Leptin, adiponectin and other adipokines in gestational diabetes mellitus and pre-eclampsia

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Summary

Proteins secreted from adipocytes – so-called adipokines – influence metabolic and vascular function. Recent data suggest that various adipokines are dysregulated in gestational diabetes mellitus (GDM) and pre-eclampsia (PE) and might be of pathophysiological and prognostic significance in these complications of pregnancy. This review gives an overview on the regulation and pathophysiology of leptin and adiponectin in GDM and PE. Furthermore, data on novel adipokines including resistin, visfatin, retinol-binding protein 4 and vaspin are summarized. (Received 5 May 2011; returned for revision 14 June 2011; finally revised 9 August 2011; accepted 19 September 2011)

Introduction

Human pregnancy is characterized by a series of endocrine, metabolic and vascular changes to provide sufficient energy and nutrients to the foetus. In early pregnancy, insulin secretion increases, whereas insulin sensitivity is unchanged, decreased or even increased. Furthermore, there is an increase in maternal fat stores and a lowering in free fatty acid (FFA) concentrations. From mid-pregnancy onwards, insulin sensitivity progressively decreases to levels that approximate insulin resistance seen in type 2 diabetes. As a result, a 2- to 2.5-fold increase in insulin secretion is necessary to maintain euglycaemia. In late pregnancy, maternal adipose tissue depots decrease, whereas postprandial FFA levels increase and insulin-mediated glucose disposal rates decline by approximately 50% as compared to prepregnancy values. Moreover, insulin shows reduced ability to suppress lipolysis. Dysregulation of these physiological changes during pregnancy contributes to the complications of pregnancy. In the current review, gestational diabetes mellitus (GDM) and pre-eclampsia (PE) are briefly summarized as complications of pregnancy, after which adipocyte-secreted factors – so-called adipokines – are introduced. The review then focuses on the key adipokines leptin and adiponectin for which extensive data in GDM and PE have been published. Furthermore, results on novel adipokines including resistin, visfatin, retinol-binding protein 4 (RBP4) and vaspin are summarized. However, data on these latter adipokines are often preliminary and remain rather descriptive.

Gestational diabetes mellitus and pre-eclampsia as complications of pregnancy

Gestational diabetes mellitus is a complication of pregnancy that is characterized by impaired glucose tolerance with onset or first recognition during pregnancy. It develops when the pancreatic β-cell reserve is not sufficient to compensate for decreased insulin sensitivity during pregnancy. As a consequence, there are greater postprandial increases in FFAs, increased hepatic glucose production, severe insulin resistance and subsequently increased blood glucose levels. The reported prevalence of GDM varies between 0.6% and 20% of pregnancies depending on screening method, gestational age and the population studied. Both mother and newborn have a significantly increased future risk for metabolic and vascular disease after a diabetic pregnancy. Furthermore, newborns of mothers with GDM are typically at increased risk for acute perinatal complications including hypoglycaemia, jaundice and being large for gestational age.2

Pre-eclampsia is a complication of pregnancy that is characterized by de-novo development of concurrent hypertension and proteinuria. It affects 2–5% of pregnancies and is a major contributor to foetal, neonatal and maternal morbidity and mortality. PE may develop from 20 weeks of gestation up to 6 weeks postpartum and is considered early onset before 34 weeks of gestation. Like GDM, PE shares risk factors with the metabolic syndrome including insulin resistance, subclinical inflammation and obesity. Women with PE are at increased risk for future cardiovascular disease. The relative risks for hypertension, ischaemic heart disease, stroke and venous thromboembolism 4.7–14.1 years after PE are 3.7, 2.2, 1.8 and 1.8, respectively. Reduced uterine perfusion pressure (RUPP) during pregnancy is an important initiating event in PE. Furthermore, abnormal placentation and an imbalance between
Adipokines

Adipose tissue is not only involved in energy storage but also functions as an endocrine organ that secretes various bioactive molecules. Proteins that are secreted by adipose tissue and that provide an extensive network of communication both within adipose tissue and with other organs are collectively called adipokines or adipocytokines. Adipokines are involved in a wide range of physiological processes including haemostasis, lipid metabolism, atherosclerosis, blood pressure regulation, insulin sensitivity and angiogenesis. Various adipokines also influence immunity and inflammation.

