Transmission of Obesity-Adiposity and Related Disorders from the Mother to the Baby

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Key Messages
- A conventional approach to non-communicable disease prevention targets unhealthy adult lifestyle.
- Epigenetic fetal programming is a novel idea.
- Human and animal studies support an ‘intrauterine programming’ of obesity, diabetes and other non-communicable diseases.
- Maternal nutritional imbalance, a deranged metabolism, stress and other factors contribute to fetal programming.
- Improving the health of young mothers will contribute to a ‘primordial’ prevention of non-communicable diseases in future generations.

Key Words
Obesity · Adiposity · Diabetes · Fetal programming · Intergenerational transmission · Primordial prevention · Mother and baby

Abstract
The conventional aetiological model of obesity and diabetes proposes a genetic predisposition and a precipitation by an unhealthy adult lifestyle. This hypothesis was challenged by David Barker who proposed that the intrauterine environment influences the risk of non-communicable diseases (NCDs). The original idea was based on fetal undernutrition because lower birth weight was associated with a higher risk of diabetes and heart disease. However, soon it was clear that the association was U shaped, and that the increased risk in large babies was driven by maternal obesity and diabetes. A number of human and animal studies have refined our ideas of ‘fetal programming’, which is now thought to be related to acquired chemical changes in DNA (methylation), histones (acetylation and other) and the role of non-coding miRNAs. Maternal nutritional disturbances are the major programming stimulus, in addition to a deranged metabolism, infections, maternal stress, extreme atmospheric temperature, etc. The first demonstration of a link between fetal ‘starvation’ and future ill-health was in the Dutch Hunger Winter studies. In the prospective Pune Maternal Nutrition Study, we found that small and thin Indian babies were more adipose compared to larger English babies, and their higher risk of future diabetes was reflected in higher insulin and leptin and lower adiponectin concentrations in the cord blood. This phenotype was partly related to a deranged 1-carbon metabolism due to an imbalance in vitamin B₁₂ (low) and folate (high) nutrition, which was also related to insulin resistance in the offspring. Maternal obesity and diabetes have made an increasing contribution to childhood obesity and diabetes at a young age. This was prominently shown in Pima Indians but is now obvious in all other populations. The best window of opportunity to prevent fetal programming of NCDs is in the periconceptional period. This is
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There is a rapidly growing epidemic of obesity in the world, both in developed and in developing countries [1]. Obesity is a risk factor for a large number of health problems including diabetes, hypertension and cancer, collectively called non-communicable diseases (NCDs). The treatment of obesity is ineffective and not without side effects. Unless a preventive strategy is quickly outlined, obesity and the NCD epidemic will have substantial adverse effects on the development of the world population.

Recent ideas have focused on the ‘first 1,000 days’ of life as the most important window in the programming of health and disease.

Since the description of the human genome, a number of genetic associations have been described for obesity and related disorders. This generated a lot of hype and hope that this will help us deal with the problem. The findings are, however, unlikely to contribute to the prevention of the epidemic. The search for modifiable risk factors has therefore expanded, and a number of risk factors (diet, inactivity, stress) are already described. Many clinical trials have shown a beneficial effect of correcting some of these risk factors, but this effect is usually small and short lived. A recent discovery that offers hope for preventing the burgeoning epidemic of obesity and NCDs is the recognition of the importance of ‘intrauterine programming’ [2]. This thought started with the demonstration that those exposed to the Dutch Hunger Winter in utero had an altered risk of obesity as adults [3]. This was followed by the ‘fuel-mediated teratogenesis’ idea in diabetic pregnancies [4] and was finally established with the ‘thrifty phenotype’ hypothesis from Southampton (UK) [5, 6]. Recent ideas have focused on the ‘first 1,000 days’ of life as the most important window in the programming of health and disease and offer hope that an intervention in early life could help prevent these disorders. We will discuss the scientific basis, observational and intervention evidence as well as future directions in this new paradigm called ‘developmental origins of health and disease’ (DOHaD) in relation to obesity and related NCDs. This article is not proposed to be a comprehensive review but an attempt to discuss some basic concepts.

