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REVIEW

The endocrine function of human placenta: an overview

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Mariana Costa holds a PhD in Pharmaceutical Sciences, Specialty of Biochemistry, by the Faculty of Pharmacy University of Porto. Her PhD work contributed significantly to unveil the importance of endocannabinoid signaling in apoptosis and differentiation of human trophoblasts, as well as in protein synthesis by these cells.

Abstract During pregnancy, several tightly coordinated and regulated processes take place to enable proper fetal development and gestational success. The formation and development of the placenta is one of these critical pregnancy events. This organ plays essential roles during gestation, including fetal nourishment, support and protection, gas exchange and production of several hormones and other mediators. Placental hormones are mainly secreted by the syncytiotrophoblast, in a highly and tightly regulated way. These hormones are important for pregnancy establishment and maintenance, exerting autocrine and paracrine effects that regulate decidualization, placental development, angiogenesis, endometrial receptivity, embryo implantation, immunotolerance and fetal development. In addition, because they are released into maternal circulation, the profile of their blood levels throughout pregnancy has been the target of intense research towards finding potential robust and reliable biomarkers to predict and diagnose pregnancy-associated complications. In fact, altered levels of these hormones have been associated with some pathologies, such as chromosomal anomalies or pre-eclampsia. This review proposes to revise and update the main pregnancy-related hormones, addressing their major characteristics, molecular targets, function throughout pregnancy, regulators of their expression and their potential clinical interest.

KEYWORDS: placental hormones, peptide hormones, pregnancy, steroid hormones, syncytiotrophoblast

Introduction

The human placenta is a specialized pregnancy organ that is responsible for essential functions for gestational success, including fetal support, nourishment and protection. The most characteristic placental cells are the trophoblasts. These epithelial cells have different phenotypes and form the in chorionic villi, finger-shaped structures present in the placenta. Cytotrophoblasts are mononucleated cells that are able to proliferate and differentiate into other trophoblast

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subtypes, functioning as a precursor pool for the syncytiotrophoblast and extravillous trophoblasts (EVT). In fact, cytotrophoblasts fuse and undergo biochemical differentiation, giving rise to the multinucleated syncytiotrophoblast. The syncytial layer has no proliferative capacity and is in intimate contact with maternal blood, participating in fetal nourishment, gas exchange and also playing important roles in other placental functions, mainly in protein biosynthesis. Cytotrophoblasts may also acquire invasive properties, forming the EVT. These trophoblasts are able to invade and remodel maternal tissues (interstitial EVT) and uterine spiral artery (endovascular EVT), reducing the resistance against blood flow that irrigates the fetus. EVT may also invade and remodel uterine glands (endoglandular EVT), which is important to provide histiotrophic nutrition to the embryo. All these trophoblast subtypes interact with each other and with the other cell types in the placental milieu, e.g. decidual cells, Hofbaüer cells, endothelial cells, vascular smooth muscle cells, providing a unique microenvironment that is crucial for pregnancy outcome and fetal development (Huppertz et al., 2014; Lunghi et al., 2007). The human trophoblast phenotypes at the maternal–fetal interface are represented in **Figure 1**.

One of the major functions of the human placenta is the capacity to synthesize important hormones and other mediators, as this placental endocrine function is crucial for gestational success. In fact, placental hormones are important throughout gestation, as they play different roles in pregnancy establishment and maintenance, fetal development and labour. The major source of placental hormones is the syncytiotrophoblast layer, which expresses the enzymatic machinery and other requirements for the biosynthesis of several hormones that intervene in numerous pregnancy-related events. Other trophoblast phenotypes, however, may also produce some placental hormones and affect the gestational course. For instance, the hormones produced by EVT contribute to vascular and uterine tissue remodelling and to regulate EVT migration and invasion (Lunghi et al., 2007; Ji et al., 2013).

The release of placental hormones into maternal circulation has been the target of intense research into their potential as biomarkers for predicting and diagnosing pregnancy-related diseases. Nevertheless, the study of hormone production by human placenta and the function of each hormone in different gestational events represent a challenge. In fact, because of ethical reasons, studies in human models are limited and are susceptible to great inter-individual variability. Currently, human placental explants or isolated primary human cytotrophoblasts are used to assess the endocrine function of human placenta. Alternatively, immortalized trophoblast cell lines have been used as models to study the human trophoblast. The choriocarcinoma-derived cell line BeWo is the most commonly used model to represent the cytotrophoblast, as these cells have the main characteristics of human cytotrophoblast cells, including the synthesis of placental hormones, e.g. human chorionic gonadotrophin (HCG), progesterone, oestrogens (Orendi et al., 2011). BeWo cells, however, still keep tumour cell properties, which raises questions about their true representation of normal human trophoblasts. On the other hand, animal models, namely mice, are frequently used to study placentation (Carter, 2007) but considerable differences are denoted between mice and human placentas. In fact, although both have haemochorial placentation, trophoblast invasion in mice is much more restricted, and placental hormone production is considerably different. For example, in mice, progesterone synthesis by corpus luteum is required throughout pregnancy, and mouse placental lactogens regulate corpus luteum function. In humans, placenta assumes progesterone synthesis from 6–8 weeks of gestation until the labour, and HCG maintains corpus luteum. Also, human trophoblasts secrete higher amounts of steroid hormones than trophoblasts of other mammals (Malassine et al., 2003). Therefore, this interspecies variability also limits the study of human placental hormones in animal models.

In this review, the main placental hormones and their functions, mechanisms of action, regulators and the most consistent evidence linking altered levels of these hormones and

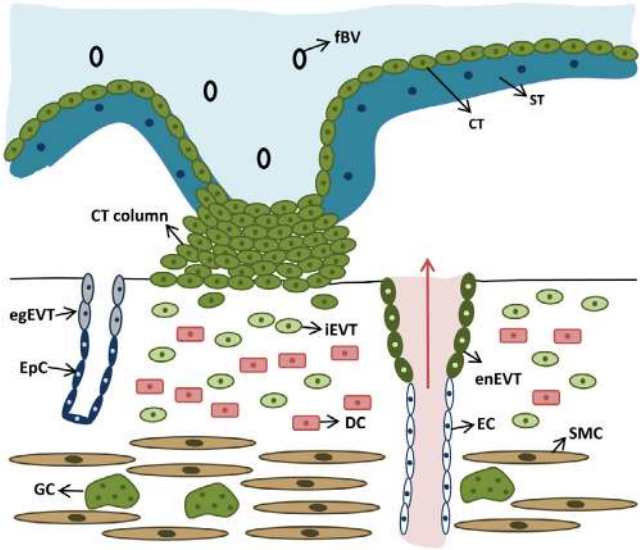

Figure 1 Placental cells at the maternal–fetal interface. Cytotrophoblasts are mononucleated cells that proliferate and undergo fusion and biochemical differentiation to originate the syncytiotrophoblast. The syncytiotrophoblast is a multinucleated cell layer devoid of proliferative activity, which is in intimate contact with the maternal blood. The cytotrophoblasts may also acquire invasive capacity, invading maternal decidua (decidual cell) and part of the myometrium (smooth muscle cell), blood vessels, and uterine glands forming the interstitial extravillous trophoblast, endovascular extravillous trophoblasts, and endoglandular extravillous trophoblasts respectively. Endovascular extravillous trophoblasts replace the endothelial cells of spiral artery, leading to the widening of artery lumen, which decreases the resistance against blood flow that irrigates the fetus (pink arrow). Interstitial extravillous trophoblast fuse and form the multinucleated giant trophoblast cells, which are unable to further invade the uterine tissues. CT = cytotrophoblast; DC = decidual cell; EC = endothelial cell; egEVT = endoglandular extravillous trophoblast; enEVTs = endovascular EpC = epithelial cell; EVT = extravillous trophoblast; fBV = fetal blood vessel; GC = giant trophoblast cells; iEVT = interstitial extravillous trophoblast; SMC = smooth muscle cell; ST = syncytiotrophoblast.

gestational-related complications will be addressed. This information is summarized in **Table 1**.

HCG

HCG is one of the most important pregnancy-related hormones. It belongs to the glycoprotein family hormone, sharing similarities with other members of this family, such as hypophysary LH and FSH. These hormones are composed of two non-covalently linked subunits, α and β: α subunit is shared by all of them, whereas β subunit is characteristic of each hormone. HCG β subunit is encoded by a cluster of genes located on chromosome 19 (Policastro et al., 1986). Therefore, HCG is a heterodimeric protein mainly synthesised by the syncytiotrophoblast (Cole, 1997), although EVT may also produce this protein (Handschuh et al., 2007). HCG mRNA is detected at six- to eight-cell embryo stage, so the human embryo begins to produce this hormone before implantation (Bonduelle et al., 1988). From day 8 after fertilization, HCG is detectable in maternal serum, and its levels peak at 10th week of gestation, decreasing then slowly until the end of pregnancy (Cole, 1997). Moreover, in first-trimester placental explants, it was reported that the secretion of this glycoprotein is pulsatile (Barnea and Kaplan, 1989). Beta-HCG detection in blood and urine is commonly used as a pregnancy test (Cole, 2012), as it is almost exclusively produced during pregnancy (some tumour cell types can also secrete this hormone).

HCG binds to G protein-coupled receptor LH–HCG, and mainly activates the enzyme adenylyl cyclase, increasing concomitantly cyclic adenosine monophosphate (cAMP) levels and protein kinase A (PKA) activity. Moreover, through an independent mechanism, HCG may also activate phospholipase C–inositol phosphate pathway (Choi and Smitz, 2014). The LH–HCG receptor is expressed in the cytotrophoblast, syncytiotrophoblast and EVT (Handschuh et al., 2007; Pidoux et al., 2007). By its activation, HCG plays pleotropic roles during gestation owing to its autocrine and paracrine actions, interfering with several processes that are vital for the pregnancy outcome. In fact, continuous intravenous infusion of exogenous HCG after therapeutic termination of pregnancy maintains preoperative levels of 17α-hydroxyprogesterone, suggesting HCG enhances progesterone synthesis by corpus luteum (Garner and Armstrong, 1977). In-vitro progesterone production by human granulosa luteal cells is also stimulated by HCG (Emi et al., 1991). These HCG-mediated effects are essential for early pregnancy maintenance, until placenta is able to produce this steroid by itself. Moreover, HCG also promotes in-vitro human cytotrophoblast differentiation into the syncytiotrophoblast, by activating LH–HCG receptor and consequently PKA pathway (Pidoux et al., 2007; Shi et al., 1993).

