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Effect of Maternal Protein Restriction during E10&11 Day of Gestation on Organ Weights, Litter Size, Placental Weight and Biochemical Analysis

Research Article

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Abstract

Environmental constraints during pregnancy results in phenotypic changes which will be associated with changes in biochemical components and alteration in body and placentae weight. The aim of the study is to investigate the effect of maternal protein restriction during embryonic day 10 (E10) and 11 (E11) (Acute protein restriction). Pregnant mice were divided into four groups (I-IV) respectively. Pregnant mice were fed on 10th and 11th day with isocaloric low protein diets (control diet 24% diet for group I, 18% diet for group II, 12% diet for group III and 6% diet for group IV) and studied at gestational day 18. Maternal body weight, visceral organ and reproductive organ weights, litter size, placental number and biochemical parameters were analyzed. The levels of various biochemical parameters including serum glucose, urea, uric acid, creatinine, cholesterol, HDL, LDL, TGL, VLDL, bilirubin (total, indirect and direct) showed significant variations ($P<0.05$) when compared to those of the control group. Similarly, SGPT, SGOT, total protein and albumin levels increased significantly in protein restricted groups, when compared with group I, whereas the body weight and organ weights showed no significant change. Among the restricted groups, group IV shows 5.0771 ± 0.128 g, group III 5.439 ± 0.059 g, group II 55.2501 ± 0.026 g and control group I with 5.5056±0.0341 g of placenta weights. While the weights of fetuses in group I26.81 ±2.993, group II 13.76 ±0.211, group III 18.3±2.151 and group IV 16.16 ±1.970 g shows reduction in placental weights. We demonstrated the effect of maternal protein restriction during 10 and 11th day of gestation, which influences the change in the visceral organ weight and reproductive organ weight. Our observation coincides with the earlier findings which showed that the increase in the blood glucose in the restricted group paved way for the development of Diabetes in the adult life and showed lower fetal weight and placental weight in the restricted groups.

Keywords: Placentae; Maternal protein restriction; Acute protein restriction; IUGR; Diabetes

Introduction

Introduction of the fetus to maternal malnutrition is well recognized causal factor for intrauterine growth restriction (IUGR), in both humans and animals. Low protein diets in particular have been related with distorted placental growth and composition, fetal growth and organ development [1-4].

Maternal nutrition during gestation has a pivotal role in the regulation of placental-fetal development and in that way affects the all-time health and productivity of the offspring in human and animal models [5]. The maternal suboptimal nourishment during pregnancy results in IUGR and newborns with low birth weight. Intrauterine growth restriction is associated with increased perinatal morbidity and death, and newborns with low birth weight have increased

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the threat for the development of adult metabolic syndrome [6]. Maternal protein restriction adversely affects nutrient supply to the fetus. Human epidemiological observations from the 'Dutch Hunger Winter' studies have revealed that adults born to mothers exposed to poor nutrition during early pregnancy displayed increased early-onset incidences of coronary artery diseases [7]. Maternal malnutrition, psychological stress or perturbed hormonal status transmit signals to the developing fetus and, depending on the timing of these exposures, permanently changing tissue structure and function [8]. In 1970's, Forsdahl, using official data on Norwegian counties, reported that scarcity during adolescence, followed by prosperity, was positively correlated with risk of death from coronary heart diseases [9]. In 1986, Barker and colleagues began publishing reports on the association between an adverse intrauterine environment, as determined primarily by low birth weight, and an increased risk of coronary heart disease later in life [10]. Collectively, the above studies generated the Forsdahl-Barker hypothesis, recognizing Forsdahl, as the original basis of the idea and Barker as the developer of the concept. The Forsdahl-Barker hypothesis has become better known as the "fetal origins" hypothesis and has created a new branch of scientific knowledge and investigation, known as "The Developmental Origins of Health and Diseases"(DOHaD) [11]. It is now broadly acknowledged that certain chronic diseases of adulthood may have their genesis in the womb. From the above literature, we hypothesized that maternal protein restriction from E10 and E11of gestation (acute protein restriction), in mouse, would result in changes in litter size, placental weight, and organ weight and variations in biochemical parameters of maternal serum.

