Overweight and Obesity before, during and after Pregnancy
Part 1: Pathophysiology, Molecular Biology and Epigenetic Consequences

Übergewicht und Adipositas in der Peripartualperiode

Teil 1: Pathophysiologische und molekularbiologische Aspekte von Übergewicht und Adipositas sowie deren epigenetische Konsequenzen für künftige Generationen

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Abstract
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Overweight and obesity before conception as well as excessive weight gain during pregnancy are associated with endocrinological changes of mother and fetus. Insulin resistance physiologically increases during pregnancy, additional obesity further increases insulin resistance. In combination with reduced insulin secretion this leads to gestational diabetes which may develop into type-2-diabetes. The adipose tissue produces TNF-alpha, interleukins and leptin and upregulates these adipokines. Insulin resistance and obesity induce inflammatory processes and vascular dysfunction, which explains the increased rate of pregnancy-related hypertension and pre-eclampsia in obese pregnant women. Between 14 and 28 gestational weeks, the fetal adipose tissue is generated and the number of fat lobules is determined. Thereafter, an increase in adipose tissue is arranged by an enlargement of the lobules (hypertrophy), or even an increase in the number of fat cells (hyperplasia). Human and animal studies have shown that maternal obesity "programmes" the offspring for further obesity and chronic disease. Pregnant women, midwives, physicians and health care politicians should be better informed about prevention, pathophysiological mechanisms, and the burden for society caused by obesity before, during and after pregnancy.

Zusammenfassung
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Übergewicht und Adipositas vor der Konzeption sowie überhöhte Gewichtszunahme während der Schwangerschaft sind mit einer Reihe von Veränderungen des endokrinen Systems von Mutter und Kind verbunden. In der Schwangerschaft steigt die Insulinresistenz ohnehin, bei zusätzlicher Adipositas wird eine schon vorhandene Insulinresistenz verstärkt. Zusammen mit einer verminderten Insulinsekretion führt dies zu einem Gestationsdiabetes, der in einen manifesten Typ-2-Diabetes mellitus konvertieren kann. Das Fettgewebe produziert TNF-alpha, Interleukine und Leptin und sorgt für eine Hochregulierung dieser Adipokine. Insulinresistenz und Adipositas sind mit inflammatorischen Prozessen und vaskulärer Dysfunktion assoziiert, die auch die erhöhte Rate von schwangerschaftsassoziiertem Hypertonus und Präeklampsie adipöser Schwangerer erklärt. Beim Feten entsteht Fettgewebe zwischen den Schwangerschaftswochen 14 und 28. In dieser Zeitspanne wird die Zahl der Fettlobulae festgelegt. Eine spätere Zunahme des Fettgewebes erfolgt durch Vergrößerung der Läppchen (Hypertrophie). Bei Entwicklung einer Adipositas kann es jedoch auch zu einer Zunahme der Zahl der Fettzellen (Hyperplasie) kommen. Studien an Mensch und Tier haben gezeigt, dass mütterliche Adipositas die Nachkommenschaft bereits in der Schwangerschaft für Adipositas und chronische Erkrankungen „programmiert". Hierüber sollten nicht nur die betroffenen Mütter, sondern auch Hebammen, Ärzte und Gesundheitspolitiker informiert sein, um Risiken zu verhindern und die damit verbundenen Kosten zu limitieren.

Introduction
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The prevalence of overweight and obesity has risen dramatically in the past 20 years also including women of child-bearing age. According to the German National Consumption Study, in 2005 and 2006 29% of 20 to 29-year-old German women were overweight and 8.7% were obese. In women of 30 to 39 years even 35.3% were overweight and in addition, 14.3% were obese [1]. There is still an increasing trend representing a challenge for future generations.

Overweight and obesity have an impact on a variety of physiological changes and molecular biological processes during pregnancy. In Part 1 of our two publications we concentrate on the pathophysiological and molecular mechanisms of a high BMI and its effects on maternal metabolism and epigenetic effects on the fetus. We have to be aware of the associated short and long-term risks.

In Part 2, we evaluate evidence-based studies and international guidelines to document steps in diagnosis, prevention and risk reduction. The WHO-classification of overweight and obesity is explained in Part 2, Tab. 2. Experimental and epidemiological data may complement each other and reflect the reality.

Overweight and Obesity during Pregnancy
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Pregnancy, overweight and obesity all cause increased insulin resistance, an initial hyperinsulinism and a reduced insulin secretion by pancreatic beta cells, leading to type-2 diabetes (T2D) [2, 3]. In pregnancy, mild changes may be physiologic [4]. In overweight and obese pregnant women there is a high risk that physiological changes turn into a pathological condition of gestational diabetes (GDM) [5]. In observational studies, a close correlation was found between overweight (BMI 25–29.9 kg/m^2) or obesity (BMI ≥ 30 kg/m^2) and the risk of GDM [6, 7]. GDM is present in only 2.3% of pregnant women within a BMI between 18.5 and 24.9 kg/m^2, but in 9.5% of obese patients [8]. A meta-analysis found a 3.76-fold increased risk for GDM in obese compared to non-obese pregnant women, with an 0.82% increase in prevalence per BMI-gain of 1 kg/m^2 [9].

Insulin resistance in obesity has been related to (pro-)inflammatory processes and subclinical inflammation [10, 11]. These are associated with vascular dysfunction, explaining the increased risk of pre-eclampsia in obese pregnant women [12–14].

Molecular Biological Mechanisms
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The molecular basis of endocrine changes is explained by the fact that adipose tissue stores triglycerides and represents a metabolically highly-active tissue [15–20]. An increase in adipose tissue is associated with an inflammatory reaction inducing insulin resistance and cardiovascular disorders [18] (⦿ Fig. 1).

