



## *Dietary Proteins, Developmental Programming, and Potential Implication in Maternal Obesity*

Alireza Jahan-mihan; PhD; RDN\*<sup>1</sup>

<sup>1</sup> Department of Nutrition and Dietetics, University of North Florida, Jacksonville, FL, USA 32224.

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#### \*Corresponding author:

alireza.jahan-mihan@unf.edu  
Department of Nutritional  
and Dietetics, Brooks College  
of Health, University of  
North Florida, 1 UNF Dr.  
BLDG 39, Room 3057A,  
Jacksonville, FL, USA.

Zip code: 32224

Tel: (904) 620-5359

### ABSTRACT

**Background:** Proteins are known mainly based on their metabolic and nutritional functions including protein synthesis and a source of energy. In spite of various physiological properties attributed to proteins, their functions have neither been addressed by assessing quality of proteins nor by nutrition and dietetic practices. **Methods:** Studies were included if they were randomized animal studies, clinical trials and systematic reviews/meta-analysis published in English language. **Results:** The effect of maternal diet in general and dietary proteins in particular during development on health of offspring has been well-studied. Protein content as well as source of protein in the diet consumed during pregnancy and lactation influenced the risk of metabolic syndrome characteristics in offspring. Both high and low protein diets showed detrimental effects on health of offspring. Moreover, comparison of maternal casein-based diet with soy protein-based diet showed more favorable effect on body weight, body composition, blood pressure, and glucose metabolism in offspring. However, the role of maternal dietary proteins in developing the risk of metabolic syndrome characteristics in offspring in gestational obesity is still unclear and needs further study. **Conclusions:** Dietary proteins are determining factors in developmental programming. Both quantity and source of proteins in maternal diet influenced the development of metabolic syndrome characteristics in offspring. However, whether they have the same function in presence of gestational obesity is still unclear and needs further study.

**Key words:** *Dietary proteins; Developmental programming; Maternal obesity; Metabolic syndrome*

### Introduction

The notion that fetal and early post-natal nutrition plays a major role in development of fetus and infant is not new and far from novel. There have been massive recommendations and

prohibitions regarding maternal nutrition during pregnancy across the cultures for thousands of years. It is well-established that nutrition during pregnancy and lactation is a predominant factor in the development of somatic structures, endocrine

systems, and homeostatic mechanisms in the fetus and infant. The novelty of this field originates from the fact that these effects influence the risk of chronic diseases including obesity, hypertension, diabetes, and cancer in later life (Adair *et al.*, 2001, Barker and Law, 1994, Eriksson and Olsson, 2004). The link between early ontogeny and later life health has been named fetal programming, which is defined as the process whereby a stimulus during a critical period of early development results in long-term physiological consequences (Kapoor *et al.*, 2006, Lucas, 2005). This critical window can be open even after birth and therefore, the developmental programming can be a more suitable term covering this crucial period. The developmental programming is the result of interaction between the in-utero and post-natal environments that has been captured in the Predictive Adaptive Response (PAR) hypothesis. According to the PAR hypothesis, offspring weaned to diets similar to those of their mothers will adapt more appropriately to their environment than those who receive an unmatched diet (Gluckman and Hanson, 2004). The role of maternal diet in general and dietary proteins in particular in developmental programming received considerable study. This review is an attempt to examine current findings in the field with more focus on maternal obesity and also to identify the gaps that need to be addressed in the future.

### Materials and Methods

Studies were included if they were randomized animal studies, clinical trials and systematic reviews/meta-analyses published in the English language.

### Results

**Maternal obesity:** Maternal obesity or gestational diabetes during pregnancy increases the risk of obesity and/or glucose intolerance in offspring (Fowden and Hill, 2001, Ogden *et al.*, 2014, Plagemann *et al.*, 1997). It is particularly important because more than two-thirds of women aged from 20 to 39 in the United States are overweight and/or obese and half of them are

