Sixty years ago, the Australian ophthalmologist Gregg was the first to describe the causation of an illness by an external influence on fetal and embryonic development: rubella embryopathy due to maternal rubella infection. Until that time, the prevailing medical opinion had considered the fetus largely able to develop autonomously, shielded from external influences.

There is no longer any question that intrauterine life is far more than just the execution of a genetic program of which the neonate is the final product. If the mother is severely undernourished, or in case of placental insufficiency (to give two examples), the fetus adapts with metabolic, endocrine, and hemodynamic changes. This adaptation is useful from an evolutionary perspective, because elevated vigilance, higher cortisol levels, and an activated vascular sympathetic system increase the chances of survival post partum in an unfavorable environment. The neonate's elevated level of stress leads to more rapid activation of mother-seeking behavior and flight reflexes and thereby promotes early mobilization. On the other hand, in an environment where the neonate is well provided for and more than adequate nourishment is available, adaptations of this type are inappropriate. If they persist long enough, they can produce cardiovascular and metabolic disturbances.

Dörner (Berlin) and Barker (Southampton) were the leading figures behind a paradigm shift in the understanding of multifactorial disease pathogenesis, e.g., in type II diabetes mellitus and arterial hypertension. These diseases arise not only because of the individual’s genetic background and external influences in childhood, adolescence, and adulthood, but also because of events during intrauterine life and around the time of birth. This concept became widely known under the names of „functional teratology“ and „fetal programming.“ It initially failed to achieve broad scientific acceptance, because the mainly retrospective epidemiologic data seemed to provide no more than speculative support for the proposed causal relationships, and because there was doubt about the applicability of findings in animal experiments to the human situation.
In recent years, however, many scientific articles have appeared that demonstrate not just epidemiological, but also pathogenetic connections between an abnormal intrauterine environment and later disease in human beings. This article will deal with a particular example, namely, the implications of intrauterine growth restriction (IUGR) for later life. The author selectively reviewed the literature obtained by Medline search on this topic, with particular attention to original articles, meta-analyses, and reviews that were considered to be particularly useful.

**Long-term sequelae of low birth weight**

It is difficult to define an abnormal intrauterine environment. In the earliest, classic studies, a birth weight below 2500 g was taken as evidence of an abnormality, though this was clearly an oversimplification. In studies on long-term sequelae, Barker and Hales found an association of low birth weight with the frequent occurrence of some of the manifestations of the metabolic syndrome, e.g., insulin resistance and dyslipidemia (1). There soon followed further studies by these authors, as well as articles from Scandinavian countries (2) and retrospective evaluations of large American cohorts, such as the Nurses’ Health Study. The last-named study also provided evidence of an association of low birth weight with type II diabetes mellitus as well as cardiovascular diseases in adulthood (3, 4). In these studies, however, adequate attention was not paid to the question whether low birth weight was due to intrauterine growth restriction, prematurity, or a constitutional state in a healthy, mature neonate whose weight was below 2500 g, or to a combination of these factors. The results of these studies are therefore open to many different interpretations.

Subsequent studies provided clearer evidence of the association of an abnormal intrauterine environment with later cardiovascular diseases. Barker et al. analyzed data concerning 1,586 men born in Sheffield from 1907 to 1924 whose weight, body length, and gestational age at birth had been recorded. It was found that men who had been „small for gestational age“ (SGA) at birth were at elevated risk of coronary heart disease, but those who had merely been small at birth because of prematurity were not at elevated risk (5). Nonetheless, restriction of a study population to SGA neonates still does not produce a homogeneous cohort, as smallness for gestational age may be due to different kinds of disturbances in the fetal environment. Ideally, epidemiologic studies of this question should concentrate on chronically undernourished fetuses, i.e., those with intrauterine growth restriction (IUGR). The Helsinki study (6) showed that low birth weight is associated with an elevated rate of death from coronary heart disease, and that the association is much stronger when the neonate has a lower ponderal index (weight in kg divided by body surface area in m², multiplied by 1000). A low ponderal index (relative „thinness“) is associated with a doubled risk (6).

