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WOMEN, DIABETES, AND PREGNANCY

Nutrient-mediated teratogenesis and fuel-mediated teratogenesis: Two pathways of intrauterine programming of diabetes

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ABSTRACT

The epidemic of diabetes is spreading quickly to the poor and the deprived. Nutrition during fetal life influences the future risk for diabetes; and both under- and overnutrition contribute and coexist in rapid-transition countries. Nutrient imbalance seems particularly important; for example, low maternal vitamin B_{12} status coupled with high folate predicted higher adiposity and insulin resistance in Indian children, suggesting a role for 1-C (methyl) group donors in fetal programming. Maternal hyperglycemia worsens the situation. Improving the early-life environment may be more cost-effective for preventing diabetes than controlling lifestyle factors alone in later life.

1. Diabetes epidemic and the developing world

The world is facing an unprecedented epidemic of obesity and diabetes. Unlike the statistics a few decades ago, today there are more diabetic patients in developing countries than in developed countries, and the major burden of diabetes is shared by the developing rather than the developed world. In many developed countries, and in some developing countries, the prevalence of obesity and diabetes is higher in low socioeconomic groups compared with affluent groups (a "reversal" of the socioeconomic gradient) [1,2]. Diabetes, considered a disease of the affluent, is fast affecting the poor. There are some striking features of diabetes in developing countries, such as India, when compared to the developed countries [3]. These include: (1) younger age at diagnosis; (2) lower body mass index; (3) higher adiposity (body fat percentage) and central adiposity (waist–hip ratio and visceral fat; "thin and fat"); and (4) higher insulin resistance. In India, over the last few decades, age at diagnosis of type 2 diabetes has decreased by many years. Children are increasingly affected by obesity and type 2 diabetes, especially those from urban and affluent backgrounds. Clearly the diabetogenic influences are operating at a much younger age and at a lower threshold of body size.

2. Current efforts at diabetes "prevention"

Popular "preventive" strategies have targeted the "at risk" middle-aged obese and impaired glucose tolerant populations [4]. This is based on the traditional model of the pathogenesis of diabetes, which ascribes susceptibility to genetic factors and precipitation to adult lifestyle (Fig. 1). In the absence of any means to control genetic susceptibility, impetus is placed on controlling lifestyle factors in adults. Improvement in glycemia by dietary modification and promotion of physical activity, and sometimes pharmacological agents, is called "diabetes prevention." This is rather naïve and reflects the popular medical practice of "fixing it." Both obesity and impaired glucose tolerance are end-stage conditions with arbitrary cut-off points (which have changed substantially over the last two decades). These attempts ignore that controlling obesity and metabolism in the postreproductive years will not curtail the epidemic, which is fueled by its increasing incidence in the young, nor will it benefit their offspring who are at a progressively increasing risk of diabetes. This is a major limitation of our current efforts to curtail the epidemic.

The problem is even more complex in countries undergoing rapid transition. It includes the double burden of disease, comprising rapidly emerging non-communicable disease (NCD; including diabetes and cardiovascular disease), in addition to the unconquered nutritional and infectious disorders. In many instances these coexist; for example, families living in urban slums may have undernourished children but overweight parents, and women from urban areas in India carry the double burden of micronutrient deficiencies and gestational diabetes. Trying to control one could have an effect on the other.

3. Early-life factors and risk of diabetes

The real issue is tracing when and how diabetes begins. The traditional model ascribes susceptibility to genetic factors. Barker [5] proposed a novel model for the susceptibility of diabetes and cardiovascular disease by demonstrating that low birth weight was a risk factor for these conditions. In addition to weight, other measures of small size at birth (eg, length, ponderal index, etc) also predict diabetes or its two pathogenic mechanisms ie, insulin resistance and

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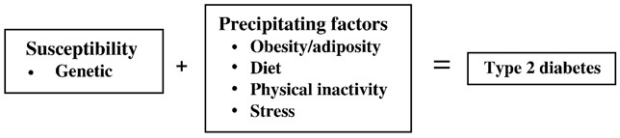

Fig. 1. The conventional model of origin of type 2 diabetes. The current diabetes prevention trials are based on the conventional model.

impaired beta-cell function. It was proposed that intrauterine growth restriction (IUGR) consequent upon maternal undernutrition contributed to this association (the "thrifty phenotype"). Many studies across different populations confirmed the association between small size at birth and diabetes later in life [6].

