Perinatal Vitamin D Insufficiency and Neonatal Health

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Vitamin D insufficiency and deficiency, especially amongst pregnant and lactating women and their newborn infants, is a global public health problem, not only in the developing countries but also amongst the developed countries of the world. The Institute of Medicine, USA defines vitamin D insufficiency as 25 (OH) D levels of 10-19 ng/mL and deficiency as < 10ng/mL. In contrast, the Endocrine Society (US) defines vitamin D insufficiency as 25 (OH) D levels of 20-30 ng/mL and deficiency as <20 ng/mL.

Magnitude of the problem

In order to create a global summary of maternal and newborn vitamin D status, Saraf R et al.[1] carried out a systematic review and meta-analysis of published studies which had reported maternal and newborn vitamin D levels. Based on the 95 studies identified for the review they reported the following average maternal 25 (OH) D levels for the WHO regions: 18.8-26 ng/mL for the Americas, 6-28.8 ng/mL for Europe, 5.2-24 ng/mL for the Eastern Mediterranean, 8-20.8 ng/mL for South East Asia, 16.8-28.8 ng/mL for the Western Pacific and 26.8 ng/mL for Africa. The prevalence of maternal 25 (OH)D levels <20 and <10 ng/mL, respectively, was reported as 64% and 9% for the Americas, 57% and 93% for Europe, 46% and79% for the Eastern Mediterranean, 87% (<20 ng/mL) for SE Asia, and 83% and 13% for the Western Pacific. The prevalence of 25 (OH)D levels <20 and <10 ng/mL, respectively, for newborns was reported as 30% and 14% for the Americas, 73% and 39% for Europe, 60% (<20 ng/mL) for the Eastern Mediterranean, 96% and 45% for SE Asia, and 54% and 14% for the Western Pacific.

Maladkar et al.[2] published an updated review of Indian studies reporting vitamin status in pregnant women. Of the 11 studies identified by the authors, eight studies used 25 (OH) D levels < 20 ng/mL to define deficiency, and the prevalence ranged from 42%-96.3% (median 75%). The authors also identified 6 studies that had reported vitamin D levels in exclusively breast fed infants (ages 2-24 weeks) and the prevalence of 25 (OH) D levels <20 ng/mL ranged from 43-100% (median 86%).

Agarwal et al.[3] in a study of Vitamin D status amongst low birth weight (LBW) neonates in Delhi reported a prevalence of 25 (OH) D <15 ng/mL within 48 hr of birth amongst LBW as 87.3% and amongst normal birth weight infants as 88.6% (the corresponding prevalence amongst their mothers ranged from 93-97%). Concurrently, parathyroid hormone (PTH) was reported to be raised in 63.6% of LBW and 41.4% of n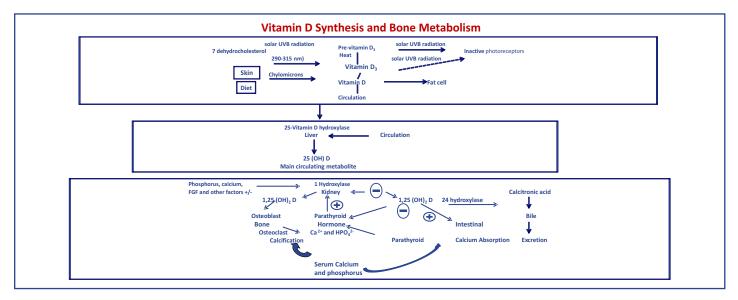ormal birth weight infants. At 12-15 weeks about 14% of these LBW and 5% of normal birth weight infants had developed clinical rickets.

Relationship between Maternal and Neonatal Vitamin D status

There is considerable evidence that there is a correlation between maternal and neonatal vitamin D levels. However, there is some controversy about the correlation between circulating 25 (OH) D levels and the active 1α, 25 (OH)$_2$ D concentrations in maternal-neonatal studies. The standard estimation of vitamin D levels measures both active and inactive forms. Karras et al.[4] measured all vitamin D forms in maternal and paired neonatal cord blood samples. Maternal samples had slightly (to an insignificant extent) higher levels of vitamin D (25 (OH) D$_2$ and 25 (OH) D$_3$) than the respective neonates. In both mother and neonate, the predominant forms of vitamin D detected were 25 (OH)D$_2$ and 25 (OH)D$_3$ (25 (OH)D3: 25 (OH)D$_2$ of 3:1), accounting for almost 75% of the total circulating vitamin D. The inactive epi- forms (3-epi-25 (OH)D2 and 3-epi-25 (OH)D3) constituted the remaining 25% of the total vitamin D estimations. The 1α, 25(OH)2D3 form was detected in very minuscule amounts only in maternal blood and not in the neonate. The overall correlation between maternal vitamin D and neonatal vitamin D was 0.543 (highly significant). The levels of the active forms of vitamin D showed a better correlation between mother and neonate than the epi- forms. The authors have hypothesized that assays that do not separately measure epimers, and those that have high cross reactivity with epimers, are likely to report higher levels of vitamin D. This may have implications for clinicians when attempting to detect vitamin D insufficiency.