Materials and Methods

Animals and experimental treatments

The experimental study was carried out using weaning Swiss albino mice weighing about 15-20 grams. The animals were housed individually and fed with control or normal diet, till conception *ad libitum*. Female mice were housed with males, of proven fertility for mating. Next morning, the vaginal plug positive animals were separated (n6) and grouped into four. Group I- IV animals were fed with normal control diet (100% protein diet). On 10^{th} and 11^{th} day of gestation, animals in groups II, III and IV were fed with protein restricted diet (25% protein restricted diet, 50% protein restricted diet and 75% protein restricted diet) respectively (Table 1). The mice were fed with modified Laboratory Animal Information Service Centre diet. The experimental design was approved by Institutional Animal Ethical Committee, St.Joseph's College (Autonomous), Tiruchirappalli.

Collection of tissue and serum sample

At day 18, animals were euthanized (Group -I, II, III, & IV with 6 animals each) with ether. After dissection, serum, organs, foetus, placentae were collected quickly. The liver, kidney, heart, spleen, placentae were dried on blotting paper and their weights were measured. The maternal serum was stored at -20 ˚C for biochemical estimations.

Determination of serum biochemical parameters: Serum from the respective groups was pooled for various biochemical parameters. All the parameters were analysed with Prietest Clinical Biochemistry reagents kits using Prietest Touch-Auto Biochemistry Analyser, (Robonik India Pvt, Ltd.).

Determination of body weight and organ weights: The body weights of all the groups were measured once in three days from conception till sacrifice. The organ weights, fetal number, and the placentae number of the respective groups were measured.

Statistical analysis

Data are presented as means ± SEM. Statistical analyses were performed using student's t-test, where significant differences were indicated. A probability of 5% or less was accepted as significant.

Result

In this study, a total of 24 female pregnant animals were studied. The growth increment of the mother, foetus and the major organs in respective groups were measured. The maternal weights of the respective groups increase with the gestational age (Table 2). The reduction in the protein content of the diet did significantly affect the weight of the dams at slaughter on day 18.The number of foetuses carried by each mother were dissimilar in mice given normal diets after protein restriction. While the weight of the placenta in restricted groups show significant reduction, the weights of the foetuses in group 3 are increased than those of the group II and IV, though the fetal number in group III is less as compared to restricted group II (Table 3).

A significant ($p< 0.05$) increase in serum glucose levels were observed in control group (Group I) animals as compared to those from other three groups (Group II, III & IV). Among the groups, the

Table 1: Composition of diet fed to pregnant animals on day 10 and 11[d].

Diet constituents	Group I[a] C	Group II R1	Group III R2	Group IV R3
			g%	
Wheat flour	22.5	-	22.5	22.5
Roasted Bengal gram flour	60.0	60.0	60.0	60.0
Skim milk powder	5.0	-	-	5.0
Casein	4.0	-	-	-
Refined ground nut oil	4.0	4.0	4.0	4.0
Starch[b]	-	31.5	9.0	4.0
Mineral mixture[2]	4.0	4.0	4.0	4.0
Vitamin mixture[1]	0.5	0.5	0.5	0.5

[1]Vitamin mix: α-tocopherol 12.0 g/500g; Menadione (K) 0.15 g/500g; Thiamine (B_1) 1.2g/500g; Riboflavin (B_2) 0.5g/500g; Pyridoxine (B_6) 0.6g/500g; Niacin 1g/500g; Pantothenic acid (Calcium Salt) 1.2g/500g; Cyanocobalamine (B_{12}) 0.5 µg/500g; Folic acid 0.1g/500g; Paraamino benzoic acid (PABA) 10.0g/500g; Biotin 40.0 mg/500g; Inositol 10.0g/500g; Choline chloride 100.0g/500g; Total vitamin put together 136.79g + Starch 363.21g.

[2]Mineral mix: Dicalcium phosphate 12.50g/kg; Calcium carbonate 5.55g/kg; Sodium chloride 3.0g/kg; Magnesium sulphate 2.292g/kg; Ferrous sulphate 0.5g/kg; Manganese sulphate 160.4mg/kg; Potassium iodide 10mg/kg; Zinc sulphate 21.92mg/kg; Copper sulphate 19.08mg/kg; Cobalt chloride 0.12mg/kg.

