

## Birth weight, gestational diabetes, and perinatal programming

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### Abstract

Over the past few years, “perinatal programming”, a novel medical research topic, has raised increasing awareness. In order to establish this new field, low birth weight infants and infants from mothers with gestational diabetes have been studied. In order to establish this new field, subjects with low birth weight and offspring of mothers with diabetes during pregnancy provided the necessary data. The aim of these studies was to investigate the correlation between prenatal and/or neonatal exposures to the prevalence of diabetes, adiposity and atherogenesis later in life. Current research focuses on causes and mechanisms of prenatal and perinatal “malprogramming”.

### Definition: perinatal programming

Perinatal programming explores how during critical prenatal and/or neonatal windows, environmental factors such as nutrition and hormones determine the future functionality of the organs and organ systems. If this process of “programming” is disturbed, the infants have a greater risk of developing chronic diseases such as obesity and diabetes later in life (Plagemann 2005; Plagemann et al. 2008).

### Obesity: epidemiology

Worldwide, the prevalence of obesity and diabetes mellitus has rapidly increased over the past years. In the USA, the prevalence of obesity among adults increased from 13% to 31% between 1960 and 2002 while the percentage of overweight increased from 45% to 65% (Flegal 2005). In Germany, approximately 70% of all men and 50% of all women are overweight (body mass index (BMI) 25–35 kg/m<sup>2</sup>) or obese (BMI > 35 kg/m<sup>2</sup>) (Mensink et al. 2005). The recently published national nutrition study (German National

Nutrition Survey) revealed that every third woman at reproductive age is overweight (Federal Ministry of Food, Agriculture and Consumer Protection, 2008). This trend can already be observed among children and teenagers. Meanwhile, in America, one in six children from the age of 9 to 19 is overweight (Hedley et al. 2004). The German Health Interview and Examination Survey for Children and Adolescents (Kinder- und Jugendgesundheitssurvey, KIGGS) showed that 15% of all children and teenagers between 3 to 17 years of age are overweight (Kurth 2007).

However, it is remarkable that this development does not originate in the childhood period, but already in the mother's womb. The above-mentioned development goes along with an increase in average birth weight. And what is more: the increase in birth weight preceded the increase in overweight prevalence (Rooth 2003). In the USA, the average birth weight increased by 116 g between 1975 and 2003 (Catalano et al. 2005). A markedly increased birth weight has been described in the newly formed German states, with an increase of 151 g between 1985 and 1997 (Hesse et al. 2003). It is alarming that this process cannot be ascribed to growth acceleration but rather to an increased fat deposition at birth, resulting in a macrosomia prevalence of up to 25% (Rooth 2003). Such a development within only a few decades probably represents a unique development in the history of evolutionary biology, of which the long-term consequences are not yet foreseeable, especially if the current trend continues (Table 1).

Table 1: Increase of average birth weight within the last three decades in Europe and North America

Author(s)	Population	Year of birth	Increase in average birth weight
Rooth 2003	Europe*	1978-1998	45–95 g
Kramer et al. 1985b	Canada	1978-1996	57 g
Catalano et al. 2005	USA	1975-2003	116 g
Hesse et al. 2003	Germany (NFGS)**	1985-1997	151 g

\* Counting Hessen as part of the old German states

\*\* NFGS: newly formed German states

It remains unclear whether the increase in average birth weight represents a valid explanation for the increased prevalence of obesity and diabetes. One possible explanation is a disturbance in prenatal development, i.e. perinatal programming. In fact, a number of studies could show a correlation between birth weight and the risk for obesity. For instance, Kramer et al. found a positive correlation between birth weight and body mass index (BMI) in childhood (Kramer et al. 1985a). Another study performed in the USA and including more than 20,000 participants describes a positive correlation between birth weight and BMI in the group aged 60 to 65 (Curhan et al. 1996). A systematic review of our group found that 89% of all published studies on this subject had found a linear association. Thus, the conclusion that an increased birth weight correlates with an increased risk for obesity later in life can be drawn. In the mentioned meta-analysis, we analyzed data from 980450 individuals from 16 different countries spread over four continents (Harder et al. 2007).

