{23, 25}. These AAs must be produced in the fetal liver or in the placenta itself. Branched-chain AAs are also not simply taken up by the placenta from maternal circulation and then released to the fetus. They are partially metabolized into their ketoacids when they enter the placenta from maternal circulation, and assist in providing nitrogen for further AA and protein synthesis at the fetal liver^{23, 25}. Both of these mechanisms demonstrate the cooperative relationship between the fetal liver and placenta in regulating AA concentration and exposure to the fetus.

Relatively little is known about the transfer of lipids to the fetal environment. Not surprisingly, fetal access to lipids is regulated and determined by the maternal diet as well as placental lipid transport²³. The first crucial step of lipid transfer involves the action of lipoprotein lipase (LPL) on the MVM²². The growing fetus is particularly reliant on arachidonic acid (omega-6) and docosahexaenoic acid (omega-3) provided by the mother²⁷. Maternal intake of both omega-3 and omega-6 fatty acids has been shown to have an effect on membrane composition²⁸. It has also been shown that consumption of high fat diets has deleterious health effects on the fetus²⁷, suggesting some alteration or insufficient regulation of placental transport. With respect to metabolism of fatty acids within the placenta, it appears that medium-chain fatty acids are preferentially provided to the fetus, as a result of chain altering metabolism within the placenta²³. The final step involves ketones, which have been shown to cross the placenta into fetal circulation, and then are readily taken up by fetal tissues for oxidative metabolism. In addition to these specific macronutrient systems, it is important to note that a number of hormonal control systems are affected by nutritional status, potentially leading to lasting effects on the "set-points" of internal homeostatic systems that will extend into postnatal life. The most

significant long-term alterations occur in the hypothalamic-pituitary-gonadal axis²⁹. Insulin levels are severely affected by a high carbohydrate diet, which may predispose to hyperinsulinism in later life³⁰. Effects on glucocorticoid levels have also been documented, which have been hypothesized to correlate to an increased set-point in the hypothalamic-pituitary-adrenal (HPA) axis³¹. The fetus has mechanisms to protect itself against these excesses, but if hormone levels rise sufficiently high they may become saturated and fail. One of the key mediators of glucocorticoid transfer across the placenta is the enzyme 11 β -hydroxysteroid dehydrogenase type-2 (11 β -HSD2) which converts the potent glucocorticoid cortisol into the much less biologically active cortisone³². In the offspring of dams fed low protein diets, placental levels of activity and mRNA expression of the 11 β -HSD2 are reduced³³. 11 β -HSD2 acts as a "gatekeeper", limiting the amount of glucocorticoids that can cross the placenta³². Exposure of the fetus to excessive levels of glucocorticoids increases later susceptibility to inappropriate stress responses, hypertension and renal injury^{34, 35}.

Another regulatory mechanism that is altered is sensitivity to leptin, one of the key regulatory hormones associated with appetite. When there are increased levels of leptin, an individual feels satiated³⁶. Rats exposed to low protein *in utero* and then allowed to self select food postnatally became hyperphagic with elevated plasma concentrations of leptin and an increased fat pad mass, suggesting that they have become resistant to normal satiety signals³⁶. Likewise, increased insulin resistance could also explain the obesity often seen in protein deficient offspring. Similar to leptin, elevated insulin levels suppress appetite through their effects on hypothalamic satiety centers³⁶. However, with reduced insulin sensitivity, this normal satiety response may be lost. Consistent with this hypothesis, selective elimination of insulin receptors in the brain has been demonstrated in mice to result in loss of normal appetite control and obesity³⁷.

EFFECTS OF MACRONUTRIENT IMBALANCE ON SPECIFIC ORGAN SYSTEMS

Congenital Malformations and Birth Weight

Poor glycaemic control in diabetic mothers is associated with numerous serious effects, including a three-fold increase in congenital malformations as well as increases in miscarriage rates and perinatal mortality, compared to those with optimal glycaemic control³⁸. The associated high glucose levels seen in these individuals also put them at an elevated risk for greater fetal and placental growth, leading to an increased risk for cesarean section deliveries³⁹⁻⁴¹. As well, there is an elevated risk for pre-eclampsia, a condition that puts both the mother and child at risk⁴². At the other end of the spectrum, a low carbohydrate intake in pregnancy has a restrictive

effect on fetal growth, indicating that maintenance of glucose levels within the normal range is important for optimal pregnancy outcome⁴³.

