Nutrition, Growth, and Body Size in Relation to Insulin Resistance and Type 2 Diabetes

Chittaranjan S. Yajnik, MD

Address
Diabetes Unit, King Edward Memorial Hospital Research Center, Rasta Peth, Pune 411011, India.
E-mail: diabetes@vsnl.com

Current Diabetes Reports 2003, **3:**108–114
Current Science Inc. ISSN 1534-4827

Nutritional and genetic factors interact in the etiology of type 2 diabetes. Undernutrition followed by overnutrition increases adiposity and the risk of diabetes. The thrifty hypotheses suggest that the nutritional challenges could have happened thousands of year ago (thrifty gene selection) or during one's intrauterine life (thrifty phenotype). Current strategies for the prevention of diabetes are related to avoiding overnutrition.

Introduction

There is an escalating epidemic of type 2 diabetes and insulin resistance syndrome in the world, especially affecting the developing countries [1]. It is estimated that more than half the diabetic patients in the world will be from the developing countries by the year 2025. Indians are particularly affected, both in India [2] and abroad [3]. Between 1972 and 2000, there was a fivefold increase in the prevalence of type 2 diabetes in urban India; the total number of diabetic patients in India was estimated to be more than 25 million in the year 2000 and predicted to rise to more than 60 million by 2025—one in five diabetic patients in the world will then be an Indian.

The causes of the diabetes "epidemic" are not clear, but rapid lifestyle changes in populations with high genetic susceptibility ("thrifty genotype") [4] or programmed by early life growth retardation ("thrifty phenotype") [5,6••] are two not necessarily mutually exclusive possibilities. In either case, inadequate or irregular food supply is thought to initiate genetic or nongenetic mechanisms, which allow the individual to survive the scarcity. These adaptations, however, predispose the individual to obesity (especially in the "central" adipose tissues) during periods of excess intake or reduced energy expenditure. In turn, obesity and the associated insulin resistance increase the risk of type 2 diabetes [7]. Thus, the two thrifty hypotheses link nutritional deficiency followed by excess with type 2 diabetes. In clinical practice attention is usually paid only to the excess nutrition and obesity in the periods immediately preceding the diagnosis of type 2 diabetes. The thrifty hypotheses, conversely, remind us of the past circumstances of food deprivation; with the thrifty genotype it might have happened thousands of years ago, in the thrifty phenotype it happens in an individual's own lifetime or during preceding few generations.

In this article, I review the role of nutrition during the life cycle of an individual in the genesis of insulin resistance and diabetes, thus relating more to the thrifty phenotype. I discuss this from the view of the "fetal insulin hypothesis," which offers a genetic basis for the same. Special comments are made on findings from India where the largest number of diabetic patients live. I did not discuss animal evidence, but excellent reviews are available.

The Two Thrifty Hypotheses

Neel proposed the thrifty genotype hypothesis in 1962 to explain the high prevalence of diabetes in Western societies. He proposed that genetic mechanisms, which favored deposition and storage of energy, were selected in the hunter-gatherer days and helped survival by tiding over lean periods. These days when food is available throughout the year and in adequate quantities, the thrifty genes promote obesity and the insulin resistance syndrome. Despite intensive efforts, no genetic markers have been shown to be consistently associated with type 2 diabetes in humans. In the absence of molecular markers, the hypothesis remains untestable and teleological. Prevention focuses attention on efforts to avoid obesity. Identification of the genetic markers will help diagnose individuals at risk, may allow targeted therapy, and in the future some form of "gene therapy."

Hales *et al.* [8] and Barker *et al.* [9] reported an inverse relationship between birth weight and hyperglycemia and insulin resistance in later life. Growth retardation rather than prematurity was thought to be responsible. The relationship was continuous and graded (*ie,* across the whole range of birth weights and not only

in the "low birth weight"). These associations were confirmed in many different countries but not in two developing countries (India and Guatemala) [10,11]. It was argued that low birth weight represents fetal undernutrition and growth retardation. Maternal undernutrition was thought to be responsible. An undernourished fetus, to tide over the crisis, alters its metabolic-endocrine pathways and becomes insulin resistant. This is reflected in reduced growth rate and small size. The persistence of metabolic-endocrine and structural changes in later life ("programming") leads to the insulin resistance syndrome and type 2 diabetes when the food supply becomes adequate or excessive. It is proposed that improvement of maternal nutrition and fetal size will reduce the prevalence of type 2 diabetes. The increased risk of obesity and diabetes in "macrosomic" children of diabetic mothers was not apparent in any of their historic cohorts. Survival bias is a likely problem, especially for studies involving the elderly who survived the second world war. Some populations showed a U-shaped relationship between birth weight and adult diabetes [12], and two reports from the developing countries showed no relationship with low birth weight [10,11]. It has recently been argued that the low birth weight and diabetes connection may not be relevant now in the well-fed populations from the developed countries [13].