obese (de Campos *et al.*, 2007). An association has been found between increased nutrient supply before birth and later obesity. Intrauterine exposure to maternal obesity is associated with an increased risk of metabolic syndrome (Boney *et al.*, 2005) and obesity (Lawlor *et al.*, 2007) in later life. Obesity in mothers has been associated with gestational hypertension, preeclampsia, gestational diabetes (GDM), and high fetal birth weights greater than 4000 g. GDM results in hyperglycemia and hyperinsulinemia in the fetus during late development and higher risk of obesity in later life compared to infants of non-diabetic mothers (Boney *et al.*, 2005, de Campos *et al.*, 2007, Lawlor *et al.*, 2007, Ogden *et al.*, 2014, Plagemann *et al.*, 1997, Silverman *et al.*, 1991). Higher concentrations of insulin in fetus can potentially influence the development of regulatory systems permanently. For example, higher concentrations of plasma insulin within the immature hypothalamus may cause permanent alterations in life-long dysplasia of the central nervous nuclei regulating food intake and body weight (Dörner and Plagemann, 1994, Plagemann *et al.*, 1999). Fetal hyperinsulinemia can also lead to hyperhomocysteinemia (Fonseca *et al.*, 2002, Jiang *et al.*, 2007) that may result in DNA hypomethylation (Jiang *et al.*, 2007), causing further adverse effects on development of fetus (Jackson *et al.*, 2002, McMillen and Robinson, 2005). Obesity during pregnancy may also influence fetal growth and post-natal outcomes independent of GDM (Boney *et al.*, 2005, Lawlor *et al.*, 2007, Schäfer-Graf *et al.*, 1998, Silverman *et al.*, 1991). It has been suggested that in obese mothers without clinical signs of GDM, fetal hyperinsulinemia may occur due to maternal mild hyperglycemia which is below the threshold as defined for GDM.

**Dietary proteins and developmental programming: protein content:** Dietary proteins contribute to regulation of food intake, body weight, glucose and lipid metabolism, and blood pressure. Both amino acid composition (Jiang *et al.*, 2007, Lucas *et al.*, 1996, Ozanne *et al.*, 1996a, Ozanne *et al.*, 1996b, Petrie *et al.*, 2002,

Rees *et al.*, 2000, Steegers-Theunissen and Steegers, 2003) and characteristics related to molecular structure of proteins including digestibility, bioactive peptides (BAPs) encrypted in their amino acid sequence (Anderson *et al.*, 2004, Daniel *et al.*, 1990, FitzGerald and Meisel, 2000, Froetschel, 1996, Jahan-Mihan *et al.*, 2011a, Lan-Pidhainy and Wolever, 2010, Leng *et al.*, 1985, Meisel, 1993, Nagata *et al.*, 2005, Nurminen *et al.*, 2000, Paroli, 1988, Pupovac and Anderson, 2002, Schusdziarra *et al.*, 1984, Teschemacher, 2003) and also their digestion kinetics (Boirie *et al.*, 1997, Fouillet *et al.*, 2002, Jahan-Mihan *et al.*, 2011a, Jahan-mihan *et al.*, 2011c, Leprohon and Anderson, 1982) are determining factors in their physiologic and metabolic properties. The effect of protein quantity in maternal diets during pregnancy on the risk of development of metabolic syndrome in offspring has been investigated. In rats, low protein maternal diets increase blood pressure (Rees *et al.*, 2000, sasaki *et al.*, 1982), body weight (Rees *et al.*, 2000), and adiposity (Leprohon and Anderson, 1982). However, high protein maternal diets increase body weight (Rees *et al.*, 2000), blood pressure, and food efficiency (Thone-Reineke *et al.*, 2006) but decrease energy expenditure (Beyer *et al.*, 2007, Daenzer *et al.*, 2002) in offspring. Nevertheless, low protein intake is less likely to be a major factor affecting majority of women's diets in developed countries. The average protein consumption in 20-39 years women in the US is 71.3 g/day (NAHNES 2011-12) which is far beyond the recommended amount of protein (46 g/day for women in the ages of 19-70+) (Nutrition for everyone, 2014). However, in spite of enormous studies on the role of maternal dietary proteins in fetal programming (Rush *et al.*, 1984), only a few studies have examined the role of a gestational high protein diet. In humans, a 40-g protein supplement added to the diets of black women during pregnancy resulted in lower birth weight in offspring compared to those born to mothers fed on a low protein supplement (6g as 7.5% energy) beverage (Rush *et al.*, 1984). The underlying mechanism is unclear at present.

