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The Story of the hungry Indian foetus

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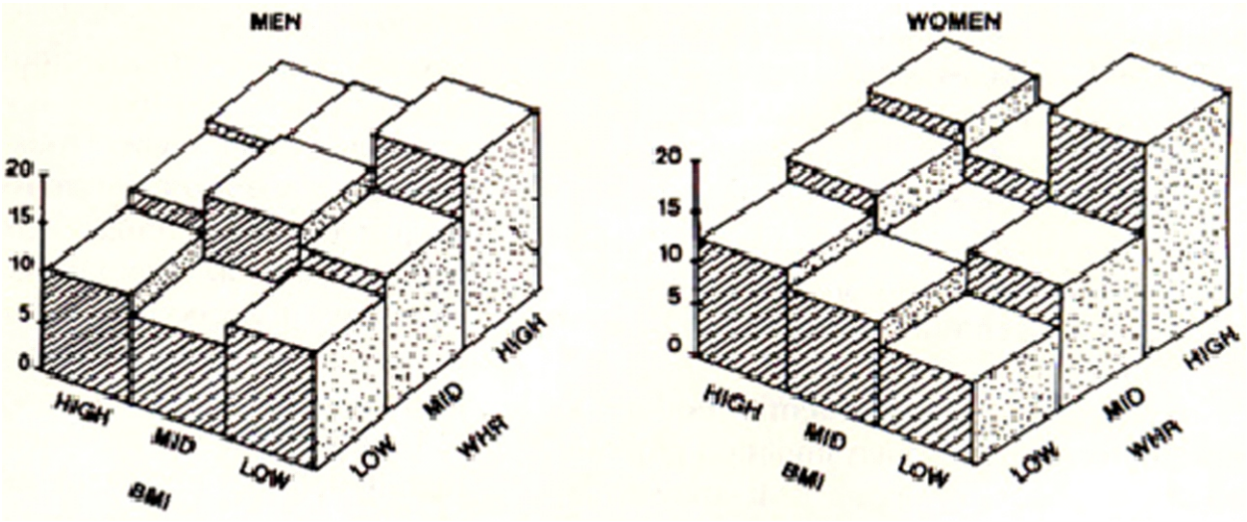
Worldwide, the prevalence of diabetes in adults has progressively increased from 4.7% in 1980, to 5.1% in 2003, to 6.0% in 2007[1] and 8.8% in 2017 as reported by the International Diabetes Foundation[2]. India has also seen a parallel rise in the incidence of diabetes. A comparison of two surveys in Tamil Nadu (conducted using similar methods) ten years apart (2006 and 2016), reported that diabetes prevalence in persons 18-65 years of age had increased significantly during the decade in a city (from 18.6% to 21.9%), in a town (16.4% to 20.3%), and in peri-urban villages (9.2% to 13.4%)[3].

Traditionally, diabetes was considered as a disease of the affluent and a person's susceptibility to it was attributed to having the thrifty genotype[4]. This genotype was thought to have evolved over millions of years out of periodic availability of food ('famine or feast') to help store calories (as body fat) to tide over the famine. It was suggested that with regular availability of food in modern times, the genotype produces obesity and led to diabetes. The precipitating factors proposed were rapid urbanization, unhealthy diets and increasingly sedentary lifestyles. This was evident as early as 1985 in a Southall survey which showed that migrant Indians had a much higher prevalence of diabetes as compared to local Europeans[5]. In recent times, however, it is apparent that people of lower socio-economic status are also increasingly being affected, and developing countries carry approximately 80% of the burden of diabetes, with China and India being the world's diabetes capitals[2]. A recent population-based ICMR-INDIAB study in 15 states of India reported the overall prevalence of diabetes at 7.3% and pre-diabetes at 24.7% (ADA criteria)[6]. The interesting finding was that in some of the states, the prevalence was higher in the urban poor as compared to the higher income group. The Indian Global Burden of Disease (GBD) report 2017, compared literature-reported diabetes prevalence in the years 1990 and 2016 and calculated the increase in diabetes burden over 25 years. The remarkable finding was that the highest increase in diabetes prevalence was in the states which have suffered financial, geographic or socio-political difficulties over many decades. Today, developing countries face a 'double burden' of malnutrition: persistent problems of undernutrition including low birth weight, stunting and infections, at the same time as increasing prevalence of obesity, diabetes and other non-communicable diseases (NCDs). It appears that rapid socioeconomic development is not well tolerated by populations which faced deprivation in the past[7]. These facts have generated interest to investigate if non-genetic factors also contribute to increased susceptibility to diabetes and other NCDs.