Background

We sometimes forget that an individual is born at conception and not at delivery. The genome of the conceptus contains all the information for the development into a new individual. The information flows from the DNA to the RNA to the protein. The factors governing this flow contribute to the development and the differentiation of cells, tissues, organs and systems which contribute to the phenotype of the individual. Waddington [7] described all these processes which link the genotype to the phenotype at birth as ‘epigenetic’. Modern epigenetics investigates the molecular basis of the regulation of the flow of information, involving gene expression and function. This does not depend on the sequence of bases in the DNA molecule which is inherited from the parents, but on the differential regulation of genes by environmental factors at different times in the life course of an individual. Currently, three mechanisms are believed to be involved in this process: (1) methylation of DNA which prevents transcription, i.e. ‘silences’ the gene; (2) chemical modifications of histones (acetylation, methylation, etc.) which alter the chromatin structure and transcription, and (3) miRNAs which interfere with the translation of the mRNA. The DOHaD theory (fig. 1) proposes that the risk of obesity-adiposity-related NCDs is substantially influenced by intrauterine and postnatal environmental modifications of the epigenome. Occurring during crucial periods of the development, there is a permanent change in the structure and function of the organism (phenotype), which is called programming.

‘Early life programming’ offers hope that investment in early life could help prevent non-communicable disorders.

Periconceptional, intrauterine and postnatal periods are the most influential in programming. The periconceptional period encompasses the natural ‘wiping out’ of the inherited epigenome and the ‘reestablishment’ of a new one [8]. This period also covers vital processes such
as gametogenesis, fertilisation, implantation, morphogenesis, embryogenesis, organogenesis and placentation, all of which have a profound influence on the growth, development, differentiation and phenotype of an individual [9] (fig. 2). If the environment is not ideal (for example, maternal nutritional imbalance, altered metabolism, infections, exposure to environmental pollutants, etc.), this might lead to undesirable programming and induce the risk for later disease.

Barker’s [2, 10] ideas about intrauterine programming and DOHaD were based on retrospective cohorts in the UK, Finland and other countries. The most frequently available measure of intrauterine nutrition and growth was birth weight with very direct measurements of maternal nutrition. These studies showed that low birth weight was a predictor of future diabetes, hypertension, coronary heart disease and other NCDs [10]. The majority of these are associated with obesity (excess weight for a given height). It is to be appreciated that the BMI, the most frequently measured index of obesity, is not a measure of body fat but only a surrogate. A higher percent of body fat is more appropriately called ‘adiposity’ and necessitates direct measurements of body fat (skinfolds, bioimpedance, isotopic dilution, DXA, CT scan, MRI, etc.). It is important to distinguish between these measurements because the interpretation could be misleading, especially when comparing two different populations [11].
Maternal Nutrition

The most investigated causes of fetal programming of obesity-adiposity and NCDs are maternal-fetal nutrition and metabolism. Intriguingly, both undernutrition and overnutrition may be responsible.

The first indication that intrauterine undernutrition may be linked to future obesity and related disorders came from the follow-up of individuals who were in utero at the time of the Dutch Hunger Winter, when the Dutch population (including pregnant women) had to survive on a few hundred calories a day for many months. When maternal undernutrition occurred in the first and second trimesters of intrauterine life, the offspring were more likely to be obese as young adults, whereas those exposed in the third trimester were less likely to be obese [3]. It was postulated that in the first two trimesters, undernutrition affected the development of hypothalamic appetite centres, leading to overeating and obesity in postnatal life, while the reduced risk of obesity observed with third-trimester undernutrition was related to a reduction in the number of fat cells which develop during this period. A number of Dutch Winter Hunger studies have linked in utero undernutrition to a variety of outcomes such as diabetes, coronary heart disease, schizophrenia, etc. [12, 13].

