FETAL ORIGIN OF ADULT DISEASE

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ABSTRACT

"Fetal origins of adult disease", often called the "Barker hypothesis" after a large proportion data of Barker and colleagues in Southampton over the last decade, that adverse influences early in development, and particularly during intrauterine life, can result in permanent changes in structure, physiology, metabolism, which result in increased disease risk in adulthood. Many further studies have provided evidence for the hypothesis that size at birth is related to the risk of developing disease in later life. In particular, links are well established between reduced birthweight and increased risk of coronary heart disease, diabetes, hypertension and stroke in adulthood. The most widely accepted mechanisms thought to underlie these relationship are those of altered fetal nutrition, genetic–epigenetic links, fetal programming and fetal excess glucocorticoid exposure. It is suggested that the fetus makes physiological adaption in response to changes in its environment to prepare itself for posnatal life. The "Fetal origin of adult disease" hypothesis is attractive. It suggests that these diseases could be prevented by improving maternal health and fetal development.

Key words: Development origin of adult disease, Chronic diseases, Heart disease, Hypertension, Diabetes, Programming.

1. FETAL ORIGIN OF ADULT DISEASE HYPOTHESIS

The "Fetal Origin of Adult Disease" hypothesis often called the "Barker hypothesis" after a large proportion of the data of Professor David Barker (1938-2013) and colleagues in Southampton over the last decades of the 20th century states that adverse influences early in growth and developmental period, particularly during intrauterine life, can result in permanent changes in structure, physiology and metabolism, which result in increased disease risk in adulthood.

Since 1986, Barker and collesgues noted that the regions in England and Wales that the highest rates of malnutrition and infant mortality in the early 20th century also had the highest rate of mortality from conorary heart disease in dacades later [1]. Two large studies of men in Shieffiel and Hertforshire from t989 to 1993 shwed a strong relationship between death from coronary heart disease and decreasing birthweight, head circumferencs or poderal index, It was particularly people who were born growth restricted rather than premature who were ar risk [2][3]. Barker showed that undernutrition during gestation was an important contributor to low birthweight, small size at birth and early origin of adult

cardiac and metabolic disorders [4]. The fetus is dependent on the nutrients from the mother and adapts to an inadequate nutrient supply in a number of ways : prioritization of brain growth at the expense of other tissues such as the abdominal viscera; reduced secretion or sensitive to the fetal growth hormones as insulin and IGF-1; and up-regulation of the hypothalamus-pituitary-adrenal (HPA) axis. Barker and al. proposed the "Thrifty phenotype" hypothesis; when the fetal environment is poor, there is an adaptive response, which optimizes the growth of key body organs to the detriment of others and leads to altered postnatal metabolism, which is designed to enhance postnatal survival under conditions of intermittent or poor nutrition [5]. The fetal has many homeostatic and homeorhetic mechanisms that confer immediate survival advantage e.g. alterations in regional blood flows and organ growth when nutrient or oxygen supply is reduced, even if there may be subsequent postnatal costs [6]. The fetal origin of adult disease (FOAD) hypothesis proposes that although occurring in response to a transient phenomen (fetal–undernutrition) these adaptions become permanent or "programmed" because they occur during critical periods of early development of the fetal [7][8]. Fetal life is a sensitive period of cellular proliferation and maturation, resulting in structural and functional changes in cells, tissues and organ systems. All organ systems undergo developmental programming in utero that predetermine subsequent physiologic and metabolic adaptions during adult life. These concepts have been referred to fetal origin of adult onset disease, also health and disease [9][10]. The origin of adult onset disease is the profound effects of "mismatch" between the early developmental environment and the subsequent environment in childhood and adult life [11].