We have investigated the characteristics of diabetes patients in India since the 1980's. In the Wellcome Diabetes Study we described that, compared to Europeans, Indians are diagnosed with the disease at a younger age, the patients have a lower BMI but greater central obesity, and have higher insulin resistance (Fig1). The population was divided by tertiles of BMI and waist-to-hip ratio (WHR). In Indians central rather than generalised obesity was related to hyperglycaemia. The highest plasma glucose concentrations were in those with a low BMI but high waist-hip ratio (WHR), thus highlighting that central obesity is more contributory to hyperglycaemia than generalised obesity in these 'lean' diabetic patients[8]. Further comparisons showed that Indians have a higher body fat percentage {measured either by fat-fold thickness measurements or by dual-energy x-ray absorptiometry (DXA)} at a given BMI as compared to their European counterparts, giving rise to the concept of a 'thin-fat Indian phenotype'[9]. This hypothesis was popularised by a frequently-cited illustration published in the Lancet, called the 'Y-Y paradox' (Fig 2). It shows that an Indian has twice the adiposity (body fat)percentage as a British counterpart with identical BMI[10]. Many proposed that this is due to genetic

CONTENTS

Fig 1 BMI and waist hip ratio and insulin resistance in Indian men and women



differences but there was little proof.

On the background of the thrifty genotype hypothesis, the extraordinary study of Hales and Barker showed that low birth weight was a risk factor for type 2 diabetes and NCDs, independent of adult BMI[11]. This was called a 'thrifty phenotype' originating during foetal and infant life, and it spotlighted early life poor growth as precursors of diabetes. It focused attention on environmental rather than genetic drivers of susceptibility to NCDs. The thrifty phenotype hypothesis reduced the period of exposure to 'deprivation' to only one or a few generations rather than millennia. It also focussed attention on gene-environment interaction and gene expression ('epigenetics') as an additional basis for susceptibility to disease. The thin-fat phenotype provided a body composition aspect to the overall hypothesis of the thrifty phenotype.

After a meeting with Prof. David Barker, we started the Pune Children's study (PCS) to investigate the thrifty phenotype hypothesis in Indians. Our cohort comprised children born in the KEM Hospital, Pune, India between 1987 and 1989. We studied these children at 4 years of age to measure their body size, glucose tolerance (oral glucose tolerance test, OGTT) and other cardiovascular risk factors. We found that lower birth weight was associated with higher glucose and higher insulin concentrations, suggestive of insulin resistance[12] extrapolating to higher risk of diabetes in the future. These observations supported the thrifty phenotype hypothesis in Indians, and we decided to continue the follow up of these children (Fig 3). At 8 years of age, we found that, in addition to the association of lower birth weight with higher levels of diabetes and CVD risk factors (blood pressure and lipids) there was an interesting interplay between birth weight and 8-year weight (Fig4)[13]. The highest levels of blood glucose and other risk factors for diabetes and CVD were found in those children who were born small but had grown big. This challenged the conventional wisdom in paediatric practice which advised promoting extra growth in small babies to make them 'normal'. Our results suggested that such a situation was associated with increased risk of NCDs. After initial disagreements, the paediatricians now accept the dangers of rapid 'catch up' growth in growth-retarded babies, and there is a general agreement to avoid such interventions. We have followed these children at 21 years of age. By tracking body size and cardio-

Fig 2 BMI and Body fat in Caucasians and Indians

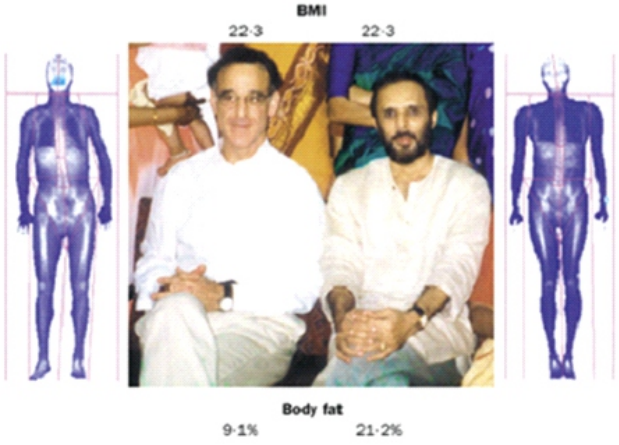


Fig 3 Association between birth weight, glucose and insulin concentrations at 4 years of age

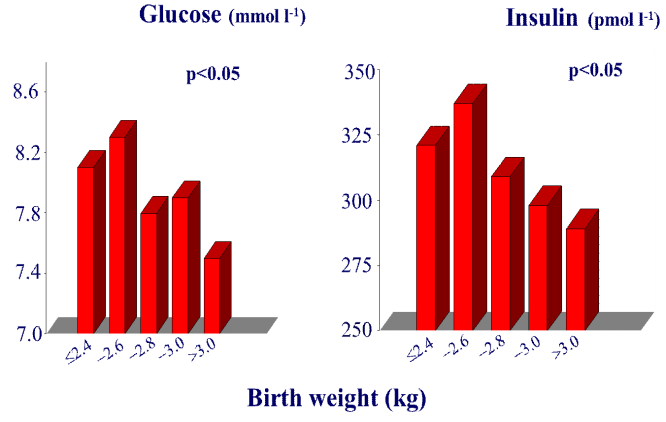


Fig 4 Mean level of insulin resistance (HOMA-R) in children at vear by tertiles of their birth weight and 8 year weight