The associations between size at birth and later disease have been explained by the concept of fetal programming. This refers to a permanent change in structure and function of a developing organism in response to an environmental factor [7]. Thus, the intrauterine environment assumes a great significance in determining the long-term prospects for the fetus. The programmed fetus will do well if the postnatal environment is similar, but if substantially different the fetal "programs" are unable to cope, resulting in disease [8].

4. Studies in Pune, India

Professor David Barker and Caroline Fall met us in 1991 and convinced us of the importance of intrauterine factors. Our first study was the Pune Children's Study (PCS). Here we studied over 400 children whose birth weights were available from the labor room records. At 4 years of age their plasma glucose and insulin concentrations 30 minutes after the glucose load were inversely related to birth weight (Fig. 2), providing the first proof for Barker's hypothesis in a developing country [9]. Given that almost one-third of babies born in India are small by international standards, this could have enormous implications for the diabetes epidemic.

We studied these children again at 8 years of age and confirmed the association between low birth weight and insulin resistance [10]. In addition, we found that the levels of risk factors for diabetes and cardiovascular disease (glucose, insulin resistance, lipids, blood pressure, leptin concentrations, etc) were highest in the children who weighed the least at birth, but weighed the most at 8 years of age (Fig. 3). This finding focused attention on rapid childhood growth as a risk factor for diabetes and cardiovascular disease. In addition, we found that children born to short parents were more insulin resistant, and those who had grown taller in relation to parental height were the most insulin resistant. A discordance of size, presumably due to

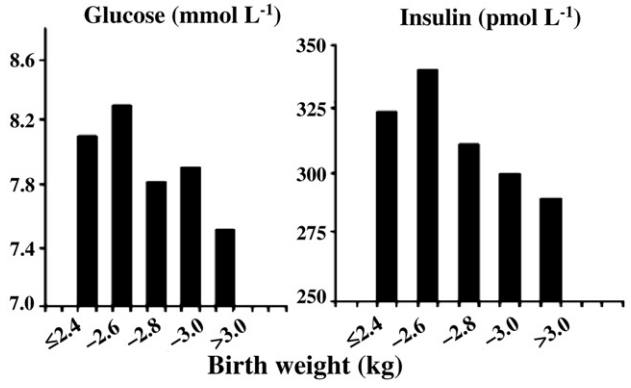

Fig. 2. Plasma glucose and insulin concentrations after oral glucose load in 4-year-old Indian children. Significance of the trend is corrected for age, gender, and current body weight. The results show that low birth weight is associated with higher glucose and insulin concentrations. Reprinted with permission from Wiley-Blackwell [11].

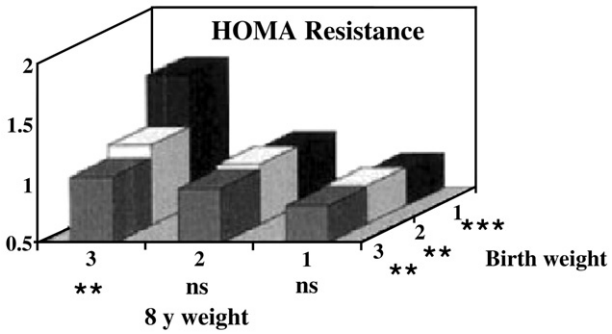

Fig. 3. Mean levels of insulin resistance (HOMA) in 8-year-old children by tertiles of birth weight and 8-year weight. Those born the lightest but grown heaviest are the most insulin resistant. The figure highlights the effect of "rapid transition" in one's lifetime, and depicts the effect of double-burden (early life undernutrition and subsequent overnutrition) in an individual. (ns, not significant, $*P<0.05$, $**P<0.01$, $***P<0.001$). Reprinted with permission from Wiley-Blackwell [11].

nutritional factors, in one's lifetime (low birth weight and being overweight later in life), as well as across generations (short parents and tall children), predicts higher metabolic risk.

