Commentary Article

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Journal of Clinical Nutrition & Dietetics
ISSN 2472-1921

2023
Vol.9 No.3:186

Effect on Development and Metabolism of Offspring Born from Japanese Underweight Model Dams

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Received date: March 21, 2023, Manuscript No. IPJCND-23-16135; **Editor assigned date:** March 23, 2023, PreQC No. IPJCND-23-16135 (PQ); **Reviewed date:** April 06, 2023, QC No. IPJCND-23-16135; **Revised date:** April 13, 2023, Manuscript No. IPJCND-23-16135 (R); **Published date:** April 21, 2023, DOI: 10.36648/2472-1921.9.3.186

Citation: Takemori K, Aoki K, Matsuo T, Taguchi T, Kometani T (2023) Effect on Development and Metabolism of Offspring Born from Japanese Underweight Model Dams. J Clin Nutr Diet Vol.9 No.3:186.

Abstract

Environmental imbalance during the early developmental period affects health and increases susceptibility to non-communicable diseases, including metabolic syndrome, in later life. Therefore, The Developmental Origins of Health and Disease (DOHaD) theory were established. Japan is unique among developed countries, in that the low-birth-weight rate was almost 10% in the past decade and the rate of underweight women of childbearing age is close to 20%. Compared to estimated energy requirements of this age group in the dietary reference intakes for Japanese 2020, the energy sufficiency is approximately 85%.

Here we established animal model rats to mimic under-nutrition of Japanese women (85% of the energy required for those with normal activity levels). The serum corticosterone concentrations and adrenal gland weight were increased in premating and prenatal in these rats. Therefore, it was clear that these maternal animals were under constant malnutrition stress.

Although the offspring born from these dams showed delayed sternal ossification, they acquired normal formation of neuronal cells, development of reflexive actions and memory/learning. It is speculated that nutrients from the underweight dams are preferentially supplied to nervous system formation which is essential for pup survival. On the other hand, these pups tend to develop glucose intolerance due to disorders of insulin-dependent glucose uptake and decreased muscle weight after growth and have the risk of developing metabolic syndrome.

Keywords: Developmental origins of health and disease; Maternal undernutrition; Metabolic syndrome

Description

Based on The Developmental Origin of Health and Disease (DOHaD) theory, environmental factors, particularly nutrition during pregnancy and early life can influence the risk of chronic diseases in later life, not only the onset of metabolic syndrome but also psychiatric and developmental disorders [1-3].

In Japan, the proportion of infants with low-birth-weight (less than 2,500 g) was 9.4% in 2019 according to the Ministry of Health, Labor and Welfare. It is a high percentage compared to other 34 Organization for Economic Co-operation and Development (OECD) member countries. One of the possible causes is the fact that nearly 20% of young adult women in their 20 s-30 s are underweight (body mass index <18.5), for whom daily energy intake is only about 85% of what is necessary for women with a normal activity level according to the Japanese dietary reference intake (2020 edition; 18-29 years: 2,000 kcal, 30-39 years: 2,050 kcal). However, it is unclear whether this level of decreased energy intake is associated with an increase in infants with low-birth-weight.

Therefore, a rat model was established to mimic undernutrition (85% of the energy required for those with normal activity levels: UN). At pre-mating and pre-parturition, serum corticosterone levels and adrenal gland weights, as markers of maternal stress, were elevated in UN [4]. Physical development (body weight, body length, osteogenesis, pinna detachment, eye opening), development of a reflexive action (righting reflex (a pup can quickly return to its feet when placed on its back); negative geotaxis (a pup turns around 180°C when placed on a board inclined at 45°C with its head pointing downward); cliff avoidance (a pup turns and crawls away from the edge of a cliff when placed beyond the edge with its forepaws)), learning and memory test (Morris water maze test, conditioned avoidance response test), neuronal development (incorporation of 5-bromo-2'-deoxyuridine in the hippocampus during brain development) and neuronal-related protein expression (neurofilament, myelin basic protein) were evaluated

[5]. Although a partial delay in 5th sternal segment ossification was observed, healthy physical and neurodevelopment was shown in UN.

Furthermore, we investigated the effects on glucose metabolism in pups. The blood glucose and plasma insulin levels were higher in UN than in control and expression of Phospho-Akt (insulin signaling factor) was suppressed. In addition, the expressions of FOXO1 (transcription factor), PDK4 (starvation) and Gadd45 (muscle atrophy) were up regulated, along with a decrease in skeletal muscle mass [4].

Previous DOHaD animal model studies used severe dietary restrictions ranging from 30% to 70% ((mild (30%), moderate (50%) and severe (70%)) undernutrition during pregnancy [6]. Moderate to severe restriction commonly leads to low-birth-weight, developmental disabilities, hypertension and impaired glucose tolerance in offspring [7]. However, no difference was found in birth weight in the UN, because we continuously kept 15% undernutrition in this study. Further investigation is needed on the result divergence between human and animal models. Although the pups show some delay in morphological development, they acquired normal growth, neuronal cell formation and memory/learning ability because they were exposed to mild maternal stress with mild malnutrition from the fetal to early postnatal period.

Conclusion

Therefore, it was speculated that maternal nutrients were preferentially supplied to nervous system development in pups. On the other hand, it was suggested these pups were at high risk of the occurrence of post-growth glucose metabolism disorder, mediated by impaired insulin transduction and decrease in skeletal muscle weight.

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