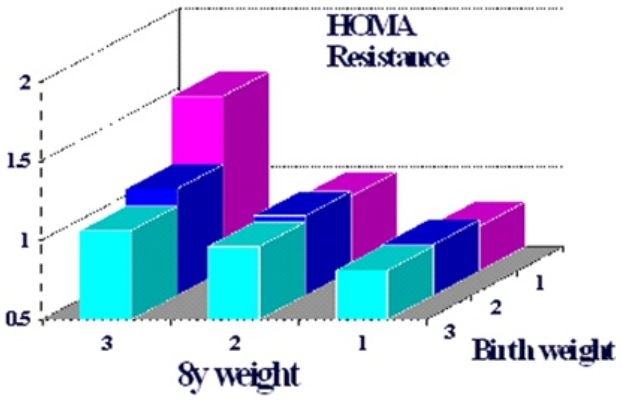
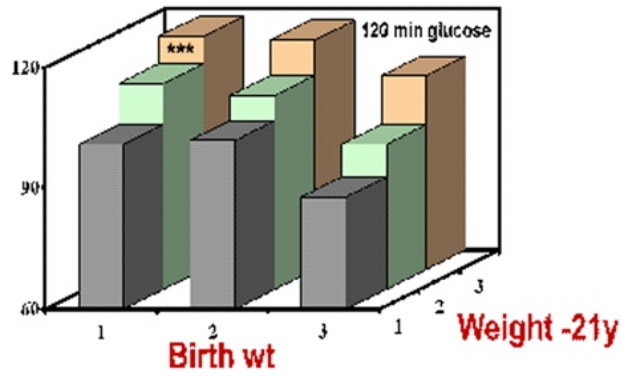


Fig 5 Mean level of 120 min glucose (OGTT) in children at 21 year by tertiles of their birth weight and 21 year weight



metabolic risk factors from childhood to early adult age we found an association between rapid gain in weight in childhood with adult adiposity and increased risk of NCDs (Fig 5)[14]. The role of 'mismatch' between intra-uterine and post-natal growth in predisposing to diabetes was also highlighted in the New Delhi Birth Cohortstudy which commenced in the late 1960s. Individuals with diabetes and pre-diabetes at 28 years of age had been born small, remained small for age till 2 years of age, and then showed a progressively more rapid increase in BMI as compared to those who did not become diabetic later. None of these participants were obese, but merely putting on weight at a very rapid rate in later childhood as compared to earlier childhood was a strong risk factor for cardio-metabolic disturbances[15]. A follow–up of individuals born in the Holdsworth Hospital in Mysore also showed that lower birth weight was associated with increased risk of CVD in later life[16]. The inferences as regards the future risk of diabetes were less clear.

Having established the role of small size at birth with increase in susceptibility to diabetes and CVD, we investigated the factors regulating intrauterine growth of Indian babies. We set up the 'Pune Maternal Nutrition Study' 1993 (PMNS), a prospective pre-conception cohort in 6 villages near Pune to study the association between maternal nutrition and foetal growth, with a plan of long-term follow up to study the evolution of cardio-metabolic risk factors (Fig 6). It is the first pre-conception cohort,with data on maternal pre-pregnancy size and socio-economic factors, and pregnancy data relating to nutrition, physical activity, biochemistry