A study in Delhi provided further proof that rapid childhood growth predisposes to type 2 diabetes [12]. In a study of over 1500 men and women, diabetes at 28 years of age was predicted by lower birth weight and slower growth in infancy, but a progressively faster growth from 3 years of age compared with those who had normal glucose tolerance (Fig. 4). Younger age at adiposity rebound increased the risk of diabetes many times.

In all of these studies, the role of nutrition was presumptive. There were little prospective nutritional data in these studies. We therefore set up a prospective, community-based study of maternal nutrition and fetal growth, called the Pune Maternal Nutrition Study (PMNS). We enrolled over 2500 eligible nonpregnant women in 6 villages near Pune, and over 800 became pregnant during the study. We measured their nutrition, physical activity, biochemistry, and fetal growth. Neonates were measured in detail at birth and every 6 months thereafter. Every 6 years we undertake a detailed assessment of body composition, and a range of risk factors for diabetes and cardiovascular disease. Over 700 children are being followed up, currently at 12 years of age.

The PMNS has made a number of interesting contributions to our understanding of fetal growth in India. We found that although Indian babies were small, short, and thin at birth, they had comparable subscapular skin-fold thickness compared with white babies born in the UK [13]. In other words, our previous description of "thin but fat" Indian adults, really started in utero, and suggested that body composition is established at birth. In a subsequent study, we also demonstrated that Indian babies have higher concentrations of insulin and leptin, but lower concentrations of adiponectin in cord blood, again suggesting that the high-risk Indian phenotype for diabetes is established at birth [14].

Another important observation from the PMNS was that maternal micronutrient nutrition was an important determinant of fetal growth in this population [15]. Maternal intake of calories, proteins, and fats did not have a significant effect on fetal growth; however, frequency of consumption of green leafy vegetables, milk, and fruits had a major effect. Higher maternal circulating concentrations of homocysteine predicted fetal growth restriction [16]. In this population, we found that two-thirds of mothers had low vitamin B_{12} concentrations, while only one woman had folate deficiency. Low B_{12} status in this population was due to low dietary intake, predominantly caused by vegetarianism. At 6 years of age the children's adiposity and insulin resistance was significantly related to maternal B_{12} and folate levels in pregnancy [17]. Higher maternal folate concentrations predicted