Moreover, postnatal high protein diet alone had no effect on body composition or metabolic rate (Beyer *et al.*, 2007). In rats, a maternal high protein diet fed throughout pregnancy and lactation resulted in higher blood pressure in male offspring compared with those born to normal protein fed dams (Langley and Jackson, 1994). In another study, maternal high protein diet resulted in higher body weight at the beginning of puberty, persisting until the end of the experiment (week 22), but just in female offspring of rats (Jahan-Mihan *et al.*, 2015). A high protein diet fed during gestation resulted in increased food efficiency (Petrie *et al.*, 2002) and lower energy expenditure (Beyer *et al.*, 2007, Daenzer *et al.*, 2002). However, the results from studies examining the effect of quantity of protein in maternal diet are not consistent. For example, "Hope Farm" and "South Hampton" low protein diets that have been used widely in various experiments in this field gave contradictory results: When the Southampton diet was given to the dams, higher systolic blood pressure was found in the offspring (Langley-Evans *et al.*, 1999, Langley and Jackson, 1994), the Hope Farm diet, resulted in normotensive, insulin-resistant offspring (Lucas *et al.*, 1996, Ozanne *et al.*, 1996a, Ozanne *et al.*, 1996b). It can be due to different protein sources that have been used in these diets.

*Dietary proteins and developmental programming: Protein source:* We previously reported that casein- and soy protein-based diets fed during pregnancy and lactation have different effects on the development of metabolic syndrome in rat dams and their offspring (Jahan-mihan *et al.*, 2012). Fasting plasma glucose and insulin were higher in dams fed the soy protein diet compared with those fed a casein diet (Jahan-mihan *et al.*, 2012). At weaning, offspring born to the dams fed the soy diet had higher fasting plasma insulin, homeostatic model of assessment-insulin resistance (HOMA-IR) and homocysteine, and at week 15, higher body weight, body fat and HOMA-IR. Higher systolic (SBP) and diastolic blood pressure (DBP) were also found in the

offspring born to the soy diet dams (Jahan-mihan et al., 2012). Offspring born to dams fed the soy diet had increased food intake compared with those born to the casein diet fed dams. In addition, higher insulin at weaning and 15 weeks post-weaning and higher hypothalamic mRNA expression of Agouti-related protein (AgRP) at weaning and higher plasma insulin, Glucagon-like peptide-1 (GLP-1) and ghrelin, in response to protein preloads characterized the offspring born to dams fed soy protein (Jahan-mihan et al., 2011b). Although weaning diet was also influential (Jahan-mihan et al., 2011c), maternal diet played a dominant role during the development and masked the effect of the weaning diet in majority of measured parameters in offspring (Jahan-mihan et al., 2011b, c, Jahan-mihan et al., 2012). Moreover, maternal diet influenced the phenotype of offspring in a sex-dependent manner. Female offspring were more resistant against changes induced by maternal diet compared with male offspring (Jahan-mihan et al., 2011d). Whether this observation is due to either the protective effect of sex-dependent hormones or due to the difference in development process in male and female offspring during pregnancy and lactation is still unclear and therefore an open window for further research.

It was also reported that structure and physicochemical properties of proteins fed during pregnancy and lactation are factors determining the effect of proteins on the development of metabolic syndrome in the offspring. In offspring born to dams fed on an amino acid-based diet (AAD), birth weight and body weight were lower while SBP and fasting blood glucose (FBG) were higher compared with those born to dams fed on an intact protein-based diet (IPD) (Jahan-mihan et al., 2017). The results of these experiments support the hypothesis that nutritionally complete diets differing in protein sources fed during gestation alone or during gestation and lactation have different effects on metabolic syndrome characteristics of offspring. Determining factors of such effects are structure and physicochemical

properties of proteins. This study also showed that extending the duration of test diets from gestation alone to gestation and lactation resulted in a more robust effect of the diet on body weight, body composition, and glucose metabolism in offspring. This can be explained by the fact that the lactation period in rats is comparable with the third trimester of pregnancy in human (Jahan-Mihan et al., 2015).

### Summary

The substantial role of consumed dietary proteins' quantity during pregnancy and lactation in developmental programming is well-established. Moreover, there are some evidences supporting the role of source as well as physicochemical properties of proteins in their effect on phenotype of offspring. Interestingly, nutritionally balanced maternal diets fed during pregnancy and lactation influenced development of various regulatory systems and eventually altered the phenotype of offspring differently when different sources of proteins were applied in these diets. It may support the notion that proteins, beyond their traditional role as the source of indispensable amino acids and energy, possess extensive physiologic and metabolic properties in a source-dependent manner. These functions of proteins cannot be simply explained by their amino acid composition. Various methods have been developed to evaluate quality of proteins including net protein utilization (NPU), biological value (BV), and more recently, the Protein Digestibility-Corrected Amino Acid Score (PDCAAS). However, their main focus is on determining the bioavailability of proteins and amino acids. Unfortunately, none of these methods can explain numerous physiologic and metabolic functions attributed to proteins. Moreover, the fact that dietary proteins can alter phenotype of offspring, even when they are given as part of a nutritionally complete diet, may suggest that the physiologic properties of proteins must be considered in nutrition recommendations when they are applicable. Lastly, in spite of abundant studies conducted in

