The Diabetic Pregnancy, Macrosomia, and Perinatal Nutritional Programming

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Abstract

Health and diseases are generally perceived to be caused genetically. It is meanwhile accepted, however, that alterations in the intrauterine and early postnatal nutritional, metabolic, and hormonal environment may also predispose to disorders and diseases throughout later life. Studies in the offspring of diabetic mothers (ODM) have decisively contributed to this perception and our understanding of causal mechanisms. It has long been known that hormones are environment-dependent organizers of the developing neuroendocrine-immune network, which regulates all fundamental processes of life. When present in non-physiological concentrations during critical periods of development, induced by altered intrauterine and/or neonatal environment, hormones can therefore also act as endogenous functional teratogens. Fetal and neonatal hyperinsulinism is the pathognomic feature in ODM. Epidemiological, clinical, as well as experimental data obtained by our group indicate that insulin itself, when occurring in elevated concentrations during perinatal life, may program the development of obesity and diabetes. Similar situations may occur due to maternal overweight accompanied by increased fetal food supply, and neonatal overfeeding. From a clinical point of view, general screening and therapy of all types of diabetes during pregnancy as well as avoidance of early postnatal overfeeding are therefore recommended. These measures might serve as causal approaches to a genuine primary prevention.

Introduction

The impact of the intrauterine and early postnatal environment on lasting determination of fundamental processes of life is becoming more and more accepted. Especially investigations and hypotheses by the groups of Hales and Barker [1] have led to the postulation of a so-called small baby syndrome...
which is explained by a thrifty phenotype acquired by poor fetal nutrition. This concept has contributed mainly to the worldwide attention to the phenomenon of early epigenetic conditioning, and terms such as nutritional programming or imprinting have been proposed to describe it. It was Günter Dörner, however, who in 1974 was the first to postulate a general etiological concept of epigenetic, perinatal programming of the lifetime function of fundamental regulatory systems and, thereby, the possibility of perinatal prophylaxis [2, 3].

**Hormone-Dependent Perinatal Programming**

Already in the early 1970s in a series of clinical as well as experimental studies Dörner [2, 3] demonstrated that especially hormones are environment-dependent organizers of the neuroendocrine system, which finally regulates all fundamental processes of life. When present in non-physiological concentrations, induced by alterations in the intrauterine and/or early postnatal environment, hormones can therefore also act as endogenous functional teratogens by malprogramming the neuro-endocrine-immune system (NEIS), leading to developmental disorders and diseases throughout life. This means that the classical science of teratology, as the discipline which addresses macroscopic malformations, should be supplemented by the science of functional teratology as the discipline of perinatally acquired malfunctions [2, 3].

**Diabetes in Pregnancy, Perinatal Hyperinsulinism, and Perinatal Programming**

Evidence for the existence of the biomedical phenomenon of fetal programming originates mainly from the fields of reproductive behavior and stress [3–5], with research addressing the significance of altered concentrations of the respective steroid hormones (sexual steroids, or gluco- and mineralocorticoids) during critical periods of perinatal development for a permanent malprogramming of the affected subsystems of the NEIS. However, the results of clinical investigations and animal experiments on the long-term effects of maternal diabetes during pregnancy in the development of the offspring have for a long time provided key support for the concept of fetal programming of disposition to diseases.

**Clinical Observations**

Pregnancy is a diabetogenic situation per se. Women with gestational diabetes, just as pre-gravid diabetic women, are classed as risk pregnancies, and
their offspring show increased perinatal morbidity and mortality. The disturbances manifested during the neonatal period, apart from a tendency to hypoglycemia, hyperbilirubinemia, and neonatal respiratory distress syndrome, are characterized above all by an increased prevalence of macrosomia. This is caused by the virtually pathognomonic fetal and perinatal hyperinsulinism, which arises because of the materno-fetal hyperglycemia and consequent overstimulation of the fetal pancreatic B cells.

Already in the 1970s it was shown in a cohort of 4,000 diabetic patients that type 2 diabetes was inherited more frequently through the mother than the father, and the difference was highly statistically significant [6]. The offspring of a mother with gestational diabetes show an increased tendency to be overweight or obese already in childhood [7–9], accompanied by disturbances in glucose tolerance, insulin secretion, and insulin sensitivity [10–12].