Adipose tissue consists of adipocytes (fat cells) and connective tissue stroma cells, which include endothelial cells, fibroblasts and haematopoetic cells. Immature adipose tissue develops in the fetus between 14 and 16 gestational weeks. Pre-adipocytes gradually differentiate from mesenchymal cell clusters, developing into fat lobules with characteristic lipid vacuoles in the cytoplasm. These fat lobules are surrounded by dense septae of perilobular mesenchymal tissue [21, 22].

Fetal adipose tissue starts to be visible in the head and throat, and later as part of the fetal body and the upper and lower extremities [23]. At around 28 gestational weeks, the adipose tissue formation is completed including the number of fat lobules. Thereafter, adipose lobules increase in size (hypertrophy). However, if obesity during childhood develops, even the number of fat cells (hyperplasia) may increase [24]. Only in extreme obesity during adulthood, the number of fat cells may still increase [25].

Two types of adipose tissue can be differentiated: white and brown adipose tissue, which have specific functions in fat storage, metabolic activity and thermogenesis respectively [26]. In humans, visceral (VAT) and subcutaneous adipose tissue (SAT) are formed. The VAT plays a key role in the development of a metabolic syndrome [16, 17, 21, 27].

In 1993, Hotamisligil et al. demonstrated that fat cells in the adipose tissue of mice produce tumour necrosis factor (TNF)-alpha and that obese mice have a greater TNF-alpha expression and higher TNF-alpha levels [28]. They also discovered the association between the TNF-alpha production in adipose tissue and insulin resistance. Only one year later, leptin, the product of the ob gene, was identified as the main secreted product of adipose tissue [15]. Excessive TNF-alpha production in human obesity leads to a subclinical inflammation; leptin regulates metabolic processes [29, 30]. Additionally, signalling cascades of the cellular metabolism are functionally disturbed. Anti-inflammatory cytokines such as adiponectin which, paradoxically, is reduced in obesity, and interleukin (IL)-10 are produced in the VAT [16, 31, 32]. In obesity, adipokines and their receptors are upregulated rather in the VAT than in the SAT [33, 34] which explains that excessive VAT is more closely associated with a metabolic syndrome than excessive SAT [35]. Adipokines from the VAT are directly absorbed by the liver via drainage through the portal veins. Thereby, the VAT has a direct impact on hepatic glucose homeostasis and insulin sensitivity [36]. Pro-inflammatory cytokines in adipose tissue are positively correlated with liver fat content and systemic arterial dysfunction and negatively correlated with insulin sensitivity [37, 38].

TNF alpha, IL-6, IL-10, leptin and adiponectin are part of more than 50 different "adipokines", peptides which are produced from the white adipose tissue. They circulate in the maternal blood and play an important role in obesity-specific morbidity [16, 17, 28, 31, 39] (⦿ Table 1).

The placenta produces adipokines similar to the white adipose tissue, only lacking adiponectin, a marker for increased insulin sensitivity [40, 41]. Challier et al. [42] demonstrated that the number of CD14+ and CD68+ macrophages in the placenta of obese women was three-fold increased compared to normal weight women. These macrophages produce pro-inflammatory

Table 1 Physiological and pathophysiological effects of selected adipokines [16, 18, 39]).

