8 Early life origins of diabetes and obesity: General aspects and the thin – fat baby paradigm

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The increasing realization that obesity and type 2 diabetes are best prevented has focused researchers' attention on the influence of early life factors. The environment in utero has been shown to program the body composition and metabolic-endocrine axes, which determine the individual's adaptability to later-life exposures. Accumulating evidence suggests that epigenetic mechanisms contribute to this programming. Thus, maternal factors (nutrition and metabolism) that influence the in utero milieu have a large role to play in the primordial prevention of chronic diseases. Optimizing adolescent health rather than focusing only on adult lifestyle modifications would be much more beneficial and cost effective in preventing obesity and diabetes.

8.1 Introduction

The escalating burden of chronic noncommunicable diseases (NCDs) such as obesity, diabetes, cardiovascular disease (CVD), and cancer is well recognized, although these do not appear in the millennium development goals. Obesity and diabetes are now epidemic in many economically developing and newly industrialized nations (low and middle income countries [LMIC]), and are considered to be the most challenging health problems in the 21st century. These conditions affect a very large number of people; more than 1 billion adults are overweight in the world (World Health Organization, 2010), and 285 million people are diabetic (International Diabetes Federation, 2009). Together, the two are major contributors to the global burden of chronic diseases and disability.

The current dogma proposes that obesity, diabetes, and other related disorders have a genetic susceptibility and are precipitated by adult lifestyle factors, including poor diet and lack of physical activity. Recent diabetes prevention trials have therefore targeted the middle-aged, obese, and glucose-intolerant subjects for *primary* prevention of diabetes. We consider these as attempts to fix the problem after the horse has bolted.

There is increasing interest in the newly established field of developmental origins of health and disease (International Society for Developmental Origins of Health and Disease, 2010). Recent discoveries have highlighted that intrauterine factors influence susceptibility to NCDs by nongenetic mechanisms. This has led to a growing belief in the possibility of primordial prevention of diabetes and related disorders.

This review focuses on the impact of the intrauterine environment on the risk of diabetes and obesity in later life.

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8.2 Nutrition and diabetes

It is interesting to see the evolution of ideas in this field. In 1965, a WHO Expert Committee on diabetes commented, "evidence that malnutrition protects adult populations from diabetes seems unassailable" (World Health Organization, 1965). In 1980, another WHO Expert Committee wrote, "malnutrition is probably a major determinant of diabetes" (World Health Organization, 1980). They introduced a new category: malnutrition-related diabetes mellitus (MRDM). However, in 1997 the Expert Committee dropped the entity of MRDM from their classification (The Expert Committee Report, 1997). Even though there can be no doubt that overnutrition precipitates type 2 diabetes (T2D), it is relevant that India, the world's capital of diabetes, also figures prominently in the world hunger map. In addition to holding more than 50 million diabetic patients in 2010, India also holds the largest number of low birth weight (LBW) babies and more than 8 million severely undernourished children. These statistics point toward contribution of both early life undernutrition and later life overnutrition in the etiology of T2D. Our research focused attention on these factors by describing the thin – fat Indian diabetic patient (Yajnik et al., 2002), which refers to poor lean mass and a relative excess of fat mass, especially deposited in and around the abdomen. More excitingly, we described that the small and thin Indian baby was adipose (Yajnik et al., 2003), thus focusing the attention on intrauterine life as an important determinant of the epidemic of diabetes and CVD.

Our findings were stimulated by the research of Hales and Barker, who caused a sensation in the 1980s by describing an association between birth weight and risk of diabetes (Hales and Barker, 1992). They proposed that fetal undernutrition disturbed the development of fetal pancreas and also promoted insulin resistance (IR) in various organs. Thus, low birth weight predicted diabetes, which they called the "thrifty phenotype" hypothesis. This idea was variously expressed as "fetal origins of adult diseases," "small baby syndrome," etc. During this period considerable stress was given on *low* birth weight, though Barker and his colleagues had described a continuous and graded association of the birth weight (Barker, 1997).