The majority of studies have shown low birth weight to predict insulin resistance rather than insulin deficiency. This relationship is usually seen after adjustment for the strong influence of current size. Some have suggested that this may indicate an association with change in size from birth rather than to size at birth itself [14]. Individuals who are born small but become big are the most affected. In studies where data is available, rapid childhood growth rate is a strong predictor of insulin resistance [15•,16] and future type 2 diabetes [17,18•]. Another significant issue is that there is a sexual dimorphism in the details of the birth weight–adult disease relationship. This may point toward different mechanisms underlying this relationship in the two sexes and will have implications for interventions. It may also point toward genetic factors involved in these relationships.

The fetal insulin hypothesis suggests that the small birth weight–diabetes relationship has a genetic basis based on the role of insulin as a growth-promoting hormone in utero [19]. Genetic defects causing reduced insulin secretion or reduced insulin sensitivity in utero will affect the size of the insulin-dependent organs. Maternal diabetes affects fetal size by stimulating fetal insulin secretion, and masks the effects of a genetic mutation. A baby's genes and maternal metabolism (*ie,* intrauterine environment) thus interact to affect the size of the baby, but the risk of diabetes is related to the genetic predisposition. No robust genetic markers of type 2 diabetes have yet been described and molecular testing of this hypothesis is difficult.

Size at Birth and Risk of Diabetes

Birth weight

The archival nature of these studies meant that the only birth measurement available in the most studies was weight. Birth weight is a crude reflector of the complexities of intrauterine growth; a given birth weight can be arrived at by different rates of growth in different intrauterine periods. Birth weight also does not tell us about the body composition, a major determinant of disease. It is clear, however, that it captures some aspect of intrauterine development that is relevant to future risk of diabetes. The mechanisms and events leading to small size at birth may be more important determinants of future risk rather than small size itself.

The relationship between birth weight and subsequent diabetes is not always linear, and biologically it may be U-shaped, suggesting an increased risk at both the lower and the higher ends of birth weights [12]. Heavy babies born to diabetic mothers have a higher risk of diabetes in later life and probably make a major contribution to the upswing of the U-shape. Thus, the factors contributing to the etiology of diabetes are different in the two arms of the U-shape. Depending on a number of factors (*ie,* the ethnic and the historic background of the population being studied, age of the subjects, characteristics of the "nonresponders," and statistic correction for current size), the relationship may deviate from the U-shape and affect the conclusions that are drawn. Extrapolation of results from one population to another is thus not advisable. The term "small baby syndrome" may also be misleading.

Gestational period and the sex of the baby are the most important determinants of birth size and may contribute variably in different populations to the size at birth. Indians deliver a week or more earlier than white Caucasians. Maternal nutrition, stress, and related hormonal disturbances may determine mildly preterm parturition and could confound the birth weight–adult disease relationship [20].

Other birth measurements

Some studies have reported a relationship with shortness at birth (*eg,* India, men in Iceland) [10,21], although women in Iceland showed a U-shaped relationship with length at birth and no relationship with birth weight. Smaller head circumference predicted diabetes in China [22], whereas diabetic Indian men had larger head circumference at birth (Raghupathy, Unpublished data). Many studies report a strong predictive value for low ponderal index (*ie,* weigh/ht^3, a measure of "thinness") [23], although in India high ponderal index was predictive [10]. Low ponderal index has been interpreted to represent poor muscle mass. However, the relationship between ponderal index and body fat is different in different populations, making interpretation difficult. Indians have a higher percentage of body fat for a given ponderal index [24]. Body fat is the most important predictor of insulin resistance

and diabetes but is not routinely measured at birth. A variable relationship between body fat and other measurements could be responsible for contradictory findings in different studies.