It is particularly noticeable that these alterations may even occur independent of genetic influences and the type of maternal gestational hyperglycemia [9, 11, 13, 14]. However, they do show marked correlations with fetal metabolic alterations of the affected children, namely the degree of fetal and perinatal hyperinsulinism [10–12]. In the Pima Indian study it was shown that the prevalence of juvenile diabetes and obesity among the offspring of mothers who had diabetes already during pregnancy was several times higher than the prevalence among the offspring of normoglycemic or also pre-diabetic mothers (the latter being those who showed a genetic predisposition to diabetes but only became diabetic after delivery) [13]. This observation was later confirmed impressively by Dabelea et al. [14].

In particular, a positive correlation was found between the level of amniotic insulin or perinatal hyperinsulinemia and the increase in relative bodyweight and risk of impaired glucose tolerance (IGT) in later life for children of diabetic mothers [10–12]. The latter has to be interpreted as a decisive indication of a persistent influence of the diabetic intrauterine milieu and consequent hyperinsulinism in the sense of a hormonally initiated malprogramming.

Experimental Observations

Animal experiments have confirmed that maternal gestational hyperglycemia leads to overweight, IGT, hyperinsulinemia and insulin resistance in the juvenile and adult offspring, regardless of any genetic disposition [15–17]. Remarkably, the female F1 offspring of gestationally diabetic dams spontaneously develop gestational hyperglycemia. In the F2 offspring exposed in utero this can then in turn lead to diabetogenic disturbances in later life, and therefore an epigenetic, materno–fetal transmission of increased disposition to diabetes is possible through a number of generations in sequence even without any genetic predisposition [15–18].
A permanent influence on the function of pancreatic B cells has been proposed, on the one hand, as an etiopathogenetic mechanism of this prenatally acquired malprogramming, in particular a persistent B cell hyperplasia and hyperactivity leading to permanent impairment of insulin secretion in the offspring [15]. On the other hand, studies have shown that permanent alterations of the programming of neuroendocrine and vegetative functional systems play a key etiopathogenetic role [18–20]. Thus the experimental induction of gestational hyperglycemia not only leads to perinatal hyperinsulinemia in the offspring but also to increased insulin concentrations within the immature hypothalamus, followed by the morphological characteristics of permanent, i.e. lifelong, dysplasia of central nervous control centers for metabolism and bodyweight. In particular this affects the ventromedial hypothalamic nucleus (VMN), which develops a permanent dysplasia and neuronal hypotrophy as a result of the exposure to increased insulin concentrations during critical periods of development [16, 18, 20]. Furthermore, as an expression of perinatally acquired hypothalamic resistance to the peripheral satiety signals, insulin and leptin, there is a permanent dysorganization and malfunction of specific neuropeptidergic neurones in the arcuate nucleus. Particularly important seems to be a lifelong increased activity and number of neurones which express the orexigenic peptides, galanin and neuropeptide Y [19, 21]. The extent to which these neuroendocrine functional impairments are attributable to perinatally acquired permanent alterations in gene expression remains an open question. Interestingly, however, the promoter regions of the neuropeptides and receptors involved show an increased CpG content [22] and are thus potential candidates for methylation-dependent alterations of the expressivity.

All this is accompanied by a permanently increased disposition for diabetes and obesity, characterized by hyperphagia, overweight, basal hyperinsulinemia, insulin resistance, and IGT. It should be emphasized that, both clinically and experimentally, these permanent disturbances occur independent of the birth weight and can also be observed in animals treated neonatally with insulin, experimentally applied either peripherally or only intrahypothalamically [16, 18, 23, 24].