Several lines of evidence support a modulator role of HCG in endometrium and placental angiogenesis. In fact, LH–HCG receptor is expressed in human uterine arteries, namely in endothelial and smooth muscle cells (Toth et al., 1994). Also, in-vivo administration of HCG decreases the resistance index in human uterine arteries, and an in-vitro study showed HCG increases vasodilatory and decreases the levels of vasoconstrictive eicosanoids in the vessels (Toth et al., 1994). In a three-dimensional in-vitro model containing uterine microvascular endothelial cells, HCG enhanced in-vitro capillary formation and promoted endothelial cells migration (Zygmunt et al., 2002). In addition, in-vitro studies have revealed that exogenous HCG enhances the production of the pro-angiogenic factor vascular endothelial growth factor (VEGF) by human cytotrophoblast cells (Islami et al., 2003), by endometrial epithelial cells and by human umbilical vein endothelial cells (HUVEC) (Berndt et al., 2006). In addition, HCG stimulates the proliferation of placental microvascular endothelial cells (Herr et al., 2007) and HUVEC independently or by an interplay with some adipokines, possibly by enhancing ERK 1/2 phosphorylation (Polec et al., 2014).

Different in-vitro studies have also reported that HCG is important for immunotolerance, as it suppresses the maternal immunological system. In fact, in-vitro migration assays revealed that cytotrophoblast-produced HCG attracts regulatory T cells (Treg), by upregulating LH–HCG receptor on these cells, which leads to an increase of Treg number at the fetal–maternal interface (Schumacher et al., 2009). As Treg cells play an important role in maintaining immunotolerance during gestation, it is suggested that HCG is a modulator of these process. It also enhances the proliferation of endometrial uterine natural killer (uNK) cells cultured *in-vitro*, through the activation of mannose receptor (Kane et al., 2009). In women who received HCG in preparation for IVF, HCG increased Th2 cells, polarized Th1/Th2 balance, increased the number of Treg and serum levels of IL-8 and the anti-inflammatory cytokine IL-10 (Koldehoff et al., 2011). All this evidence points towards an immunosuppressive role for HCG during pregnancy.

Trophoblast invasion is also stimulated by HCG, by modulating the production of matrix metalloproteinases (MMP) and their inhibitors (TIMP). In fact, co-cultures of human first-trimester cytotrophoblasts and decidualized endometrial stromal cells (ESC) exposed to HCG showed an increased secretion of MMP-2 and MMP-9 by cytotrophoblasts and decreased levels of TIMP-1, -2, and -3 in ESC (Fluhr et al., 2008). In-vitro migration of first-trimester villous explants and of cytotrophoblast model SGHPL-5 is also promoted by HCG, through the activation of extracellular signal-regulated kinases 1/2 (ERK 1/2) and AKT signalling pathways (Prast et al., 2008). Similarly, human ESC treated with HCG express increased levels of MMP-2 and reduced levels of TIMP-1 and conditioned media of HCG-treated ESC enhances the invasive properties of HTR8/SVneo cell line, an EVT model (Tapia-Pizarro et al., 2013).

Additionally, HCG induces a relaxant effect in human myometrial tissue (Slattery et al., 2001), suggesting a direct contribution of this hormone for the maintenance of myometrial quiescence during pregnancy. In fact, human myometrium expresses HCG–LH receptors and HCG decreases connexin-43 expression in myometrial cells, downregulating gap junctions, via a mechanism mediated by PKA signalling and that may also involve progesterone receptors (Ambrus and Rao, 1994). All this evidence, particularly the promotion of immunotolerance and uterine quiescence, suggests that HCG enhances endometrial receptivity and, so, it is also important for embryo implantation (Perrier d'Hauterive et al., 2007).

Several mediators control HCG secretion by trophoblasts. It is stimulated by the signalling pathways cAMP–PKA (Keryer et al., 1998; Knofler et al., 1999), mitogen-activated protein kinases (MAPK) p38 and ERK 1/2 (Daoud et al., 2005) and Src kinases (Daoud et al., 2006). Interestingly, the nuclear receptor peroxisome proliferator-activated receptor gamma (PPAR-γ) enhances HCG secretion by the syncytiotrophoblast, but inhibits its production by EVT (Handschuh et al.,

2009). In addition to these signalling pathways, HCG synthesis may also be enhanced by other hormones and growth factors, such as gonadotrophin-releasing hormone (GnRH) (Islami et al., 2001; Siler-Khodr et al., 1986), leptin (Cameo et al., 2003; Chardonnens et al., 1999), activin (Petraglia et al., 1989), calcitriol (Barrera et al., 2008), cortisol (Wang et al., 2014c) and epidermal growth factor (EGF) (Morrish et al., 1987). On the other hand, progesterone (Szilagyi et al., 1993; Wilson et al., 1984) and inhibin (Petraglia et al., 1989) hinder the secretion of this hormone.

Progesterone

Progesterone is a steroid hormone crucial for gestational maintenance, so it is also called the 'hormone of pregnancy'. The name progesterone comes from the Latin *pro* and *gestare*, which means a substance that favours pregnancy. Corpus luteum is the main producer of progesterone during the first weeks of pregnancy, owing to HCG stimulation. After 6–8 weeks of gestation until the end of pregnancy, as HCG concentration declines, the placenta gradually becomes the main source of progesterone, owing to the formation of the syncytial layer (Tuckey, 2005). This steroid hormone is mainly synthesised from the maternal cholesterol, through a two-step reaction occurring in the syncytiotrophoblast mitochondria (**Figure 2**). In contrast to other steroidogenic organs, placenta does not express the steroidogenic acute regulatory protein, a protein that transfers cholesterol towards mitochondrial inner membrane, which is a critical and limiting step for progesterone synthesis (Sugawara et al., 1995). Instead, in the syncytiotrophoblast, metastatic lymph node 64 (MLN64) is responsible for intramitochondrial translocation of cholesterol. MLN64 is an endosome protein that shares the cholesterol-binding domain with steroidogenic acute regulatory protein (Watari et al., 1997). In the mitochondrial inner membrane, maternal cholesterol is a substrate for cholesterol side-chain cleavage cytochrome P450 (CYP450scc), which converts it into pregnenolone. This reaction requires electrons from the reduced form of nicotinamide adenine dinucleotide phosphate-(NADPH), which are transferred via the mitochondrial adrenodoxin and adrenodoxin reductase. Then, pregnenolone is metabolized into progesterone by the type 1 3beta-hydroxysteroid dehydrogenase/Δ^5-Δ^4-isomerase (3β-HSD), using NAD^+ as cofactor. It may also be the substrate for other enzymes, producing other steroids (Tuckey, 2005). Progesterone blood levels increase throughout pregnancy, peaking during the last 4 weeks of gestation and decreasing after labour and placental delivery (Csapo et al., 1971).

Progesterone exerts genomic and non-genomic actions, by activating different receptors. The classic nuclear progesterone receptors (NPR), PRα and PRβ, are ubiquitously expressed in female reproductive tract and placenta and dimerize after progesterone binding, mediating its genomic action by binding to specific DNA elements in the promotor of target genes. In addition, these receptors may also mediate cytoplasmic signalling pathways. The non-genomic actions are mediated by the membrane-associated progesterone receptors (MPR) and include MAPK activation, decrease of cAMP production and intracellular Ca^{2+} mobilization (Goldman and Shalev, 2007).

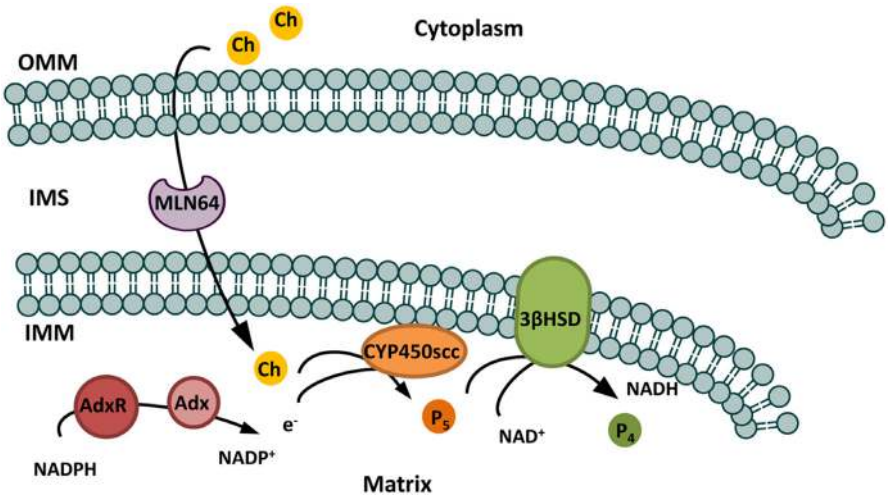

Figure 2 Biosynthesis of progesterone in the syncytiotrophoblast. Cholesterol from maternal circulation is transported from the outer mitochondrial membrane of the syncytiotrophoblast to the inner mitochondrial membrane by the transporter metastatic lymph node 64, through the intermembrane space. In the mitochondrial matrix, adrenodoxin reductase transfers electrons from the reduced form of nicotinamide adenine dinucleotide phosphate to the electron transfer protein adrenodoxin, which transfer these electrons to the enzyme cholesterol side-chain cleavage cytochrome P450 (CYP450scc). Then, CYP450scc converts cholesterol into pregnenolone, which is metabolized into progesterone by type 1 3beta-hydroxysteroid dehydrogenase/Δ_5-Δ_4-isomerase, using micotinamide adenine dinucleotide as cofactor. ADX = adrenodoxin; AdxR = adrenodoxin reductase; Ch = cholesterol; e^- = electrons; CYP450scc = cholesterol side-chain cleavage cytochrome P450; IMM = inner mitochondrial membrane; IMS = intermembrane space; MLN64 = metastatic lymph node 64; NAD^+ = nicotinamide adenine dinucleotide; NADPH = nicotinamide adenine dinucleotide phosphate (reduced form); OMM = outer mitochondrial membrane; P_4 = progesterone; P_5 = pregnenolone; ST = syncytiotrophoblast; 3β-HSD = 3beta-hydroxysteroid dehydrogenase/Δ_5-Δ_4-isomerase.