Further epidemiologic studies addressed the possible association of low birth weight with arterial hypertension. Huxley examined this question in a meta-analysis (7) of data on birth weight and blood pressure at various ages in over 440,000 persons. An inverse correlation between birth weight and blood pressure was found. The meta-analysis revealed that a 1 kg increase in birth weight was associated with a 2 mm Hg decrease in blood pressure, on average. This difference seems slight, but, because it is an average value, it implies that persons born with a growth restriction will be more likely to suffer from arterial hypertension.

The meta-analyses of the correlation between birth weight and blood were criticized, however (8), for including studies that contained no information about the gestational age at birth, current weight, sex, or socioeconomic status of the persons in the study. These studies permit no firm conclusion as to whether the abnormal intrauterine environment had an independent effect on blood pressure or whether a genetic predisposition was the cause of both low birth weight and hypertension. They do not inform us, either, whether hypertension in adulthood is the result of an abnormal intrauterine environment or of external environmental influences in childhood and adolescence.

Interestingly, animal experiments on maternal-fetal malnutrition due to maternal protein restriction revealed a significant effect mainly when prenatal undernourishment was followed by neonatal overnourishment (9). The same studies provided indirect clues implying that the pathophysiological causes of increased metabolic and cardiovascular risk in low-birth-weight individuals must be sought not just in the prenatal period, but also in the...
neonatal period (1). „Overfeeding“ of low-birth-weight neonates may lead to disproportionate neonatal weight gain. A number of epidemiologic studies have identified rapid early weight gain as a risk factor for overweight and diabetogenic disturbances (11, 12).

**Consequences of placental insufficiency for the fetus**

Even though inadequate maternal nutrition is a rare cause of an abnormal intrauterine environment in Western countries, fetal nutritional deficiencies are nonetheless common, manifesting themselves as intrauterine growth restriction. This problem affects about 5% of all pregnancies; in Germany, this corresponds to about 34,000 per year. The cause is usually chronic placental insufficiency (box), a condition in which an inadequately developed placenta supplies insufficient amounts of oxygen and/or nutrients to the fetus.

| Causes of intrauterine growth retardation due to inadequate fetal supply of oxygen and nutrients |
| Maternal diseases |
| • severe anemia and persistent high fever |
| • hypertension and pre-eclampsia |
| • chronic maternal illness (congenital heart diseases, chronic renal diseases, diabetes mellitus, autoimmune diseases) |
| Maternal abnormalities |
| • severe eating disorder with inadequate nutrition |
| • toxic effects of cigarette smoking, alcohol, illicit drugs, and other substances |
| • living at high altitude |
| Placental abnormalities (placental insufficiency) |
| • abnormal placation with abnormal structure or maturation of the placenta |
| • placenta previa |
| • isolated chromosomal changes in the placenta |

Chronic placental insufficiency is an important problem in obstetrics and neonatology because the affected fetuses and neonates are at elevated risk of perinatal asphyxia, intrauterine fetal death, operative vaginal delivery, neonatal encephalopathy, and sudden infant death. Further neonatological problems include hypoglycemia, hyperthermia, hypocalcemia, and polycythemia due to the metabolic, hemodynamic, and endocrine abnormalities of the growth-restricted fetus.

Placental insufficiency is associated with fetal hemodynamic and endocrine changes that can affect the development, functional programming, and final function of the regulatory circuits for blood pressure, sympathetic and parasympathetic function, the renin-angiotensin-aldosterone system (RAAS), and the hypothalamic-pituitary-adrenal (HPA) axis, all of which are still plastic in the fetus.

