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ENDOCRINE AND METABOLIC CONSEQUENCES OF BEING BORN SMALL- OR LARGE-FOR-GESTATIONAL AGE: A REVIEW

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ABSTRACT:

In this review article, the genetics of size at birth, prenatal metabolic programming and the endocrine and metabolic consequences of abnormal size at birth are discussed. In addition, the relevance of fetal origin of adult disease in developing countries and the public health implication as well as future perspectives are also discussed. Being born either small- or large-for-gestational age affects such children and adults in several ways. These include increased risk of type 2 diabetes mellitus, metabolic syndrome, oxidative stress, persistent reduction in growth, cardiovascular disease, osteoporosis and premature pubarche as well as adrenarche. Individuals with abnormal size at birth who experienced rapid growth in the first three years of life have the greatest risk for future metabolic abnormalities. The mechanisms involved in prenatal (fetal) metabolic programming in infants with abnormal size at birth are just beginning to be explored. Both the "thrifty genes" and the "thrifty phenotype" could result in adverse health consequences later in life on exposure to plentiful nutrition. The most important epigenetic reactions affecting genetic transcription are acetylation and methylation. However, the major challenge at this point in time is to link such alterations with modifications in gene expression and ultimately, with metabolic abnormalities encountered in adult life. Thus, developmental origins of health and disease (DOHaD) represent a relatively new frontier of research and with time, some of the discrepancies may be resolved.

KEYWORDS: *Endocrine effects, metabolic effects, birth size, large-for-gestational age, small-for-gestational age*

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INTRODUCTION:

Size at birth is defined by measurement of weight, length or both and is influenced by the quality of nutrition during fetal life [1,2]. Several decades ago, concerns over abnormal size at birth centered on survival and health of the offspring in the immediate neonatal period. Today, the emphasis has shifted to long-term consequences of such abnormal fetal growth, and ultimately size at birth. In man, diseases in adulthood are increasingly associated with growth patterns in early life, implicating early nutrition as an underlying mechanism [3].

Genetics of size at birth:

Birth size is influenced by genetic and environmental factors [1]. Reports from epidemiological studies indicate that genetic factors account for 38 to 80 percent of birth weight variance with environmental influences accounting for the remainder [4,5]. The relative contributions of genetic and environmental factors vary, not only from individual to individual, but also between populations [1]. Fetal genes have a greater influence on birth size variance (18% - 69.4%) than parental genes (3 % - 20%) [4,5]. Several animal knockout experiments have identified the important role played by insulin-like growth factor 1 (IGF-I), IGF-II, insulin and their respective receptors in regulating fetal growth and ultimately, size at birth [6-8].

