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Review

# Adipokines underlie the early origins of obesity and associated metabolic comorbidities in the offspring of women with pregestational obesity☆,☆☆

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ABSTRACT

Maternal pregestational obesity is a well-known risk factor for offspring obesity, metabolic syndrome, cardiovascular disease and type 2 diabetes. The mechanisms by which maternal obesity can induce alterations in fetal and later neonatal metabolism are not fully elucidated due to its complexity and multifactorial causes. Two adipokines, leptin and adiponectin, are involved in fetal and postnatal growth trajectories, and both are altered in women with pregestational obesity. The placenta synthesizes leptin, which goes mainly to the maternal circulation and in lesser amount to the developing fetus. Maternal pregestational obesity and hyperleptinemia are associated with placental dysfunction and changes in nutrient transporters which directly affect fetal growth and development. By the other side, the embryo can produce its own leptin from early in development, which is associated to fetal weight and adiposity. Adiponectin, an insulin-sensitizing adipokine, is downregulated in maternal obesity. High molecular weight (HMW) adiponectin is the most abundant form and with most biological actions. In maternal obesity lower total and HMW adiponectin levels have been described in the mother, paralleled with high levels in the umbilical cord. Several studies have found that cord blood adiponectin levels are related with postnatal growth trajectories, and it has been suggested that low adiponectin levels in women with pregestational obesity enhance placental insulin sensitivity and activation of placental amino acid transport systems, supporting fetal overgrowth. The possible mechanisms by which maternal pregestational obesity, focusing in the actions of leptin and adiponectin, affects the fetal development and postnatal growth trajectories in their offspring are discussed.

## 1. Introduction

During pregnancy, a significant amount of complex interactions between the mother and the fetus are established to promote fetal growth and development. After implantation, during the embryonic development (first 8 weeks after conception), organogenesis, maturation and integration of the most relevant systems occurs to ensure the forthcoming extrauterine life. This stage of development is characterized by a high rate of cell proliferation and it is a critical period of vulnerability. Therefore, adverse factors during this decisive period of embryonic and fetal (from 8 weeks post-conception until delivery) development can alter the programming of physiological processes, leading to permanent metabolic or structural changes [1,2]. For example, key factors such as a deficit in the supply of nutrients from the mother to the fetus, or an excess of maternal glucose, fatty acids, or inflammatory markers, leads to 1) alterations in placental formation, structure and function, 2) alterations in secretion of inflammatory mediators by the trophoblast and 3) important changes in nutrient transport towards the fetal circulation. The latter leads to a metabolic, hormonal and immunological reprogramming, resulting in altered growth trajectories, contributing to fetal programming during intrauterine life.

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The prevalence of obesity, defined by a body mass index (BMI) equal or higher than 30 kg/m$^2$, has increased worldwide and is currently considered a public health problem, particularly in women in reproductive age [3,4]. In addition to this prevalence, there are comorbidities associated with obesity, such as insulin resistance, type 2 diabetes and cardiovascular diseases [5–7]. Although the development of obesity is mostly due to modifiable causes, the mechanisms by which obesity in women in reproductive age affects fetal development are not well established. Systematic reviews and meta-analysis have linked higher maternal BMI with a higher risk of associated comorbidities in their offspring [8,9]. Pregestational obesity as well as high gestational weight gain [10,11], are important health issues for the mother [12] and a known handicap for offspring's health.

Pregestational obesity has been associated with different complications for the mother, as spontaneous abortion, gestational diabetes, pre-eclampsia and pregnancy-induced hypertension. By the other hand, the offspring have a higher risk of congenital malformations, preterm birth, neonatal complications and admission to a neonatal intensive care unit [13,14], lower neurocognitive development [15–18] and higher prevalence of neurological, metabolic, allergic and cardiovascular diseases in infancy and adulthood [19–21]. The offspring of women with pregestational obesity have higher birthweight [12,22–24], higher risk of being Large for Gestational Age (LGA, > percentile 90 for gestational age) and being macrosomic (> 4 kg) at birth, as well as being overweight or obese during infancy, childhood and adulthood [25–27]. Maternal pregestational obesity has a programming effect in the offspring, which confers them a higher risk of developing metabolic diseases later in life, such as obesity, metabolic syndrome, cardiovascular disease and type 2 diabetes, but the mechanisms by which these changes occur are still controversial. It has been proposed that several cytokines modulate placental growth and function, and therefore the fetus development.

Leptin and adiponectin are adipokines predominantly produced by the adipose tissue. Leptin is also produced by the placenta and is released mainly to the maternal and in a lower quantity to the fetal circulation [28]. The expression and synthesis of adiponectin in the placenta is at present controversial [29–32]. These two hormones, leptin and adiponectin, have high relevance in fetal growth and adiposity and several studies relate their cord blood levels to childhood and infant growth trajectories [33,34], and therefore could contribute to confer a higher susceptibility in the offspring, of mothers with pregestational obesity, to develop metabolic conditions later in life. The role of other cytokines, such as tumor necrosis factor alpha (TNF-α) and interleukin 6 (IL-6) have been recently reviewed [35]. In this review, the question of how leptin and adiponectin are affected by maternal obesity, and the possible mechanisms by which they modify fetal growth and adiposity in the offspring of mothers with pregestational obesity is addressed.

## 2. Leptin and leptin receptors in pregnancy

Leptin is a 16-kDa peptide which acts as a regulator of satiety and energy expenditure in the central nervous system (Table 1). Six leptin receptor (LepR) isoforms are generated by alternative splicing of the LEPR gene located in chromosome 7. LepR-a, -b, -c, -d and -f are membrane-bound receptors but only LepR-b is full length with an intracellular signaling domain. It is the most important receptor in the hypothalamus and responsible for the control of energy intake and expenditure. LepR-e is a soluble receptor which binds circulating leptin [36,37] (Table 2).

During pregnancy, leptin plasma levels increase in the first and second trimester, having a peak at around week 28 of gestation [38–40]. During the first trimester, circulatory leptin levels are correlated with maternal BMI and the amount of maternal visceral fat [41], but the increment in leptin levels during pregnancy can not only be explained by the increase in the volume of adipose tissue, but also by the production of leptin by the placenta [42,43]. Estradiol positively correlates with leptin levels in pregnant women [38] and directly upregulates leptin gene expression in placental cells through genomic and non-genomic pathways [44]. Likewise, human chorionic gonadotropin (hCG), synthesized by the trophoblast during pregnancy, induces the leptin mRNA expression in human placenta explants [45,46]. These data suggest that pregnancy hormones are, at least in part, responsible for the placental production of leptin and for the raise in leptin levels along gestation. Likewise, the high secretion of leptin during pregnancy is maintained by the raise in the circulatory levels of the soluble leptin receptor (LepR-e) [47], which increases leptin clearance making it less available to membrane-bound receptors, concordant with the well-known leptin resistance state in pregnancy [48]. After birth, a drastic decrease of maternal leptin levels occurs and 6 weeks after delivery circulating leptin concentration returns to pre-pregnancy values [47], which supports a role of placental leptin secretion into the maternal circulation.

The leptin mRNA and protein are expressed and synthesized in the placenta, specifically by the syncytiotrophoblast (facing maternal circulation) and villous vascular endothelial cells (facing fetal circulation), while the membrane-bound isoforms of LepR have been localized in the syncytiotrophoblast [49–51] and in villous stroma [51] of early (7–14 weeks) and late (third semester) placenta [50]. The short form of the receptor is localized in both the microvillous and basal membrane [52,53], as well as in the apical membrane of the syncytiotrophoblast [49,54–56]. The mRNA expression of leptin, its receptors and their proteins in term pregnancy umbilical cord and fetal membranes, support the hypothesis that leptin acts as an autocrine and paracrine regulator in these tissues. These are also expressed in the distal extravillous cytotrophoblast cells of cell columns invading the basal plate, which suggest that leptin and its receptors could have a role in the invasive processes of these cells by modulating the expression of matrix metalloproteinases [57].

A role as a leptin transporter to fetal tissues has been suggested for LepR-e, the soluble leptin receptor, which has been found in both umbilical and maternal blood [58]. This isoform is increased in placentas of pre-eclamptic and diabetic women which synthesize more leptin compared to uncomplicated pregnancies [50].

The induction of leptin gene expression involves the cyclic AMP/Protein kinase A (cAMP/PKA) or cAMP/exchange protein directly activated by cAMP (cAMP/Epac) pathways which have important functions in human trophoblast [59]. The activation of the phosphoinositide 3-kinase (PI3K) and the mitogen-activated protein kinase (MAPK) pathways also participate in leptin gene expression [60] in the placenta. Various regulatory elements have been identified within the leptin promoter such as a response elements to cAMP, glucocorticoid, CCAAT/enhancer-binding proteins (C/EBPs) and specificity protein 1 (Sp1) binding sites, suggesting a direct regulation of leptin expression through different transcriptional pathways [61]. A placental-specific enhancer located 1,9 kb upstream of the human leptin gene has been described in choriocarcinoma cell lines but not in adipose cells [62]. The leptin promoter has active elements in placental cells: the transcription factors cAMP response element-binding protein (CREB), Activator protein 1 (AP1), Sp1, nuclear factor kappa B (NF-κB) and the coactivator CREB binding protein (CBP), are involved in placental leptin expression [63].

By the other hand, the major signaling pathways known to be triggered by the activation of leptin receptors are Janus kinase2/signal transduction and activator of transcription 3 (JAK2/STAT-3), MAPK and PI3K pathways in placental cells [60]. The RNA-binding protein Sam68, a member of the signal transduction and activation of RNA metabolism (STAR), is involved in leptin receptor signaling in the human trophoblastic cell line JEG-3 and Sam68 tyrosine phosphorylation-dependent on JAK-2 activity, mediates the proliferative and trophic effects of leptin in the placenta [64].

