NFI BULLETIN

Bulletin of the Nutrition Foundation of India

Volume 42 Number 3 July 2021

Primordial Prevention of Adult Chronic Disease in the "First 1000 Days": An Indian Perspective

Sumaira Khalil, and H.P.S. Sachdev

Introduction

Epidemiological studies indicate that various insults during the intrauterine period are associated with adult chronic diseases. The term "First 1000 Days", first articulated by Hillary Clinton, includes the period from conception till the child is two years of age, and is considered to be crucial in this context. This vulnerable period in humans can be influenced by several adverse maternal-infant factors including maternal health, psychological stress, and nutrition, breast feeding, complementary feeding and socio-economic factors, all of which can affect the growth and development of the child, and lead to long-term outcomes extending into adult and geriatric life.

Foetal programming

In the 1980s Professor David Barker hypothesized that the combined effect of environmental factors and inherited genes during this critical period of the first 1000 days could lead to the origin of adult disease[1]. This theory was later termed as the Developmental Origin of Health and Disease (DOHaD)[2]. Prof. Barker proposed that a stimulus or insult during this sensitive or critical period of development could have a lasting or lifelong significance through alterations of structure, physiology and metabolism. Foetal programming is one of the adaptive mechanisms to maintain homeostasis when the foetus is exposed to a hostile environment during critical periods of development of essential organs. Evidence indicates an association between intra-uterine stress and permanent phenotypic changes secondary to foetal programming, leading to the development of future health problems. Placental function plays an important role in maintaining normal gestational environment. Any condition such as maternal psychological stress, psychosis, depression, anxiety or foetal hypoxia, and oxidative stress to the foetus disrupts placental function, thereby triggering foetal programming and initiation of epigenetic alterations[3]. The mechanism of foetal programming and epigenetic memory is graphically summarized in Figure 1. Epigenetic memory is defined as a heritable change in the DNA and histones without an alteration in the DNA sequence, having the effect of modifying the genetic expression in response to environment stimuli. Epigenetic mechanisms like DNA methylation and histone modification[3] are known to be associated with an increase in the occurrence of chronic conditions such as obesity, insulin resistance, type 2 diabetes mellitus and cardiovascular diseases.

First 1000 days: supportive human evidence

There is substantial observational evidence in support of the DOHaD hypothesis, especially from long-standing birth cohorts from Low-and-Middle-Income-

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Countries (LMICs). In this context, the New Delhi Birth Cohort (NDBC) from India is one of the longest standing birth cohorts. It was initiated in 1969, has had follow-ups for five decades by now, and includes four generations. Data from this birth cohort have been pooled with data from four other similar cohorts from other LMICs, namely, Guatemala, South Africa, Philippines and Brazil, to form the COHORTS collaboration[4]. In 2008, data from these five cohorts were reviewed to look for association between maternal and child under-nutrition on the one hand, and the risk of developing adult-onset diseases on the other. Maternal and child under-nutrition markers, including maternal height, birth weight, intra-uterine growth restriction, and weight, height and body mass index (BMI) at 2 years of age were related to adult outcomes such as height, schooling, birth weight of the off-spring, BMI, blood pressure and glucose concentration. It was concluded that larger size of the child at birth and in childhood was positively associated with higher BMI in adulthood, and to a lesser extent with higher blood pressure, but no association was seen with blood glucose concentration. Lower birth weight and under-nutrition in childhood were positively associated with later onset of high blood pressure and high glucose concentrations, leading to increased risk of developing adult chronic diseases[5].

In the NDBC, the association between growth in early life and the incidence of glucose intolerance was evaluated in 1492 men and women between 26-32 years of age; these participants had been measured at birth and followed every 3-6 months throughout infancy, childhood and adolescence[6]. Participants who developed impaired glucose tolerance or diabetes at 32 years of age had been thin at birth, became slightly thinner till 2 years of age, and then showed a gradual and sustained increase in BMI; the change in BMI from the nadir to the peak was ~0.5SD. Another important observation was that among those who had developed diabetes or impaired glucose tolerance in adult life, <1% had been obese in infancy and childhood, while one third or half (30-50%) of them had been underweight till 12 years of age. Similar findings have now been reported from other global datasets.