CONTENTS

Vitamin D Synthesis and Bone Metabolism

Thomas et al.[5] in a study amongst Australian mother-infant dyads reported a significant correlation between maternal third trimester 25 (OH) D levels and neonatal values. When the estimations of vitamin D were compared using enzyme immune assay (EIA) and LC/MS-MS, the correlation was very good (r=0.9) and the authors have therefore suggested than EIA may be a good method for estimation of maternal and neonatal vitamin D levels.

Maternal Vitamin D and Foetal growth

The effect of maternal vitamin D insufficiency on foetal growth has been insufficiently studied. Bodnar et al.[6] carried out a nested case control study amongst nulliparous singleton pregnancies. They observed a U-shaped relationship between maternal 25 (OH) D levels and foetal growth restriction (small for gestational age, SGA) in white women only. The odds for SGA at maternal serum vitamin D levels < 37.5 and >75 nmol/L (15 and 30 ng/mL) were 7.5 (95% CI 1.8-31.9) and 2.1 (95% CI 1.2-3.8), respectively. They also noted that some single nucleotiode polymorphisms (SNPs) in the vitamin D receptor (VDR) genes were associated with SGA. The authors have suggested that the relationship of vitamin D to foetal growth is complex and may be related to race/ethnicity.
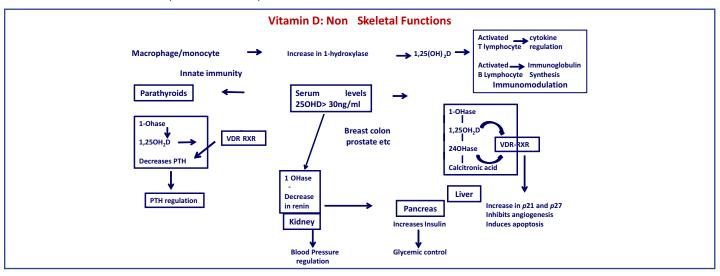
In a systematic review of maternal vitamin status and pregnancy and neonatal outcomes, Aghajafari et al.[7] reported a significant association between maternal vitamin D insufficiency SGA infants. The odds ratio for SGA was 1.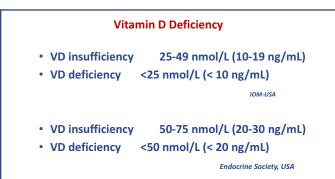85 (95% CI 1.52-2.26). This association remained significant even when stratified for maternal vitamin D levels (<37.5 and < 80 nmol/L) and study designs.

In a systematic review of 13 randomized clinical trials (enrolling a total of 2299 women) on the effects of vitamin D supplementation on pregnancy and birth outcomes, Lopez et al.[8] reported that infants born to the vitamin D supplemented group of mothers were significantly heavier (mean difference 107.6 g; 95% CI 59.9-155.3 g) and longer (mean difference 0.3 cm; 95% CI 0.1-0.41 cm) than the control group.

Neonatal Effects

Respiratory Function. In a systematic review of animal, laboratory and human studies on the effect of vitamin D on foetal and neonatal lung maturation, Lykkedegn et al.[9] found no association between vitamin D receptor polymorphism and broncho-pulmonary dysplasia (BPD). However, the authors observed positive effects of vitamin D on the alveolar type II cell, fibroblast proliferation, surfactant synthesis, and alveolarization. The authors suggested that human studies should be carried out to explore the relationship between hypovitaminosis D and respiratory distress syndrome (RDS) in the newborn. Koroglu et al.[10] observed that VDR gene polymorphism of Fok I was associated with an increase in the risk of BPD in preterm neonates (adjusted OR 4.1, 95% CI 1.08-15.6).
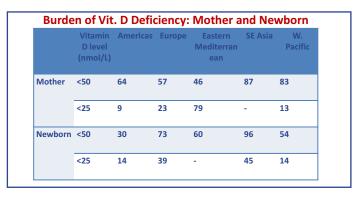
Vitamin D: Non Skeletal Functions