Chronic placental insufficiency is regularly associated with changes of the flow pattern in the fetal arteries that serve the purpose of conserving oxygen for the fetal brain. The fetal cerebral vessels are dilated at the expense of the blood supply of the rest of the body, with the exception of the heart and adrenal glands (diagram 1, figure 1). This phenomenon is known as „brain sparing.“

Fetuses with intrauterine growth restriction manifest activation of the RAAS with significantly elevated serum levels of angiotensin (AT) II and an unchanged AT II receptor density (13). The HPA axis, too, is activated: cortisol concentrations in the cord blood of IUGR fetuses are significantly elevated (14). The placenta is a structural and biochemical barrier for maternal adrenocorticotropic hormone (ACTH), glucocorticoids and catecholamines, so that the fetus is largely shielded from these substances. In placental insufficiency, however, placental 11β-hydroxysteroid dehydrogenase 2 (HSD), an enzyme that catalyzes the transformation of cortisol and corticosterone into mostly inactive metabolites, is expressed in a lesser amount (15). As a result, the fetus is
exposed to additional maternally-derived steroids, particularly when the mother is under elevated stress. Gitau et al. estimate that 40% to 50% of fetal cortisol is maternally derived (16).

**Intrauterine growth restriction as a risk factor for arterial hypertension**

Intrauterine growth restriction can lead to arterial hypertension through a number of different pathophysiological mechanisms. Hypertension, in turn, is the most important risk factor for stroke (17) and other cardiovascular diseases in later life (table).

The fetal metabolic, hemodynamic, and endocrine changes associated with intrauterine growth retardation can directly affect arterial wall structure and endothelial function. Leeson et al. showed that low birth weight is associated with impaired endothelial function in large arteries, both in children aged 9 to 11 and in young adults aged 20 to 28 (18). A recent study by Skilton et al. revealed that neonates with intrauterine growth restriction already have a significantly greater intimal and medial thickness of the abdominal aorta, as measured by ultrasound, than neonates without growth restriction (19). The sonographically measured intimal and medial thickness of the abdominal aorta is accepted as a precise and sensitive marker of the risk of arteriosclerosis in children (20).

**TABLE**

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<td>Changes of endocrine functional systems</td>
<td>RAAS activation</td>
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RAAS, renin-angiotensin-aldosterone system; HPA, hypothalamic-pituitary axis; BP, blood pressure; NO, nitric oxide; PGI₂, prostacyclin; EDHF, endothelium-derived hyperpolarizing factor; T-II, angiotensin II; ↑, elevated; ↓, reduced.
Our own studies have shown that the umbilical arteries of fetuses with growth restriction are less elastic than control arteries of normal fetuses (diagram 2, illustration 2). There may be a further relevant pathophysiological mechanism relating to structural changes of the kidneys. Epidemiologic studies have shown a positive correlation between birth weight and the number of nephrons (21), while autopsy data reveal a lower number of nephrons in persons with essential hypertension (22). The studies of Phillips et al. support the hypothesis that intrauterine growth restriction permanently alters HPA axis function and elevates the fasting plasma cortisol concentration in the adult (23). Although individual measurements of plasma cortisol concentration are of limited meaning, these observations do at least suggest a connection between birth weight and adrenocorticotropic hormone activity in adulthood. Elevated plasma cortisol concentrations are associated with hypertension, hyperlipidemia, and elevated insulin resistance and should therefore be regarded as a risk factor for arteriosclerosis, type II diabetes mellitus, and the metabolic syndrome.

A fetus with intrauterine growth restriction manifests tachycardia and low heart rate variability (HRV), both of which are signs of sympathetic activation of the cardiovascular system (figure 3). Studies in human beings have yielded conflicting answers to the question whether sympathetic activation of the cardiovascular system in utero persists after birth. In a number of different animal models, adult animals that had suffered from intrauterine growth restriction were found to have elevated serum norepinephrine levels, a sign of sympathetic activation (24).

Thus, in intrauterine growth restriction, changes of the cardiovascular, autonomic nervous, and endocrine systems all promote arterial hypertension (table). Because of a lack of longitudinal studies, we do not know whether these changes persist in human beings after birth, leading to hypertension in the adult, or whether they regress. Only animal experiments can be standardized well enough to isolate the effect of intrauterine growth restriction on blood pressure independently of the organism’s genetic make up and post partum environmental conditions. Alexander showed, in animal experiments, that both female and male animals with intrauterine growth restriction have elevated blood pressure at various ages (25).