Progesterone acts in several events throughout the gestational period. Its main functions are exerted in the uterus. In fact, it stimulates in-vitro decidualization of human ESC, by increasing cAMP levels and activating PKA signalling pathway (Brar et al., 1997). This steroid also promotes embryo implantation in animal models, by blocking oestrogens proproliferative effect in uterine epithelial cells and inducing genes that promote uterine receptivity, e.g. *Hand2*, *forkhead box O1* (*FOXO1*), *HoxA-10*. Therefore, these genomic actions of progesterone enhance embryo attachment and implantation (Halasz and Szekeres-Bartho, 2013). For ethical reasons, implantation studies in human models are limited, so the role of progesterone in human implantation still needs further clarification.

In addition, progesterone participates in immunotolerance, as it enhances the expression of profertility Th2 cytokines by maternal type 2 T-helper lymphocytes and inhibits uNK cells activity. Indeed, in-vitro cultures of lymphocytes of women undergoing recurrent spontaneous abortion showed progesterone enhances the production of Th2 cytokine IL-4 and decreases Th1 cytokines INF-γ and TNF-α, promoting a shift from Th1 to Th2 bias (Raghupathy et al., 2005). Moreover, in human $CD4^+$ T cell lines, progesterone promotes the differentiation of human Th2 lymphocytes (Piccinni et al., 1995). In addition, progesterone decreases cytolytic activity of uNK and blocked perforin exocytosis, an effect mediated by progesterone-inducing binding factor (PIBF) (Laskarin et al., 2002).

Progesterone also inhibits myometrium contractility and promotes uterine quiescence throughout pregnancy. Indeed, this steroid inhibits spontaneous contractility of human myometrial tissues *in vitro* (Ruddock et al., 2008). It was reported that progesterone exerts this effect by activation of MPR, directly modulating intracellular cAMP and Ca^{2+} levels and the transactivation of nPRβ, which decreases the expression of genes encoding proteins involved in contraction (Karteris et al., 2006; Mesiano, 2007).

Moreover, in-vitro studies revealed progesterone inhibits endocrine function of human placenta, by reducing HCG (Szilagyi et al., 1993; Wilson et al., 1984), leptin (Coya et al., 2005) and resistin (Lappas et al., 2005b). Progesterone also hinders in-vitro trophoblast invasion, by decreasing MMP-2 and MMP-9 activities of ESC (Shimonovitz et al., 1998; Zhang et al., 2000) and EVT (Chen et al., 2011) and enhancing the expression of TIMP-3 during in-vitro decidualization of human ESC (Higuchi et al., 1995). Similarly, PIBF also impairs this process by repressing the expression and activity of MMP-2 and MMP-9 in human trophoblast cells. This effect possibly results from PIBF-downregulation of EGF and leptin, which are invasion-promoting molecules, and from prevention of STAT3 activation (Halasz et al., 2013; Miko et al., 2011). On the other hand, other evidence suggests that progesterone promotes EVT migration by genomic actions, caused by upregulation of insulin-like growth factor binding protein-1 and Dickkopf-related protein-1 (Halasz and Szekeres-Bartho, 2013).

In addition to placentation, progesterone also prepares the mammary gland for lactation by enhancing the proliferation of mammary epithelium, but also prevents lactation until labour, antagonizing the prolactin effect (Pang and Hartmann, 2007). Moreover, this steroid hormone participates in metabolic changes during pregnancy, promoting hyperphagia, fat storage and insulin resistance (Butte, 2000; Kalkhoff, 1982).

Progesterone synthesis by human placenta is controlled by several factors. In fact, PKA stimulates this steroid synthesis, by promoting cholesterol transport into the mitochondria, but not interfere with 3β-HSD activity (Gomez-Chang et al., 2014; Gomez-Concha et al., 2011). On the other hand, p38 and ERK 1/2 phosphorylation increase 3β-HSD transcripts (Costa et al., 2015). Other modulators of progesterone synthesis have been described: oestradiol (Shanker and Rao, 1997), insulin and insulin-like growth factor 1 (IGF-1) (Nestler, 1989), calcitriol (Barrera et al., 2007) stimulate the synthesis of this steroid, whereas leptin (Cameo et al., 2003) and corticotrophin-releasing hormone (CRH) (Gao et al., 2012; Yang et al., 2006) inhibit progesterone production by the syncytiotrophoblast.

Oestrogens

Placental oestrogens are a group of four different steroid hormones: oestrone (E_1), 17β-oestradiol (E_2), oestriol (E_3) and oestetrol (E_4). During the first weeks of gestation, the oestrogens are produced by corpus luteum but then, placenta undertakes the synthesis of these steroids. Blood levels of all oestrogens increase throughout pregnancy in maternal plasma, peaking at term. Oestradiol is the most abundant oestrogen (Loriaux et al., 1972).

The synthesis of placental oestrogens reflects the interdependence between mother, fetus and placenta (**Figure 3**). In fact, compared with other steroidogenic organs, placenta is devoid of 17alpha-hydroxylase/17, 20-lyase, so it is unable to convert pregnenolone and progesterone (C_{21}) into androgens (C_{19}). In this way, placenta uses the circulating androgen dehydroepiandrosterone sulphate provided by fetal and maternal adrenal glands, converting it into androstenedione and testosterone. In the syncytiotrophoblast, the enzyme CYP450 aromatase converts them into oestrone and oestradiol, respectively, using NADPH as cofactor. Moreover, the enzyme 17beta-hydroxysteroid dehydrogenase interconverts oestradiol and oestrone, and also androstenedione and testosterone (Levitz and Young, 1977).

Oestrogens play several roles during gestation, and their effects are classically mediated by the activation of nuclear oestrogens receptors, ERα and ERβ. Similarly to progesterone receptors, these receptors dimerize after ligand binding and modulate the expression of several genes. Oestrogens, however, may also activate membrane-associated oestrogens receptors, exerting nongenomic actions that include intracellular Ca^{2+} mobilization, activation of adenylyl cyclase and consequently increase of cAMP levels and MAPK activation (Bjornstrom and Sjoberg, 2005). In placenta, ERα expression is mainly confined to the cytotrophoblast (Bechi et al., 2006; Bukovsky et al., 2003) whereas ERβ is more expressed in the syncytiotrophoblast (Bechi et al., 2006).

Oestriol is a weak oestrogen and the most abundant oestrogen in urine. Apparently, its main function is to increase the uteroplacental blood flow (Resnik et al., 1974). Oestriol, however, may also induce the contraction of isolated human myometrial cells by increasing connexin-43 expression, which indicates this steroid increases gap junction communication in myometrium and a plausible role in labour initiation (Di et al., 2001). It is also synthesised in placenta

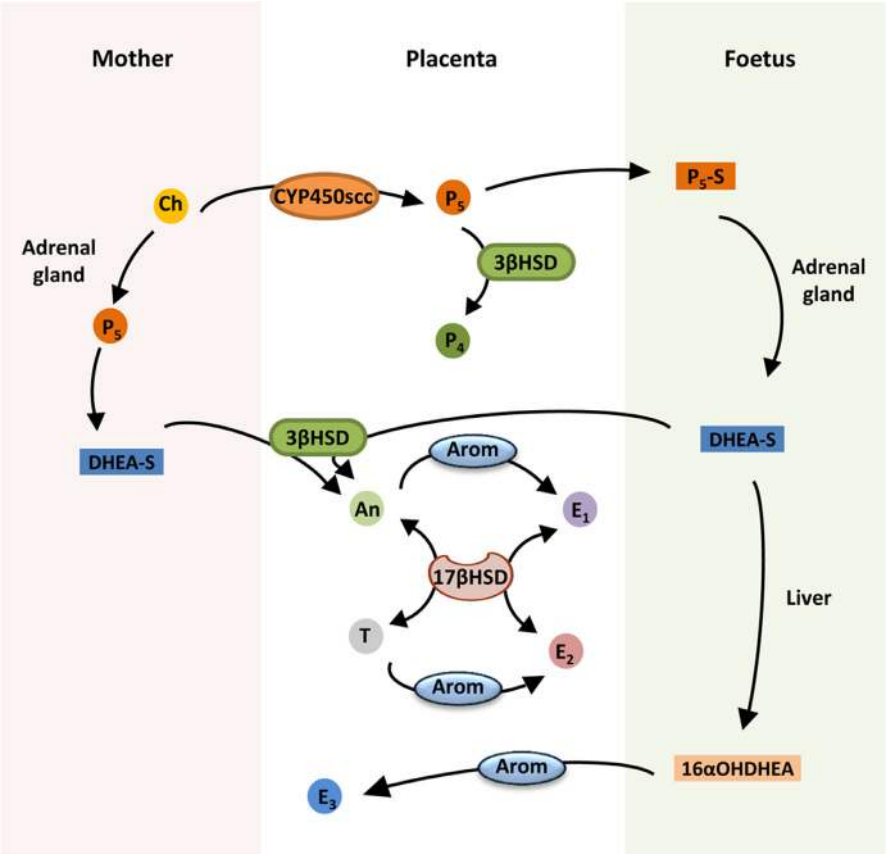

Figure 3 Steroidogenesis at the maternal–fetus interface. Maternal cholesterol is the substrate of cholesterol side-chain cleavage cytochrome P450, producing pregnenolone, which is converted into progesterone by type 1 3beta-hydroxysteroid dehydrogenase/Δ^5-Δ^4-isomerase. The placental biosynthesis of oestrogens uses the androgen dehydroepiandrosterone sulphate as precursor. This is provided by fetal and maternal adrenal glands and is metabolized into androstenedione by 3beta-hydroxysteroid dehydrogenase/Δ^5-Δ^4-isomerase. Androstenedione is then converted into oestrone by cholesterol side-chain cleavage cytochrome P450 aromatase. The enzyme 17beta-hydroxysteroid dehydrogenase interconverts oestrone and oestradiol and also androstenedione and testosterone. Testosterone may also be converted into oestradiol by aromatase. Oestriol is synthesised by aromatase from the precursor 16alpha-hydroxy- dehydroepiandrosterone sulphate, which has fetal origin. An = androstenedione; Arom = aromatase; CYP450scc = cholesterol side-chain cleavage cytochrome P450; DHEA-S = dehydroepiandrosterone sulphate; E_1 = oestrone; E_2 = oestradiol; E_3 = oestriol; P_4 = progesterone; P_5 = pregnenolone; P5-S = pregnenolone sulfate; T = testosterone; 3β-HSD = 3beta-hydroxysteroid dehydrogenase/Δ^5-Δ^4-isomerase; 16α-OHDHEA = 16alpha-hydroxy-DHEA-S; 17β-HSD = 17beta-hydroxysteroid dehydrogenase.

by aromatase from the 16α-hydroxy- dehydroepiandrosterone sulphate, which has fetal origin (Levitz and Young, 1977).