In recent years, the adipokines adiponectin and leptin have been shown to play a role in normal pregnancy, as well as in complications of pregnancy, including GDM and PE. Furthermore, dysregulation of other adipokines including resistin, visfatin, RBP4 and vaspin has been demonstrated in GDM and PE; however, the significance of these findings remains to be established.

Adipokines in GDM and PE

Leptin

Function of leptin. Leptin is a 16-kDa protein hormone discovered in 1994 that plays a key role in the regulation of energy intake and energy expenditure. Further, leptin is involved in a number of physiological processes including regulation of endocrine function, inflammation, immune response, reproduction and angiogenesis. Thus, it increases insulin sensitivity by influencing insulin secretion, glucose utilization, glycogen synthesis and fatty acid metabolism, regulates gonadotrophin releasing hormone secretion from the hypothalamus and activates the sympathetic nervous system. Leptin is produced mainly by adipocytes. Leptin-deficient ob/ob mice are hyperphagic and obese. Serum leptin levels are directly proportional to fat mass. Leptin is transported across the blood–brain barrier where it binds to specific receptors of appetite-modulating neurons most notably in the arcuate nucleus.4

Leptin in normal pregnancy. Besides its effect on regulating gonadotrophin releasing hormone secretion, leptin plays a functional role in implantation.5 Moreover, it induces human chorionic gonadotrophin production in trophoblast cells, regulates placental growth, enhances mitogenesis and stimulates amino acid uptake.5 Leptin and leptin receptor mRNA and protein have been identified in human placental tissue.6,7 In addition, the adipokine is found in amniotic fluid and cord blood at birth.8 Placental leptin mRNA production is upregulated by tumour necrosis factor (TNF) α and interleukin (IL)-6.7 From the earliest stages of pregnancy, maternal leptin concentrations increase implying that the increases are not only originating from maternal weight gain.10 Circulating leptin levels reach two- to three-fold higher concentrations as compared to nonpregnant conditions with a peak occurring around 28 weeks of gestation and a decrease to pre gravid concentrations observed immediately after delivery (Table 1).11 Pregnancy is considered a leptin resistant state, which is associated with impaired leptin signalling in the hypothalamus. Thus, in rats, the long isoform of leptin receptor mRNA is reduced in the ventromedial nucleus of the hypothalamus during pregnancy as compared to nonpregnant controls. Furthermore, reduced levels of the soluble isoform of leptin receptor have been found in the choroid plexus of pregnant rats. Hence, diminished transport of leptin into the brain may also contribute to pregnancy-induced leptin resistance.12

One possible function of increased maternal leptin levels is to enhance the mobilization of maternal fat stores to increase availability and to support transplacental transfer of lipid substrates.5

There is strong evidence that the placenta, rather than maternal adipose tissue, contributes a substantial part to the rise in maternal leptin concentrations during pregnancy.13 Thus, the human placental leptin gene has a specific promoter region suggesting that placental leptin is differentially regulated as compared to leptin originating from adipose tissue.13 Furthermore, the foetus itself contributes to leptin production starting early in the second trimester,14 although to a much lesser extent than the placenta. Moreover, leptin concentrations in umbilical cord plasma positively correlate with birth weight of newborns.15