Once bound to placental receptors, leptin triggers local and peripheral effects. Placental leptin induces hCG production in trophoblast

**Table 1**
Leptin and adiponectin characteristics.

| Gene | Gene location | Protein | Synthesis | Function |
|---|---|---|---|---|
| LEP | 7q32.1. | 167 amino acids, 16 kDa | Adipose tissue placenta (syncytiotrophoblast) | Hormone<br>Regulator of satiety and energy expenditure in the central nervous system |
| ADIPOQ | 3q27.3. | 244 amino acids. 27 kDa<br>Full-length adiponectin (fADN)<br>Globular adiponectin (gADN)<br>Three types of complex:<br>· Low molecular weight (LMW, 67 kDa)<br>· Middle molecular weight (MMW, 136 kDa)<br>· High molecular weight (HMW, > 300 kDa). | Adipocytes<br>Lower amounts are produced in maternal white blood cells | Hormone<br>Insulin-sensitizing, anti-inflammatory, antiatherogenic, and anti-proliferative.<br>Glucose uptake in skeletal muscle. |

cells [65], enhances mitogenesis, stimulates amino acid uptake, and increases the synthesis of extracellular matrix proteins and metalloproteinases. Leptin may also have a local autocrine immunomodulatory or anti-inflammatory role [66]. The endocrine effects of leptin in human placenta involve proliferation and survival of trophoblast cells, protein synthesis [67] and anti-apoptotic action in placenta controlling the expression of p53 master cell cycle regulator under different stress conditions [68]. Placental leptin is also a target of different placental regulatory molecules like hCG [46], insulin [69], steroids [44] and hypoxia [70]. These studies suggest an important role of leptin and its receptor in implantation and maintenance of pregnancy and a relevant function in placental health.

Placental leptin is secreted into the fetal circulation in minimum amounts (around 5%) and most is secreted into the maternal circulation [42,43,71]. It has been reported that human embryos (6 to 10 weeks) express leptin mRNA in preadipocytes, which suggests that fetal adipose tissue could produce leptin when preadipocytes differentiate and begin to accumulate fat [72]. In the same direction, it has been reported that fetal white adipose tissue (20 to 38 weeks of gestation) expresses and secretes leptin [42]. To date it is recognized that fetal leptin levels are independent of maternal or placental secretion and are more correlated with birth weight and fetal fat mass [40,42,73–76], than with maternal leptin concentration. Cord blood leptin levels are correlated with higher birthweight and also correlates with maternal pre-pregnancy BMI and gestational weight gain [77].

Since umbilical cord blood leptin concentration is correlated with some indicators of fetal growth such as birth weight and length, head circumference, ponderal index and adiposity [76–79], it has been proposed that placental leptin has an indirect influence on fetal growth, since its role in the control of placental growth and function.

In JEG-3 and BeWo cell lines, endogenous leptin, stimulates their proliferation through the progression of the cell cycle by the increase of Cyclin D1 expression. Also, leptin increases cell survival by an anti-apoptotic mechanism involving the inhibition of caspase 3 [80] and, increase protein translation in human trophoblastic cells by activation of translational machinery [81]. In placental explants, leptin increases the production of the vasodilator agent nitric oxide and increment placental lipid catabolism. Both mechanisms could increase nutrient availability and transport to the fetus, consequently, modulating fetal growth [82]. Finally, it has been reported that leptin activates System A, a sodium-dependent neutral amino acid transporter in human placental villous fragments at term, but not in placentas obtained during the first trimester, increasing, therefore, amino acid transport to the fetus in the second half of pregnancy [83,84]. It seems that leptin increases System A activity by stimulating JAK-STAT3 signaling pathways in an autocrine/paracrine manner [85]. These studies suggest that leptin influences placental nutrient transport supporting the hypothesis for its role as a regulator of fetal growth.

## 3. Leptin and leptin receptors in pregestational obesity

It has been extensively reported that women with pregestational obesity have higher leptin levels throughout gestation compared to normal weight women [86–89], although the mechanisms for this have not been fully elucidated. One of the reasons for this could be the higher adipose tissue mass in obese women, since some reports showed no increase in leptin placental production or gene expression between normal weight and obese pregnant women [51,90,91]. However, it seems that women with pregestational obesity produce lower amounts of leptin per unit of body mass or placental tissue than normal-weight pregnant women during the course of gestation [87,88].

Beside the increase in circulatory levels of leptin, a state of leptin resistance in the placenta has been proposed in pregnancies affected by obesity. Although it is still debated, some have shown that the long form of the leptin receptor is less expressed in placentas from women with pregestational obesity [51,89,91].

Some studies have proposed that maternal obesity and hyperleptinemia are associated with placental dysfunction [92] and changes in nutrient transporters in the placenta. The activity of placental transporter of taurine is decreased in placentas from obese mothers, which has a negative relationship with maternal BMI. This could be probably related to alterations in fetal development since taurine is relevant in organogenesis, fetal growth and placental function due to its role in facilitating cell renovation and survival [93].

Contrary to what has been reported in placentas from normal weight women [83–85], in placentas from women with obesity a decrease [51] or no change [94,95] in System A activity and therefore in the placental transport of amino acids to the developing fetus has been described. It has been stated is that this transporter's activity correlates with fetal birth weight [94].

Regarding glucose transport across the placenta, glucose transporter 1 (GLUT1) is the most relevant transporter expressed both in the basal and apical trophoblast membrane. In obese mothers without gestational diabetes, no association has been found between GLUT1 expression and maternal BMI, although there is a positive correlation between the basal membrane expression of this glucose transporter and fetal birth weight. No change in the activity of GLUT1 in placentas from obese compared to normal weight women has been evidenced [96]. Additional studies, with a higher number of subjects, are needed to clarify the effect of maternal obesity on placental glucose transport.

Some studies suggest that maternal obesity alters placental lipid transport and metabolism, producing changes in the lipid profile of newborns from obese mothers. Dube et al. [97] found changes in the expression of important lipid metabolism proteins such as lipoprotein lipase, lipid binding protein 1 and 3, and the lipid transporter FATP4 (fatty acid transport protein 4 or SLC27A4), which affects placental uptake of fatty acids without altering fetal growth. Others have not

**Table 2**
Leptin and adiponectin receptors characteristics.

| Gene | Gen location | Protein | Tissue localization and synthesis | Receptor affinity | Function |
|---|---|---|---|---|---|
| LEPR | 1p31.3. | Leptin receptor (LepR). 1.165 amino acids, 132.494 Da.<br>Six isoforms (a–f).<br>Cell membrane bound receptor, extracellular, with trans-membrane, and intracellular sections.<br>LepR-b has intracellular signaling.<br>LepR-e is a soluble receptor and binds circulatory leptin. | Isoform a: expressed in fetal liver and in hematopoietic tissues and choroid plexus.<br>In adult highest expression in heart, liver, small intestine, prostate and ovary. Low level in lung and kidney.<br>Isoform b: highly expressed in hypothalamus, but also in skeletal muscle. Detected in fundic and antral epithelial cells of the gastric mucosa. Syncytiotrophoblast | High-affinity interaction | On ligand binding, mediates leptin central and peripheral effects through the activation of different signaling pathways such as JAK2/STAT3 and MAPK cascade/FOS, through phosphorylation of Tyr986 and Tyr1141 of LepR.<br>Hypothalamus: appetite-regulating factor and an increase in energy consumption by inducing anorexinogenic factors and suppressing orexigenic neuropeptides.<br>Regulates bone mass and secretion of hypothalamo-pituitary-adrenal hormones.<br>Periphery: increases basal metabolism, influences reproductive function, regulates pancreatic beta-cell function and insulin secretion, is pro-angiogenic and affects innate and adaptive immunity.<br>Control of energy homeostasis and melanocortin production (stimulation of POMC and full repression of AgRP transcription) is mediated by STAT3 signaling, whereas distinct signals regulate NPY and the control of fertility, growth and glucose homeostasis.<br>Involved in the regulation of counter-regulatory response to hypoglycemia by inhibiting neurons of the parabrachial nucleus.<br>Specific effect on T lymphocyte responses, differentially regulating the proliferation of naive and memory T-cells.<br>Leptin increases Th1 and suppresses Th2 cytokine production. |
| ADIPOR1 | 1q32.1. | Adiponectin receptor 1 (AdipoR1). 375 amino acids. 42.616 Da.<br>Localized at cell membrane and intracellular organelles.<br>Seven transmembrane domains, cytoplasmic N-terminus and extracellular C-terminus. | Widely expressed. Highly expressed in heart and skeletal muscle.<br>Expressed at intermediate level in brain, spleen, kidney, liver, placenta, lung and peripheral blood leukocytes.<br>Weakly expressed in colon, thymus and small intestine | High affinity for globular adiponectin.<br>Low affinity for full-length adiponectin | Required for normal glucose and fat homeostasis and for maintaining a normal body weight.<br>Adiponectin binding activates a signaling cascade that leads to increased AMPK activity, and ultimately to increased fatty acid oxidation, increased glucose uptake and decreased gluconeogenesis. |
| ADIPOR2 | 12p13.33. | Adiponectin receptor 2 (AdipoR2). 386 amino acids. 43.884 Da.<br>Localized at cell membrane and intracellular organelles.<br>Seven transmembrane domains, cytoplasmic N-terminus and extracellular C-terminus. | Ubiquitous. Highly expressed in skeletal muscle, liver.<br>Expressed at intermediate level in placenta<br>Weakly expressed in brain, heart, colon, spleen, kidney, thymus, small intestine, peripheral blood leukocytes and lung. | Intermediate affinity for globular and full-length adiponectin | Required for normal body fat and glucose homeostasis.<br>Adiponectin binding activates a signaling cascade that leads to increased PPARα activity, and ultimately to increased fatty acid oxidation and glucose uptake.<br>Required for normal revascularization after chronic ischemia caused by severing of blood vessels.<br>Adiponectin through AdipoR2 activates p38 MAPK and PPARα, which inhibits IGF-1.<br>Decreases the transfer of glucose through the placenta to the fetus, regulating birth weight |

found differences in the expression of fatty acid transporters in placentas affected by maternal obesity [95].

Tsai et al. [89] found a linear increase in the leptin levels in the placental villous vascular endothelial cells (fetal side of the placenta), but not in syncytiotrophoblast cells (facing maternal side of the placenta) with pre-pregnancy BMI. This could indicate that more placental leptin is reaching the developing fetus, which is consistent with the finding of higher levels of cord blood leptin in children born from obese mothers [77,89,98–101].

