Review Article

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Fetal Origin of Adult Disease

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Abstract

The risk of number of chronic diseases in adulthood may have their origins before birth search diseases include non-insulin dependent Diabetes, hypertension and coronary heart disease. Alteration in fetal nutrition and endocrine status may result in adaptations that permanently change the structure physiology and metabolism of the offspring predisposing individuals to metabolic endocrine and cardiovascular diseases in adult life. The developmental origin of adult disease hypothesis is called Barker hypothesis. Under nutrition is programming stimulus when events during critical period of development and change structure and function of the organism. Insulin resistance is early feature of metabolic syndrome and is associated with fetal effects. Adverse events during pregnancy can affect not only the offspring of that pregnancy but also the next generation, women on growth, diet and body composition before and during pregnancy play a major role in programming the future health of her children.

Keywords: Fetus; Adult; Barkar; Programming; Thrifty Phenotype; Diabetes.

Introduction

It is now widely accepted that the risks of a number of chronic diseases in adulthood may have their origins before birth. Such diseases include non-insulin-dependent diabetes mellitus, hypertension and coronary heart disease [1]. Such relationships have been shown to hold in many different populations and are apparent from early childhood [2, 3].

There is considerable evidence for the fact that early life environment in human beings are associated with future development of various metabolic diseases. Fetal programming and perinatal events appear to exert effects on later life that are independent of environmental risk factors in adults.

In this review, we amalgamate facts from several disciplines to support this hypothesis.

"The devil has put a penalty on all things we enjoy in life. Either we suffer in health or we suffer in soul or we get fat." Albert Einstein, 1879–1955.

Nutrition is the major intrauterine environmental factor that alters expression of the fetal genome and may have lifelong consequences. This phenomenon, termed "fetal programming," has led to the recent theory of "fetal origins of adult disease." Namely, alterations in fetal nutrition and endocrine status may result in developmental adaptations that permanently change the structure, physiology, and metabolism of the offspring, thereby predisposing individuals to metabolic, endocrine, and cardiovascular diseases in adult life.

Barker Hypothesis

The 'developmental origins of adult disease' hypothesis, often called the 'Barker hypothesis' states that adverse influences early in development,and particularly during intrauterine life, can result inpermanent changes in physiology and metabolism, whichresult in increased disease risk in adulthood. Nevertheless, the undisputable achievement of Hales and Barker was that, in an unselected population sample from Hertfordshire, UK, they proved a direct

link between low weight at birth and increased risks of developing type 2 diabetes, hypertension, elevated triacylglycerols and insulin resistance later in life [4].

Poor development of pancreatic α-cell mass and function (including islet of Langerhans vasculature and possibly innervation) were key elements linking poor early nutrition to later type 2 diabetes. Fetal malnutrition led to insulin resistance. Fetal nutrition thereby set in train mechanisms of fetal nutritional thrift, which had a differential impact on the growth of different organs, with selective protection of brain growth. Altered growth permanently changes the structure and function of the body.

The thrifty phenotype hypothesis and predictiveadaptive responses

The 'thrifty phenotype' hypothesis first proposed by Halesand Barker suggested that adult insulin resistance and type 2diabetes could result from the persistence of a fetal glucoseconservingadaptation in response to intrauterine hypoglycaemia [5]. This adaptive response is detrimental as low birth weight was associated with increased risk of obesity, dyslipidemia, hypertension, ischemic heart disease, Type 2 diabetes, and polycystic ovarian syndrome (PCOS) in adults. Thrifty phenotype hypothesis suggested that in a nutritionally deprived environment, the fetus undergoes intrauterine programming and channels the nutrient resources toward the development of vital organs like brain at the expense of other organs like beta cell islets [6,7].

Adaptive Responce

The evolution of the human species through a process of survival of the fittest has necessitated a complex interaction between maternal and fetal genotypes. The thrifty genotype theory suggests that the relative scarcity of food during the early periods of human evolution leads to an adaptive response of enriched thrifty genes, which is conducive in a nutritionally poor environment. However, with relative easy availability of food and nutritional enrichment, this adaptation becomes counterproductive [8].

Gluckman and Hanson have recently revised and extended this hypothesis [9]. They propose that when there is a changein the intrauterine environment, for example, nutrient restriction or high glucocorticoid levels, the fetus will make adaptations to improve its immediate chances of survival. These adaptations are often reversible. However, if the environmental changes persist, the fetus is forced to make irreversible adaptations that may or may not be immediately beneficial, but that will manifest themselves in later life. In this way the fetus is preparing itself for life in an extrauterine environment with, for example, low food availability or highlevels of stress. Gluckman and Hanson coined the term 'predictive adaptive response' (PAR) for this phenomenon.

Programming

Programming describes the process when events during critical periods of development may change structure and function of the organism [10] the term "programming" was introduced to describe the processes by which physiological development is altered *in utero* so as to impact on adult pathophysiology. As yet, programming remains a conceptual term rather than having any precise biological basis.

Programming Stimulus

The question concerns the nature of the programming stimulus. Undernutrition was proposed early as a likely programming stimulus, although others such as excessive fetal exposure to glucocorticoids have also been proposed [11,12,13].

Period of Developmental Programming

Studies of third trimester fetal growth rate pointed towards effects prior to or after the third trimester (i.e. all periods except the third trimester) being the most important periods during development relevant to programming of components of the metabolic syndrome [14].

Programming

1 IGF-I, insulin-like growth factor I; Ig, immunoglobulin.

Ref: Keith M Godfrey and David JP BarkerFetal nutrition and adult disease1–3The American journal of clinical nutrition2000; 71suppl:1344s-52s.