Leptin in gestational diabetes mellitus. Data on leptin in GDM have been controversial (Table 1). Most studies have found increased16–19 leptin concentrations in GDM. Moreover, hyperleptinaemia in early pregnancy appears to be predictive of an increased risk to develop GDM later in pregnancy independent of maternal adiposity. Thus, Qiu et al.20 have studied 823 pregnant women from 13 weeks of gestation to delivery. After adjusting for maternal pre-pregnancy adiposity and other confounders, women with leptin concentrations of ≥310 ng/ml at 13 weeks of gestation had a

| Table 1. Up- (†), down- (↓) and no (↔) regulation of circulating maternal adipokines in pregnancy complications compared with regulation in normal pregnancy. Reference numbers are indicated |
|---------------------------------|---------------------------------|---------------------------------|
| Normal pregnancy | GDM | PE |
| **Leptin** | Two- to three-fold higher as compared to nonpregnant conditions; peak occurring around 28 weeks of gestation1 | ↑16–19 | ↑32–45 |
| | | ↓23,24 | ↓44 |
| **Adiponectin** | Progressive decline during pregnancy31 | ↓56–62 | ↑34,72–74,76,77 |
| **Resistin** | Higher as compared to nonpregnant controls34 | ↑86 | ↓57 |
| | | ↓34 |
| **Visfatin** | Peak between 19 and 26 weeks of gestation; nadir between 27 and 34 weeks of gestation90 | ↑95 | ↓98 |
| **RBP4** | Inconsistent data104,105 | ↑106 | ↓110 |
| | | ↓107 | ↑111 |
| | | ↓108 | ↓113 |
| **Vaspin** | Lower levels at 24–30 weeks of gestation116 | ↓117 | ↓117 |

GDM, gestational diabetes mellitus; n.d., not determined; PE, pre-eclampsia; RBP4, retinol-binding protein 4.
4.7-fold increased risk of GDM as compared to women with leptin levels of ≤143 ng/mL. Furthermore, a strong linear correlation between increased maternal plasma leptin and increased risk of GDM could be observed with each 10 ng/mL increase in leptin concentration being associated with a 20% increase in GDM risk. An increase in maternal serum leptin concentrations before the onset of GDM has also been shown by other authors. Moreover, D’Anna et al. demonstrate significantly higher amniotic fluid leptin concentrations at 15–17 weeks of gestation in 32 women with subsequent GDM as compared to 43 women with normal glucose tolerance during the course of pregnancy. They note that a 1 ng/mL increase in leptin concentration is associated with a 4% increased risk to develop GDM. Furthermore, amniotic fluid leptin values at 15–17 weeks of gestation are directly correlated with amniotic insulin concentration. However, some investigators have observed decreased or unchanged maternal leptin concentrations in patients with overt GDM. These discrepancies may be partly attributed to differences in severity of GDM or to ethnic differences.

Gestational diabetes mellitus is characterized by an amplification of the low-grade inflammation already existing in normal pregnancy. This hypothesis is supported by increased circulating concentrations of inflammatory molecules like TNFα and IL-6 in GDM pregnancies. TNFα is one of the candidate molecules responsible for causing insulin resistance. Comparison of the placental gene expression profile between normal and diabetic pregnancies indicates that increased leptin synthesis in GDM is associated with a higher production of proinflammatory cytokines, e.g. IL-6 and TNFα causing a chronic inflammatory environment that enhances leptin production. Thus, compared with normal pregnant women, placental leptin expression in patients with GDM is increased. Conversely, leptin itself increases production of TNFα and IL-6 by monocytes and stimulates the production of CC-chemokine ligands. Thus, a vicious circle develops, aggravating the inflammatory situation. Chronic insulin administration increases leptin secretion by adipocytes. Thus, hyperinsulinaemia in GDM might further stimulate leptin production. Elevated leptin concentrations in turn amplify inflammation.