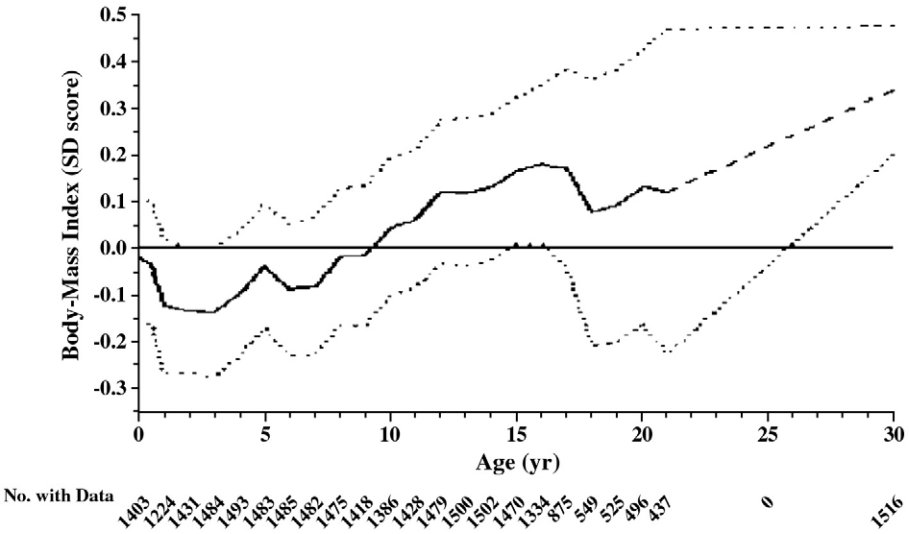

Fig. 4. Mean sex-specific unadjusted SD scores for body mass index, according to age, for subjects in whom impaired glucose tolerance or diabetes developed. The mean SD scores (solid lines) are obtained by linear interpolation of yearly means, with one additional observation at 6 months. The dotted lines represent 95% confidence intervals. The dashed portions of lines indicate years in which there was no follow-up. The SD score for the cohort is set at zero (solid horizontal lines). Reprinted with permission from: Bhargava SK, Sachdev HS, Fall CH, Osmond C, Lakshmy R, Barker DJ, et al. Relation of serial changes in childhood body-mass index to impaired glucose tolerance in young adulthood. N Engl J Med 2004;350(9):865–75. Copyright © 2004 Massachusetts Medical Society. All rights reserved.

higher adiposity and children born to mothers with low B_{12} concentrations but high folate concentrations were the most insulin resistant. This is the first demonstration in a prospective study of a relationship between maternal nutrition in pregnancy and risk of diabetes in the offspring.

5. Size at birth, intrauterine environment, and risk of diabetes

It must be appreciated that size at birth is only representative of the events during intrauterine life. The relationship between birth size and later risk is a continuous one, and there are no cut-off points. The birth weight story provides a unique explanation for the distribution of risk across the population and indicates that intrauterine life is an important determinant of the health of the population. For diabetes, the risk distribution is U-shaped (as shown in Pima Indians), where both low and high birth weight (contributed by maternal diabetes) increase the risk of diabetes [18]. The common mistake is to equate birth weight as the "exposure" in this relationship. It is only an intermediate variable, which is neither very sensitive nor specific for a particular exposure. Overall, maternal size and nutrition are major determinants of the offspring's size and therefore potential targets for the intervention. Interventions should target the intrauterine environment rather than birth weight.

5.1. Maternal glycemia and fuel mediated teratogenesis

Norbert Freinkel and colleagues in Chicago developed the concept of fuel-mediated teratogenesis to describe the wide-ranging fetal effects of maternal hyperglycemia and related metabolic abnormalities [19]. The concept was predominantly based on animal studies. Pettit and colleagues made very interesting observations in Pima Indians. Using prospective serial databases from a Pima Indian community, they assessed the contribution of genetics and the intrauterine environment to the risk of obesity and diabetes in the offspring [20,21]. They demonstrated that children of diabetic mothers had a higher risk of being obese. Subsequently, they showed that risk of diabetes in the child was many times higher if the mother had diabetes during pregnancy (intrauterine exposure) compared with the risk in the children whose mothers developed diabetes after pregnancy (genetic risk). These results suggest that intrauterine hyperglycemia is more important in intergenerational propagation of diabetes compared with genetic factors. Diabetes in young girls is, therefore, a major factor in the escalating epidemic of diabetes. A subsequent analysis showed that 70% of cases of diabetes in young Pima Indians could be ascribed to maternal diabetes. Studies in Chicago also showed that children of diabetic mothers had a higher risk of glucose intolerance at a young age; this was related to higher amniotic fluid insulin concentrations [22]. Studies in India have confirmed the high risk of glucose intolerance in 5-year-old children of mothers with gestational diabetes [23].

5.2. Maternal nutrition and nutrient-mediated teratogenesis

The low birth weight story and a large body of animal studies have shown that maternal undernutrition of calories, proteins, and a number of micronutrients have a profound "programming" effect on the fetus and increase its risk of metabolic and vascular disease. Until recently, little information on the role of specific nutrients in humans was available. The PMNS has provided a role for maternal vitamin B_{12} and folate as potential candidates [17]. We know from clinical experience that deficiency or imbalance of these two vitamins is associated with a spectrum of fetal outcomes: early abortion, congenital anomalies (neural tube and cardiac defects), intrauterine growth restriction, neurocognitive affection, adiposity, and insulin resistance. The situation is analogous to the description by Norbert Freinkel in a diabetic pregnancy, and we have proposed the term "nutrient-mediated teratogenesis" to describe these phenomena. We expect that a spectrum of fetal effects will be described for a number of other nutrients.