The thin-fat Indian baby

In the Pune Maternal Nutrition Study, we measured detailed anthropometry at birth in six villages near Pune [24]. The mean birth weight of these babies was 2614 g and 28% were low birth weight (*ie*, < 2500 g). We thus confirmed that Indian babies are among the smallest in the world. In comparison with the white Caucasian British babies (measured using comparable techniques), the Indian babies were lighter, shorter, and thinner (ponderal index). The abdominal circumference was the smallest comparative measurement in Indian babies, skinfolds were closest to those of the British babies, and the head circumference was in between. Thus, the Indian babies are thin in the abdominal viscera and skeletal muscle (*ie*, "protein-rich" tissues) but relatively "fat." In a subsequent study, we confirmed these findings and also showed that the cord leptin concentrations in Indian babies are comparable with those in the British babies [25]. Indian neonates have a higher body fat percent compared with British babies.

The rural Indian mothers were considerably smaller (42 kg, 1.52 m, and 18.0 kg/m^2) compared with the British mothers (63 kg, 1.62 m, 23.5 kg/m^2) and delivered about a week earlier. Different body measurements of the mother are "mirrored" in her neonate [26]. Maternal anthropometric measurements may be interpreted as reflecting her "nutritional history" [15•]. Thus, maternal head circumference (reflecting her growth in early life) was the most consistent predictor of all the measurements of the baby. The fattest babies were born to mothers who were short and fat (suggesting poor growth in early life but positive energy balance in later years).

Is 'brain-sparing' a precursor to obesity?

The Indian baby's propensity to retain body fat at the cost of muscle and visceral organs could be contributed by genetic mechanisms about which we know little. The "body composition" suggests that there is a selective failure of growth in protein-rich tissues (*eg*, skeletal muscle and abdominal viscera) but not the brain and the lipid-rich adipose tissue. This could represent a tissue-selective or nutrient-selective resistance to the growth-promoting action of insulin. The brain does not need insulin for transfer of nutrients across the cell membrane and thus continues to grow despite changing insulin response of the pancreas in the face of variable nutrient supply. This is the classic "brain-sparing" of a growth-retarded fetus [27]. Seventy percent of dry weight of the brain consists of lipids, and therefore its growth will depend on adequate supply of precursors (*eg*, triglycerides, phospholipids, cholesterol and its derivatives). Adipose tissue will supply some of these. The mother achieves higher circulating levels of nutrients by being insulin resistant, thus promoting transplacental transfer [28]. Preductal diversion of blood flow in the developing fetus ensures supply to the brain but the postductal organs will be deprived, including liver, kidneys, pancreas, and muscle.

Thus, the teleological origin of insulin resistance and obesity may be in the brain-sparing of a jeopardized fetus rather than the need to store energy in the hunter-gatherer days. It will be useful to follow up these babies to study if the neonatal body composition influences adult body composition and predicts susceptibility to different diseases. Adult Indians have higher body fat percent and central fat compared with white Caucasians and black African Americans, and this contributes to their insulin resistance and increased cardiovascular risk [29].

Parental size

Maternal influence

The thrifty phenotype implies that small-sized "malnourished" mothers would increase the risk of diabetes in the offspring. The thrifty genotype predicts that diabetes may be more common in the offspring of obese mothers. Studies show variable associations. In China, lighter babies born to low body mass index (BMI) mothers had increased risk of diabetes [30]; in Finland, lighter and thinner babies born to mothers with larger BMI had increased risk [17,18•]; and in India, fatter babies born to heavier mothers had a higher risk of diabetes [10]. Insulin resistance (usually measured as fasting hyperinsulinemia) in light and thin babies is predicted by mothers with low BMI; but in macrosomic babies, it is predicted by overweight gestational diabetic mothers [31]. Thus, the relationship between maternal size, offspring birth size, and later, insulin resistance and diabetes, is variable.

Part of the explanation for the above differences may lie in the determinants of small size at birth. Placental insufficiency and smoking are major causes of small size at birth in the well-fed populations from the developed countries, whereas small maternal size (maternal constraint), undernutrition, and infections are major determinants in developing countries like India. These underlying causes may be major determinants of the future risks for the fetus, and some of these may be genetic.

Paternal influence

Fathers do not figure into the thrifty phenotype hypothesis. Paternal size (especially height) is a determinant of size at birth and during subsequent life [32]. When corrected for the socioeconomic status and the "assortative mating" effect (maternal size), this would be interpreted as genetic effect. The fetal insulin hypothesis predicted that paternal insulin resistance would be associated with lower birth weight. This was true in babies of diabetic Pima Indian fathers [33] and in the United Kingdom [34], but not in babies of insulin-resistant Indian fathers [35]. Paternal

influences on birth size may be masked because of "maternal constraint" and manifest only after birth. A recent report from Sweden demonstrated an association between higher nutrition in paternal grandfathers and risk of diabetes in the offspring, and it raises interesting possibilities of intergenerational transmission [36].