Oestetrol is a unique steroid in human pregnancy, which is exclusively produced by fetal liver. It is detectable from ninth week of gestation, but is biological function remains to be identified (Holinka et al., 2008).

Oestradiol is the most abundant oestrogen throughout pregnancy and different roles are attributed to this hormone. Indeed, this oestrogen promotes embryo implantation, as it stimulates endometrial growth and differentiation (Groothuis et al., 2007). In primary co-cultures of endometrial epithelial cells (EEC) and ESC, oestradiol enhances ESC-induced proliferation of EEC, and it is suggested that this effect is at least partially mediated through ESC-secreted IGF-1 (Pierro et al., 2001). In human endometrial explant cultures, oestrogen modulates the expression of several genes that participate in endometrial maturation and differentiation (Punyadeera et al., 2005).

Oestradiol also promotes angiogenesis and vasodilatation, which indicates a role in the regulation of human uteroplacental blood flow. Indeed, this steroid induces vasodilatation of uterine and placental arteries (Corcoran et al., 2014). Oestradiol also promotes angiogenesis, as it causes HUVEC proliferation by activating classical ERα, ERβ receptors, (Jobe et al., 2010). Another report supported this evidence, as it showed that oestradiol enhances the migration and proliferation of HUVEC by triggering oestrogen receptors, which activates RhoA–ROCK pathway and increases cell-cycle-related protein expression (Oviedo et al., 2011).

In addition, similarly to oestriol, oestradiol increases the contraction of human myometrial cells by promoting the formation of gap junctions, suggesting its involvement in labour initiation (Di et al., 2001). Moreover, in term myometrium explants, this steroid induces the expression of the gene encoding the pro-contraction protein oxytocin receptor by a mechanism that implies an ERα-dependent activation of ERK 1/2 signalling (Welsh et al., 2012).

The role of oestradiol in trophoblasts, however, remains unclear. Oestradiol enhances syncytialization of human primary cytotrophoblasts via ERα (Bukovsky et al., 2003; Cronier et al.,

1999). It also induces leptin expression in BeWo cells by triggering genomic and nongenomic actions involving a crosstalk between ERα and ERK 1/2 and phosphoinositide 3-kinase (PI3K)/AKT signal transduction pathways (Gambino et al., 2010). Furthermore, oestradiol inhibits resistin release by human placental explants (Lappas et al., 2005b).

In addition to these local functions, oestradiol also stimulates the proliferation of mammary epithelium, preparing the breast for breastfeeding (Pang and Hartmann, 2007). Oestrogen is also involved in the metabolic alterations of pregnancy, inhibiting lipolysis and promoting hyperlipidaemia and fat storage (Butte, 2000).

The biosynthesis of oestrogens is regulated by different mechanisms, including substrate availability and the expression or activity of enzymes involved in their synthesis. In fact, aromatase is enhanced by cAMP (Lobo and Bellino, 1989), cortisol, HCG (Wang et al., 2014c), oestradiol (Kumar et al., 2009), p38 phosphorylation and ERK 1/2 inhibition (Costa et al., 2015). Moreover, oestradiol synthesis is stimulated by calcitriol (Barrera et al., 2007), CRH (Gao et al., 2012) and diminished by insulin (Hochberg et al., 1983) and leptin (Coya et al., 2006).

Placental lactogen

The human placental lactogen (HPL), also known as human chorionic somatomammotropin, is a polypeptide hormone encoded by a cluster of five genes localized on chromosome 17. These genes encode pituitary growth hormone, placental growth hormone (HPGH) and the other three encode placental lactogen (*HPL-A*, *HPL-B*, *HPL-L*). The genes *HPL-A* and *HPL-B* encode identical mature proteins that contribute to HPL serum levels, whereas the product protein of HPL-L has not been detected in maternal blood (Handwerger and Freemark, 2000). This hormone is mainly biosynthesised by the syncytiotrophoblast but EVT can also produce HPL (Kliman et al., 1986; Tarrade et al., 2001a). From the second week of gestation HPL is detected in the placenta; after the third to the sixth week it is mainly released into maternal circulation, though it is also present in fetal circulation. Until the end of pregnancy HPL serum levels increase greatly, disappearing after placental delivery (Handwerger and Freemark, 2000). In fact, HPL production seems to mirror the increase in placental mass, specifically the syncytiotrophoblast mass (Sciarra et al., 1968).

The HPL acts by binding to the membrane-bound receptor of pituitary growth hormone, the growth hormone receptor, though with lower affinity than its main ligands. In addition, HPL has also affinity for prolactin receptor (Handwerger and Freemark, 2000; Lowman et al., 1991).

The main HPL functions are the regulation of maternal lipid and carbohydrate metabolism, being important for mother and fetus energy homeostasis. Indeed, HPL promotes lipolysis of human adipose tissue *in-vitro*, increasing the circulating free fatty acids. These can be used as energy source by producing ketone bodies, which act as fuel for the fetus (Handwerger and Freemark, 2000; Williams and Coltart, 1978). This evidence has led to the hypothesis that HPL is responsible for the insulin resistance emerging in mid to late pregnancy, although this hypothesis still remains to be deciphered (Freemark, 2006). On the other hand, HPL promotes the increase of primary human pancreatic islets function and enhances insulin secretion (Brelje et al., 1993). In these cells, HPL-A inhibits apoptosis through the phosphorylation of PI3K/AKT and p38 pathways (Lombardo et al., 2011). In addition, this hormone also enhances the intracellular expression of pancreatic and duodenal homeobox 1 (PDX-1), a factor that activates insulin transcription, suggesting HPL-A improves islets functionality (Lombardo et al., 2011). Therefore, HPL effects may contribute to postprandial hyperglycaemia and hyperinsulinaemia in the mother during mid to late pregnancy (Handwerger and Freemark, 2000). In in-vitro studies with human fetal cells, HPL also promotes growth and synthesis of IGF-1 in hepatocytes (Strain et al., 1987), myoblasts and fibroblasts (Hill et al., 1985), and stimulates insulin and IGF-1 production by pancreatic tissues (Swenne et al., 1987). Nevertheless, the autocrine–paracrine role of HPL in human trophoblast is still poorly understood, although it was reported that it inhibits leptin production by primary human syncytiotrophoblast (Coya et al., 2005).

The secretion of HPL is regulated by several molecules. In fact, cAMP (Harman et al., 1987), growth hormone-releasing factor (Hochberg et al., 1988), insulin (Hochberg et al., 1983), EGF (Morrish et al., 1987), PPAR-γ /retinoid X receptor alpha (RXR-α) activation (Tarrade et al., 2001b), apolipoproteins (Handwerger et al., 1987), calcitriol, interleukins IL-1 and IL-6 (Handwerger and Freemark, 2000) enhance HPL secretion by placenta.

Placental growth hormone

A polypeptide hormone that shares high homology with HPL is the HPGH, and is encoded by the same gene cluster (Handwerger and Freemark, 2000). It is encoded by *GH-V* gene, from which results two different size transcripts. The minor, *GH-V2*, is translated into an integral membrane protein. The major, *GH-V*, is translated into a secreted protein (HPGH), which differs from the pituitary growth hormone by 13 amino acids. This hormone is mainly synthesised by the syncytiotrophoblast in a non-pulsatile way, but EVT are also able to produce it (Alsat et al., 1998; Lacroix et al., 2005). In maternal serum, HPGH is detected at 15–20 weeks' gestation, and its levels highly increase during the third trimester. Therefore, HPGH becomes the principal growth hormone, as the maternal levels of hypophysary growth hormone decrease at this stage. Compared with HPL, however, HPGH secretion and serum levels are lower and it is not released into fetal circulation (Alsat et al., 1998).

HPGH activates growth hormone receptor and has also affinity for prolactin receptor. In this way, HPGH shares growth hormone receptor with HPL, although the latter has lower affinity for the receptor (Alsat et al., 1998; Lowman et al., 1991).

During gestation, HPGH assumes several growth hormone functions, including the enhancement of maternal IGF-1 synthesis (Caufriez et al., 1993). Similarly to HPL, HPGH is important for metabolic regulation, as it induces insulin resistance. In fact, this hormone promotes gluconeogenesis, lipolysis and anabolism, increasing the nutrient availability for fetal nourishment (Alsat et al., 1998). In addition, growth hormone receptors are also expressed in human placenta (Frankenne et al., 1992), and HPGH plays an autocrine role in this organ by stimulating the in-vitro invasion of primary

human EVT through the activation of Janus kinase 2/signal transducers and activators of transcription (JAK-STAT) pathway (Lacroix et al., 2005).

The production of HPGH is regulated by different factors, as it is enhanced by cAMP (Alsat et al., 1998), hypoglycaemia (Bjorklund et al., 1998), PPAR-γ /RXR-α activation (Tarrade et al., 2001b) and visfatin and decreased by leptin, insulin and cortisol (Zeck et al., 2008).