The fetal undernutrition theory gained prominence with the publication of the ‘thrifty phenotype’ hypothesis of Hales and Barker [5]. They observed that low birth weight was a risk factor for diabetes, independent of the adult BMI and family history, and proposed that ‘diabetes was a result of the fetus having to be thrifty during its intrauterine life and in infancy’. This caused a considerable upset in the field because it challenged the dogma that diabetes resulted from genetic predisposition and an unhealthy adult lifestyle. Even though fetal nutrition depends on a complex supply line [14], maternal nutrition is the ultimate source of fetal nutrition. Therefore, improvement in the health and nutrition of women in their reproductive age might provide an intergenerational solution to the rapidly escalating epidemic of obesity and diabetes.

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The original studies of the thrifty phenotype were all conducted in European populations. Barker [personal communication] predicted that the link between fetal undernutrition and diabetes may be even more important in a country like India, where there is a history of multigenerational undernutrition. It is well recognised that macronutrition and diabetes may be even more important in India even in the absence of the conventional risk factor of obesity, and ‘malnutrition-related diabetes’ was reported from different parts of India [17, 18]. In collaboration with Prof. Barker and Caroline Fall, we set up a study in 4-year-old children born in our hospital (Pune Children’s Study) [19]. The average birth weight was 2.8 kg. Lower birth weight in these children was associated with higher glucose and insulin concentrations after glucose load, suggesting insulin resistance. When we followed up these children at 8 years of age, we were able to confirm the original observation and additionally found that the children who were born small but grown big at 8 years had the highest levels of adiposity, central obesity, insulin resistance and other cardiovascular risk factors [20]. This was the first demonstration of DOHaD in a developing population which suggested that a mismatch between intrauterine and postnatal experiences was conducive to an increased risk of NCDs. We therefore set up the Pune Maternal Nutrition Study (PMNS) to investigate the influence of maternal nutrition on fetal growth and the future risk of diabetes and other NCDs in 6 villages near Pune. This study has provided some notable findings.

The newborn Indian babies were small and thin (average birth weight = 2.7 kg, ponderal index = 2.4). However, a comparison of detailed anthropometric measurements of newborns in Pune and Southampton (UK) revealed an interesting story. The Indian babies were, on average, 800 g lighter than the English babies but had almost similar subscapular skinfold measurements, suggesting that the Indian babies had a low lean mass but a relatively high fat mass, what we called the ‘thin-fat’ Indian baby (fig. 4) [21]. This observation was similar to the findings in adult Indians and Europeans [11] and demonstrated that the adipose Indian body composition, which predisposes to a higher risk of diabetes and related disorders.
disorders, originates in intrauterine life, and that it is not a result of an unhealthy adult lifestyle. The use of MRI revealed that the Indian babies have a very small abdominal circumference (a marker of intrauterine growth restriction) but higher abdominal fat in both the subcutaneous and intra-abdominal compartments compared to the English babies [23]. Thus, visceral adiposity, a major risk factor for diabetes, is present in Indians from their intrauterine life, suggesting that the interventions to reduce the risk of diabetes should start intergenerationally. It has been suggested that this characteristic body composition of Indians may be due to genetic factors. This might be true to a certain extent, but as yet we have found only small differences in the genetic predisposition to diabetes and obesity-adiposity between Indians and Europeans. The major implication of our finding is that the nutrition of the fetus may be a modifiable risk factor to reduce the risk of NCDs in Indians.

The PMNS analysed the association between maternal nutrition and fetal growth and body composition. The mothers investigated lived in rural areas, were predominantly vegetarians and consumed on average 1,800 calories and 45 g protein per day, which is much below the recommended intakes. There were only a few associations between maternal macronutrient intake and neonatal size. On the other hand, the intake of micronutrient-rich foods (green leafy vegetables, milk and fruits) was strongly related to birth size (fig. 5) [24].