One of the difficulties for the scientists to appreciate the association of lower birth weight with diabetes was the previously described association between macrosomia and future risk of diabetes in babies born to diabetic mothers. These two ideas have stimulated a considerable amount of research in the link between intrauterine growth and future risk of diabetes. This chapter discusses some aspects of this association.

8.3 Maternal nutrition, fetal growth, and future health

More than 50 years ago, McCance wrote, 'The size attained in utero depends on the services which the mother is able to supply; these are mainly food and accommodation' (McCance, 1962). Thus, maternal size and the nutrients transferred through placenta determine the size of the fetus.

Pedersen and Freinkel were the first to highlight the role of maternal diabetes in influencing the long-term health of the offspring. Pedersen proposed that maternal glucose and other fuels cross the placenta and cause fetal islet hyperplasia and hyperinsulinism, which causes overgrowth in *insulin sensitive* organs (Pedersen, 1977).

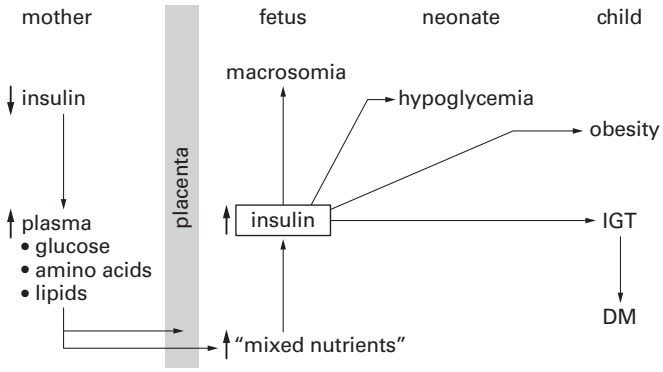

Fig. 8.1: Fuel mediated teratogenesis of Pedersen and Freinkel. Maternal fuels cross the placenta and influence islet development and fetal insulin secretion. In diabetic pregnancies there is islet hyperplasis, hyperinsulinism, and excess growth of insulin responsive tissues and organs. This leads to macrosomia, perinatal metabolic problems, and early onset obesity and type 2 diabetes (modified from Freinkel, 1980).

Freinkel expanded the use of the term *teratogenesis* from the conventional reference to fetal malformation to include fetal macrosomia and future obesity and diabetes (fuel mediated teratogenesis) (Freinkel, 1980) (▶Fig. 8.1).

During development, different organs and systems are susceptible to the maternal metabolic changes at different times based on the developmental schedule. Freinkel (1980) suggested that pregestational diabetes, which affects the fetus until conception, would have more wide-ranging effects than *gestational* diabetes (GDM), which begins later. Severity of maternal metabolic disturbance will determine the size of the effect.

Data from Pima Indians in Arizona, US, showed that the risk of obesity and diabetes was higher in offspring who were born to mothers who were diabetic during the pregnancy, compared with those born to nondiabetic mothers and mothers with pre-diabetes (Pettitt et al., 1988). This finding indicates a stronger role for intrauterine hyperglycemia in the etiology of obesity and diabetes compared to genetics. However, it is possible that mothers who are diagnosed with diabetes at a younger age might transmit an excess of genetic risk. A subsequent study of siblings in the same population showed that those born after the mother was diagnosed with diabetes were heavier and more likely to have diabesity (diabetes and obesity) compared with those who were born before mother was diagnosed with diabetes (Dabelea, Hanson, and Lindsay, 2000). There was no corresponding paternal influence. These findings confirm a role for pregnancy hyperglycemia rather than genetics or postnatal environment in the risk of childhood obesity. Studies in Chicago (Silverman et al., 1995) showed similar findings in the offspring of diabetic mothers and also showed an association between amniotic fluid insulin concentration and risk of obesity-hyperglycemia in the offspring.

On the other hand, a follow-up study of people born in Hertfordshire, UK, demonstrated that lower birth weight increased the risk of diabetes and associated disorders (Barker, 1997). Interesting findings were reported in children of Dutch women who were exposed to Hunger Winter, providing a more direct proof of association between

intrauterine undernutrition and risk of NCDs (Roseboom, de Rooij, and Painter, 2006). One of the first studies involving these offspring showed that if the exposure to famine was in the third trimester of pregnancy, offspring were less likely to be obese in adult life, but exposure to famine during the first and second trimesters was associated with higher risk of obesity (Ravelli, Stein, and Susser, 1976).