this field, the role of source and quantity of proteins in maternal diet in gestational obesity is still elusive. Whether a high protein diet plays a positive role in controlling appetite and calorie intake in obese mothers and consequently results in an improved pregnancy outcome or it deteriorates the development of the fetus and offspring, as it is reported in previous studies in normal weight mothers, is unclear currently and needs further investigation.

### References

- Adair LS, Kuzawa CW & Borja J** 2001. Maternal energy stores and diet composition during pregnancy program adolescent blood pressure. *Circulation*. **104 (9)**: 1034-1039.
- Anderson GH, Tecimer SN, Shah D & Zafar TA** 2004. Protein source, quantity, and time of consumption determine the effect of proteins on short-term food intake in young men. *The journal of nutrition*. **134 (11)**: 3011-3015.
- Barker D & Law C** 1994. Birth weight and blood pressure in adolescence. Studies may be misleading. *British medical journal*. **308 (6944)**: 1634.
- Beyer M, et al.** 2007. Effects of dietary energy intake during gestation and lactation on milk yield and composition of first, second and fourth parity sows. *Archives of animal nutrition*. **61 (6)**: 452-468.
- Boirie Y, et al.** 1997. Slow and fast dietary proteins differently modulate postprandial protein accretion. *Proceedings of the national academy of sciences*. **94 (26)**: 14930-14935.
- Boney CM, Verma A, Tucker R & Vohr BR** 2005. Metabolic syndrome in childhood: association with birth weight, maternal obesity, and gestational diabetes mellitus. *Pediatrics*. **115 (3)**: e290-e296.
- Daenzer M, Ortmann S, Klaus S & Metges CC** 2002. Prenatal high protein exposure decreases energy expenditure and increases adiposity in young rats. *The journal of nutrition*. **132 (2)**: 142-144.
- Daniel H, Vohwinkel M & Rehner G** 1990. Effect of casein and beta-casomorphins on gastrointestinal motility in rats. *Journal of nutrition*. **120 (3)**: 252-257.
- de Campos KE, Sinzato YK, de Paula Pimenta W, Rudge MVC & Damasceno DC** 2007. Effect of maternal obesity on diabetes development in adult rat offspring. *Life sciences*. **81 (19)**: 1473-1478.
- Dörner G & Plagemann A** 1994. Perinatal hyperinsulinism as possible predisposing factor for diabetes mellitus, obesity and enhanced cardiovascular risk in later life. *Hormone and metabolic research*. **26 (05)**: 213-221.
- Eriksson R & Olsson B** 2004. Adapting genetic regulatory models by genetic programming. *Biosystems*. **76 (1)**: 217-227.
- FitzGerald RJ & Meisel H** 2000. Milk protein-derived peptide inhibitors of angiotensin-I-converting enzyme. *British journal of nutrition*. **84 (S1)**: 33-37.
- Fonseca V, et al.** 2002. The effect of troglitazone on plasma homocysteine, hepatic and red blood cell S-adenosyl methionine, and S-adenosyl homocysteine and enzymes in homocysteine metabolism in Zucker rats. *Metabolism*. **51 (6)**: 783-786.
- Fouillet H, Bos C, Gaudichon C & Tomé D** 2002. Approaches to quantifying protein metabolism in response to nutrient ingestion. *The journal of nutrition*. **132 (10)**: 3208S-3218S.

### Conclusions

Dietary proteins are determining factors in developmental programming. Both quantity and source of proteins in maternal diet influenced the development of metabolic syndrome characteristics in offspring. However, whether they have the same function in presence of gestational obesity is still unclear and needs further study.

### Conflicts of interest

The author declares no conflict of interest.