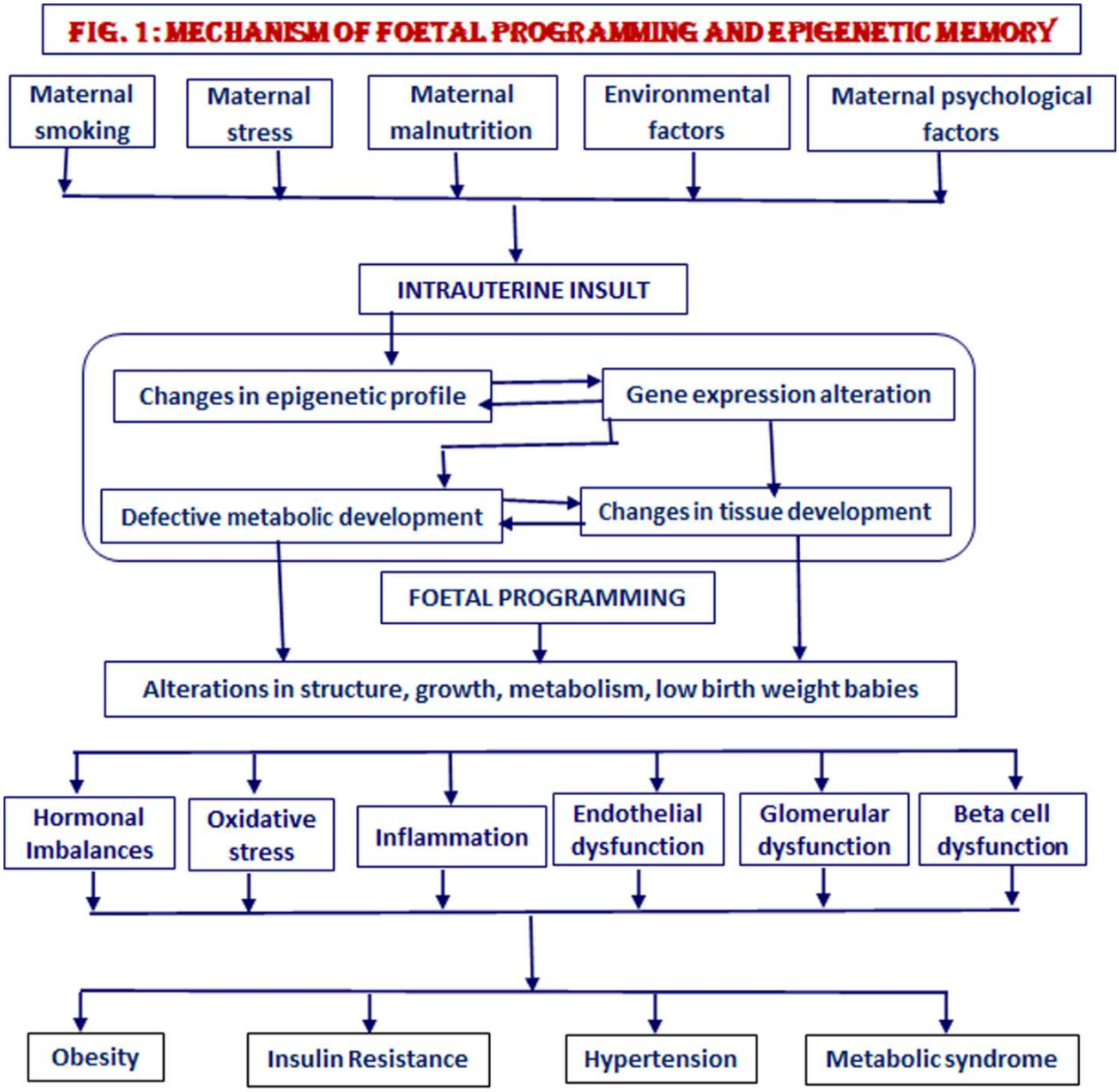
Recently, NDBC data have been used for evaluating the association between human capital and physical growth from birth to adulthood. Higher linear growth in the first 2 years was associated with better school education, and with a better occupation and financial status in adulthood. The small effect persisted even after adjusting for several confounders, although from 2-5 years this effect was lower and inconsistent[7]. The above evidence reinforces the crucial importance of the first 1000 days and the need to explore relevant interventions during this period for improving human capital and preventing development of adult chronic diseases.