The hypothesis is supported by examples in experimental animals of permanent structural and metabolic changes resulting from transient nutritional insults in utero. Maternal rats protein restriction in pregnancy leads to higher blood pressure, impaired glucose tolerance, insulin resistance and altered hepatic architecture and function in the offspring. Fetal undernutrition results in susceptivity to disease in later life, as reduced insulin sensitivity, low muscle mass, pancreatic beta cell mass and nephron numbers, altereial structure, and up-regulation of the HPA axis and sympathic nervous system [12][[13].

After the first studies of Barker and al., many other studies in various countries and regions note also that reduced birthweight and size at birth have been associated with an increased incidence of adult chronic disease in later life. Many diseases were well accepted association,with small birth size as hypertension, coronary heart disease, non–insulin dependant disorders, stroke, dislipidemia [14]; and some others were less well association with small birth size as chronic lung disease, depression, schizophrenia, breast cancer, testicular cancer [15]]16].

Table 1. Diseases linked with birthweight

Diseases	Reference
Strong association with small birth size	
Hypertension	Huxley RR và cs, 2000
Conorary heart disease	Barker DJ và cs, 1989
Non insulin dependent diabetes	Newsome CA và cs, 2003
Stroke	Roseboom JJ và cs, 2000
Dislipidemia	Henry JA và cs, 1997
Elevated clotting factors	Henry JA và cs, 1997
Impaired neurodevelopment	McCartoon CM và cs, 1996
Less association with small birth size	
Chronic lung disease	Lal MK và cs, 2003
Depression	Gale CR và cs, 2004
Schizophrenia	Kunugi H và cs, 2001
Behavioural problems	Hack M và cs, 2004
Left handedness	James WH, 2001
Reduced uterine and ovarian size	Ibanez L. và cs, 2000
Precocious pubarche	Ibanez L. và cs, 2000
Breast cancer	Elias SG. và cs, 2004
Testicular cancer	English PB và cs, 2003
Described association with large birth size	
Polycystic ovaty disease	Cresswell JL. và cs, 1997
Breast cancer	Michels KB. và cs, 1996
Prostate cancer	Nilsen TI. và cs, 2005
Testicular cancer	Richiardi I. và cs, 2003
Childhood leukemia	Hjaldrim LL. và cs, 2004
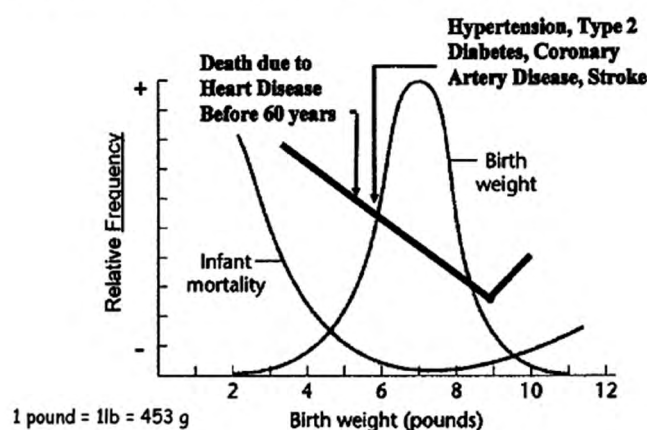
Figure 1. Birthweight with infant mortality and adult disease

Fetal nutrition affects strongly to adult disease in later life. The Dutch famine at the end of the Second World War, 1944-1945 showed that: After 60 years, adults exposed to Dutch famine during gestation had been higher incidence of chronic diseases, as obesity, type 2 diabetes, aarterosclerosis, coronary heart disease, breast cancer, Alzheimer than others who were not exposed [17][18][19].

Acute maternal stress in pregnancy effects also to diseases of offspring in later life. A cohort study of 88.829 born in Jerusalem from 1964 to 1976, Malaspina D (2008) showed that adults who were born from the mothers in the 3rd month of pregnancy during the Arab - Israel Six day War at 1967 had been high incidence of schizophrenia. The schizophrenia has been linked with intrauterine exposure to maternal stress due to bereavement, famine and major disorders [20].