**Leptin in pre-eclampsia.** Leptin protein and mRNA levels are increased in placentas from PE women as compared to healthy pregnant controls. Moreover, increased levels of circulating leptin in PE even before the clinical onset of the disease have been shown in the majority of studies, and elevated leptin levels seem to have a prognostic significance for the development of PE (Table 1). Thus, Ning et al. demonstrate 78% higher first trimester plasma leptin levels at 13 weeks of gestation in 55 patients with subsequent PE as compared to 487 normal pregnant controls. Compared with women with leptin concentrations <27.4 ng/mL, those with leptin levels ≥27.4 ng/mL show a 2.3-fold increased risk for PE development. Each 10 ng/mL increase in leptin concentrations is associated with a 30% increase in PE risk. Another study determining plasma leptin at 13 weeks of gestation in 37 women who subsequently developed PE and 53 normotensive controls even demonstrates a 18.8-fold increased risk for PE in women with leptin concentrations ≥25.3 ng/mL. Moreover, the observation that leptin rises before the clinical onset of the disease suggests a pathophysiological role of leptin rather than an elevation caused by reduced renal leptin clearance, because renal dysfunction rarely precedes the clinical onset of PE. Moore et al. have performed animal experiments in Sprague–Dawley rats using the RUPP rat model to imitate PE by placement of clips on the aorta and the ovarian arteries providing 35% occlusion of the vessels. Maternal serum leptin was significantly increased in the animal group with occluded vessels (2.21 ± 64 ng/mL) as compared to controls (1.66 ± 38 ng/mL), suggesting that reduced placental perfusion results in an increase in maternal serum leptin. Hypoxia might play a role in upregulation of placental leptin in PE as the adipokine...
Adiponectin

**Function of adiponectin.** Adiponectin (also referred to as AdipoQ, Acrp30 and adipocyte complement-related protein) is a 30-kDa protein that is synthesized almost exclusively by adipocytes. It exists in three major oligomeric forms: a low-molecular-weight trimer, a middle-molecular-weight hexamer and high-molecular-weight (HMW) 12- to 18-mer adiponectin.45 Adiponectin is considered an insulin-sensitizing, anti-inflammatory and antiatherogenic adipokine. It stimulates glucose uptake in skeletal muscle and reduces hepatic glucose production through AMP-activated protein kinase.46 Moreover, adiponectin levels are inversely correlated with plasma triglyceride levels and positively associated with HDL cholesterol concentration.46 Plasma adiponectin levels are affected by multiple factors including gender, age and lifestyle. Furthermore, adiponectin gene expression is inhibited by β-adrenergic stimulation, glucocorticoids and TNFα.47,48 Oxidative stress has also been suggested to inhibit expression of the adipokine.49 Low adiponectin serum levels are significantly associated with type 2 diabetes mellitus, insulin resistance, obesity, hypertension and left ventricular hypertrophy.50

**Adiponectin in normal pregnancy.** During the course of pregnancy, maternal adiponectin secretion progressively declines (Table 1).51 This decrease is associated with a 60% reduction of adiponectin mRNA levels in white adipose tissue.51 Both plasma adiponectin concentrations and mRNA are negatively correlated with fat mass suggesting that adipose tissue accretion is associated with signals for lowering adiponectin production even in the absence of obesity.51 In contrast, umbilical vein adiponectin concentrations are higher than maternal serum adiponectin levels.52 Moreover, there is a striking increase in cord plasma adiponectin levels with gestational age reaching more than 20-fold higher concentrations at term compared with 24 weeks of gestation.53 In view of these findings, the human placenta might be a source of adiponectin. Moreover, Chen et al.54 show that adiponectin is expressed in human term placenta, primarily in the syncytiotrophoblast. Furthermore, adiponectin and its receptors are differentially regulated in placenta by various cytokines including TNFα, IFNγ, IL-6 and leptin in vitro.54 However, it is still a matter of debate whether adiponectin is also expressed in placenta besides adipose tissue because some authors33,55 are unable to detect adiponectin mRNA expression.

**Adiponectin in GDM.** Circulating adiponectin levels are reduced in patients with GDM as compared to pregnant controls independent of prepregnancy body mass index (BMI) and insulin sensitivity in various studies (Table 1).56–62 In agreement with these findings, adiponectin mRNA is downregulated in placental tissue in women with GDM.54 Furthermore, circulating adiponectin concentrations are decreased postpartum in women with a history of GDM.63–65 Foetuses of mothers with diabetes exhibit significantly lower adiponectin levels as compared to normal foetuses of same gestational age independent of birth weight.57,58 Moreover, downregulation of adiponectin in the first trimester of pregnancy is an independent predictor of impending GDM. Thus, Lain et al.67 demonstrate that women with first trimester adiponectin concentrations below the 25th percentile are 10 times more likely to be diagnosed with GDM as compared to women with higher adiponectin levels. Williams et al.68 analysed plasma adiponectin in 111 pregnant women at 13 weeks of gestation. They showed a 4.6-fold increased risk of subsequent GDM for women with adiponectin concentrations below 6.4 mg/ml as compared to pregnant women with higher concentrations of the adipokine. Similar results are published by other authors.21 Moreover, quantification of adiponectin has been included in a prediction model using a panel of maternal demographic and clinical characteristics.69–71