Subsequent to the demonstration of the association of birth weight and type 2 diabetes, Lucas defined fetal programming as "a process whereby a stimulus applied in utero establishes a permanent response in the fetus leading to enhanced susceptibility to later disease" (Lucas, 1991). There is now ample evidence that maternal nutritional imbalance involving both macro- and micronutrients has a *programming* effect on the fetus. Data on the role of specific nutrients is now accumulating from animal and human studies. We have coined the term *nutrient mediated teratogenesis* to describe this phenomenon (Yajnik, 2009).

Maternal obesity without hyperglycemia can also have substantial effect on the risk of obesity in the child (Catalano et al., 2009). This raises the possibility that nonglucose fuels (e.g., lipids) might also be important. In clinical practice we have been too glucocentric and have forgotten about the original concept of *mixed nutrients* in the teratogenic process.

8.4 Developmental plasticity, programming, teratogenesis, and predictive adaptive response

The ability of the growing fetus to respond to the environmental cues and assume different sizes and functional characteristics is called *developmental plasticity* (Bateson, Barker, and Clutton-Brock, 2004). It describes the ability of the fetus to achieve different phenotypes with a given genotype. An intrauterine challenge puts constraint on the structural and functional development of the fetus, limiting its ability to respond effectively to a changing environment. It is thought that the fetus perceives these environmental cues as indicative of the postnatal environment, and the adaptations are appropriate for such an environment (predictive adaptive response) (Gluckman, Hanson, and Spencer, 2005). If the postnatal environment is different, the adaptations may become inappropriate, and the individual has an increased susceptibility to disease.

The concept of *nutrient mediated teratogenesis* and *fuel mediated teratogenesis* refers to different ends of the spectrum of the effects of nutritional and metabolic challenges in utero, and can be looked upon as the two sides of the same coin. We have used the term *dual teratogenesis* to describe the situation in rapidly transiting populations (▶Fig. 8.2) (Yajnik, 2009).

Intrauterine undernutrition produces small, thin, and adipose babies who are insulin resistant and remain so (small, thin, and insulin resistant) if postnatal nutrition is not excessive. These individuals have low rates of NCD, as seen in rural populations in India. Postnatal overnutrition promotes obesity and hyperglycemia, frequently without correction of the micronutrient deficiencies. For example, in a study in Mysore, India, GDM was associated with low circulating vitamin B_{12} concentrations (Krishnaveni et al., 2009). In such a condition, the fetus is exposed to multiple adverse programming influences, resulting in a phenotype of excess adiposity, pancreatic islet dysfunction, and a tendency toward diabetes and CVD at a young age. Such a dual teratogenesis