2. POSSIBLE MECHNISMS

The most widely theory of development origin hypothesis is 'programming". Programming is a concept whereby a stimulus or insult during a sensitive or critical period of growth and development long-term irreversible effects on structure, physiology, metabolism in tossues or organ system. Many mechanisms can explain the fetal origin of adult disease, but well - recognized mechanisms include alterd fetal nutrition, genetic–epigenetic links, fetal programming and glucocorticoid exposure.

2.1. Altered fetal nutrition

Fetal nutrition is a key regulator of fetal growth, as a nutritional programming influence [21]. Fetal undernutrition affects clearly to birthweight and adult disease in later life. Maternal rat, both global undernutrition and specific protein restriction result in reduced birhweight [22], hypertension [23], and impaires glucose tolerance 24] in offspring. Similar effects have been reported in guinea pig [25] and sheep [26].

In human pregnancy, both birthweight and placental weight were low due to undernutrition [27]. Imbalance of protein and carbohydrate intake during pregnancy has been associated with reduced birthweight and hypertension in offspring [28]. Micronutrients may also play an important role in programming of postnatal disease. India pregnancy women intake of green vegetables and fruit were associated with birth size and glucose tolerance in offspring [29] Higher calcium intake during pregnancy has been associated with hypotension in offsprings [30].

Fetal overnutrition may be related with posnatal disease. Infants of diabetic mothers also expeience fetal overnutrition, they are exposed to increased glucose and fatty acid in blood before birth, and increased risk of glucose intolerance and type 2 dibetes in later life [[31].

Alterd fetal nutrition may be lead to stimulate common programming in increasing risk of adult disease [31]. The following schema describes of altered fetal nutrition directly or indirectly leading to altered growth and maturation of various fetal organ systems influencing to disease in later life.
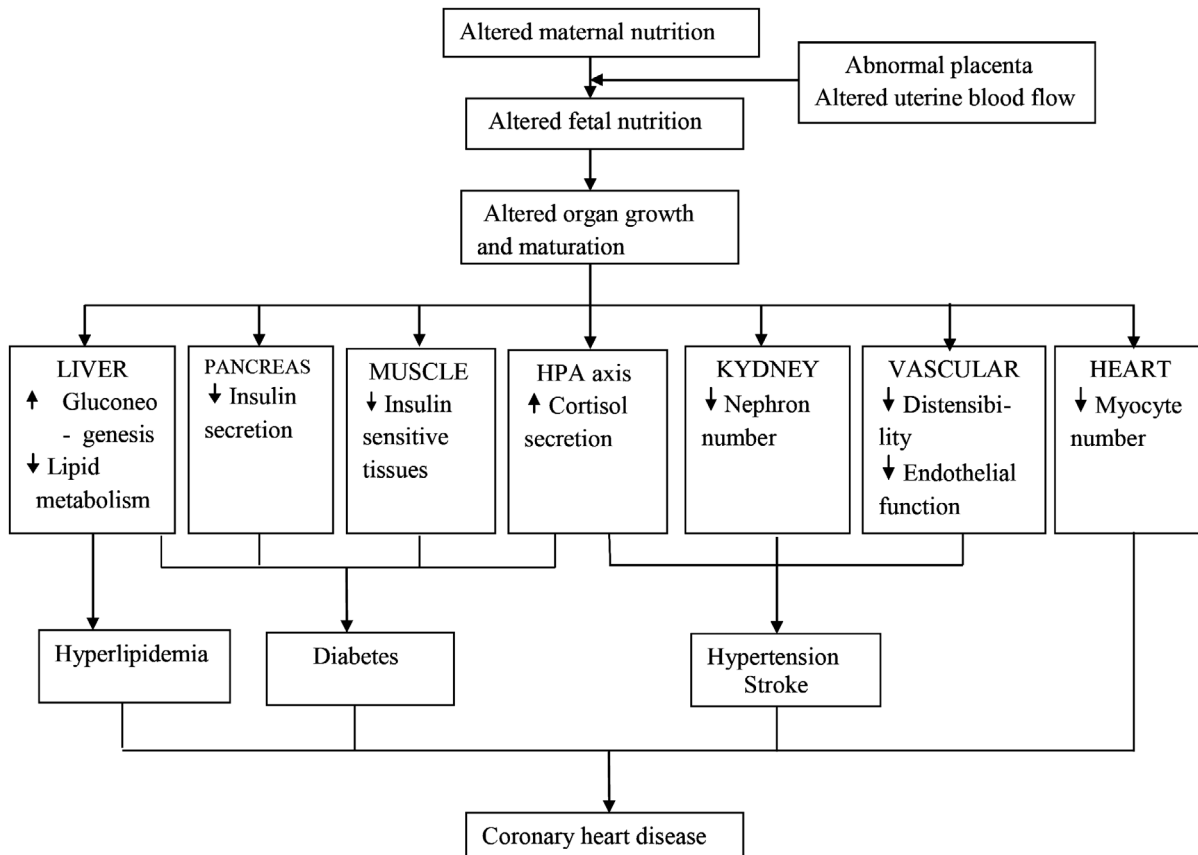
Figure 2. Altered fetal nutrition on growth and maturation of fetal organ systems and their links with adult disease