**Abnormal intrauterine environment and other illnesses**

Metabolic syndrome, type II diabetes mellitus, and cardiovascular diseases are the best studied and best documented long-term sequelae of an abnormal intrauterine environment. Large-scale epidemiologic studies have shown that negative influences during intrauterine life can also significantly elevate the risk of developing breast cancer, schizophrenia, or depression (e1, e2, e3, e4, e5, e6).
An association of schizophrenia with perinatal complications was postulated as early as 30 years ago (e6). The best evidence for an association between severe maternal malnutrition during early pregnancy and schizophrenia in later life is derived from an observational study of pregnancies during the „hunger winter“ of 1944-5 in the Netherlands (e4); further support comes from studies of pregnancies during the Chinese famine of 1959-61 (e2). Large-scale epidemiologic studies based on Finnish and Swedish birth registries reveal an association of low birth weight (e7) and low body length at birth (e8) with the later development of schizophrenia. A study of 90 discordant twin pairs (one twin with schizophrenia, one without) also showed an association of fetal intraterine growth restriction with later schizophrenia (e9). The mechanisms underlying this association remain unclear. In other studies, the presence of such an association could not be confirmed.

There seems to be a surprising association of abnormal birth weight with breast cancer in young women (e1, e5). Innes et al. found a higher probability of developing breast cancer in persons with low birth weight as well as in persons with very high birth weight (e1). A recently published meta-analysis of 26 original studies confirmed that there is a significant

![Figure 3](image-url)
connection between abnormal birth weight and the risk of breast cancer, even though not all of the individual studies included in the meta-analysis had shown this association (e19).

High birth weight is associated with elevated placental weight; thus, large fetuses have higher serum levels of estrogens, progesterone, human placental lactogen (HPL), and placental growth hormones. As some of these substances are thought to be involved in the pathogenesis of breast cancer, this might explain the higher rate of breast cancer in persons with high birth weight. On the other hand, the association of low birth weight with breast cancer remains unexplained.

Overview
The most common reason for an abnormal intrauterine environment in Western countries is not maternal malnutrition but rather placental insufficiency. Placental insufficiency leads to hemodynamic, endocrine, and morphological changes in the fetus, which, if they persist after birth, are themselves risk factors for type II diabetes mellitus and cardiovascular diseases. According to our current understanding, based on studies published to date, fetal growth restriction cannot be corrected by nutritional supplementation, the administration of vitamins or other supplementary foodstuffs, or intravenous therapy after diagnosis.

Psychosocial stress during pregnancy, unfavorable working conditions, an unbalanced diet, maternal diseases, smoking, and the consumption of illicit drugs are modifiable causes of intrauterine growth restriction. Further research must be directed to the questions of how gestation can be made as healthy and safe as possible for mother and child, what kind of advice relating to health is best for pregnant mothers, and what sorts of occupational activity are compatible with a healthy pregnancy. Research of this type may well yield multiple approaches to the primary, early prophylaxis of type II diabetes mellitus and cardiovascular diseases in neonates at elevated risk, if studies that are currently underway do indeed confirm that an abnormal intrauterine environment is an independent risk factor for these diseases.

Conflict of Interest Statement
The author declares that he has no conflict of interest as defined by the guidelines of the International Committee of Medical Journal Editors.

Manuscript received on 9 October 2006; final version accepted on 30 January 2007.

Translated from the original German by Ethan Taub, M.D.

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For e-references please refer to the additional references listed below.


ADDITIONAL REFERENCES


Corresponding author
PD Dr. med. Ernst Beinder
University Hospital Zurich
Dept. of Gynecology (Frauenheilkunde)
Frauenklinikstrasse10
8091 Zurich, Switzerland
ernst.beinder@usz.ch