One of the goals of the metabolic adaptations to fetal malnutrition appears to be to spare the brain from the effects of an inadequate nutrient supply as much as possible. Nevertheless, effects of prenatal malnutrition on brain development are still observed¹³. As the body attempts to adapt to reduced caloric intake by reducing rates of metabolism, it is hypothesized that decreased cerebral metabolism is maintained after birth¹³. Epidemiological studies have shown neurological, emotional and cognitive effects of prenatal malnutrition¹³. A decrease in dendritic numbers was noted in malnourished offspring⁴⁴. This decline could be associated with a decreased blood flow due to reduced nutrient supply¹³. A diet unbalanced in fatty acids can affect the fetal transfer of essential fatty acids. For example, improper fat intake has been reported to have adverse cerebral effects, with decreased docosahexaenoic acid levels due to reduced fetal transfer⁴⁵.

Congenital abnormalities are seen with increased frequency in fetuses exposed to high glucose levels throughout birth⁴⁶. These outcomes include an increased risk for renal agenesis, obstructive abnormalities of the urinary tract, cardiovascular and multiple congenital abnormalities⁴⁶. Specifically, a 200-fold increase is seen in the incidence of caudal regression in diabetic mothers. While it is a relatively rare condition in healthy mothers, it affects 1 in 350 diabetic births⁴⁷. It is difficult to separate the diabetic effects from the effects of hyperglycemia⁴⁶ since the two conditions usually occur concurrently.

Liver

The liver is one of the most important organs involved in glucose homeostasis, being sensitive to the effects of both insulin and glucocorticoids. It is therefore not surprising that fetal malnutrition has lasting effects on the liver. In rats exposed *in utero* to a low protein diet, there are fewer but larger liver lobules⁴⁸. In adulthood, the response of these livers to glucagon or glucagon plus insulin infusion is altered, glucose output consequent to glucagon stimulation being reduced while addition of insulin resulted in an anomalous initial increase in glucose output followed later by the expected reduction. These changes were associated with both a reduction in glucagon receptors and an increase in insulin receptors in the liver⁹.

Urogenital System

Effects of an unbalanced diet on the urogenital system include increased risks of hypertension and renal dysfunction. A low protein diet predisposes offspring to problems with renal structure and function⁴⁹. Overall, kidney weight in proportion to body weight is smaller⁵⁰, the development of the kidney is impeded and progression to renal failure occurs much sooner than normal^{7,51}.

Low protein and high glucose studies have demonstrated that the offspring of altered nutritional status dams have fewer renal glomeruli^{49, 51}. As a result, the glomeruli undergo compensatory postnatal hypertrophy⁵¹. In turn, this increases the average glomerular volume and elevates protein levels, such as albumin and creatinine, excreted in the urine⁴⁹. Individuals with proteinuria often have kidney disease⁴⁹, as this indicates a decreased permeability of the glomerular membranes⁵⁰. Eventually, this pathway results in renal disorders, particularly hypertension⁵¹.

Part of the mechanism for this effect is probably upregulation of the renin-angiotensin pathway. Studies have observed that low protein diet in pregnancy results in an increased vascular reaction when Angiotensin II (AngII) is administered⁵². Administration of drugs that work to reduce hypertension (e.g. captopril, an angiotensin converting enzyme inhibitor) will counteract this effect in early postnatal life⁵². The offspring of pregnant rats fed a high fat diet exhibit decreased renin and the Na⁺, K⁺-ATPase activity but other than that, it does not appear that a high fat diet has a significant effect on renal function⁵³. By contrast, a maternal low protein diet induces hypertension in the offspring and is associated with a higher level of reactive oxygen species and an increased immune cell infiltration into the kidney⁵⁴, indicating a greater potential for renal damage. Sexual maturation is also affected by prenatal nutritional status. In general, decreased nutrition dampens the ability of fetus to produce gonadotrophins, resulting in a delayed sexual maturation¹². The consequences of reduced fetal gonadotrophin output appear to be particularly severe in males, at least in part because of the dependence of the male on testicular androgen production, for normal sexual differentiation of both the reproductive organs and the brain and pituitary systems responsible for reproductive control. In protein deficient male offspring, one study found higher levels of glucocorticoids in the dams, as well as an increase in ano-genital distance and a delay in testicular descent, markers of sexual differentiation¹². Male rats exposed to any stress *in utero* have less sexual activity⁵⁵.

Cardiovascular System

The heart and major blood vessels are one of the first organ systems to develop. These begin functioning during the first trimester in humans, and continue to develop into late gestation. Since development of the heart and vasculature begins early and continue for the remainder of pregnancy, it is not surprising that significant effects are seen in response to maternal diet.

Relatively few studies have focused specifically on prenatal abnormalities in glucose regulation and their potential long term cardiovascular sequelae, but what has been done suggests that glucose regulation is critical for normal cardiac development. It is known that a high blood glucose concentration in the mother is transferred to the fetus⁵⁶. It has also been determined that high concentrations of

Table 1: Effects of high prenatal lipid intake on offspring.