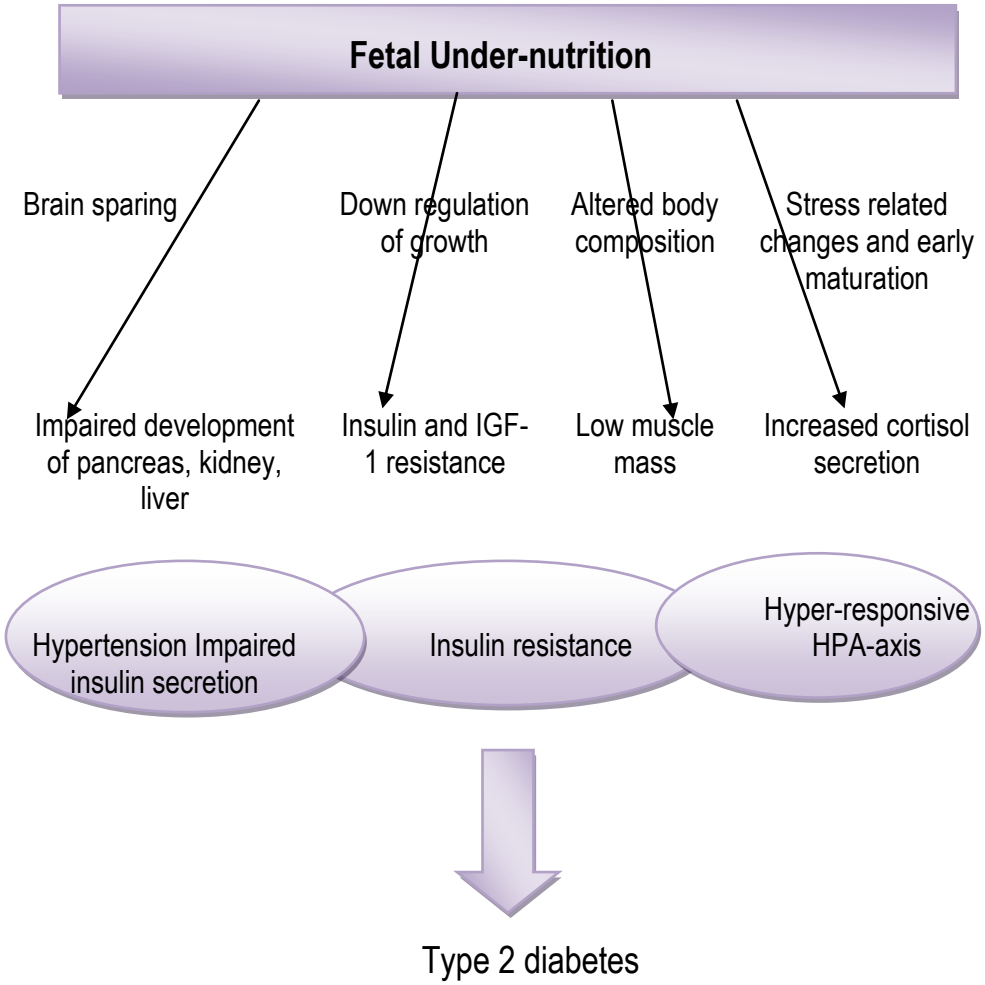
Prenatal (fetal) metabolic programming:

The term “programming” refers to a permanent change in the structure and function of an organism as a result of a transient stimulus or insult occurring at a critical or sensitive period of development [9]. The mechanisms by which programming could occur at a tissue or cellular level may be categorized into structural changes or changes in cellular homeostatic process. An example of a structural change which has been described in low birth weight infants is reduction in pancreatic beta cell mass, which could increase disease risk later, if it persists [10]. Growth-restricted human fetuses have an altered endocrine profile. For instance, they have low circulating insulin and insulin-like growth factor (IGF) concentrations [11]; an example of changes in cellular homeostatic process. Programming is well described in endocrine systems. Some examples include (i) female rats given testosterone in the first 4 days of life fail to develop normal pattern of female sexual behaviour [11]; (ii) vaginal adenocarcinoma in young women has been linked to a transient intrauterine exposure to diethylstilbesterol and shown to have a long latent period between exposure and disease [12]. Thus, both represent

programming stimuli in fetal life. The hypothalamus has been implicated as the key site that is programmed by transient changes in prenatal endocrine status [13].

The existence of prenatal metabolic programming is captured in the concept represented by the terms “thrifty phenotype” coined by Hales and Barker [14] and “thrifty genotype” coined by Neel [15]. Neel suggested that type 2 diabetes is caused by ‘thrifty’ genes which were selected for during man’s phylogenetic evolution when food supply was precarious, but became diabetogenic in a modern setting of plentiful nutrition. In contrast, the thrifty phenotype hypothesis (also called the small-baby-syndrome) describes the metabolic adaptations adopted as a survival strategy by an under-nourished fetus. In later life, such a phenotype must be thrifty and help affected individuals to cope better with conditions of food shortage. However, under conditions of abundant food intake and decreased energy expenditure, this advantage turns into a disadvantage, leading to metabolic syndrome, type 2 diabetes and cardiovascular diseases. Thus, both the thrifty genes and the thrifty phenotype could become detrimental on exposure to plentiful nutrition [12,16]. This idea is widely accepted and is a source of concern for societies undergoing a transition from sparse to better nutrition [17]. Risk factors of thrifty phenotype include advanced maternal age and placental insufficiency [18]. The gestational age at which the nutritional deprivation occurred influence the metabolic consequences. For instance, if fetal exposure to nutritional deprivation occurs during early pregnancy it will affect lipid metabolism (associated with higher LDL/HDL cholesterol concentrations and (in women) higher BMI and waist circumference), but if it occurs in late pregnancy, it will affect glucose metabolism (associated with glucose intolerance, insulin resistance and some increase in type 2 diabetes) [19]. In most cases, programming is beneficial for health and survival of the organism. However, the problem of “mismatch” occurs when individuals developmentally adapted to one environment are exposed to another, resulting in detrimental effects on health [20]. The effects of fetal under-nutrition on structure and metabolism, which may lead to later disease is illustrated in figure 1.