Maternal Nutrition, Metabolism, and Fetal Size

At the heart of the thrifty phenotype hypothesis is the concept of fetal undernutrition. Small size at birth is used as a surrogate for fetal undernutrition, poor growth, and maternal undernutrition. Body size, growth, and nutrition may not be used interchangeably. Small fetal size may reflect small parental size rather than any disturbance of its nutrition and growth. The maternal-fetal supply line is long and controlled at different points [37•]. Small fetal size, even when a result of fetal undernutrition and poor growth rate, need not necessarily be due to poor maternal nutrition. Infections, inflammation, and placental pathology may be important.

Maternal food intake

Macronutrients

Assessment of food intake is difficult, and many times unreliable. There is a poor relationship between maternal caloric intake and fetal size both in well-fed women from the developed countries as well as in rural Indian women. A recent study from Southampton showed that small and thin babies were born to mothers who ate high amounts of carbohydrates in early pregnancy and low amounts of dairy protein in late pregnancy [38]. The placenta was smaller and cord levels of insulin, proinsulin, and split proinsulin were lower. However, in the Pune Maternal Nutrition Study a similar pattern of food intake did not predict thinness at birth [39], only fat intake predicted birth size. In these women who ate approximately 1800 kcal/d, more than 70% of calories came from carbohydrates and average daily intake of proteins was 45 g and fats 35 g. Of the many trials of maternal feeding in recent years, one that has shown a clear benefit was the Gambian trial of feeding pregnant women 1200-cal biscuits, which caused an increase in birth weight of more than 200 g in the lean season and reduced perinatal mortality [40].

An issue frequently forgotten but now revived is the "quality" of the calories consumed. A small but intensive study in the United States showed symmetrical overgrowth of the baby in mothers who ate "cafeteria" type (high glycemic index) rather than the "aboriginal" type (low glycemic index) carbohydrates [41]. Larger studies with follow-up of the offspring to study their growth and metabolism will be crucial.

Shiell *et al.* [42] have investigated two groups of people born in Scotland whose mothers were fed high-protein diet in pregnancy or their dietary intakes were carefully recorded. High maternal intake of proteins (*eg,* meat, fish, and beef) and fats predicted smaller increments in insulin concentrations during an oral glucose tolerance test in middle-aged subjects. It is not easy to interpret these findings, but they may suggest that imbalances in maternal macronutrient intake may affect the development of fetal systems that control insulin secretion.

Exposure of the mothers to Dutch famine during the first trimester of pregnancy increased risk of obesity in the offspring at a young age [43] and also increased cardiovascular risk (*eg,* blood pressure, lipids, fibrinogen) in middle age [44]. Exposure to famine in the middle and the last trimester led to a small increase in glucose and insulin concentrations after an oral glucose load, but no increase in diabetes [45]. All risk factors were worse in those who became obese later. These effects were independent of birth weight. The epidemiologic design of these studies necessarily has a number of limitations, including survivor bias and smaller numbers. The most severely affected women will be less fertile, have higher pregnancy wastage, and have higher chances of dying in pregnancy. People exposed to the Leningrad Siege failed to reveal any abnormalities of glucose insulin metabolism or other cardiovascular risk factors [46].

Micronutrients

There is a lot of interest in relating maternal micronutrient nutrition with fetal growth and risk of later disease; these have been recently reviewed [47,48]. The strongest predictors of fetal size in the Pune Maternal Nutrition Study were the frequencies of consumption of foods high in micronutrients (*ie,* green leafy vegetables, fruits, and milk) [39]. These relationships remained significant when controlled for potential confounders (*ie,* maternal size, macronutrient intake, socioeconomic status). Circulating levels of folate and vitamin C predicted fetal size.

Maternal physical activity

Mild to moderate physical exercise in pregnancy will have beneficial metabolic-endocrine and cardiovascular effects. Excessive maternal physical activity, especially involving certain postures and large muscle groups, predicts reduced fetal size and increases risk of low birth weight [49]. In relating maternal nutrition to fetal growth, the activity aspect is frequently forgotten. Long-term effects on the offspring of maternal physical activity need to be carefully studied.

