International Journal of Health Sciences and Research
www.ijhsr.org ISSN: 2249-9571

*Review Article*

# Maternal Protein Restriction Determines the Fate of the Fetus - A Review

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*Received: 20/05/2016* *Revised: 10/06/2016* *Accepted: 13/06/2016*

## ABSTRACT

Maternal nutrition proffers the major intrauterine environmental conditions that govern and signal changes in the expression of the fetal genome. Any untoward alterations may have long term consequences that may even last lifelong. This phenomenon is termed as fetal programming and led to Dr. Barker propounding the theory of fetal origins of adult diseases. [1] Maternal protein restriction, whether it occurs before conception, throughout gestation or during lactation, may lead to physiological adaptations in the fetus that will affect the health of the offspring in adult life. The impact of the insult varies with the duration and composition of the nutrition. [2] The placenta, a maternofetal organ joining mother and offspring during pregnancy in mammals, serves as an endocrine organ in the maternal placental fetal complex. [3] Successful placental development is decisive for optimal growth, maturation and survival of the embryo or fetus. The fetal origin hypothesis proposes that adult cardiovascular and metabolic disease originate through developmental plasticity and fetal adaptations. Evidences show that alterations in placental growth and vascular resistance altered nutrient and hormone metabolism in the placenta and changes in nutrient transfer and partitioning between the mother, placenta and fetus all have important effects on the fetal adaptations thought to be central in fetal endocrine programming. [4]

***Keywords:*** Maternal nutrition, maternal protein restriction, placenta, FEPAD.

## INTRODUCTION

Maternal nutrition is a key player during gestation. The composition and the timely intake of essential nutrients during early, mid and late gestation is understood to be crucial for proper fetal development and organ differentiation. The central roles played by maternal protein in the process of fetal development during gestation are now being recognized and widely acknowledged. Upon survey of the pertinent literature, much evidence from research employing appropriate animal models over the past few decades has revealed both the significance of adequate maternal protein and the possible ramifications thereof in human scenarios. Undernutrition was proposed very early on to be a likely programming stimulus, although others such as excessive fetal exposure to glucocorticoids have also been proposed and proved in the etiology of FEPAD (Fetal Endocrine Programming of Adult Disorder).[5] During normal gestation, the placenta undergoes a variety of physiological changes that are regulated by angiogenic factors, hormones and nutrient-related genes to maximize the efficiency in meeting the ever-increasing demand for nutrients during the different phases of gestation. Perturbations in the fetomaternal environment following protein restriction or under nutrition will adversely alter the above changes. Ecological influences may lead an organism along certain pathways

during sensitive and often brief periods of development, so that it may adapt distinctively better to the future environment in which it is likely to live. [6] The developmental plasticity during intrauterine development is beneficial if the extra uterine environment is consistent with that signaled via the mother before birth. This review attempts to discuss the influence of the nature of maternal under nutrition or restriction on key issues such as placental development and weight, body weight, intrauterine growth restriction, fetal weight, organ weight, hormones secretion, gene expression and fetal programming.

**Nature of Maternal nutrient restriction**

Although the majority of studies had analyzed the effects of maternal under nutrition on the developing fetus and investigated global under nutrition and sufficiently examined the effects of deficiencies of particular dietary components, there is increasing evidence showing that altered gestational macronutrient balance, [7] micronutrient intake [8] and overall caloric intake, [9] can each influence postnatal disease risk. Protein deficiency during pregnancy has been frequently investigated. Studies performed earlier showed an inverse relationship between maternal protein intake and the systolic blood pressure of rat offspring, and that the hypertension witnessed in offspring from low-protein-fed dams was associated with increased pulmonary angiotensin-converting enzyme activity. [10] Additional studies have consistently demonstrated hypertension in offspring following maternal protein restriction, with some studies also reporting increased fetal mortality. Low-protein diets throughout gestation also have been shown to decrease serum estradiol concentrations in the female offspring. [11] In humans, an isocaloric low-protein diet during pregnancy has also been associated with augmented systolic blood pressure in adolescent males, independent of birth weight and maternal triceps skin fold thickness throughout pregnancy. [12] Protein underfeeding throughout gestation reduced the lifespan of mice when dams were allowed to overfeed throughout lactation. [13] The progeny of rat dams subjected to protein under nutrition throughout gestation and lactation usually become considerably more obese, insulin resistant, hyperlipidemic and hypertensive. [14] It is not clear how maternal protein restriction supply affects fetal growth. The embryonic cells are able to respond directly to amino acid deficiency by increasing the expression of a variety of genes, whose products regulate growth and differentiation. [15]