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TNF-alpha	Inflammation, apoptosis, impact on insulin resistance, stimulation of endothelial dysfunction and atherogenesis
IL-6	Inflammation, immune regulation (modulation of the insulin receptor), insulin resistance, atherogenesis
Adiponectin	Stimulation of insulin secretion, increase in insulin sensitivity, stimulation of glucose uptake in the muscle, inflammation reduction, plasma lipid reduction, atheroprotective effect
Leptin	Saturation, increase in energy utilization, weight control, modulation of insulin sensitivity, reduction of insulin secretion, angiogenesis
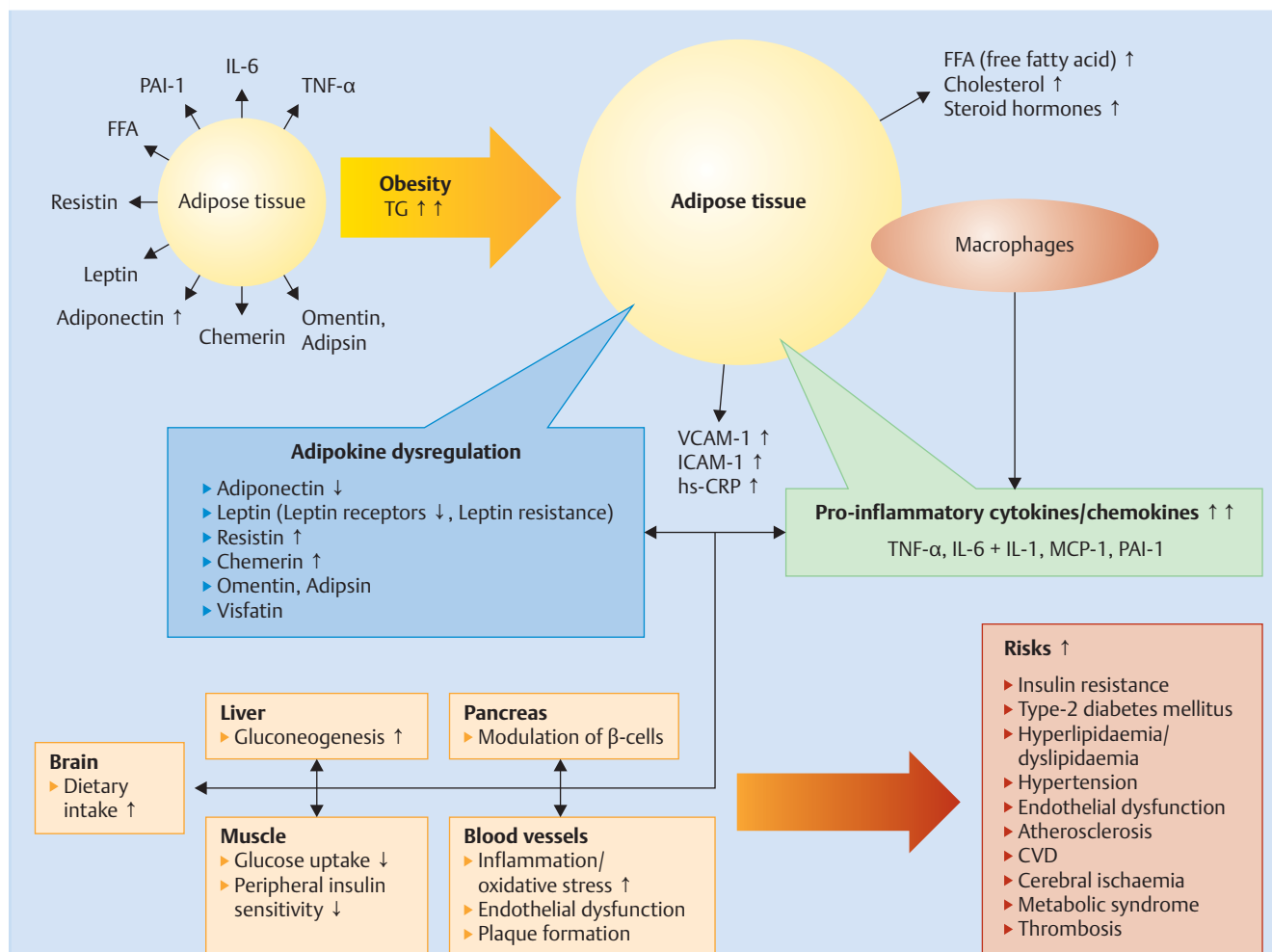
Fig. 1 Adipokines, obesity and risk factors. Fatty acids are stored as triglycerides (TG) by adipocytes. Hypertrophy of adipocytes results in obesity. This increases secretion of monocyte chemotactic protein 1 (MCP-1) and an accumulation of macrophages leading to a pro-inflammatory status with an increase in adipokines secreted by macrophages (TNF-α, IL-6 and -1). Chronic inflammation with high ectopic levels of muscular lipids, disruptions in mitochondrial β-oxidation and insulin-stimulated glucose transportation are the consequence. Adipokines increase the production of endothelial adhesion molecules such as intercellular adhesion molecule-1 (ICAM-1), vascular adhesion molecule-1 (VCAM-1) and of C-reactive protein (hs CRP) contributing to endothelial dysfunction and atherosclerosis (modified in accordance with [18]).

cytokines as TNF-alpha and IL-6. Local inflammatory changes in obese pregnant women are also reflected in increased plasma concentrations of C-reactive peptide (CrP) and IL-6. Interestingly, the CD14+ macrophages were of a maternal but not fetal origin [43].

Up to now few studies have investigated the effect of overweight and obesity on inflammation during pregnancy. Ramsay et al. [13] found higher serum concentrations of leptin, CrP and IL-6 in obese compared to normal weight women. These circulating pro-inflammatory cytokines were also correlated to higher levels of TNF-alpha- and IL-6-mRNA produced by maternal peripheral mononuclear cells [42]. However, the invasion of macrophages into the VAT have up to now only been demonstrated in non-pregnant obese adults [44,45]. In obese baboons, Farley et al. demonstrated a marked macrophage infiltration into the adipose tissue [46]. With increasing degree of obesity macrophages increasingly produce transcription factors, adipokines and inflammatory molecules [47] which also results in insulin resistance [44].

Visceral obesity associated with glucose intolerance and insulin resistance [13,48], may lead to GDM in obese women [20]. Unfortunately, there is a paucity of research related to biochemical pathways of GDM in pregnant women. According to Kirwan et al. [49] TNF-alpha levels in normal weight pregnant women can predict insulin resistance during later stages of pregnancy. Disturbances in the insulin signalling cascade in obese pregnant women with normal glucose tolerance could be demonstrated in both the adipose tissue as well as in the skeletal muscle [50]. The negative effects of overweight and obesity become more obvious in glucose intolerance and insulin resistance [21,51,52]. The inflammatory processes are closely related to the prevalence of pregnancy-induced hypertension or pre-eclampsia in obese pregnant women [53].