Limitations in translating evidence into interventions

There are some inherent limitations in translating the relevant human evidence into potential interventions, particularly in the Indian context. First, the exposure time required for primordial prevention spans at least one generation, and long-term evidence of this nature may not be available. Thus, intermediary outcomes have to be used as surrogates (for example, hyperlipidemia instead of coronary artery disease). Second, several studies focus only on the anthropometric parameters, with limited information on relevant metabolic phenotyping of over-nutrition. Third, sometimes observational evidence has to be utilized, as randomized controlled trials would be unethical (for example, risk of developing coronary artery disease or diabetes mellitus with infant milk substitutes). Fourth, indirectness of the evidence, resulting from extrapolation from High-Income-Countries settings to LMICs. Fifth, there has been intermingling of faith and evidence in some proposed interventions. Within this backdrop, the ensuing section summarizes the pertinent global evidence for potential preventive interventions in the mother and baby, with a primary focus on studies from India, where available.

Observational evidence

In 2015, the COHORTS collaboration reported a significant U-shaped relationship between the maternal age at childbirth and plasma glucose level and systolic blood pressure of offspring when they reach adulthood. The confounder-adjusted U-shaped quadratic trend was statistically significant (P=0.005) for offspring of both young (<19 years) and old (>35 years) mothers to have a tendency for high plasma glucose as compared to 25-34 year age group which, in some datasets, translated into impaired glucose tolerance tests or diabetes; however, this trend was



not statistically significant for systolic blood pressure[8]. There is thus a case for propagating an optimal age of child bearing (25-34 years) for lowering the incidence of adult Non-Communicable Diseases (NCDs).

In the Parthenon study conducted at Mysore, maternal Gestational Diabetes Mellitus (GDM) was found to be associated with adiposity and higher glucose and insulin concentrations in female offspring at 5 years age. The absence of similar associations in offspring of diabetic fathers suggested a programming effect in the diabetic intra-uterine environment[9]. In a subsequent follow-up (9.5 years), the offspring of diabetic mothers had higher risk factors for diabetes and cardiovascular diseases, and the effects strengthened with increasing age during childhood[10]. Similarly, observational evidence from several global studies indicates that maternal obesity, gestational diabetes, overt diabetes, and pregnancy-induced hypertension predispose both the mothers and the offspring to develop hypertension, diabetes and metabolic syndrome in later life, with biomarkers often being discernible in early childhood for the children[11-13]. However, there is limited evidence evaluating the effect of optimal treatment of these maternal conditions on subsequent reduction of risk of adult-onset disease in offspring. A pragmatic approach would, therefore, combine optimal maternal management with inculcating healthy life style habits in the offspring, along with their frequent screening for early indicators of developing a tendency for adult-onset chronic disease.

Systematic reviews indicate that prenatal maternal smoking is associated with an increased risk of

overweight and obesity (ORs: 1.37-1.55) in the offspring till 18 years of age, which can track into adulthood[14-15]. However, the role of tobacco chewing, a practice prevalent in rural India, has not been systematically evaluated in this context. Maternal caffeine consumption at 50 mg/day during pregnancy was found to be associated with a higher risk of childhood overweight or obesity, the association becoming even stronger when the coffee intake was ≥300 mg/day. The current recommendation of <200 mg/day of caffeine during pregnancy is likely to be associated with a lower risk of overweight or obesity in offspring, but avoidance of the substance has been recommended[16].

In comparison to vaginal delivery, Caesarean section has been associated with an increased risk of overweight and obesity in the offspring (ORs: 1.15-1.33) at ages ranging from childhood to early adulthood[17-19]. In a large study evaluating 22068 children born to 15271 mothers aged 20-28 years, a vaginal delivery following a first Caesarean section resulted in a 31% (17-47%) lower risk of an obese offspring[19]. The biological postulates for this include changes in the microbiome and a greater propensity towards breast feeding, or Caesarean delivery could be a proxy for underlying conditions such as vascular disease or pregnancy-induced hypertension.

Exclusive breast feeding for the first 6 months of life is the global recommendation, based on the findings of systematic review by the WHO in 2013. Children who were exclusively breastfed were more likely to have lower levels of total blood cholesterol, less likely to have elevated blood pressure, had a lower risk of developing overweight, obesity and diabetes mellitus, and performed better on intelligence quotient tests[20].