Leptin

Leptin was the first adipocyte-derived signalling protein (adipokine) identified. It is a peptide hormone, product of *Ob* gene and was identified for the first time in mice adipocytes (Zhang et al., 1994). Leptin is mainly secreted by adipocytes into circulation, has important roles in regulation of body weight, appetite and energy homeostasis and its plasma levels are proportional to body fat. Moreover, this adipokine is expressed in several other tissues and organs and plays different functions, including in angiogenesis, immune function, bone metabolism and reproductive events (Park and Ahima, 2015). During pregnancy, the human placenta synthesises large amounts of leptin, which is released into maternal and fetal circulation and amniotic fluid (Henson et al., 1998; Schubring et al., 1997). The main source of leptin is the syncytiotrophoblast (Henson et al., 1998; Senaris et al., 1997), but EVT are also able to secrete this adipokine (Castellucci et al., 2000). Furthermore, its placental synthesis is higher in early pregnancy than at term (Henson et al., 1998; Yura et al., 1998). Leptin serum levels are increased in pregnant women. In fact, leptin levels increase during the gestation, peak in late second or early third trimester, and then remain stable until labour (Sivan et al., 1998; Stock et al., 1999).

Leptin exerts its effects by binding to leptin receptor (LepR). This receptor is a single transmembrane glycoprotein that belongs to the class I cytokine receptor family and is ubiquitously expressed in human tissues. Six isoforms of LepR resulting from alternative splicing were already identified (LepRa-LepRf) (Peelman et al., 2014). LepRb or LepR long form seems to be the isoform that mediates most leptin effects, activating JAK-STAT, ERK1/2 and PI3K pathways. The other isoforms, however, may also mediate some leptin effects, depending on the tissues where they are expressed (Allison and Myers, 2014; Peelman et al., 2014).

In early and term human placentas, LepRb is expressed in the syncytiotrophoblast, although other isoforms of this receptor are also detected in this tissue. Moreover, leptin receptors are also expressed in other trophoblast phenotypes (Castellucci et al., 2000; Challier et al., 2003). In this way, placental leptin may act locally, modulating several reproductive events. In fact, leptin has pleotropic effects in trophoblasts, as it modulates the endocrine function of primary human syncytiotrophoblasts by enhancing HCG secretion (Cameo et al., 2003; Chardonnens et al., 1999) and inhibiting progesterone (Cameo et al., 2003), oestradiol (Coya et al., 2006) and HPGH (Zeck et al., 2008) production. Leptin also stimulates in-vitro proliferation of cytotrophoblast cells, by promoting cell-cycle progression to G2/S phase and by upregulating cyclin D1 expression (Magarinos et al., 2007). It also prevents the apoptosis of first-trimester Swan-71 cells and placental explants, by increasing Bcl2–Bax ratio and downregulating p53 and by inhibiting caspase-3 activation and preventing Poly [ADP-ribose] polymerase-1 cleavage (Toro et al., 2014). In-vitro experiments demonstrated this adipokine also induces the expression of metalloproteinases involved in trophoblast invasion in primary human trophoblasts (MMP-2, MMP-9 and MMP-14) (Castellucci et al., 2000; Wang et al., 2014a). In the EVT cell line HTR-8/SVneo, MMP-14 is upregulated via a mechanism involving a crosstalk between Notch1 and PI3K/AKT signalling pathways (Wang et al., 2014a). In addition, leptin increases nitric oxide levels (White et al., 2006) and enhances the production of pro-inflammatory cytokines and prostaglandins in human placental explants through the activation of NF-κB, PPAR-γ and ERK 1/2 pathways (Lappas et al., 2005a), suggesting a pro-inflammatory role of this adipokine.

In addition to its functions in placentation, leptin is important for pre-implantation, implantation and embryo development in animal models (Perez-Perez et al., 2015). Corroborating the above evidence, leptin expression is decreased in endometrial biopsies of women with recurrent implantation failure (Dos Santos et al., 2012).

Leptin promotes angiogenesis, as it enhances HUVEC proliferation through the activation of LepR and of ERK 1/2 signalling pathways and promotes capillary-like tube formation in an in-vitro angiogenesis assay (Bouloumie et al., 1998). In addition, this adipokine decreases VEGF production human cytotrophoblasts (Islami et al., 2003).

Leptin also seems to intervene in immunomodulation (Perez-Perez et al., 2015). In fact, it stimulates human leukocyte antigen G expression on trophoblast cell model Swan-71 cells, through the activation of ERK and PI3K pathways (Barrientos et al., 2015). Leptin also has a slight inhibitory effect on in-vitro contraction of human pregnant myometrial tissues (Mumtaz et al., 2015).

After second-trimester, pregnancy is generally a physiology state of leptin resistance. In this way, in spite of the high leptin levels, there is a loss of satiety sensation, leading to hyperphagia, gain of weight and hyperinsulinaemia. This resistance is required for the nutrient supply to the fetus, to prepare the body for metabolic demands of lactation and seems to be caused by other gestational hormones, like progesterone, oestrogens or HPL (Ladyman et al., 2010). Central leptin resistance in pregnancy may also result from the increased levels of circulating leptin and soluble isoform of LepR, as it was proposed that leptin is unable to dissociate from this receptor, decreasing the levels of free leptin available to trigger the membrane-bound LepR and exert its effects (Tessier et al., 2013). In addition, leptin promotes lipid catabolism in human placental explants and decreases cholesterol and triglyceride levels (White et al., 2006).

The secretion of leptin is regulated by other pregnancy hormones. Indeed, HCG (Ge et al., 2011), insulin (Perez-Perez et al., 2013) and oestradiol (Gambino et al., 2010) enhance leptin secretion, whereas HPL and progesterone (Coya et al., 2005) inhibit it. Moreover, cAMP (Maymo et al., 2010), PKA, PKC (Yura et al., 1998), Epac/cAMP (Maymo et al., 2012), p38 (Ge et al., 2011) and ERK1/2 pathways (Maymo et al., 2010) and RXR-α receptors (Guibourdenche et al., 2000) also promote leptin expression. On the other hand, hypoxia diminishes leptin synthesis (Nusken et al., 2015).

Adiponectin

Adiponectin is another important adipokine for placentation and gestational outcome. It is a member of complement 1q family encoded by *ADIPOQ* gene, exclusively produced in white adipose tissue, and it is secreted into the circulation in three forms: trimers, hexamers and high molecular weight multimers. Moreover, it exists as a full length or a globular truncated form. Adiponectin promotes insulin sensitivity, has anti-inflammatory and anti-atherogenic properties and its levels negatively correlate with body fat (Kadowaki and Yamauchi, 2005; Liu and Liu, 2014). Previous studies have shown that human placenta produces adiponectin (Caminos et al., 2005; Chen et al., 2006), but more recent reports do not confirm these findings (Haghiac et al., 2014; McDonald and Wolfe, 2009). Moreover, no significant differences are found in the adiponectin levels between pregnant and non-pregnant women, although inconsistences are found in the adiponectin levels throughout gestation. Indeed, some studies have shown that its serum levels decline in the second half of gestation (Cortelazzi et al., 2007; Fuglsang et al., 2006), whereas another report indicated that no alterations occur throughout pregnancy (Mazaki-Tovi et al., 2007).

Adiponectin effects are mediated by the activation of its receptor, AdipoR1 and AdipoR2, seven-domain transmembrane proteins that are expressed in several organs and tissues. Their activation triggers AMP-activated protein kinase (AMPK) and PPARs and decreases ceramide levels (Yamauchi et al., 2014). In human placenta, AdipoR1 and AdipoR2 were detected in all trophoblast phenotypes (Benaitreau et al., 2010a; McDonald and Wolfe, 2009) and adiponectin is a regulator of human trophoblast biology. Indeed, it diminishes the endocrine function of term syncytiotrophoblast, as it decreases HCG, progesterone and HPL secretion (McDonald and Wolfe, 2009). On the other hand, it enhances in-vitro syncytialization of primary cultures of first trimester cytotrophoblast via AdipoR1 and AdipoR2 and a subsequent PKA activation (Benaitreau et al., 2010b), and has antiproliferative effects on trophoblastic cell lines BeWo and JEG-3 (Benaitreau et al., 2009). Moreover, adiponectin stimulates the migration and invasion of first trimester EVT, by upregulation of MMP-2 and MMP-9 and downregulation of TIMP-2 (Benaitreau et al., 2010a). This adipokine also inhibits insulin placental signalling, function and insulin-stimulated amino acid transport in in-vitro cytotrophoblasts cell cultures, through the activation of PPAR-α and ceramide synthesis (Aye et al., 2014; Jones et al., 2010). In spite of its anti-inflammatory action in other systems, adiponectin has a pro-inflammatory role in placenta, as it enhances the production of pro-inflammatory cytokines and prostaglandins in human placental explants, by activating NF-κB, PPAR-γ and ERK 1/2 pathways (Lappas et al., 2005a). It also increases the expression of the pro-inflammatory proteins CD24 and Siglec10, although these molecules may also be involved in downregulation of maternal immune response, promoting maternal immunotolerance to the foetus (McDonald and Wolfe, 2011). Adiponectin may also modulate angiogenesis, as it stimulates differentiation, proliferation and migration of human microvascular endothelial cells (HMEC-1), as well as VEGF expression (Adya et al., 2012). Additionally, this adipokine also promotes HUVEC migration and differentiation into tube-like structures by triggering AMPK pathway, which in turn enhances endogenous nitric oxide synthase and PI3K/AKT pathway (Ouchi et al., 2004). Another report, however, shows that this adipokine induces apoptosis in these cells, by the activation of a cascade of caspases-8, -9, and -3 (Brakenhielm et al., 2004). Therefore, further studies in placenta microvasculature are required to understand the function of adiponectin in placental angiogenesis.

As information is conflicting about adiponectin production by human placenta, data about the regulation of its placental synthesis is scarce. Chen et al. (2006) reported that adiponectin produced by placental explants is regulated by leptin, TNF-α and IL-6.

Resistin

Resistin is a cysteine-rich polypeptide that was first identified in mouse white adipocytes. In contrast to mice, in humans, resistin is mainly expressed by macrophages, circulates as trimeric and oligomeric isoforms and there is no clear evidence about a link among resistin, obesity and insulin resistance. Therefore, the main function of resistin in humans seems to be the modulation of inflammation, as it stimulates the expression of pro-inflammatory cytokines (Park and Ahima, 2013). Recently, a decorin isoform and the adenylyl cyclase-associated protein 1 were identified as resistin receptors in adipose stromal cells and monocytes, respectively (Daquinag et al., 2011; Lee et al., 2014). The molecular targets of this adipokine in human placenta, however, still remain to be identified.