Fig 6 Cohort profile of Pune Maternal Nutrition Study from 1993-2019

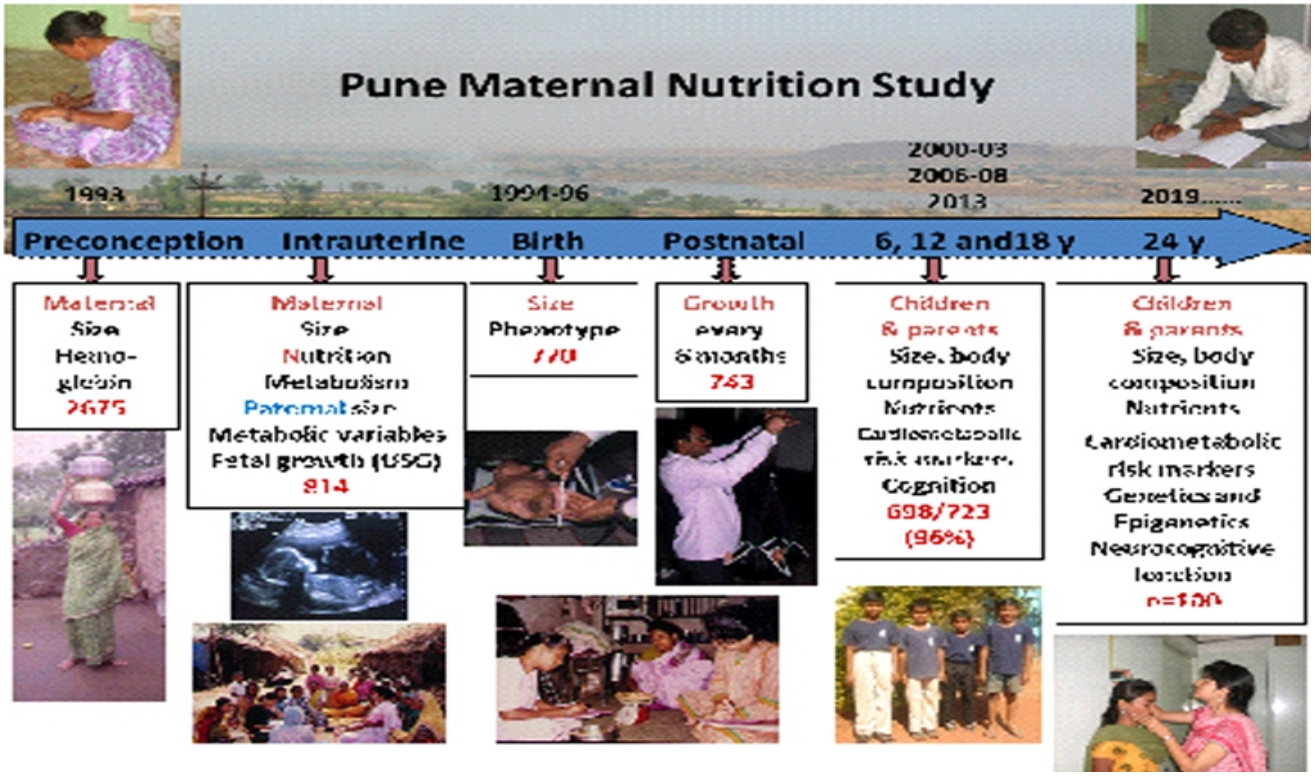


Fig 7 Intake of green leafy vegetables during pregnancy and birth weight

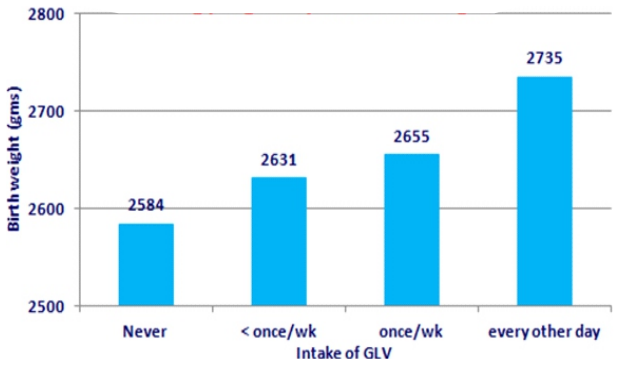
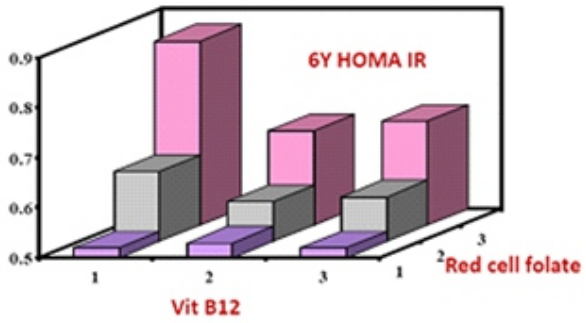


Fig 8 Folate, Vitamin B12 and Homa IR at 6 years of age



Adjusted for sex, age and fat%; maternal adiposity, protein intake, birth size, vitamin B12

and metabolism. The setting of this cohort was in a deprived, drought-prone community which has subsequently undergone rapid socio-economic transition.

Babies were measured by ultrasound in utero and by detailed anthropometry at birth and every 6 months thereafter. In addition, at 6, 12 and 18 years we studied the children and their parents for risk factors for diabetes, cardiovascular diseases and neuro-cognitive development. The cohort are now adults in their 20's, and provide a unique opportunity to study the role of maternal nutrition in influencing the unfolding of the risk of chronic disease (foetal programming).

The mothers from the initial cohort (F0 generation mothers) in the PMNS had a mean age of 21 years, mean height of 1.52 m, and mean BMI of 18.1 kg/m^2. The women were physically active in household activities as well as on the farm, but reportedly ate less than 2000 calories and 45 g proteins per day[17,18]. Deficiencies of iron, vitamin B12 and vitamin D were common but folate status was good. Small parental size, lower maternal intake of micronutrient-rich foods (green leafy vegetables, milk and fruits)[17] (Fig 7), excessive physical activity of the mother18, lower circulating nutrient concentrations (vitamin B12, folate, vitamin D) and disturbed one-carbon metabolism (higher homocysteine concentrations) were associated with higher insulin resistance (Fig 8) and with poor foetal growth (Fig 9)[19] which resulted in small and thin-looking babies (average weight 2.7 kgs). Given our earlier experience with the 'thin-fat' Indian adult phenotype, we planned to compare the measurements with those in English babies. Indian babies were smaller in all parameters as compared to English babies (average weight 3.5 kg). However, for a given weight, they had higher fat fold thickness[20] (Fig 10). Thus the Indian babies were thin-fat as compared to the English babies. This finding highlighted the important point that this diabetes-prone phenotype originates during intra-uterine life and is not related to adult lifestyle[20]. This phenotype has been demonstrated in a number of other studies of Indian babies (migrants in the UK and Canada, multi-generational migrants in Surinam, Pakistanis in the UK and in Oslo). There could be genetic basis for this phenotype, but multi-generational under-nutrition in the mothers especially deficiency of micronutrients, seems a strong possible contributing cause. Gestational diabetes seems to exaggerate this phenotype. It seems to be epigenetically 'imprinted' and persists across generations, as seen in babies of multigenerational migrant Indians in Surinam. The original description was based on anthropometric comparisons (Fig10)[21] but it was validated by MRI measurements in the Indian and English new-borns which showed that sub-cutaneous as well as intra-abdominal fat is higher in Indian babies (Fig 11)[22]. It will be interesting to attempt to increase the lean mass and reduce fat-mass in Indian babies to reduce the risk of NCDs.