**Timing of maternal protein restriction**

Studies on offspring of women affected by the Dutch famine have shown that early gestational under nutrition primarily affects the cardiovascular system, leading to a greater occurrence of coronary heart disease, a more atherogenic lipid profile and troubled blood coagulation profiles. [9] Studies in ruminants also have established that undernutrition can have profound, untoward effects in the fetus. In sheep, restricted maternal nutrition in early to mid-gestation was related to an increase in placental weight, an increase in crown-rump length, and lower fetal to placental weight ratios. [16] Gheorghe and Goyal reported considerable changes in mouse placental gene expression in response to maternal hypoxia for 48 hours, from the $15.5^{th}$ day post coitus to $17.5^{th}$ day post coitus and demonstrated an insightful down-regulation of cell growth and proliferation and an up-regulation of genes coding for apoptotic proteins. [17] Maternal low protein diet treatment exclusively during mouse oocyte maturation 3.5days prior to conception is sufficient to alter postnatal phenotypes, resulting in behavioral and cardiovascular changes indicative of adult disease. [18]

Maternal protein restriction during mid-gestation in mouse resulted in ketone body metabolism. [19] Rats fed a diet leading to 50% global maternal under nutrition during the last week of gestation experienced decreased glucose levels in

maternal plasma. [20] Rats fed on 6% casein low-protein diet from day 5 of gestation showed 27% reduced transfer of the non-metabolizable amino acid C-α amino isobutyric acid from the maternal-fetal circulations. [21] Noblet *et al*. suggested that when energy is limited in early gestation, the cellular growth of the placenta is limited, resulting in its inability to respond to nutritional rehabilitation. [22] Maternal protein restriction during embryonic day 10 produced a predictable stress reaction in the mother, as evidenced by prominent maternal plasma corticosterone, and a reduction in fetal weight and hypotrophy of the basal and labyrinth zones of the placenta. The reduction in fetal and placental weights was observed in both mid and proximal horn positions, the uterine regions which receive the least and greatest levels of maternal blood flow, respectively. [23]