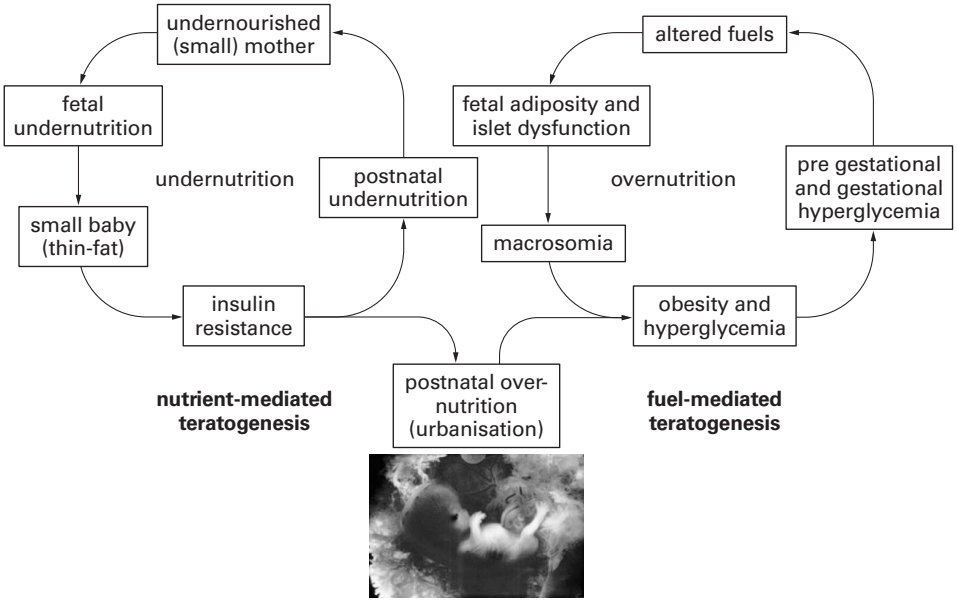

Fig. 8.2: The figure shows the interrelationship of two major maternal factors (undernutrition and overnutrition) in fetal programming. An undernourished mother produces a small (thin-fat), insulin resistant baby. If this baby remains undernourished in postnatal life, the cycle is propagated. If the thin-fat insulin-resistant baby is overnourished it becomes obese and hyperglycemic. An obese and hyperglycemic mother produces a *macrosomic* baby at higher risk of obesity and hyperglycemia. Thus, the intergenerational insulin resistance – diabetes cycle is propagated through a girl child. Rapid transition shifts the balance from undernutrition to overnutrition and contributes to escalation of the diabetes epidemic. Improving health of a girl child is of paramount importance in controlling the diabetes epidemic (Yajnik, 2009).

is proposed to contribute to the rapidly rising epidemic of obesity – diabetes in modern India (Yajnik, 2009).

8.5 Birth weight: An exposure, an intermediate variable, or only a marker?

It is important to note that the biological association between birth weight and diabetes is U-shaped, that is, both low and high birth weight are associated with higher risk of diabetes. The risk associated with large birth weight is mostly ascribed to the effect of maternal hyperglycemia, but risk of maternal obesity also is increasingly recognized.

A recently published systematic review (Whincup et al., 2008) covering data from 31 populations examined the association of birth weight and type 2 diabetes in 152,084 individuals, including 6,090 diabetes cases. The association between birth weight and type 2 diabetes was inverse in 23 populations (statistically significant in 9) and positive in 8 (statistically significant in 2 native North American populations). Overall,

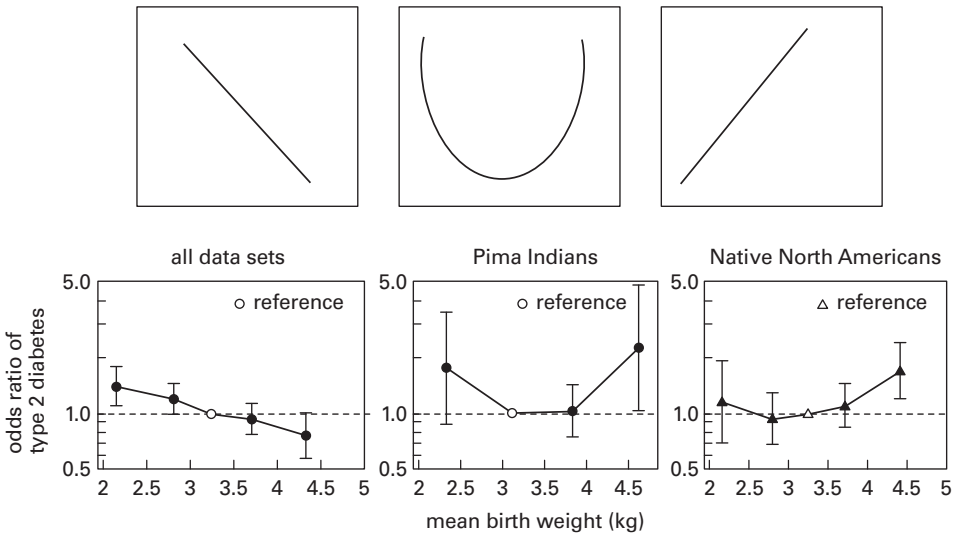

Fig. 8.3: Associations of birth weight with type 2 diabetes. The biological association appears to be U-shaped, that is, both low and high birth weight are associated with the risk of diabetes. Depending on the relative role of maternal undernutrition (nutrient mediated teratogenesis) and overnutrition (fuel mediated teratogenesis), the shape of the graph varies as shown from the systematic review by Whincup et al. (Compiled from Yajnik, 2004 and Whincup et al., 2008).