The follow-up of these Indian babies born in the PMNS cohort,

Fig 9 Risk of low birthweight in relation to biochemical parameters

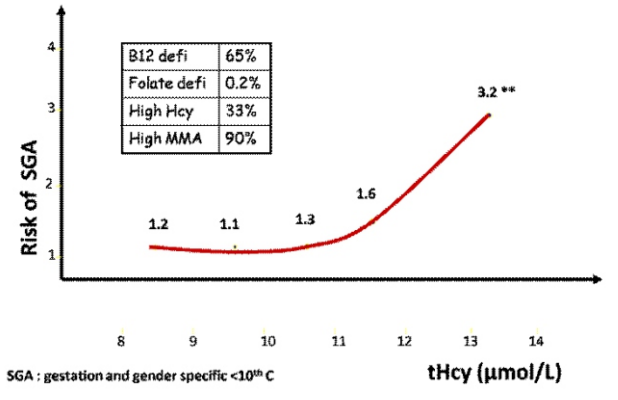
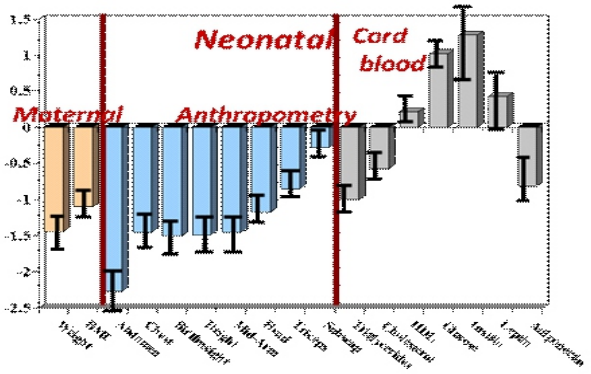


Fig 10 The thin fat Indian neonate



revealed that low maternal circulating vitamin B12 and high folate concentrations in pregnancy were associated with higher levels of diabetes risk factors (adiposity and insulin resistance), and that lower vitamin B12 was also associated with lower neurocognitive performance in childhood[23]. Such an imbalance (low B12, high folate) is contributed by vegetarian dietary habits which provide folate but not vitamin B12, and is exaggerated by the prescription of large doses of folic acid by obstetricians to reduce the risk of neural tube defects. Unfortunately, the tablet commonly used in India contains 5mg of folic acid (5000mcg) which is 12 times higher than the recommended dose of 400mcg. In a setting of low B12 status it exaggerates the imbalance. The Indian national programmes prescribe iron and folic acid to adolescents and pregnant woman, without any vitamin B12. Our findings provide potential points of action at a policy level.

There has been rapid socio-economic development in the study villages because of regular water supply from a dam to some of the villages and establishment of an industrial complex which has provided employment. This has led to improved economic status, movement away from subsistence farming, changes in diet, and substantial reduction in physical activity. This reflects in the exaggerated secular trend of body size. At the age of 18 years, children (F1 generation) were on average, 5 cm taller than their parents. The downside is that despite a relatively low BMI of 19 kg/m2 (45% underweight by WHO criteria) there is a high prevalence of pre-diabetes: 18% in females and 35% inmales[24]. Interestingly, the mismatch which we described 25years ago was related to diabetes risk: those born light in weight but grown relatively heavier are at the highest risk. Our results support a role for intra-uterine under-nutrition and subsequent rapid transition as a risk factor for NCDs.

We found that substantial vitamin B12 deficiency in our population is mainly caused by low dietary intakes and not malabsorption.We also used the technique of Mendelian Randomization to support causality of high maternal homocysteine in causing foetal growth restriction. Equipped with these data we performed a pilot trial of physiological oral doses of vitamin B12 (2µg daily) over 12 months to demonstrate safety and efficacy of this intervention in this population[25,26]. Following this, we planned a randomized, placebo-controlled intervention study, 'Pune Rural Intervention in Young Adolescents (PRIYA)' to investigate whether improving women's vitamin B12 status from adolescence improves foetal growth and reduces the intergenerational transmission of diabetes risk. The results of this trial will have a significant impact on public health policy. It offers hope for 'primordial' prevention of the escalating epidemic of diabetes in future generations. This is unlike the current prevention strategies which focus on controlling the lifestyle factors responsible for the increased risk for diabetes in later life.