Fig 1: The effects of fetal under-nutrition on structure and metabolism, which may lead to later disease. Source: Fall CHD [11]



Today, there is emerging evidence that epigenetic mechanisms are involved in such "programming" of offspring to either maintain health or develop disease in adults [21]. A clear-cut "cause and effect" can be seen in rodent model of intrauterine growth restriction (IUGR). When fetal rats are growth-retarded by diminishing uterine blood flow, they develop diabetes as adults due to reduced β-cell mass [22]. This occurs because the expression of

pancreatic and duodenal homeobox 1 (PDX 1); a transcription factor involved in pancreatic islet development) is compromised as a result of specific alteration in DNA methylation and histone acetylation. Epigenetic factors, by different types of reactions, could mediate the interplay between genes and the environment, resulting in activation or repression of genetic transcription or even silencing the genetic transcription [23]. The most important epigenetic reactions affecting genetic transcription are acetylation and methylation. These reactions occur mainly in the tail of histones which are part of the protein component in chromosomes [24]. Thus, epigenetic processes such as DNA methylation and histone modification allow the developmental environment to modulate gene transcription and many of these changes may then be stable throughout the individual's life time. A report by Einstein et al [25] identified epigenetic alterations that could provide a mechanism linking IUGR with type 2 diabetes later in life. In that animal model study, they identified 56 candidate loci and performed detailed analyses on a subset. They found consistent differences in loci near genes controlling growth such as those involved in cell cycle. Of particular interest was the observed reduction in DNA methylation in the hepatocyte nuclear factor-4-α (HNF4 A) promoter. It is has been established that mutation in HNF4 A is associated with the pathogenesis of maturity onset diabetes of the young, type 1. Several studies using different methods, have identified regions of differential DNA methylation in the placenta of IUGR infants [26-28], supporting this concept in human. Epigenetic modifications are frequently tissue specific, so findings in the placenta may not apply to muscle, adipose tissue, or the pancreatic β-cell. Despite these limitations, this is an area of research that has diagnostic, prognostic and therapeutic implications [29].

A review of the literature suggests that impaired intrauterine growth and development are linked to several diseases in adulthood. Some examples include coronary heart disease, hypertension, and type 2 diabetes [30]. There is also emerging evidence that mitochondrial dysfunction and oxidative stress play important role in the pathogenesis of the Fetal Origin of Adult Disease (FOAD) [30,31]. It is believed that oxidative stress is the primary link between adverse fetal growth and later risks of the metabolic syndrome and type 2 diabetes [30].The fetus is entirely dependent on the nutrients from the mother and adapts to an inadequate nutrient supply in a number of ways: (i) prioritization of brain growth and metabolism at the expense of other tissues such as abdominal viscera; (ii) reduced secretion of and sensitivity to the fetal

growth hormone, insulin and IGF-I; and (iii) up-regulation of the hypothalamic-pituitary-adrenal axis [32]. This preferential distribution of nutrients to the brain impairs the growth of the liver and may underlie permanent abnormalities in the regulation of cholesterol and clotting factors [28]. The FOAD hypothesis proposes that although the events occur in response to a transient phenomenon (fetal under-nutrition), the resultant adaptation become permanent or "programmed" because they occur during a critical period of early development [30]. Tissues and systems for which there is evidence of programming in humans are summarized in Table 1.