Table 1: Tissues and systems for which there is evidence of programming in humans (159)

Tissue or system	Examples of programming
Cardiovascular system	Vascular compliance Endothelial function

Respiratory system	Lung volume
Endocrine system	Hypothalamic-pituitary-adrenal axis Glucose-insulin metabolism Growth hormone–IGF-I axis
Reproductive system	Age at menarche Polycystic ovary syndrome
Central nervous system	Schizophrenia
Skeletal muscle	Insulin resistance Glycolysis during exercise
Bone	Bone mineral content
Kidney	Renin-angiotensin system
Liver	Cholesterol metabolism Fibrinogen and factor VII synthesis
Immune system	Thyroid autoantibodies IgE concentrations

Programming Due to Excess Metabolism

There are many possible mechanisms by which alteredfetal nutrition might lead to increased risk of disease in theoffspring [15].

Glucocorticoids

Another mechanism by which adult cardiovascular andmetabolic disease may be programmed is via exposure toexcess glucocorticoid levels are elevated, if exogenous synthetic glucocorticoidsare administered, or if the placental barrier thatprotects the fetus from high levels of maternal glucocorticoidsis impaired. These effects appear to be mediated at least in partvia permanent changes in the regulation of the hypothalamo-pituitary–adrenal axis in the offspring. Intrauterine glucocorticoidexposure leads to reduced numbers of glucocorticoid receptors in the hypothalamus, resulting in impaired negativefeedback and hence long-term up-regulation of the hypothalamo–pituitary–adrenal axis after birth. This, in turn, could contributeto increased blood pressure and glucose

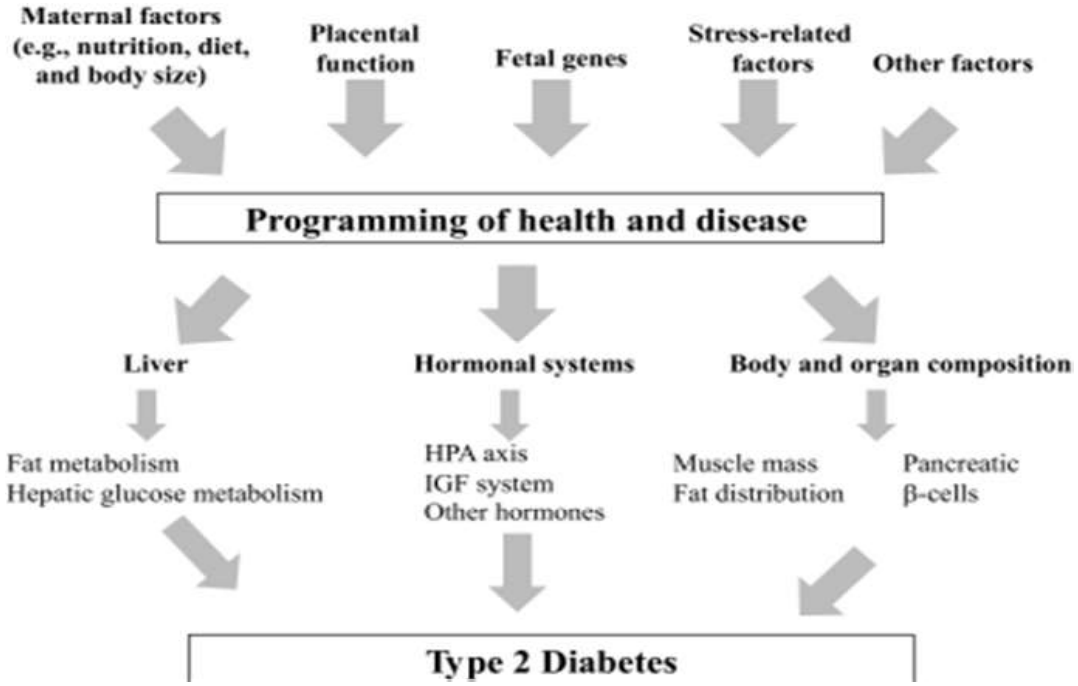

Chart 2

intolerancein the offspring. Maternal dietary restriction increasesmaternal glucocorticoid secretion in rats, reduces placental 11!-HSD-2 activity and alters neonatal hypothalamopituitary–adrenal axis function [16]. Thus, the effects ofnutrition and glucocorticoids as programming stimuli mayact via similar pathways to produce long-term changes inhomeostatic regulation leading to increased risk of adultdisease.

An unfavorable programming of body composition could be one mechanism linking early childhood growth with later increased risk for type 2 diabetes [17]. Potential underlying mechanisms explaining the early programming of adult health and disease are schematically presented in Table 2. These include maternal factors, placental function, genetic and epigenetic mechanisms, as well as a large number of other factors. These factors could program organ and body function and composition as well as hormonal and growth factors. Within the context of type 2 diabetes, the factors could have an effect on insulin sensitivity and secretion, on hepatic glucose production, and on hormones involved in glucose and insulin metabolism.

Ref: Ylihärsilä H, Kajantie E, Osmond C, Forsén T, Barker DJ, Eriksson JG. Body mass index during childhood and adult body composition in men and women aged 56–70 y. Am J Clin Nutr2008; 87: 1769–1775.

Developmental Plasticity

The response to these adaptations in later life is based on an environmental mismatch with respect to the nutritional availability and requirement. The intrauterine programming in a nutritionally challenged environment provides a survival advantage in a nutrient-deficient extrauterine environment and becomes detrimental in a nutrient-rich environment. Hence, there is a developmental plasticity by which a single genotype may give rise to different phenotypes by adjusting their phenotype to match the environment they have to survive in [18,19]. The complex interactions of environment and nutrition with maternal and fetal genotypes influence maternal and fetal well-being. We also do know that nutrition, stress, and other environmental factors can modify the epigenome. Coronary heart disease and type 2 diabetes may originate through two widespread biological phenomena—developmental plasticity and compensatory growth.