Observations in offspring	Implications	References
- increased blood pressure in females - abnormal plasma lipids and triglycerides	- leads to hypertension and other vascular abnormalities	11, 60, 61 60, 61
- fatty acid abnormalities in aortic tissue composition - vascular fatty acid profile pronounced in females in adulthood	- decreased functionality	61 61
- decreased relaxation by acetylcholine	- increased vascular dysfunction	62
- decreased maximum relaxation of arteries		

fetal blood glucose lead to the premature fetal secretion of insulin²². A large study on the outcomes of 4180 pregnancies complicated by gestational or type II diabetes found that initial fasting serum glucose and glycosylated hemoglobin levels were significantly higher in pregnancies with major congenital abnormalities. Cardiac malformations accounted for 37.6% of these major abnormalities⁵⁷.

Low maternal protein and high maternal fat intake diets have both been demonstrated to have serious effects on the cardiovascular system. In offspring of female rats who consumed a low protein diet, increased apoptosis of the cardiac myocytes has been observed during the fetal period, leading to hypertrophy⁵⁸. In particular, the left ventricles were found to initially have a thin muscular wall, which then thickened past the point of normalcy. This increased rate of cell division predisposes the myocytes, and therefore the heart, to dysfunction or disease later in life⁵⁸.

Since lipids are the main structural component of cell membranes, it is not surprising that maternal fatty acid status appears to affect fetal development of the cardiovascular system. Most studies to date have been done using the rat model. A low arachidonic acid diet has been found to have a profound influence on cardiovascular development *in utero*: in both rats and humans exposure to a low arachidonic acid diet in pregnancy reduces birth weight, increases resting heart rate and reduces the number of insulin receptors on heart muscle, which can lead to increased cardiac muscle insulin resistance later in life⁵⁹. A high fat maternal diet also appears to predispose the fetus to cardiovascular dysfunction. It is known that endothelial dysfunction causes an increased risk in cardiovascular disease, and any developmental irregularities in early gestation will lead to endothelial dysfunction of the vasculature⁶⁰.

In general, increased lipid consumption during pregnancy leads to decreased ability of the vasculature to adapt to pressure changes, which adds to the already impaired functionality of the heart and blood vessels. In humans, an

elevated level of fatty atherosclerotic streaks has been observed in the fetus when the maternal diet was high in saturated fats⁶².

The Mammary Gland: Breast Cancer Incidence

The prevalence of breast cancer is steadily increasing in countries with high dietary fat consumption. In comparison, countries with low fat intake such as those in East Asia demonstrate a far lower level of breast cancer occurrence¹⁰. While there is a substantial genetic component in breast cancer, genetics are not the regulating factor behind this higher incidence in Western over East Asian countries, as shown by the increase in breast cancer rates among Asian immigrants to the West¹⁰. There has been intense research into the correlation between a high fat diet and breast cancer incidence. Investigations have focused on the role of maternal diet to determine if any correlations can be detected, in order to determine the origins of breast cancer.

It has previously been observed that a high estrogenic environment *in utero*, such as in the case of dizygotic female twins, increases the risk of breast cancer in female offspring⁶³. It has been hypothesized that the greater occurrence of breast cancer in offspring of mothers ingesting a high fat diet may be due to increased aromatization in fat tissue, as well as activation of P450 aromatase by fatty acids resulting in a higher rate of conversion of androstenedione to estrone¹⁰. A 1997 study conducted by Hilakivi-Clarke et al has shown that in comparison to low-fat offspring, prenatal exposure to a diet high in n-6 PUFA (polyunsaturated fatty acids) causes an increase in the levels of circulating estrogens by 30%, associated with an increased risk of breast cancer in the offspring⁶⁴. No increase in breast cancer was noted if the levels of estrogen were not raised, giving further support to the role of estrogen in the initiation of breast cancer¹⁰. As there is no change in the offspring's production of estrogen postnatally, the influence of the estrogen must have effect during the *in utero* period. It also appears that changes are

restricted to exposure occurring during the initial rapid growth period⁶⁴, thereby indicating a critical period when exposure can affect neoplastic occurrence.

A high estrogenic *in utero* environment is also associated with alterations to mammary gland development¹⁰. In offspring of rats fed a high-fat diet, the mammary fat pad was larger, epithelial cell density was greater and there were more terminal end buds (TEB's)⁶³. These changes in mammary morphology of rats are theorized to play a role in the increased incidence of breast cancer. TEB's are the sites of carcinogen-induced malignant transformation, therefore, any increase in the number of these structures potentially increases the number of sites from which carcinoma could arise^{63, 64}. This correlates with the location of malignant alteration in the human, the terminal ductal-lobular units, which arise directly from TEB's. An increase in locations for neoplastic transformations suggests that the greater incidence of breast cancer in high fat-exposed offspring may at least partially arise through alterations in mammary structure.