A systematic review of 282 studies documented some additional potential risk factors for developing childhood obesity. These include (i) excess gestational weight gain, (ii) high birth weight, (iii) accelerated infant weight gain, (iv) insufficient level of maternal-infant relationship and (v) antibiotic exposure of the infant[21]. However, no definitive priority interventions are agreed upon for the first three of the above, while the jury is still out for the other two. Recent evidence suggests that childhood exposure to particulate and nitrogen dioxide air pollution inside the home, and urine cotinine levels indicative of second-hand smoke exposure, are associated with overweight and obesity[22].

Interventional evidence

Project Sarasin Mumbai conducted a randomized controlled trial of a micronutrient-rich food supplementation given to over 6000 women prior to their conceiving a child and during their pregnancy[23]. Of the 6513 randomized women, 1826 received the food supplements for more than 3 months before they became pregnant. The intervention effect on birth size was 50 grams overall but, paradoxically, the effect was greater in obese mothers than in normal or thin ones. Using the WHO-1999 criterion, gestational diabetes mellitus was halved (7.1% vs 13%) but not reduced significantly as per the WHO-2013 criterion. It is, therefore uncertain whether multi-micronutrient food supplementation prevents gestational diabetes in the Indian context.

A systematic review evaluated the benefits of antenatal multiple micronutrient supplements on offspring 2.5-8.5 years after birth. The review included studies (n=1-4 for various outcomes) conducted in South East Asia. There was no evidence of any beneficial effect on the evaluated outcomes including surrogates of adult-onset cardio-metabolic diseases. The various outcomes investigated included childhood survival, growth, body composition, blood glucose, glycosylated haemoglobin, blood pressure, serum cholesterol, micro-albuminuria, renal volume, and respiratory and cognitive measures[24].

In 29 randomized controlled trials involving 11,487 pregnant women, the effect of lifestyle intervention on the risk of GDM was evaluated[25]. In the pooled analysis, either diet or physical activity or their combination resulted in an 18% (95%CI 5-30%) reduction in the risk of GDM (P=0.009). Subgroup analysis showed that such intervention was effective among women who received the intervention before the 15th gestational week (relative risk: 0.80, 95%CI 0.66-0.97), but not among women who received it beyond this window. The effect was similar across the BMI spectrum of the mothers (thin to obese). Two of the trials showed evidence of a lower maternal weight gain and a potential for reduction in the risk of pregnancy-induced hypertension. It was concluded that lifestyle modification during pregnancy, especially before the15th gestational week, can reduce the risk of GDM.

The concern about potential adverse effects of maternal exercise on the offspring has been addressed in systematic reviews[26,27]. There was no evidence of higher incidence of foetal loss, prematurity or small-for-gestational-age babies, but there was a 31% reduction in large-for-gestational-age new born babies, 20% fewer Caesarean section deliveries, and a 5-year insulin resistance (one trial). The mean birthweight of the new born babies was 30 grams lower (95% CI 4, 57 grams). In another review of 20 trials comprising 11,385 women, lifestyle interventions during pregnancy were not associated with differences in weight, length, BMI, or corresponding z-scores, in children aged 1 month to 7 years[27]. The findings remained consistent when the studies were stratified by maternal baseline BMI or other risk factors, intervention content and duration. It was concluded that prenatal lifestyle interventions do not influence childhood weight or growth; nevertheless, women should be encouraged to pursue a healthy lifestyle during pregnancy[27]. In the Indian context, pregnant women who are thin or those from lower socio-economic strata are generally advised rest rather than lifestyle modification and physical activity during pregnancy.

In a Vitamin D supplementation trial conducted in New Delhi, 1400 IU per week was given to term new-borns of low birth weight till 6 months of age[28]. The effects of the intervention on blood pressure and body composition were evaluated between 3 and 6 years of age. There was no evidence of any effect of Vitamin D supplementation on fat free mass, fat percentage, fat mass, or systolic and diastolic blood pressure.

Emerging evidence indicates that early taste preferences track well into later life. All infants display an innate preference for sugar, salt and high energy foods with a dislike or lower preference for sour or bitter foods, as in some vegetables. The period of complementary feeding, therefore, presents a golden opportunity for modulating these innate tastes by limiting the child's exposure to sugar, salt and high energy foods, while simultaneously offering bitter and sour foods repeatedly to develop these tastes. The former tastes form an integral part of the ultra-processed foods, which are known to increase the risk of NCDs, whereas the latter tastes form a component of fruits and vegetables, which protect against NCDs. It is difficult to initiate these taste preferences in pre-school children, as they have 'neophobia', namely, a tendency to reject unfamiliar tasting foods[29]. In this context, two[30-31] of the three randomized controlled trials from HMICs[30-32] indicate that sodium intake in infancy is positively associated with elevated blood pressure in the short term (6 months to 15 years) with average elevations of systolic blood pressure ranging from 2-5 mmHg.