### Gestational diabetes: epidemiology

Gestational diabetes is any degree of glucose intolerance, which first occurs or is first identified during pregnancy. This definition is independent of whether or how much insulin is needed for substitution. It also includes those diabetes types that continue beyond delivery, including primary manifestations of diabetes type 1 and type 2. Within the past years, the worldwide prevalence of gestational diabetes has increased (Dabelea et al. 2005; Engel et al. 2006; Fuhrmann et al. 1988; Kleinwechter et al. 2000; Weiss 1988). This is undoubtedly caused by the above-mentioned increase in overweight, of which also women of reproductive age are affected. It is an example for the known association between overweight, insulin resistance and diabetic metabolic condition.

In Germany, the prevalence of gestational diabetes was thought to be below 1% referring to data from perinatal studies (Günter et al. 2006). However, the prevalence was underestimated considerably, as glucose intolerance screening had not been widely implemented and thus no valid data was available. Recent studies indicate that a more realistic prevalence of gestational diabetes among all pregnant women in Germany is around 20%. (Engel et al. 2006; Kleinwechter et al. 2000). However, due to the missing routine screening, only one in ten gestational diabetes cases is being diagnosed and treated (Bühling et al. 2000). As obesity is an important risk factor for the development of gestational diabetes (Galtier-Dereure et al. 2000), it is likely that an increased prevalence will correlate with an increased prevalence of gestational diabetes.

The effects of gestational diabetes on the infant in peripartal and perinatal stages as well as the long-term effects of gestational diabetes, for example on the risk to develop obesity, have been analyzed in numerous clinical and animal studies (Bergmann et al. 1984; Plagemann et al. 1997; Silverman et al. 1991). They include disturbances of glucose metabolism, insulin secretion and insulin sensitivity (Weiss et al. 2000). Already in the 1970s, Dörner and Mohnike discovered in a cohort study with more than 4000 patients, that the predisposition for type 2 diabetes was significantly more often transmitted maternally than paternally (Dörner and Mohnike 1976). Thus, Dörner and Plagemann postulated more than 15 years ago, that exposure of the fetus to the mother's diabetes during pregnancy as well as neonatal overnutrition permanently increases obesity and diabetes disposition by fetal or neonatal hyperinsulinemia. This is largely caused by a dysfunction of hypothalamic regulation of body weight and metabolism (Dörner and Plagemann 1994). Ever since, additional clinical and epidemiological studies that support this hypothesis have been published. A data analysis of siblings from the Pima Indian Study is especially noteworthy (Dabelea et al. 2000). The results confirm that the BMI and the frequency of type 2 diabetes are increased in adulthood if the mother developed diabetes prior to or during pregnancy, compared to the siblings of these participants, who were born in a period when the mother was metabolically healthy. The risk to develop diabetes was threefold increased in the group exposed to the maternal gestational diabetes compared to their siblings. Exposure to a diabetic intrauterine milieu thus represents an independent risk factor for obesity and diabetes in the offspring, also in later stages of life, even in a population with a high genetic risk for obesity and type 2 diabetes such as the Pima Indians.

### Perinatal programming and the “small baby syndrome”

Maternal gestational diabetes often leads to macrosomic offspring if not detected or treated early enough and is unlikely to cause reduced birth weight. How do these data match with the “Barker-hypothesis” on a “small baby

syndrome”? Here, an early study by McCance et al. is worth mentioning. Similar to the other study, it was also carried out in Pima Indians. The aim was to investigate the correlation between birth weight and the development of type 2 diabetes in adulthood (McCance et al. 1994). Interestingly, the correlation was U-shaped (Fig. 1). In a meta-analysis, our group could show that such a U-shaped correlation is also present when summarizing all existent study data (Harder et al. 2007; Plagemann et al. 2005). In subjects who weighed more than 4500 g at birth, McCance and colleagues observed that diabetes susceptibility was associated with maternal gestational diabetes (McCance et al. 1994). In an analysis of published data, B. Vohr and C. Boney could show that the development of a metabolic syndrome in children correlated with maternal adiposity, gestational diabetes, hyperglycemia in the last trimester of pregnancy as well as neonatal (macrosomia) and postneonatal obesity (Vohr et al. 2008). In the only large randomized intervention study on this topic, Crowther et al. could show that the consequent therapy of gestational diabetes halves the rate of macrosomia in all newborns (Crowther et al. 2005). These data indicate that routine glucose screening with consequent therapy of gestational diabetes is of utmost importance for the prevention of overweight and diabetes, also in future generations.