As summarized in the leptin section, GDM is characterized by an amplification of low-grade inflammation already existing in normal pregnancy and increased circulating concentrations of inflammatory cytokines including TNFα and IL-6.1 TNFα and IL-6 are putative negative regulatory factors of the adiponectin gene.48 Thus, TNFα and other proinflammatory mediators suppress the transcription of adiponectin in adipocytes, and this might explain the lower levels of the adipokine in individuals with GDM. As adiponectin has insulin-sensitizing effects, low levels of this adipokine might further aggravate insulin resistance. Moreover, insulin is able to suppress plasma adiponectin concentrations,48 and hyperinsulinaemia seen in GDM might cause a significant decrease in plasma adiponectin levels (Fig. 2).

**Adiponectin in PE.** In PE, a paradoxical and significant increase in circulating adiponectin of 30–87% has been described in
Adiponectin in normal pregnancy

- Aggravation of insulin resistance
  - Inflammatory cytokines e.g. TNFα and IL-6
  - Transcription of adiponectin
  - Insulin resistance
  - Hyperinsulinemia

Adiponectin in GDM
- Insulin resistance
- Hypoinsulinemia

Adiponectin in PE
- NFκB signaling
- CRP production
- Nitric oxide production

- Attenuation of inflammatory response in the vascular wall and improved vascular function and/or adiponectin resistance

Fig. 2 Hypothetical model of pathophysiological significance of adiponectin in gestational diabetes mellitus (GDM) and pre-eclampsia (PE).

Adipokines in pregnancy

**Potential role in normal pregnancy:**
- Progressive decline during pregnancy
- Anti-inflammatory

**Regulation in normal pregnancy:**
- Stimulation of glucose uptake in skeletal muscle
- Reduction of hepatic glucose production
- Anti-inflammatory

**Dysregulation in complications of pregnancy:**
- Insulin resistance
- Hyperinsulinemia
- Aggravation of inflammatory response in the vascular wall

**Adipokines in GDM and PE:**
- Resistin
- Visfatin
- RBP4
- Vaspin

**Other adipokines:**
- Resistin
- Visfatin
- RBP4
- Vaspin

The physiological role of the novel adipokines resistin, visfatin, RBP4 and vaspin in nonpregnant conditions is only briefly summarized as an extensive review of the (patho)physiology of these adipokines is beyond the scope of the current manuscript and can be found in several excellent recent papers. It needs to be emphasized that various groups have addressed regulation of these adipokines in GDM and PE recently. However, data have been mostly descriptive, and the physiological significance of adipokine dysregulation in these complications of pregnancy remains to be established in future experiments.

