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CHAPTER 18

Fetal Programming of Type 2 Diabetes Mellitus

K Kumaran, CS Yajnik

CURRENT STRATEGIES FOR PREVENTION OF TYPE 2 DIABETES MELLITUS

It is generally believed that individual susceptibility to type 2 diabetes mellitus (T2DM) has its roots in genes. The genetic susceptibility is thought to be exacerbated by lifestyle behaviors such as high energy and fat intake and reduced physical activity, leading to the development of the disease (Fig. 18.1). Of the known risk factors, obesity or excessive body mass index (BMI) is one of the most common features associated with T2DM.[1] The prevalence of obesity has been increasing in many populations.[2] Even in individuals who are not apparently obese, or meet definitions of obesity by western standards, there may be a high proportion of body fat relative to muscle mass (adiposity). The accumulation of body fat in the abdominal areas leads to higher diabetes risks.[3] This strong interrelation between obesity or adiposity and T2DM is now well recognized and together called "diabesity".[1]

Most of the current preventive strategies and recommendations to reduce the burden of T2DM focus mainly on reducing adult lifestyle risk factors in middle-aged individuals with pre-existing disease or risk factors. However, these measures can at best be termed secondary prevention and do not address the impact of the disease on future generations. Genetic research has so far also failed to provide any major breakthrough towards primary prevention. In order to stem the epidemic of T2DM, it is imperative to find etiologic clues that will help develop strategies to prevent the condition in unborn generations.

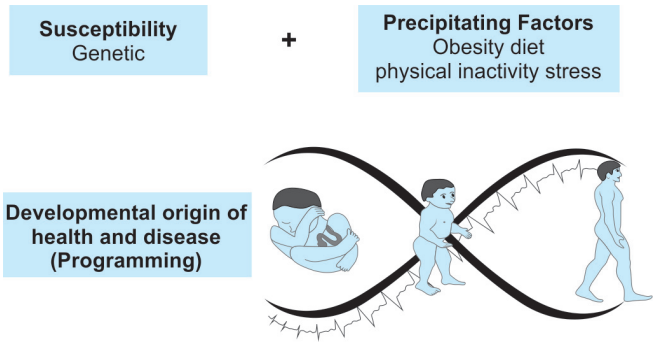


Fig. 18.1: Type 2 diabetes mellitus—the conventional dogma (genetic + lifestyle) and the alternative explanation (programming) for its etiology

PROGRAMMING HYPOTHESIS AND THE DEVELOPMENTAL ORIGINS OF HEALTH AND DISEASE

The most promising possibility for primary prevention comes from David Barker's programming hypothesis. He suggested that alterations in the nutritional supply during critical stages of intrauterine development permanently alter the structure and metabolism of the fetal organs (fetal programming).[4] The growing fetus depends on the mother for its nutritional needs, and therefore any disturbance in the maternal nutritional status or its supply to the fetus will adversely impact fetal growth. When there is a poor nutritional supply, the available nutrition is utilized for the growth of the fetal brain, which is vital for survival. This compromises the growth and functions of "less important" insulin sensitive organs like the pancreas, liver and skeletal