A possible explanation for this is that, following an intra-uterine lesion regulatory mechanisms may maintain homeostasis for many years until further damage, due to age, obesity or other influences, initiates a self-perpetuating cycle of progressive functional loss [20]. In particular, rapid childhood weight gain increases the risk of disease associated with small body size at birth and during infancy. Examination of the risk of disease attributable to early development therefore requires data on fetal, infant and childhood growth. The Hertfordshire studies showed, for the first time, that people who had low birthweight and low weight at age one year were at increased risk of developing coronary heart disease (CHD) and type 2 diabetes. So-called 'phenotypic plasticity' enables one genotype to give rise to a range of different physiological or morphological states in response to different environmental conditions during development [21].

Diabetes Mellitus in Adulthood

Dutch Hunger Winter study, findings from which suggested that malnutrition—and stress—during prenatal life have a long-term effect by increasing the risk of coronary heart disease and type 2 diabetes in later life. These effects also depend upon timing of the exposure [22].

Maternal Obesity and Diabetis

Maternal diabetes predisposes to adult-onset obesity and diabetes in the fetus even after other influencing factors are adjusted for. Children born to mothers who were diabetic at the time of pregnancy were found to be more obese than their siblings who were born before the onset of diabetes [23]. It was also seen that diabetes was more common in children who were born to mothers who had diabetes at the time of pregnancy when compared to infants who were born to mothers who did not have diabetes at the time of pregnancy, though they developed diabetes subsequently [24].

Infants with high birth weight are also prone to develop obesity and insulin resistance later in life [25]. A study by Yajnik et. al. showed that higher birth weight in children was associated with adiposity in the parents and metabolic syndrome in mother 8 years after the child birth [26]. The metabolic abnormalities that are present in the obese and diabetic mothers are transferred to the fetus during intrauterine period, conferring a risk of subsequent obesity [27]. Multiple pathways including upregulated placental transporters and altered fetal gene expression are proposed [28]. Another interesting mechanism is probably early-onset endothelial dysfunction. Studies have shown that the levels of endothelial progenitor cells are reduced in neonates born to mothers with

type 1 diabetes mellitus [29]. Endothelial progenitor cells play an important role in vascular repair and neovascular formation, and endothelial dysfunction plays a pivotal role in the development of cardiovascular diseases.

Hypercholesterolemia has been shown to induce islet cell apoptosis and glucokinase downregulation, resulting in decreased insulin secretion.Further studies are required to highlight the effects of hypercholesterolemia and a nutrient-rich environment on fetal insulin secretion.

Risk Factors for Diabetis Mallietus

Importantly, comparative studies of low birthweight in humans and protein-undernourished rats in utero identified strikingly similar changes in the expression of key insulin signalling proteins and of the glucose transporter GLUT4 in both skeletal muscle and adipose tissue [30].

The extent to which the global diabetes epidemic may be driven by a mismatch between being born with a low birthweight and the fast propagation of overnutrition and physical inactivity seen over recent years in developing countries needs to be determined to provide a focus for efforts to prevent metabolic diseases. GDM may be considered an early manifestation of type 2 diabetes that is unmasked by pregnancy-induced insulin resistance, and studies in both animals and humans have indicated that exposure to an adverse fetal environment is a significant risk factor for GDM per se [31].

Insuline Resistance

During periods of maternal undernutrition the fetusreduces insulin secretion and increases peripheral insulinresistance, thus directing more glucose to the brain and heartand less to insulin-dependent tissues such as skeletal muscle [32]. Type 2 diabetes genes have appeared to be more selective in their influence on organ dysfunctions, with defective pancreatic insulin secretion being the most important [33].

Hales and Barker and colleagues were the first to document the association between low birthweight and insulin resistance in humans [34]. Insulin resistance is a very prominent and early feature of the metabolic syndrome and has consistently been associated with fetal programming in humans, regardless of whether the exposure is low birthweight, prematurity independent of low birthweight, gestational diabetes mellitus (GDM) or twin/zygosity status [35,36,37].

Intergenerational Effects

Multigenerational Effects

Much debate has surrounded the role of genetic influences in the relationship between size at birth and later disease risk. The associations between maternal hypertension, reduced birth size and hypertension in the next generation, for example, could be at least partly of genetic origin. Nutritional influences, too, may have effects on more than one generation.

Intergenerational Effects

Adverse events during pregnancycan affect not only the offspring of that pregnancy butalso the next generation. It has long been recognised that thebirthweight of the mother is related to the birthweight of herchildren. This epigenetic process of imprintingis thought to particularly affect many of the genes regulatingfetal and placental growth. There was a 5-month period of severe famine at the end of theSecond World War. Women who were severely undernourishedduring the first trimester of pregnancy gave birth tobabies who were on average of normal birthweight, butthose babies themselves then went on to give birth to smaller babies in the next generation [38].

The hormonal environmentof the uterus of undernourished mothers may affectthe developing reproductive tract of the fetus. Indeed, motherswho were small at birth have reduced uterine and ovarian size [39]. It is proposed that smaller uterine size may impose agreater 'maternal constraint' on the fetus, thereby reducingits growth, although there is not yet any direct evidencefor such an effect. Second, any epigenetic changes to thegenome may be passed on to the second generation.

There are also intergenerational effects on risk factors forcardiovascular disease [40].Lower maternal birthweight is associatedwith an increased risk of hypertension during pregnancy, which in turn is associated with lower birthweight of the off spring [41].

This effect maybe mediated by exposure to excess glucocorticoids Experimental studies in animals have shown that undernutrition over many generations can have cumulative effects on reproductive performance over several generations .Strong evidence of major intergenerational effects in humanshas come from studies showing that a woman's birth weight influences the birth weight of her offspring [42,43].

Diabetis Mallietus in Adulthood

Prenatal Stress Affects HPA Axis

Confounders such as infections and stress might predispose subjects to unfavourable health outcomes similar to those caused by the famine itself.Prenatal stress is known to affect the hypothalamic- pituitary-adrenal (HPA) axis and primarily cortisol secretion. This could be one plausible mechanism explaining the association between prenatal programming and a higher prevalence of hyperglycaemia in adult life [44].