Mammary structure alone may not, however, completely explain the observed increases in breast cancer incidence. In one study, the onset of puberty was advanced in the offspring of mothers fed the high-fat diet⁶³. An association between early puberty and breast cancer risk has previously been identified in humans⁶⁵. Precocious sexual maturation may further enhance the susceptibility of those exposed to high levels of prenatal estrogen.

Different pathways have been proposed as possible links between a high n-6 PUFA diet resulting in n-3 deficiency and increased breast cancer risk. These pathways, while not fully investigated, are important to consider. For one, prostaglandins, products of arachidonic acid metabolism, are lower in those who consume increased levels of n-3 PUFA⁶⁶. While it seems biologically plausible that the protective mechanisms of n-3 PUFA work through a decrease in prostaglandin, no increase in prostaglandin levels has yet to be documented as a correlation with tumour growth¹⁰. Another suggested pathway is the decrease of the compounds 12-hydroxyeicosatetraenoic (12-HETE) and 15-hydroxyeicosatetraenoic (15-HETE) in the mammary tumour tissue of those fed increased levels of n-3 PUFA⁶⁶. It has also been proposed that a change in lipid peroxidation activity resulting from the addition of n-3 PUFA may provide additional protection⁶³. Cells that exhibit increased lipid peroxidation are more likely to undergo apoptosis and therefore have less probability of malignant transformation⁶³.

SUMMARY AND CONCLUSIONS

The value of prenatal nutritional intervention as a means of improving long term population health has been amply demonstrated by experience with micronutrients. In the

1990s, for example, it was established that the incidence of neural tube defects in pregnancy could be dramatically reduced by supplementation of the diet with folic acid³. Since 1998, when the US Government instituted folate supplementation of grain products, the incidence of neural tube defects in the US population has substantially declined⁶⁷.

It now seems likely that even greater long-term health advantages could result from preventing macronutrient imbalance in pregnancy. All three macronutrient imbalances discussed here have detrimental outcomes that could be prevented with proper care and education. Unfortunately, current education programs are criticized for not offering enough information for the most at risk groups, specifically those with gestational diabetes⁶⁸. For example, education centers helped to prevent abortion risk, but women were still at increased risk for severe malformations due to improper glycaemic control⁶⁸. Many of the drugs available for the treatment of diabetes, other than insulin, are however still under review to investigate their potentially teratogenic effects, which limits the potential for therapeutic intervention⁶⁹.

Increased fat intake in the Western world is a great concern for the entire population, but especially for women of child-bearing age. The high-fat diets in the rat studies that have demonstrated adverse pregnancy outcome are representative of the fat intake of Caucasian women in Westernized countries. There is a great need for further education, not only on the amount of fat consumed, but also the type of fat. In most Western countries, the diet is high in arachidonic acid and deficient in docosahexaenoic acid¹⁰. Saturated fats need to be limited in the diet for many reasons, not the least of which is the disruption of the fetal transfer of essential fatty acids²⁷.

Protein deficiency in the developing world will always be a concern but greater understanding of its consequences may improve long term health outcomes. Insufficient levels of protein directly affect the number of enzymes available for lipid metabolism⁴⁵. Similarly, altering the levels of nutrients available appears to affect levels of potential methyl donors, thereby affecting the expression of certain genes⁷⁰ via epigenetic mechanisms⁷¹. Modifiers of gene expression such as DNA methylation or histone acetylation essentially turn genes off so proteins are not produced⁷². It has been suggested that supplementation of low protein diets with methionine, to provide methyl groups⁷³, could ameliorate some of the long term adverse consequences, but whether or not this is an effective practice is still unclear⁷¹.

Through these educational and prenatal programs, care must be taken to address cultural and ethnic differences between the groups to ensure that any cultural food requirements are properly addressed. Differences have also been found between food purchasing behaviour and socioeconomic class, with those in the lower end more likely

to purchase less nutritionally dense foods, indicating a target group where increased focus must be placed on changing food buying habits⁷⁴.

More research is needed to determine the mechanisms of macronutrient pathology. However, this should not prevent the implementation of programs to help expecting mothers provide for their growing fetus. In light of all the evidence presented, it appears that the best recourse is patient education and providing access to premium prenatal programs⁶⁸. This is required to protect the health of not only the offspring, but also of the mother. It has been stated repeatedly in the scientific literature that the prevention is the best defense. By providing the mother with information and therapy to avoid many of the pathologies noted, the offspring is given the optimal chance at survival.

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