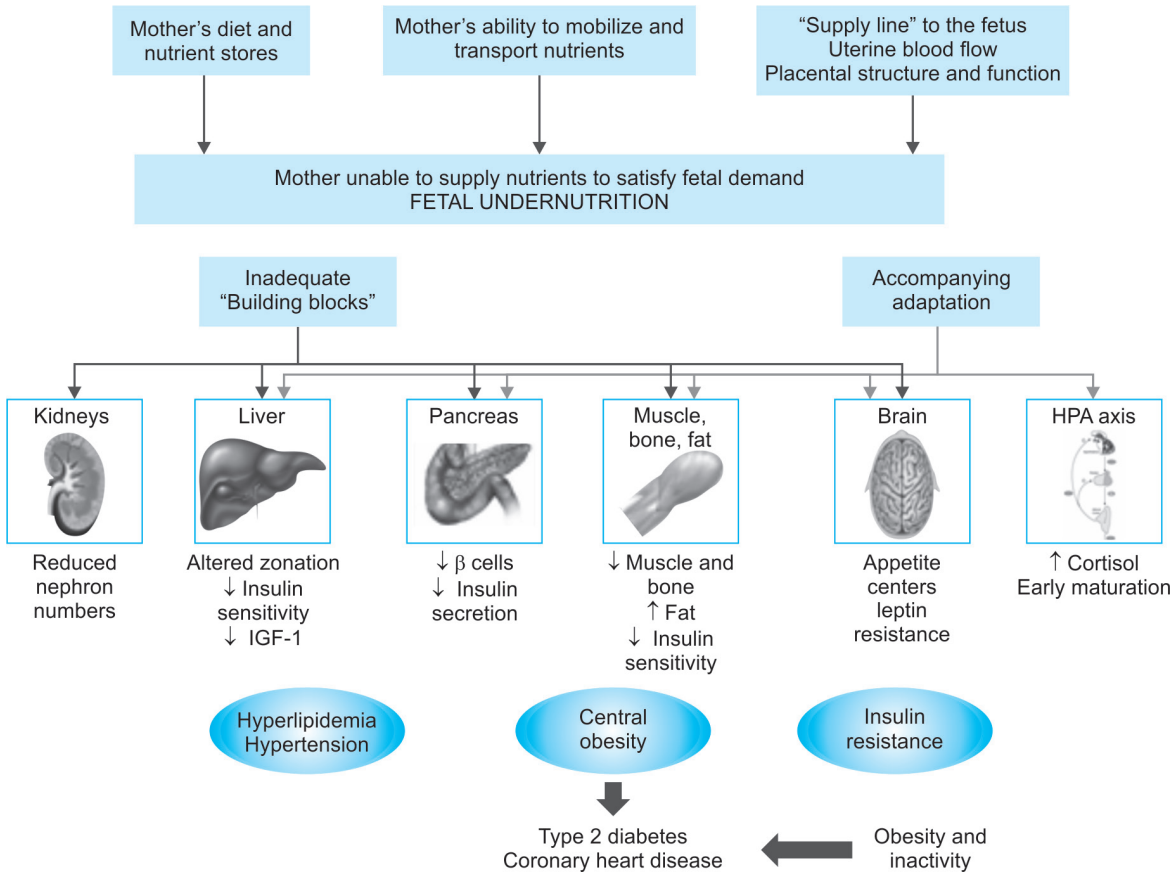


Fig. 18.2: Programming hypothesis—different pathways by which fetal undernutrition influences risk of adult chronic noncommunicable diseases; inadequate maternal nutrition or disturbances in maternal ability to transport nutrients to the growing fetus leads to fetal undernutrition. The fetus adapts by altering the structure and metabolism of its organs and tissues; these adaptations result in permanent changes which "program" the development of risk factors for noncommunicable diseases in later life
IGF: Insulin-like growth factor

muscles. It is suggested that these organs "fail" to function optimally in later life leading to disease. These individuals have higher adiposity, insulin resistance and increased risk of T2DM, similar to obese individuals, but at lower levels of BMI (Fig. 18.2).

Early work in this field of research dates to the 1970s when Forsdahl demonstrated a significant positive correlation between arteriosclerotic heart disease in middle-aged adults and the prevailing infant mortality rates during their childhood in twenty counties in Norway.[5] He attributed this finding to poor living conditions in childhood followed by affluence in later life. Subsequently, Barker and colleagues in Southampton showed a positive significant correlation between coronary heart disease (CHD) mortality rates in local authorities in England and Wales in the 1970s and corresponding infant mortality rates in the earlier part of the century.[6] There was a strong relationship with neonatal mortality also, and as low birth weight was the most common cause of neonatal mortality in the early 1900s, Barker suggested low birth weight as the link between neonatal and infant mortality and adult CHD. The group then moved on from ecological studies to studies on individuals and demonstrated that the prevalence of CHD in Hertfordshire in the UK was highest in adults who had the lowest birth weights.[7] Further work showed similar findings for T2DM and impaired glucose tolerance (Fig. 18.3).[8] The relationship with birth weight was continuous and graded, without any threshold. These findings have subsequently been replicated in several parts of the world including developing countries.[9-12] It was however soon apparent that birth weight was not the major issue, and in fact, both low and high birth weights were associated with later T2DM indicating a U-shaped relationship.[13] It was suggested that birth weight was a marker of a multitude of exposures during fetal life, and not one single exposure.

Subsequently, postnatal growth has also been shown to be associated with risk of T2DM; individuals with the highest risk of T2DM are those who had low birth weight but high current BMI.[11,14] Thus, the fetal programming