- Fowden AL & Hill DJ** 2001. Intra-uterine programming of the endocrine pancreas. *British medical bulletin*. **60** (1): 123-142.
- Froetschel M** 1996. Bioactive peptides in digesta that regulate gastrointestinal function and intake. *Journal of animal science*. **74** (10): 2500-2508.
- Gluckman PD & Hanson MA** 2004. The developmental origins of the metabolic syndrome. *Trends in endocrinology & metabolism*. **15** (4): 183-187.
- Jackson AA, MARCHAND MC & LANGLEY-EVANS SC** 2002. Increased systolic blood pressure in rats induced by a maternal low-protein diet is reversed by dietary supplementation with glycine. *Clinical science*. **103** (6): 633-639.
- Jahan-Mihan A, Luhovyy BL, El Khoury D & Anderson GH** 2011a. Dietary proteins as determinants of metabolic and physiologic functions of the gastrointestinal tract. *Nutrients*. **3** (5): 574-603.
- Jahan-Mihan A, Rodriguez J, Christie C, Sadeghi M & Zerbe T** 2015. The role of maternal dietary proteins in development of metabolic syndrome in offspring. *Nutrients*. **7** (11): 9185-9217.
- Jahan-mihan A, Smith CE & Anderson GH** 2011b. Effect of protein source in diets fed during gestation and lactation on food intake regulation in male offspring of Wistar rats. *American journal of physiology-regulatory, integrative and comparative physiology*. **300** (5): R1175-R1184.
- Jahan-mihan A, Smith CE & Anderson GH** 2011c. Soy protein–and casein-based weaning diets differ in effects on food intake and blood glucose regulation in male Wistar rats. *Nutrition research*. **31** (3): 237-245.
- Jahan-mihan A, Smith CE, Hamedani A & Anderson GH** 2011d. Soy protein–based compared with casein-based diets fed during pregnancy and lactation increase food intake and characteristics of metabolic syndrome less in female than male rat offspring. *Nutrition research*. **31** (8): 644-651.
- Jahan-mihan A, Szeto IM, Luhovyy BL, Huot PS & Anderson GH** 2012. Soya protein-and casein-based nutritionally complete diets fed during gestation and lactation differ in effects on characteristics of the metabolic syndrome in male offspring of Wistar rats. *British journal of nutrition*. **107** (02): 284-294.
- Jahan- mihan A, Labyak C & Arikawa A** 2017. The effect of characteristics of proteins fed during gestation and lactation on development of metabolic syndrome in dams and male offspring of Wistar rats. *Obesity science & practice*.
- Jiang Y, et al.** 2007. Hyperhomocysteinemia-mediated DNA Hypomethylation and its Potential Epigenetic Role in Rats. *Acta biochimica et biophysica sinica*. **39** (9): 657-667.
- Kapoor A, Dunn E, Kostaki A, Andrews MH & Matthews SG** 2006. Fetal programming of hypothalamo- pituitary- adrenal function: prenatal stress and glucocorticoids. *The journal of physiology*. **572** (1): 31-44.
- Lan-Pidhainy X & Wolever TM** 2010. The hypoglycemic effect of fat and protein is not attenuated by insulin resistance. *The American journal of clinical nutrition*. **91** (1): 98-105.
- Langley-Evans SC, Welham SJ & Jackson AA** 1999. Fetal exposure to a maternal low protein diet impairs nephrogenesis and promotes hypertension in the rat. *Life sciences*. **64** (11): 965-974.
- Langley SC & Jackson AA** 1994. Increased systolic blood pressure in adult rats induced by fetal exposure to maternal low protein diets. *Clinical science*. **86** (2): 217-222.
- Lawlor DA, et al.** 2007. Epidemiologic evidence for the fetal overnutrition hypothesis: findings from the mater-university study of pregnancy and its outcomes. *American journal of epidemiology*. **165** (4): 418-424.
- Leng G, et al.** 1985. Central opioids: a possible role in parturition? *Journal of endocrinology*. **106** (2): 219-224.
- Leprohon CE & Anderson GH** 1982. Relationships among maternal diet, serotonin metabolism at weaning, and protein selection of progeny. *The journal of nutrition*. **112** (1): 29-38.