Vitamin B_{12} and folate are important methyl group donors involved in a multitude of processes, including cell growth and division, which includes DNA synthesis. Animal models have provided exciting information on the role of methyl groups in fetal programming. Waterland and Jirtle [24] fed genetically obese Agouti mice a methylating cocktail (B_{12}, folic acid, choline, and betaine) and showed that the offspring had a different coat color and were less obese, despite inheriting the Agouti mutation. This was related to methylation status of the promoter region of the Agouti gene. Lillycrop et al. [25] demonstrated that the folate rescue in the rat model of maternal protein deficiency was related to methylation in some of the genetic sequences. Sinclair et al. [26] produced methionine deficiency in female sheep (by dietary restriction of methionine, $B_{12,}$ and folate).

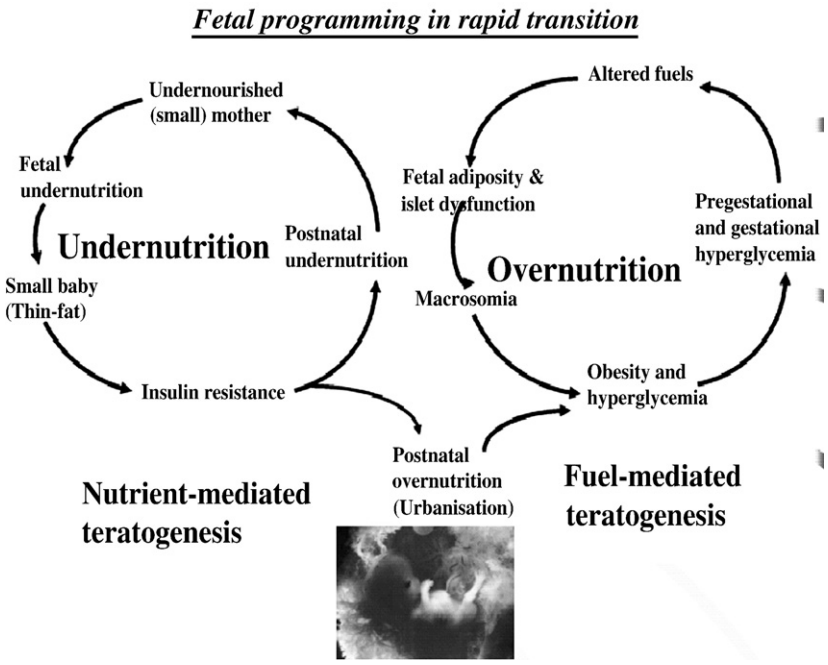

Fig. 5. Interrelationship of two major maternal factors (undernutrition and overnutrition) in fetal programming. An undernourished mother produces a small (thin–fat) insulin resistant baby. If this baby remains undernourished in postnatal life, the cycle is propagated. If the thin–fat insulin resistant 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.

Ova from these sheep were fertilized in vitro, and the blastocysts were transferred to normal methionine status surrogate mothers. The offspring were obese and insulin resistant, especially males. They demonstrated a differential methylation at a number of sites in the genome of these animals. This model highlights the importance of periconceptional 1-C (methyl) metabolism in fetal programming. These phenomena are included under the concept of epigenetics, which refers to heritable modifications in the genome that are not associated with a change in the base sequence [27]. These could potentially result in production of different phenotypes from the same genotype by altering gene expression and increasing or decreasing the amount of encoded protein.

6. Fetal programming, DOHaD, and life-course model

We propose that nutrient-mediated teratogenesis and fuel-mediated teratogenesis are two sides of the same coin (Fig. 5). Intrauterine undernutrition produces small, thin, and fat babies who are insulin resistant and remain so if postnatal nutrition is not excessive. These individuals have low rates of NCD, such as in rural India. When postnatal nutrition is relatively plentiful it promotes obesity and hyperglycemia, many times without correction of the micronutrient imbalance. In a female, such a situation exposes her fetus to multiple adverse programming influences, resulting in a complex phenotype including exaggerated adiposity (macrosomia) and pancreatic islet dysfunction with a tendency to develop diabetes, cardiovascular disease, and other disorders at a young age. Such a situation seems to be happening in urban India. Therefore, the nutritional history of a population becomes an important determinant of its current health.