Maternal metabolism in pregnancy

The role of maternal glycemia, even in the "normal" range, in promoting fetal growth is well known [50]. Gestational diabetes is a strong risk factor for diabetes in the offspring [51]. Gestational diabetes accounts for 70% of the risk of diabetes in the young in Pima Indians. There is growing interest in maternal circulating lipids and fetal growth [52]. In the Pune Maternal Nutrition Study, circu-

lating maternal triglycerides and cholesterol had a strong relationship to fetal size. Maternal insulin resistance is a major determinant of circulating lipid concentrations. In gestational diabetes, these levels are high and affect fetal size and adiposity. Adequate treatment with insulin may help to an extent. Controlling maternal insulin resistance may offer an opportunity to prevent fetal adiposity and reduce its future risk of diabetes; the role of metformin is being investigated.

Breast-feeding and weaning foods

The protective role of breast-feeding for type 2 diabetes was first demonstrated in Pima Indians [53]. The underlying mechanism needs further studies. This could be an important factor in prevention strategies in a community.

Childhood Growth ('Catch-up')

Diabetes usually affects obese people, and childhood obesity is a strong risk factor for diabetes. Conversely, small size at birth and at 1 year of age predicted later diabetes [8]. Those born small but who grow big have the highest risk. Studies in children showed that accelerated childhood growth and larger size at the time of the study were strong determinants of the insulin resistance syndrome [15•]. In urban India, it was demonstrable at 4 and 8 years of age [54]. In South Africa, there was a strong relationship between growth velocity and insulin resistance in childhood [16]. Serial childhood growth data in Finland showed that diabetic people were born light and thin (low ponderal index), and continued to be small and thin in infancy, but that their growth rate accelerated from 2 years onward and they grew faster in height and weight throughout childhood compared with those who did not become diabetic [17,18•]. A component of accelerated childhood growth is the "adiposity rebound" (*ie,* the age at which BMI starts rising). In Finland, earlier age at the adiposity rebound was a strong risk factor for type 2 diabetes [18•].

In these Finnish cohorts, the effect of childhood growth was more pronounced in those who weighed less than 3 kg at birth. These people were born to mothers who were heavier and had higher BMI. These findings indicate that maternal undernutrition in pregnancy was unlikely to be a problem, and that placental dysfunction or other distal factors contributed to the small size of the fetus.

What are the determinants of the accelerated growth in childhood? More availability of food is one possibility. Excess hunger is another possibility. In Pune urban children, we found that childhood growth velocity is more related to paternal size than maternal size. It would be interesting to study the genetics of childhood growth, which might lead us to genes for type 2 diabetes. At present, there is little information on the relationship between pubertal growth and type 2 diabetes. Further research should clarify if the risks of accelerated growth in childhood are continued, exaggerated, or reversed during this period.

A synthesis

I have discussed and highlighted the importance of nutritional history, growth pattern, and size of an individual in the evolution of type 2 diabetes. There is a complicated interaction between the genome of the individual and his or her nutrition throughout life, starting from conception, and it is influenced by what happened in previous generations. Nutritional pressures many generations ago might have led to genetic selection of "'fit genotypes"; current interest has focused on events in one's early life and a few generations before. Hales and Barker deserve special applause for pointing out this important fact. Undernutrition and overnutrition are both involved; if the latter follows the former it promotes insulin resistance and increased risk of type 2 diabetes.

The current controversies in this field focus on genetic versus nutritional (environmental) determinants of metabolism, growth, and size. Size at birth is an important predictor of future diabetes but the relationship is U-shaped. Birth weight does not tell about body composition, which is a strong determinant of type 2 diabetes. Maternal nutrition has a complex influence on fetal size and body composition, and genetics is an important player in the outcome. There is only preliminary information on the effects of individual nutrients; when available, such information will help ideas of intervention. Maternal insulin resistance, glycemic level, and concentration of circulating lipids in pregnancy are important determinants of obesity and diabetes in the offspring. Current information does not permit a uniform nutritional intervention in the intrauterine life to reduce the risk of diabetes in the offspring. Excess feeding is likely to be as detrimental as underfeeding, and the balance of nutrients seems very important.

Accelerated growth after birth is associated with insulin resistance. Further research is needed to understand what aspect is detrimental. The prevention of childhood obesity is a priority and may be more beneficial in those born small. Whether nutritional intervention will modify accelerated childhood growth and prevent diabetes remains to be seen. Avoiding obesity and promoting physical fitness at any time of life has a salutary effect on metabolism and helps prevent type 2 diabetes.