Finally, even type 1 diabetes susceptibility is increased in the offspring of diabetic mothers. Multiple low dose streptozocin (STZ) treatment is a well-known model for type 1-like diabetes in rats accompanied by cell-mediated immune responses which closely resemble the autoimmune processes associated with infantile type 1 diabetes in the human. In maternal-side F1 and even F2 offspring of STZ-treated gestational diabetic mother rats (F0) spontaneous gestational diabetes, basal hyperinsulinemia from birth into adulthood, indicating persisting basal overstimulation of the pancreatic B cells, and, most important, a severe insulin-deficient type 1-like diabetes after a single low dose STZ treatment were observed in contrast to the offspring of control mothers [16]. The offspring of mother rats with gestational diabetes responded to multiple low dose STZ treatment with increased spleen cell cytotoxicity to syngeneic
B cells. Exogenous insulin treatment of newborn rats, even when only intra-hypothalamically performed, was also followed by increased susceptibility to low dose STZ type 1-like diabetes in further life [23, 24]. Moreover, these experimental data were accompanied by some clinical and epidemiological observations indicating that prevention of gestational diabetes in the mother may prevent increased type 1 diabetes susceptibility in the offspring [18].

**Conclusions**

Taking together the epidemiological, clinical, and experimental observations, it seems obvious that fetal hyperinsulinism induced by maternal hyperglycemia has functionally teratogenic significance for a permanently increased disposition to obesity, diabetes, the metabolic syndrome, and subsequent cardiovascular diseases in the children affected (fig. 1). Given that gestational diabetes has in the mean time probably reached a prevalence in excess of 10% in developed industrialized countries, it is urgent that all pregnant women are screened for glucose intolerance and adequately treated as a primary prevention measure.
Birthweight, Neonatal Nutrition, and Lasting Programming

The widely discussed data and hypotheses of the groups working around Barker and Hales have led to the postulation of a small baby syndrome, according to which fetal undernutrition, growth restriction, and low birthweight predispose to the later development of alterations in metabolism, bodyweight, and the cardiovascular system in terms of type 2 diabetes, metabolic syndrome, and cardiovascular diseases [1, 25].

Clinical Observations

Since the early 1990s, an impressive number of studies in various populations have been published which clearly show a persuasive link between a low birthweight and a subsequently increased risk for aspects of the metabolic syndrome. Even in the Pima Indian study, a long-term investigation in a North American population with a particularly high disposition to diabetes and obesity, it was shown that type 2 diabetes associated with overweight in adulthood was more prevalent in patients who had been overweight at birth, but also in patients who were neonatally underweight [26]. By means of meta-analysis of a variety of studies beyond that in the Pima Indians, we were recently able to confirm these observations [27]. This leads to the postulation that, in fact, no linear-inverse but a U-shaped relationship exists between birthweight and subsequent diabetes, obesity, and the metabolic syndrome.

Whereas the pathogenetic context seems more or less obvious for neonatal overweight, no clear etiopathogenetic link has been established for reduced perinatal weight [18, 28]. In particular it should be emphasized that no causal link has been established between intrauterine growth restriction and a subsequently increased disposition to obesity, i.e., the pathophysiological key for subsequent diabetes and cardiovascular diseases. It remains to be clarified whether fetal growth restriction and neonatal underweight, per se or rather the quality and quantity of early postnatal nutrition and weight gain in early infancy have pathophysiological significance for the prospective risk.

The central pathogenetic importance of later overweight is clear, for example, within the context of the metabolic syndrome, but although a positive correlation has frequently been demonstrated between weight at birth and weight or overweight in later life, an independent inverse relationship has never been shown [29]. Increased weight gain in early infancy, on the other hand, leads to increased disposition for obesity in later life [30]. It also seems remarkable that increased weight gain in early childhood, in particular in underweight newborns, leads to early manifestation of insulin resistance [31, 32]. Finally, it has been variously shown that increased weight gain in early childhood is a predictive factor for a disposition to the metabolic syndrome.
and cardiovascular risk in adulthood, in particular in the case of low birth-weight [33–35].

**Experimental Observations**

Against the background of the thrifty phenotype hypothesis, investigations on the small baby syndrome frequently use animal models of maternal underfeeding during gestation and lactation, which leads to a pronounced intrauterine and neonatal growth restriction in the offspring [36]. However, examination of the results on the long-term effects obtained with these and similar models showed no congruence with the observations after intrauterine growth restriction and low birthweight in humans.

Thus, for example, the animal experiments of Hales' group [36] have shown that offspring born to rat dams that were malnourished during gestation and lactation do not become overweight, but rather show a life-long persistence of low weight. This is associated with a permanently reduced food intake [36]. The animals predominantly show increased instead of decreased glucose tolerance. In contrast to the metabolic syndrome in humans, hyperinsulinemia and insulin resistance do not occur, but rather lower insulin secretion. All these findings persist even after dietary provocation [36, 37].