Recently Nogues et al. [102] studied the expression of the leptin pathway in the placenta, determining a much higher expression of the leptin gene (*LEP*) in the fetal compared to the maternal side of the human placenta of both normal weight women and those with obesity with a lower expression or *LEP* on the placenta of the later. Conversely the placental leptin receptor (*LEPR*) protein levels from women with pregestational obesity where significantly lower than control. This finding was associated with higher methylation of the *LEP* gene, with no changes in the methylation status at the *LEPR* gene promoter in the placenta of women with obesity. This lower expression of the leptin receptor could be central in the proposed leptin resistance largely suggested in the offspring of women with pregestational obesity.

## 4. Leptin at birth and in early postnatal life

The concentration of leptin is higher in LGA and lower in Small for Gestational Age (SGA) newborn, whereas placental leptin is higher in SGA infants and inversely correlated with placental weight, independent of maternal weight and gestational age. Both the short and long LepR isoforms expression are lower in SGA infants, while the short isoform is positively correlated with the neonate's birth weight and placental weight. These results suggest that placental leptin and LepR protein expression may influence placental growth and therefore birth weight [103].

As previously mentioned, cord blood leptin significantly correlates with indicators of fetal growth and fat mass [76–79,104]. It has been proposed that leptin at birth influences growth trajectories during infancy. Low cord blood leptin levels are associated with higher rates of weight gain in infancy, and higher cord blood levels are associated with a slower weight gain between birth and at 2 years of age, independent of birth weight [79,105,106]. These studies suggest that newborn and infants are sensitive to leptin actions even if their plasma levels are higher, which could be an adaptation or a response to intrauterine adverse conditions.

Further investigations are required to clarify how maternal leptin levels and obesity affects intrauterine fetal growth, since its role in modifying placental nutrient transport is still under debate, since several reports indicate changes in transporters of fatty acids and amino acids, while others have not been able to see these differences. Maternal obesity, and cord blood hyperleptinemia affects infant and child growth trajectories and could represent a link between maternal obesity and propagation of obesity and metabolic risk in the next generation (Fig. 1).

## 5. Leptin in pregnancies affected by other perinatal complications associated with pregestational obesity

### 5.1. Gestational diabetes mellitus (GDM)

Leptin and its receptors show a higher expression in placentas from women with GDM compared to controls [67,107], where it activates protein synthesis mediated by signaling molecules such as the Mammalian target of rapamycin (mTOR), Ribosomal protein S6K (S6 kinase), Eukaryotic translation initiation factor 4E-binding protein 1 (EIF4E-BP1), and Eukaryotic elongation factor 2 (eEF2). The higher placental protein synthesis in part explains the increase in placental and fetal growth in GDM [67].

### 5.2. Fetal growth restriction and oxygen deprivation

Fetal growth restriction during pregnancy is characterized by low concentrations of placental and cord blood leptin compared to normal placentas, without changes in the leptin receptor expression [49]. The transmembrane leptin receptor expression is induced in a time-dependent manner under hypoxic conditions, but its signal transduction remains unaffected in choriocarcinoma cell lines. The soluble receptor expression does not change under oxygen deprivation, perhaps playing a role in modulating free leptin in the placenta [108]. In normal term placental explants cultured under severe hypoxia (0.1% oxygen), reduced leptin synthesis without changes in the LepR expression in trophoblasts has been described [70].

### 5.3. Preeclampsia

A higher expression of leptin in the placental bed of patients with preeclampsia has been reported, when compared to normal placentas, whose high leptin levels in early pregnancy have been associated with the onset of preeclampsia [109]. In women with mild/severe preeclampsia no changes have been reported in the leptin transmembrane receptor in the apical or basal syncytiotrophoblast membranes, when compared to normal pregnancies [110].

## 6. Adiponectin and adiponectin receptors in pregnancy

Adiponectin is an adipokine with insulin-sensitizing, anti-inflammatory, antiatherogenic, and anti-proliferative effects [111]. This protein, recognized as an hormone, is encoded by a gene identified as AdipoQ or Acrp30 in murine cell lines [112,113], apM1 cloned from human adipose tissue [114] and GBP28 isolated from human plasma [115]. Adiponectin is expressed mainly in adipose tissue [116]. These genes encode a full-length adiponectin (fADN) with 248 amino acids and four domains based on the primary amino acid sequence: a N-terminal signal peptide, a variable region, a collagenous domain and a globular domain at the C-terminal end. This protein is encoded in the long arm of chromosome 3 *locus* 3q27 [116] (Table 1).

The globular fragment of adiponectin (gADN) has 137 amino acids and is formed by the proteolytic cleavage of the fADN, has potent biological activities, which in many tissues displays similar properties to fADN. However gADN and fADN have distinct, and sometimes opposing, biological effects in different tissues including the placenta [117]. Most of the circulating adiponectin is fADN, while gADN is only present in very low concentrations in the human plasma [118].

In human circulation, three types of fADN have been described and are constituted by trimers, hexamers and multimers. These are of low molecular weight (LMW, 67 kDa), middle molecular weight (MMW, 136 kDa) and high molecular weight (HMW, > 300 kDa) [118], being the HMW the most abundant in plasma. Low serum levels of HMW adiponectin, rather than other oligomeric forms, are associated with several metabolic disorders including type 2 diabetes mellitus [119], childhood obesity [120] and metabolic syndrome in different populations [121] (Table 1).

Adiponectin gene is expressed in maternal adipose tissue and in lower amounts in maternal white blood cells [32]. In normal weight healthy women, adiponectin decreases late in gestation and this has been correlated with lower mRNA adiponectin expression in their white adipose tissue [98]. In pregnant women, adiponectin promotes insulin sensitivity and glucose uptake in skeletal muscle, reducing nutrient availability for placental transfer [122].

The HMW adiponectin is the most abundant multimeric form in non-pregnant women and in pregnant women along gestation [123]. However, it is possible that not all adiponectin forms change with gestation in the same way. While the HMW, LMW and HMW/total adiponectin ratio were different between pregnant and non-pregnant women, total and MMW did not change with gestation. Maternal

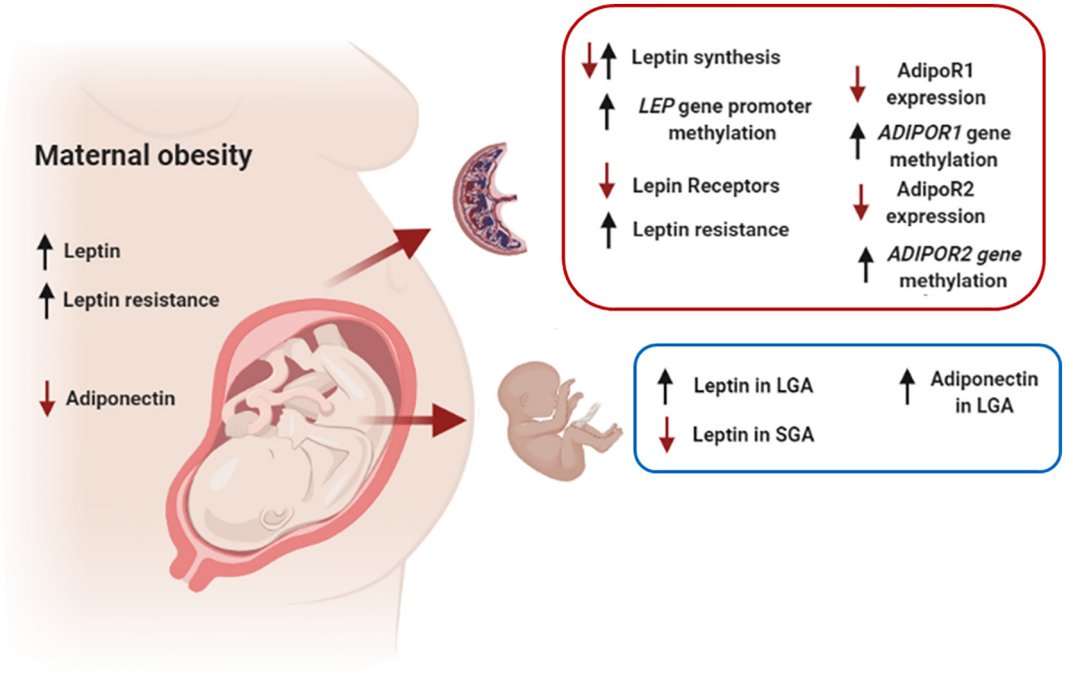


**Fig. 1.** Leptin and adiponectin in pregnant women with pregestational obesity, in the placenta and their offspring. In pregestational obesity, there is an increase in leptin levels in the mother and a decrease in leptin synthesis in the placenta, however there is controversy on this point (indicated by up and down arrow). Leptin gene promoter in the offspring of women with obesity is methylated. The evidence about less leptin receptors expression and the existence of a leptin resistance in the placenta of women with pregestational obesity is not conclusive but supported by some groups. Cord leptin levels in large for gestational age (LGA) offspring are higher and lower in small for gestational age (SGA) offspring compared to newborn of normal weight women. On the other hand, in women with pregestational obesity adiponectin levels are decreased. There is no adiponectin synthesis in the placenta, nevertheless *ADIPOR1* and *ADIPOR2* show high methylation in the promoter and regulatory regions and this is concordant with lower gene expression in the placenta of the offspring of women with pregestational obesity. There are few studies that show that adiponectin levels are higher in LGA newborn of women with pregestational obesity, although this needs more evidence to be stated categorically.

adiponectin levels are inversely related to their BMI [123] and insulin resistance at delivery [31,32].

The expression of adiponectin in the placenta is still controversial. Although the expression of adiponectin mRNA was observed in the syncytiotrophoblast of human term placenta [124,125], others have not been able to detect both the mRNA and the protein in primary cytotrophoblasts [30,126]. In term human placenta Pinar et al. did not detect adiponectin mRNA expression in placental endothelial cells and trophoblast, although they found adiponectin mRNA expression at the limit of detection in placental villi [31]. Haghiac observed very low adiponectin mRNA expression in term placentas but this expression was totally absent after including a washing step of the trophoblast in the protocol [32] leading to the actual concept that the human placenta does not express adiponectin.

The biological actions of adiponectin are mediated via two receptors: AdipoR1 and AdipoR2 [116]. Both AdipoRs have 7 helix, with an inverse transmembrane architecture of the G-protein coupled receptors [116,127]. AdipoR1 is ubiquitously expressed with a high expression in the skeletal muscle, whereas AdipoR2 expression is more restricted, with high expression in the liver [127]. AdipoR1 binds gADN with high affinity and fADN with low affinity, whereas AdipoR2 binds both gADN and fADN with intermediate affinity [128]. The expression of these receptors has been reported in the brain, ovaries, endometrium and also in the placenta [129]. In human cytotrophoblast cells from term placentas, the transcripts for both adiponectin receptors, are abundantly expressed [30] (Table 2).