Kuh and Ben-Shlomo [28] synthesized a "life course" model for NCD stressing that risk for these conditions operates cumulatively throughout life. A WHO committee adopted these ideas to include many disorders [29]. To accommodate the new evidence since the coining of the original term "fetal origins of adult disease (FOAD)," the International Society for Developmental Origins of Health and Disease also adopted the new term, "developmental origins of health and disease" (DOHaD) [30].

There is a growing recognition of the importance of environmental factors acting on the genotype throughout the life cycle of an individual to progressively modify its phenotype. Clearly there are windows of time in the lifecycle when the susceptibility of the genome to such an influence is very high. The periconceptional and intrauterine period seem to be the most crucial, when a small change in environment could have a large effect on the phenotype. Any preventive intervention will therefore have to start in utero, and improving the health of young girls will be a very important aspect of such an approach. The slogan of the UN Expert Meeting held in April 2008, "Woman's Health is a Nation's Wealth" reflects this philosophy [31]. This must represent a paradigm shift in the prevention of the NCD epidemic.

7. Conflict of interest statement

The author declares that there is no duality of interest associated with this manuscript.

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References

[1] International Diabetes Federation. Diabetes atlas. 3rd edition. Brussels: IDF; 2006.
[2] Wild S, Roglic G, Green A, Sicree R, King H. Global prevalence of diabetes: estimates for the year 2000 and projections for 2030. Diabetes Care 2004;27(10):1047–53.
[3] Yajnik CS. The insulin resistance epidemic in India: fetal origins, later lifestyle, or both? Nutr Rev 2001;59:1–9.