Vitamin D Deficiency

- VD insufficiency   25-49 nmol/L (10-19 ng/mL)
- VD deficiency   <25 nmol/L (< 10 ng/mL)

IOM-USA

- VD insufficiency   50-75 nmol/L (20-30 ng/mL)
- VD deficiency   <50 nmol/L (< 20 ng/mL)

Endocrine Society, USA

Burden of Vit. D Deficiency: Mother and Newborn

	Vitamin D level (nmol/L)	Americas	Europe	Eastern Mediterranean	SE Asia	W. Pacific
Mother	<50	64	57	46	87	83
	<25	9	23	79	-	13
Newborn	<50	30	73	60	96	54
	<25	14	39	-	45	14

Ataseven et al.[11] studied the association of vitamin D deficiency and RDS in 152 preterm neonates (born between 29-35 weeks). Severe vitamin D deficiency (< 10 ng/mL) was detected in 64% of the neonates, and the rest showed moderate to mild deficiency (10-30 ng/mL). RDS was significantly more common in preterm neonates with severe deficiency (28%) as compared to those with mild-moderate deficiency (14%). These findings support the hypothesis proposed by Lykkendegn et al9. The link between vitamin D deficiency and respiratory morbidity in preterms is further supported by the study of Onwuneme et al.[12] The latter study noted a significant association between low vitamin D levels (< 12 ng/mL) at birth in preterm neonates (< 32 weeks) and the requirement for longer duration of intermittent positive pressure ventilation (IPPV) in the delivery room and increased need for oxygen supplementation and mechanical ventilation during the stay in the neonatal intensive care unit (NICU). The risk of respiratory morbidity is also higher in term neonates who are vitamin D deficient. Konca et al.[13] observed that term neonates with transient tachypnea of the newborn (TTNB) had significantly lower levels of vitamin D as compared to those with no respiratory distress. However, they found no association between vitamin D levels and severity of TTNB.

Miller et al.[14] studied the relationship between maternal vitamin D intakes in early pregnancy and neonatal airway epithelial cell (AEC) response to various stimuli. They observed that an increased intake of vitamin D by the mother in early pregnancy (10-12 weeks gestation) was associated with an increased release of IL-10 by neonatal AEC in response to stimulation by TNF-α/IL-1β or House dust mite. The authors suggest that these findings could have implications for later onset asthma or allergic rhinitis. Thus, not only maternal vitamin D deficiency, but also excess maternal intake of vitamin D in pregnancy may have adverse effects on their infants.

Immune Function There have been several reports on the role of vitamin D in immune function. Chary et al.[15] studied the relationship between maternal vitamin D status and cord blood immune function in Indian women. They observed that T*reg* cell levels were significantly lower in the cord blood of neonates born to women who were vitamin D deficient as compared to those who were insufficient/sufficient. Also, the B cell populations of CD 23 and CD 21 were significantly higher in the cord blood of neonates born to

vitamin D-deficient mothers as compared to those born to mothers who were insufficient/sufficient. The authors have suggested that these alterations may be linked to asthma and allergy in neonates. Walker et al.[16] observed that monocytes cultured in severely vitamin D deficient (< 10 ng/mL) cord plasma resulted in decreased Toll like receptor (TLR)-induced cathelicidin expression as compared to those cultured in vitamin D-sufficient plasma. They also noted that in vitro supplementation with vitamin D increased the expression of the antimicrobial peptide gene. The authors suggested that there was a need to investigate this relationship further in human neonates. In a study on neonates with early onset sepsis, Cetinkaya et al[17] noted that neonates with early onset sepsis had significantly lower levels of vitamin D as compared to non-infected normal neonates. These observations further strengthen the hypothesis that vitamin D has a role in innate immunity in neonates.

Metabolic Consequences. There is sufficient evidence that vitamin D deficiency in the neonate is associated with higher risk of hypocalcemia[18]. However, vitamin D insufficiency/deficiency has not been noted to be associated with metabolic bone disease in preterm infants. There is limited evidence of a correlation between umbilical cord plasma vitamin D levels and neonatal fat mass[19]. However, its clinical implications need to be elucidated.