Table 1: Tissues and systems for which there is evidence of programming in humans [32]

Tissue or system	Examples of programming
Endocrine system	Hypothalamic-pituitary-adrenal axis Glucose-insulin metabolism Growth hormone-IGF-1 axis
Reproductive system	Age at menarche Polycystic ovary syndrome
Skeletal muscle	Insulin resistance Glycolysis during exercise
Bone	Bone mineral content
Liver	Cholesterol metabolism Fibrinogen and factor VII synthesis
Kidney	Renin-angiothensin system
Cardiovascular system	Vascular compliance Endothelial function
Immune system	Thyroid authoantibodies IgE concentrations
Respiratory system	Lung volume
Central nervous system	Schizophrenia

IGF-I = insulin-like growth factor I; Ig = immunoglobulin

Infants who are born large-for-gestational age (LGA) are at risk of long-term metabolic complications. The effects of fetal "over nutrition" may, therefore, contribute to the rising prevalence rates of type 2 diabetes [12]. Plagemann et al [34-36], in three separate

studies, using animal models suggested that over-nutrition in prenatal period can lead to alteration in DNA methylation patterns within the promoter regions of genes whose products are involved in the hypothalamic regulation of appetite, body weight and metabolism. In the promoter region of proopiomelanocortin (POMC), the most important anorexigenic neurohormone, neonatally overfed rats developed hypermethylation of activating transcription factor binding sites in parallel with hypomethylation at an inhibitory transcription binding site. The promoter region of the hypothalamic insulin receptor gene promoter was found to be hypermethylated. The findings of these studies suggest that perinatal programming of long-term increased obesity and diabetes risk due to neonatal (by extension fetal) over-nutrition may occur via altered methylation patterns of the promoter regions of central nervous body weight-regulating neuropeptides and receptors [34-36]. St Jeor et al [37], reported that a higher birth weight is associated with a higher BMI and an increase in prevalence of obesity in adulthood. Data from the study also suggest rapid weight gain during infancy is associated with obesity later in childhood, perhaps reflecting a combination of genetically determined catch-up growth and postnatal environmental factors [37].

Postnatal growth pattern:

The pattern of growth in the postnatal period is also an important issue. Data from longitudinal studies have shown that after infancy, in individuals born small, crossing BMI centiles upwards during childhood or adolescence is strongly associated with adult disease [37,38]. The phenomenon of adiposity rebound (the point in early childhood when BMI starts to rise, having fallen during infancy) plays an important role in subsequent glucose metabolism. Early adiposity rebound was a strong risk factor for impaired glucose tolerance and development of type 2 diabetes [38,39]. Rapid postnatal catch-up growth contributes actively to insulin resistance, at least during the first years of life [40]. There are a number of possible explanations for the observation that weight gain in childhood in individuals born small might be associated with disease. The process of catch-up may be disadvantageous in itself. Studies, using animal models have shown that compensatory growth can lead to adverse short- and long-term effects, operating through a variety of mechanisms [41]. Such mechanisms include (i) LBW babies undergo catch-up growth in the postnatal period and the rapidity of such growth may simply be a reflection of the severity of the growth retardation; (ii) rapid weight gain may be disadvantageous in itself because of excess demand on tissues that are not capable

compensatory hyperplasia, such as the pancreas; (iii) rapid weight gain may lead to altered body composition; good nutrition in childhood may enhance the development of fat, which maintains the capacity for growth throughout life, but may not restore muscle tissue, which may lose the capacity for cell division early in life; (iv) it is possible that hormones driving catch-up growth have adverse cardiovascular and metabolic effects [42].

Endocrine and Metabolic Consequences:

Several longitudinal studies have demonstrated that being born small-for-gestational age (SGA) is detrimental with adverse metabolic effects, such as insulin resistance and dyslipidaemia as well as hypertension [43]. Together, these contribute to the "multimetabolic" syndrome (Syndrome X); an association that is independent of obesity in later life and a family history of metabolic problems [44]. In the literature, there is increasing evidence that has linked some diseases in adulthood to being born SGA. Such diseases result from fetal programming of certain metabolic and endocrine systems, which may affect health in childhood and adolescence [45]. There is also emerging evidence that epigenetic mechanisms are involved in such "programming" of offspring to either maintain health or develop disease in adulthood [21]. In addition, genetic variations that affect the insulin axis might influence both birth weight and subsequent development of type 2 diabetes and could also explain transgenerational effects [46,47]. The endocrine and metabolic effects of being born SGA and LGA are summarized in Tables 2 and 3 respectively.