Maternal obesity associated with GDM and hypertension is thus related to an inflammatory reaction in the white adipose tissue, in the plasma and the placenta. This "pro-inflammatory state" is supposed to be the primary mechanism underlying the insulin resistance and hypertension in obese pregnant women [20].
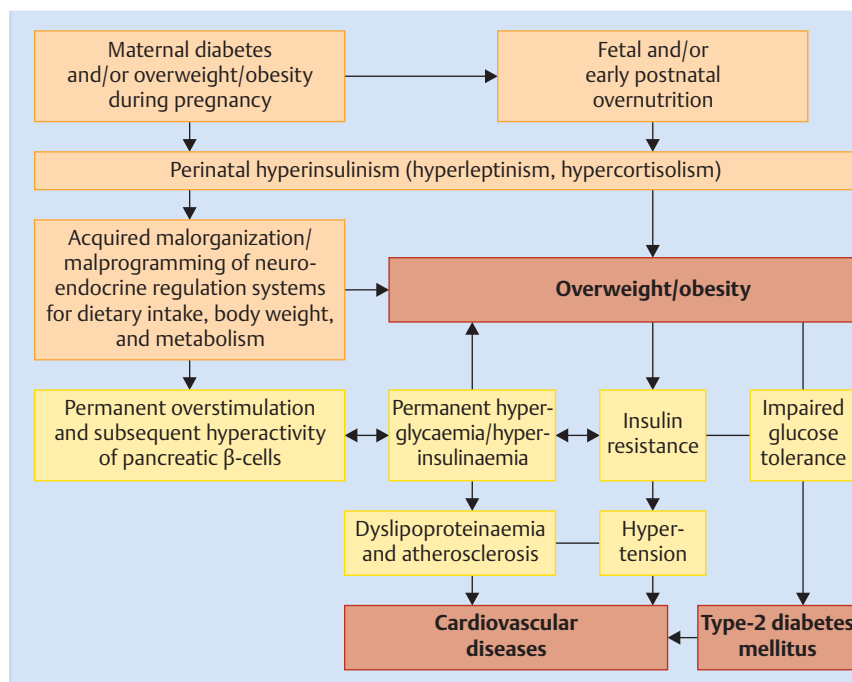
Fig. 2 Pathogenetic mechanisms, and consequences of perinatal malprogramming. Aetiology of pre- and neonatal overfeeding and hyperinsulinism for excessive weight gain, overweight/obesity, type-2 diabetes mellitus and subsequent cardiovascular diseases in later life (modified in accordance with [58]).

Perinatal Programming of Overweight and Obesity
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"Perinatal programming" has meanwhile been established as a field of research for dealing with the impact of the intrauterine and early postnatal environment on fundamental mechanisms of health and disease [54–59] (○ **Fig. 2**). The main focus is the phenomenon of an epigenetic, maternal-fetal transmission of acquired conditions.

Results from epidemiological, clinical and animal experimental studies indicate the impact of nutrition during the pre-natal and early post-natal development and its impact on the occurrence of overweight, obesity, T2D and cardiovascular diseases in later life [60, 61]. The metabolic state during pregnancy and the kind of nutrition in the neonatal period (e.g. breast-feeding and its long-term effect) may both have negative or positive sequelae for the growing child up to adulthood [62–65].

Günter Dörner at Charité postulated in the 1970s that T2D is "transmitted" more frequently from the maternal line than from the paternal line [66]. He developed the concept of "perinatal programming" and established a "functional teratology" [67]. In the 1990s the groups of Hales and Barker described the concept of "prenatal origin of adult disease" in growth-retarded fetuses and newborns [68].

Apart from genetic factors, maternal diet and nutritional status during pregnancy have a critical impact on intrauterine growth and birthweight. In developed countries, overall birthweight increased by 126 g during the last 20 to 30 years. Accordingly, the rate of macrosomia rose by 25% per decade [69–72] whereby epigenetic causes are supposed to be the underlying mechanism.

The risk of macrosomia (birthweight > 4000 g) is more than doubled or even tripled in children of obese or morbid obese women [73], and mainly combined with excessive weight gain [69, 76]. In Part 2, we explain the clinical consequences and complications [74]. Regardless of the pre-conceptional weight, maternal weight gain during pregnancy positively correlates with the birthweight [69, 75].

Epidemiological studies showed a positive correlation between birthweight and the body weight in adulthood signifying that maternal obesity-related fetal macrosomia is associated with obesity in later life [77, 78]. A meta-analysis of a total of 643 902 individuals between 1 and 75 years of age from 26 countries revealed a positive linear connection between birth weight and the later overweight in 59/66 (89.4%) of studies. In four of the studies (6.1%), no correlation was observed. In three studies (4.5%) a U-shaped relation was described, i.e. a similar risk increase in low and high birth weight. However, no linear inverse relation was described. Based on adjusted estimation, it was shown that the risk of overweight in later life in children with high birth weight was almost doubled (OR 1.96, 95% CI 1.43–2.67) compared to children of normal birthweight (2500–4000 g) [78].

A meta-analysis on the correlation between birth weight and the subsequent risk of T2D accordingly revealed a U-shaped relation in all published studies explaining that children with low birth and high birth weight exhibit an increased risk for T2D in later life [79].

It seems to be a vicious circle that obesity during pregnancy causes maternal GDM and an increased birth weight and obesity in the offspring who then develop associated diabetic metabolic disorders, e.g., GDM in females [80–84].

Similarly, animal studies showed that not only maternal overweight and obesity but also the nutrition during pregnancy have an impact on the offspring: Pregnant female Japanese macaques that received either a high-fat (35% fat) or a normal diet (13% fat) during pregnancy showed differences in the juvenile microbiome of the gastro-intestinal tract during the first year of life [85]. Campylobacter was not detectable in the juvenile microbiome after the high-fat-diet. These changes were very stable and could not even be corrected postnatally by a normal diet.

Maternal obesity and a high-fat diet during pregnancy seem to lead to a malprogramming of the hepatic fatty acid metabolism resulting in upregulated lipogenesis and obesity in the offspring which is indicated by an increased desaturation index (DI), e.g. a ratio of unsaturated (C16 and C18) versus saturated fatty acids.

Rats that either received a high-fat or a normal diet did not differ in birth weight, however showed a reduced DI in the offspring of obese rats [86]. At the age of six months, the male offspring were significantly heavier (800 vs. 659 g), more obese (26 vs. 20 %) and showed an increased DI in the plasma (0.1 vs. 0.06) and in the liver (0.09 vs. 0.06). A high-fat diet during pregnancy initially suppresses the DI of the newborns but subsequently upregulates the DI despite a normal postnatal diet. Bytautiene et al. demonstrated significantly shorter telomeres and a reduced expression of the *Klotho* gene in the female and male offspring of obese mice in comparison to normal weight mice, which is a surrogate parameter of an accelerated ageing process [87]. A dysfunctional VAT in the offspring of obese mice was described by the same group [88]. Obesity before conception was generated by a high-fat diet. The offspring received a normal diet until the age of six months. A reduced expression of the hypoxia-inducible factor 1 alpha (HIF-1 α) and of the angiotensin 2 receptor as well as an increased expression of angiotensin (ANG) were found in the VAT of the offspring of obese mice. These alterations may disturb developmental cascades leading to fetal programmed hypertension and a metabolic syndrome in later life even in following generations.