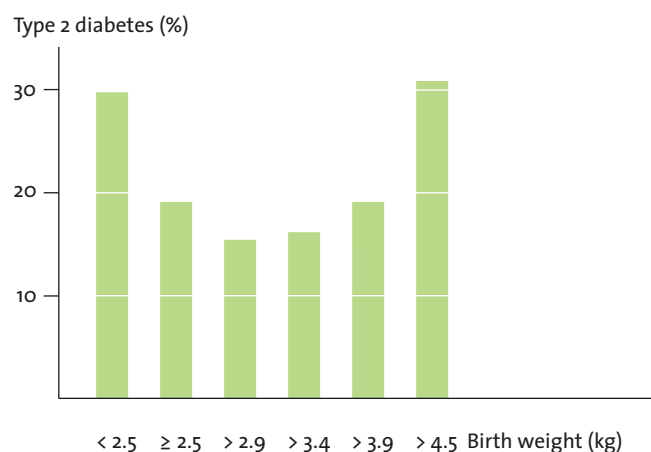


Figure 1: Prevalence of type 2 diabetes in PIMA Indians (n = 1179) at the age of 20 to 39 depending on their birth weight (taken and modified from McCance et al. 1994)

### Perinatal under- and overnutrition: long-term effects

Hales and Barker hypothesized that the observed association between reduced birth weight and increased health risks later in life is a consequence of prenatal undernutrition (Hales et al. 1992, 2001). However, the coherence and consistency of the observations underlying the hypothesis have to be reconsidered, given those on the consequences of maternal diabetes during pregnancy on the newborn.

In this context, a remarkable almost “historical” study is the one by Ravelli et al. (1976) on the repercussions of intrauterine undernutrition during the Second World War on the later development of body weight. Data were obtained from the Dutch famine of 1944, the “Hunger Winter”. Parts of the Netherlands were occupied by German troops from September 1944 until being released from the Allied in 1945. During this period, the population in the affected territories was partly cut from nutritional supplies. Ravelli et al. compared the body weight of recruits with an average age of 19 of whom the pregnant mothers had been affected by the occupation with the body weight of recruits, whose mothers had been living in unoccupied territories in the Netherlands during the same period. One frequently cited result is that undernutrition within the first and second trimester was associated with an increased risk for obesity of the offspring. A lesser-known fact, however, is that undernutrition during the third trimester and within the first five months of life correlated with a reduced risk of obesity in the offspring (Fig. 2). One interpretation could be that the long-term risk for the offspring to develop obesity due to early life undernutrition depends largely on the time of exposure. On the other hand, there is a possibility that an increased risk for adiposity as a consequence of undernutrition during early pregnancy is caused by relative overnutrition during late pregnancy and especially during early infancy of the underweight newborns.

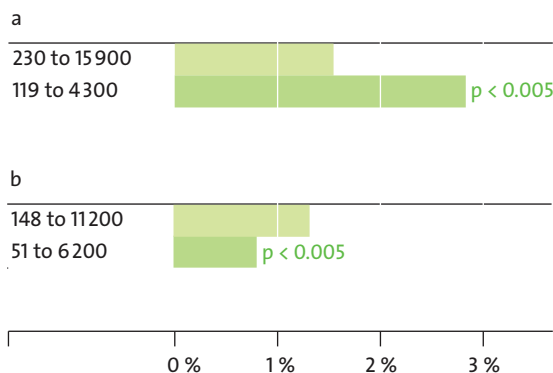


Figure 2: Obesity in sons from women exposed to undernutrition during the first and second pregnancy trimester (a) and the third trimester and the first five months (b) (taken and modified from Ravelli et al. 1976); light green: “controls”, dark green: mothers with undernutrition