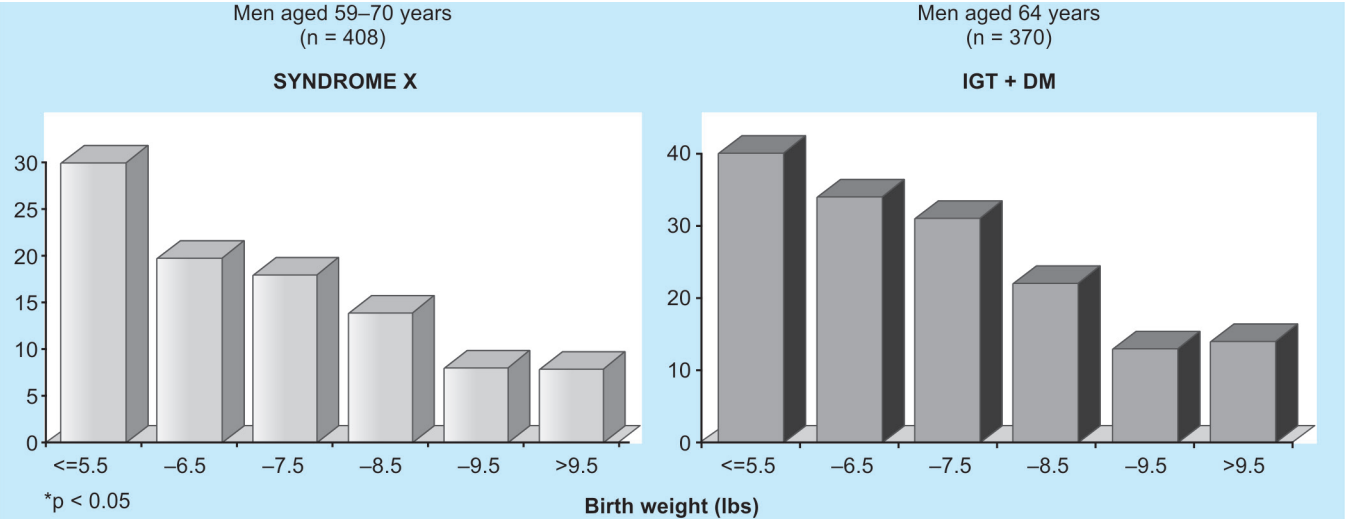


Fig. 18.3: Birth weight and type 2 diabetes mellitus and impaired glucose tolerance in Hertfordshire men aged 60–70 years; as birth weight increases, the prevalence of type 2 diabetes mellitus (T2DM) and impaired glucose tolerance (IGT) decreases

Source: Hales CN, Barker DJP, Clark PMS, et al. Fetal and infant growth and impaired glucose tolerance at age 64 years. BMJ. 1991;303:1019-22.

hypothesis was expanded to include postnatal factors and is now referred to as the "developmental (or early) origins of health and disease" hypothesis (DOHaD).

The DOHaD hypothesis is strongly supported by animal studies showing that maternal nutritional status can influence disease outcomes in the offspring. Obesity, hypertension and diabetes can be programmed by under- or overnourishing the fetus, by changing the pregnant mother's diet.[15-17]

The fetal insulin hypothesis offers an alternative explanation to the association between birth weight and diabetes and suggests that low birth weight, insulin resistance and ultimately T2DM are all linked through genetic factors.[18] However, a study examining the associations between birth weight differences and glucose tolerance in monozygous and dizygous twins suggested that shared genetic determinants for birth weight and glucose tolerance were neither very prevalent nor powerful.[19] Allan[illegible]g paper Birth weight is only partly determined by genetic factors and the relative importance of genes and environment has been an active area of research over the past 2 decades. It is therefore likely that an interaction between genetic and environmental factors influences not only fetal growth but also the development of T2DM. Rach[illegible]eathy.

