Adipocytokines in Particular Pregnancy Disorders

**Canverenler Emre[1],
Buke Baris[2],
Akkaya Hatice[2],
Akarsu Suleyman[3] and
Isık Ahmet Zeki[3]**

1 Department of Obstetrics and Gynecology, Sinop Ataturk State Hospital, Sinop, Turkey
2 Department of Obstetrics and Gynecology, Kayseri Education and Research Hospital, Kayseri, Turkey
3 Department of Obstetrics and Gynecology, İzmir University, İzmir, Turkey

Corresponding author: Canverenler Emre

✉ canverenleremre@gmail.com

Department of Normal Anatomy, Wrocław Medical University, Poland

Tel: 905555643212

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Abstract

Human pregnancy is affected by placental hormones which cause insulin resistance. In normal pregnancy, insulin resistance may lead to some problems associated with disturbed placental function, such as gestational diabetes mellitus, preeclampsia, and intrauterine growth restriction. These pregnancy conditions may result in the future development of metabolic syndrome. The pathogenetic mechanisms underlying the association between abnormal placental development, insulin resistanc and maternal metabolic syndrome are not fully understood. Adipose tissue may have an important role in the regulation of insulin resistance in both nonpregnant and pregnant participants. In this respect, adipocytokines, which are adipocyte derived hormones, have been implicated in the regulation of maternal metabolism and gestational insulin resistance. Adipocytokines, including leptin, adiponectin, tumor necrosis factor a, interleukin 6, as well as the recently ascertained resistin, visfatin, and apelin, are also known to be produced within the intrauterine environment. Release of adipocytokines in normal and abnormal pregnancy is still not clear and partially conflicting. This review aims to summarize reported findings concerning the role of adipocytokines (leptin, adiponectin, ghrelin, tumor necrosis factor [TNF], interleukin-6 [IL-6], visfatin, resistin, apelin). In early life, while attempting to speculate mechanisms through which differential regulation of adipocytokines in pregnancy complications may influence the risk for development of chronic diseases in later life.

Keywords: Adipocytokines, Preeclampsia, Gestational diabetes mellitus, İntrauterine growth restriction, Metabolic syndrome

Pregnancy is a condition that can affect fetus via insulin resistance. A progressive decrease in insulin sensitivity facilitates the diversion of glucose to the fetus [1]. İnsulin resistance can lead in some pregnancy complications in pregnancy, such as gestational diabetes mellitus (GDM) [2], preeclampsia (PE) [3], and intrauterine growth restriction (IUGR) [4]. These pregnancy disorders thought to be associated with future maternal metabolic syndrome.

Gestational diabetes is like a marker for the future development of type 2 diabetes. Similarly, preeclampsia is a marker for future heart disease. Especially in the early onset and recurrent form preeclampsia constitutes a rise in IUGR [5]. Despite reduced placental perfusion, one third of fetuses of preeclamptic women are growth restricted [6].

Many problems occur because of pregnancy related placental hormones and increased maternal adiposity [7]. So new studies have focused on a group of hormone so called ''adipocytokines'' secreted by adipose tissue [8,9]. During pregnancy, adipocytokines, including leptin, adiponectin, tumor necrosis factor a (TNF-a), interleukin 6 (IL-6), and the newly discovered resistin, visfatin,

and apelin, are also secreted by the placenta [10,11]. İn addition to regulate the mother's metabolism, adipocytokines have been implicated in pregnancy complications, including GDM, PE, and IUGR [12,13].

This review aims to summarize the reported findings concerning the role of adipocytokines in pregnancy complications, while attempting to identify mechanisms through which these factors may influence the risk of developing pregnancy complications.

Leptin

Leptin, the protein product of the ob gene [14], is mainly synthesized in white adipose tissue. It can also be produced in other sites, including the placenta [15]. Leptin is a hormone of 16 kDa comprising 167 amino acids [16]. It is an important metabolic hormone, influencing insulin secretion, glucose utilization, glycogen synthesis and fatty acid metabolism [14]. Stimulates a negative energy balance by increasing energy expenditure and reducing food intake [17]. Rodents and humans lacking leptin or functional leptin receptors develop severe obesity and hyperphagia [18]. Furthermore, leptin plays a key role in the immune response and T-cell activation [19].