Fetal Growth: Insulin and Nutrient

The major hormonal mediators of fetal growth are insulin and the insulin-like growth factors (IGF)[45,46]. These in turn are regulated by fetal nutrient supply[47,48]. Thus reduced glucose supply to the fetus results in reduced circulating insulin and IGF concentrations and in reduced fetal growth. Since nutrition has such a central role in the regulation of fetal growth, it is a good candidate for a programming stimulus, holding a central role in the link between size at birth and subsequent disease risk. Mammalian fetus grows at the end of a long and sometimes precarious 'supply line', which links maternal diet at one end with fetal tissue uptake at the other [49].

Relatively large changes in maternal diet may have little impact on fetal nutrition if the capacity of the fetal supply line allows a large margin of safety for fetal growth. Conversely, common clinical causes of impaired fetal growth such as maternal hypertension associated with reduced uterine blood flow, or placental infarcts resulting in reduced placental transfer capacity, may severely limit fetal nutrient supply without a corresponding change in maternal nutrition The fetal 'diet' of the late gestation is remarkably consistent in different species, comprising glucose, lactate and amino acids as the major fuels for oxidative metabolism. However, the relative proportions of these fuels varies with the species and with the time in gestation. The human fetus is very dependent on glucose as a major oxidative substrate

In the protein undernutrition model, increased apoptosis has been reported in the fetal pancreas that might explain the altered β cell mass observed [50]; in the kidney, reduced nephron number has been reported [51]; in the brain, there is reduced cerebral and mesenteric vascularity [52]; and in the liver a change in pattern of hepatic zonation [53,54], as reflected in altered expression patterns of gluconeogenic enzymes.

At a more synthetic level it has been suggested that multiple hormone insensitivity including GH, IGF-1, insulin, and leptin might be involved [55]. Hypothalamic dysfunction may also be involved: there being evidence of central disturbance of the HPA axis and of vegetative functions, including appetite [56]. Other authors have suggested endothelial dysfunction, or alterations in the autonomic nervous system as core elements [57, 58].

Many other outcomes in adult life have been linked tosize at birth. Reduced birthweight has been associated withan increased incidence of chronic lung disease, and psychologicaloutcomes, and with characteristic changes in fingerprintpatterns [59,60], while larger birthweight has been associatedwith increased risk of polycystic ovarian disease and thehormone-related cancers: breast, prostate and testicular cancer [61]. This suggests that, whatever the mechanisms underlyingthese relationships, they must act within the normalphysiologicalprocesses regulating intrauterine development, ratherthan involving pathological mechanisms applying only toabnormal pregnancy. The effect of small size at birth is modulated by patterns of childhood growth.Timing of the adverse event during gestation must also be considered. In the Dutch winter famine, early gestational exposure had no effect on the development of postnatal carbohydrate intolerance, whereas third trimester exposure had a marked effect [62].

SGA children who have weight gain are at risk of developing insulin resistance, PCOS, premature adrenarche during adolescent period, and hypertension, diabetes, and cardiovascular disease in adulthood [63,64]. Low birth weight may be associated with decreased number of glomeruli, which when exposed to hyperfiltration associated with weight gain can accelerate glomerulosclerosis and contribute to hypertension [65]. It is important to note that those infants who do not have significant catch-up growth are not at risk for most of these diseases [66].

Acute undernutrition in pregnancy profoundly activates the maternal HPA axis sufficient to affect the fetal HPA axis secondary to transplacental corticosterone transfer. This is of relevance in that other experimental paradigms in both rats and sheep have demonstrated that maternal exposure to betamethasone or dexamathasone can induce hypertension in the offspring [67,68].

Maternal Undernutrition in Preconceptional Period

Experimental animals and inhuman pregnancy suggest that altered risk of adult disease maybe linked

with the maternal nutritional status around conceptionand implantation in the absence of altered size at birth.In sheep, maternal undernutrition only around the timeof conception is associated with preterm birth, prematurematuration of the fetal hypothalamo–pituitary–adrenal axis, [69] altered fetal growth trajectory and altered insulin secretion inthe fetus [70].

Mother's Low Birth Weight

The effect of maternalbirth weight on thinness at birth is consistent with the hypothesisthat the maternoplacental supply line may be unable to satisfyfetal nutrient demand in low-birth-weight mothers. Potential mechanisms underlying this effect include alterations in the uterineor systemic vasculature, programmed changes in maternal metabolic status, and impaired placentation. The strong effect ofpaternal birth weight on crown-heel length may reflect paternalimprinting of genes important for skeletal growth, such as thoseregulating the concentrations of insulin-like growth factors [71].

Father's Low Weight

Godfrey et al in their study found that whereas low-birth-weight mothers tend to havethin infants with a low ponderal index, the father's birth weightis unrelated to ponderal index at birth; crown-heellength at birth is, however, more strongly related to the father'sbirth weight than to the mother's [72].

Fetal Micronutrient Deficincy

Bothbirthweight and placental weight are affected by the balanceof macronutrients in the maternal diet [73,74]. Imbalance ofprotein and carbohydrate intake during pregnancy has beenassociated with reduced birthweight and increased blood pressure in the offspring [75,76].

Micronutrients may also playan important role in programming of postnatal pathophysiology. In an Indian study, maternal intake of fruit and greenvegetables during pregnancy was positively associated withbirth size and glucose tolerance in the offspring [77,78]. Infants of diabetic mothers also experience fetalovernutrition, as they are exposed to increased glucose andfatty acid concentrations before birth.

IUGR

One common assumption is that body proportions provide information about the timing of nutritional insults leading to the limitation of fetal growth. Thus a baby which is proportionately small in weight, length and head circumference at birth is presumed to have suffered from nutrient limitation in early pregnancy, while a baby of similarly low birthweight who is relatively long and thin is presumed to have suffered nutrient limitation in late pregnancy [62-64].