[a]Animals in this group received normal diet throughout the gestation period.

[b]Starch is added to compensate the protein value of the prepared food.

[d]Diet were provided to animals as pellets.

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Table 2: Body weights of animals once in three days from conception till sacrifice.

Days	Total body Weight in grams			
	GROUP 1† (n=6)	GROUP 2†† (n=6)	GROUP 3‡ (n=6)	GROUP 4§ (n=6)
0	30.49 ± 3.310	31.14 ± 3.111(102%)	28.70 ± 3.112 (94%)	27.04 ± 1.001 (88%)
3	34.35 ± 4.612	32.75 ± 2.721 (95%)	30.79 ± 2.810 (89%)	28.93 ± 1.131 (84%)
6	34.57 ± 1.182	33.64 ± 2.610 (97%)	31.76 ± 2.912 (91%)	29.92 ± 1.256 (86%)
9	35.83 ± 1.767	35.035 ± 2.501 (97%)	33.01 ± 2.508 (92%)	30.84 ± 1.102 (86%)
12	36.59 ± 1.421	36.02 ± 2.480 (98%)	34.09 ± 2.244 (93%)	31.41 ± 1.057 (85%)
15	37.55 ± 1.454	36.03 ± 1.852 (95%)	35.30 ± 4.245 (94%)	31.17 ± 0.950 (83%)
18	38.37 ± 1.326	37.14 ± 1.725 (96%)	34.87 ± 1.986 (90%)	32.01 ± 0.656 (83%)

*Data are mean ± SEM
† Mice were fed with 100% protein diet from day 0 to day 18 of gestation
†† Mice were fed with 75% protein diet between day 10 and day 11 of gestation
‡ Mice were fed with 50% protein diet between day 10 and day 11 of gestation
§ Mice were fed with 25% protein diet between day 10 and day 11 of gestation
[a]Significant difference between control group and other groups: P<0.05.
[b]Significant difference between respective groups: P<0.05.

Table 3: Total fetal, placental weight, and fetal number of mice during E18 of gestation*.

	GROUP 1† (n=6)	GROUP 2†† (n=6)	GROUP 3‡ (n=6)	GROUP 4§ (n=6)
No. of Foetus and placenta	46	47	41	39
Weight of all Placenta	5.5056±0.0341	5.2501±0.026	5.439±0.059	5.0771±0.128
Weight of all foetus	26.81±2.993	13.76±0.211	18.3±2.151	16.16±1.970

*Data are mean ± SEM
† Mice were fed with 100% protein diet from day 0 to day 18 of gestation
†† Mice were fed with 75% protein diet between day 10 and day 11 of gestation
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[a]Significant difference between control group and other groups: P<0.05.
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highest concentration of serum glucose level was recorded in protein restricted group IV 101.50 ± 1.76 mg/dL, which is 122% increase as compared to control group I 83.00 ± 1.41mg/d/L, followed by group II 90.00 ± 1.41mg/dLwith 108% increase and group III 80.83 ± 0.76 mg/dL with 92% increase (Table 4). A significant (P0.05) raise in serum urea level was noted in group III50.00 ± 0.90mg/dL and group IV54.83 ± 0.75mg/dL as compared to group I44.33 ± 1.63mg/dL. Creatinine levels in the restricted group III 2.71 ± 0.15mg/dLincreases significantly as compared to the control group I 2.38 ± 0.17mg/dL. Increase in cholesterol levels were also noticed in the protein restricted groups (Group III 80.66 ± 0.82; 101% and Group IV 87.33 ± 0.82mg/dL; 109%) as compared to the control group I79.67 ± 1.03mg/dL; 100%. In case of HDL and LDL cholesterol levels, the serum concentration of the above two were increased significantly in the group IV when compared to the control group.