**Placental weight and gene expression**

Placental weight is associated with dietary intake in mammalian pregnancies. The result of maternal under nutrition on placental weight is unequivocal; the timing, length and etiology of nutritional restriction can each differently affect placental mass. Women subjected to starvation in their third trimester of pregnancy had light placentas and newborns with low birth weight, but an unaltered placental weight: birth weight ratio when compared to non-starved women. [24] A wide array of genes are required for proper development of the placenta; research points to increasing numbers of genes known to have active roles in the process, in part, due to the discovery of numerous lethal embryonic null mutants secondary to placental failure. [25] In the human trophoblast *in vitro*, several gene classes are strongly up- regulated and down-regulated during the course of differentiation. [26] Global maternal undernutrition during early to mid-pregnancy in sheep increased the placental weight: fetal weight ratio by enhancing placental weight at term without altering fetal weight. [16] A low protein diet administered to mice during pregnancy caused major variations in both body mass and gene expression profiles of liver and skeletal muscle of the newborn mice. The expression changes were chiefly related to mitochondrial genes but were significantly different in liver and skeletal muscle. [27] In the spontaneously hypertensive rat placenta, several proteins, angiotensin receptor type I and inducible nitric oxide synthase were upregulated, while angiotensin converting enzyme and peroxisome proliferator-activated receptors (PPAR's) alpha and gamma were down regulated. [28] Gheorghe *et al*., compared gene expression levels between normal placentas at embryonic day 17.5, and those from pregnancies in which, the mothers were exposed to seven days of protein deprivation from embryonic day 10.5 to embryonic day 17.5. They inferred that protein deprivation altered the expression of several genes involved in DNA methylation, histone acetylation, and epigenetic regulation of gene expression. The expression levels of histone deacetylase 7A and methionine adenosyltransferase II alpha were elevated several fold. A number of genes involved in the p53 oncogene pathway were up-regulated. In addition to p53 itself, its positive regulators Zmis, Jmy, and Hipk2, as well as genes activated by p53, were induced. These p53 pathway proteins are important regulators of cell growth and proliferation [29] The molecular mechanisms whereby genes are repressed or active in a stable manner are exceedingly complex. The best studied of these epigenetic modifications is that of DNA methylation, which first was suggested. [30] DNA methylation and posttranscriptional gene regulations are triggered by MicroRNAs. [31] The expression of leptin and its secretion from the placenta are species-specific, under the acute regulation of cAMP, but not glucocorticoids [32] We found that maternal protein restriction by 75% during mid-gestation in mouse results in the over expression of the Ornithine Decarboxylase gene in placenta (Unpublished) by 77%. The ornithine decarboxylase enzyme is the prime rate-

limiting enzyme in polyamine metabolism. Polyamines plays important role in angiogenesis and are essential for the normal growth and development of the fetus.

**Changes in angiogenesis and vasculogenesis**

Angiogenesis is formation of new vessels from a preexisting blood supply vessel and vasculogenesis is afresh pattern of blood vessels from mesoderm precursor cells; both are processes critical to maternal-fetal exchange. The vascular endothelial growth factor (VEGF) and angiopoietin proteins are critical to these processes. [33] Insult induces compromise in placental vasculogenesis and angiogenesis, and impairs exchange between the maternal and fetal circulations, [34] ultimately resulting in IUGR fetuses. Endothelium derived nitric oxide (NO), is an intermediary of angiogenesis and plays a role in modulating vascular resistance. Vascular endothelial growth factor stimulates the release of NO and up regulates the expression of NO synthetase. A critical role for NO during pregnancy is suggested by studies of fetuses with intrauterine growth retardation. [35]

**Remodeling of nutrient transfer ability**

Fetal nutrient accessibility results from the interrelationships of maternal food intake, accessibility of nutrients in the maternal circulation, and the capacity of the placenta to powerfully transport substrates to the fetal conduction. Global maternal nutritional status affects transporters in the placenta, there by influencing the rate of nutrient delivery through the placenta. For example, rats fed a 50% global maternal under nutrition during the last week of gestation incident caused glucose levels to decrease in maternal plasma. [36] The maternal-to-fetal glucose concentration gradient, which drives facilitative glucose diffusion across the placenta, is also abridged and glucose transporter 3 expressions are noticeably decreased, suggesting a mechanism for placental glucose transport dysfunction. Although glucose represents the prime metabolic fuel during gestation, specific possessions of maternal dietary glucose restriction on placental and fetal development have not been extensively studied. Placental transport of amino acids is pivotal for fetal maturity, and is affected by the activity and location of amino acid transporter systems. In humans, reduced circulating concentrations of essential amino acids, such as leucine and lysine, in growth restricted human fetuses [37,38,39] and imply that there is a global alteration of placental amino acid transport activity in intrauterine growth retardation. In animal models, rats fed 6% casein low protein diet, from day 5 of gestation show reduced transfer of non-metabolizable amino acid C-α amino isobutyric acid from maternal to fetal circulations, compared to well-fed controls. Adequate placental transport of fatty acids to the fetus is critical for normal fetal improvement and growth, as fatty acids play multiple roles as cell membrane components, energy sources, and precursors to cellular signaling molecules. Intrauterine growth retarded placentas show disrupted lipid metabolism and altered microvillus plasma membrane lipid hydrolase actions. Both these factors impact flux of fundamental fatty acids and preformed long chain-polyunsaturated fatty acids to the human fetus. [40]