DOHaD Work in India

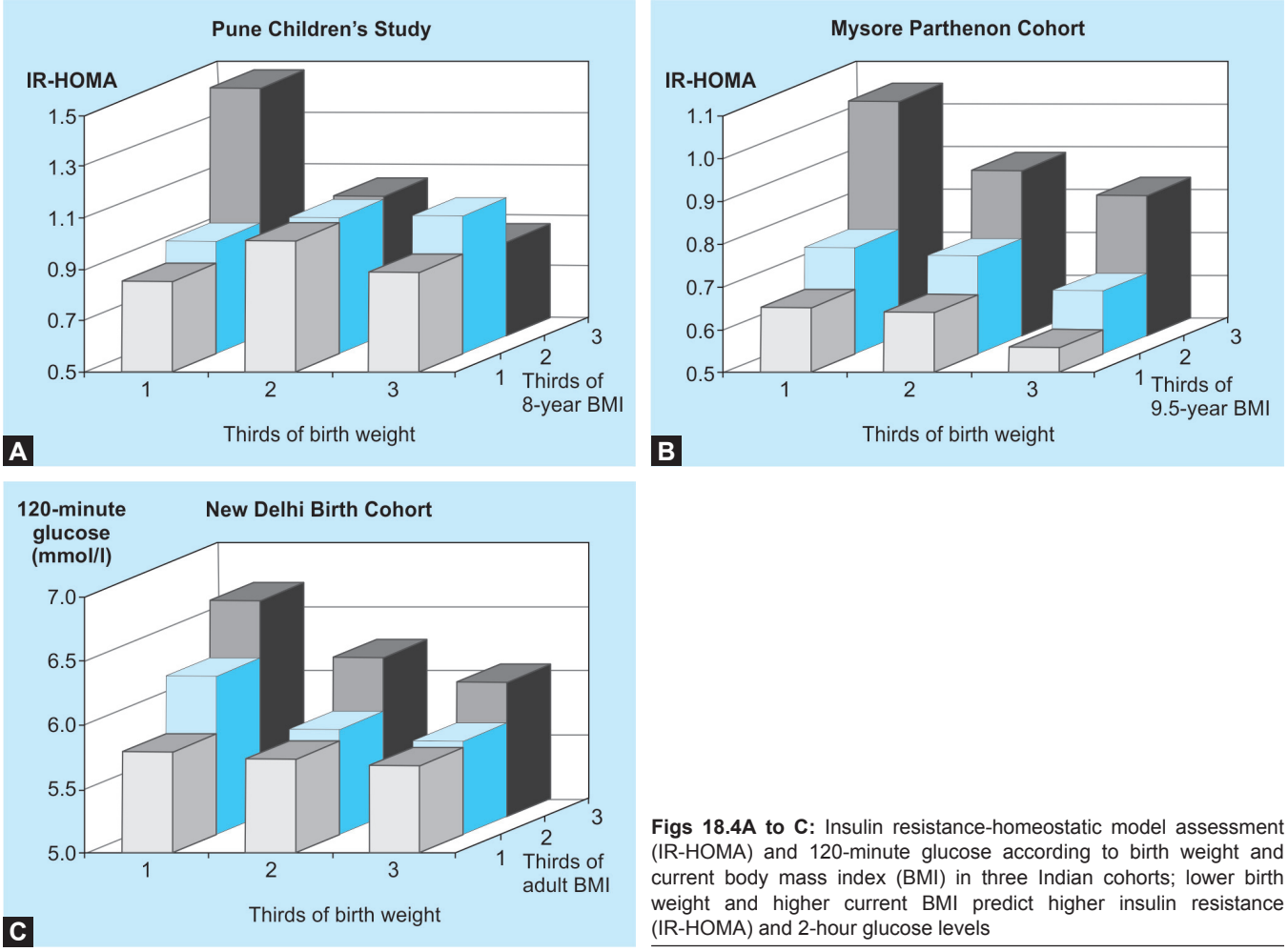
Consider chan[illegible] position

The DOHaD hypothesis may be particularly applicable to the Indian situation with a high burden of maternal malnutrition and low birth weight.[20] India is also considered one of the diabetes capitals of the world and is estimated to have the highest number of people with T2DM by 2030 (10.1 crores).[21] More importantly, it will disproportionately affect the young and economically productive age groups resulting in significant social and economic consequences. Indian diabetic patients are known to be younger, shorter and thinner compared to western patients but tend to be centrally more obese (as measured by waist-hip ratio), with greater subcutaneous fat and insulin resistance. Metabolic syndrome is common in Indians, and occurs at a young age and low BMI compared to white Caucasians, attributed to Indians' typically low lean mass and high percentage body fat (thin-fat Indian phenotype).[22]

The DOHaD work in India was sparked off by the visit of David Barker and Caroline Fall in the early 1990s. They established collaborations with a group of interested researchers after contacting approximately 300 hospitals across India and initial studies in India were set up in Pune and Mysore. This collaboration led to the formation of the Society for the Natal Effects of Health in Adults (SNEHA) which has grown in strength and is currently the longest established "fetal origins" society. This group organized the first world congress on fetal origins of disease at Mumbai in 2001. The growing work in this field across the world led to the formation of the International DOHaD Society with a world congress organized every 2 years.

DOHaD research in India date back to 1991 when a study in Pune showed that children with lower birth weights had higher insulin and glucose levels.[23] At 8 years of age, the children of lower birth weight who had the

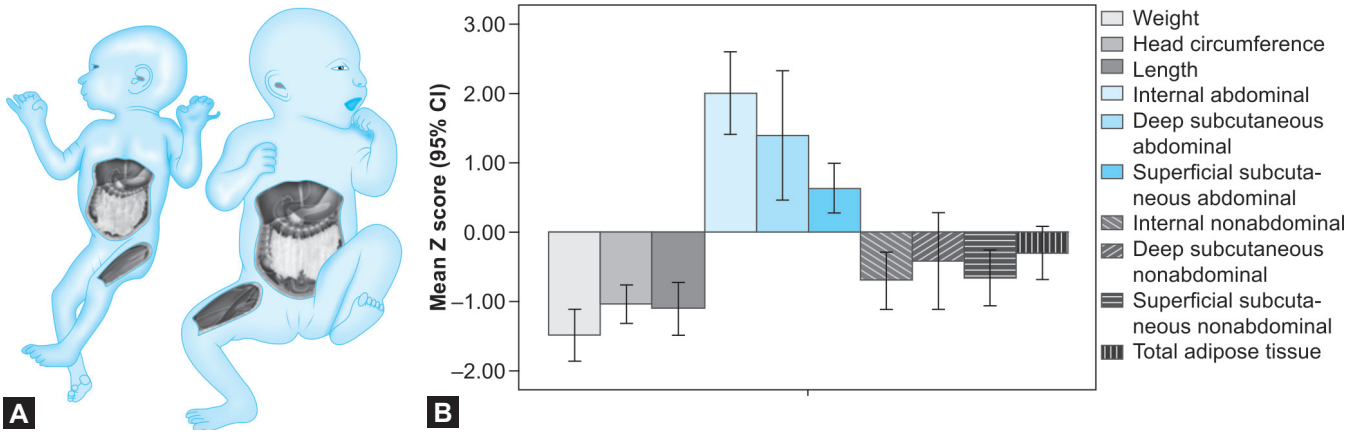
highest current weight had higher insulin resistance.[24] In 40–60 year old adults in Mysore, the risk of CHD was higher in those who had been small at birth as measured by birth weight, birth length and head circumference at birth.[25] In Mysore however, the prevalence of T2DM was higher in those with a greater ponderal index (a ratio of birth weight to birth length; heavier weight and shorter length leads to greater ponderal index).[10] This led to the suggestion that these heavier babies may have been offspring of diabetic mothers and that further work was necessary to look beyond birth size measurements. Younger adult cohorts with detailed childhood growth data were retraced in Delhi and Vellore; these studies demonstrated that lower birth weight followed by higher childhood weight gain were associated with adult insulin resistance and glucose intolerance.[26,27] In Delhi, those with impaired glucose tolerance or T2DM had a low BMI up to the age of two years, followed by early adiposity rebound (the age after infancy when body mass starts to rise) and an accelerated increase in BMI until adulthood. However, none of these subjects were obese at the age of 12 years despite this increase in BMI in childhood.[24] Conditional growth analysis was performed to separate out associations of linear growth and weight-for-height gain (relative weight gain) with adult body composition and risk of CHD and T2DM. Faster linear growth throughout childhood and faster relative weight gain in the first 6 post-natal months were associated more strongly with adult lean mass than fat mass (unpublished data).[28] In contrast, faster relative weight gain after 11 years was associated more strongly with adult fat mass, and with a higher risk of impaired glucose tolerance and T2DM. The studies in India therefore confirmed western findings that lower birth and infant weight, followed by rapid childhood or adolescent weight gain are associated with adiposity, insulin resistance and glucose intolerance in later life (Figs 18.4A to C).