Role of Leptin in Normal Pregnancy

Leptin seems to be a critical factor for overall fetal development [20,21]. The hormone is produced in both maternal and fetal adipose tissues and the placenta [22], Fetal adipose tissue is an important source of leptin and fetal leptin levels are strongly related to birth weight and fetal adiposity [23].

Maternal levels of leptin increase during the third trimester of pregnancy [23-26]. There is evidence to suggest that the placenta makes a substantial contribution to maternal leptin levels. The increase in leptin levels precedes the physiologic increase in maternal body mass index (BMI). and maternal leptin levels rapidly decline after delivery [24,26]. The human placenta expresses high amounts of leptin messenger RNA (mRNA). and its receptors are abundant in the uterine endometrium, trophoblast and the fetus [25,27]. Placental leptin mRNA production is upregulated by TNF-a and IL-6 [26,28]. İn addition, leptin regulates placental growth, nutrient transfer, angiogenesis, and trophoblast invasion [27-30].

Furthermore, a strong association between neonatal leptin levels, bone mineral content and estimated bone density has been confirmed, supporting a role for leptin in the process of fetal bone remodeling [31].

Role of Leptin in Pathologic Pregnancies

Leptin may play a significant role in many different pregnancy complications via regulating mother's metabolism.

Leptin in GDM

GDM is associated with a considerable increase in placental leptin expression [32]. Blood leptin levels of gestational diabetic women vary in studies, this discrepancy could be a result of the differences in the time of maternal blood sampling [ie, gestational age]. İncreased leptin synthesis is associated with a higher production of inflammatory cytokines (IL-6, TNF-a) [20]. Thus, this increased placental leptin expression in GDM may represent a protective response to counterbalance the effects of inflammatory cytokines, which characterizes GDM [21].

Leptin in PE

There is no consensus about preeclampsia leptin levels in pregnant women. Some investigators argue that pregnancies complicated with PE are associated with increased placental leptin synthesis [33,34]. and increased maternal leptin levels [23,35], correlating with the severity of the disease, even before its clinical onset [36,37]. Other investigators have concluded that either maternal leptin levels are reduced in PE [38,39]. or similar in both ways [40].

According to the researchers argue that leptin is increased in preeclampsia, as an induced compensatory response, and aiming to increase nutrient delivery to an underperfused placenta [41].

Furthermore, leptin may play a role in the development of thrombosis in endothelial damage with platelet leptin receptor [38].

Alternatively, leptin may have a local immunomodulatory effect or stimulate placental angiogenesis [42]. It is interesting to note that inflammatory cytokines, such as TNF-a and IL-6, are significantly correlated with leptin in both normal and preeclamptic pregnant women suggesting a relationship between inflammatory and metabolic events involved in the pathogenesis of PE [43].

Measurements of maternal plasma leptin can be used as a marker in the development PE and leptin has been suggested to play a role in the pathogenesis of the disease [35]. There is a need for more comprehensive studies on this topic.

Leptin in IUGR pregnancy

There are different opinions in leptin levels in IUGR pregnancy. For some of the researchers lower circulating leptin levels were observed in normotensive women with IUGR offspring. possibly due to lower placental response to reduced placental perfusion. Fetal leptin may be involved in an adaptive response. In accordance, Laivuori et al and Lepercq et all demonstrated higher placental leptin expression and maternal plasma levels in PE. But all the authors concluded that leptin levels in PE may be associated with inflammatory stimuli [44-49].

There are various animal studies on this topic. Altered hypothalamic leptin receptor distribution very recently has been shown in IUGR piglets, while leptin supplementation partially reversed the IUGR phenotype, by correcting growth rate and body composition in the offspring [50]. Furthermore, in the sheep fetus, moderate maternal undernutrition does not seem to influence fetal plasma leptin levels, while severe maternal undernutrition leads to suppression of fetal leptin synthesis, secondary to profound fetal hypoglycemia or hypoinsulinemia [51].