The levels of HDL and LDL were decreased in group III when compared to the group IV. The serum VLDL levels in the respective groups show significant decrease in the restricted group IV 18.16 ± 1.47mg/dL; 89% as compared to the control group I 20.25 ± 0.5mg/dL; 100%. In comparison with control group I 64.20 ± 0.78mg/dL; 100%, TGL is elevated 128% in group II 82.33 ± 1.03mg/dL as compared to group III 63.00 ± 1.26 mg/dL and group IV 65.50 ± 1.04 mg/dL. No significant change is observed in group IV (102%).

Serum bilirubin (Total, direct and indirect) was significantly increased in the restricted groups II, III & IV when compared to that of the control group. In protein metabolism, the utilization of the tissue/serum proteins in the restricted groups results in the decrease of the total protein and albumin levels when compared to the control group.

Serum enzyme levels were significantly increased in SGPT and ALP. The level of SGOT in group 2 increased (13%) when compared to that of the other restricted groups.

Organ weights in the restricted group IV showed significant increase. The percentage of increase in the weights of liver 2.14 ± 0.21g; spleen 0.20 ± 0.05g; and, uterus and ovary 0.84± 0.20 g; are 138%, 166% and 116% respectively. While the weight of heart in the restricted group remains the same, the weight of the kidney in the restricted group IV shows a slight decrease (3%) and the weight in group II was significantly reduced (13%) (Table 5).

Discussion

The present study addressed the effects of maternal protein restriction mediated maternal stress during E10 and E11 day of gestation on fetal body weight, organ weight, placental number and biochemical parameters. Maternal protein restriction produced a predictable stress response in the mother, as evidenced by elevated maternal plasma glucose levels in the restricted groups. Our results showed decrease in the fetal weight and placenta in the E10 and E 11 day of the pregnancy in mice. Langley-Evans *et al.* (1996) and Gonzalez *et al.*, observed a similar early increase in the growth of the foetuses in pregnant rats of the Wistar strain [12,13].

Numerous animal studies have investigated the effect of maternal low-protein diet on glucose metabolism in the off-spring [14]. We hypothesized the impact of maternal low protein diet during E10 and E11 day of gestation in mice, which shows significant increase in serum glucose in the protein restricted groups (Group II and IV). Similarly, a low protein diet during gestation (10% protein in the restricted group) shows no significant difference in serum glucose during E19 in rats [15]. The levels of TGL show no significant change in previous study by Nimbe Torres *et al.*, (2010) [16]. We previously reported that maternal protein restriction determines the fate and development of the foetus during development and the origin of adult disease in later life [17].

Conclusion

Concept and importance of nutritional programming was recommended by epidemiological studies in human during pregnancy and confirmed by animal experiments (Swine, Sheep, Rat and Mice). In humans, as it was proved by numerous papers, scientific field of nutritional programming is hopeful and represents a theme

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Table 4: Levels of various biochemical components during E18 of gestation*.