1 kg increase in birth weight reduced type 2 diabetes risk by 25%, and by 30% after adjusting for adult BMI. The association was strongly graded and continuous (▶Fig. 8.3).

It is important to understand that the story is not about birth weight but about fetal programming and that intergenerational prevention of type 2 diabetes and obesity will need to target maternal nutrition and metabolism.

8.6 Role of postnatal growth

Longitudinal follow up in birth cohorts from both developing and developed populations has helped our understanding of the interactions between intrauterine and postnatal growth and risk of type 2 diabetes and CVD.

In the Pune Children's Study (PCS) at the King Edward Memorial Hospital, Pune, we followed up more than 400 children whose birth weights were available from the labor-room record. At 4 years of age we studied their anthropometry, glucose tolerance, and circulating insulin concentrations. We demonstrated that after oral glucose load, 30 min plasma glucose and insulin concentrations were inversely related to the birth weight (Yajnik et al., 1995). This provided the first proof for Barker's hypothesis in a developing country. We followed up these children at 8 years of age to study their metabolic characteristics. In addition to confirming the association of low birth weight with increased insulin resistance, we observed that the levels of risk factors for diabetes and CVD (glucose, insulin resistance, lipids, blood pressure, leptin concentrations, etc.) were highest in children who were born the lightest but were heaviest at 8 years of age

(Bavdekar et al., 1999). The offspring from New Delhi Birth Cohort who are followed from birth were studied at 28 years of age (Bhargava et al., 2004). Those who were diabetic were born lighter, had grown slower during infancy but had grown progressively faster from 3 years of age, and had an earlier adiposity rebound compared to those who were normal glucose tolerant.

Glucose tolerance was tested in adults participating in the Helsinki Birth Cohort Study (1934–1944) (Eriksson et al., 2006). Both, impaired glucose tolerance and type 2 diabetes, were associated with low birthweight ($p < 0.0001$, adjusting for current BMI), and low weight gain between birth and 2 years increased the risk. A one standard deviation (*SD*) increase in weight at 2 years protected against hyperglycemia (odds ratio [OR] 0.76, 95% confidence interval [CI] 0.69–0.84); the effect was greatest in those with low birth weight. Thus, this study defined intrauterine life, infancy, and childhood as critical periods for future risk of insulin resistance and hyperglycemia.

8.7 Contributions of the Pune Maternal Nutrition Study

The Pune Maternal Nutrition Study (PMNS) cohort was established between 1992 and 1996 in six villages near Pune, India, to investigate the influence of maternal body size and nutrition during pregnancy on fetal growth and future metabolic risks in the offspring (Rao et al., 2001). More than 800 pregnancies were studied. The average mother in the PMNS was aged 21 years, weighed 42 kg (BMI 18.1 kg/m^2), and had a dietary intake of 1700 kcal/day and 45 g proteins/day during pregnancy. The newborns