A possible explanation for these contradictory results may rely on the fact that studies have not consistently characterized IUGR and have not consistently considered maternal BMI and other confounding factors.

Adiponectin

Adiponectin is one of the most abundant adipose tissue-specific proteins and is predominantly expressed and secreted from adipose tissue [52]. and has antiinflammatory, antiatherogenic, and insulin sensitizing properties. Adiponectin is postulated to play a role in the modulation of glucose and lipid metabolism in insulin sensitive tissues [53]. Circulating adiponectin levels decrease in insulin resistant states, including type 2 diabetes, obesity, and coronary vascular disease [54]. Adiponectin levels are inversely correlated with BMI [55].

Adiponectin in Pregnancy

Recent study indicates that, maternal adiponectin levels negatively correlated with maternal BMI, however others failed to verify such a correlation [56-59]. The high fetal adiponectin levels may be attributed to the lack of negative feedback on adiponectin production, resulting from the lack of adipocyte hypertrophy or a different distribution of neonatal fat depots [60]. On the contrary, other investigators failed to demonstrate a relationship between fetal adiponectin and birth weight [61].

Adiponectin in Pregnancy Complications

Highman et all indicates, no significant difference in the release of adiponectin among diabetic and non-pregnant women [24]. By contrast, in another study, lower adiponectin gene expression has been noted in placentas of diabetic pregnant women [16]. Tsai et al demonstrated that decrease in maternal adiponectin levels may increase the risk of fetal overgrowth in GDM [62].

In fact, lower adiponectin levels in GDM have been associated with subclinical inflammation [63]. In this respect, Ategbo et al. [64]. speculated a physiological importance of concomitant high maternal TNF-a/IL-6 and low adiponectin levels in GDM [12].

In a interesting study, maternal adiponectin levels in early pregnancy predicts GDM, months before the clinical diagnosis of the disease, independently of maternal BMI [65]. Therefore, because GDM is a prediabetic state, hypoadiponectinemia may explain the high rate of progression to type 2 DM.

Given the significance of glucose and insulin in fetal growth and the fundamental role of adiponectin in insulin metabolism, it is reasonable to assume that adiponectin may play a role in IUGR. A number of studies [66-68]. demonstrated lack of significant differences in fetal adiponectin levels between IUGR cases and AGA controls. However, SGA fetuses have been recently reported to shift their adiponectin pattern toward the high-molecular-weight isoform [which specifically correlates with insulin sensitivity]., thus sensitizing their body to insulin and preparing for neonatal catch-up growth. By contrast, in the recent new studies , low adiponectin levels may be a marker for future development of metabolic syndrome [69,70]. Interestingly, in support of this view, adiponectin levels in IUGR children were particularly low in those who showed postnatal catch-up growth, compared with IUGR children who remained small during childhood [71,72]. This may indicate that the low adiponectin levels in IUGR infants may predict the insulin resistance. On the other hand, normal or higher adiponectin concentrations in IUGR

insulin-resistant children have also been recently reported [73]. A possible explanation for these conflicting results may rely on the fact that all the above studies have not consistently characterized IUGR or by differences in specific methodological ways.

Taken together, lack of adiponectin in IUGR children and adults may be a reasonable explanation for metabolic disorders. The relationship between IUGR and postnatal circulating adiponectin is not stationary, indicating that the modifying effects of early and late postnatal growth characteristics may not completely explain the changeability in adiponectin levels [74].

TNF-a and IL-6 in Pregnancy

A chronic in adipose tissue may lead to pregnancy induced insulin resistance such as TNF-a and IL-6. In this respect, a rise in TNF-a and IL-6 during pregnancy, mainly due to placental production [75] has been related to pregnancy associated insulin resistance [76].