Figs 18.4A to C: Insulin resistance-homeostatic model assessment (IR-HOMA) and 120-minute glucose according to birth weight and current body mass index (BMI) in three Indian cohorts; lower birth weight and higher current BMI predict higher insulin resistance (IR-HOMA) and 2-hour glucose levels

All these initial studies were retrospective, based on obstetric birth records. These were followed by setting up of new prospective cohorts in Pune and Mysore, collecting detailed maternal data and following up the children at birth and into childhood and adolescence. The Pune Maternal Nutrition Study was the first ever study in the developing world to prospectively study the effects of maternal nutrition (even before conception) on the cardiovascular risk of the offspring. The study recruited married nonpregnant women in six villages near Pune consisting mostly of subsistence farming communities in a drought-prone area. Anthropometry (height, weight, circumferences and skinfolds) was recorded every 3 months. Women missing two successive periods underwent an ultrasound examination to confirm pregnancy and assess gestational age. During pregnancy, information was collected on socioeconomic status, dietary intake and physical activity. Anthropometry, glucose and insulin, and lipids were also measured. At birth, newborn measurements included birth weight, length, head circumference and skinfolds. These children have subsequently been followed up every 6 months for anthropometry and detailed cardiometabolic measurements at 6 and 12 years. This study for the first time demonstrated a link between maternal micronutrient intake and offspring size; mothers who had the most frequent intake of green leafy vegetables and who had the highest red cell folate levels gave birth to the heaviest babies.[29] Interestingly, there were no relationships with total energy or protein intake. The study also demonstrated that the "thin-fat" Indian phenotype was present at birth and not a consequence of post-natal life as previously presumed (Figs 18.5A and B).[30] When the Pune babies were compared to babies born in UK, the Indian babies were 700 gm lighter but had comparable subscapular skinfold compared to the English babies. Further studies using whole body magnetic resonance imaging (MRI) in the newborn confirmed that Indian babies have higher intra-abdominal fat at birth compared to the English babies,[31] and also that they have higher insulin levels in the cord blood.

Follow-up work demonstrated a direct association between maternal micronutrient levels and risk factors for diabetes in the children. Higher folate concentrations in the mothers during pregnancy predicted higher adiposity in the offspring at 6 years.[32] Vitamin B12 deficiency in the pregnant mothers was associated with increased insulin resistance in their children at 6 years of age; the highest insulin resistance was in children born to mothers with low vitamin B12 and high folate during pregnancy (Fig. 18.6). The 1-carbon metabolism cycle, a network of inter-related biochemical reactions that involve the transfer of 1-carbon groups from one compound to another, is crucial for cell growth and differentiation. Both vitamin B12 and folate (along with other B group vitamins) are coenzymes for several of these reactions. Insufficiency or imbalance of these micronutrients can cause an increase in homocysteine levels, which has been linked to higher CHD risk.[33] In the Pune study, lower vitamin B12 was also associated with higher homocysteine, which predicted lower birth weight.[34] These findings were particularly significant in a context where the population was folate sufficient (0.2% deficiency) but vitamin B12 deficient (~70% deficiency).