Endocrine and Metabolic Effects of Being Born Small-For-Gestational Age:

Alterations in endocrine axes/functions:

Hypothalamic-pituitary-adrenal (HPA) axis:

Animal studies have shown that the early environment can permanently modify the HPA axis [60,61]. In most species, maternal stress during pregnancy leads to hyper-responsiveness of the HPA axis in the offspring, with increased peak and prolonged duration of glucocorticoid secretion [12]. Different types and timings of maternal stress have different long-term effects, and there may be sexual dimorphism; for example, female rat fetuses are more susceptible to HPA effects induced by maternal stress [12]. The placenta forms a partial barrier to glucocorticoids because of the enzyme 11β-hydroxysteroid dehydrogenase (11β-HSD), which converts cortisol and corticosterone to inactive metabolites. It has been observed that levels and activity of 11β-HSD and thus fetal protection from glucocorticoid exposure, are reduced in animal models of intrauterine growth restriction and

maternal under-nutrition [60,61] and in human pregnancies complicated by intrauterine growth restriction [62]. Subtle programmed abnormalities of the HPA axis may play a role in the development of hypertension, insulin resistance, and type-2 diabetes in humans and their link with low birth weight [61]. Growth-restricted fetuses have higher circulating cortisol concentrations [63]. An association between LBW and a syndrome of exaggerated adrenarche, hyperinsulinaemia, precocious puberty, and ovarian hyperandrogenism in girls has been reported [64]. The mechanisms are unknown but the authors postulated that it might indicate either programming by the prenatal environment or genetic disorder of serine kinase activity, leading to abnormal phosphorylation of hormone receptors.

Table 2: Summary of endocrine and metabolic effects of being born small-for-gestational age (SGA)

Organ/System involved	**Biochemical abnormality or clinical disorder**
Growth, puberty and body composition [47-51]	Decrease in growth hormone (GH) action and secretion; Short stature; Accelerated gain in fat mass
Adrenal function [46,52]	Increase in cortisol secretion; Increase in dehydroepiandrosterone sulphate; Exaggerated adrenarche
Gonadal function / Genitalia [47,53]	Polycystic ovary syndrome; Anovulation; Small ovaries and uterus; Male subfertility; Cryptoorchidism; Precocious pubarche
Bone metabolism [54]	Reduction in bone mineral density; increase in risk of osteoporosis and fracture in adulthood
Changes in other hormones [31,55]	Decrease in adiponectin and follistatin in children. Increase in Prostaglandin factor-2α
Metabolic; Resetting of insulin-like growth factor and insulin systems [49-51]	Insulin resistance; Hyperinsulinism; Decrease in insulin-like growth factor-binding protein-1; Hypercholesterolaemia; Increase in prevalence of metabolic syndrome; Ketotic hypoglycaemia (accelerated starvation) in childhood
Increased risk of adult disease [30,56]	Stroke; Heart failure; Type 2 diabetes; Obesity; Hypertension

Table 3: Summary of endocrine and metabolic effects of being born large-for-gestational age (LGA)

Organ/System involved	Biochemical abnormality or clinical disorder
Growth, puberty and body composition [57]	At the age of 9-10 years and 23-25 years, individuals born LGA remain heavier and taller than individuals born AGA. Young adults born LGA present higher BMI, waist circumference and blood pressure than controls
Metabolic [31,37,58]	Insulin resistance Increase in risk of obesity Increase in risk of type 2 diabetes Increase in prevalence of metabolic syndrome Increase in risk of oxidative stress Increase in risk of hypertension
Changes in other hormones [31,59]	Increase in levels of plasma IGF-1 Increase in levels of Prostaglandin factor-2α

AGA = appropriate for gestational age

Growth hormone (GH) and insulin-like growth factors (IGF):

