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/m², 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, circulating 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 up-regulates 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-kB) 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 kinases2/signal transduction and activator of transcription 3 (JAK2/STAT-3), MAPK and PI3K pathways in placental cells [60]. The mRNA-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
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.

### Table 1

<table>
<thead>
<tr>
<th>Gene</th>
<th>Gene location</th>
<th>Protein</th>
<th>Synthesis</th>
<th>Function</th>
</tr>
</thead>
<tbody>
<tr>
<td>LEP</td>
<td>7q22.1</td>
<td>167 amino acids, 16 kDa</td>
<td>Adipose tissue placenta (syncytiotrophoblast)</td>
<td>Hormone regulator of satiety and energy expenditure in the central nervous system</td>
</tr>
<tr>
<td>ADIPOQ</td>
<td>3q27.3</td>
<td>244 amino acids, 27 kDa</td>
<td>Adipocytes Lower amounts are produced in maternal white blood cells</td>
<td>Hormone insulin-sensitizing, anti-inflammatory, antiatherogenic, and anti-proliferative. Glucose uptake in skeletal muscle.</td>
</tr>
</tbody>
</table>

#### 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

<table>
<thead>
<tr>
<th>Gene</th>
<th>Gen location</th>
<th>Protein</th>
<th>Tissue localization and Synthesis</th>
<th>Receptor affinity</th>
<th>Function</th>
</tr>
</thead>
<tbody>
<tr>
<td>ADIPOR1</td>
<td>1q32.1</td>
<td>Adiponectin receptor 1 (AdipoR1).</td>
<td>375 amino acids. 42.616 Da.</td>
<td>Localised at cell membrane and intracellular organelles.</td>
<td>Ubiquitous. Highly expressed in skeletal muscle, liver, adipose tissue, and white blood cells. Weakly expressed in brain, thymus, kidney, lung, and small intestine. Intermediate affinity for globular and full-length adiponectin. Required for normal glucose and fat homeostasis and for maintaining a normal body weight. 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.</td>
</tr>
<tr>
<td>ADIPOR2</td>
<td>12p13.33</td>
<td>Adiponectin receptor 2 (AdipoR2).</td>
<td>386 amino acids. 43.884 Da.</td>
<td>Localised at cell membrane and intracellular organelles.</td>
<td>Ubiquitous. Highly expressed in skeletal muscle, liver, adipose tissue, and white blood cells. Weakly expressed in brain, thymus, kidney, lung, and small intestine. Intermediate affinity for globular and full-length adiponectin. Required for normal glucose and fat homeostasis and for maintaining a normal body weight. 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.</td>
</tr>
</tbody>
</table>

**Gene function:**
- On ligand binding, adiponectin binds to AdipoR1 and AdipoR2 through a two-step mechanism involving dimerization, oligomerization, and receptor activation.
- Adiponectin regulates many metabolic, cardiovascular, and other processes through these receptors.

**Receptor properties:**
- LEPR: Six isoforms, extracellular, trans-membrane, and intracellular sections.
- ADIPOR1: Ubiquitous expression in various tissues.
- ADIPOR2: Ubiquitous expression in various tissues.

**Function:**
- Adiponectin is involved in glucose and lipid metabolism, cardiovascular health, and inflammatory processes.
- LEPR and ADIPOR1/2 receptors are key components in the signaling pathways of adiponectin's effects.

**Adiponectin signaling:**
- Activation of AMPK and other signaling pathways.
- Modulation of insulin sensitivity.
- Regulation of adipocyte differentiation and lipolysis.
- Inhibition of fat accumulation.

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

Tsaï 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 [109].

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], aPp1 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 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
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, adipo-nectin 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 cas-pase 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 [122,32].

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 cytrophoblasts 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 [3H]-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 placentas 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 de

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 obeseogenic 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

The 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.

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