Perinatal mal-programming may also involve the central nervous regulatory centres of metabolism and body weight control. Thus, maternal overweight and/or maternal diabetes (hyperglycaemia) during pregnancy and early postnatal overnutrition lead to increased insulin, glucose, protein and/or leptin levels during critical development stages (e.g. fetal hyperinsulinism). Malprogramming via epigenetic mechanisms results in a life-long disposition for overweight, obesity and diabetic metabolic disorders across generations [54,58,63,89,90].

Epigenetic mechanisms are DNA-methylation, the modification of histones and the regulation of microRNAs. Methylation of cytidine bases in cytosine-guanosine nucleotide dimers (CpG) (DNA methylation) has been investigated [91]. Highly-methylated DNA (especially the so-called promoter regions) reduces the gene expression [91]. Only a few studies have investigated the contribution of epigenetic mechanisms to fetal metabolic programming on a molecular level [92–96]. In placentas of women with gestational diabetes, modifications in the methylation of the leptin and adiponectin genes (*LEP* and *ADIPOQ*) have been found. *LEP* and *ADIPOQ* are classified as candidate genes for obesity and GDM [93,96]. Furthermore, it was shown that total methylation in the placentas of obese women is significantly higher than in normal-weight women [97]. These changes have lasting effects on the regulation of the metabolism of the offspring if they reflect DNA methylation in other tissues, thus triggering the development of chronic metabolic disorders.

In maternal obesity without glucose intolerance the microRNA expression remains unchanged. In a study on 16 obese and 20 normal-weight pregnant women, with a normal glucose tolerance, the microRNA expression in the umbilical cord blood did not differ significantly [98]. The authors concluded that in fetal programming other mechanisms are more relevant.

Future prevention should start before conception to avoid maternal obesity, GDM, and the epigenetic modifications. In pregnant rats it was demonstrated that an exercise programme during pregnancy could have positive effects on the metabolic phenotype of the offspring [99]. The percentage of fat-free body mass in the male offspring was increased and the fat mass reduced. Interventions and longitudinal studies might help to detect whether we can also modify epigenetics and perinatal programming of GDM, overweight or obesity.

Conclusions
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Overweight and obesity lead to an increase in maternal and perinatal morbidity and mortality. The molecular biological mechanisms as gestational diabetes or metabolic syndrome, have not yet been sufficiently investigated. Local and systemic inflammatory processes, triggered by the adipose tissue, seem to play a key role. Despite the increasing prevalence of overweight and obesity in pregnant women in Western countries including Germany, clinical research on mechanisms and interventions are scarce although the diagnosis is easy. Further investigations of the biology of adipose tissue and its association with insulin resistance, the formation of adipokines and endothelial dysfunction are necessary.

Primary prevention programmes have to be implemented. Avoiding overweight and obesity in childhood and adolescence and appropriate weight gain during pregnancy [100] are essential. Educational programs prior to conception are important. The promotion of breast-feeding for newborns should also be considered.

Conflict of Interest
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None.

Literatur

1 *Max Rubner-Institut.* Nationale Verzehrsstudie II. Ergebnisbericht, Teil 1. 2008. Online: www.mri.bund.de; last access: 20.01.2014
2 *Abbasi F, Brown BW jr., Lamendola C et al.* Relationship between obesity, insulin resistance, and coronary heart disease risk. J Am Coll Cardiol 2002; 40: 937–943
3 *McLaughlin T, Allison G, Abbasi F et al.* Prevalence of insulin resistance and associated cardiovascular disease risk factors among normal weight, overweight, and obese individuals. Metabolism 2004; 53: 495–499
4 *Catalano PM, Tyzbir ED, Roman NM et al.* Longitudinal changes in insulin release and insulin resistance in nonobese pregnant women. Am J Obstet Gynecol 1991; 165 (6 Pt 1): 1667–1672
5 *Catalano PM, Huston L, Amini SB et al.* Longitudinal changes in glucose metabolism during pregnancy in obese women with normal glucose tolerance and gestational diabetes mellitus. Am J Obstet Gynecol 1999; 180: 903–916
6 *Athukorala C, Rumbold AR, Willson KJ et al.* The risk of adverse pregnancy outcomes in women who are overweight or obese. BMC Pregnancy Childbirth 2010; 10: 56
7 *Ovesen P, Rassmussen S, Kesmodel U.* Effect of prepregnancy overweight and obesity on pregnancy outcome. Obstet Gynecol 2011; 118 (2 Pt 1): 305–312
8 *Weiss JL, Malone FD, Emig D et al.; FASTER Research Consortium.* Obesity, obstetric complications and cesarean delivery rate – a population-based screening study. Am J Obstet Gynecol 2004; 190: 1091–1097
9 *Torloni MR, Betran AP, Horta BL et al.* Prepregnancy BMI and the risk of gestational diabetes: a systematic review of the literature with meta-analysis. Obes Rev 2009; 10: 194–203
10 *Challis JR, Lockwood CJ, Myatt L et al.* Inflammation and pregnancy. Reprod Sci 2009; 16: 206–215
11 *Wang Z, Nakayama T.* Inflammation, a link between obesity and cardiovascular disease. Mediators Inflamm 2010; 2010: 535918
12 *Mangge H, Almer G, Truschnig-Wilders M et al.* Inflammation, adiponectin, obesity and cardiovascular risk. Curr Med Chem 2010; 17: 4511–4520