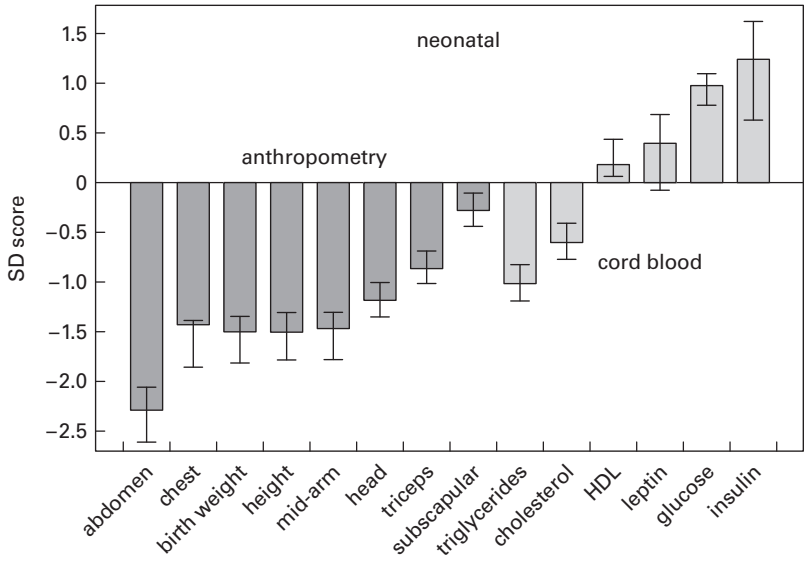

Fig. 8.4: Comparison of Indian and UK babies. UK measurements are used as a reference (0). The Indian babies were smaller than the British babies in all measurements of size. Cord plasma leptin concentration was similar, and cord plasma glucose and insulin concentrations were higher in the Indian babies. (Yajnik et al., 2002).

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weighed on average 2700 gm with a ponderal index of 24.1 kg/cm^3; 28% were LBW (<2500g). In comparison with babies born in the UK (3500 gm, ponderal index 27.3 kg/cm3), Indian babies were lighter, shorter (47.3 cm vs. 50.2 cm), and thinner, but the sub-scapular skin-fold measurements were relatively well preserved (*z* score −0.53; 95% CI −0.61, −0.46) (▶Fig. 8.4) (Yajnik et al., 2002, 2003). Thus, the Indian babies were short and thin but fat, corroborating our description of Indian adults.

Recently, we compared whole body magnetic resonance imaging (MRI) measurements of adipose tissue and its distribution in healthy full-term Indian babies (Pune) with those in white European newborns (London, UK) (Modi et al., 2009). Though smaller in weight (95% CI for difference −0.757 to −0.385 kg, $p < 0.001$), head circumference (−2.15 to −0.9 cm, $p < 0.001$) and length (−2.9 to −1.1 cm $p < 0.001$), the Indian babies had similar whole body adipose tissue content (−0.175 to 0.034 l, $p = 0.2$) (▶Fig. 8.5).

Adipose tissue distribution was distinctly different. Indian babies had significantly greater absolute adiposity in all three abdominal compartments, internal (visceral) (0.012 to 0.023 l, $p < 0.001$), deep subcutaneous (0.003 to 0.017 l, $p = 0.006$), and superficial subcutaneous (0.006 to 0.043 l, $p = 0.011$) but a significant reduction in non-abdominal superficial subcutaneous adipose tissue (−0.184 to −0.029 l, $p = 0.008$). Thus, this study confirmed that differences in adipose tissue distribution exist at birth, which could be an important risk factor for diabetes and related disorders. Conventional measurements of birth size are not sensitive to these vital differences. Further research must focus on periconceptional, intrauterine, and early postnatal exposures that modify the tissue deposition pattern. In yet another study we demonstrated higher insulin and leptin concentrations but lower adiponectin concentrations in the cord blood of Indian babies compared to the European babies (▶Fig. 8.4) (Yajnik et al., 2002).