Further epidemiological data question whether prenatal undernutrition can be considered an independent risk factor for adiposity and diabetes. Stanner et al. analyzed data from adult participants who suffered starvation in utero or in their infancy during the Second World War in the occupied territory of Leningrad, similar to the study on the Dutch Hunger Winter. The control participants were born in the exact same period but in unoccupied territory (Stanner et al. 1997). The exposure to a much more severe famine compared to the Dutch Famine Winter (approximately 300 kcal/day, protein restriction) largely affected both intrauterine stages as well as infancy. Interestingly, the prevalence of diabetes mellitus and impaired glucose tolerance during adult life was not increased but, instead, decreased. The control group did not differ in terms of body-mass index or the systolic and diastolic blood pressure. With regard to the “small-baby-syndrome” hypothesis, it is remarkable here that in none of the two studies, birth weight was decreased after intrauterine undernutrition.

In addition, also clinical studies raise doubts about whether prenatal undernutrition is an independent risk factor in the pathogenesis of the “small-baby-syndrome”, and thus the long-term effects of a relatively low birth weight. As a consequence, Hofman et al. analyzed whether preterm birth predisposes to insulin resistance (Hofman et al. 2004). They found that normal weight preterm infants had an increased risk for developing insulin resistance already during childhood. However, the risk was the same in term infants who were small for their gestational age. Thus, normal weight (normal nutrition during intrauterine life) preterm babies have an equally increased risk for insulin resistance later in life compared to mature newborns that were exposed to intrauterine undernutrition. The only similar characteristic of these two groups lies in the fact that they have a relatively low birth weight. However, as this is not a risk factor by itself, we have to assume that,

considering the rather divergent prenatal nutritional situation in both cases, a postnatal mechanism was responsible for the outcome (Plagemann and Harder 2005). Such a pathophysiological risk factor could be the early postnatal overnutrition of underweight infants, independent of their gestational age. Already in the 1970s, Dörner and Mohnike had examined the relationship between weight gain in early infancy, an important indicator for infant nutrition, and the later risk for overweight (Dörner et al. 1977). They observed that the rate of overweight was highest in those children that had gained a relatively large amount of weight. Of those infants who had gained more than 3 kg within the first three months, 18% developed obesity at the age of 15 compared to 4% of those infants who had gained less than 3 kg in the first three months. Bearing in mind the situation at that time, an obesity prevalence of 18% is rather high. In the already-mentioned study by Kramer and colleagues (1985a), there was an additional positive correlation between the body mass index at the age of six to twelve months and the body mass index in later childhood. This correlation proved to be even stronger than that between birth weight and later BMI. 20 years later, Stettler et al convincingly confirmed and expanded these findings by further significant aspects. For example, in addition to birth weight, they observed that the weight gain within the first four months was associated with an increased risk for overweight in late childhood. Interestingly, those kids who belonged to the highest birth weight quintile as well as to the highest quintile of early weight gain had the highest risk for overweight.

To summarize, epidemiological and clinical data indicate that prenatal and neonatal overnutrition increases the risk for overweight and metabolic diseases, in addition to and even independent of genetic predisposition.

#### **Long-term effects of perinatal under- and overnutrition: experimental data**

In the context of the above-mentioned epidemiological and clinical data, animal studies provide further insight on the long-term effects of perinatal over- and undernutrition. The most commonly used animal models here include prenatal and neonatal maternal undernutrition (e.g. “low-protein model”) and early postnatal overnutrition (e.g. “small-litter model”).

colleagues, the inaugurator of the “thrifty phenotype hypothesis” show that intrauterine undernutrition in the “low-protein model” does not lead to a higher risk of overweight in later life but persistent underweight in the offspring (Ozanne et al. 1999; Petry et al. 1997) as well as lower insulin concentrations in adult life compared to the control animals, even after overfeeding. Likewise, our work demonstrated that the offspring from rats exposed to a low protein diet during gestation had no increased risk for overweight in contrast to what was to be expected from the epidemiological and clinical data (Plagemann 2001). Moreover, the offspring of undernourished mothers had a long-term reduction in body weight and reduced nutritional intake. Glucose tolerance was rather improved, and no tendency towards hyperinsulinemia, insulin resistance or increased blood pressure was observed. These results, from our as well as from other research groups, did not change even after dietetic provocation (Moura et al. 1997; Petry et al. 2000), and no parameter was comparable to the metabolic syndrome in humans. Moreover, part of the parameters even showed contrary associations.