Figs 18.5A and B: (A) The "thin-fat" Indian baby; (B) Figure showing the Indian babies at birth had considerably lower birth weight, were shorter and had smaller head circumferences but were relatively adipose compared to UK babies[30,31]

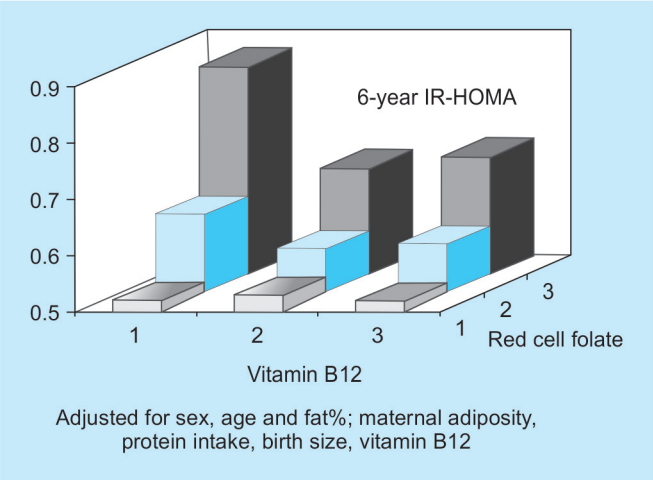


Fig. 18.6: Maternal vitamin B12, folate and insulin resistance in the offspring; children whose mothers had low vitamin B12 and high folate levels during pregnancy had the highest insulin resistance at 6 years[32]

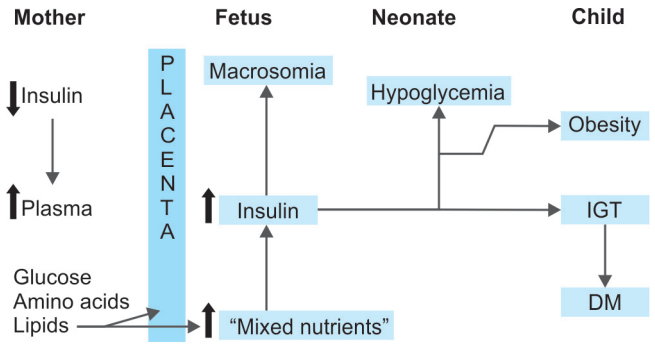


Fig. 18.7: A diagrammatic representation of the Pedersen and Freinkel hypotheses;[36,37] transfer of maternal fuels during pregnancy influence newborn size as well as the future development of risk factors for type 2 diabetes mellitus (T2DM)

Fetal overnutrition (due to maternal obesity and hyperglycemia) may also program the offspring for T2DM. These babies are born "larger", and develop early obesity, central obesity, higher insulin resistance and impaired glucose tolerance and T2DM similar to the offspring of undernourished mothers. The Pima Indian studies provide support that the association between high birth weight and T2DM may be linked through maternal diabetes.[35] Maternal diabetes mellitus [gestational diabetes mellitus (GDM)] provides classical example of fetal programming by intrauterine oversupply of fuels including glucose, lipids and amino acids. Pedersen proposed that the transfer of excess maternal glucose in a diabetic pregnancy stimulates fetal islets to produce fetal hyperinsulinemia which leads to macrosomia.[36] Freinkel suggested that a "mixture" of maternal nutrients (glucose, lipids and amino acids) affects not only fetal growth and development but also influences risk of future obesity, diabetes and neurocognitive development (fuel-mediated teratogenesis) (Fig. 18.7).[37] Though the mechanisms are poorly understood, the inheritance of genes responsible for both obesity and GDM has been suggested as a cause.[38] However, it has been shown that offspring born to diabetic mothers had higher rates of obesity and T2DM compared to the offspring born before the diagnosis of the mother's diabetes.[39] These findings suggested that it is the intrauterine diabetic environment, rather than genes that predicted offspring diabetes in this population. The Mysore Parthenon Study was specifically set up to study the long-term effects of GDM on the offspring. The study recruited women during pregnancy in a charitable hospital which attracts patients from all strata of society. Measurements during pregnancy included anthropometry, glucose and insulin, and lipids. This study showed that the children born to GDM mothers were larger at birth and had higher subcutaneous adiposity compared to the newborns of non-GDM mothers.[40] The difference in adiposity continued to increase throughout childhood, and at 9 years, the children of GDM mothers had higher glucose and insulin concentrations and higher insulin resistance (Fig. 18.8).[41] Maternal vitamin B12 deficiency was also associated with an increased risk of GDM and subsequent T2DM in the mother.[42]

Thus, the prospective cohorts in India have enabled the identification of nutritional and metabolic factors in the mothers that predict fetal growth and later outcomes in their offspring.

MECHANISMS OF NUTRITIONAL FETAL PROGRAMMING

Findings from across the world have now demonstrated that an individual's fetal, infant and childhood nutritional history influences their adult risk of T2DM. In women, their nutritional and metabolic status influences fetal nutrition and the birth size, body composition, and risk of T2DM in the next generation. The possible mechanisms are still poorly understood. It has been suggested that permanent structural changes in an organ due to suboptimal conditions during a critical period of development[43] may result in T2DM (e.g. the permanent reduction in beta cell mass in the pancreas).