Adiponectin binds to AdipoR2 in the trophoblast and activates p38 MAPK and Peroxisome Proliferator-Activated Receptor alpha (PPAR-α), which inhibits the insulin/insulin-like growth factor 1 (IGF-1) signaling pathway [122], having an important role in regulating fetal birth weight in normal pregnancies and in pregnancies associated with altered maternal adiponectin levels such as pregestational obesity and GDM [122,130]. Adiponectin increases p38 MAPK phosphorylation and PPARγ activation due to the increase in ceramide synthase expression and ceramide production in primary human term trophoblasts [130], which inhibits placental insulin signaling and systems A and L transport of amino acids, resulting in reduced fetal nutrient availability.

In human cytotrophoblasts from first trimester placenta, adiponectin inhibits the expression of glucose transporter 1 (GLUT1) and GLUT2, and the sodium-coupled neutral amino acid transporters (SNAT1, SNAT2, and SNAT4). It also enhances total ATP production but decreases lactate production; inhibits mitochondrial biogenesis and function, and stimulates cell death by enhancing the expression of the pro-apoptotic B-cell lymphoma-2 (BCL-2)-associated X protein (BAX) and tumor protein p53 (TP53) gene expression and inducing the caspase activity [131]. Adiponectin prevents the insulin-stimulated amino acid and glucose uptake in cultured primary human trophoblast cells by modulating the phosphorylation of the insulin receptor substrate IRS-1 [122,132].

In addition to the role of adiponectin in the transport of nutrients in placenta and its anti-proliferative effects, Benaitreau et al. [133] demonstrated that in human extravillous trophoblast cell lines from first-trimester placenta (HTR-8/SVneo cells), adiponectin stimulates cell migration and enhanced invasion in a dose-independent manner. These pro-invasive effects of adiponectin in human trophoblasts are mediated by matrix metalloproteinases (MMP2 and MMP9) activities and via repression of Tissue inhibitor of metalloproteinases 2 (*TIMP2*) mRNA expression.

In human cytotrophoblast cells, both AdipoR1 and AdipoR2 receptors are expressed after the induction of the syncytium formation by exogenous epidermal growth factor. The treatment of cytotrophoblasts with adiponectin resulted in a significant drop in the expression of a

number of genes involved in endocrine functions in the placenta, including the chorionic gonadotropin subunits, placental lactogen, and some steroidogenic enzymes [30].

JEG-3 and BeWo cells express AdipoR1 and AdipoR2 and respond to human recombinant adiponectin by AMPK activation and induce a reduction in cell number and [$^{(3)}$H]-thymidine incorporation, demonstrating that adiponectin has antiproliferative effects in trophoblastic cells. These effects are mediated in part by the mitogen-activated protein kinase (MAPK) and phosphoinositide-3-kinase (PI3K) signaling pathways [134]. Adiponectin was shown to cause placental insulin resistance in cultured primary human trophoblast cells [135,136].

These studies suggest that adiponectin regulates human placental function by limiting nutrient transporters expression and inducing apoptosis. It has been described as a key factor linking the regulation of metabolic homeostasis and apoptosis in the placenta, and therefore modulating fetal growth.

## 7. Adiponectin and its receptors in women with pregestational obesity

Studies with large samples sizes have described lower adiponectin levels in mothers with pregestational obesity. Pregestational maternal obesity was associated with lower total and HMW adiponectin concentration in the second trimester of gestation and without changes in DNA methylation marks in the maternal adipose tissue [32]. It has been reported that overweight pregnant women have lower HMW/total adiponectin ratio and higher LMW/total adiponectin ratio than normal weight pregnant women during the first, second and third trimester of the gestation [123]. However, some studies with rather small sample sizes did not show differences in adiponectin levels between normal and obese pregnant women [86,98,101,137,138]. By the other hand, the insufficient or excessive weight gain during gestation does not change the plasma concentration of adiponectin at delivery [138].

We have evidenced higher AdipoR1 mRNA levels in human umbilical artery endothelial cells (HUAEC)-derived from LGA newborn from women with pregestational obesity compared to AGA. In this last study higher total eNOS and active AMPK (p-Thr172) protein expression was observed in LGA-HUAEC [141]. Recently a role for adiponectin in the regulation of chorionic plate vascular tone has been described [141], where the placental arterial vessels of LGA fetuses from women with pregestational obesity showed lower vasodilatation capacity and eNOS phosphorylation in Ser1177 in response to an adiponectin receptor agonist. This vasoactive effect of adiponectin was mediated by nitric oxide (NO).

By the other hand Powell et al. [35] have proposed that low adiponectin levels in women with pregestational obesity enhance placental insulin sensitivity and activation of placental amino acid transport systems, supporting fetal overgrowth.

The information regarding the behaviour of adiponectin and its receptors in pregnant women with obesity is rather limited, and most of studies revising the effect of maternal obesity on placental adiponectin receptors have been made in animal models. Very recently the expression and methylation of the adiponectin (*ADIPOQ*) and the receptors *ADIPOR1* and *ADIPOR2* genes in the fetal and maternal side of the placenta in normal weight and women with obesity was studied [102]. As previously stated, the placenta does not express the *ADIPOQ* gene. Very interestingly this lack of expression does not seem to be due to genomic DNA methylation of the *ADIPOQ* gene promoter, since its promoter is barely methylated, but possibly alternative epigenetic mechanisms, including histone methylation, could be involved. This needs to be demonstrated. The study of the expression of *ADIPOR1* and *ADIPOR2* in placenta revealed that both genes show a lower expression in the maternal side of placentas from women with obesity compared to the fetal side of these or to samples from normal weight subjects.

## 8. Adiponectin at birth and early in life

Adiponectin is expressed in fetal subcutaneous and omental adipose tissue, white blood cells and vascular cells of several organs including skeletal muscle, kidney, skin and brain cortex [31]. There are no gender differences in the umbilical cord total adiponectin levels [142–145]. Total adiponectin concentrations in the umbilical cord blood increase with gestational age and this increment is 81% due to the HMW form [146]. The type of delivery and duration of labor are not associated with adiponectin concentrations in the umbilical cord blood [147].

The relationship between maternal adiponectin levels and newborn size has been studied. According to the evidence, mothers of SGA newborns showed lower adiponectin levels than mothers of Adequate for Gestational Age (AGA) newborns [139]. Others have shown lower maternal adiponectin levels with an even higher decrease in LGA offspring compared to AGA newborns [140].

Total and multimeric adiponectin concentrations decrease between birth and infancy [148,149]. Although total, HMW and HMW/total adiponectin ratio at birth and 12 months [148] and at 3 years of life [144] are directly associated in healthy infants, when describing adiponectin trajectories the newborns with the highest adiponectin in umbilical cord blood showed the greatest reduction during infancy [149]. The largest drop of adiponectin levels in infancy has been described in girls with higher weight [150].

It is well-known that maternal adiponectin levels at the second and third trimester of gestation are positively associated with their offspring levels at birth [131,143,151] and fetal growth velocity in the third trimester of pregnancy [143]. Some studies report no differences in adiponectin concentration in umbilical cord blood between newborns from normal weight, overweight and obese mothers [86,98,101,138]. However, in a cohort of over 200 newborns the umbilical cord concentration of total adiponectin was higher in the offspring of obese mothers compared to those of normal-weight mothers (authors unpublished results). It is possible that the most important effect of maternal obesity on the offspring is on the adiponectin trajectory in infancy [149] and not only on its levels at birth [152] (Fig. 1).

Maternal adiponectin in the third trimester was negatively related to weight and subcutaneous fat in their offspring at birth [143]. Maternal HMW adiponectin at the third trimester of gestation was positively associated with peritoneal fat in their offspring at 1 week and with subcutaneous adipose tissue at 4 months of life [153]. Also, total and LMW adiponectin in the umbilical cord blood were positively associated with subcutaneous fat at birth [143]. The total adiponectin and HMW concentration in the umbilical cord blood has been positively associated with central body fat at 3 years of age [154] and with total fat mass at 3 and 4 years [144]. While an inverse association has been shown between adiponectin levels and the change of weight at 6 months [154] and the BMI during infancy [149,155].

There is still a lack of consensus about the effects of pregestational obesity on maternal and newborn adiponectin levels, and if maternal BMI is associated with adiponectin concentrations in newborns. It seems clear that the adiponectin level at birth is an important determinant of growth trajectories and adiposity during childhood. Maternal obesity could be a risk factor in predisposing their offspring to a higher adiposity gain during the first years of life. More studies are needed to elucidate the role of prepregnancy BMI in modifying adiponectin levels at birth.

## 9. Adiponectin in pregnancies affected by other metabolic complications associated with maternal obesity

### 9.1. Gestational diabetes mellitus (GDM)

Maternal adiponectin concentration has been studied in diseases associated with pregnancy. Lower levels of total and HMW adiponectin in the second and third trimester [86,151] and at delivery [156] of

women with GDM have been determined. Furthermore, when GDM is accompanied with pregestational obesity the decrease in adiponectin is greater than in normal weight women with GDM [153]. By the other hand adiponectin concentration decreases even more in the case of insulin-treated GDM compared to only diet-treated patients [151]. In the placenta of women with GDM, there is a significant downregulation of adiponectin mRNA and an upregulation of AdipoR1 expression compared with controls [124].

### 9.2. Preeclampsia

Plasma adiponectin increases in every trimester of normal pregnancy but in women with preeclampsia very small variations can be evidenced [157]. Only AdipoR2 is expressed in the cytoplasm of both placental cytotrophoblasts and syncytiotrophoblasts in the placenta of women with mild and severe preeclampsia; protein and mRNA levels are higher in severe preeclampsia, suggesting that Adipo-R2 may be associated with the pathogenesis of this condition [158].

The evidence shows that maternal adiponectin, mainly synthesized in the adipose tissue, is an important signal for fetal growth, fat mass determination and growth and adipose trajectory in the offspring. How the placenta participates in this process is up to date defined by the expression and activation of AdipoR1 and AdipoR2 receptors.