TNF-a and IL-6 in Pregnancy Complications

Recent data have shown that maternal plasma levels of TNF-a and IL-6 are increased in GDM [76]. In this respect, TNF-a has been thought to make an inhibitory effect on insulin secretion and insülin regulated glucose uptake in GDM [45].

TNF-a and IL-6 are also produced by the placenta during pregnancy [77], but very few and conflicting data exists in the literature, regarding the IUGR state. In this respect, reduced [78,79]. and also increased [80]. fetal IL-6 levels have been documented in IUGR, possibly due to impaired trophoblast function and severe placental insufficiency in the former and to hypoxia and/or nutrient deficiency in the latter, supporting the hypothesis that IL-6 may be related to fetal growth in the fetomaternal interface. According to other opinions, normal [81]. and also decreased. fetal TNF levels have been demonstrated, proposing a role for TNF in the pathogenesis of IUGR. Casano-Sancho et al. reported that SGA children show increased frequency of the TNF-308G allele, which is associated with prenatal growth and postnatal insulin resistance. On the other hand, upregulation of TNF-a has been thought to be a survival mechanism in the IUGR fetus, by inducing muscle insulin resistance. This may lead glucose to enter brain sparing pathway [82,83].

It would be plausible to suggest that perinatal stressors could lead to the reprogramming of TNF-a regulation with overproduction that persists in postnatal life and causes insulin resistance. The authors speculate that downregulation of TNF-a may be one of the mechanisms leading to insulin resistance in these subjects.

Nevertheless, IUGR is a heterogeneous state, including cases of fetal malformations, infections, or placental insufficiency due to preeclampsia [84]. This fact, as well as differences in disease severity, might explain the contradictory results of the above studies. Pregnancies [85].

Resistin

Specifically, resistin, a newly discovered hormone secreted by human adipocytes and mononuclear cells [86]. Resistin is thought to impair glucose tolerance [87]. Several human and animal

studies showed that circulating resistin levels are proportional to the degree of adiposity. Furthermore, resistin is expressed in the human placenta and has been postulated to play a role in regulating energy metabolism in pregnancy [88,89]. Recent reports [90], have also demonstrated markedly high levels of resistin in umbilical plasma samples, affecting adipose tissue in utero. Nevertheless, most studies failed to show a correlation between plasma resistin levels and insulin sensitivity in humans [91].

Resistin in Pregnancy

Resistin is expressed in the human placenta, upregulated in the third trimester, and has been postulated to play a role in the regulation of maternal energy metabolism [17]. In addition, placental resistin gene expression is more significant as pregnancy advances, while the release of resistin from human placenta has been shown to be stimulated by insulin [24]. Such changes may contribute to the decreased insulin sensitivity in pregnant women in the second half of pregnancy, which may relate to the development of postprandial hyperglycemia and be beneficial for rapid fetal growth [92]. Though, maternal BMI do not seem to correlate with plasma resistin levels during pregnancy [92].

Resistin in Pregnancy Complications

There are conflicting studies on resistin levels in pregnancy. In this respect, lack of maternal resistin changes in GDM has been reported in humans and in animals [93], challenging the role of resistin in reducing insulin sensitivity during pregnancy. Megia et al reported lower resistin levels in GDM. Other investigators have documented elevated maternal resistin levels in GDM, supporting the status of insulin resistance [94,95].

On the other hand, in vitro studies in human placentas have showed a biphasic effect of insulin in the release of resistin. At low concentrations, insulin significantly increases the release of resistin, whereas it returns to basal levels when the placenta is exposed to higher insulin concentrations, suggesting a downregulation of resistin expression in a high insulin medium [24]. This biphasic action of insulin may lead to low resistin levels shown in GDM [95].

Conclusively, it could be speculated that resistin may mediate the state of insulin resistance present during pregnancy, whereas the role of the adipocytokine in pregnancy complications, associated with insulin resistance, remains controversial, in accordance with reports from other fields, challenging the role of resistin in reducing insulin sensitivity in humans and animals.