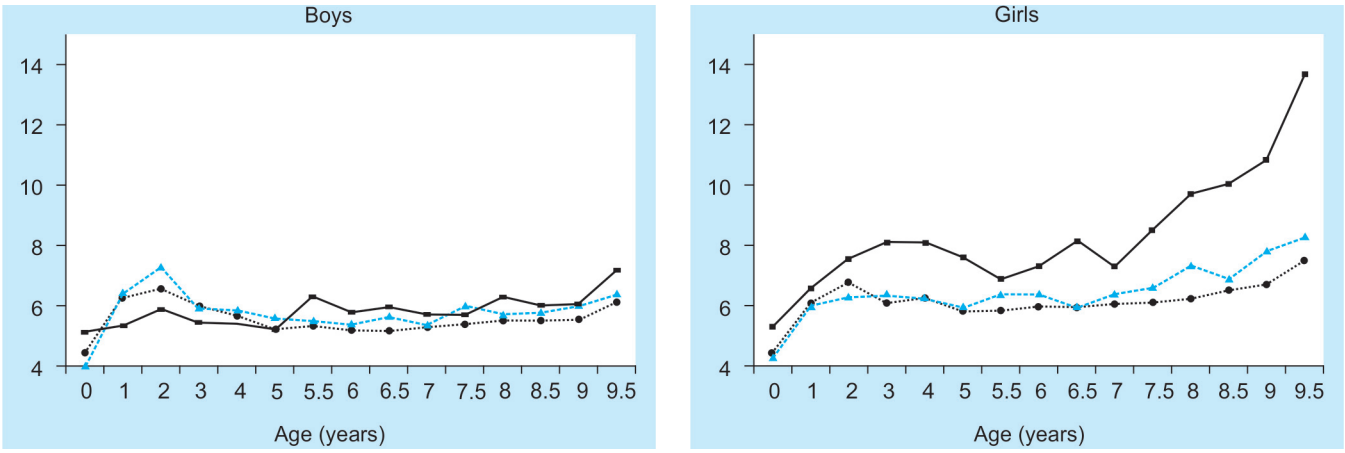


Fig. 18.8: Median subscapular skinfold thickness (mm) for offspring of diabetic mothers (ODM), offspring of diabetic fathers (ODF) and controls 0–9.5 years;[41] offspring of diabetic mothers had greater skinfold thicknesses suggestive of subcutaneous fat through early childhood
(Continuous lines with black squares: offspring of diabetic mothers (ODM); long-dashed lines with cyan triangles: offspring of diabetic fathers (ODF); short-dashed lines with black circles: Control offspring. P for difference between ODM and controls was significant (<0.05) at birth for boys, and all time points, except 1-year for girls.)

However, more recent research suggests these effects may act through "epigenetic" mechanisms that alter expression of genes without altering the base sequence (i.e. change in phenotype independent of change in genotype). The most likely mechanisms may be through methylation of deoxyribonucleic acid (DNA) and modification (acetylation) of histones; both processes modify gene expression and could result in different phenotypes for the same genotype.[44] Vitamin B12 and folate are both methyl donors and therefore may influence epigenetic methylation reactions, which is well shown in many animal models. Animal studies have shown that epigenetic changes during early development may be an important mechanism linking early nutrition to later health. The normal process of demethylation and remethylation of fetal DNA in early gestation is nutritionally sensitive. Nutritional interventions in pregnant mothers (mostly using methyl donors in 1-carbon metabolism such as vitamin B12, folic acid, betaine and choline) induce permanent changes in DNA methylation, gene expression, and later phenotype in the offspring.[45-47]

Dual Burden in India

In populations undergoing rapid economical and demographic changes, both maternal undernutrition and overnutrition coexist creating a double burden of disease. India is still burdened with widespread maternal undernutrition and low birth weight. At the same time, more and more women exposed to urban lifestyle are becoming obese and glucose intolerant during pregnancy. The combination of poor fetal growth followed by rapid weight gain in later life is most evident in India's urban populations as they are increasingly exposed to a calorie rich diet with high saturated fats, sugar and salt as well as reduced levels of physical activity. However, rural areas are also rapidly urbanizing. Given their greater early life undernutrition, we would expect the consequences to be worse in these communities as urbanization increases.