[4] Gillies CL, Abrams KR, Lambert PC, Cooper NJ, Sutton AJ, Hsu RT, et al. Pharmacological and lifestyle interventions to prevent or delay type 2 diabetes in people with impaired glucose tolerance: systematic review and meta-analysis. BMJ 2007;334(7588):299.
[5] Barker DJ. Fetal nutrition and cardiovascular disease in later life. Br Med Bull 1997;53(1):96–108.
[6] Barker DJ. Mothers, babies and health in later life. 2nd ed. Edinburgh: Churchill Livingstone; 1998.
[7] Lucas A. Programming by early nutrition in man. In: Bock GR, Whelan J, editors. The childhood environment and adult disease. CIBA Foundation Symposium Chichester: John Wiley; 1991. p. 38–55.
[8] Gluckman PD, Hanson MA. Living with the past: evolution, development, and patterns of disease. Science 2004;305(5691):1733–6.
[9] Yajnik CS, Fall CH, Vaidya U, Pandit AN, Bavdekar A, Bhat DS. Fetal growth and glucose and insulin metabolism in four-year-old Indian children. Diabet Med 1995;12(4):330–6.
[10] Bavdekar A, Yajnik CS, Fall CH, Bapat S, Pandit AN, Deshpande V, et al. Insulin resistance syndrome in 8-year-old Indian children: small at birth, big at 8 years, or both? Diabetes 1999;48(12):2422–9.
[11] Yajnik CS. The lifecycle effects of nutrition and body size on adult adiposity, diabetes and cardiovascular disease. Obes Rev 2002;3(3):217–24.
[12] Bhargava SK, Sachdev HS, Fall CH, Osmond C, Lakshmy R, Barker DJ, et al. Relation of serial changes in childhood body-mass index to impaired glucose tolerance in young adulthood. N Engl J Med 2004;350(9):865–75.
[13] Yajnik CS, Fall CH, Coyaji KJ, Hirve SS, Rao S, Barker DJ, et al. Neonatal anthropometry: the thin-fat Indian baby: The Pune Maternal Nutrition Study. Int J Obes Relat Metab Disord 2003;27(2):173–80.
[14] Yajnik CS, Lubree HG, Rege SS, Naik SS, Deshpande JA, Deshpande SS, et al. Adiposity and hyperinsulinemia in Indians are present at birth. J Clin Endocrinol Metab 2002;87(12):5575–80.
[15] Rao S, Yajnik CS, Kanade A, Fall CH, Margetts BM, Jackson AA, et al. Intake of micronutrient-rich foods in rural Indian mothers is associated with the size of their babies at birth: Pune Maternal Nutrition Study. J Nutr 2001;131(4):1217–24.
[16] Yajnik CS, Deshpande SS, Panchanadikar AV, Naik SS, Deshpande JA, Coyaji KJ, et al. Maternal total homocysteine concentration and neonatal size in India. Asia Pac J Clin Nutr 2005;14(2):179–81.
[17] Yajnik CS, Deshpande SS, Jackson AA, Refsum H, Rao S, Fisher D, et al. Vitamin B_{12} and folate concentrations during pregnancy and insulin resistance in the offspring: The Pune Maternal Nutrition Study. Diabetologia 2008;51(1):29–38.
[18] McCance DR, Pettitt DJ, Hanson RL, Jacobsson LT, Knowler WC, Bennett PH. Birth weight and non-insulin dependent diabetes: thrifty genotype, thrifty phenotype, or surviving small baby genotype? BMJ 1994;308(6934):942–5.
[19] Freinkel N. Banting Lecture 1980. Of pregnancy and progeny. Diabetes 29(12): 1023-1035.
[20] Pettitt DJ, Aleck KA, Baird HR, Carraher MJ, Bennet PH, Knowler WC. Congenital susceptibility to NIDDM. Role of intrauterine environment. Diabetes 1988;37(5): 622–8.
[21] Dabelea D, Knowler WC, Pettitt DJ. Effect of diabetes in pregnancy on offspring: follow-up research in the Pima Indians. J Matern-Fetal Med 2000;9(1):83–8.
[22] Silverman BL, Rizzo TA, Cho NH, Metzger BE. Long-term effects of the intrauterine environment: the Northwestern University Diabetes in Pregnancy Center. Diabetes Care 1998;21(Suppl 2):B142–9.
[23] Krishnaveni GV, Hill JC, Leary SD, Veena SR, Saperia J, Saroja A, et al. Anthropometry, glucose tolerance, and insulin concentrations in Indian children: relationships to maternal glucose and insulin concentrations during pregnancy. Diabetes Care 2005;28(12):2919–25.
[24] Waterland RA, Jirtle RL. Transposable elements: targets for early nutritional effects on epigenetic gene regulation. Mol Cell Biol 2003;23(15):5293–300.
[25] Lillycrop KA, Phillips ES, Jackson AA, Hanson MA, Burdge GC. Dietary protein restriction of pregnant rats induces and folic acid supplementation prevents epigenetic modification of hepatic gene expression in the offspring. J Nutr 2005;135(6):1382–6.
[26] Sinclair KD, Allegrucci C, Singh R, Gardner DS, Sebastian S, Bispham J, et al. DNA methylation, insulin resistance, and blood pressure in offspring determined by maternal periconceptional B vitamin and methionine status. Proc Natl Acad Sci U S A 2007;104(49):19351–6.
[27] Robertson K. DNA methylation and human disease. Nat Rev Genet 2005;6(8): 597–610.
[28] Kuh D, Ben-Shlomo Y. A life-course approach to chronic disease epidemiology. 1st ed. Oxford: OUP; 1997.
[29] Aboderin I, Kalache A, Ben-Shlomo Y. Life course perspectives on coronary heart disease, stroke and diabetes: key issues and implications for policy and research. Geneva: WHO; 2001.
[30] International Society for Developmental Origins of Health and Disease: DOHaD. Accessed August 31, 2008: www.mrc.soton.ac.uk/dohad/.
[31] World Diabetes Foundation, Global Alliance for Women's Health. Diabetes, Women, and Development. Meeting summary, expert recommendations for policy action, conclusions, and follow-up actions. Int J Gynecol Obstet 2009.