In contrast, it has early been postulated that transition from fetal malnutrition to early postnatal overfeeding could play a key role in the etiopathogenesis of the small baby syndrome [18], especially since it seemed quite possible that growth-restricted neonates, also in the epidemiological studies, had been overfed and possibly fattened. Similar hypotheses on the possible significance of early postnatal nutrition for the long-term outcome of underweight neonates have since been formulated by other authors, around Barker and Hales [32, 34].

The influence of this early postnatal nutritive situation on the later outcome of metabolism and bodyweight has often been investigated using the small litter model. Rats which were overfed in the early postnatal period show phenotypic alterations through juvenile age into adulthood, such as overweight, hyperphagia, glucose intolerance, hyperinsulinemia, dyslipidemia and increased blood pressure, which correspond in important aspects to those of the metabolic syndrome in humans [38]. This is all the more remarkable because clinical findings suggest that early postnatal overfeeding in humans also predisposes for an increased risk of metabolic syndrome in later life (see above). But here too the causes are not clear.

As already mentioned, neuropeptidergic hypothalamic centers play a key role in the regulation of food intake, bodyweight, and metabolism. It is of note that, very similar to the offspring of diabetic dams, neonatally overfed small litter rats show persisting disorganization and malprogramming of these regulatory systems, including malfunction of the VMN and especially resistance of the arcuate nucleus to the satiety signals, insulin and leptin, which may explain their neonatally acquired long-term risk [16, 18, 38, 39].
Conclusions

From an epidemiological point of view there is a clear phenomenological link between reduced birthweight and subsequently elevated risks. The critical integration of epidemiological, clinical, and experimental observations, however, cast doubt on a causal relationship. However, neonatal overfeeding and rapid early weight gain with increased fat deposition could be of lifelong pathophysiological importance especially for underweight newborns (fig. 1). Therefore, prophylactic recommendations should focus on the recognition, avoidance, and optimal treatment of the causes of intrauterine growth restriction (nicotine, alcohol, stress, gestosis, etc.), and also on the avoidance of neonatal overfeeding.

Synopsis

Globally, diabetes mellitus, obesity, and the metabolic syndrome are life-shortening diseases, and the continual dramatic increase in their prevalence represents a health problem of the greatest relevance, so that there is an urgent need for prevention strategies.

Generally, complex pathogenetic processes, in particular those relating to the so-called diseases of civilization, originate from an impaired interaction or an imbalance between environmental factors and the genetic matrix. From a practical clinical viewpoint, therefore, it is extremely important to characterize epigenetic risk factors with long-term malprogramming effects which can be influenced by preventive measures in critical periods of early development.

At least every tenth pregnancy in developed industrialized countries is probably affected by a disturbed glucose tolerance. The great majority of cases go unrecognized and thus untreated, because there is no universal screening for glucose intolerance of all pregnant women.

Fetal or early postnatal hyperinsulinism (and also hyperleptinism), induced as a result of maternal gestational hyperglycemia and/or early postnatal overfeeding, acts as a functional teratogen during critical periods of differentiation and maturation, especially of the NEIS. This can lead to irreversible, lifelong malprogramming of fundamental control systems and hypothalamic regulation centers for metabolism, food intake, and bodyweight. The result is a disposition to become overweight, and the development of obesity and associated metabolic disturbances such as hyperinsulinemia, insulin resistance, IGT, type 2 diabetes and metabolic syndrome, including undesirable clinical outcomes such as cardiovascular disease (fig. 1). Even an increased disposition to the manifestation of insulin-dependent type 1 diabetes may be pre-programmed in this way [18, 40, 41]. Here once again, the complex malprogramming of the NEIS is probably of causal significance, so that, for example, an under-functioning of the VMN as well as basal hyperglycemia lead to a permanent basal
overstimulation of the pancreatic B cells. But a permanent basal B cell over-
stimulation not only contributes to hyperinsulinemia, but also to increased
autoimmune reactivity to the constantly hyperactive B cells [42, 43], particu-
larly in otherwise predisposed individuals and/or together with exposure to
noxae (e.g. viruses), with the consequence of increased susceptibility to type
1 diabetes [18]. Remarkably, these aspects have also been substantially sup-
ported in recent years by observations and interpretations according to which
accelerated growth and overweight in childhood can have pathogenetic signif-
icance for the manifestation of type 1 diabetes [44].