In this predominantly vegetarian rural population, folate deficiency was rare, but two thirds of the mothers were vitamin B12 deficient. Circulating folate, vitamin C, vitamin D and iron were associated with fetal growth. Maternal circulating homocysteine concentration (a marker of 1-carbon metabolism) predicted fetal growth restriction [25]. Further, at 6 years of age, maternal folate status in pregnancy was a predictor of the child’s adiposity and insulin resistance [26]. The most insulin-resistant children were born to mothers who had low vitamin B12 but high folate levels, suggesting that a balance between these two vitamins is essential. The importance of folate in fetal growth has been well demonstrated in non-vegetarian European populations, but the role of vitamin B12 is less clear. Studies in Bangalore [27], Nepal [28] and Mysore [29] have supported different aspects of our findings in Pune. Folate as well as vitamins B12, B6 and B2 regulate maternal 1-carbon metabolism (usually assessed by circulating homocysteine concentration), which influ-
ences cellular growth by helping synthesis of nucleic acids and providing the essential amino acid methionine. In addition, methylation of DNA is one of the major mechanisms of epigenetic regulation, thus influencing the genetic regulation of growth and differentiation. The role of 1-carbon metabolism and these vitamins in fetal growth and programming has been recently reviewed [30–32].

**Maternal Metabolism**

In addition to nutrition, maternal metabolism exerts a major influence on fetal growth and programming. Substantial evidence has now accumulated that maternal diabetes and obesity (causing fetal overnutrition) influence future obesity and diabetes in the child. The common perception is that this mechanism must be genetic, but a series of studies have shown a prominent role for non-genetic mechanisms.

The central observation in this field was made by Pedersen [33], who suggested that an excess transfer of glucose and other fuels to the baby in a diabetic pregnancy stimulates fetal islets and causes hyperinsulinaemia. Insulin is a major growth hormone in utero and promotes the growth of insulin-sensitive tissues and organs, leading to fetal adiposity and macrosomia at birth. Freinkel [4] expanded this idea to suggest that the increased risk of postnatal obesity and diabetes was a ‘fuel-mediated teratogenesis’ by comparing these common long-term outcomes with rare disfiguring birth defects (for example, neural tube defects). He proposed that this was mediated by a ‘stable change in gene expression’, which we now call epigenetic programming, and not on the inherited genetic trait (fig. 6).

The Pima Indian studies [34–37] critically investigated the genetic-versus-intrauterine environmental aetiology of obesity and diabetes in the offspring of diabetic mothers. The Pima study has an unparalleled design where every member of the community more than 5 years of age, including all pregnant women, if not already diabetic, was serially investigated with an oral glucose tolerance test every 2 years. This allowed a more confident classification of the in utero exposure of the fetus to maternal diabetes.

![Graphs showing the impact of maternal nutrition and metabolism on fetal growth and programming.](image-url)
The first investigation showed that the children exposed to maternal diabetes in pregnancy were more likely to be obese (and glucose intolerant) compared to the children born to prediabetic (non-diabetic during pregnancy, diagnosed diabetic later and, therefore, genetically predisposed) and non-diabetic mothers (non-diabetic at serial tests and, therefore, genetically not predisposed) (fig. 7) [35]. This suggested that the intrauterine diabetic environment could be more important than the genetic factors in the aetiology of obesity and diabetes in the children of diabetic mothers. Interestingly, the risk was independent of macrosomia at birth and manifest as early as 5 years of age. To investigate the possibility that the mothers who were diagnosed as having diabetes at a younger age will transmit a stronger genetic predisposition, a subsequent study [36] investigated the risk of obesity and diabetes in the siblings (expected to inherit similar amounts of diabetes and obesity genes) who were discordant both for the exposure to intrauterine hyperglycaemia (born before or after the development of maternal diabetes) and outcome (obese or non-obese, normal glucose tolerant or hyperglycaemic). This study showed that the risk of obesity and diabetes was higher in the siblings who were born after the diagnosis of maternal diabetes.