## 10. Conclusions

Altogether the information discussed in this review highlights the role of leptin and adiponectin levels in maternal circulation on placental transport of nutrients and growth signals to the fetus. The associations of maternal adipokine levels and fetal size at birth, as well as postnatal growth have been evidenced. Nevertheless, the scarce consensus regarding the mechanism of how signals coming from the maternal adipose tissue, such as adiponectin and leptin, modulate placental function and fetal physiology are pending. The greatest gap in this respect is the participation of the placenta and the fetal immune system in early obesogenic and metabolic cues in the newborn. Much is pending to be unveiled regarding to the early origin of adiposity and metabolic functions in the offspring and the long-term effects of maternal obesity.

## Transparency document

The Transparency document associated with this article can be found, in online version.

## Declaration of competing interest

he authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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## Author contributions

PC conceived the review. PC, VAJ, AJ, ECM, KCN and ML drafted the article. The final version was approved by all the authors.

## References

[1] D.J. Barker, In utero programming of chronic disease, Clin Sci (Lond). 95 (1998) 115–128.
[2] M.A. Hanson, P.D. Gluckman, Early developmental conditioning of later health and disease: physiology or pathophysiology? Physiol. Rev. 94 (2014) 1027–1076.
[3] Ng M, Fleming T, Robinson M, Thomson B, Graetz N, Margono C, et al. Global, regional, and national prevalence of overweight and obesity in children and adults during 1980–2013: a systematic analysis for the Global Burden of Disease Study 2013. Lancet. 2014;384:766–81.
[4] P.M. Catalano, K. Shankar, Obesity and pregnancy: mechanisms of short term and long term adverse consequences for mother and child, BMJ 36 (2017) j1, https://doi.org/10.1136/bmj.j1.
[5] World Heatlh Organization, Physical Status: The Use and Interpretation of Anthropometry: Report of a World Health Organization (WHO) Expert Committee, Geneva, Switzerland, 1995.
[6] World Heatlh Organization, Obesity and Overweight, WHO, 2016.
[7] World Health Organization, Mean Body Mass Index (BMI), WHO, 2017.
[8] C.S. Yajnik, Transmission of obesity-adiposity and related disorders from the mother to the baby, Ann Nutr Metab. 64 (2014) 8–17.
[9] M.A. Faucher, M.K. Barger, Gestational weight gain in obese women by class of obesity and select maternal/newborn outcomes: a systematic review, Women and Birth. 28 (2015) e70–e79.
[10] K.M. Rasmussen, Yaktine AL, Guidelines PW, Board N. Weight Gain During Pregnancy, 2009.
[11] E.Y. Lau, J. Liu, E. Archer, S.M. McDonald, J. Liu, Maternal weight gain in pregnancy and risk of obesity among offspring: a systematic review, J. Obes. 2014 (2014).
[12] L. Poston, R. Caleyachetty, S. Cnattingius, C. Corvalán, R. Uauy, S. Herring, et al., Preconceptional and maternal obesity: epidemiology and health consequences, Lancet Diabetes Endocrinol. 4 (2016) 1025–1036.
[13] S.S. Kim, Y. Zhu, K.L. Grantz, S.N. Hinkle, Z. Chen, M.E. Wallace, et al., Obstetric and neonatal risks among obese women without chronic disease, Obstet. Gynecol. 128 (2016) 104–112.
[14] S.K. Berglund, L. García-Valdés, F.J. Torres-Espinola, M.T. Segura, C. Martínez-Zaldívar, M.J. Aguilar, et al., Maternal, fetal and perinatal alterations associated with obesity, overweight and gestational diabetes: an observational cohort study (PREOBE), BMC Public Health 16 (2016) 207.
[15] M. Casas, L. Chatzi, A.E. Carsin, P. Amiano, M. Guxens, M. Kogevinas, et al., Maternal pre-pregnancy overweight and obesity, and child neuropsychological development: two southern european birth cohort studies, Int. J. Epidemiol. 42 (2013) 506–517.
[16] E. Basatemur, J. Gardiner, C. Williams, E. Melhuish, J. Barnes, A. Sutcliffe, Maternal prepregnancy BMI and child cognition: a longitudinal cohort study, Pediatrics. 131 (2013) 56–63.
[17] L. Huang, X. Yu, S. Keim, L. Li, L. Zhang, J. Zhang, Maternal prepregnancy obesity and child neurodevelopment in the Collaborative Perinatal Project, Int. J. Epidemiol. 43 (2014) 783–792.
[18] R.M. Gardner, B.K. Lee, C. Magnusson, D. Rai, T. Frisell, H. Karlsson, et al., Maternal body mass index during early pregnancy, gestational weight gain, and risk of autism spectrum disorders: results from a Swedish total population and discordant sibling study, Int. J. Epidemiol. 44 (2015) 870–883.
[19] Z. Yu, S. Han, J. Zhu, X. Sun, C. Ji, X. Guo, Pre-pregnancy body mass index in relation to infant birth weight and offspring overweight/obesity: a systematic review and meta-analysis, PLoS One 8 (2013).
[20] P.M. Catalano, K. Shankar, Obesity and pregnancy: mechanisms of short term and long term adverse consequences for mother and child, BMJ. 356 (2017) j1.
[21] K.M. Godfrey, R.M. Reynolds, S.L. Prescott, M. Nyirenda, V.W.V. Jaddoe, J.G. Eriksson, et al., Influence of maternal obesity on the long-term health of offspring, Lancet Diabetes Endocrinol. 5 (2017) 53–64.
[22] K.J. Stothard, P.W.G. Tennant, R. Bell, J. Rankin, Maternal overweight and obesity and the risk of congenital anomalies: a systematic review and meta-analysis, JAMA. 301 (2009) 636–650.
[23] A.S. Poobalan, L.S. Aucott, T. Gurung, W.C.S. Smith, S. Bhattacharya, Obesity as an independent risk factor for elective and emergency caesarean delivery in nulliparous women–systematic review and meta-analysis of cohort studies, Obes. Rev. 10 (2009) 28–35.
[24] J. Marchi, M. Berg, A. Dencker, E.K. Olander, C. Begley, Risks associated with obesity in pregnancy, for the mother and baby: a systematic review of reviews, Obes. Rev. 16 (2015) 621–638.
[25] R.C. Whitaker, Predicting preschooler obesity at birth: the role of maternal obesity in early pregnancy, Pediatrics. 114 (2004) e29–e36.
[26] H.C. Tan, J. Roberts, J. Catov, R. Krishnamurthy, R. Shypailo, F. Bacha, Mother's pre-pregnancy BMI is an important determinant of adverse cardiometabolic risk in childhood, Pediatr. Diabetes 16 (2015) 419–426.
[27] A.M. Stuebe, M.R. Forman, K.B. Michels, Maternal-recalled gestational weight gain, pre-pregnancy body mass index, and obesity in the daughter, Int. J. Obes. 33 (2009) 743–752.
[28] J. Lepercq, M. Cauzac, N. Lahlou, J. Timsit, J. Girard, J. Auwerx, et al., Overexpression of placental leptin in diabetic pregnancy: a critical role for insulin, Diabetes. 47 (1998) 847–850.
[29] S. Corbetta, G. Bulfamante, D. Cortelazzi, V. Barresi, I. Cetin, G. Mantovani, et al., Adiponectin expression in human fetal tissues during mid- and late gestation, J. Clin. Endocrinol. Metab. 90 (2005) 2397–2402.
[30] E.A. McDonald, M.W. Wolfe, Adiponectin attenuation of endocrine function within human term trophoblast cells, Endocrinology. 150 (2009) 4358–4365.
[31] H. Pinar, S. Basu, K. Hotmire, L. Laffineuse, L. Presley, M. Carpenter, et al., High molecular mass multimer complexes and vascular expression contribute to high adiponectin in the fetus, J. Clin. Endocrinol. Metab. 93 (2008) 2885–2890.

[32] M. Haghiac, S. Basu, L. Presley, D. Serre, P.M. Catalano, S. Hauguel-de Mouzon, Patterns of adiponectin expression in term pregnancy: impact of obesity, J. Clin. Endocrinol. Metab. 99 (2014) 3427–3434.

[33] Palcevska-Kocevska S, Aluloska N, Krstevska M, Shukarova-Angelovska E, Kojik L, Zisovska E, et al. Correlation of serum adiponectin and leptin concentrations with anthropometric parameters in newborns. Srp Arh Celok Lek. n.d.;140:595–9.

[34] E. Horosz, D.A. Bomba-Opon, M. Szymanska, M. Wielgos, Third trimester plasma adiponectin and leptin in gestational diabetes and normal pregnancies, Diabetes Res. Clin. Pract. 93 (2011) 350–356.

[35] K.R. Howell, T.L. Powell, Effects of maternal obesity on placental function and fetal development, Reproduction. 153 (2017) R97–108.

[36] H. Munzberg, C.D. Morrison, Structure, production and signaling of leptin, Metabolism. 64 (2015) 13–23.

[37] P. Trayhurn, N. Hoggard, J.G. Mercer, D.V. Rayner, Leptin: fundamental aspects, Int. J. Obes. Relat. Metab. Disord. 23 (Suppl. 1) (1999) 22–28.

[38] L. Hardie, P. Trayhurn, D. Abramovich, P. Fowler, Circulating leptin in women: a longitudinal study in the menstrual cycle and during pregnancy, Clin. Endocrinol. 47 (1997) 101–106.

[39] P. Tamas, E. Sulyok, I. Szabo, M. Vizer, T. Ertl, W. Rascher, et al., Changes of maternal serum leptin levels during pregnancy, Gynecol Obs Invest. 46 (1998) 169–171.

[40] T. Tamura, R.L. Goldenberg, K.E. Johnston, S.P. Cliver, Serum leptin concentrations during pregnancy and their relationship to fetal growth, Obstet. Gynecol. 91 (1998) 389–395.

[41] C. Fattah, S. Barry, N. O'Connor, N. Farah, B. Stuart, M.J. Turner, Maternal leptin and body composition in the first trimester of pregnancy, Gynecol. Endocrinol. 27 (2011) 263–266.

[42] J. Lepercq, J.C. Challier, M. Guerre-Millo, M. Cauzac, H. Vidal, S. Hauguel-de Mouzon, Prenatal leptin production: evidence that fetal adipose tissue produces leptin, J. Clin. Endocrinol. Metab. 86 (2001) 2409–2413.