In a similar vein, relative preservation of head circumference at birth ('head sparing') is commonly assumed to occur as a consequence of blood flow redistribution in fetal life. There is certainly good evidence of redistribution of cardiac output in fetuses exposed to hypoxia, with maintenance of blood flow to essential organs such as the brain and heart at the expense of other organs such as the gut and skin [71]. There is also ultrasound evidence that such redistribution does occur in chronically hypoxaemic intrauterine growth restricted (IUGR) human fetuses, and can be partly reversed by administration of oxygen [79, 80].

Other nutritional mechanisms may allow relative preservation of brain growth in the substrate limited fetus. Glucose uptake into many tissues is mediated by insulin, and fetal insulin secretion is regulated by glucose and amino acid supply. However glucose uptake into the brain does not require insulin. Thus limitation of glucose and amino acid supply to the fetus will reduce circulating insulin concentrations and glucose uptake into peripheral tissues such as muscle, sparing the available glucose for uptake into the brain which is insulin independent. In addition, fasting in women increases the supply of ketones to the fetus and the fetal brain has been shown to preferentially take up and oxidize ketones.

Hormones in IUGR

SGA children have elevated levels of growth hormone,insulin like growth factor binding proteins 1 and 2 (IGFBP1, and IGFBP2), with low levels of IGF-1 and IGFBP3, which is a pattern consistent with growth hormone insensitivity and insulin resistance [81,82,83]. In most of these children, growth hormone dynamics normalizes in the initial few months of life [84].

Adipocytokinesis

Subsequently, when they progress to childhood and adulthood, the leptin levels are higher compared to normal cohort. This leptin resistance may be an adaptive response which may serve as a stimulus for food intake and promote catch-up growth [85].

Other adipocytokines under active investigation for their role in IUGR and subsequent adult-onset

adiposity and insulin resistance include tumor necrosis factor-alpha (TNF-α), interleukin-6 (IL-6), resistin, apelin, and visfatin [86].

Disproportion in body length relative to head size is thoughtto result from cranial redistribution of oxygenated blood awayfrom the trunk to sustain brain metabolism—an adaptiveresponse present in mammals [87]. This impairs the growth ofthe liver and may underlie permanent abnormalities in the regulation of cholesterol and clotting factors Inembryo transfer studies, it is the recipient mother rather than thedonor mother that more strongly influences the growth of thefetus; a fetus transferred to a larger uterus will achieve a largerbirth size.

Mitochondria and IUGR

Epidemiological studies have recorded a subnormal mitochondrial function in patients with hypertension and diabetes. Since mitochondrial DNA is inherited from the mother, it may be a player that determines the transfer of maternal nutritional stress to fetus. So it is not surprising that mitochondria contributes to thrifty phenotype [88].

The central mechanism here is possibly free radical induced mitochondrial DNA damage. Studies have associated IUGR with increased oxidative stress in fetus [89,90]. Reactive oxygen species (ROS) can induce several intramitochondrial changes like shutting down of mitochondrial energy production and various other cellular changes [91].

An apt example of free radical induced mitochondrial damage occurs in β cell. The β cells have a high oxidative energy requirement for their normal function. The antioxidant machinery of β cell is suboptimal, which makes it more prone for free radical induced injury [92].

Islets affected by IUGR have increased oxidative stress secondary to increased ROS production. Complexes I and III of the electron transport chain are shown to function below par. IUGR is associated with decreased mitochondrial gene content and progressive damage of the mitochondrial DNA content with free radicals [93].

These dysfunctions can manifest functionally as decreased glucose-mediated insulin secretion and cell death, with diabetes as the end result [94,95].

Neonatal Abdominal Circumference

Neonatal abdominal circumference has been shown topredict plasma cholesterol and fibrinogen levels in men laterin life. Both of these are risk factors for the developmentof coronary heart disease [96,97]. It has been suggested thatabdominal circumference at birth is at least partly reflectingliver size, growth of which may be impaired in babies bornsmall, perhaps as a result of blood flow redistribution to vitalorgans such as the heart and brain at the expense of abdominalorgans such as the liver. However, there is not yet any direct evidence of such a causal link.

Clinical Period of Adverse Uterine Environment

The varying critical periods during which organs and systemsmature indicate that an adverse intrauterine environment atdifferent developmental stages is likely to have specific shortandlong-term effects. A critical period for gonadal development exists, for example, very early in gestation [98], as comparedwith a critical period for renal development later in gestation, between 26 and 34 wk of pregnancy [99]. Consistent with thesediffering critical periods, follow-up studies of babies that weresymmetrically small, short, or thin at birth showed that theseinfants are predisposed to different disorders in adult life.

Proportionately small babies are at increased risk of high adultblood pressure but do not appear to develop coronary heart diseaseWith respect to timing, it is important to appretiate that effect that are manifest late in pregnancy may commonly originate earlier in gestation As adults, individuals who were disproportionatelyshort at birth tend to have abnormalities of systems controlledby the liver, and have increased rates of coronary heart disease [100]. These may reflect adverse effects on liver development associated with cranial redistribution of blood flow later in gestation [101].

Outside the setting of famine, both animal and human studies indicate that fetal undernutrition late inpregnancy is, however, more commonly a consequence of aninadequate maternoplacental supply capacity set up earlier ingestation [102,103]. These studies suggest that a mother's own fetal growth and her dietary intakes and body composition can exert major effects on the balance between the fetal demand for nutrients and the maternoplacental capacity to meet that demand.

Failure of the maternoplacental supply line to satisfy fetal nutrient requirements results in a range of fetal adaptations and developmental changes; although these adaptations may be beneficial for short-term survival, they may lead to permanent alterations inthe body's structure and metabolism and thereby to cardiovascularand metabolic disease in adult life.