Cord blood IGF-I concentrations are low in growth-restricted fetuses and newborns, suggesting a possible growth hormone resistance [12]. On the other hand, insulin-like growth factor binding protein-1 (IGFBP-I) concentrations are increased in such fetuses and newborns. GH deficiency is associated with osteoporosis [12]. Data from follow-up studies of children with IUGR and subsequent short stature indicate that they have persistent abnormalities of the GH-IGF axis with low-amplitude GH peaks and high baseline GH secretion [50,65]. In addition, they have low serum IGF-I, IGF-II , and IGFBP-3 concentrations compared with non-IUGR children of normal stature [50,66] but higher concentrations than non-IUGR short children, suggesting that they may be resistant for both IGF and GH. Infants affected by IUGR have low concentrations of insulin and IGF-I at birth and normalization of these parameters occur in the postnatal period [67]. It is thought that tissues chronically depleted of insulin and IGF-I throughout fetal life and then suddenly exposed to increased concentrations of the two hormones shortly after birth may counteract the actions of insulin by developing insulin resistance. Thus, in this proposed scenario, insulin resistance is serving as a metabolic

defense mechanism to protect the organism against hypoglycaemia [68].

Puberty and reproductive function:

Report of some studies indicate that girls born SGA have earlier menarche [69,70], particularly if they experienced accelerated growth in infancy and accelerated BMI gain from birth to 7 years of age [71]. Data from Nordic countries indicate that the risk of cryptoorchidism and hypospadias was higher in babies born SGA than babies born AGA [72,73].

Body composition and obesity:

In a study involving Danish conscripts, the prevalence of obesity, defined as a BMI of 30kg/m^2 or more, rose from 3.5% in those with birth weight of 2.5 kg or less to 11.4 % in those with birth weight greater than 4.5kg [74]. However, there is good evidence that the positive correlation between birth weight and adult BMI reflects increased lean and muscle mass rather than adiposity [13]. In a small study involving 22 young Korean men, no association was observed between birth weight and visceral fat area measured by computed tomography [75].

Bone metabolism and osteoporosis:

Fetal growth has been linked to osteoporosis later in life [76]. Being born SGA has been associated with reduced bone mineral density and an increased risk of osteoporosis and fracture in adulthood, particularly in those born short [54]. It has been postulated that fetal programming of bone mass may be mediated through the effects of environmental stressors during intrauterine or early postnatal life on the sensitivity of the growth plate to growth hormone and cortisol [45]. The consequences of such fetal programming might be to reduce peak skeletal size and perhaps, mineralization, thus predisposing to an accelerated rate of bone loss during later life.

Metabolic abnormalities:

Obesity, type-2 diabetes and the metabolic syndrome:

Several epidemiological studies have demonstrated the long-term impact of being born SGA on metabolic health in adulthood. For instance, increased risk of type 2 diabetes and metabolic syndrome have been demonstrated in such individuals, both during childhood and adulthood [77-79]. Leunissen et al [80] demonstrated that rapid weight gain during the first 3 months of life in individuals born SGA was associated with reduced insulin sensitivity, lower HDL-cholesterol, and higher serum triglycerides.

Endocrine and Metabolic Effects of being Born Large-For-Gestational Age:

Endocrine function:

Growth, puberty, body composition and polycystic ovarian syndrome:

At the age of 9-10 years and 23-25 years, individuals born LGA were found to remain heavier and taller than individuals born AGA [56]. In the same study, the authors also found that young adults born LGA present higher BMI, waist circumference and blood pressure than controls [57]. Some studies have shown that 30% of children born LGA had early adiposity rebound and is associated with a larger body size in childhood [81]. There is evidence that prenatal factors play a role in the aetiology of polycystic ovarian syndrome (PCOS). Cresswell et al [82] observed that some women with high birthweight and whose mothers were above average weight in pregnancy were at increased risk of developing PCOS. The authors linked it to an ovarian defect, either of genetic origin or resulting from some effect of maternal obesity, leading to hypersecretion of androgens.

Hormone-related cancer:

Higher birth weight is associated with an increased risk of breast cancer (relative risk 1.5 - 1.7 for birth weights > 4000g compared with normal birth weights 2500-2999 g) [83].

Metabolic abnormalities:

Infants who are born LGA are at risk of potentially long-term metabolic complications.