During pregnancy, resistin is produced by placenta, mainly in the syncytiotrophoblast and EVT, and its levels are higher in term placentas than in the first-trimester chorionic villi (Yura et al., 2003). Resistin serum levels are increased during pregnancy but some studies indicate its levels increase in the third trimester (Nien et al., 2007; Palik et al., 2007), whereas others claim it decreases throughout gestation (Cortelazzi et al., 2007). During gestation, resistin increases MMP-2 and decreases TIMP-1 and TIMP-2 in BeWo cells, promoting cell invasion (Di Simone et al., 2006). Moreover, resistin stimulates the expression of glucose transporter 1 through the activation of ERK 1/2 pathway, increasing placental glucose uptake (Di Simone et al., 2009). Nevertheless, further research in primary trophoblast is required to confirm these resistin effects in human placentation. This adipokine also stimulates angiogenesis, as it enhances the formation of endothelial cell tube and VEGF production by HUVEC (Di Simone et al., 2006). Furthermore, resistin stimulates the proliferation and migration of human coronary artery endothelial cells, by triggering p38 and ERK 1/2 signalling pathways, and also upregulates some angiogenesis-related factors, including VEGFR-2, VEGFR-1, MMP-1 and MMP-2 (Mu et al., 2006).

Little information is available about the regulation of resistin synthesis by placenta but its secretion is inhibited by oestradiol and progesterone (Lappas et al., 2005b).

Other adipokines

In addition to leptin, adiponectin and resistin, other adipocyte-derived proteins are produced by human placenta, and they

may also contribute to the development and maintenance of this organ and to gestational outcome. Nevertheless, the information about these adipokines in pregnancy events is still scarce and further studies focusing on their effects in placental development are required.

Visfatin is a newly identified adipokine, which was originally isolated from human peripheral blood lymphocytes and named pre-B-cell colony-enhancing factor (Samal et al., 1994). Later, this adipokine was identified as a nicotinamide phosphoribosyltranferase, an enzyme involved in nicotinamide adenine dinucleotide biosynthesis (Rongvaux et al., 2002). Visfatin is mainly secreted by visceral and omental adipose tissue and is an insulinomimetic peptide, as it binds to insulin receptor, triggering downstream phosphorylation events, promoting glucose transport (Katwa and Seidel, 2009). Visfatin is expressed in human placenta, especially in the syncytiotrophoblast and fetal capillary endothelium (Morgan et al., 2008). Serum levels of this adipokine are increased during pregnancy (Fasshauer et al., 2007; Mastorakos et al., 2007). Notwithstanding, the role of visfatin in placentation and other pregnancy-related events is still poorly elucidated. In fact, it was reported visfatin increases in-vitro secretion of HPGH by primary human syncytiotrophoblasts (Zeck et al., 2008). Also, visfatin inhibits in-vitro contractility of human myometrium tissues (Mumtaz et al., 2015) and contributes to VEGF-mediated increase of human placental amnion's permeability by inducing VEGFR2 upregulation, indicating a role in the control of amniotic fluid volume throughout gestation (Astern et al., 2013). Moreover, visfatin also stimulates the release of prolabour mediators. Indeed, it increases cyclooxygenase 2 (COX-2) expression in human placental explants and the secretion of prostaglandins E_2 and F2α (PGE2, PGF2α), IL-6 and IL-8, by inducing the degradation of the NF-κB inhibitor IκB-α, increasing consequently NF-κB activity (Lappas, 2012).

Fibroblast growth factor 21 (FGF21) is a metabolic regulator and a plausible target for treatment of metabolic diseases. It is primarily synthesised by the liver but also expressed by adipose tissue, thymus and pancreas (Nishimura et al., 2000). It regulates lipid and carbohydrate metabolism by enhancing insulin sensitivity, decreasing triglyceride levels, increasing energy expenditure and causing weight loss. These effects are mediated by the activation of membrane-bound FGF receptors 1-4 (FGFR1-4). Moreover, high blood concentrations of FGF21 are registered in humans diagnosed with type 2 diabetes (Li et al., 2013). Recently, the presence of FGF21 mRNA and protein was demonstrated in human placenta, namely in the syncytiotrophoblast, endothelial cells and stromal cells (Dekker Nitert et al., 2014). Also, FGFRs 1-4 are expressed by this organ throughout gestation (Anteby et al., 2005), which suggests a role for FGF21 during placentation and in placental metabolism. The effects of FGF21 in these processes, however, have not yet been documented. In fact, it was only recently reported that FGF21 expression is increased in gestational diabetes mellitus (GDM) placentas (Dekker Nitert et al., 2014) and the secretion of this adipokine by GDM placental explants is lower compared with controls (Tan et al., 2013), indicating an altered FGF21-mediated signalling in this pregnancy-related disease. In addition, no information is available about the profile of FGF21 blood levels throughout gestation.

Pregnancy-associated plasma protein A

Pregnancy-associated plasma protein A (PAPP-A), also known as pappalysin-1, is a metalloproteinase belonging to metzincin superfamily, more precisely to pappalysin family, which was identified for the first time in plasma from pregnant women (Lin et al., 1974). It specifically cleaves the insulin-like growth factor binding protein 4 (IGFBP-4) (Lawrence et al., 1999), but IGFBP-2 and IGFBP-5 are also described as substrates for this metalloproteinase (Kumar et al., 2005; Laursen et al., 2001). Moreover, PAPP-A can cleave itself and the resultant autocleaved form is inactive (Boldt et al., 2001). It is secreted as a disulphide-bound homodimer and circulates as a covalent heterotetrameric 2:2 complex with the preform of eosinophil major basic protein (proMBP), which functions as a physiological inhibitor of PAPP-A (Overgaard et al., 2000; Oxvig et al., 1993).

Pregnancy-associated plasma protein A is mainly synthesised by the syncytiotrophoblast and EVT, although its expression has also been reported in cytotrophoblasts (Guibourdenche et al., 2003; Handschuh et al., 2006). According to Bonno et al. (1994) proMBP, is synthesised by EVT. During pregnancy, PAPP-A levels increase with gestational age and decrease after delivery (Leguy et al., 2014; Sutcliffe et al., 1982).

The role of PAPP-A during pregnancy is still poorly understood. Because of its protease activity, PAPP-A decreases IGFBP-4 affinity for IGF-1 and 2. As IGFBP-4 antagonizes the action of IGF action by preventing its interaction with IGF receptor, PAPP-A enhances the activation of this receptor, promoting IGF-regulated processes, including glucose metabolism, cell proliferation, differentiation, invasion and survival (Oxvig, 2015). Recently, it was shown that IGFBP-4 and IGFBP-5 inhibit IGFs-induced in-vitro migration of a cellular model of EVT, suggesting a role for PAPP-A in the regulation of EVT migration (Crosley et al., 2014). Corroborating this evidence, PPAR-γ activation in primary cultures of human EVT inhibits cell invasion and PAPP-A expression, suggesting that reduced PAPP-A levels may decrease bioactive IGF-2, a factor that promotes trophoblast invasion (Handschuh et al., 2006). PAPP-A also enhances in-vitro proliferation of the trophoblastic cells JAR, as well as their adhesion to uterine epithelial cell lines, indicating a role in embryo implantation (Wang et al., 2014b). Further studies in primary trophoblasts, however, are required to clarify PAPP-A function in these invasive and proliferative events.

Little information is available about the factors that regulate placental expression of PAPP-A. Progesterone increases the expression of this metalloproteinase (Wang et al., 2014b), whereas PPAR-γ activation inhibits PAPP-A expression by EVT but not by the syncytiotrophoblast (Handschuh et al., 2006). In addition, p38 and ERK 1/2 pathways increase *PAPP-A* mRNA levels (Costa et al., 2015).

It is worth mentioning that, besides placenta, PAPP-A is ubiquitously expressed in other cell types, including fibroblasts, osteoblasts, endothelial cells or smooth-muscle cells, suggesting that this metalloproteinase has a function outside of pregnancy (Conover, 2012). In addition, recently, PAPP-A2 (another pappalysin) was identified in human placenta, namely in the syncytiotrophoblast and EVT (Wang et al., 2009; Winn et al., 2009). This metalloproteinase circulates as a monomer and cleaves IGFBP-5, increasing the IGF bioavailability during gestation (Overgaard et al., 2001; Yan

et al., 2010). Nevertheless, the biological effects of PAPP-A2 in placentation are still unexplored.

Placental protein 13

Placental protein 13 (PP13) or galectin-13 is a member of galectin superfamily encoded by the gene *LGALS13*, which was identified in human placental tissues. PP13 is a homodimer constituted by two subunits linked by disulphide bonds and has the capacity of binding to β-galactoside residues of several cellular proteins and extracellular matrix (Bohn et al., 1983; Than et al., 2004). It is predominantly synthesized by the syncytiotrophoblast and released into the circulation, but fetal vessel endothelium also expresses this protein (Sekizawa et al., 2009; Than et al., 2004). PP13 levels slowly increase during gestational course, particularly during the third trimester, decreasing after labour (Burger et al., 2004; Huppertz et al., 2008).

The role of PP13 during pregnancy is not fully elucidated. It is suggested that this galectin participates in immunotolerance, as PP13 seems to induce apoptosis of immune cells (Than et al., 2014a). In early pregnancy, immunohistochemistry studies of human placentas of the first trimester revealed that PP13 forms aggregates around decidual veins and induces the formation of decidual zones of necrosis (ZONEs) (Kliman et al., 2012). These ZONEs contain activated T-cells, neutrophils and macrophages, and it was hypothesised that they divert the maternal immune cells away from spiral artery, allowing the trophoblast invasion and vessel remodelling (Kliman et al., 2012). Furthermore, PP13 also enhances the secretion of IL-1a and IL-6 by human peripheral blood lymphocytes, suggesting a pro-inflammatory action (Kliman et al., 2012). PP13 purified from normal human placentas induces calcium depolarization of human cytotrophoblasts, leading to a release of linoleic and arachidonic acids and a subsequent increase of prostacyclin and thromboxane levels (Burger et al., 2004). Nevertheless, these effects were negligible if PP13 was purified from pathological placentas (Burger et al., 2004), suggesting a defective PP13-mediated signalling in these placentas. It was postulated that this effect may result from the intrinsic mild phospholipase-A activity of PP13 (Than et al., 1999). Moreover, because of PP13-induced increase of vasoactive prostaglandins levels, it has been suggested that this protein may regulate blood pressure of utero–placental vasculature (Huppertz et al., 2013). The vasodilator effect of PP13 was demonstrated in rodents, where PP13 also promotes angiogenesis (Gizurarson et al., 2013; Sammar et al., 2014).