I conceptualize the interaction between nutrition and genetic factors in the evolution of diabetes to be a continuous process throughout life and it reflects in growth, size, and glucose-insulin metabolism. Even though continuous, there are well-defined stages in life in which the interaction has long-term implications (critical periods: *ie,* the intrauterine period, childhood, puberty, and pregnancy). The interactions are interactive and iterative, the system learns from its previous experiences, and what happened before has an important bearing on the result of an "insult" in later life. Solutions to the problem will have to take into account the complexity of such a system.

Conclusions

The rising epidemic of type 2 diabetes seems to be related to a biphasic nutritional insult, undernutrition followed by overnutrition. The "thrifty genes" originated thousands of years ago, the thrifty phenotype originates in early life. Susceptibility to type 2 diabetes is traceable to altered growth in utero and childhood and obesity at any time in lifetime. The markers of genetic and nutritional (environmental) determinants are inadequately understood, nor is their relative contribution clear. Both mechanisms seem to change body composition and affect insulin action. Prevention of obesity throughout life, including during intrauterine life, is crucial in the prevention of type 2 diabetes. Gestational hyperglycemia is a major risk factor for diabetes in the offspring as well as the mother; its prevention and effective treatment will make an important contribution to intergenerational transmission of type 2 diabetes.

Acknowledgments

I am grateful to all subjects, colleagues, and collaborators who helped my studies. Special thanks to Professor Jeffrey Robinson (Adelaide, Australia) for useful discussions and comments, to Ms. Hannah Farrant (Southampton, UK) for help in the literature search, and The Wellcome Trust, London, for funding my research.

References and Recommended Reading

Papers of particular interest, published recently, have been highlighted as:

- • Of importance
- •• Of major importance

1. King H, Aubert RE, Herman WH: **Global burden of diabetes, 1995–2025; prevalence, numerical estimates and projections.** *Diabetes Care* 1998, **21:**1414–1431.
2. Ramchandran A, Snehalatha C, Kapur A, *et al.*: **High prevalence of diabetes and impaired glucose tolerance in India: National Urban Diabetes Survey.** *Diabetologia* 2001, **9:**1094–1101.
3. McKeigue PM, Shah B, Marmot MG: **Relation of central obesity and insulin resistance with high diabetes prevalence and cardiovascular risk in South Asians.** *Lancet* 1991, **337:**971–973.
4. Neel JV: **Diabetes mellitus: a "thrifty" genotype rendered detrimental by "progress"?** *Am J Human Genet* 1962, **14:**353–362.
5. Hales CN, Barker DJP: **Type 2 (non-insulin dependent) diabetes: the thrifty phenotype hypothesis.** *Diabetologia* 1992, **35:**595–601.
6. •• Hales CN, Barker DJP: **The thrifty phenotype hypothesis.** *Brit Med Bull* 2001, **60:**5–20.

An updated version of the hypothesis with recognition of the importance of maternal hyperglycemia and childhood growth.

7. Reaven G: **Role of insulin resistance in human disease.** *Diabetes* 1988, **37:**1595–1607.
8. Hales CN, Barker DJP, Clark PMS, *et al.*: **Fetal and infant growth and impaired glucose tolerance at age 64.** *BMJ* 1991, **303:**1019–1022.
9. Barker DJP, Hales CN, Fall CHD, *et al.*: **Type 2 (non-insulin dependent) diabetes mellitus, hypertension and hyperlipidemia (syndrome X): relation to reduced fetal growth.** *Diabetologia* 1993, **36:**62–67.
10. Fall CHD, Stein CE, Kumaran K, *et al.*: **Size at birth, maternal weight, and type 2 diabetes in South India.** *Diabet Med* 1998, **15:**220–227.
11. Stein AD, Conlisk AJ, Torun B, *et al.*: **Cardiovascular disease risk factors are related to adult adiposity but not birth weight in young Gualemalan adults.** *J Nutr* 2002, **132:**2008–2014.
12. McCance DR, Pettitt DJ, Hanson RL, *et al.*: **Birth weight and non-inslin dependent diabetes: thrifty genotype, thrifty phenotype, or surviving small baby genotype?** *BMJ* 1994, **308:**942–945.
13. Wilkin T, Metcalf BS, Murphy MJ, *et al.*: **The relative contributions of birth weight, weight change, and current weight to insulin resistance in contemporary 5-years-olds.** *Diabetes* 2002, **12:**3468–3472.
14. Lucas A, Fewtrell MS, Cole TJ: **Fetal origins of adult disease—the hypothesis revisited.** *BMJ* 1999, **319:**245–249.
15. • Yajnik CS: **Interactions of perturbations in intrauterine growth and growth during childhood on the risk of adult-onset disease.** *Proc Nutr Soc* 2000, **59:**257–265.