Glucose homeostasis and lipid metabolism:

Exposure to fetal over-nutrition, resulting in LGA at birth is associated with increased risk of type 2 diabetes and obesity (additional to any inherited predisposition) [82]. This is often referred to as the "fuel-mediated teratogenesis hypothesis". Children who are LGA at birth are at increased risk of insulin resistance and oxidative stress [31,85]. There is a strong positive correlation between oxidative stress and obesity in childhood [86]. In the beginning of adult life, subjects born LGA, especially those who did not experience a catch-down of weight during childhood appear to be at increased risk of higher BMI, central adiposity and higher blood pressure [57]. Boney et al [58] have demonstrated that children who were LGA at birth and were exposed to an intrauterine environment of either diabetes or maternal obesity were at increased risk of metabolic syndrome during childhood.

The Relevance of FOAD in Nigeria and Other Developing Countries:

Worldwide, there is a linear and graded trend in cardiovascular mortality in relation to birth weight [87]. This observation suggests that majority of the world's population experience sub-optimal fetal growth, particularly in developing countries; also referred to as "resource-limited countries". In Nigeria and other developing countries, the prevalence of low birth weight range from 17% to

38% [88]. In addition, some developing countries are witnessing a rapid increase in incidence of obesity among children and adults because of economic development, nutrition transition and changing lifestyle [89,90]. Thus, the combination of high prevalence of fetal growth retardation and rising incidence of obesity, create a potential greater risk for adult cardiovascular disease and type 2 diabetes mellitus, ultimately reducing life expectancy. Studies have shown that within the same country, obesity-related health burden is disproportionately experienced by children from low income and ethnic minority families and this serves to perpetuate health disparities between rich and poor families [91,92].

The Public Health Implications and Future Perspective:

The knowledge that fetal growth retardation is linked to endocrine and metabolic disease later in life, suggests that such diseases could be prevented by improving fetal growth and development via improved maternal health and nutrition. Data from the study by Boney et al [57] provided strong evidence that a mother's nutrition programs the metabolism and growth of her offspring. Perinatal epigenetic analysis may have utility in identifying individual vulnerability to later obesity and metabolic disease. The epigenetic changes induced by maternal/fetal environment are not necessarily immutable, but they can be reversed during critical developmental windows. For example, the programming of diabetes in IUGR rats can be avoided by injection of a glucagon-like peptide analogue at birth with restoration of β-cell mass [23]. Thus, with a clear understanding of how maternal conditions affect the pathway that lead to diabetes, obesity and the metabolic syndrome, we may one day be able to "vaccinate" children to reverse potentially detrimental epigenetic alterations and thereby prevent the manifestation of adult disease [28].

Future research should focus on exploring the relationship between prenatal, natal and postnatal growth pattern on one hand and nuero-endocrine and metabolic effects in later life on the other hand. In addition, studies focusing on the mechanisms by which metabolism, body composition and growth may be permanently affected in individuals born either SGA or LGA is necessary. There are ongoing research projects in various institutions in India addressing these subjects [31].

CONCLUSIONS:

Individuals born SGA are at increased risk of development of endocrine dysfunction and metabolic abnormalities in later life. This detrimental effect manifests as insulin resistance, gonadal and somatotropic axes abnormalities and premature adrenarche. SGA birth has been linked to the escalating prevalence of type 2

diabetes in the paediatric age group. Individuals born LGA are at increased risk of metabolic syndrome and obesity later in life. The rising incidence of type 2 diabetes in childhood and adolescence has been attributed to the rising incidence of obesity in various populations. Thus, the persistent rise in incidence obesity will result in a perpetual increase in incidence of type 2 diabetes with the attendant adverse health consequences in subsequent generations. Thus, abnormal size at birth represents a significant public health concern. This public health importance of being born either SGA or LGA, underlie the relevance of careful follow-up of children born either SGA or LGA to detect the development of metabolic abnormalities during childhood. Health intervention strategies directed at mothers and aimed at reducing the frequency of delivery of babies with abnormal size at birth will be beneficial, not only to the individual's health but also the health of future generations.

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