13 *Ramsay JE, Ferrell WR, Crawford L et al.* Maternal obesity is associated with dysregulation of metabolic, vascular, and inflammatory pathways. J Clin Endocrinol Metab 2002; 87: 4231–4237

14 *Roberts JM, Bodnar LM, Patrick TE et al.* The role of obesity in preeclampsia. Pregnancy Hypertens 2011; 1: 6–16

15 *Zhang Y, Proenca R, Maffei M et al.* Positional cloning of the mouse obese gene and its human homologue. Nature 1994; 372: 425–432

16 *Ronti T, Lupattelli G, Mannarino E.* The endocrine function of adipose tissue: an update. Clin Endocrinol (Oxf) 2006; 64: 355–365

17 *Fischer-Posovszky P, Wabitsch M, Hochberg Z.* Endocrinology of adipose tissue - an update. Horm Metab Res 2007; 39: 314–321

18 *Gelsinger C, Tschoner A, Kaser S et al.* [Adipokine update – new molecules, new functions]. Wien Med Wochenschr 2010; 160: 377–390

19 *Denison FC, Roberts KA, Barr SM et al.* Obesity, pregnancy, inflammation, and vascular function. Reproduction 2010; 140: 373–385

20 *Catalano PM.* Trying to understand gestational diabetes. Diabet Med 2014; 31: 273–281

21 *Poissonnet CM, Burdi AR, Bookstein FL.* Growth and development of human adipose tissue during early gestation. Early Hum Dev 1983; 8: 1–11

22 *Martin RJ, Hausman GJ, Hausman DB.* Regulation of adipose cell development in utero. Proc Soc Exp Biol Med 1998; 219: 200–210

23 *Poissonnet CM, Burdi AR, Garn SM.* The chronology of adipose tissue appearance and distribution in the human fetus. Early Hum Dev 1984; 10: 1–11

24 *Knittle JL, Timmers K, Ginsberg-Fellner F et al.* The growth of adipose tissue in children and adolescents. Cross-sectional and longitudinal studies of adipose cell number and size. J Clin Invest 1979; 63: 239–246

25 *Spalding KL, Arner E, Westermark PO et al.* Dynamics of fat cell turnover in humans. Nature 2008; 453: 783–787

26 *Cinti S.* Transdifferentiation properties of adipocytes in the adipose organ. Am J Physiol Endocrinol Metab 2009; 297: E977–E986

27 *Després JP, Lemieux I.* Abdominal obesity and metabolic syndrome. Nature 2006; 444: 881–887

28 *Hotamisligil GS, Shargill NS, Spiegelman BM.* Adipose expression of tumor necrosis factor-alpha: direct role in obesity-linked insulin resistance. Science 1993; 259: 87–91

29 *Lago F, Dieguez C, Gómez-Reino J et al.* The emerging role of adipokines as mediators of inflammation and immune responses. Cytokine Growth Factor Rev 2007; 18: 313–325

30 *Maury E, Brichard SM.* Adipokine dysregulation, adipose tissue inflammation and metabolic syndrome. Mol Cell Endocrinol 2010; 314: 1–16

31 *Hu E, Liang P, Spiegelman BM.* AdipoQ is a novel adipose-specific gene dysregulated in obesity. J Biol Chem 1996; 271: 10697–10703

32 *Milan G, Granzotto M, Scarda A et al.* Resistin and adiponectin expression in visceral fat of obese rats: effect of weight loss. Obes Res 2002; 10: 1095–1103

33 *Huber J, Kiefer FW, Zeyda M et al.* CC chemokine and CC chemokine receptor profiles in visceral and subcutaneous adipose tissue are altered in human obesity. J Clin Endocrinol Metab 2008; 93: 3215–3221

34 *Fain JN, Madan AK, Hiler ML et al.* Comparison of the release of adipokines by adipose tissue, adipose tissue matrix, and adipocytes from visceral and subcutaneous abdominal adipose tissues of obese humans. Endocrinology 2004; 145: 2273–2282

35 *Demerath EW, Reed D, Rogers N et al.* Visceral adiposity and its anatomical distribution as predictors of the metabolic syndrome and cardiometabolic risk factor levels. Am J Clin Nutr 2008; 88: 1263–1271

36 *Tordjman J, Poitou C, Hugol D et al.* Association between omental adipose tissue macrophages and liver histopathology in morbid obesity: influence of glycemic status. J Hepatol 2009; 51: 354–362

37 *Apovian CM, Bigornia S, Mott M et al.* Adipose macrophage infiltration is associated with insulin resistance and vascular endothelial dysfunction in obese subjects. Arterioscler Thromb Vasc Biol 2008; 28: 1654–1659

38 *Poulain-Godefroy O, Lecoeur C, Pattou F et al.* Inflammation is associated with a decrease of lipogenic factors in omental fat in women. Am J Physiol Regul Integr Comp Physiol 2008; 295: R1–R7

39 *Staiger H, Häring HU.* Adipocytokines: fat-derived humoral mediators of metabolic homeostasis. Exp Clin Endocrinol Diabetes 2005; 113: 67–79

40 *Radaelli T, Varastehpour A, Catalano P et al.* Gestational diabetes induces placental genes for chronic stress and inflammatory pathways. Diabetes 2003; 52: 2951–2958

41 *Hauguel-de Mouzon S, Guerre-Millo M.* The placenta cytokine network and inflammatory signals. Placenta 2006; 27: 794–798

42 *Challier JC, Basu S, Bintein T et al.* Obesity in pregnancy stimulates macrophage accumulation and inflammation in the placenta. Placenta 2008; 29: 274–281