The regulation of placental PP13 secretion is still unexplored. Indeed, it was only reported that its release is enhanced by calcium influx and ischaemia (Balogh et al., 2011; Burger et al., 2004). Moreover, p38 phosphorylation also enhances *LGALS13* transcription (Costa et al., 2015). As PP13 expression increases with syncytialization, cAMP and PKA pathways, enhancers of this process, also stimulate the expression of this galectin (Orendi et al., 2010; Than et al., 2014b).

Inhibins and activins

Inhibins and activins are disulphide-linked dimeric glycoproteins belonging to transforming growth factor beta (TGF-β) superfamily and are functional antagonists. Inhibins were firstly identified in bovine and porcine follicular fluid as a suppressive agent of secretion of FSH by hypophysis (Ling et al., 1985; Robertson et al., 1985). Subsequently, activins were characterized in porcine follicular fluid (Ling et al., 1986; Vale et al., 1986). Inhibins are heterodimers composed by an α and a β subunit, whereas activins are homo or heterodimers of inhibin β subunits. In humans, one α subunit and four β subunit isoforms (β_A, β_B, β_C, β_E) were identified, but the dimers constituted by β_C and β_E are still poorly studied. There are two best characterized inhibins, inhibin A ($\alpha\beta_A$) and inhibin B ($\alpha\beta_B$) and three activins, activin A ($\beta_A\beta_A$), activin B ($\beta_B\beta_B$) and activin AB ($\beta_A\beta_B$). Each subunit is synthesized as a precursors and the prodomains of α and β subunits enable the folding and dimerization of mature domains (de Kretser et al., 2002; Walton et al., 2012). In addition to these dimeric hormones, another FSH-modulating protein was identified. In fact, follistatin is a single-chain glycoprotein that suppresses FSH release by hindering activin capacity to activate its receptor, neutralizing its effect (Robertson et al., 1987; Ueno et al., 1987).

Inhibins, activins and follistatin are expressed in several organs and tissues, including reproductive organs, brain, pancreas and placenta, and participate in cell proliferation, differentiation, apoptosis, steroidogenesis, folliculogenesis and immunomodulation (Tsuchida et al., 2009; Xia and Schneyer, 2009). Inhibins A and B, activin A and follistatin are expressed in human placenta, mainly the syncytiotrophoblast, although cytotrophoblasts also express these hormones. Concerning activins B and AB, conflicting studies about their expression in placenta were reported (McCluggage et al., 1998; Petraglia, 1997). The β_c and β_E subunits were also identified in this organ (Gingelmaier et al., 2011; Weissenbacher et al., 2010).

Inhibin A and B, activin A and follistatin serum levels increase throughout gestation, whereas activin AB is undetectable during this period (Fowler et al., 1998; O'Connor et al., 1999).

Activin effects are mediated by the activation of activin receptors, ActRIIA, ActRIIB, which are type II transmembrane serine/threonine kinase receptors. After activin binding, these receptors phosphorylate type I receptors, the activin receptor-like kinase ALK4, ALK5 and ALK7, forming a ternary receptor complex. The activated type I receptor phosphorylates and activates the second messengers Smad-2 and Smad-3, which enters the nucleus and modulates the transcription of different genes. Moreover, activation of activin receptors may trigger other signalling pathways, including MAPKs or AKT/PI3K or Wnt/β-catenin pathways (Tsuchida et al., 2009; Walton et al., 2012). Type I and type II activin receptors are expressed in human placenta, predominantly in the syncytiotrophoblast (Schneider-Kolsky et al., 2002; Shinozaki et al., 1995). By acting on its receptors, activin plays several roles in pregnancy. In fact, this hormone promotes in-vitro syncytialization of isolated human cytotrophoblasts (Gerbaud et al., 2011; Song et al., 1996) and enhances endocrine function of these cells, by increasing HCG, inhibin A (Song et al., 1996), progesterone and GnRH secretion (Petraglia et al., 1989; Steele et al., 1993), as well as aromatase activity (Song et al., 1996). Furthermore, activins stimulate the differentiation of human cytotrophoblasts into EVT, by promoting trophoblast outgrowing and MMP-2 and MMP-9 expression (Caniggia et al., 1997; Jones et al., 2006) and also by *N*-cadherin up-regulation

through Smad 2/3 phosphorylation (Li et al., 2014). In addition, in primary EVT and HTR8/SVneo cells, a recent report described that activin A stimulates the expression of MMP-2 and of SNAIL and SLUG, which are downstream transcription factors of ALKs (Li et al., 2015). This study also showed activin A promotes trophoblast invasion by triggering ALK4, in a Smad 2/3-Smad4-dependent way, inducing SNAIL-mediated upregulation of MMP-2 (Li et al., 2015). Besides, activin A stimulates the production of proMMPs-2, -3, -7, -9 and active MMP-2 by human ESC and EEC and also promotes in-vitro decidualization of human endometrium by up-regulating these metalloproteinases (Jones et al., 2002, 2006), promoting endometrial receptivity. On the other hand, inhibin and follistatin hinder the aforementioned activin-mediated effects.

The placental secretion of activins and inhibins is regulated by different mediators. Indeed, HCG, EGF (Qu and Thomas, 1993b), prostaglandins (Qu and Thomas, 1993a), GnRH (Keelan et al., 1994; Li et al., 1994), cAMP (Li et al., 1994), dexamethasone (Keelan et al., 1994), transcription factor AP-2 (Debieve et al., 2011) enhance inhibin secretion whereas activin A (Qu and Thomas, 1993b) and hypoxia (Manuelpillai et al., 2003) decrease inhibin production. Regarding activin, its secretion is enhanced by CRH, endothelin 1 (Reis et al., 2002), pro-inflammatory cytokines (Mohan et al., 2001) and oxidative stress (Mandang et al., 2007) and diminished by hypoxia (Manuelpillai et al., 2003).

Kisspeptin

Kisspeptins are a family of neuropeptides encoded by *Kiss1* gene. *Kiss1* was identified for the first time as a metastasis-suppressor gene in human melanoma (Lee et al., 1996), and later kisspeptin was characterized and called metastin (Kotani et al., 2001; Ohtaki et al., 2001). The product of *Kiss1* is a 145-amino acid peptide (Kp-145), which undergoes a post-translational cleavage into four shorter bioactive peptides of the carboxyl terminus region, containing 54 (Kp-54), 14 (Kp-14), 13 (Kp-13) or 10 (Kp-10) amino acids. The latter corresponds to a decapeptide shared by all kisspeptins, which is crucial for their biological effects (d'Anglemont de Tassigny and Colledge, 2010; Kotani et al., 2001). Kisspeptins are produced by kisspeptin neurones in the hypothalamus, and their main function is to stimulate the release of GnRH by GnRH neurones. In this way, these neuropeptides lead to an increase in LH and FSH, mediate sex steroid hormones positive and negative feedback and may also link energy, metabolic status and reproduction, having an important role in pubertal development and fertility (Skorupskaite et al., 2014). Kisspeptin effects are mediated by the G protein-coupled receptor GPR54, also known as Kiss1 receptor (Kiss1R). Kiss1R is coupled to Gq/11 subunits and activates phospholipase C, increasing IP3 and diacylglycerol intracellular levels, which leads to Ca^{2+} mobilization and PKC and ERK 1/2 activation (d'Anglemont de Tassigny and Colledge, 2010).

Besides the hypothalamic neuronons, kisspeptins and Kiss1R are also detected in other organs and tissues, including human placenta (Kotani et al., 2001; Ohtaki et al., 2001). In fact, *Kiss1*, the four bioactive peptides and Kiss1R are detected in trophoblasts, with higher expression in the syncytiotrophoblast, although cytotrophoblasts and EVT also express Kiss1R (Bilban et al., 2004). Moreover, *Kiss1* and Kiss1R expression is higher in first trimester than in term placentas (Bilban et al., 2004; Cartwright and Williams, 2012). Regarding plasma levels, Kp-54 levels increase throughout pregnancy (Horikoshi et al., 2003; Jayasena et al., 2014).

A role for kisspeptin/Kiss1R signalling in pregnancy was already documented. In human placenta, Kp-10 inhibits in-vitro migration and invasion of trophoblasts in placental explants and of primary cultures of first trimester EVT, by suppressing MMP-2 activity (Bilban et al., 2004). Moreover, Francis et al. (2014) corroborated these findings, reporting kisspeptin inhibits EVT invasion, downregulates the transcripts of several MMPs and increases TIMP-1 and TIMP-3 mRNA levels. Kisspeptin also enhances in-vitro adhesion of a cellular model of human EVT to type-I collagen by triggering Kiss1R, which activates PKC and ERK 1/2 pathways (Taylor et al., 2014). Moreover, Kp-10 has a role in placental angiogenesis, as it inhibits in-vitro proliferation, migration and tube formation of HUVECs, and inhibits new vessels sprouting from human placenta artery explants (Ramaesh et al., 2010). Kisspeptin also downregulates VEGF-A transcripts (Francis et al., 2014), hindering the angiogenic process. Nevertheless, the factors controlling placental expression of kisspeptins still remain to be identified.