[43] K. Linnemann, A. Malek, R. Sager, W.F. Blum, H. Schneider, C. Fusch, Leptin production and release in the dually in vitro perfused human placenta, J. Clin. Endocrinol. Metab. 85 (2000) 4298–4301.

[44] Y.P. Gambino, A. Pérez Pérez, J.L. Dueñas, J.C. Calvo, V. Sánchez-Margalet, C.L. Varone, Regulation of leptin expression by 17beta-estradiol in human placental cells involves membrane associated estrogen receptor alpha, Biochim. Biophys. Acta 1823 (2012) 900–910.

[45] J.L. Maymo, A. Perez Perez, V. Sanchez-Margalet, J.L. Duenas, J.C. Calvo, C.L. Varone, Up-regulation of placental leptin by human chorionic gonadotropin, Endocrinology. 150 (2009) 304–313.

[46] Y.C. Ge, J.N. Li, X.T. Ni, C.M. Guo, W.S. Wang, T. Duan, et al., Cross talk between cAMP and p38 MAPK pathways in the induction of leptin by hCG in human placental syncytiotrophoblasts, Reproduction. 142 (2011) 369–375.

[47] C. Schubring, P. Englaro, T. Siebler, W.F. Blum, T. Demirakca, J. Kratzsch, et al., Longitudinal analysis of maternal serum leptin levels during pregnancy, at birth and up to six weeks after birth: relation to body mass index, skinfolds, sex steroids and umbilical cord blood leptin levels, Horm. Res. 50 (1998) 276–283.

[48] T.J. Highman, J.E. Friedman, L.P. Huston, W.W. Wong, P.M. Catalano, Longitudinal changes in maternal serum leptin concentrations, body composition, and resting metabolic rate in pregnancy, Am J Obs Gynecol. 178 (1998) 1010–1015.

[49] R.G. Lea, D. Howe, L.T. Hannah, O. Bonneau, L. Hunter, N. Hoggard, Placental leptin in normal, diabetic and fetal growth-retarded pregnancies, Mol. Hum. Reprod. 6 (2000) 763–769.

[50] J. Challier, M. Galtier, T. Bintein, A. Cortez, J. Lepercq, S. Hauguel-de Mouzon, Placental leptin receptor isoforms in normal and pathological pregnancies, Placenta. 24 (2003) 92–99.

[51] D.M. Farley, J. Choi, D.J. Dudley, C. Li, S.L. Jenkins, L. Myatt, et al., Placental amino acid transport and placental leptin resistance in pregnancies complicated by maternal obesity, Placenta. 31 (2010) 718–724.

[52] F. Akerman, Z.M. Lei, C.V. Rao, Human umbilical cord and fetal membranes co-express leptin and its receptor genes, Gynecol. Endocrinol. 16 (2002) 299–306.

[53] C.F. Ebenbichler, S. Kaser, M. Laimer, H.J. Wolf, J.R. Patsch, N.P. Illsley, Polar expression and phosphorylation of human leptin receptor isoforms in paired, syncytial, microvillous and basal membranes from human term placenta, Placenta. 23 (2002) 516–521.

[54] M.C. Henson, K.F. Swan, J.S. O'Neil, Expression of placental leptin and leptin receptor transcripts in early pregnancy and at term, Obstet. Gynecol. 92 (1998) 1020–1028.

[55] J. Bodner, C.F. Ebenbichler, H.J. Wolf, E. Müller-Holzner, U. Stanzl, R. Gander, et al., Leptin receptor in human term placenta: in situ hybridization and immunohistochemical localization, Placenta. 20 (1999) 677–682.

[56] B. Toth, A. Fischl, C. Scholz, C. Kuhn, K. Friese, M. Karamouti, et al., Insulin and leptin receptors as possible new candidates for endocrine control in normal and disturbed human pregnancy, Mol. Hum. Reprod. 15 (2009) 231–239.

[57] M. Castellucci, R. De Matteis, A. Meisser, R. Cancello, V. Monsurrò, D. Islami, et al., Leptin modulates extracellular matrix molecules and metalloproteinases: possible implications for trophoblast invasion, Mol. Hum. Reprod. 6 (2000) 951–958.

[58] S. Schulz, C. Häckel, W. Weise, Hormonal regulation of neonatal weight: placental leptin and leptin receptors, BJOG. 107 (2000) 1486–1491.

[59] J.L. Maymó, A. Pérez Pérez, B. Maskin, J.L. Dueñas, J.C. Calvo, V. Sánchez Margalet, et al., The alternative Epac/cAMP pathway and the MAPK pathway mediate hCG induction of leptin in placental cells, PLoS One 7 (2012) e46216.

[60] J.L. Maymó, A. Pérez Pérez, Y. Gambino, J.C. Calvo, V. Sánchez-Margalet, V.C.L. Review, leptin gene expression in the placenta–regulation of a key hormone in trophoblast proliferation and survival, Placenta. 32 (Suppl. 2) (2011) S146–S153.

[61] L.J. Slieker, K.W. Sloop, P.L. Surface, A. Kriauciunas, F. LaQuier, J. Manetta, et al., Regulation of expression of ob mRNA and protein by glucocorticoids and cAMP, J. Biol. Chem. 271 (1996) 5301–5304.

[62] S. Bi, O. Gavrilova, D.W. Gong, M.M. Mason, M. Reitman, Identification of a placental enhancer for the human leptin gene, J. Biol. Chem. 272 (1997) 30583–30588.

[63] M. Schanton, J.L. Maymó, A. Pérez-Pérez, V. Sánchez-Margalet, C.L. Varone, Involvement of leptin in the molecular physiology of the placenta, Reproduction. 155 (2018) R1–12.

[64] F. Sánchez-Jiménez, A. Pérez-Pérez, C. González-Yanes, C.L. Varone, V. Sánchez-Margalet, Sam68 mediates leptin-stimulated growth by modulating leptin receptor signaling in human trophoblastic JEG-3 cells, Hum. Reprod. 26 (2011) 2306–2315.

[65] P. Cameo, P. Bischof, J.C. Calvo, Effect of leptin on progesterone, human chorionic gonadotropin, and interleukin-6 secretion by human term trophoblast cells in culture, Biol. Reprod. 68 (2003) 472–477.

[66] C.J. Ashworth, N. Hoggard, L. Thomas, J.G. Mercer, J.M. Wallace, R.G. Lea, Placental leptin, Rev. Reprod. 5 (2000) 18–24.

[67] A. Pérez-Pérez, J.L. Maymó, Y.P. Gambino, P. Guadix, J.L. Dueñas, C.L. Varone, et al., Activated translation signaling in placenta from pregnant women with gestational diabetes mellitus: possible role of leptin, Horm. Metab. Res. 45 (2013) 436–442.

[68] A.R. Toro, J.L. Maymó, F.M. Ibarbalz, A. Pérez-Pérez, B. Maskin, A.G. Faletti, et al., Leptin is an anti-apoptotic effector in placental cells involving p53 down-regulation, PLoS One 9 (2014) e99187.

[69] A. Pérez-Pérez, J. Maymó, Y. Gambino, P. Guadix, J.L. Dueñas, C. Varone, et al., Insulin enhances leptin expression in human trophoblastic cells, Biol. Reprod. 89 (2013) 20.

[70] E. Nüsken, Y. Herrmann, M. Wohlfarth, T.W. Goecke, S. Appel, H. Schneider, et al., Strong hypoxia reduces leptin synthesis in purified primary human trophoblasts, Placenta. 36 (2015) 427–432.

[71] N. Hoggard, J. Crabtree, S. Allstaff, D.R. Abramovich, P. Haggarty, Leptin secretion to both the maternal and fetal circulation in the ex vivo perfused human term placenta, Placenta. 22 (2001) 347–352.

[72] P. Atanassova, L. Popova, Leptin expression during the differentiation of subcutaneous adipose cells of human embryos in situ, Cells Tissues Organs 166 (2000) 15–19.

[73] D. Jaquet, J. Leger, C. Levy-Marchal, J.F. Oury, P. Czernichow, Ontogeny of leptin in human fetuses and newborns: effect of intrauterine growth retardation on serum leptin concentrations, J. Clin. Endocrinol. Metab. 83 (1998) 1243–1246.

[74] P.J. Tsai, C.H. Yu, S.P. Hsu, Y.H. Lee, C.H. Chiou, Y.W. Hsu, et al., Cord plasma concentrations of adiponectin and leptin in healthy term neonates: positive correlation with birthweight and neonatal adiposity, Clin. Endocrinol. 61 (2004) 88–93.

[75] A.A. Mellati, S. Mazloomzadeh, A. Anjomshoaa, M. Alipour, F. Karimi, S. Mazloomi, et al., Multiple correlations between cord blood leptin concentration and indices of neonatal growth, Arch. Med. Res. 41 (2010) 26–32.

[76] P. Karakosta, L. Chatzi, E. Plana, A. Margioris, E. Castanas, M. Kogevinas, Leptin levels in cord blood and anthropometric measures at birth: a systematic review and meta-analysis, Paediatr. Perinat. Epidemiol. 25 (2011) 150–163.

[77] P. Karakosta, V. Georgiou, E. Fthenou, E. Papadopoulou, T. Roumeliotaki, A. Margioris, et al., Maternal weight status, cord blood leptin and fetal growth: a prospective mother-child cohort study (Rhea study), Paediatr. Perinat. Epidemiol. 27 (2013) 461–471.

[78] M. Valuniene, R. Verkauskiene, M. Boguszewski, J. Dahlgren, D. Lasiene, L. Lasas, et al., Leptin levels at birth and in early postnatal life in small- and appropriate-for-gestational-age infants, Med. 43 (2007) 784–791.

[79] C.N. Chaoimh, D.M. Murray, L.C. Kenny, A.D. Irvine, J.O. Hourihane, M. Kiely, Cord blood leptin and gains in body weight and fat mass during infancy, Eur. J. Endocrinol. 175 (2016) 403–410.

[80] M.P. Magarinos, V. Sanchez-Margalet, M. Kotler, J.C. Calvo, C.L. Varone, Leptin promotes cell proliferation and survival of trophoblastic cells, Biol. Reprod. 76 (2007) 203–210.