In all these studies, there was no corresponding association with paternal obesity and diabetes, which supports a stronger role for the intrauterine diabetic environment compared to genetic predisposition in the aetiology of obesity and diabetes in the children of diabetic mothers. It is estimated that up to 70% of diabetes in Pima Indian children is due to maternal diabetes [37]. It is of note that most of the diabetic Pima Indian women had pregestational rather than gestational diabetes, and, therefore, the children were exposed to an abnormal metabolic mi-
lieu periconceptionally rather than only late in the pregnancy. In this context, it may also be important to note that the subsequent risk of obesity and diabetes was independent of birth size which is largely 'fueled' in the last trimester. The follow-up of children born to mothers with gestational diabetes in the Parthenon study in Mysore, India, has shown an increased risk of obesity and prediabetes below 10 years of age especially in girls [38]. A Danish study which followed children of type 1 and type 2 diabetic mothers as well as children born to mothers with gestational diabetes showed that all these children had a higher risk of diabetes in later life [39]. Many of the diabetic mothers in the Chicago Diabetes Pregnancy studies were also pregestationally diabetic [40].

**Findings suggest that even subtle alterations in the maternal intrauterine environment can have profound effects on the development of the fetal systems and that these effects last for the rest of the child’s life.**

The relative importance of periconceptional versus late-pregnancy exposure to diabetes needs to be further investigated. This has a major effect on the current practice of diagnosis and management of gestational diabetes in the third trimester. The majority of women with gestational diabetes have an excess of preconceptional risk factors (family history, obesity, previous abnormalities of glucose tolerance, low birth weight, short height, etc.) which may confound the association of later glucose intolerance and mislead about its importance for fetal programming [41]. As of today, there is little information about the long-term benefits to the offspring of treating maternal diabetes (either pregestational or gestational).

**Other Intrauterine Exposures**

In addition to maternal nutrition and metabolism, a number of other factors have been implicated in the regulation of fetal growth and for programming of NCDs in the offspring. These include maternal smoking, exposure to extreme (high) atmospheric temperature, pollutants and toxins (especially the 'endocrine disruptors'). Another major programming exposure may be maternal stress. All these findings suggest that even subtle alterations in the maternal intrauterine environment can have profound effects on the development of the fetal systems and that these effects last for the rest of the child’s life.

The importance of the time of exposure during pregnancy (window) can be easily understood by the sequence of fetal development and has been described for the periconceptional period earlier in the article.

**Synthesis**

It is now well established that, in addition to the conventional genetic inheritance (the so-called fixed inheritance), there are additional ‘malleable’ epigenetic influ-
ences (the so-called soft inheritance) which shape the future of the growing fetus. These mechanisms translate the environmental messages to the structure and the function of the developing fetus and leave a permanent mark. They are described under the general term of ‘epigenetic’ and represent gene-environment interactions. These new exciting findings describe a modifiable component of the intergenerational transmission of health and disease traits and offer hope of curtailting the rapidly expanding epidemic of NCDs across the world populations. Specific evidence is available for susceptibility to obesity-adiposity, diabetes, cardiovascular disease, neuropsychiatric disorders and cancers. The life-course evolution of these disorders includes a series of changes in the epigenome which start from the periconceptional period and continue to occur in the later life, producing an evolving phenotype which finally ends in a clinically recognisable disorder (fig. 8). Both undernutrition and overnutrition contribute to these processes. In the developing countries undergoing rapid socioeconomic and nutritional transition, the two cycles could operate one after the other in one life time, producing an even more detrimental effect on the phenotype (dual teratogenesis) (fig. 9). This may contribute to the high prevalence of these conditions. Preventive measures will depend on identifying specific exposures, demonstrating an effect of acting on them. Given the difficulties in identifying specific exposures among the multitude as well as the long latency between exposure and disease manifestation, this is not an easy task. Despite these limitations, substantial progress has been made in the last 25 years in this field both in animal and human models. The science of DOHaD is now well established, and preventive trials are in progress. Considering the difficulty of implementing long-term lifestyle modifications in adults to control the risk of NCDs, the model of primordial prevention by influencing the lifestyle of young girls and pregnant women in the relatively short period of periconceptional and gestational windows offers a more attractive alternative. The success of such interventions will be an appropriate tribute to the brilliant research of pioneers in this field over the last many decades.

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