2.2. Genetic and Epigenetic links - Fetal programming

The relation between fetal growth and adult disease must ultimately involve changes in gene expression, which are very likely in involve epigenetic phenomena. During early embryogenesis, DNA undergoes demethylation and remethylation; some genes from maternal or paternal origin have been inactivation, that affect many genes regulating fetal and placental growth [33] Fetal nutrition is an important environment factor of DNA regulating, and also the source of methyl and acetyl affecting to methylation and acetylation of epigenetic mechanisms leading to phenotype changes and adult disease later (Cartin và cs., 2013). Intrauterine environment affects to epigenetic mechanism establishing fetal developmental genotype, fetal programming - early life programming, leading to programmed a large number of metabolic and phusiological genes influencing to health and adult chronic diseases [34].
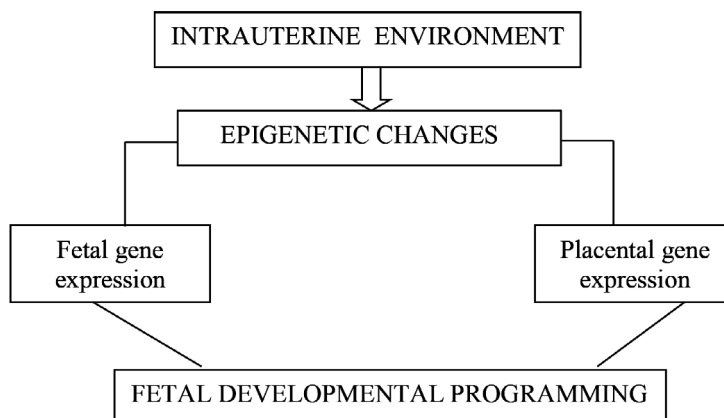
Figure 3. Effects of intrauterine environment and fetal developmental programming.

2.3. Thrifty phenotype hypothesis and Adaptive response

The "Thrifty phenotype" hypothesis first proposed by Hales and Barker suggested that adult insulin resistance and type 2 diabetes could result from the persistence of the fetal adaptive response in intrauterine hypoglycemia due to fetal undernutrition [35]. During periods of maternal undernutrition, the fetal reduces insulin secretion and increases insulin resistance, thus directing more glucose to the brain and heart, and less to insulin-dependent tissues such as skeletal muscles [36]. When nutrient is abundant in postnatal life, this pancreatic beta-cell defect and peripheral insulin resistance could then cause glucose intolerance and diabetes. This would explain why thin babies become overweight during childhood who are prone to developing type 2 diabetes in later life [37].