Fetal Growth Inlate Gestation

Fetal growth in late gestation is normally limited by maternal size and her capacity to supply nutrients to her fetus, a phenomenon known as maternal constraint. Thus fetal growth in late gestation is normally regulated by fetal nutrient supply [104].

Markers for Low Birth Weight

Measurements made on babies at birth, including birthweight, length, body proportions and placental weight, are strongly related to either later disease incidence (coronary heart disease mortality, non-insulin-dependent diabetes) [105,106]. The relationship between early life events and adult disease had been raised many years earlier [107].

Large Fetus

There are many possible mechanisms by which alteredfetal nutrition might lead to increased risk of disease in theoffspring [108]. However, altered fetal nutrition is leading, directly or indirectly, toaltered growth and maturation of various fetal organ systems

Fetal Environment

Those with a thrifty phenotype who actually develop in an affluent environment may be more prone to metabolic disorders, such as obesity and type II diabetes, whereas those who have received a positive maternal forecast will be adapted to good conditions and therefore better able to cope with rich diets. This idea is now widely (if not universally) accepted and is a source of concern for societies undergoing a transition from sparse to better nutrition [109]. These changes are also believed to possibly be inherited across generations. Leptin has been identified as a possible gene for the acquisition of these thrifty traits. On a larger anatomic scale, the molecular mechanisms are broadly caused by a suboptimal environment in the reproductive tract or maternal physiological adaptations to pregnancy.

Diseases Linked with birth Weight

In humans, the demonstration of adult disease can be viewed as a mismatch between prenatal adaptation and postnatal environment. These observations suggest a teleological explanation of programming. Namely, that there are multiple mechanisms designed to achieve an evolutionary goal of survival of the species; these mechanisms must act via a transient environmental change too brief a period for genetic selection to act.

Rapid Growth after Birth

None of these are sufficient explanations for the programming of metabolic syndrome. At a more synthetic level it has been suggested that multiple hormone insensitivity including GH, IGF-1, insulin, and leptin might be involved [110].

Genetic Link

Genetic and epigenetic links

The link between fetal growth and adult onset disease mustultimately involve changes in gene expression, which are verylikely to involve epigenetic phenomena. During early embryogenesis,DNA undergoes demethylation and remethylation;a process that involves 'labelling' of some genes as ofmaternal or paternal origin, and marks these genes for subsequentinactivation [111]. Maternal progester one treatment can, for example, permanently alter thetrajectory of fetal growth by changing the allocation of cellsbetween the inner cell mass that develops into the fetus and theouter trophectoderm that becomes the placenta [112,113]. The trajectory of fetal growth is thought to increase with improvements inpericonceptional nutrition, and is faster in male fetuses [115].

Dutch Hunger Winter Study

Ravelli et al. studied a population cohort born during the Dutch famine of 1944–1945. Infants who were subjected to mid or late gestation calorie restriction had a lower birth weight and impaired glucose tolerance (IGT) as adults. Infants of mothers who endured the famine in early gestation had a normal birth weights, but had obesity and atherogenic lipid proûle as adults [115,116].

Barker and associates proposed the Barker hypothesis which suggested that an environment which produces poor fetal and infant growth is followed by an adult environment that determines high risk for ischemic heart disease.Human evidence about the importance of nutrition in the periconceptional period again comes from the Dutch hungerwinter studies. The offspring of women exposed to famine midand late gestation were born smaller than unexposed babies [103] and had an increased risk of impaired glucose tolerance asadults. However, the offspring of women exposed to faminein early gestation, although of normal birthweight, had a threefold increased risk of coronary heart disease as adults, 105 increasedrisk of obesity [117] and raised plasma fibrinogen levels [118].

Other notable long-term effectsof alterations in maternal nutrition include changes in cholesterolmetabolism, insulin secretion, and renal development [119]. Although some effects of nutrition may be direct consequencesof alterations in substrate availability, several are thought to bemediated by hormonal effects. These may alter the development of specific fetal tissues during sensitive periods of development [120,121], or may lead to long-lasting changes in hormone secretionor tissue hormone sensitivity [122]. Experiments in animals haveimplicated the fetal hypothalamus as a key site that can be programmed by transient changes in prenatal endocrine status [119]. Studies have found that a wide range of organs and systems may be programmed by the intrauterine environment.

Observations linking the intrauterine environment with later hypertension, diabetes, elevated blood cholesterol and fibrinogen concentrations, and polycystic ovary syndrome serve to illustrate some of the principles that underlie fetal programming. It has been argued that people who were exposed to anadverse environment in utero and failed to grow well continue tobe exposed to adverse influences in childhood and adult life, andit is these later influences that produce the effects attributed to programming in utero. There is, however, little evidence to support this argument. Rather, associations between birth weight and adult blood pressure, for example, are found in each socialgroup and are independent of influences such as smoking, alcohol intake, and obesity in adult life [123,124].

Placenta

Genomic imprinting also plays a role in epigenetic modifications. *IGF2* gene is imprinted and plays a major role in placental nutritional transfer. Placental insufficiency can decrease the production of pancreatic transcription factor product of pdx1 by CpG methylation in animals and they can develop diabetes at a later date [125].

Although the size of the placenta gives only an indirect measure of its capacity to transfer nutrients to the fetus, it is none the less strongly associated with fetal size at birth. Women who delivered at term, those with high dietary intakes inearly pregnancy, especially of carbohydrate, had smaller placentas, particularly if combined with low intakes of dairy protein inlate pregnancy (Table 3) [126]. These effects were independent ofthe mother's body size, social class, and smoking status, and resulted in alterations in the ratio of placental weight to birthweight (placental ratio). Confirmation that maternal diet canalter placental growth has come from analyses of the Dutchfamine of 1944–1945, in which famine exposure in early pregnancy increased placental weight [128].

Whereas babies with a disproportionately small placenta may suffer as a consequence of an impaired placental supply capacity, those with a disproportionately large placenta may experience fetal catabolism and wasting to supply aminoacids for placental consumption [129,130]. Consequent fetal adaptations may under lie the increased death rates of adult coronary heart disease in those with both low and high placental ratios.