Resistin. Resistin is a signalling molecule expressed in monocytes, macrophages and adipocytes. In the latter, resistin gene expression is induced during fat cell differentiation. In vitro and in vivo studies suggest that resistin impairs glucose tolerance by inducing insulin resistance at least in rodents. Plasma resistin levels in pregnant women are significantly higher as compared to nonpregnant controls (Table 1). Furthermore, circulating concentrations of the adipokine increase with advancing gestation. Results on circulating resistin in patients with GDM have been inconsistent (Table 1). Thus, levels of the adipokine are not altered in patients with GDM as compared to healthy pregnant women in some reports, whereas other authors demonstrate elevated or decreased levels of resistin in women with GDM. In agreement with the former results, Lappas...
et al. are unable to show a difference in the release of resistin from placental and subcutaneous adipose tissue obtained from normal pregnant subjects and women with GDM. Despite increased resistin levels in GDM, Kuzmicki et al. are unable to demonstrate an independent relationship between insulin resistance and serum resistin concentrations. Similar to GDM, conflicting results about regulation of circulating resistin are reported in PE (Table 1). Haugen et al. reported elevated circulating resistin concentrations in patients with PE as compared to normal pregnant controls. However, differences in resistin plasma levels between PE and normal pregnancies are lost after controlling for insulin resistance. Moreover, resistin mRNA expression in abdominal subcutaneous tissue and placenta does not correlate with plasma resistin concentrations. As resistin plasma concentrations depend on glomerular filtration and increase with progressive renal impairment, altered renal function in PE might contribute to elevated circulating resistin levels. In contrast to the above-summarized report, other studies demonstrate lower circulating resistin levels in PE as compared to normotensive healthy pregnant women of similar gestational age. The authors hypothesize that lower levels of resistin in PE might be related to a reduction in placental production of the adipokine because of the smaller size of the placenta. Hendler et al. were unable to find a difference in circulating resistin concentrations between pregnant women with and without PE.

Visfatin. Visfatin is a 52-kDa protein that is highly enriched in the visceral fat of both humans and mice, and plasma levels of which increase during the development of obesity. It is also known as pre-B cell colony-enhancing factor, a cytokine expressed in lymphocytes. The initial report on visfatin suggests that it has insulin-mimetic effects in vitro and in vivo; however, this study has subsequently been retracted. In normal weight women, median maternal plasma concentrations of visfatin peak between 19 and 26 weeks of gestation and have a nadir between 27 and 34 weeks of gestation (Table 1). Visfatin is expressed by foetal membranes and secreted from amniotic epithelial cells during pregnancy. The adipokine has antiapoptotic properties. Furthermore, recombiant human visfatin treatment of human foetal membranes causes a significant increase in inflammatory cytokines including IL-1β, TNFα and IL-6. Moreover, visfatin might play a role in foetal growth. In women with GDM, both increased and decreased visfatin concentrations are reported (Table 1). Furthermore, serum visfatin levels in the first trimester of pregnancy positively predict insulin sensitivity in the second trimester in 80 pregnant nonobese, nondiabetic white women. Similar to GDM, conflicting results have been published for PE (Table 1). Thus, circulating visfatin concentrations are increased in PE in some studies, whereas other investigators show similar or even decreased visfatin concentrations in patients with PE as compared to healthy pregnant women. Differences in the specificity of the visfatin immunosays utilized might potentially contribute to the inconsistencies observed in patients with GDM and PE.

Retinol-binding protein 4. Retinol-binding protein 4 is a 21-kDa protein synthesized in hepatocytes and adipocytes, which serves as a carrier for retinol in the blood stream. Overexpression of RBP4 or injection of recombinant RBP4 in normal mice induces insulin resistance. Increased circulating RBP4 levels have been reported in several metabolic complications including obesity, insulin resistance, polycystic ovary syndrome and cardiovascular disease. RBP4 is a physiological constituent of amniotic fluid. Median amniotic fluid concentrations of RBP4 are elevated in pregnancies complicated by intra-amniotic infection and inflammation. Studies investigating RBP4 serum concentrations in normal pregnancy show conflicting results (Table 1). Thus, maternal fasting RBP4 concentrations are significantly increased between early and late pregnancy, which is associated with a decline in insulin sensitivity. In contrast, Inoue et al. report that RBP4 levels tend to decrease after early gestation and no significant difference is found between mid- and late-gestation. In GDM, significantly increased RBP4 levels are shown by some authors, whereas other investigators do not find any difference or even lower concentrations of the adipokine as compared to healthy pregnant controls (Table 1). As a positive association exists between RBP4 concentrations on one hand and BMI, as well as insulin resistance, on the other hand in nonpregnant subjects, studies not adequately controlling for insulin resistance and/or not matching for BMI might be biased. Reports on circulating RBP4 in PE have also yielded conflicting results (Table 1). Whereas some studies suggest that maternal circulating RBP4 concentrations are higher in patients with PE as compared to normal pregnant subjects, others have been unable to show a significant difference in RBP4 levels between patients with PE and normal controls. Interestingly, RBP4 concentrations are significantly higher in the subgroup of overweight patients with late-onset PE as compared to overweight pregnant controls. In contrast to the above-summarized reports, one study suggests that both maternal and umbilical cord RBP4 levels are significantly lower in 16 patients with PE as compared to 16 normal pregnant women in the third trimester of pregnancy.