A widely used and established animal model for neonatal overnutrition is the “small litter model”. Reducing the original litter size in rats and raising the pups in “small nests” lead to relative overnutrition. Rats from small litters develop symptoms that have a striking resemblance with the human metabolic syndrome. Apart from increased nutritional intake, i.e. hyperphagia with increased appetite, these animals have an increased body fat mass, increased blood pressure and reduced glucose tolerance with insulin resistance and increased leptin levels (Plagemann et al. 1999). Over the past few years, these findings have been confirmed by other groups (Boullu-Ciocca et al. 2005; López et al. 2005).

What are the underlying mechanisms? The existing data of our group indicate that fetal or perinatal hyperinsulinemia, which develops as a consequence of maternal gestational

Interestingly, animal experiments performed by Hales and

diabetes or as a consequence of neonatal overnutrition,

causes neuroendocrine “malprogramming” and thus lifelong dysfunction of the regulation of nutritional intake, body weight and metabolism (Plagemann 2004). Here, insulin works as a physiological satiety signal from the periphery. It inhibits the hypothalamic (predominantly the nucleus arcuatus hypothalamic, ARC) expression of orexigenic neuropeptides which stimulate nutritional intake, such as neuropeptide Y (NPY), while the expression and release of anorexigenic neuropeptides which inhibit nutritional intake, such as proopiomelanocortin (POMC), is stimulated. Leptin released from adipocytes works synergistically in an intact system. However, fetal or perinatal exposure to hyperinsulinemia/hyperleptinemia can cause hypothalamic, permanent resistance of this control system, leading to central nervous leptin resistance or insulin resistance, which causes a permanent disposition to hyperphagia, obesity and consecutive metabolic and cardiovascular disorders (Plagemann 2004).

Hyperinsulinemia during the fetal or neonatal period, especially caused by maternal diabetes during pregnancy as well as neonatal overnutrition, results in a permanent malprogramming of hypothalamic control systems, which regulate food intake, body weight and metabolism. Such malprogramming leads to a lifelong increase in the risk for overweight, diabetes mellitus and consequent diseases (Fig. 3). The optimization of fetal and early postnatal environmental factors can permanently and positively modify risks for diseases. A preventive measure here is the detection and early therapy of gestational diabetes. Diabetes screening for all pregnant women as part of the maternity regulations (“Mutterschaftsrichtlinien”) is thus urgently needed. During the neonatal period, overnutrition should be avoided, e.g. by encouraging breastfeeding as the optimal nutrition for the newborn but also by further optimization of infant nutrition.

The detection and consideration of these associations in perinatal programming opens various chances for a future primary prevention of, for example, obesity and diabetes mellitus as two main examples.