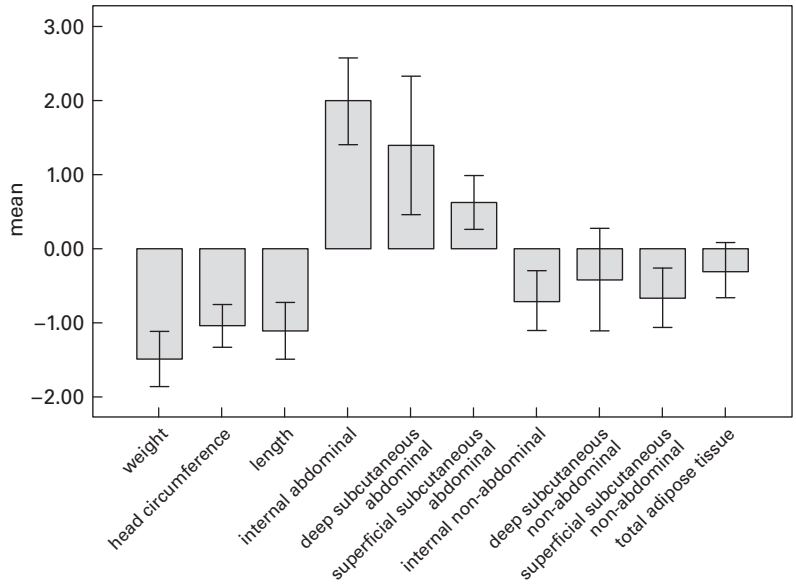

Fig. 8.5: Anthropometry and adipose tissue compartments: Z scores (mean ± 95% CI) for Indian babies with white European babies as baseline (Modi et al., 2009). (Error bars: 95% CI).

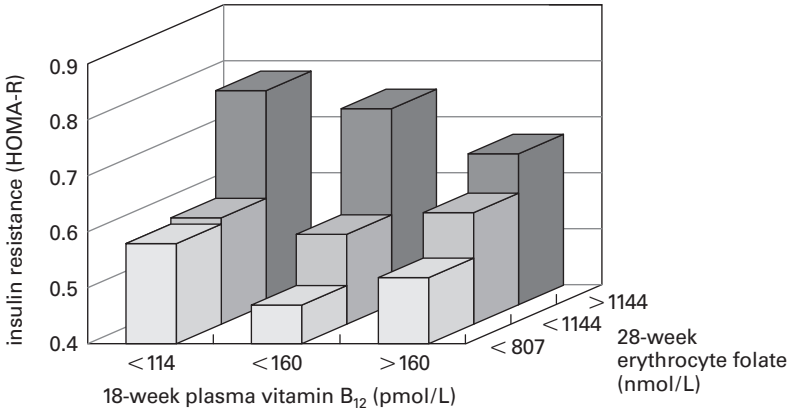

Fig. 8.6: Pune Maternal Nutrition Study: Insulin resistance (HOMA-R) in the children at 6 y in relation to maternal plasma vitamin B_{12} (at 18 wk) and erythrocyte folate (at 28 wk) concentrations. Maternal folate concentrations in pregnancy directly predict insulin resistance in the child. The most insulin-resistant children were born to mothers who had the lowest vitamin B_{12} and highest folate concentrations (Yajnik et al., 2008).

The PMNS also improved our knowledge of maternal determinants of fetal growth. More frequent intake of green leafy vegetables, fruit, and milk (foods rich in micronutrients) by mother predicted larger newborn size, whereas macronutrient intake (calories and proteins) did not, highlighting the importance of micronutrients in fetal growth (Rao et al., 2001). About two-thirds of women had low vitamin B_{12} concentrations; hardly anyone was folate deficient. About one-third had high total homocysteine (tHcy) concentrations, and more than 90% had high methyl malonic acid (MMA) concentrations, attributable to the deficiency of vitamin B_{12} (Yajnik et al., 2008).

High maternal tHcy concentration predicted intrauterine growth restriction (Yajnik et al., 2005). Higher maternal frequency of consumption of green leafy vegetables and milk and higher erythrocyte folate concentrations during pregnancy predicted higher offspring adiposity. The effect of maternal folate was exaggerated by vitamin B_{12} deficiency; the offspring of mothers who had lowest vitamin B_{12} and highest folate concentrations were the most insulin resistant (▶Fig. 8.6) (Yajnik et al., 2008).

Thus, attention was focused on the importance of maternal one-carbon metabolism for fetal growth and programming of diabetes and related disorders. One-carbon metabolism is important for nucleic acid and protein synthesis and epigenetic methylation of DNA. This regulates cellular growth and differentiation.

8.8 Genetics and epigenetics of fetal growth and diabetes-obesity

Do genetic factors have a role in fetal growth and programming of NCDs? One obvious pathway to investigate was insulin mediated fetal growth, which was proposed as an important mechanism for fuel mediated teratogenesis. Hattersley et al. (1998) investigated the possibility that genetic determinants of insulin secretion and activity could explain the association between fetal size and future risk of diabetes (fetal insulin hypothesis).

