

## Review article

**Does the intrauterine condition dictate chronic metabolic disorders in the adult life?**Megha Bhat Agni<sup>1</sup>, Pramukh Subrahmanya Hegde<sup>1</sup>, Praveen Rai<sup>2</sup>, Damodara Gowda K.M.<sup>1</sup><sup>1</sup>Department of Physiology, K.S. Hegde Medical Academy, <sup>2</sup>Nitte University Centre for Science Education and Research, Nitte (Deemed to be University), Mangalore, 575018, Karnataka, India

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Corresponding author: **Damodara Gowda K. M.** Email: dr\_damodar@nitte.edu.in**ABSTRACT**

Foetal development has dictated by maternal gestational diet and intrinsic factors, physical activity, and environmental stimulations. Many studies provided evidence for metabolic disorders in adult life who underwent under nutrition during their foetal life. This review is an effort to use the published data to know the effect of the intrauterine environment on chronic metabolic disorders. Here, we discuss the impact of foetal under nutrition on the development of chronic metabolic diseases. Intrauterine under nutrition negatively influences health after birth. In adults, under-nutrition in utero results in metabolic impairments and cognitive impairments. Under nutrition during foetal/embryonic development influences human physiology and has a lifelong effect, often called foetal programming. This review concludes that the intrauterine environment and foetal nutrition play a significant role in developing chronic metabolic disorders. Therefore, this study provides the necessary insight into target timely interventions in the earliest possible time to prevent offspring from developing chronic diseases in adult life.

**Keywords:** Intrauterine environment; foetal under nutrition; chronic metabolic disorders; foetal programming.**INTRODUCTION**

**I**ntrauterine under nutrition negatively influences health after birth. An undernourished foetus is more likely to develop hypertension, insulin resistance, diabetes mellitus, obesity, and cognitive function impairment in adulthood. This paper describes the influence of undernourishment during the perinatal period on postnatal health.

Programming of the foetus occurs during the critical period of development, which involves rapid cell division and the formation of tissues and organs. Under nutrition during foetal/embryonic development influences programming human body and has a lifelong effect, often called foetal programming. An insult or stimulus during a critical period of development can have long-lasting effects on life after birth, a process known as foetal programming (1). When the foetus is exposed to an altered intrauterine environment, it alters its structural and physiological function. Once changes occur, the phenotype will be permanent and may decide the future health problems (2).

It was a British Epidemiologist, David Barker, who developed the first theory of foetal programming, which showed the correlation between low birth weight and coronary heart disease, high blood pressure, and type-2 diabetes mellitus (1). Adverse nutrition in early life has been linked to adult metabolic disease according to Barker's hypothesis (3), proposed that early childhood undernourishment is associated with metabolic syndrome. It includes obesity, type-2 diabetes, hypertension,

hyperlipidaemia, coronary heart disease, and stroke (4).

**METHODOLOGY**

We conducted database searches using Google Scholar, PubMed, and Science direct until September 2021 to include up-to-date documented information in the present review. We limited the search to English language papers. The data mining was done by following MeSH words such as Foetal under nutrition, chronic metabolic disorders, the effect of under nutrition, cognitive impairment. In almost all cases, we obtained the original articles and extracted the relevant data.

**Foetal and maternal under nutrition**

Foetal development had dictated by maternal gestational diet and intrinsic factors, physical activity, and environmental stimulations. Among the crucial factors that influence the programming of the body are maternal nutrition, maternal body composition, dietary pattern, and blood flow to the uterus and placenta. The altered metabolic response of the foetus to malnutrition reduces the substrate use and decreasing the metabolic rate to increase the foetal viability results in insulin resistance in adulthood. It may also be due to decreased foetal insulin, IGF, and glucose levels that ultimately reduce foetal growth (5). Insufficiency of macronutrients, proteins, and carbohydrates during pregnancy causes fetoplacental modifications. As a result, low birth weight, high blood pressure, type-2 diabetes, cardiovascular disease, and adiposity develop during adulthood.

Conversely, the thrifty phenotype hypothesis postulates that the association between poor foetal and infant growth and subsequent type II diabetes and metabolic syndrome is caused by poor nutrition in early life (6). The lack of nutrients during foetal development decreases the size and mass of specific organs. Due to under-nutrition during rapid cell division, the endocrine pancreas does not develop properly, leading to insufficient insulin production. In adulthood, if the under nutrition continues, and when insulin requirement increases, the body develops diabetes mellitus (3-6). In adults, hypertension is more likely to occur due to under nutrition during pregnancy as it alters nitric oxide production, leading to the inadequate endothelium structure of blood vessels (7). Furthermore, a low protein diet during embryonic development leads to insufficient pancreatic cell proliferation, and it also affects the receptor system of insulin-dependent tissue, which may develop insulin resistance (8, 9).