43 *Basu S, Leahy P, Challier JC et al.* Molecular phenotype of monocytes at the maternal-fetal interface. Am J Obstet Gynecol 2011; 205: 265.e1–265.e8

44 *Xu H, Barnes GT, Yang Q et al.* Chronic inflammation in fat plays a crucial role in the development of obesity-related insulin resistance. J Clin Invest 2003; 112: 1821–1830

45 *Hotamisligil GS.* Inflammation and metabolic disorders. Nature 2006; 444: 860–867

46 *Farley D, Tejero ME, Comuzzie AG et al.* Feto-placental adaptations to maternal obesity in the baboon. Placenta 2009; 30: 752–760

47 *Lumeng CN, Bodzin JL, Saltiel AR.* Obesity induces a phenotypic switch in adipose tissue macrophage polarization. J Clin Invest 2007; 117: 175–184

48 *Martin AM, Berger H, Nisenbaum R et al.* Abdominal visceral adiposity in the first trimester predicts glucose intolerance in later pregnancy. Diabetes Care 2009; 32: 1308–1310

49 *Kirwan JP, Hauguel-De Mouzon S, Lepercq J et al.* TNF-alpha is a predictor of insulin resistance in human pregnancy. Diabetes 2002; 51: 2207–2213

50 *Colomiere M, Permezel M, Riley C et al.* Defective insulin signaling in placenta from pregnancies complicated by gestational diabetes mellitus. Eur J Endocrinol 2009; 160: 567–578

51 *Metzger BE, Lowe LP, Dyer AR et al.; HAPO Study Cooperative Research Group.* Hyperglycemia and adverse pregnancy outcomes. N Engl J Med 2008; 358: 1991–2002

52 *Boomsma CM, Eijkemans MJ, Hughes EG et al.* A meta-analysis of pregnancy outcomes in women with polycystic ovary syndrome. Hum Reprod Update 2006; 12: 673–683

53 *Bodnar LM, Ness RB, Harger GF et al.* Inflammation and triglycerides partially mediate the effect of prepregnancy body mass index on the risk of preeclampsia. Am J Epidemiol 2005; 162: 1198–1206

54 *Plagemann A.* 'Fetal programming' and 'functional teratogenesis': on epigenic mechanisms and prevention of perinatally acquired lasting health risks. J Perinat Med 2004; 32: 297–305

55 *Catalano PM, Hauguel-De Mouzon S.* Is it time to revisit the Pedersen hypothesis in the face of the obesity epidemic? Am J Obstet Gynecol 2011; 204: 479–487

56 *Plagemann A, Harder T, Schellong K et al.* Early postnatal life as a critical time window for determination of long-term metabolic health. Best Pract Res Clin Endocrinol Metab 2012; 26: 641–653

57 *Pinney SE, Simmons RA.* Metabolic programming, epigenetics, and gestational diabetes mellitus. Curr Diab Rep 2012; 12: 67–74

58 *Plagemann A.* Toward a unifying Concept on perinatal Programming: vegetative Imprinting by Environment-dependent Biocybernetogenesis. In: Plagemann A, ed. Perinatal Programming. The State of the Art. Berlin, Boston: de Gruyter; 2012: 243–282

59 *Ruchat SM, Hivert MF, Bouchard L.* Epigenetic programming of obesity and diabetes by in utero exposure to gestational diabetes mellitus. Nutr Rev 2013; 71 (Suppl. 1): S88–S94

60 *Plagemann A.* Perinatal programming and functional teratogenesis: impact on body weight regulation and obesity. Physiol Behav 2005; 86: 661–668

61 *Plagemann A, Harder T, Dudenhausen JW.* The diabetic pregnancy, macrosomia, and perinatal nutritional programming. Nestle Nutr Workshop Ser Pediatr Program 2008; 61: 91–102

62 *Harder T, Rodekamp E, Schellong K et al.* Adipositas und perinatale Programmierung. In: Plagemann A, Dudenhausen JW, Hrsg. Adipositas als Risiko in der Perinatalmedizin. München: Springer; 2010: 72–81

63 *Plagemann A.* Maternal diabetes and perinatal programming. Early Hum Dev 2011; 87: 743–747

64 *Plagemann A, Harder T.* Fuel-mediated teratogenesis and breastfeeding. Diabetes Care 2011; 34: 779–781

65 *Stupin JH, Harder T, Plagemann A.* [Fetal programming during diabetic pregnancy.] Adipositas 2011; 5: 134–140

66 *Dörner G, Mohnike A.* Further evidence for a predominantly maternal transmission of maturity-onset type diabetes. Endokrinologie 1976; 68: 121–124

67 *Dörner G.* Perinatal Hormone Levels and Brain Organization. In: Stumpf W, Grant LD, eds. Anatomical Neuroendocrinology. Basel: Karger; 1975: 245–252

68 *Hales CN, Barker DJ.* Type 2 (non-insulin-dependent) diabetes mellitus: the thrifty phenotype hypothesis. Diabetologia 1992; 35: 595–601

69 *Bergmann RL, Richter R, Bergmann KE et al.* Secular trends in neonatal macrosomia in Berlin: influences of potential determinants. Paediatr Perinat Epidemiol 2003; 17: 244–249

70 *Harder T, Plagemann A.* The intrauterine environmental adipogenesis. J Pediatr 2004; 144: 551–552

71 *Hesse V, Voigt M, Sälzler A et al.* Alterations in height, weight, and body mass index of newborns, children, and young adults in eastern Germany after German reunification. J Pediatr 2003; 142: 259–262

72 *Sewell MF, Huston-Presley L, Super DM et al.* Increased neonatal fat mass, not lean body mass, is associated with maternal obesity. Am J Obstet Gynecol 2006; 195: 1100–1103