We chose to start the intervention pre-conceptionally so as to influence the processes such as conception, gametogenesis, post-conceptional epigenetic reprogramming, placentation, embryogenesis and foetal organogenesis. The adolescent girls are individually randomized to receive a daily supplement of: (1) vitamin B12, 2µg; or (2) vitamin B12, 2µg + multiple micronutrients (MMN) + 5 g milk protein; or (3) a placebo for at least 3 years or until their first delivery. The composition of multiple micronutrient supplements were guided by the UNIMAPP formulation[32], providing approximately 1 RDA of 15 vitamins and minerals, but with 2µg

Fig 11 MRI measurements of Subcutaneous and abdominal fat in babies from Pune & London

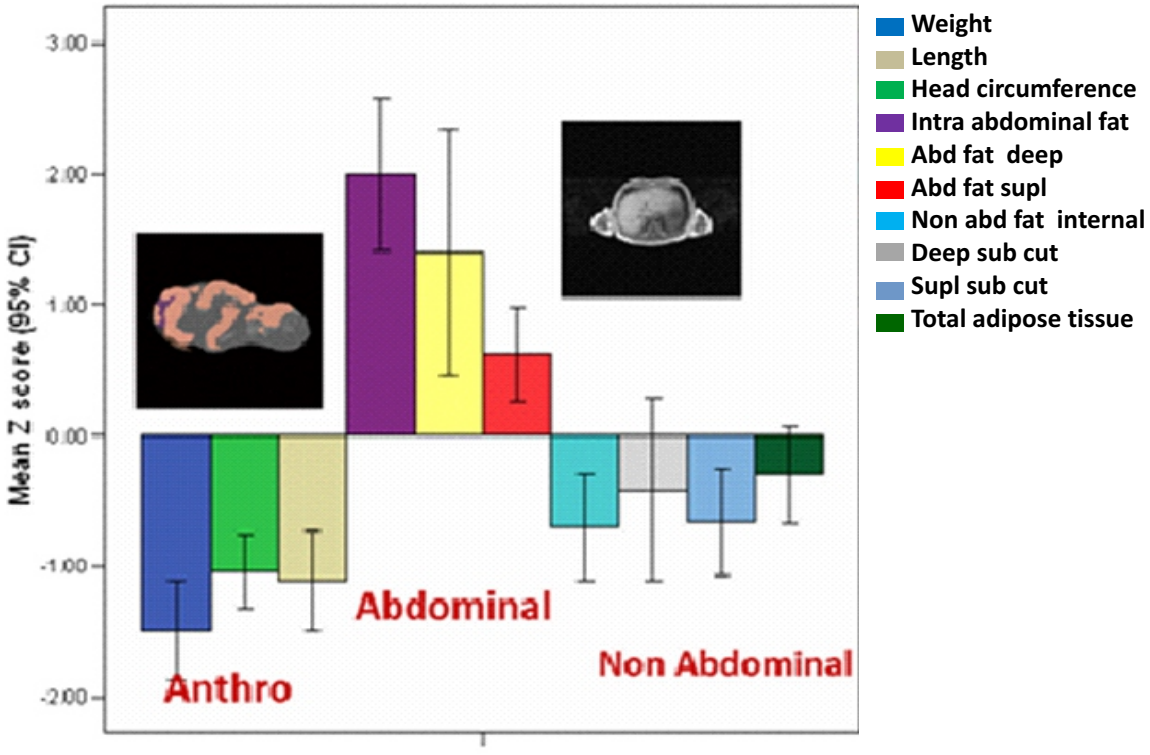
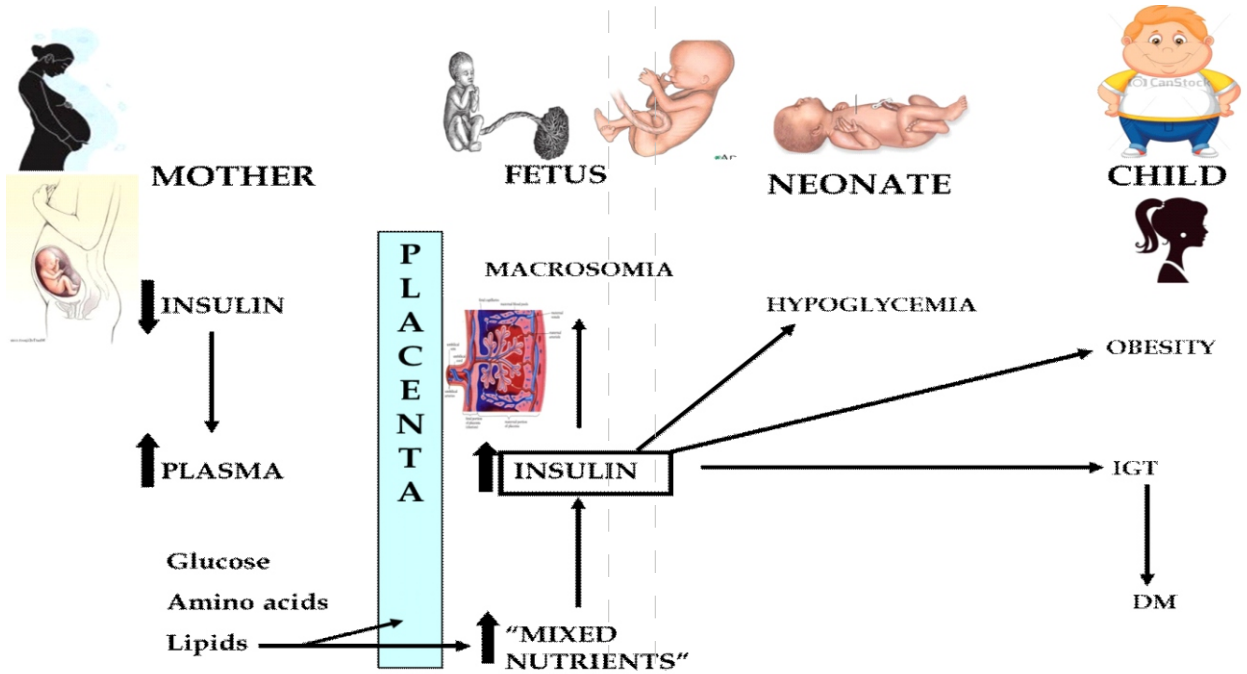
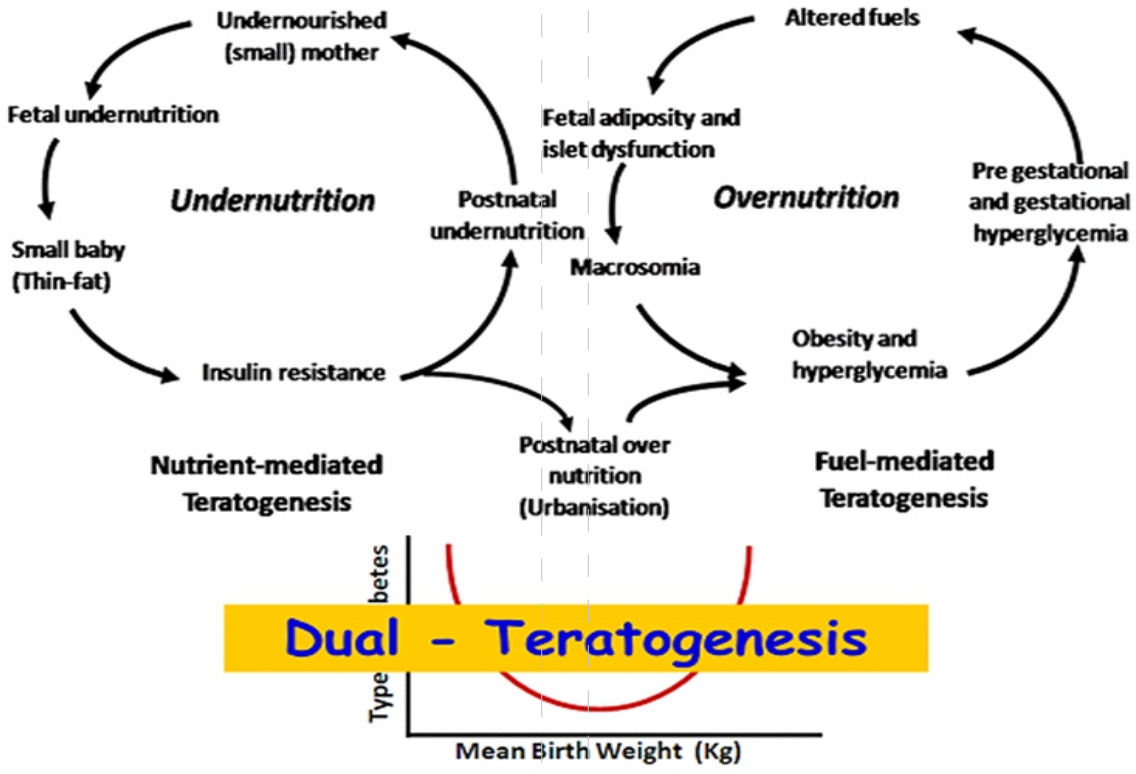


Fig 12 Fuel-mediated teratogenesis in diabetic pregnancies



vitamin B12 instead of 1µg. Iron and folic acid are prescribed separately for participants of all 3 groups as a standard care practice according to Indian guidelines[27]. The trial is ongoing. Despite of the fact that these young women are postponing their marriages

Fig 13 Dual Nutrition teratogenesis



because of educational and professional aspirations, we expect that data from at least 200 deliveries will become available overall. At the present time, more than half of the expected births have occurred. Serial data collection in PMNS and PRIYA allows us to construct a two-generational landscape of maternal size and metabolism, and pregnancy outcomes. The prevalence of gestational diabetes in the daughters (F1) is many times higher than that in their mothers (F0), and the birth weight of the granddaughters (F2) is 200 gm more than that of their mothers[28]. We are currently blinded to the intervention and therefore, unable to relate the outcomes to the intervention. In the follow upstudy we will be collecting and exploring the data on many important areas including methylation, gut microbiomes, genomics, protiomics, transcriptomics and metabolomics.