**Variations in hormone secretion:**

Secretion of hormones can be affected by maternal protein restriction, which in turn, can affect fetal development. Glucocorticoids, IGFs and leptin play essential regulatory roles in fetal development and homeostasis. Glucocorticoids are essential for maturation of fetal tissues so that the organs they form can cope with extra uterine life. [41] Excessive exposure to endogenous glucocorticoids *in utero* decreases fetal growth and is a predisposing factor for anxiety disorders in adult rats. [42] Insulin like growth factors (IGF) are a family of hormones acting in autocrine, paracrine and endocrine fashions to modulate growth. [43] The IGF ligands (IGF1 and IGF2) are controlled by a family of proteins known as

the IGF binding proteins (IGFBPs), and these interactions regulate fetal development. In pregnant women, the concentration of the IGFBP1 is negatively associated with birth weight. [44] Apart from satiety, leptin plays a key role in the regulation of energy homeostasis in adults, and has such a likely role in fetuses as well. In humans, plasma leptin concentrations in growth restricted newborns are low; however these concentrations increase in infants by one year of age. [45] The enhanced plasma leptin in infants is connected with a weight gain and an increase in subcutaneous tissue. [46] Offspring of sheep [47] and rodents [48] with intrauterine growth retardation show resistance to the anorexigenic effects of leptin as adults, which clearly suggests *in utero* programming as a predisposing factor for obesity in adults. The conclusions in humans and in animal models gleaned from a careful survey of the pertinent literature indicate that under nutrition *in utero* programs leptin dysregulation to signally cause early obesity in later adult life.

## CONCLUSION

Poor maternal nutrition and child nutrition is common in developing and developed countries. Optimal growth, development, survival and maturation of the fetus into healthy adults necessitate fully developed placental growth. Various experimental and epidemiologic studies have suggested the key influence of the intrauterine environment on life, and the diseases to which individual is susceptible to acquire as an adult. For the most part, these odious influences, whether maternal hypoxia, protein or caloric deficiency/ excess, amongst a host of other factors, characterize types of maternal stress. In the present review, we examine certain aspects of maternal protein or under nutrition on placental weight, fetal weight, maternal hormone changes and gene expression in the placenta as a consequence of maternal stressors. To examine these matters in a controlled mode, and in a species in which the genome has been sequenced, most of these reported studies have been performed in the mouse, rat and swine. While each individual maternal stress is reflected by up- or down-regulation of specific genes in the placenta, functional analysis reveals some patterns of gene expression common to the several forms of stress. Amongst the host of genes involved, of paramount importance are the genes involved in DNA methylation and his tone adaptation, cell cycle regulation, and related global pathways of great relevance to epigenesis and the developmental origins of adult health and disease like diabetes and hypertension. Hence, it is concluded that maternal protein restriction is signally involved in programming and in predisposing the fetus to the development of several metabolic disorders in adult life.

## ACKNOWLEDGMENTS

We sincerely thank Dr. Daniel Andrew, Post Doc Fellow, Department of Biochemistry, Indian Institute of Science, Bangalore for technical assistance and Dr. B. Chitra, Assistant Professor, Department of Biotechnology, Srimad Andavan Arts and Science College, T.V kovil, Trichy for her assistance.

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How to cite this article: Vijayakumar ABS, Gomez M P. Maternal protein restriction determines the fate of the fetus - a review. Int J Health Sci Res. 2016; 6(7):341-348.

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