Higher maternal resistin levels have been demonstrated in PE, although placental gene expression of resistin was found to be unchanged [94]. Recent evidence suggests that circulating resistin levels increases with the progressive decline of renal function and depends on glomerular filtration rates [95]. Thus, changed renal function in PE may be related to elevated resistin levels [23].

In contrast, other researchers reported that the physiological increase of maternal resistin during gestation is less evident in PE [25], possibly due to reduced placental production.

The inconsistency of the above findings is uncertain, but differences in sample size and study design, might have contributed to the conflicting findings.

Visfatin

Visfatin, a 52 kDa protein, has been recently identified as a visceral fat specific adipocytokine [96], probably linking the expansion of adipose depot to insulin resistance [97]. Visfatin was initially thought to be upregulated in obesity and in states of insulin resistance, while exerting insulin mimetic effects in tissues. However, following studies have generated different findings with regard to the role of visfatin in obesity and insulin resistance and the pathophysiological role of visfatin in humans remains controversial and largely unknown [98,99].

Visfatin is identical to pre-B-cell colony enhancing factor (PBEF), a cytokine involved in B-cell precursor maturation. The PBEF protein is immunolocalized in both normal and infected human fetal membranes and is significantly upregulated by labor [100]. Moreover, data of a recent study indicate that visfatin is present in cord blood in substantial amounts, probably due to placental production [101,102].

Visfatin in Pregnancy

The existence of visfatin has been documented in human fetal membranes and the placenta. Histological examination put forth that visfatin distribution is limited to the villous capillary of the fetal endothelium. Thus, it is appealing to speculate that given this distribution, visfatin could play a role in the transfer of glucose from the maternal to the fetal circulation. Besides, visfatin mRNA expression has been recently shown to be significantly related to TNF-a and IL-6 mRNA expression in placental tissues [103,104].

Visfatin levels have been documented to be either comparable between nonpregnant women and women in the third trimester of pregnancy, suggesting that the placenta may not contribute to maternal circulating visfatin levels [104]. A recent study demonstrated a 7-fold increase in visfatin gene expression and protein in omental fat of pregnant women, as compared to controls, but only a small increase in serum visfatin levels, suggesting that visfatin may act locally as a paracrine/ autocrine agent, not as a hormone [103]. Furthermore, visfatin mRNA in fat increases in late pregnancy in a rat model similar to that seen for leptin mRNA [105]. There is evidence to suggest that both these adipocytokines can set against insulin resistance, so it is possible that this increase is an attempt to set against insulin resistance, as the rat enters lactation [105]. Finally, serum visfatin levels in the first trimester of pregnancy positively predict insulin sensitivity in the second trimester, however, this close association disappears later, possibly due to an increase in visfatin secretion by an additional source other than adipose tissue [104].

It may be speculated that adipose tissue derived visfatin may act as an insulin mimetic agent, aiding insulin sensitivity during the second and third trimester of pregnancy.

Visfatin in Pregnancy Complications

Although some investigators have reported lower maternal visfatin levels in GDM [105,106], others indicated increased visfatin levels with a worsening degree of maternal glucose. Gestational

diabetes mellitus is a state of transient insulin resistance and elevated visfatin levels might set against high glucose and insulin levels. Thus, elevated maternal visfatin levels in GDM may reflect an impairment of visfatin function in target tissues, dysregulation of biosynthesis, or a response to hyperglycemia. Moreover, TNF-a is known to improve visfatin expression in human placental cells. Chronic inflammation, including elevated levels of TNF-a, is present in women with GDM [92]. Thus, the placenta could be a source of increased visfatin in GDM.

Maternal serum visfatin have been recently demonstrated to be elevated in PE, irrespectively of the severity of the disease [107]. In contrast, Hu et al demonstrated markedly decreased visfatin levels in PE, irrespectively of maternal BMI [108].