Results from two more trials that studied the effects of primordial prevention efforts on adolescent blood pressure outcomes have been summarized[33]. These two trials were: (i) STRIP (Special Turku Coronary Risk factor Intervention Project) trial from Finland, and (ii) PROBIT (Promotion of Breast feeding Intervention) trial in Belarus. In the individually randomized STRIP trial, mothers/children were counselled from infancy right through to 15 years of age to consume healthy fats and more fruits, vegetables, and whole grains while reducing their intake of salt and sodium-rich foods. A decrease in systolic blood pressure of -1mmHg (-1.7, -0.2 mmHg) was observed at 15 years of age. Also, at 15-20 years of age, metabolic syndrome halved in the intervention group as compared to the controls (6-7% *vs* 10-13%)[34]. The STRIP trial concluded that ongoing and personalized dietary counselling lowered glucose and cholesterol levels, mitigated endothelial dysfunction and reduced the risk of metabolic syndrome. The PROBIT trial was a cluster randomized trial in which breast-feeding promotion was done in infancy and children were followed up till 11.5 years of age. There was no evidence of a beneficial effect on blood pressure in this trial.

A systematic review of interventions for childhood obesity in the first 1,000 days identified 26 completed and 47 ongoing trials, mostly from high- and middle-income countries, primarily focusing on anthropometric criteria, especially Body Mass Index[35]. Of the 26 unique identified interventions, nine were effective, but the effect sizes were small. A high-protein and nutrient-rich formula led to greater risks of obesity and fat mass at 5-8 years of age. A combination of diet, physical activity and sleep counselling in five trials showed a positive effect. Effective interventions were focused on individual or family-level behavioural changes through home visits, individual counselling or group sessions in clinical settings, and a combination of home and group visits in a community setting. It may be concluded that, even though the effect size between

1 and 10 years of age was small, obesity prevention interventions may have the greatest effect if begun early in life. A combination of individual, family-centred and community interventions focusing on several components including diet and physical activity are more likely to be successful.

A recent systematic review evaluated the effect of early-life randomized controlled nutrition interventions on long-term cardio-metabolic outcomes[36]. It included 33551 participants from 21 countries. Interventions were initiated as early as conception, and the longest went on until 7 years of age (except 1 study that ran from infancy to 20 years of age). The cohorts were followed up for between 3 and 73 years. The authors identified seven types of interventions (protein-energy supplements, long-chain PUFAs, single micronutrient, multiple micronutrients, infant and young child feeding, dietary counselling, and other) and four types of cardio-metabolic outcomes (biomarkers, cardiovascular, body size and composition, and subclinical/clinical outcomes). Most findings were null. In the intervention groups, fasting glucose was lower (0.04 mmol/L; 95% CI: −0.05, −0.02) in 15 studies, but BMI was higher (0.20 kg/m^2; 95% CI: 0.12, 0.28) in 14 studies. There was no evidence of effect for total cholesterol (12 studies) or blood pressure (17 studies). Ongoing and personalized dietary counselling was associated with lower glucose and cholesterol, better endothelial function, and reduced risk of metabolic syndrome. The timing of intervention mattered, with earlier initiation conferring greater benefit (improved lipid profile and marginally lower glucose concentration) as per the findings of two studies. The review concluded that maternal and child nutrition interventions should be evidence-based and tailored to specific populations to promote long-term cardio-metabolic health. Some futuristic interventions are under evaluation. These include designer diets depending on the child's genotype, new born and infants' gyms to build up muscle and improve the uptake of insulin, sleep kits and "poop" pills to transplant microbiome from NCD-free individuals.