Vaspin. Visceral adipose tissue-derived serpin A12 (vaspin) is a member of the serine protease family, which is expressed in visceral adipose tissue. Vaspin has insulin-sensitizing properties, and expression of the adipokine decreases with worsening diabetes in rats. In humans, serum vaspin concentrations positively correlate with age, BMI and insulin resistance; however, these associations are abrogated in patients with type 2 diabetes. Vaspin is expressed in rat and human placenta. In first trimester human placentas, vaspin immunostaining is found in cytotrophoblasts and syncytiotrophoblasts, whereas in third trimester, only syncytiotrophoblasts express the adipokine. Vaspin expression is low in early pregnancy, rises with advancing gestational age and shows highest expression at the end of pregnancy. In first trimester human placentas, vaspin immunostaining is found in cytotrophoblasts and syncytiotrophoblasts, whereas in third trimester, only syncytiotrophoblasts express the adipokine. Vaspin expression is low in early pregnancy, rises with advancing gestational age and shows highest expression at the end of pregnancy. To the best of our knowledge, no study to date has investigated vaspin serum concentrations during the complete course of pregnancy. Data on regulation of circulating vaspin in pregnancy complications are scarce. We have recently shown that vaspin serum levels are not significantly altered in patients with GDM and PE. Furthermore, vaspin serum levels are not associated with markers of insulin resistance in pregnant patients.
Summary and conclusions

Adipokines are involved in many physiological processes and might contribute to pregnancy complications. In the past few years, the role of leptin and adiponectin in gestational diabetes mellitus and pre-eclampsia has been elucidated in more detail. Thus, abnormally high leptin levels are found in most patients with gestational diabetes mellitus and pre-eclampsia. Increased leptin levels in gestational diabetes mellitus might amplify the inflammatory process, whereas elevated leptin concentrations in pre-eclampsia are suggested to be a compensatory response to increase nutrient delivery to the underperfused placenta. For adiponectin, decreased concentrations are found in gestational diabetes mellitus, whereas circulating levels of the adipokine are increased in pre-eclampsia. In gestational diabetes mellitus, the decrease in adiponectin might further exacerbate insulin resistance seen in this condition. Increased adiponectin concentrations in pre-eclampsia have been hypothesized to be part of a physiological feedback mechanism to attenuate the excessive inflammatory response and improve vascular function in pre-eclampsia. Furthermore, regulation of novel adipokines including resistin, visfatin, retinol-binding protein 4 and vaspin in gestational diabetes mellitus and pre-eclampsia has been studied in more detail recently. However, the physiological significance of these adipokines in these pregnancy complications remains far from clear. Future studies need to assess in more detail whether or not dysregulation of adipokines directly contributes to the pathophysiology of gestational diabetes mellitus and pre-eclampsia and/or might be a useful marker for these pregnancy complications. Here, prospective long-term studies of sufficient size in patients with gestational diabetes mellitus and pre-eclampsia and their children, as well as animal studies, need to be performed to address these important questions.

Acknowledgements

This study was supported by grants to M.F. from the Deutsche Forschungsgemeinschaft (DFG, KFO 152 ‘Atherobesity’, FA476/4-1), the Federal Ministry of Education and Research (BMBF), Germany, FKZ: 01EO1001 (IFB AdiposityDiseases, project K7-9) and the Deutsche Hochdruckliga e.V.

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Leptin, adiponectin and other adipokines in GDM and PE


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