A review of information from different parts of the world, including challenges to the thrifty phenotype concept.

16. Crowther NJ, Cameron N, Trusler J, Gray IP: **Association between poor glucose tolerance and rapid post natal weight gain in seven-year-old children.** *Diabetologia* 1997, **41:**1163–1167.
17. Forsen T Eriksson J, Tuomilehto J, *et al.*: **The fetal and childhood growth of persons who develop type 2 diabetes.** *Ann Intern Med* 2000, **133:**176–182.
18. • Eriksson JG, Forsen T, Tuomilehto J, *et al.*: **Early adiposity rebound in childhood and risk of type 2 diabetes in adult life.** *Diabetologia* 2003, in press.

A classic paper tracing early life growth and adiposity rebound of people who develop diabetes.

19. Hattersley AT, Tooke JE: **The fetal insulin hypothesis: an alternative explanation of the association of low birth weight with diabetes and vascular disease.** *Lancet* 1999, **353:**1789–1792.
20. Gibb W, Challis JR: **Mechanisms of term and preterm birth.** *J Obstet Gynaecol Can* 2002, **24:**874–883.
21. Birgisdottir BE, Gunnarsdottir I, Thorsdottir I, *et al.*: **Size at birth and glucose intolerance in a relatively genetically homogeneous, high birth weight population.** *Am J Clin Nutr* 2002, **76:**399–403.
22. Mi J, Law C, Zhang K, *et al.*: **Association of body size at birth with impaired glucose tolerance during their adulthood [in Chinese].** *Zhonghua Yu Fang Yi Xue Za Zhi* 1999, **33:**209–213.
23. Phillips DI, Barker DJ, Hales CN, *et al.*: **Thinness at birth and insulin resistance in adult life.** *Diabetologia* 1994, **37:**150–154.
24. Yajnik CS, Fall CHD, Rao S, *et al.*: **Neonatal anthropometry: the thin fat Indian baby. The Pune Maternal Nutrition Study.** *Int J Obesity* 2003, in press.
25. Yajnik CS, Lubree HG, Rege SS, *et al.*: **Adiposity and hyperinsulinemia in Indians are present at birth.** *J Clin Endocrinol Metab* 2002, **12:**5575–5580.
26. Fall CHD, Yajnik CS, Rao S, Coyaji KJ: **The effects of maternal body composition before pregnancy on fetal growth. The Pune Maternal Nutrition Study.** In *Fetal Programming Influences on Development and Disease in Later Life.* Edited by Shaughn PM, *et al.* London: Royal College of Obstetrics and Gynecology; 1999:231–245.
27. Winnick M, Noble A: **Cellular response in rats during malnutrition at various stages.** *J Nutr* 1966, **89:**300–306.
28. Catalano PM, Thomas AJ, Huston LP, Fung CM: **Effect of maternal metabolism on fetal growth and body composition.** *Diabetes Care* 1998, **(suppl 2):**B85–B90.
29. Banerji MA, Faridi N, Atluri R, *et al.*: **Body composition, visceral fat, leptin, and insulin resistance in Asian Indian men.** *J Clin Endocrinol Metab* 1999, **84:**137–144.
30. Mi J, Law C, Zhang K-L, *et al.*: **Effects of infant birth weight and maternal body mass index in pregnancy on components of the insulin resistance syndrome in China.** *Ann Intern Med* 2000, **132:**253–260.