[81] A. Perez-Perez, J. Maymo, Y. Gambino, J.L. Duenas, R. Goberna, C. Varone, et al., Leptin stimulates protein synthesis-activating translation machinery in human trophoblastic cells, Biol. Reprod. 81 (2009) 826–832.

[82] V. White, E. Gonzalez, E. Capobianco, C. Pustovrh, N. Martinez, R. Higa, et al., Leptin modulates nitric oxide production and lipid metabolism in human placenta, Reprod. Fertil. Dev. 18 (2006) 425–432.

[83] N. Jansson, S.L. Greenwood, B.R. Johansson, T.L. Powell, T. Jansson, Leptin stimulates the activity of the system A amino acid transporter in human placental villous fragments, J. Clin. Endocrinol. Metab. 88 (2003) 1205–1211.

[84] A. Ericsson, B. Hamark, N. Jansson, B.R. Johansson, T.L. Powell, T. Jansson, Hormonal regulation of glucose and system A amino acid transport in first trimester placental villous fragments, Am J Physiol Regul Integr Comp Physiol. 288 (2005) R656–R662.

[85] F. von Versen-Hoynck, A. Rajakumar, M.S. Parrott, R.W. Powers, Leptin affects system A amino acid transport activity in the human placenta: evidence for STAT3 dependent mechanisms, Placenta. 30 (2009) 361–367.

[86] Luo Z-C, Nuyt AM, Delvin E, Fraser W, Julien P, Audibert F, et al. Maternal and Fetal Leptin, Adiponectin Levels and Associations With Fetal Insulin Sensitivity. vol. 21. 2013.

[87] V.K. Misra, J.K. Straughen, S. Trudeau, Maternal serum leptin during pregnancy and infant birth weight: the influence of maternal overweight and obesity, Obes

(Silver Spring). 21 (2013) 1064–1069.
[88] V.K. Misra, S. Trudeau, The influence of overweight and obesity on longitudinal trends in maternal serum leptin levels during pregnancy, Obes (Silver Spring). 19 (2011) 416–421.
[89] P.J. Tsai, J. Davis, G. Bryant-Greenwood, Systemic and placental leptin and its receptors in pregnancies associated with obesity, Reprod. Sci. 22 (2015) 189–197.
[90] M. Allbrand, M. Bjorkqvist, K. Nilsson, I. Ostlund, J. Aman, Placental gene expression of inflammatory markers and growth factors–a case control study of obese and normal weight women, J. Perinat. Med. 43 (2015) 159–164.
[91] J. Martino, S. Sebert, M.T. Segura, L. Garcia-Valdes, J. Florido, M.C. Padilla, et al., Maternal body weight and gestational diabetes differentially influence placental and pregnancy outcomes, J. Clin. Endocrinol. Metab. 101 (2016) 59–68.
[92] J. Lepercq, M. Guerre-Millo, J. Andre, M. Cauzac, S. Hauguel-de Mouzon, Leptin: a potential marker of placental insufficiency, Gynecol Obs Invest. 55 (2003) 151–155.
[93] A.M. Ditchfield, M. Desforges, T.A. Mills, J.D. Glazier, M. Wareing, K. Mynett, et al., Maternal obesity is associated with a reduction in placental taurine transporter activity, Int. J. Obes. 39 (2015) 557–564.
[94] N. Jansson, F.J. Rosario, F. Gaccioli, S. Lager, H.N. Jones, S. Roos, et al., Activation of placental mTOR signaling and amino acid transporters in obese women giving birth to large babies, J. Clin. Endocrinol. Metab. 98 (2013) 105–113.
[95] K.E. Brett, Z.M. Ferraro, M. Holcik, K.B. Adamo, Placenta nutrient transport-related gene expression: the impact of maternal obesity and excessive gestational weight gain, J. Matern. Fetal Neonatal Med. 29 (2016) 1399–1405.
[96] O. Acosta, V.I. Ramirez, S. Lager, F. Gaccioli, D.J. Dudley, T.L. Powell, et al., Increased glucose and placental GLUT-1 in large infants of obese nondiabetic mothers, Am. J. Obstet. Gynecol. 212 (2015) 227.e1–227.e7.
[97] Dube E, Gravel A, Martin C, Desparois G, Moussa I, Ethier-Chiasson M, et al. Modulation of fatty acid transport and metabolism by maternal obesity in the human full-term placenta. Biol Reprod. 2012;87:1–11,14.
[98] P.M. Catalano, L. Presley, J. Minium, S. Hauguel-de Mouzon, Fetuses of obese mothers develop insulin resistance in utero, Diabetes Care 32 (2009) 1076–1080.
[99] F. Cifuentes-Zúñiga, V. Arroyo-Jousse, G. Soto-Carrasco, P. Casanello, R. Uauy, B.J. Krause, et al., IL-10 expression in macrophages from neonates born from obese mothers is suppressed by IL-4 and LPS/INFgamma, J. Cell. Physiol. 232 (2017) 3693–3701.
[100] G. Ferretti, A.M. Cester, T. Bacchetti, F. Raffaelli, A. Vignini, F. Orici, et al., Leptin and paraoxonase activity in cord blood from obese mothers, J. Matern. Fetal Neonatal Med. 27 (2014) 1353–1356.
[101] J.L. Josefson, D.M. Zeiss, A.W. Rademaker, B.E. Metzger, Maternal leptin predicts adiposity of the neonate, Horm Res Paediatr. 81 (2014) 13–19.
[102] P. Nogues, E. Santos, Dos, Jammes H, Berveiller P, Arnould L, Vialard F, Maternal Obesity Influences Expression and DNA Methylation of the Adiponectin and Leptin Systems in Human Third-Trimester Placenta (2019) 1–18.
[103] Lazo-de-la-Vega-Monroy M-L, González-Domínguez MI, Zaina S, Sabanero M, Daza-Benítez L, Malacara JM, et al., Leptin and its receptors in human placenta of small, adequate, and large for gestational age newborns, Horm. Metab. Res. 49 (2017) 350–358.
[104] H. Sn, S. Rawal, D. Liu, J. Chen, T. My, C. Zhang, Maternal adipokines longitudinally measured across pregnancy and their associations with neonatal size, length, and adiposity, Int. J. Obes. (2018) 10–11.
[105] K.K. Ong, M.L. Ahmed, A. Sherriff, K.A. Woods, A. Watts, J. Golding, et al., Cord blood leptin is associated with size at birth and predicts infancy weight gain in humans, ALSPAC Study Team. Avon Longitudinal Study of Pregnancy and Childhood. J Clin Endocrinol Metab. 84 (1999) 1145–1148.
[106] J.L. Kaar, J.T. Brinton, T. Crume, R.F. Hamman, D.H. Glueck, D. Dabelea, Leptin levels at birth and infant growth: the EPOCH study, J Dev Orig Heal Dis. 5 (2014) 214–218.
[107] P.S. Uzelac, X. Li, J. Lin, L.D. Neese, L. Lin, S.T. Nakajima, et al., Dysregulation of leptin and testosterone production and their receptor expression in the human placenta with gestational diabetes mellitus, Placenta. 31 (2010) 581–588.
[108] D. Klaffenbach, U. Meissner, M. Raake, F. Fahlbusch, M.A. Alejandre Alcazar, I. Allabauer, et al., Upregulation of leptin-receptor in placental cells by hypoxia, Regul. Pept. 167 (2011) 156–162.
[109] M.-J. Park, D.-H. Lee, B.-S. Joo, Y.-J. Lee, J.-K. Joo, B.-S. An, et al., Leptin, leptin receptors and hypoxia-induced factor-1α expression in the placental bed of patients with and without preeclampsia during pregnancy, Mol. Med. Rep. 17 (2018) 5292–5299.
[110] R.H.W. Li, S.C.S. Poon, M.Y. Yu, Y.F. Wong, Expression of placental leptin and leptin receptors in preeclampsia, Int. J. Gynecol. Pathol. 23 (2004) 378–385.
[111] S. Esmaili, A. Xu, J. George, The multifaceted and controversial immunometabolic actions of adiponectin, Trends Endocrinol. Metab. 25 (2014) 444–451.
[112] P.E. Scherer, S. Williams, M. Fogliano, G. Baldini, H.F. Lodish, A novel serum protein similar to C1q, produced exclusively in adipocytes, J. Biol. Chem. 270 (1995) 26746–26749.
[113] E. Hu, P. Liang, B.M. Spiegelman, AdipoQ is a novel adipose-specific gene dysregulated in obesity, J. Biol. Chem. 271 (1996) 10697–10703.
[114] K. Maeda, K. Okubo, I. Shimomura, T. Funahashi, Y. Matsuzawa, K. Matsubara, cDNA cloning and expression of a novel adipose specific collagen-like factor, apM1 (adipose most abundant gene transcript 1), Biochem. Biophys. Res. Commun. 221 (1996) 286–289.
[115] Y. Nakano, T. Tobe, N.H. Choi-Miura, T. Mazda, M. Tomita, Isolation and characterization protein purified from human of GBP28, Plasma a Novel. J Biochem. 120 (1996) 803–812.
[116] J.T. Heiker, D. Kosel, A.G. Beck-Sickinger, Molecular mechanisms of signal transduction via adiponectin and adiponectin receptors, Biol. Chem. 391 (2010).
[117] P. Bobbert, S. Antoniak, H.-P. Schultheiss, U. Rauch, Globular adiponectin but not full-length adiponectin induces increased procoagulability in human endothelial cells, J. Mol. Cell. Cardiol. 44 (2008) 388–394.
[118] H. Waki, T. Yamauchi, J. Kamon, Y. Ito, S. Uchida, S. Kita, et al., Impaired multimerization of human adiponectin mutants associated with diabetes, J. Biol. Chem. 278 (2003) 40352–40363.
[119] R. Basu, U.B. Pajvani, R.A. Rizza, P.E. Scherer, Selective downregulation of the high molecular weight form of adiponectin in hyperinsulinemia and in type 2 diabetes: differential regulation from nondiabetic subjects, Diabetes. 56 (2007) 2174–2177.
[120] S. Araki, K. Dobashi, K. Kubo, K. Asayama, A. Shirahata, High molecular weight, rather than total, adiponectin levels better reflect metabolic abnormalities associated with childhood obesity, J. Clin. Endocrinol. Metab. 91 (2006) 5113–5116.
[121] C. Lara-Castro, N. Luo, P. Wallace, R.L. Klein, W.T. Garvey, Adiponectin multimeric complexes and the metabolic syndrome trait cluster, Diabetes. 55 (2006) 249–259.
[122] I. Aye, T. Powell, T. Jansson, Review: adiponectin–the missing link between maternal adiposity, placental transport and fetal growth? Placenta. 34 (Suppl) (2013) S40–S45.
[123] S. Mazaki-Tovi, R. Romero, J.P. Kusanovic, O. Erez, E. Vaisbuch, F. Gotsch, et al., Adiponectin multimers in maternal plasma, J Matern Neonatal Med. 21 (2008) 796–815.
[124] J. Chen, B. Tan, E. Karteris, S. Zervou, J. Digby, E.W. Hillhouse, et al., Secretion of adiponectin by human placenta: differential modulation of adiponectin and its receptors by cytokines, Diabetologia. 49 (2006) 1292–1302.
[125] J.E. Caminos, R. Nogueiras, R. Gallego, S. Bravo, S. Tovar, T. García-Caballero, et al., Expression and regulation of adiponectin and receptor in human and rat placenta, J. Clin. Endocrinol. Metab. 90 (2005) 4276–4286.
[126] M. Meller, C. Qiu, S. Vadachkoria, D.F. Abetew, D.A. Luthy, M.A. Williams, Changes in placental adipocytokine gene expression associated with gestational diabetes mellitus, Physiol. Res. 55 (2006) 501–512.
[127] C.M. Deckert, J.T. Heiker, A.G. Beck-Sickinger, Localization of novel adiponectin receptor constructs, J. Recept. Signal Transduct. Res. 26 (2006) 647–657.
[128] T. Yamauchi, J. Kamon, Y. Ito, A. Tsuchida, T. Yokomizo, S. Kita, et al., Cloning of adiponectin receptors that mediate antidiabetic metabolic effects, Nature. 423 (2003) 762–769.
[129] G. Angelidis, K. Dafopoulos, C.I. Messini, V. Valotassiou, P. Tsikouras, N. Vrachnis, et al., The emerging roles of adiponectin in female reproductive system-associated disorders and pregnancy, Reprod. Sci. 20 (2013) 872–881.
[130] I. Aye, X. Gao, S. Weintraub, T. Jansson, T. Powell, Adiponectin inhibits insulin function in primary trophoblasts by PPARα-mediated ceramide synthesis, Mol. Endocrinol. 28 (2014) 512–524.
[131] F. Duval, S.E. Dos, Poidatz D, Sérazin V, Gronier H, Vialard F, et al. Adiponectin inhibits nutrient transporters and promotes apoptosis in human villous cytotrophoblasts: involvement in the control of fetal growth, Biol. Reprod. 94 (2016) 111.
[132] H.N. Jones, T. Jansson, T.L. Powell, Full-length adiponectin attenuates insulin signaling and full-length adiponectin attenuates insulin signaling and inhibits insulin-stimulated amino acid transport in human primary trophoblast cells, Diabetes. 59 (2010) 1161–1170.
[133] D. Benaitreau, E. Dos Santos, M.-C. Leneveu, N. Alfaidy, J.-J. Feige, P. de Mazancourt, et al., Effects of adiponectin on human trophoblast invasion, J. Endocrinol. 207 (2010) 45–53.
[134] D. Benaitreau, M.-N. Dieudonné, E. Dos Santos, M.-C. Leneveu, Mazancourt P de, Pecquery R. Antiproliferative effects of adiponectin on human trophoblastic cell lines JEG-3 and BeWo, Biol. Reprod. 80 (2009) 1107–1114.
[135] H.N. Jones, T. Jansson, T.L. Powell, C. Children, S. Antonio, Full-length adiponectin attenuates insulin signaling and inhibits insulin-stimulated amino Acid transport in human primary trophoblast cells, Diabetes 59 (2010) (2010) 1161–1170, https://doi.org/10.2337/db09-0824.
[136] I.L.M.H. Aye, T.L. Powell, T. Jansson, Review: adiponectin–the missing link between maternal adiposity, placental transport and fetal growth? Placenta. 34 (Suppl) (2013) S40–S45.
[137] M.K. Ozias, S. Li, H.R. Hull, W.M. Brooks, S.E. Carlson, Relationship of circulating adipokines to body composition in pregnant women, Adipocyte. 4 (2015) 44–49.
[138] M. Solis-Paredes, S. Espinoy Sosa, G. Estrada-Gutierrez, S. Nava-Salazar, V. Ortega-Castillo, M. Rodriguez-Bosch, et al., Maternal and fetal lipid and adipokine profiles and their association with obesity, Int. J. Endocrinol. 2016 (2016).
[139] C. Meral, F. Cekmez, O. Pirgon, I.A. Tanju, O.M. Ipcioglu, F. Karademir, et al., The relationship between serum visfatin, adiponectin, and insulin sensitivity markers in neonates after birth, J Matern Neonatal Med. 24 (2011) 166–170.
[140] T. Lekva, M.C. Paasche Roland, A.E. Michelsen, C.M. Friis, P. Aukrust, J. Bollerslev, et al., Large reduction in adiponectin during pregnancy is associated with large-for-gestational-age newborns, J. Clin. Endocrinol. Metab. 102 (2017) 2552–2559.
[141] E. Muñoz-Muñoz, B.J. Krause, R. Uauy, P. Casanello, LGA-newborn from patients with pregestational obesity present reduced adiponectin-mediated vascular relaxation and endothelial dysfunction in fetoplacental arteries, J. Cell. Physiol. 223 (2018) 6723–6733, https://doi.org/10.1002/jcp.26499.
[142] M. Inoue, K. Itabashi, Y. Nakano, Y. Nakano, T. Tobe, High-molecular-weight adiponectin and leptin levels in cord blood are associated with anthropometric measurements at birth, Horm Res Paediatr. 70 (2008) 268–272.
[143] I. Simón-Muela, S. Näf, M. Ballesteros, J. Vendrell, V. Ceperuelo-Mallafre, M. De La Flor, et al., Gender determines the actions of adiponectin multimers on fetal growth and adiposity, Am. J. Obstet. Gynecol. 208 (2013) 481.e1–481.e7.
[144] D.M. Meyer, C. Brei, L. Stecher, D. Much, S. Brunner, H. Hauner, Cord blood and