Reorienting the ongoing programmes

India is currently witnessing a rapid escalation in over-nutrition-associated NCDs. Importantly, the phenomenon has its origins in infancy and childhood, and the related signals are seen in an alarmingly high proportion of children and adolescents at a national level, even among rural settings and socio-economically deprived segments. In the recently concluded Comprehensive National Nutrition Survey (2016-18), in 19143 participants of 5-19 years age, "metabolic obesity", characterized by the presence of at least one abnormal cardio-metabolic risk factor, was investigated[37]. Proportions with ≥1 abnormal "metabolic obesity" biomarker(s) (dysglycemia, dyslipidemia) were 56.2% in the entire dataset, 54.2% in thin (BMI-for-age <-2SD) and 59.3% in stunted (height-for-age <-2SD) participants. Among economically disadvantaged participants, triglyceride, glucose and High-Density Lipoprotein abnormalities were higher. It is, therefore crucial to prevent potential worsening of this situation through unintended consequences of some ongoing public health programmes, introduced at a time when under-nutrition and hunger were rife. The following three notable examples illustrate the urgent need for re-examining the prescribed food and energy-dense product supplementation in the first 1000 days.

The Integrated Child Development Services programme provides for Take Home Ration (THR) of 500 Calories per day for children from 6 month to 2 years of age. This quantum was based on the energy gap calculated from the Recommended Dietary allowance (RDA), which is intended to cover the needs of 97.5% of the population. However, the energy gap at the population level in the latest National Nutrition Monitoring Bureau survey, using the appropriate Estimated Average Requirement (EAR), is 250 Calories per day (Kurpad A, personal communication). Providing for supplementation up to double this energy requirement gap has potentially adverse implications, particularly in initiating or fuelling over-nutrition. The expense saved can be utilized for improving the quality (proteins, fruits and vegetables) of THR provided, which may be beneficial.

For severe acute malnutrition (weight-for-height <-3SD of WHO reference), supplementation with therapeutic foods or ultra-processed energy-dense product (Ready to Use Therapeutic Food) supplementation has been evaluated[38], and advocated to provide for supplementation of 175-200 Cal/Kg/day. However, considering the total energy requirement for a weight gain of 5-10 g/kg/day, as also the WHO recommendations[39], supplementation with 100-130

Cal/Kg/day are sufficient. It would be pragmatic, therefore, to reduce the Calorie supplementation, and provide these calories through food instead of energy-dense products. Further, the need for providing supplements to those with moderate acute malnutrition (weight-for-height <-2SD of WHO reference) must be carefully re-examined against the finding that, in apparently healthy children in India, the BMI is shifted to the left by ~1SD in comparison to the WHO reference[40], and similar thin children who become obese relative to themselves by ~0.5 SD, tend to develop impaired glucose tolerance or diabetes as adults[6].

The WHO recommendations on antenatal care for a positive pregnancy experience state that "in under-nourished populations, balanced energy and protein dietary supplementation is recommended for pregnant women to reduce the risk of stillbirths and small-for-gestational-age neonates"[41]. This recommendation is being misused for commercial promotion of energy dense products. Recent evidence from pregnancy cohorts[23, personal communication] indicates that the incidence of gestational diabetes is alarmingly high, ranging from 10-20% overall and 8-14% in undernourished women (BMI<18.5 kg/m^2). There is thus an urgent need for refining guidelines to accurately identify undersized pregnant women who will benefit from energy-dense or other nutrient supplements without escalating the risk of metabolic obesity and related diseases.

Concluding comments

In conclusion, there is limited evidence to dogmatically recommend effective interventions in the first 1000 days for prevention of adult-onset diseases; "one size does not fit all" and the interventions need specific tailoring for individuals. The effect size is quite modest with no "magical bullets" on the horizon. A combination of individual, family-centred and community interventions, focusing on several components including diet and physical activity, are more likely to be successful, especially if these begin early and continue over several years. Fortunately, most of the promising interventions are in concurrence with the clinical guidelines and public health programmes. However, moral and ethical considerations obligate evidence-based reorientation of a few programmes to prevent escalation of metabolic obesity and related diseases

The authors of this article are Prof. H.P.S. Sachdev, Senior Consultant, Paediatrics and Clinical Epidemiology, Sitaram Bhartia Institute of Science and Research, New Delhi; and Dr. Sumaira Khalil, Assistant Professor, Department of Paediatrics, University College of Medical Science, Delhi. The article is based on the C Ramachandran Memorial Lecture delivered by Prof. H.P.S. Sachdev on the Foundation Day of Nutrition Foundation of India, at New Delhi on 27.11.2020.

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NUTRITION NEWS

Nutrition Society of India will be organising the Gopalan Oration to be delivered by Dr Duggan in virtual mode on 12th July 2021 at 4.30 pm IST