73 *Cedergren MI.* Maternal morbid obesity and the risk of adverse pregnancy outcome. Obstet Gynecol 2004; 103: 219–224

74 *Mission JF, Marshall NE, Caughey AB.* Obesity in pregnancy: a big problem and getting bigger. Obstet Gynecol Surv 2013; 68: 389–399

75 *Galtier-Dereure F, Boegner C, Bringer J.* Obesity and pregnancy: complications and cost. Am J Clin Nutr 2000; 71 (5 Suppl.): 1242S–1248S

76 *Helms E, Coulson CC, Galvin SL.* Trends in weight gain during pregnancy: a population study across 16 years in North Carolina. J Obstet Gynecol 2006; 194: e32–e34

77 *Harder T, Schellong K, Stupin J et al.* Where is the evidence that low birthweight leads to obesity? Lancet 2007; 369: 1859

78 *Schellong K, Schulz S, Harder T et al.* Birth weight and long-term overweight risk: systematic review and a meta-analysis including 643,902 persons from 66 studies and 26 countries globally. PLoS One 2012; 7: e47776

79 *Harder T, Rodekamp E, Schellong K et al.* Birth weight and subsequent risk of type 2 diabetes: a meta-analysis. Am J Epidemiol 2007; 165: 849–857

80 *Dabelea D, Hanson RL, Lindsay RS et al.* Intrauterine exposure to diabetes conveys risks for type 2 diabetes and obesity: a study of discordant sibships. Diabetes 2000; 49: 2208–2211

81 *Pettitt DJ, Baird HR, Aleck KA et al.* Excessive obesity in offspring of Pima Indian women with diabetes during pregnancy. N Engl J Med 1983; 308: 242–245

82 *Plagemann A, Harder T, Kohlhoff R et al.* Overweight and obesity in infants of mothers with long-term insulin-dependent diabetes or gestational diabetes. Int J Obes Relat Metab Disord 1997; 21: 451–456

83 *Plagemann A, Harder T, Kohlhoff R et al.* Glucose tolerance and insulin secretion in children of mothers with pregestational IDDM or gestational diabetes. Diabetologia 1997; 40: 1094–1100

84 *Silverman BL, Rizzo T, Green OC et al.* Long-term prospective evaluation of offspring of diabetic mothers. Diabetes 1991; 40 (Suppl. 2): 121–125

85 *Prince A, Ma J, Bader D et al.* Maternal diet persistently alters the developing juvenile microbiome in a primate model of obesity (abstract). Am J Obstet Gynecol 2014; 210 (Suppl. 1): S30

86 *Seet E, Yee J, Ross M et al.* Programmed adipogenesis and obesity in offspring of obese dams (abstract). Am J Obstet Gynecol 2014; 210 (Suppl. 1): S33

87 *Bytautiene E, Kechichian T, Syes T et al.* Accelerated aging in the offspring of mothers with pre-pregnancy obesity in a mouse model of developmental programming of metabolic syndrome (abstract). Am J Obstet Gynecol 2014; 210 (Suppl. 1): S30–S31

88 *Bytautiene E, Banerjee D, Kechichian T et al.* Adipose tissue dysfunction in a model of developmental programming of metabolic syndrome. Am J Obstet Gynecol 2014; 210 (Suppl. 1): S97

89 *Dörner G, Plagemann A.* Perinatal hyperinsulinism as possible predisposing factor for diabetes mellitus, obesity and enhanced cardiovascular risk in later life. Horm Metab Res 1994; 26: 213–221

90 *Plagemann A, Harder T, Brunn M et al.* Hypothalamic proopiomelanocortin promoter methylation becomes altered by early overfeeding: an epigenetic model of obesity and the metabolic syndrome. J Physiol 2009; 587 (Pt 20): 4963–4976

91 *Bird A.* DNA methylation patterns and epigenetic memory. Genes Dev 2002; 16: 6–21

92 *Heijmans BT, Tobi EW, Stein AD et al.* Persistent epigenetic differences associated with prenatal exposure to famine in humans. Proc Natl Acad Sci U S A 2008; 105: 17046–17049

93 *Bouchard L, Thibault S, Guay SP et al.* Leptin gene epigenetic adaptation to impaired glucose metabolism during pregnancy. Diabetes Care 2010; 33: 2436–2441

94 *Tobi EW, Heijmans BT, Kremer D et al.* DNA methylation of IGF2, GNA-SAS, INSIGF and LEP and being born small for gestational age. Epigenetics 2011; 6: 171–176

95 *Filiberto AC, Maccani MA, Koestler D et al.* Birthweight is associated with DNA promoter methylation of the glucocorticoid receptor in human placenta. Epigenetics 2011; 6: 566–572

96 *Bouchard L, Hivert MF, Guay SP et al.* Placental adiponectin gene DNA methylation levels are associated with mothers' blood glucose concentration. Diabetes 2012; 61: 1272–1280

97 *Nomura Y, Lambertini L, Rialdi A et al.* Global methylation in the placenta and umbilical cord blood from pregnancies with maternal gestational diabetes, preeclampsia, and obesity. Reprod Sci 2014; 21: 131–137

98 *Ghaffari N, Parry S, Durnwald C.* The role of miRNA in fetal programming of obesity. Am J Obstet Gynecol 2014; 210 (Suppl. 1): S70

99 *Nathanielsz PW, Ford SP, Long NM et al.* Interventions to prevent adverse fetal programming due to maternal obesity during pregnancy. Nutr Rev 2013; 71 (Suppl. 1): S78–S87

100 *Institute of Medicine (IOM).* Weight Gain during Pregnancy: re-examining the Guidelines. Committee to Reexamine IOM Pregnancy Weight Guidelines. Washington: National Research Council; 2009