child plasma adiponectin levels in relation to childhood obesity risk and fat distribution up to 5 y, Pediatr. Res. 81 (2017) 745–751.
[145] V.L.V. Euclydes, N.P. Castro, L.R. Lima, C. Brito, L. Ribeiro, F.A. Simões, et al., Cord blood concentrations of leptin, zinc-α2-glycoprotein, and adiponectin, and adiposity gain during the first 3 mo of life, Nutrition. 54 (2018) 89–93.
[146] N. Odden, L. Mørkrid, High molecular weight adiponectin dominates in cord blood of newborns but is unaffected by pre-eclamptic pregnancies, Clin. Endocrinol. 67 (2007) 891–896.
[147] C.A. Logan, L. Thiel, R. Bornemann, W. Koenig, F. Reister, H. Brenner, et al., Delivery mode, duration of labor, and cord blood adiponectin, leptin, and C-reactive protein: results of the population-based Ulm birth cohort studies, PLoS One 11 (2016) e0149918.
[148] S. Hibino, K. Itabashi, Y. Nakano, M. Inoue, D. Tanaka, T. Maruyama, Longitudinal changes in high molecular weight serum adiponectin levels in healthy infants, Pediatr. Res. 65 (2009) 363–366.
[149] V. Volberg, B. Heggeseth, K. Harley, K. Huen, P. Yousefi, V. Davé, et al., Adiponectin and leptin trajectories in Mexican-American children from birth to 9 years of age, PLoS One 8 (2013).
[150] Iñiguez G, Soto N, Avila A, Salazar T, Ong K, Dunger D, et al. Adiponectin Levels in the First Two Years of Life in a Prospective Cohort: Relations With Weight Gain, Leptin Levels and Insulin Sensitivity. vol. 89. 2004.
[151] M. Ballesteros, I. Simón, J. Vendrell, V. Ceperuelo-Mallafré, R.M. Miralles, G. Albaiges, et al., Maternal and cord blood adiponectin multimeric forms in gestational diabetes mellitus: a prospective analysis, Diabetes Care 34 (2011) 2418–2423.
[152] G.K.B. Ong, J.K. Hamilton, M. Sermer, P.W. Connelly, G. Maguire, B. Zinman, et al., Maternal serum adiponectin and infant birthweight: the role of adiponectin isoform distribution, Clin. Endocrinol. 67 (2007) 108–114.
[153] K. Uebel, K. Pusch, K. Gedrich, K.T.M. Schneider, H. Hauner, B.L. Bader, Effect of maternal obesity with and without gestational diabetes on offspring subcutaneous and preperitoneal adipose tissue development from birth up to year-1, BMC Pregnancy Childbirth. 14 (2014) 1–13.
[154] C.S. Mantzoros, S.L. Rifas-Shiman, C.J. Williams, J.L. Fargnoli, T. Kelesidis, M.W. Gillman, Cord blood leptin and adiponectin as predictors of adiposity in children at 3 years of age: a prospective cohort study, Pediatrics. 123 (2009) 682–689.
[155] Volberg V, Harley K, Aguilar Schall R, Goldman Rosas L, Huen K, Yousefi P, et al. Associations Between Perinatal Factors and Adiponectin and Leptin in 9-year-old Mexican-American Children. vol. 8. 2013.
[156] J.M. Atègbo, O. Grissa, A. Yessoufou, A. Hichami, K.L. Dramane, K. Moutairou, et al., Modulation of adipokines and cytokines in gestational diabetes and macrosomia, J. Clin. Endocrinol. Metab. 91 (2006) 4137–4143.
[157] F. Herse, B. Youpeng, Staff AC, J. Yong-Meid, R. Dechend, Z. Rong, Circulating and uteroplacental adipocytokine concentrations in preeclampsia, Reprod. Sci. 16 (2009) 584–590.
[158] Tie Weiwei, Yu Haiyan, Chen Juan, Wang Xiaodong, Chen Weibo, Zhou Rong. Expressions of adiponectin receptors in placenta and their correlation with preeclampsia. Reprod. Sci. 2009;16:676–84.