They investigated the influence of the glucokinase gene (GCK) on fetal growth, and showed an important interaction between maternal genotype (GCK mutation) and phenotype (hyperglycemia) with fetal genotype in influencing offspring birth weight (Hattersley et al., 1998). After the discovery of many type 2 diabetes predisposing polymorphisms in the genome wide association studies (GWAS), they have demonstrated that some of these markers are also associated with birth weight (e.g., fat mass and obesity-associated gene [FTO]). Additionally, in GWAS of birth weight (Freathy et al., 2009), they found that some of the polymorphisms predicting birth weight are also type 2 diabetes genes. These findings will no doubt improve our understanding of regulation of fetal growth and etiology of type 2 diabetes. However, the effect of maternal nutrition and metabolism is crucial for fetal growth. This is obvious from the variability of birth weight between and within populations, between the first and later pregnancies, and from the description of a reduction in offspring birth weight after maternal bariatric surgery (Smith et al., 2009).

Animal data also highlights the role of maternal rather than paternal influence on fetal growth. It is interesting, however, that skeletal growth of the fetus seems to be more influenced by paternal factors (presumably genetic) (Knight et al., 2005).

One recent exciting development is the discovery of the factors regulating gene expression. These factors have improved our understanding of the interactions between the environment and genes. Developmental plasticity is largely a function of regulation of gene function. Waddington called these processes *epigenetic* (Van Spebroeck, 2002). Current understanding is that the methylation of DNA bases, acetylation of histones, and noncoding RNAs (iRNA) are important mechanisms that regulate the gene expression. Methylation of cytosine residues in the cytosine-phosphatidylguanosine (CpG) islands is regulated by methyl donors in the diet, including folate, vitamin B_{12}, betaine, and choline (Waterland and Jirtle, 2003). Our demonstration of the role of folate and vitamin B_{12} in regulation of fetal growth, body composition, and programming of insulin resistance therefore assumes a special significance (Yajnik et al., 2008).

Waterland and Jirtle (2003) fed agouti mice with a methylating cocktail during pregnancy. The progeny had varying coat color and were less obese compared to controls, despite inheriting the same genotype. This was related to methylation of the promoter region of the agouti gene, which is responsible for determining coat color. Such epigenetic changes are heritable for many generations and potentially may be involved in fetal programming.

This idea is also supported by experiments in sheep. Ewes were made methionine deficient, their ova were fertilized in vitro, and the blastocysts were transferred to surrogate mothers with normal methionine status (Sinclair et al., 2007). The offspring (especially males) were obese and insulin resistant and had alterations in DNA methylation at a number of sites within the genome. Epigenetic regulation of glucocorticoid receptor and peroxisome proliferator activator alpha (PPAR-α) genes have been shown to be involved in fetal programming due to a low protein diet in rodents (Lillycrop et al., 2005). The first evidence in humans supporting the hypothesis that early-life environmental conditions can cause epigenetic changes in humans that persist throughout life has been provided in the Dutch Hunger Winter Families Study (Heijmans et al., 2008). They showed that individuals who were prenatally exposed to famine during the Dutch Hunger Winter in 1944–45 had, 6 decades later, less DNA methylation of the imprinted

IGF2 gene compared with their unexposed, same-sex siblings. The association was specific for periconceptional exposure.

The GWAS polymorphisms associated with birth weight, obesity, and type 2 diabetes are the obvious candidates for future epigenetic studies to inform on the important environmental regulators.

8.9 Conclusion

We suggest a modification to the conventional gene-lifestyle dogma of type 2 diabetes. The susceptibility to diabetes and other NCDs is also influenced by epigenetic processes and fetal programming. Maternal nutrition and metabolism are major determinants of these processes. Prevention of obesity, type 2 diabetes, and other NCDs should start with improvement of the health of young girls who would be mothers tomorrow. The current models of diabetes prevention in postreproductive, obese, glucose intolerant women are unlikely to reduce the escalating epidemic in the young. Along with efforts to control hyperglycemia in the elderly, there is an urgent need to plan intergenerational prevention by improving nutrition and metabolism of young girls before conception. This could provide a multigenerational benefit and should be the focus of future research.

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