31. Pettitt DJ, Baird HR, Aleck KA, *et al.*: **Excessive obesity in offspring of Pima Indian women with diabetes during pregnancy.** *N Engl J Med* 1983, **308:**242–245.
32. Godfrey K, Walker-Bone K, Robinson S, *et al.*: **Neonatal bone mass: influence of parental birthweight, maternal smoking, body composition and activity during pregnancy.** *J Bone Miner Res* 2001, **16:**1694–1703.
33. Lindsay RS, Dabelea D, Roumain J, *et al.*: **Type 2 diabetes and low birth weight. The role of paternal inheritance in the association of low birth weight and diabetes.** *Diabetes* 2000, **49:**445–449.
34. Hypponen E, Smith GD, Power C: **Parental diabetes and birth weight of offspring: intergenerational cohort study.** *BMJ* 2003, **326:**19–20.
35. Yajnik CS, Coyaji K, Joglekar CV, *et al.*: **Paternal insulin resistance and fetal growth: problem for the "fetal insulin" and the "fetal origins" hypotheses.** *Diabetologia* 2001, **9:**1197–1198.
36. Kaati G, Bygren LO, Edvinsson S: **Cardiovascular and diabetes mortality determined by nutrition during parents' and grandparents' slow growth period.** *Eur J Hum Genet* 2002, **10:**682–688.
37.• Harding JE: **The nutritional basis of the fetal origins of adult disease.** *Int J Epidemiol* 2001, **30:**15–23.

An authoritative review of the complexities of the relationship between maternal nutrition and fetal nutrition.

38. Godfrey K, Robinson S, Barker DJ, *et al.*: **Maternal nutrition in early and late pregnancy in relation to placental and fetal growth.** *BMJ* 1996, **312:**410–414.
39. Rao S, Yajnik CS, Kanade A, *et al.*: **Intake of micronutrient rich foods in rural Indian mothers and size of their babies at birth.** *J Nutr* 2001, **131:**1217–1224.
40. Ceesay SM, Prentice AM, Cole TJ, *et al.*: **Effect on birth weight and perinatal mortality of maternal dietary supplemenation in rural Gambia.** *BMJ* 1997, **315:**786–790.
41. Clapp JF: **Exercise in pregnancy: a clinical update.** *Clin Sports Med* 2000, **19:**273–286.
42. Shiell AW, Campbell DM, Hall MH, Barker DJ: **Diet in late pregnancy and glucose-insulin metabolism of the offspring 40 years later.** *BJOG* 2000, **107:**890–895.
43. Ravelli GP, Stein ZA, Susser MW: **Obesity in young men after famine exposure in utero and early infancy.** *New Engl J Med* 1976, **295:**349–353.
44. Roseboom TJ, van Der Meulen JH, Ravelli AC, *et al.*: **Effects of prenatal exposure to the Dutch famine on adult disease in later life: an overview.** *Twin Res* 2002, **4:**293–298.
45. Ravelli AC, Van der Meulen JHP, Michels RPJ, *et al.*: **Glucose tolerance in adults after prenatal exposure to famine.** *Lancet* 1998, **351:**173–177.
46. Stanner SA, Bulmer K, Andres C, *et al.*: **Does malnutrition in utero determine diabetes and coronary heart disease in adulthood? Results from the Leningrad siege study, a cross sectional study.** *BMJ* 1997, **315:**1342–1348.
47. McArdle HJ, Ashworth CJ: **Micronutrients in fetal growth and development.** *Brit Med Bull* 1999, **55:**499–510.
48. Fall CHD, Yajnik CS, Rao S, *et al.*: **Micronutrients and fetal growth.** *J Nutr* 2003, in press.
49. Clapp JF III: **Diet, exercise and feto-placental growth.** *Arch Gynecol Obstet* 1997, **260:**101–108.
50. Sermer M, Naylor CD, Gare DJ, *et al.*: **Impact of increasing carbohydrate intolerance on maternal-fetal outcomes in 3637 women without gestational diabetes. The Toronto Tri-Hospital gestational diabetes project.** *Am J Obstet Gynecol* 1995, **173:**146–156.
51. Pettitt DJ, Aleck KA, Baird HR, *et al.*: **Congenital susceptibility to NIDDM: role of intrauterine environment.** *Diabetes* 1988, **37:**622–628.
52. Knopp RH, Warth MR, Charles D, *et al.*: **Lipoprotein metabolism in pregnancy, fat transport to the fetus, and effects of diabetes.** *Biol Neonate* 1986, **50:**297–317.
53. Pettitt DJ, Forman MR, Hanson RL, *et al.*: **Breastfeeding and incidence of non-insulin-dependent diabetes mellitus in Pima Indians.** *Lancet* 1997, **350:**166–168.
54. Bavdekar A, Yajnik CS, Fall CHD, *et al.*: **Insulin resistance in 8 year old Indian children.** *Diabetes* 1999, **48:**2422–2429.