Placenta has multiple roles as an important component of the fetal supply line, and hence of the potential dissociation between maternal and fetal nutrition. Perhaps the most obvious placental influence on fetal nutrition is via its capacity to transport nutrients from the maternal to the fetal circulation. This transfer capacity is influenced by such factors as placental surface area and availability of specific nutrient transporters on the membranes. Recent evidence suggests that these may be influenced in turn by the maternal nutritional environment [131,132]. There are also important species differences in placental structure and function [133,134,135]. Species which are relatively fat at birth such as the guinea pig and human have placentas which are relatively permeable to fatty acids and related molecules in late gestation. Fatty acids may thus form a small but important component of the fetal 'diet' in these species at the end of pregnancy [136].

Links with Placental Weight

Increased risk of various adult diseases has been describednot only in babies born small, but also in those with unusual relationships between birth weight and placental weight. Babies born small in relation to the size of their placenta havean increased risk of developing hypertension [137,138]. It is interesting in this regard to note that low birth weight in relation to placental weight has also been associated with failure ofcatch-up growth in the first 18 months in babies born growth restricted [139]. On the other hand, babies who later developed type 2 diabetes, sometimes in combination with hypertension,were reported to have small placentas in relationto their birthweight [140,141].

Insulin Resitance

Insulin resistance, the key component of type 2 diabetes mellitus (T2DM), is linked to a multitude of

diseases like obesity, hypertension, coronary artery disease (CAD), and dyslipidemia. These diseases exert a major toll on resources across the world with wide ramifications on physical, psychological, and financial well-being. Intrauterine environment provides an individual with a sneak preview of the conditions one may be exposed to during childhood growth and adult life. This information in turn leads to an adaptive response in metabolism, which provides a survival advantage. Though fat can act as an energy reservoir for vital organ functions, in a nutritionally rich environment with limited energy expenditure, fat deposition occurs. This fat deposition promotes insulin resistance, inflammation, and finally diabetes and coronary vascular disease [142].

The hormonal programming concept points out that an adverse intrauterine environment leads to metabolic and endocrine adaptations programmed toward energy conservation. These adaptations prove counterproductive in adulthood as the body finds it difficult to adjust to a nutritionally enriched environment and excess nutrients become deposited as adipose tissue. Animal study have shown that those that are born small are prone to adult-onset hyperglycemia, blood pressure, anxiety, and increased hypothalamic pituitary adrenal (HPA) axis activity [143,144].

Insulin Resistance in Skeletal Muscle

Adult insulin resistance could indicate persistence of a fetal glucose-conserving adaptation. In fetal life, the glucose–insulin–insulin-like glucose factor I axis has a key role in stimulating cell division [145]. Insulin resistance in specific tissues, including skeletal muscle, might conserve glucose by reducing growth and result in diminished muscle mass and thinness at birth. In adult life, persistence of insulin resistance in skeletal muscle would, however, result ina range of metabolic abnormalities and could underlie the strong association between low birth weight and thinness at birth andthe insulin resistance syndrome in adult life.These abnormalities were found particularly in those who had had abnormal body proportions at birth and a short body in relation to their head size.

The HPA axis activity may vary depending on the sex of the fetus, and time and nature of the stimulus. Placental corticotropin-releasing hormone (CRH), sympathoadrenal system, and glucocorticoid and mineralocorticoid receptors in the hippocampus and other areas of brain are supposed to play a role in the programming of HPA axis [146].

One of the key regulators of fetal cortisol levels is placental 11 Beta Hydroxy Steroid Dehydrogenase 2 (11βHSD2) enzyme which converts cortisol to cortisone and keeps fetal cortisol levels at a lower level.

Maternal cortisol is an important way in which maternal experience can be signaled to the fetus. The paper by Lesage et. al. [147] provides further evidence of the interaction between the maternal and fetal HPA axis. There are changes in neuroendocrine control in the neonate that if persistent would lead to defective negative feedback within the HPA axis. In other models of programming, such persistence has been shown [148]. This perspective is relevant to the increasing use of betamethasone in human pregnancy. Since the original studies of Liggins and Howie [149], it has become commonplace to offer glucocorticoids to pregnant women in premature labor to promote lung maturation. However, endocrine changes are observed in human newborns following betamethas one treatment to induce lung maturation [150].

Antenatal Glucocortiocoid

There is no doubt that a single dose of glucocorticoid treatment is well-validated as an essential therapy in the prophylactic management of the premature infant, but there has been an increasing tendency – not supported by clinical trials—toward repeated glucocorticoid administration. Clearly excessive fetal exposure to glucocorticoids can cause IUGR in experimental animal models with supportive data in humans, and the complications of IUGR and prematurity increase morbidity and mortality. Furthermore, excess glucocorticoid exposure in utero has been implicated experimentally to impact on neural development.

Twins Studies

Twin studies from the 1980s suggested an almost exclusive role of genetics in type 2 diabetes, with nearly 100% concordance rates among genetically identical monozygotic twins [151]. Twins generally have lower birthweights than singletons [153-158], so the fetal origins hypothesis might predict a higher incidenceof adult disease in this population. However, mortalityrates from coronary heart disease were not found to be increased in twins compared to singletons [153-155]. Furthermore, adult blood pressure did not differ between twins and their singleton siblings [156]. In contrast, there is some evidence for an increased incidence of diabetes in the twin population [156,157] and twins have been found to have increased insulin resistance compared to singletons independent of birthweight [158]. Finally, it has been argued that the regulation of fetal growth in twins may be fundamentally different from that

insingletons. Birth weight-specific mortality is lower in twins than in singletons. Furthermore, the off spring of twins are generally of average birth weight while the offspring of growth restricted singletons are themselves at increased risk of being born growth restricted. Few studies have compared long-term outcomes of twins with appropriate singleton controls. Thus, studies on the fetal origins of adult disease in twins need tobe interpreted with caution

Future Prospects

Quite apart from any long-term effects on health in adult life, specific issues that have not been adequately addressed in previousstudies of maternal nutrition include

1. Effects on the trajectoryof fetal growth,
2. Intergenerational effects,
3. Paradoxical effects on placental growth,
4. Effects on fetal proportions and specific tissues, and
5. The importance of the balance of macronutrients in the mother's diet and of her body composition.