2.4. Glucocorticoids

Another mechanism by which adult cardiovascular and metabolic disease may be program-med in via expocure in excess glucocorticoids. This may be occur in utero if maternal glucocortioid level is elevated due to exogenous glucocorticoid administered; or if the placental barrier that protects the fetus from high level of maternal glucocorticoid is impaired. Intrauterine glucocorticoid exposure leads to reduce number of glucocorticoid receptors in the hypothalamus, resulting in impaired negative feedback and hence long-term up-regulation of hypothalamus– pituitary–adrenal axis after birth [38], contributing to increased blood pressure and glucose intolerance in offspring.

Rats given dexamethsone during pregnancy have reduced birthweight and increased blood pressure, glucose intolerance in adulthood [39]. Similar effects are seen in human pregnancy, babies born small to have higher plasma cortisol, lower activity of 11betaHSD-2 (11 beta hydroxysteroid dehydrogenase-2) in placenta. Repeated administration of betamethasone or dexamethasone during pregnancy has been associated with reduced size at birth [40].

2.5. Fetal insulin hypothesis

Hatterley proposed that the relation between small size at birth with impaired glucose tolerance in adult can explain by inherited deficits in nsulin secretion or action [41]. Insulin is an important regulator of fetal growth, impaired insulin secretion would have impaired growth before birth and would have also impaired glucose tolerance in adulthood [42].

2.6. Intergenerational effects

Adverse events during pregnancy can affect not only the offspring of that pregnancy but also

the next generation. It has long been recognized that birthweight of the mother is related to the birthweight of her children. Studies in Dutch hunger winter 1944-1945, women who were severely undernutrition during the first trimester of pregnancy gave birth to babies with normal average birthweight, but those babies themselves then went on to give birth to small babies in the next generation [43]. There are several possible explainations for these intergenerational effects on birthweight : (1) The humonal environment of the uterus of undernourished mothers may affect the developing reproductive tract of the fetus with reduced uterine and ovarian size, thereby reducing fetal growth of next generation [44]; (2) Any epigenetic changes at the genome may be passed on the second generation [45].

2.7. Intergrated mechanism

There are some possible mechanisms on explaining the fetal origin of adult disease. Some mechanisms can integrate in any individual to developing adult disease in later life. The following schema describes the integrating mechanism.
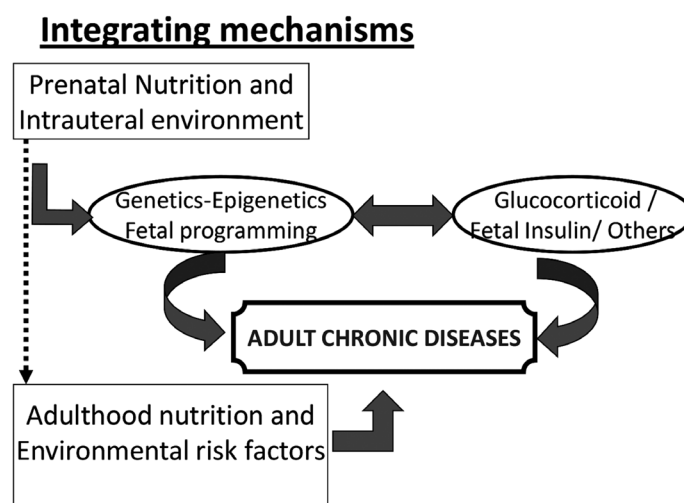
Integrating mechanisms

Figure 4. Intergrating mechanism

3. CONCLUSIONS

Fetal Origin of Adult Disease hypothesis is widely accepted. Large number of studies have provided evidence for that reduced size at birth, fetal undernutrition, also other adverse insults during pregnancy are related of adult onset chronic disease in later life. There are several possible mechanisms, the most widely accepted mechanisms are altered fetal nutrition, genetic-epigenetic links, fetal programming and glucocorticoid exposure. All risk factors of low birthweight eliminate and prenatal care, including mother, fetal and neonatal care, are crucial prevention of number adult chronic disease.

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