The DOHaD studies in India suggest problems with both undernutrition and overnutrition. Maternal undernutrition is associated with low birth weight and stunting in the children, who develop metabolic incompetence in the form of lower lean mass, poorer cognitive function and insulin resistance (nutrient-mediated teratogenesis). If fetal undernutrition is followed by rapid childhood weight gain, the result is excess adiposity, a further increase in insulin resistance and adult cardiometabolic disease. In women, this leads to gestational diabetes, which exposes the fetus to "fuel-mediated teratogenesis" and exacerbates diabesity in the next generation (Fig 18.9).[48]

IMPLICATIONS FOR PREVENTION AND POLICY

Current recommendations to reduce the burden of T2DM do not address the impact on the next generation. It is vital that measures to combat T2DM focus on the health

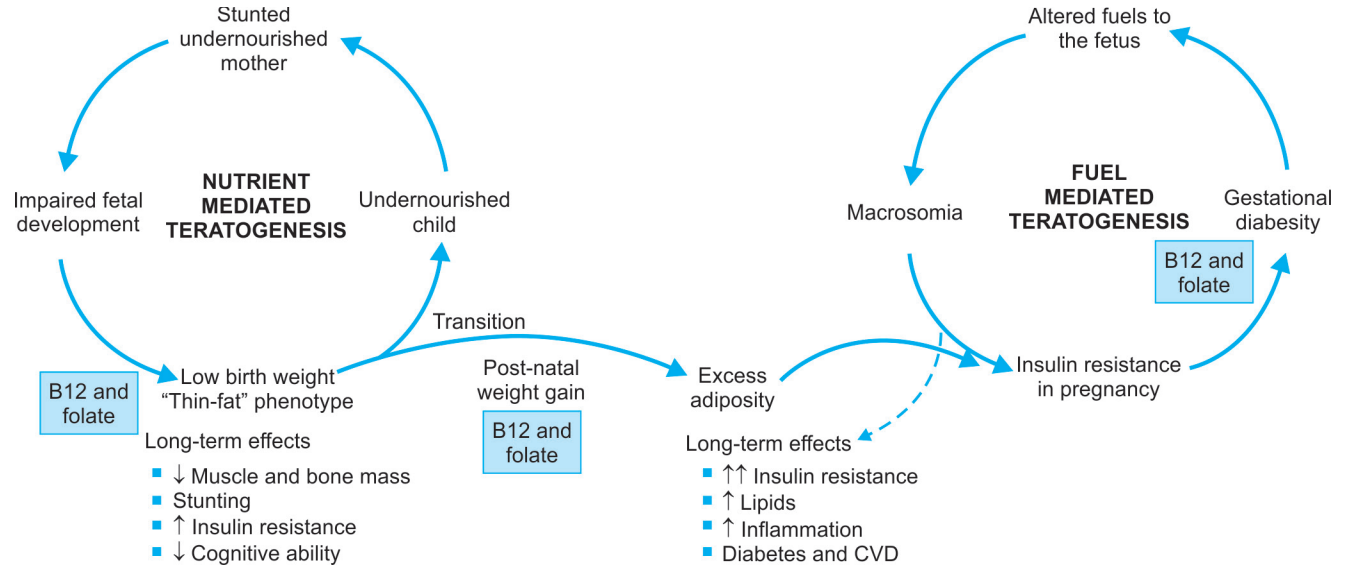


Fig. 18.9: Nutritional transitions causing disease—double burden of under and overnutrition. Both undernutrition and rapid transition to an overnourished state influence the future risk of developing type 2 diabetes mellitus (T2DM); preventive measures should address breaking the cycle at an earlier stage[48]

and nutrition of young women before they become pregnant so that the incidence of diabetes in future generations will be minimized. The only sustainable way of tackling the epidemic is to protect the young and stop the intergenerational transmission of susceptibility to diabetes. The DOHaD hypothesis suggest several potential ways to break this intergenerational transmission: improving the nutrition of pregnant women, intervening in adolescence or the periconceptional period, or optimising nutrition to achieve good linear growth in infancy and/or prevent excessive childhood adiposity.

However, evidence in humans is largely limited to observational studies, using birth weight or extreme nutritional situations (e.g. famine) as exposures, with little information on maternal nutrition. Some recent studies have followed up children whose mothers took part in nutritional supplementation trials. Indian adolescents whose pregnant mothers were supplemented with energy and protein had lower insulin resistance and arterial stiffness,[49] and Nepali children whose mothers were supplemented with multiple micronutrients had lower blood pressure.[50] In contrast, supplementation of Gambian women with energy and protein had no effect on the children's body composition or blood pressure.[51] However, these trials all started in mid-pregnancy, after important early-gestation processes such as epigenetic programming, placentation, and fetal organogenesis. Epigenetic studies applied to DOHaD in humans are limited but maternal nutrition has been shown to influence gene-specific differences in DNA methylation at birth and in later life and DNA methylation at birth has been related to later adiposity.[52-54]

Based on Indian research findings, the field of DOHaD in India has now moved on to intervention studies with two randomized controlled studies in Mumbai and Pune. The trial in Mumbai involved food based micronutrient supplementation of women before and during pregnancy; the study is now complete and results are being analyzed. The Pune trial which has just commenced involves offering preconceptional vitamin B12 supplements in capsule form to adolescents. The trial offers a unique opportunity to investigate not only the effects of maternal supplementation on offspring health, but also examine epigenetic changes in the offspring. The results of these trials will have significant implications for public health policy in India. If successful, they offer, for the first time, a primordial prevention approach to reduce and halt the epidemic of T2DM in India.

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