Woman's own fetal growth and diet and body composition before and during pregnancy play a major role in programming the future health of her children, mothers will want toknow what they can do to optimize the intrauterine environment they provide for their babies. We also need to define how the fetus adapts to a limited nutrient supply, how these adaptations program the structure and physiology ofthe body, and by what molecular mechanisms nutrients and hormones alter gene expression. Further research requires a strategyof interdependent clinical, animal, and epidemiologic investigations. Such an approach may allow us to use the information outlinedhere to reduce the prevalence of major diseases [159].

Studies of identical twins show that fetal environment is important'. There is a major need for molecular markers for metabolic programming infetal life.

Discussion

Fetus makes physiological adaptation in response to changein its environment to prepare itself for post-natal life The adaptational response in a fetus to a nutritionally challenging environment is preservation of its vital organ function, namely the brain, at the expense of other organs in the body. The mechanisms by which the fetus achieves this include blood and nutritional diversion to the brain, along with insulin and growth hormone resistance in the periphery. Starvation or nutritional deficiency is associated with reduced basal metabolic rate (BMR). If energy is stored when BMR is low, there is a relative preference to fat storage. The insulin resistance associated with reduced lean muscle mass along with hyperin-sulinemia directs the excess glucose toward fat storage in adipose tissue [160-162].

The balance of protein and carbohydrate in the diet, and the balance of different amino acids, can have critical effects on fetal growth and thus may be important nutritional programming influences which have yet to be explored in detail. Fluctuations in nutrient supply to the fetus may also have important effects on fetal growth and the programming of later disease risk. Maternal diabetes in pregnancy is a relatively common cause of altered fetal nutrient supply, with increased glucose availability resulting in increased fetal growth and impaired pancreatic function which persists over more than one generation.

When nutrient availability is abundant in postnatal life, this pancreatic cell defect and peripheral insulin resistance could then cause glucose intolerance and eventually diabetes. This would explain why it is mainly thin babies who then become overweight during childhood who are prone to developing type 2 diabetes later in life [163,164].

Adult obesity does, however, add to the intrauterine effects, such that the highest prevalence of type 2 diabetesand impaired glucose tolerance is seen in people who were small at birth but obese as adults [165,166].

It was particularly people who were born growth restricted rather than premature who were at risk.

To understand the full potential of the thrifty phenotype hypothesis as a platform to implement primary prevention of type 2 diabetes there is an urgent need to determine the extent to which developmental programming influences the development of type 2 diabetes in different populations and to understand the long-term effects of exposures during pregnancy and the distinct molecular mechanisms involved.

Programming is a well-established biological phenomenon. Nutrition can be an important and probably central programming stimulus. However, clear distinctions need to be drawn between maternal nutrition and size at birth on the one hand, and between fetal nutrition and fetal growth on the other. Maternal nutrition may bear little or no relationship to size at birth, but fetal nutrition is critically important

in fetal growth. Many common assumptions about the relationship between body proportions and prenatal physiological events lack a sound experimental basis. Furthermore, important species differences in physiology, metabolism, placental structure and function necessitate cautious interpretation of animal experiments in their application to human situations. Details of these nutritional influences are likely to be very species dependent. Altered fetal nutrition can influence both fetal growth and later disease risk. There is indeed a nutritional basis for the fetal origins of adult disease.

Adult noncommunicable diseases are associated with different patterns of early growth. Importantly, from a public health point of view we should remember that adult diseases are not programmed, but the tendency toward these unfavorable health outcomes does seem to be programmed. The early life risk factors are largely modifiable by later lifestyle, and obviously lifestyle matters from the cradle to the grave. Ensuring the optimal health of women of reproductive age will have long-term health consequences for their offspring.

Insulin resistance, [167] elevated fasting insulinlevels, [168] and elevated plasma cortisol levels have also been reported in young adults born preterm. If a relationship between adult disease risk and gestation length is confirmed, then this may provide some interesting new challenges for obstetric practice, since elective early delivery, even close toterm, may have implications for life-long health of the baby Furthermore, programming can be demonstrated even when the insult is applied in the preimplantation period [169].

Both macronutrient and micronutrient supply may influence fetal development directly and indirectly, and that additionally glucocorticoid exposure can also impact on fetal development. The adult phenotype presumably is the net sum of genomic factors, and fetal and postnatal environmental influences. In interpreting adult metabolic, endocrine, and cardiovascular phenotypes greater consideration must be given to the fetal experience.

Conclusion

Genetic, nutritional and hormonal environmental factors determine fetal growth. Size at birth for gestational age serves as a marker for fetal nutrition. Maternal nutrition in pregnancy can influence both size at birth and disease process in offspring. Both maternal undernutrition and over nutrition stunt fetal growth. Fetal programming has impact in the origin of type 2 Diabetes mellitus, metabolic syndrome and cardiovascular disease. Disease originate through biological phenomena, developmental plasticity and compensatory growth due to programming. Stimulus during critical period has irreversible long term effects on development. Thrifty phenotype hypothesis propose that environmental factors are main causes of type 2 Diabetes mellitus. Fetal undernutrition triggers the process. Response to fetal malnutrition involves selective preservation of vital organs. Barkar states that coronary heart disease may be result of fetal adaptations to undernutrition which are beneficial for short term survival through detrimental to health in adulthood. In future, preventive nutritional modification with genomic and hormonal targets may be invented for disease prevention.

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