Long Term Outcomes

Vitamin D deficiency appears to impact immunity and consequent infectious morbidity in neonates. However, the same does not appear to hold true in infancy. In a randomized controlled trial of vitamin D supplementation in deficient LBW neonates from birth to 6 months in India, Kumar et al.[20] observed that while supplementation improved the vitamin D status of the infant at 6 months, it did not affect CRP levels or cytokine levels in plasma, nor affect the recent illness episodes.

In a cohort study of 960 women and their offspring in Vietnam, Hanieh S et al.[21] observed that, at 6 months, infants born to mothers with vitamin D deficiency had lower language development scores as compared to infants born to vitamin D sufficient mothers. In an Australian cohort (Western Australia Pregnancy Cohort study) of

Vitamin D: Neonatal Respiratory function

- ➢ Vitamin D deficiency increases respiratory morbidity in pre-term neonates. There is
- ✓ increased oxygen requirement
- ✓ increased duration intermittant positive pressure ventilation PPV during delivery room resuscitation
- ✓ increased duration of mechanical ventilation in neonatal ICU
- ➢ Lower Vitamin D levels in neonates with transient tachypnea (TTNB) of preterm neonates but no association with severity of TTNB
- ➢ Respiratory distress syndrome in preterm neonates is more common with severe Vitamin D Deficiency (28%) compared to mild-moderate deficiency (14%).

Vitamin D: Neonatal Respiratory function

- ➢ Vitamin D receptor Fok 1 genotype polymorphism increases risk for broncho- pulmonary dysplasia in preterm neonates
- ➢ Vitamin D Alters Airway epithelial Cell (AEC) response
- ✓ Increased intake of vitamin D by the mother in early pregnancy (10-12 weeks gestation) was associated with an increased release of IL-10 by neonatal AEC in response to stimulation by TNF-α/IL-1β or House dust mite and may predispose to allergy / asthma .
- ✓ Both vitamin D deficiency and excess may be associated with adverse health consequences

Long term health consequences of maternal vitamin D deficiency on the offspring

Maternal Vitamin D Deficiency at 18 weeks pregnancy is associated with increased risk in the offspring

➢ **Impaired lung function at 6 years**
➢ **Neurocognitive difficulties at 10 years**
➢ **Eating disorders in adolescence**
➢ **Lower peak bone mass at 20 years**

Long term health consequences of high neonatal vitamin D levels

Higher neonatal Vitamin D associated with

• **Higher fasting adult insulin**
• **Higher triglyceride**
• **Higher cholesterol**
• **Higher risk of overweight and obesity in women**
•

901 mother-offspring pairs, Hart et al.[22] reported that maternal vitamin D deficiency was significantly associated (after adjusting for covariates) with impaired lung development in the offspring at 6 years, neurocognitive difficulties at 10 years, increased risk of eating disorders during adolescence and lower peak bone mass at 20 years. In a Swedish cohort study, Tornhammar et al.[23] reported the association between neonatal vitamin D levels and cardiovascular disease risk at 35 years of age. After adjusting for relevant co-variates, they observed that higher neonatal vitamin D levels was associated with higher adult fasting insulin, triglycerides, and cholesterol in women. It was also associated with increased risk of adult overweight and obesity in women.

Summary

Vitamin D levels in neonates are correlated to maternal vitamin D levels. Maternal vitamin D deficiency appears to increase the risk of foetal growth restriction, leading to low birth weight. Vitamin D deficiency in newborns affects their respiratory function, innate immunity and calcium metabolism. Neonatal vitamin deficiency also appears to be associated with long term adverse outcomes on lung development and neuro-cognitive behaviors. On the other hand, high neonatal vitamin D levels may have implications for increased cardiovascular risk in adult women. Future research studies may show the way to improve maternal and foetal vitamin status without incurring the risk of high neonatal vitamin D levels and associated health hazards.

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Nutritional Concepts in Fetal Programming

Vandana Jain

India and many other developing countries are presently in a state of rapid socioeconomic and demographic transition, resulting in a dual burden of under- and over-nutrition. Evidence suggests that while today's obesogenic lifestyle and environment are primarily responsible for the pandemic of obesity, diabetes and cardiovascular disease in the population, factors operating in early life may also play a key role in its genesis.