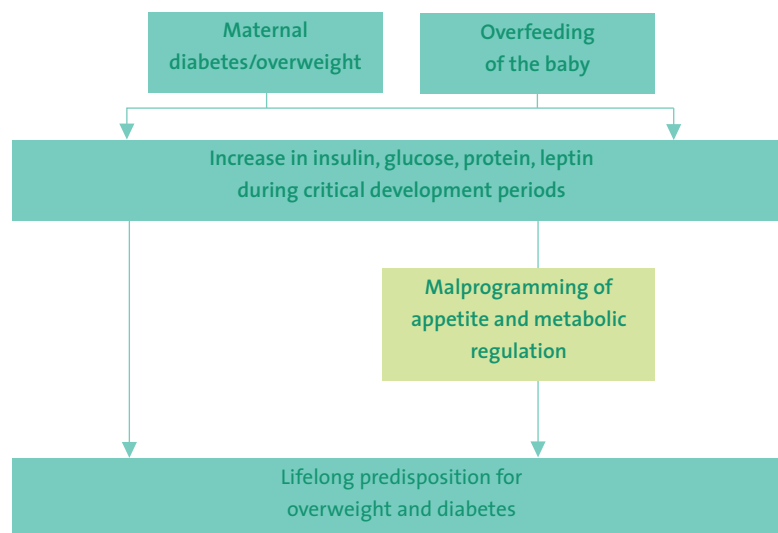


Figure 3: General concept of perinatal programming of increased risk for adiposity and diabetes



### Keywords

Prenatal imprinting, perinatal programming, gestational diabetes, small-baby syndrome

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#### Conflict of interest

The author declares that there is no conflict of interest as defined by the guidelines of the International Committee of Medical Journal Editors (ICMJE; [www.icmje.org](http://www.icmje.org)).

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## Birth weight, gestational diabetes, and perinatal programming

### Question 1

Perinatal programming is a process in which

- external factors such as medication and noise can transiently change the functionality of organs,
- during a certain “critical development period” (early childhood), the functionality of the musculoskeletal system can be improved by orthopedic measures within the first years of life,
- during a certain “critical development period” (prenatal/neonatal), the functionality of organs and organ system can be determined permanently by the impact of external factors such as nutrition and hormones,
- highly gifted newborns write computer programs,
- LINUX or other UNIX-like operating systems have to be utilized.

### Question 2

The prevalence of obesity in women in their reproductive age in Germany is:

- 1%
- 5%
- 30%
- 60%
- 80%

### Question 3

The German Health Interview and Examination Survey for Children and Adolescents (KIGGS) showed that the percentage of obese children and teenagers aged 3 to 17 years is:

- 1%
- 5%
- 10%
- 15%
- 30%

### Question 4

The association between birth weight and the risk for developing diabetes type 2 later in life is

- a strong positive linear correlation
- a strong inverse linear correlation
- W-shaped,
- U-shaped,
- non-existent.

### Question 5

Data from the so-called Dutch Hunger Winter have pointed out that

- undernutrition during the third trimester and within the first five months is associated with a reduced risk for obesity in the offspring,
- overnutrition during the third trimester and within the first five months is associated with a reduced risk for obesity in the offspring,
- undernutrition during the first trimester is associated with a reduced risk for obesity in the offspring,
- overnutrition during the first twelve months is associated with a reduced risk for obesity in the offspring,
- undernutrition during the third trimester and within the first five months is associated with an increased risk for obesity in the offspring.

### Question 6

The long-term effects of perinatal overnutrition can experimentally be analyzed in the:

- “low-protein model”
- “low-calory model”
- “big-litter model”
- “small-litter model”
- “small-cage model”

### Question 7

Crowther and colleagues have observed that

- therapy of gestational diabetes has no influence on the rate of macrosomia,
- the consequent therapy of gestational diabetes halves the rate of macrosomia in the newborn offspring,
- the consequent therapy of preeclampsia halves the rate of cesarian sections,
- SGA babies (SGA: small for gestational age) have an increased risk for becoming overweight later in life,
- the predisposition to type 2 diabetes mellitus is significantly more often transferred to the offspring maternally than paternally.

**Question 8**

Long-term effects of perinatal undernutrition can experimentally be examined in the:

- a. "low-water model"
- b. "low-protein model"
- c. "big-brother model"
- d. "small-litter model"
- e. "small-cage model"

**Question 9**

Experimentally, perinatal overnutrition does not lead to:

- a. Hyperphagia
- b. Increased body fat
- c. Increased blood pressure
- d. Insulin resistance
- e. Decreased leptin levels

**Question 10**

Regulation of nutritional intake, body weight and metabolism by insulin is regulated mainly in the:

- a. Nucleus arcuatus hypothalami
- b. Nucleus motorius nervi trigemini
- c. Nucleus nervi hypoglossi
- d. Nucleus nervi trochlearis
- e. Nucleus spinalis nervi accessorii