Higher visfatin levels were found in IUGR neonates compared with AGA counterparts, probably due to increased visceral adiposity or altered fetal development of adiposity in IUGR subjects [109,110]. In this respect, which may predispose to the later development of insulin resistance. Higher visfatin levels in IUGR could probably serve as an early marker with prognostic value for the later development of the metabolic syndrome [111]. A recent study demonstrated higher maternal visfatin levels at term in the IUGR state, suggesting that visfatin may be a novel marker upregulated in this pregnancy disorder [27], a finding further confirmed by Fasshauer et al. [8]. The physiological relevance of increased maternal visfatin levels in IUGR remains to be determined.

We may speculate that, because visfatin improves glucose tolerance through insulin mimetic effects, upregulation of maternal visfatin levels in insulin resistance associated pregnancy complications may be part of a physiological feedback mechanism.

Apelin

Apelin is a novel bioactive peptide, identified as the endogenous ligand of the orphan G protein coupled receptor, APJ [112]. It has a common pattern of expression in human tissues and it is produced in several organs. Apelin is required for normal vascular development and has properties consistent with a role in both normal and pathologic angiogenesis [113]. Additionally, numerous cardiovascular effects have been reported intravenous administration of apelin in rats was found to lower blood pressure through the release of nitric oxide [114].

Apelin has recently been identified as a novel adipocytokine, secreted in substantial amounts by adipose tissue in a regulated manner. In this respect, apelin is upregulated by obesity and hyperinsulinemia in both humans and mice [115]. Because of its angiogenic activity, apelin secreted by adipocytes is likely to stimulate blood vessel growth, leading to increase growth of adipose tissue [116]. The overproduction of apelin observed in obesity has been suggested to be an adaptive response that attempts to prevent the onset of obesity related disorders. Thus, current research focuses on the potential link of apelin with obesity associated insulin resistance [117].

Apelin in Pregnancy

Embryonic expression studies demonstrated that apelin is an angiogenic factor required for normal blood vessel growth and endothelial cell proliferation [118]. Furthermore, the presence of apelin has been documented in human placental tissue, indicating an important role of in pregnancy. A recent study indicated an increase in apelin fat mRNA expression only in early pregnancy, suggesting that apelin expression is associated with hyperinsulinemia of obesity. The reason for this increase of apelin expression in fat in early pregnancy is related to fat accumulation [119].

Apelin in Pregnancy Complications

Apelin expression strongly increases in preeclamptic placentas, probably inducing a vasoconstrictor effect, which determines the onset and/or worsening of the disease. In contrast, a recent study showed a gradual decrease of apelin expression in placentas of patients with hypertensive disorders of pregnancy compared to normal controls, and a gradual decrease in apelin expression between gestational hypertension, mild PE, and severe PE.

Eventually, a recent study indicated lack of noteworthy differences in maternal apelin levels between IUGR and normal pregnancies and lack of connection between apelin and insulin levels, suggesting that apelin may not be involved in the regulation of maternal insulin sensitivity.

Collectively, very few studies have addressed the expression and function of apelin in human pregnancy. This novel adipocytokine is highly implicated in angiogenesis and glucose homeostasis and, thus, further explanation of its role is needed in pregnancy complications [119].

Conclusions

In summary, maternal levels of leptin, resistin, TNF-a, and IL-6 [hormones that produce insulin resistance]. are elevated, while maternal levels of adiponectin and visfatin [insulin-sensitizing or insulin-mimetic hormones]. are remain unchanged or decreased during pregnancy. This pattern of changes in adipocytokines is known to increase insulin resistance and, thus, may take part in the formation of the insulin resistance in pregnancy.

Adipocytokines are unlikely regulated in pregnancy complications. The secretion patterns of adipocytokines in complicated pregnancies strongly suggest an involvement of leptin, adiponectin, TNF-a, and IL-6 in GDM, PE, and IUGR, while the role of resistin, visfatin, and apelin remains controversial. Further research is needed to explain role of adipocytokines in normal and complicated pregnancies. In addition, a deeper understanding of how prenatal and postnatal nutrition interact and influence molecular pathways involved in the development of obesity will support the development of more effective preventive strategies and therapeutic approaches to curb the worldwide epidemic of type 2 diabetes and obesity.

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