BIOCHEMICAL COMPONENTS	GROUP 1† (n=6)	GROUP 2†† (n=6)	GROUP 3‡ (n=6)	GROUP 4§ (n=6)
GLUCOSE (mg/dL)	83.00 ± 1.41	90.00 ± 1.41[a]	80.83 ± 0.76[a]	101.50 ± 1.76[a]
UREA (mg/dL)	44.33 ± 1.63	44.00 ± 1.67	50.00 ± 0.90[a]	54.83 ± 0.75[a]
CREATININE (mg/dL)	2.38 ± 0.17	1.80 ± 0.09[a]	2.00 ± 0.90[a]	2.71 ± 0.15[a]
URIC ACID (mg/dL)	6.80 ± 0.15	6.9 ± 0.12	6.13 ± 0.12[a]	7.11 ± 0.11[a]
CHOLESTEROL (mg/dL)	79.67 ± 1.03	75.00 ± 1.26[a]	80.66 ± 0.82	87.33 ± 0.82[a]
HDL (mg/dL)	9.95 ± 0.187	9.68 ± 0.34	9.91 ± 0.13	12.66 ± 1.03[a]
LDL (mg/dL)	70.01 ± 0.82	50.00 ± 1.26[a]	69.66 ± 1.03	89.83 ± 2.31[a]
TGL (mg/dL)	64.20 ± 0.78	82.33 ± 1.03[a]	63.00 ± 1.26	65.50 ± 1.04[a]
VLDL (mg/dL)	20.25 ± 0.51	20.33 ± 0.81	20.83 ± 0.98	18.16 ± 1.47[a]
TOTAL BILIRUBIN (mg/dL)	0.40 ± 0.14	0.30 ± 0.01[a]	0.59 ± 0.10[a]	0.64 ± 0.20[a]
DIRECT BILIRUBIN (mg/dL)	0.20 ± 0.01	0.20 ± 0.01	0.19 ± 0.01	0.29 ± 0.01[a]
INDIRECT BILRUBIN (mg/dL)	0.20 ± 0.10	0.20 ± 0.01	0.39 ± 0.16[a]	0.35 ± 0.02[a]
TOTAL PROTEIN (g/dL)	6.06 ± 0.81	5.82 ± 0.76[a]	5.01 ± 0.13[a]	5.70 ± 0.17[a]
ALBUMIN (g/dL)	3.95 ± 0.10	4.27 ± 1.20[a]	3.77 ± 0.15[a]	3.70 ± 0.06[a]
GLOBULIN (g/dL)	1.97 ± 0.10	1.58 ± 0.20[a]	1.20 ± 0.14[a]	2.01 ± 0.07
SGOT (IU/L)	20.66 ± 0.81	23.50 ± 0.83[a]	19.66 ± 1.03	21.50 ± 1.04
SGPT (IU/L)	17.00 ± 0.63	15.33 ± 1.03[a]	18.33 ± 0.81[a]	20.66 ± 0.81[a]
ALP (IU/L)	50.00 ± 0.63	63.66 ± 1.03[a]	51.16 ± 0.75[a]	60.00 ± 1.09[a]

*Data are mean ± SEM.
† Mice were fed with 100% protein diet from day 0 to day 18 of gestation; †† Mice were fed with 75% protein diet between day 10 and day 11 of gestation.
‡ Mice were fed with 50% protein diet between day 10 and day 11 of gestation; § Mice were fed with 25% protein diet between day 10 and day 11 of gestation.
[a]Significant difference between control group and other groups: P<0.05.; [b] Significant difference between respective groups: P<0.05.

Table 5: Weights of visceral and reproductive organs during E18 of gestation*.

Organs	Weight in grams			
	GROUP 1† (n=6)	GROUP 2†† (n=6)	GROUP 3‡ (n=6)	GROUP 4§ (n=6)
Liver	1.55 ± 0.69	1.79 ± 0.45	1.73 ± 0.23[ab]	2.14 ± 0.21[ab]
Kidney	0.39 ± 0.04	0.34 ± 0.022	0.39 ± 0.17	0.38± 0.07
Spleen	0.12 ± 0.04	0.14 ± 0.08	0.10 ± 0.01[b]	0.20 ± 0.05[ab]
Heart	0.16 ± 0.009	0.14 ± 0.033	0.14 ± 0.007[a]	0.16 ± 0.030
Uterus & Ovary	0.72 ± 0.189	0.69± 0.107	0.80± 0.127	0.84± 0.20

*Data are mean ± SEM.
† Mice were fed with 100% protein diet from day 0 to day 18 of gestation; †† Mice were fed with 75% protein diet between day 10 and day 11 of gestation.
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[a]Significant difference between control group and other groups: P<0.05.; [b]Significant difference between respective groups: P<0.05.

of major public health and clinical significance. In this perspective, it is necessary to define defensive and predisposing effects of early nutrition on the development of later chronic diseases, since early nutrient feeding can be potentially modified to minimize the risk of diseases in later life. In conclusion, our study also showed that the dietary protein restriction during mid gestation in mouse (Acute protein restriction) resulted in decreased fetal and placental weight as evident from various works. Our observation coincides with the early findings of increased blood glucose in the restricted group paved the way for the development of Diabetes during adult life. Further insight is essential in the Developmental Origins of Health and Diseases (DOHaD) in later life and the involvement of placenta or placental gene expression of the same.

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