One of the manifestations of the trend towards younger age at onset of diabetes in Indians is that the prevalence of gestational diabetes is rapidly increasing. We have treated over 1000 gestational diabetes pregnancies over the last 25 years in our clinic. In a recent programme of investigations (Intergenerational programming of 'diabesity' in offspring of women with Gestational Diabetes Mellitus, InDiaGDM), we studied the prevalence of overweight, obesity and hyperglycemia in children born in diabetic pregnancies and compared them with those in children born in non-diabetic pregnancies. At an average age of 10 years the risk of overweight and obesity and risk of glucose intolerance were more than twice as high in children born to women with gestational diabetes as compared to children born to women who did not have gestational diabetes. Five% of the children born to those who had gestational diabetes developed diabetes at a young age, while none of the children born to women who did not have gestational diabetes were diabetic. Transfer of excess of maternal 'mixed fuels' across placenta in diabetic pregnancies stimulates foetal hyperinsulinaemia. This results in greater tissue anabolism, neonatal macrosomia, and offspring adiposity and diabetes in later life[29,30].

The study will report on epigenetic signatures in the cord blood of diabetic pregnancies and study the stability of these epigenetic signatures in childhood. Our results support the concept of 'fuel-mediated teratogenesis' in diabetic pregnancies in India (Fig 12)[29,30]. Interestingly, a substantial number of babies in GDM pregnancies in India are still small-for-gestational age (SGA) due to the small size of the mother and perhaps also due to strict control of diabetes in pregnancy. Unravelling the role played by such a phenotype on future risk of diabetes will be of great interest.

Summary

Over the past 30 years, we have investigated the enigma of high susceptibility of Indians to diabetes despite the absence of classic risk factors. We described the risk of central obesity for diabetes in relatively thin Indians, and subsequently described the 'thin-fat' phenotype of Indians which denotes excess fat for each measure of obesity as compared to Europeans. We confirmed David Barker's 'thrifty phenotype' concept in Indians by showing higher levels of glucose and insulin in low-birth-weight children, and further showed that those who had rapid gain in BMI in childhood were at high risk of future diabetes. We then demonstrated that the 'thin-fat' phenotype of Indians is present at birth and is influenced by the mother's nutrition and physical activity. Maternal consumption of micro-nutrient rich foods like GLV, milk and fruits were associated with larger size of the new-born. Higher homocysteine concentrations, predominantly due to vitamin B12 deficiency was associated with higher incidence of small-for-gestational-age (SGA). Higher maternal folate status predicted higher BMI in the offspring at 6years of age, and if combined with low vitamin B12 status it was associated with higher insulin resistance. Our research highlighted the role of micro-nutrients in foetal growth and body composition and showed that low maternal vit B12 and high folate levels in pregnancy predispose the offspring to higher risk of adiposity and insulin resistance (nutrient-mediated teratogenesis)[31]. We have started the world's first pre-conceptional micro-nutrient intervention in adolescent girls to reduce the vulnerability to diabetes in the next generation (PRIYA). This ongoing study will provide multi-OMICs signatures of micro-nutrient supplementation in the cord blood. We have also investigated the effects of foetal over-nutrition (in diabetic pregnancies). The current nutritional scenario in India promotes 'dual teratogenesis' (Fig 13), and the double jeopardy of multi-generational maternal malnutrition along with rising rates of adiposity and pregnancy hyperglycaemia seem to be responsible for rapidly rising rates of diabetes in Indians[31]. Our research highlights the imperative of improving nutrition of adolescent girls to reduce the epidemic of NCDs.

Future Research

We are now into the 24th year of PMNS and are planning the 24-year follow up of the PMNS offspring for risk factors for diabetes and CVDs. We are currently also examining these offspring for neuro-cognitive performance and brain MRI measures (structural and functional) to understand the long-term effects of maternal nutritional status and foetal growth on brain development. We are hopeful that the findings from our work will enable us to make recommendations for public health policy, which could translate to reducing the risk of diabetes for Indians.

The author is Director, Diabetes Unit, KEM Hospital, Pune. The write up is based on the Dr C Gopalan oration he delivered in the Golden Jubilee Conference of the Nutrition Society of India in November, 2018.

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NUTRITION NEWS

The 51st Annual Conference of the Nutrition Society of India will be held at Thiruvananthapuram in November 2019

FOUNDATION NEWS

Dr Prema Ramachandran attended the meeting of Expert Committee for reviewing the recently revised draft of the Recommended Dietary Allowances for Indians held at Indian Council of Medical Research on 24th May 2019

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