Finally, regardless of the quality and quantity of the neonatal nutrition of
underweight newborns, it is probable that they are exposed to a further form
of hormone-dependent malprogramming. They probably show considerable
pre- and perinatal alterations of the glucocorticoid levels, at least in the form
of temporary hypercortisolism, with the potential consequence of glucocorti-
coid-induced malprogramming of the hypothalamic-pituitary-adrenal axis.
This, in turn, may substantially contribute to long-term risk of central obesity
and accompanying metabolic and cardiovascular disorders.

In all, from a clinical point of view this suggests the possibility of primary
prevention of increased disposition for overweight, diabetes mellitus, and car-
diovascular diseases by preventing fetal and/or early postnatal hyperinsulin-
ism, and also hyperleptinism and hypercortisolism, during critical periods of
development. A key to the approach is the prevention of any glucose intoler-
ance during pregnancy, and probably also the avoidance of early postnatal
overfeeding and thus consecutive hyperinsulinism during critical periods of
early development. In particular, universal screening of all pregnant women
for glucose intolerance seems to be urgent.

**Prospects**

The aspects presented here have a model character and, by way of exam-
ple, show the long-term pathophysiological significance of abnormal nutritive,
metabolic, and first of all hormonal conditions during critical fetal and perina-
tal periods of development, implying at the same time that primary prophylactic
management is possible by optimizing the fetal and early postnatal environ-
mental conditions. In this context, the general etiopathology should be
extended to include epigenetic dispositions, as exemplarily illustrated in
figure 2. For example, the molecular causes could lie in perinatally acquired
alterations in the DNA methylation pattern of receptors and/or neurohor-
mones which are involved at a cybernetically key position in the regulation of
the NEIS. All this may be of critical importance for the development and life-
long functioning, or permanent malfunctioning, of fundamental regulatory sys-
tems and life processes, and in the future should therefore be taken into
account in research into etiopathogenesis and preventive medicine.
Fig. 2. Fundamental concept on the multi-etiological origin of obesity, diabetes mellitus, the metabolic syndrome, and subsequent cardiovascular diseases (CVD), pre-programmed critically by the pre- and perinatal nutritional conditions.

References


Discussion

Dr. Spivey-Krobath: Which substrates play a role in early postnatal overfeeding and subsequent obesity and diabetes: protein, energy or both?

Dr. Plagemann: I would like to suppose that both increased energy intake as well as increased protein supply might play a crucial role. Clinical and experimental data clearly suggest that increased energy intake itself, when leading to rapid neonatal growth and, particularly, increased neonatal fat deposition accompanied by respective hormonal alterations, like hyperleptinism and hyperinsulinism, is critically involved in processes of perinatal programming of obesity and diabetes. That means, nutritional malprogramming may occur regardless of the composition of the diet but due to general overfeeding. However, increased protein content might indeed be particularly problematic since increased levels of amino acids are capable of inducing overstimulation of developing pancreatic B cells, as it occurs in utero as a result of increased glucose levels in the case of maternal diabetes. This may cause perinatal hyperinsulinism, which appears to be a pathophysiological key factor in perinatal programming of obesity and diabetes, as I illustrated in my talk. In this sense, a potential role of the protein content of the neonatal diet for the long-term risk of obesity is also supported by data from animal models. For instance, in rats a maternal low protein diet during gestation and lactation leads to a decreased susceptibility in the offspring to develop obesity during later life, while the offspring of rat dams fed a high protein diet have an increased risk of developing overweight. In recent years a maternal high fat diet has also been intensively discussed as playing an important role in programming the offspring for later overweight. Altogether, increased glucose, protein, as well as fat may be unfavorable during critical time windows of early development, and it remains to be determined by future research at which time which components of the maternal and neonatal diet have the most important long-term influence, and especially which of them are most easily and effectively modifiable in terms of perinatal nutritional prevention of later health risks. In my opinion, this could become one of the most important aspects and challenges in the field of infant nutrition and, thereby, primary preventive medicine in the future.