- Lucas A** 2005. The developmental origins of adult health and well-being. In *Early nutrition and its later consequences: new opportunities*, pp. 13-15. Springer.
- Lucas A, Baker B, Desai M & Hales C** 1996. Nutrition in pregnant or lactating rats programs lipid metabolism in the offspring. *British journal of nutrition*. **76 (04)**: 605-612.
- McMillen IC & Robinson JS** 2005. Developmental origins of the metabolic syndrome: prediction, plasticity, and programming. *Physiological reviews*. **85 (2)**: 571-633.
- Meisel H** 1993. Casokinins as bioactive peptides in the primary structure of casein. *Food proteins: structure and functionality*. 67-75.
- Nagata H, et al.** 2005. Characteristics of an aminopeptidase from Japanese cedar (*Cryptomeria japonica*) pollen. *Journal of agricultural and food chemistry*. **53 (13)**: 5445-5448.
- Nurminen M-L, et al.** 2000.  $\alpha$ -Lactorphin lowers blood pressure measured by radiotelemetry in normotensive and spontaneously hypertensive rats. *Life sciences*. **66 (16)**: 1535-1543.
- Ogden CL, Carroll MD, Kit BK & Flegal KM** 2014. Prevalence of childhood and adult obesity in the United States, 2011-2012. *The journal of the American medical association*. **311 (8)**: 806-814.
- Ozanne S, Smith G, Tikerpae J & Hales C** 1996a. Altered regulation of hepatic glucose output in the male offspring of protein-malnourished rat dams. *American journal of physiology-endocrinology and metabolism*. **270 (4)**: E559-E564.
- Ozanne S, Wang C, Coleman N & Smith G** 1996b. Altered muscle insulin sensitivity in the male offspring of protein-malnourished rats. *American journal of physiology-endocrinology and metabolism*. **271 (6)**: E1128-E1134.
- Paroli E** 1988. Opioid peptides from food (the exorphins). In *Sociological and medical aspects of nutrition*, pp. 58-97. Karger Publishers.
- Petrie L, Duthie SJ, Rees WD & McConnell JM** 2002. Serum concentrations of homocysteine are elevated during early pregnancy in rodent models of fetal programming. *British journal of nutrition*. **88 (05)**: 471-477.
- Plagemann A, et al.** 1999. Malformations of hypothalamic nuclei in hyperinsulinemic offspring of rats with gestational diabetes. *Developmental neuroscience*. **21 (1)**: 58-67.
- Plagemann A, Harder T, Kohlhoff R, Rohde W & Dörner G** 1997. Overweight and obesity in infants of mothers with long-term insulin-dependent diabetes or gestational diabetes. *International journal of obesity*. **21 (6)**: 451-456.
- Pupovac J & Anderson GH** 2002. Dietary peptides induce satiety via cholecystokinin-A and peripheral opioid receptors in rats. *The journal of nutrition*. **132 (9)**: 2775-2780.
- Rees WD, Hay SM, Brown DS, Antipatis C & Palmer RM** 2000. Maternal protein deficiency causes hypermethylation of DNA in the livers of rat fetuses. *The journal of nutrition*. **130 (7)**: 1821-1826.
- Rush D, et al.** 1984. The effects of dietary supplementation during pregnancy on placental morphology, pathology, and histomorphometry. *The American journal of clinical nutrition*. **39 (6)**: 863-871.
- Sasaki A, nakagavwa I & kajimoto M** 1982. Effect of protein nutrition throughout gestation and lactation on growth, morbidity and life span of rat progeny. *Journal of nutritional science and vitaminology*. **28 (5)**: 543-555.
- Schäfer-Graf UM, et al.** 1998. Hyperinsulinism, neonatal obesity and placental immaturity in infants born to women with one abnormal glucose tolerance test value. *Journal of perinatal medicine-official journal of the WAPM*. **26 (1)**: 27-36.
- Schusdziarra V, Lenz N, Rewes B & Pfeiffer E** 1984. Endogenous opioids modulate the effect of cholecystokinin on insulin release in dogs. *Neuropeptides*. **4 (6)**: 507-517.
- Silverman BL, et al.** 1991. Long-term prospective evaluation of offspring of diabetic mothers. *Diabetes*. **40 (Supplement 2)**: 121-125.

**Stegers-Theunissen R & Steegers E** 2003. Nutrient-gene interactions in early pregnancy: a vascular hypothesis. Elsevier.

**Teschmacher H** 2003. Opioid receptor ligands derived from food proteins. *Current pharmaceutical design*. **9 (16)**: 1331-1344.

**Thone-Reineke C, et al.** 2006. High-protein nutrition during pregnancy and lactation programs blood pressure, food efficiency, and body weight of the offspring in a sex-dependent manner. *American journal of physiology-regulatory, integrative and comparative physiology*. **291 (4)**: R1025-R1030.