In the early 1990s, Prof. David Barker proposed his hypothesis of early-life origins of chronic diseases. Since then, numerous epidemiological studies, including elegant cohort studies from India, have supported this theory. In recent years, the focus of research in this area has also included the following three issues: a) effect of maternal overnutrition and gestational diabetes mellitus on foetal programming b) modulatory role of early postnatal growth trajectory on the future risk of cardiovascular disease and diabetes, and c) unravelling of the mechanistic paradigms of developmental programming. The newer cohort studies have incorporated measurement of body composition, anthropometric measurements at closer intervals during the first year, and the study of genetic and endocrine parameters to try and understand the pathophysiology of programming.

This paper, reviews the literature dealing with evidence for the programming effects of the maternal nutritional status, the role of early postnatal growth in modifying the risks accrued due to foetal programming, and the new insights into the mechanisms of foetal programming.

Epidemiological evidence for the programming effects of maternal under- and over-nutrition

The initial interest in the 'early origins' hypothesis arose from studies by Barker and colleagues, carried out in adult males. These studies demonstrated that men who had been born with the lowest birth weights had a several-fold higher likelihood of developing ischemic heart disease and type 2 diabetes in late adulthood than those who had been heaviest at birth[1,2]. The direct role of maternal undernutrition in the causal pathway of later adulthood diseases was strongly suggested by studies in the 1990s, carried out in a group of adult males in their fifties. These men were part of the population which had been affected by the Dutch famine, a short, defined period of famine lasting around 5 months at the end of World War II. Those who had been in utero during the famine had higher plasma glucose levels 2 hours after a standard oral glucose tolerance test as compared to individuals born the year before the famine[3].

Over the years, studies have emerged that indicate that not just maternal under-nutrition, but over-nutrition too is detrimental to the offspring's long term health. This was first noted in studies of the Pima Indian population, in which maternal obesity and gestational

diabetes are common. The relationship curve between birth weight and type 2 diabetes was found to be U-shaped[4]. Maternal over-nutrition is rapidly becoming a major concern in India also. As per the third National Family Health Survey in 2005-6, 15% of Indian married women are overweight or obese[5]. Between 7-18% of pregnancies in Indian mothers are complicated by gestational diabetes mellitus (GDM)[6]. Both of these conditions, individually, and possibly synergistically, impose a risk of greater adiposity and perturbations in lipid and carbohydrate metabolism and intergenerational transfer of risk of obesity to the offspring.

Newborn offspring of mothers with pre-pregnancy overweight or with excessive gestational weight gain (GWG) have been noted to have higher total as well as abdominal fat mass[7], and greater weight gain during infancy[8]. The association of maternal overweight with childhood obesity has also been noted in a systematic review of 30 studies[9]. In a recent paper, the persistence of the association between maternal pre-pregnancy overweight/excessive GWG with cardio-metabolic risk factors in the offspring in young adulthood has also been documented[10].

The studies on the offspring of mothers with pregnancies complicated by GDM show less unanimity. Aris et al. have reported that there is a continuous linear association between maternal glycaemia and newborns' adiposity[11]. At the same time, it has been suggested that even in mothers with GDM, the perturbations in lipid metabolism may be more closely linked to foetal effects[12]. While some studies report higher BMI z-scores at ages 1-7 years among offspring of GDM women,[13,14] a systematic review suggested that, after adjusting for maternal pre-pregnancy BMI, the association is inconsistent[15]. At ages 9 and 11 years, the offspring of GDM women were noted to have higher prevalence of insulin resistance, especially if they were themselves overweight[16,17]. It emerges that, rather than the mother's GDM status, it is her pre-pregnancy BMI, and the family's lifestyle after the birth of the infant, that have a more definitive bearing on the offspring's risk of future obesity and cardio-metabolic outcomes.

Among Indian studies, one carried out by Kale et al. from Pune observed that Indian mothers with GDM were more obese than non-GDM mothers, and that their newborns were heavier and had greater skinfold thickness as compared to those of non-GDM mothers[18]. Krishnaveni et al., in an extended follow-up of the offspring of women with GDM from Mysore, noted that these babies were heavier at birth compared to those of non-GDM mothers, but not at 1 year. At 5 years, the female offspring of diabetic mothers had larger subscapular and triceps skinfold thicknesses, and at age 9.5 years, both male and female offspring were noted to have higher HOMA-IR as compared to offspring of non-GDM women[19,20]. There is a paucity of Indian studies on the effect of maternal overweight on adiposity or metabolism of the offspring. Veena et al. reported that maternal and paternal adiposity had equal positive association with

children's BMI and insulin levels at 9.5 years of age, suggesting that shared obesogenic habits and lifestyle rather than programming played a greater role in familial perpetuation of obesity, diabetes and cardiovascular disease[21].