### **Effects of under nutrition**

#### **Obesity**

Obesity and overweight are serious public health problems around the world. In 2005, 33% of the adult population worldwide was overweight or obese, a significant and growing burden on public health. In addition, by 2030, 57.8% of adults in the world may be overweight or obese (8). Furthermore, several epidemiological and experimental studies have suggested overweight and obesity in developing chronic diseases such as diabetes, cardiovascular diseases, hypertension, cancer, and premature death (9).

When the intrauterine environment has altered, the foetus will adjust to the changing climate through phenotypic plasticity, an adaptive mechanism to increase foetal viability. DOHaD suggested that if there is a mismatch between the environments where the foetus develops, phenotypic plasticity may provide an underlying mechanism for long-term disease (9). According to Parsons and colleagues, low birth weight increases the risk of developing obesity as an adult. When foetal growth is followed by compensatory childhood growth, children become predisposed to obesity as they become adults (10). In addition, compensatory growth between ages zero and two is associated with more centralized adipose tissue at age five compared to other children (11-15).

#### **Type-2 diabetes mellitus**

CL Hanes and DJ Barker proposed Thrifty Phenotype Hypothesis to explain the etiology of type-2 diabetes (3). The hypoplasia of the endocrine pancreas caused by maternal malnutrition during embryonic development results in inadequate insulin secretion. Increased requirement of insulin in adulthood triggers the development of diabetes mellitus. If calorie

restriction decreases after birth, this will result in insulin sensitivity (3- 6). Impaired adipogenesis increases insulin resistance and insulin production, which contributes to type 2 diabetes mellitus (16).

### **Blood pressure and hypertension**

Keller et al. found that blood pressure and the number of nephrons are influenced by hereditary and environmental variables (17), supported by several clinical and experimental studies showing that low nephron number is associated with arterial hypertension (18). Renal development is affected by intrauterine growth restriction, and the kidney plays a critical role when it comes to the pathogenesis of arterial hypertension (19). Reduced protein intake during pregnancy decreases the number of functioning nephrons in humans (20). During pregnancy, micronutrient (Iron and Zinc) deficiency reduces the number of nephrons in offspring (21).

### **Impaired cognitive function**

Early life experiences and environmental conditions such as maternal composition, maternal food intake, stress, physical inactivity, exposure to toxins, and maternal diseases influence brain development and behaviour. It also depends on the foetus's stage exposed to adversities (22).

Evidence from animal studies shows that delayed physical growth and neurobiological development in pups result from maternal low protein diet during gestation and lactation. And this protein insufficiency during important development period programs behaviour of the offspring's in a sex independent manner (18). Adulthood aggression is also associated with early-life social behaviour, and early-life social play deprivation results in abnormal social interaction and sexual behaviour (23). The early life interactions may lead to valuable strategies and fundamental skills to train the animal for competent social activity in its environment in adulthood (24).

Early postnatal protein restriction significantly reduces the social play interaction, especially pinning behaviour in rats (25-28). Maternal protein malnutrition enhances the anxiety and depressive-like behaviour in mice, and it also results in the impairment of locomotive activity, motivation, investigative and exploratory behaviour in mice (29-31). Moderate nutritional stress differentially affects mice's learning and memory patterns depending on exposure time, i.e., during perinatal, adolescence, or adulthood. Protein malnutrition during the perinatal period increases the risk of physical and cognitive disorders later in life. And protein malnutrition during adolescence enhances the aversive memory (32, 33).

Nutritional insufficiency in the initial stages of brain development, mainly prenatal, induces developmental brain retardation leading to cognitive impairment and

learning and memory deficits. Nutritional deprivation is associated with intellectual disabilities such as cognitive impairment and attention deficit disorder (14). Studies in animals (pigs) have shown that low birth weight is associated with lower cognitive performance compared to normal birth weight piglets (15).

Advances in brain research (34) have uncovered important insights into how the brain, the most immature of all the organs at birth, develops and grows after birth. This growth, however, was thought to be determined primarily by genetics and highly dependent on the experiences of the child. Growing evidence suggests that experiences affect how genes are expressed (i.e., turned on and off) in the developing brain. The brain develops best after having positive early experiences. However, neglect and abuse can result in some genetically normal children becoming mentally disabled or developing severe emotional challenges.

## CONCLUSION

The foetal programming paradigm allows taking preventative measures against the known factors to ensure a more favourable health outcome for future generations. Insufficiency of macronutrients, proteins, and carbohydrates during pregnancy causes fetoplacental modifications. It results in lower birth weight and eventually high blood pressure, type-2 diabetes, cardiovascular disease, cognitive decline, and adiposity in adulthood. This review concludes that the intrauterine environment and foetal nutrition play a significant role in developing chronic metabolic disorders. Therefore, this study provides the necessary insight onto target timely interventions as early in life as possible to prevent offspring from developing chronic diseases in adult life.

## CONFLICT OF INTEREST

None declared

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