Role of nutrition and growth velocity in the early postnatal period in modifying the risks accrued in the foetal period

Infancy is a period characterized by rapid growth. This is considered to be a critical period that can aggravate or reduce the programmed risks accrued during the foetal period. The adverse impact on long-term metabolic health appears to be exaggerated if foetal growth restriction is followed by accelerated postnatal growth and/or obesity. Apart from modulating the effects of foetal growth, there is strong evidence that growth and nutrition during the neonatal period also influence future health independently. In a prospective study among term low birth weight babies, we had observed that infants who showed catch-up growth (change in weight for age z-score of > 0.67) within the first 6 weeks, and had greater weight gain between birth and 3 months, had greater adiposity (assessed by DEXA) at 7.2 months of age[22]. A follow-up of the New Delhi Birth Cohort had suggested that individuals who had rapid weight gain in the first two years of life were at higher risk of developing metabolic syndrome in adulthood[23]. The relationship between rapid weight gain in infancy and overweight in childhood has also been indicated by a systematic review[9].

Factors such as infants' nutritional intake and activity levels, mothers' dietary habits and, for overweight / GDM mothers, changes in their BMI or glycemic status, have been noted to influence the infants' growth pattern[24]. In a follow-up study of a Mysore birth cohort, it was noted that weight gain between 0-2 years of age was positively related to BMI at 5 years of age,[19] and that longer duration of breastfeeding and later introduction of solids were negatively related to BMI at 5 years[25]. In a Canadian study in infants of GDM women, faster weight gain in the first year predicted HOMA-IR[26]. In China, a health survey of GDM mothers and their offspring 1-5 years after delivery showed that the offspring of mothers who developed diabetes had higher BMI Z-scores as compared to those whose mothers remained non-diabetic, thereby suggesting that efforts to improve the mother's glycemic status will be of benefit to the offspring as well[27].

A longer duration of breastfeeding has been shown to have a protective influence against overweight in offspring of mothers with overweight/ excessive GWG[28]. The lactating mother's own nutritional intake has an effect on her baby's weight gain in the first 6 months[29]. This may be mediated by the concentration of hormones and nutrients in the breast milk[30]. Leptin is present in human milk, produced and secreted by mammary epithelial cells in milk fat globules. Leptin may play a role in the short-term control of food intake in neonates by acting as a satiety signal and could also exert a long-term effect on energy balance and body weight regulation. Insulin and IGF-1 are also present in human milk and may have an influence on the infant's growth. Post-weaning, the age at introduction and the quality of the complementary foods have been noted to affect weight gain in infants born to overweight mothers[30]. Specifically, the introduction of solid foods in infants under the age of 4 months, and juice intake have been noted to increase weight

gain[31]. If the mother is more responsive and less indulgent or intrusive while feeding the child, the rate of weight gain is slower[31].

These observations are important as they represent the diverse ways in which the programmed risks accrued during the foetal period can be potentially ameliorated.

Mechanistic paradigms underlying developmental programming

Early life events shape the future. The foetal and early neonatal periods are characterized by developmental plasticity or the ability to develop in various ways, depending on the particular environment or setting. The foetus responds to suboptimal conditions during critical periods of cellular proliferation, differentiation and maturation by producing structural and functional changes in cells, tissues and organ systems. If the adaptation is permanent, it is considered a "programming" change with persistent effects in structure and/or function.

Some of the hypotheses that have been put forward to explain the mechanisms of these programming effects are as follows:

- Thrifty genotype hypothesis (Neel, 1962): Thrifty genes enabled efficient processing of food so as to deposit fat during abundance, thus favouring survival during famine. These genes became detrimental when food supply became abundant[32].
- Thrifty phenotype hypothesis (Barker and Hales, 1992): Economization of resources by the foetus in the face of undernutrition diverts nutrients to the brain at the expense of "non-essential" organs. This results in reduction in the number of pancreatic β-cells, nephrons, and cardiomyocytes, thus predisposing the affected foetus to diabetes, hypertension and ischemic heart disease in adulthood[1,2].
- Foetal salvage hypothesis (Hofman, Cutfield, Menon, Sperling 1997): The foetus develops peripheral insulin resistance to ensure glucose delivery to the brain with reduced delivery to skeletal muscle. On the one hand, this results in a permanent reduction in the number or function of muscle glucose transporters, while on the other, insulin resistance leads to eventual β-cell exhaustion[33].
- Foetal insulin hypothesis (Hattersley and Tooke, 1999): The hypothesis is that there is no cause and effect relationship; rather, genetically determined insulin resistance results in both impaired insulin-mediated growth in the foetus as well as type 2 diabetes in adulthood (common roots)[34].
- Growth Acceleration Hypothesis (Singhal and Lucas, 2004): Accelerated postnatal growth is detrimental. Tissues chronically depleted of insulin and IGF-1 during intrauterine life, when exposed to higher concentrations in the postnatal period develop insulin resistance as a protective mechanism against hypoglycemia[35].
- Predictive Adaptive Mismatch (Hanson and Gluckman, 2004): Cardiometabolic disorders result from a mismatch between the postnatal environment and the phenotype that had been predicted based on the nutritionally restricted environment in utero[36].

Recent studies, primarily in animal models, have elucidated several

programming mechanisms. These can be broadly categorised into three major groups that closely interact with each other:

a. Permanent Structural Changes: Structural effects on the endocrine pancreas, including reductions in ß-cell mass and reduced islet cell vascularization, have been noted in rodent models. Some of the structural changes, such as islet fibrosis, develop in late adult life, highlighting the interaction between the early environment and the ageing process[37]. Leptin and insulin are hormones that play an important role in development of satiety responses and energy homeostasis. Suboptimal levels of these hormones during neonatal life have been identified in animal models of both maternal under-nutrition as well as over-nutrition, and this could represent a common programming mechanism operating at both ends of the nutritional spectrum[38]. The development of the kidney has also been shown to be particularly susceptible to changes in the early environment. One of the major programmed structural differences is a reduction in nephron number, which is associated with an increased risk of hypertension and renal disease[39].

b. Epigenetic Programming of Gene Expression: Alterations in the early environment are associated with permanent changes in gene expression mediated via epigenetic alterations (e.g., changes in DNA methylation and histone modifications). Transcription factors are particularly attractive targets of developmental programming because, through modulation of their expression, a whole network of other genes that are implicated in growth and metabolism can be modulated[40].

c. Accelerated Cellular Ageing: Many of the conditions associated with a suboptimal early environment, such as type 2 diabetes and cardiovascular heart disease, are associated with the ageing process. Cellular ageing or senescence can be induced by oxidative stress, as occurs in foetal hypoxia[41]. Reactive oxygen species can cause oxidative damage to lipids, proteins and DNA. One region of the DNA that is particularly vulnerable to oxidative stress is the telomeres. Telomere shortening triggers cell senescence and is therefore associated with ageing and age-related pathologies[42].

To summarise, while the importance of maternal undernutrition in foetal programming of obesity and cardio-metabolic disorders in adulthood has long been recognized, recent studies have indicated that maternal overnutrition also increases the offspring's risk of adiposity and insulin resistance. Specifically, maternal pre-pregnancy overweight is implicated in higher birth weight and continued excessive postnatal weight gain. For mothers with gestational diabetes, their BMI and glycemic control play a role in determining the offspring's growth rate and insulin resistance. The postnatal growth trajectory modulates the expression of the risks accrued due to developmental programming. There is evidence to suggest that faster postnatal growth, as early as during the first few weeks of life, increases the future risk of obesity and related cardio-metabolic complications. The mechanistic paradigms have begun to be unravelled in interesting studies in animal models. Permanent structural changes, such as reduction in cell mass and nephron numbers, epigenetic changes that modify the expression of genes

that regulate growth and metabolism, and accelerated cellular senescence induced by oxidative stress are some of the mechanisms that are partially able to explain the phenomena of developmental programming. We hope that in future, with further insight into this field, effective interventions to prevent or ameliorate the effects of adverse developmental programming will become available.

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FOUNDATION NEWS

Dr Prema Ramachandran, Director, Nutrition Foundation of India, will be delivering the Fourteenth Rajmmal P Devadas Oration on "Millennium Development Goals-Tamil Nadu's achievements" at Avinashilingam University , Coimbatore, on 7.4.2016.

NUTRITION NEWS

The 48th Annual National Conference of NSI will be held at St John's Medical College, Bangalore .