The clinical interest of placental hormones

Placental-related hormones play important roles during several gestational events, including implantation, placentation, vascular remodelling, immunomodulation, breastfeeding and labour. An abnormal production of these hormones may imply significant alterations in these processes and negatively affect gestational course and fetal development. Several researches have, therefore, attempted to establish a linkage between abnormal levels of different placental hormones and pregnancy-related conditions. In fact, altered levels of these hormones are noticed in women diagnosed with pre-eclampsia, ectopic pregnancy or spontaneous abortion or in chromosomal anomalies or in women that later develop these pathologies. Nevertheless, a direct causality linkage between these alterations and the gestational complications has not been established. For instance, if altered hormone levels are detected before the diagnosis of these diseases, it is a hypothesis that abnormal production of placental hormones may affect development and gestational course, thus contributing to propitiate the development of pathological conditions. The actual existence of these cause-effect relationships, however, still remains unclear. On the other hand, altered levels registered only after manifestation and diagnosis of gestational complications may rather be a consequence of this pathology than the cause. In fact, it is plausible that these changes may be a placental response to the disease, in order to attempt to adapt to the pathophysiological condition.

The implementation of reliable and robust serum biomarkers to diagnose and predict these conditions has been a challenge, as similar alterations in pregnancy-related hormones levels are found in different pathological conditions. In this way, to meet clinical needs by improving the efficiency of screening tests for prediction and early diagnosis of pregnancy complications, the measurement and integration of different serum biomarkers has been studied. In this section, the most consistent data concerning this topic will

be discussed, and this information is presented in **Table 1**. It is worth mentioning that the research on this subject is extensive, but several conflicting reports have been published. In fact, for a specific pregnancy-related condition, the levels of the same hormone were reported as decreased, increased or unchanged, compared with gestational age-matched controls. Notwithstanding, heterogeneity caused by different factors (e.g. gestational age at sampling, severity of disease) is found among the studies. Therefore, in these cases, the results should be cautiously interpreted and the reliability of these hormone measurements as predictive or diagnostic biomarkers is questionable.

Pre-eclampsia

Pre-eclampsia is the major cause of maternal morbidity and mortality during pregnancy, affecting 2–8% of pregnant women. It is characterized by de-novo manifestation of hypertension (≥140/90 mmHg) and proteinuria (≥300 mg/24 h), diagnosed after the 20th week of gestation (Steegers et al., 2010). At placental level, it has bee verified as a deficient development resulting from an incomplete remodelling of uterine tissues and spiral artery by trophoblasts, which leads to an increased resistance against the blood flow and, consequently, to an impaired supply of oxygen and nutrients to the fetus (Ji et al., 2013). Moreover, pre-eclamptic cytotrophoblasts have a decreased capacity for in-vitro syncytialization (Langbein et al., 2008; Pijnenborg et al., 1996) and a decreased syncytiotrophoblast amount is found in pre-eclampsia placentas (Sheridan et al., 2012). Nevertheless, the cause of these deficiencies has not been identified yet.

Owing to its high incidence, the research for biomarkers able to predict and early diagnose pre-eclampsia has been intense, and alterations of blood levels of some pregnancy hormones have been associated with this pathology. In fact, different studies reported that decreased HCG serum levels were registered in the first trimester in women that were later diagnosed with pre-eclampsia (Asvold et al., 2014; Ong et al., 2000). In the following trimesters, however, HCG serum levels are increased in serum of women with pre-eclampsia women (Ashour et al., 1997; Kalinderis et al., 2011; Olsen et al., 2012). PP13 has been suggested as a biomarker for pre-eclampsia, as its serum levels are decreased in the first trimester of gestation of women that subsequently develop this pathology (Huppertz et al., 2008; Wortelboer et al., 2010). For this reason, PP13 replenishment has been proposed as a new approach for the treatment of this pregnancy-related complication (Huppertz et al., 2013). Similarly to HCG, however, the PP13 levels are increased in the third trimester of women with pre-eclampsia (Huppertz et al., 2008; Than et al., 2008).

In addition, low PAPP-A (D'Antonio et al., 2013; Dugoff et al., 2004; Yliniemi et al., 2015) and kisspeptin levels are detected in the first trimester of women who later develop pre-eclampsia (Armstrong et al., 2009; Logie et al., 2012), compared with normal pregnancies. Moreover, these low PAPP-A levels are associated with pregnancies that are later diagnosed with pre-eclampsia and with abnormal placenta morphometry at term (Odibo et al., 2011). On the other hand, increased levels of inhibin A (Aquilina et al., 1999; Ree et al., 2011), activin A (Akolekar et al., 2009; Muttukrishna et al., 2000) and leptin (Anim-Nyame et al., 2000; Hendler et al., 2005; Masuyama et al., 2010) are observed in women that later developed pre-eclampsia. High adiponectin (D'Anna et al., 2006; Fasshauer et al., 2008; Ramsay et al., 2003) and resistin (Haugen et al., 2006; Seol et al., 2010) levels are also registered in pre-eclamptic women, although another study reported low adiponectin levels and no alteration in resistin concentration (Hendler et al., 2005) in this pathology. Reports about the production of adiponectin by placenta, however, are divergent, and the cause of the increased levels of this adipokine in this pregnancy-related condition still remains to be elucidated. Similarly, contradictory evidence about visfatin levels in pre-eclampsia have also been published. In fact, some studies have reported that in the third trimester, pre-eclamptic women register increased (Adali et al., 2009; Zulfikaroglu et al., 2010), not altered (Mazaki-Tovi et al., 2010) or decreased (Hu et al., 2008) visfatin levels. A study on FGF21 described that its circulating levels are increased in women with pre-eclampsia, compared with controls (Stepan et al., 2013) but another report showed that no alterations were detected in late-onset pre-eclampsia (Dekker Nitert et al., 2015).

Chromosomal anomalies

Alterations in the normal human karyotype, either in number or structure of chromosomes, may have major clinical conditions as a consequence. In fact, different types of chromosomal aberration result in different chromosomal syndromes. Trisomy 21, also known as Down's syndrome, is the most prevalent chromosomal anomaly and the main genetic cause of mental retardation (Megarbane et al., 2009). Cytotrophoblasts isolated from trisomy 21 placentas have a reduced fusion capacity (Massin et al., 2001), and produce a less bioactive form of HCG (Frendo et al., 2004), indicating that a deficient placentation may be associated with this syndrome. Trisomy 18 or Edwards syndrome is the second most common autosomal trisomy syndrome. It is characterized by the presence of major malformations in vital organs, and only 5–10% of babies diagnosed with this condition survive beyond the first year (Cereda and Carey, 2012). These, and other chromosomal anomalies, are effectively diagnosed by amniocentesis or chorionic villous sampling. Less invasive screening tests, however, have been investigated to detect these pathologies before the birth. Nowadays, it is possible to prenatally predict chromosomal anomalies with a good sensitivity based on maternal age, maternal serum markers and ultrasound scan. In this way, it was found that altered levels of pregnancy hormones are related to these anomalies, which indicates their importance for gestational course and fetal development. Prenatal screening for chromosomal anomalies has integrated β-HCG quantification, as increased levels correlate with trisomy 21 whereas reduced levels are associated with trisomy 18 (Alldred et al., 2012; Bestwick et al., 2013; Nicolaides, 2011). The oestrogen oestriol has a fetal precursor, so its levels reflect the fetal steroidogenic activity. Therefore, the measurement of unconjugated oestriol (uE3) in the second trimester is also integrated in the prenatal biochemical screening for fetal anomalies (Alldred et al., 2012; Levitz and Young, 1977). Moreover, PAPP-A levels in the first trimester are also determined in the prenatal screening, as reduced PAPP-A serum levels correlate with Down's syndrome and also with trisomy

Table 1 The main pregnancy-related hormones, their roles, regulators and potential interest as biomarker.

Hormone	*Type*	*Major source*	*Molecular targets*	*Regulated by*	*Function*	*(Potential) Interest as biomarker*
HCG	glycoprotein	ST	LH/HCG receptor	➢ cAMP/PKA (↑) ➢ p38, ERK 1/2 (↑) ➢ Src kinases (↑or ↓) ➢ PPAR-γ (↑) ➢ GnRH (↑) ➢ EGF (↑) ➢ Leptin (↑ 1stT) ➢ Progesterone (↓) ➢ Activin (↑), inhibin (↓)	➢ ↑ Progesterone production by corpus luteum ➢ Syncytialization ➢ Angiogenesis ➢ Immunotolerance ➢ ↑ Trophoblast invasion ➢ Uterine quiescence ➢ Endometrial receptivity and embryo implantation	β-HCG ➢ Pregnancy test* ➢ T21, ↑1st-2nd T* ➢ T18 ↓1st-2nd T* ➢ PE ↓1st T, ↑2nd-3rd T ➢ IUGR ↓or = 1st T, ↑2nd ➢ HG ↑1st T ➢ EP ↓1st T
Progesterone	steroid	ST	nPRs, mPRs	➢ PKA (↑) ➢ Oestradiol (↑) ➢ Insulin (↑) ➢ IGF-1 (↑) ➢ Calcitriol (↑) ➢ Leptin (↓) ➢ CRH (↓) ➢ p38, ERK 1/2 (↑ *3βHSD*)	➢ Decidualization ➢ Endometrial receptivity and embryo implantation ➢ Relaxation of myometrium; uterine quiescence ➢ ↑ Th2 cytokine production ➢ ↓ uNK cells activity ➢ ↓ Trophoblast invasion; ↑ trophoblast migration ➢ ↓ HCG, leptin and resistin placental synthesis ➢ Preparation of breast for lactation ➢ Hyperphagia, fat storage	➢ SM ↓1st T ➢ EP ↓1st T
Oestradiol	steroid	ST	nERs, mERs	➢ cAMP (↑ *Aromatase*) ➢ HCG (↑ *Aromatase*) ➢ Oestradiol (↑ *Aromatase*) ➢ Cortisol (↑ *Aromatase*) ➢ p38 (↑ *Aromatase*) ➢ ERK 1/2 (↓ *Aromatase*) ➢ Calcitriol (↑) ➢ CRH (↑) ➢ Leptin (↓) ➢ Insulin (↓)	➢ Endometrial receptivity and embryo implantation ➢ Angiogenesis ➢ Regulation of human uteroplacental blood flow ➢ ↑ myometrium contraction, labour induction ➢ Syncytialization ➢ ↑ Leptin and ↓ resisitin placental synthesis ➢ Preparation of breast for lactation ➢ Hyperlipidaemia and fat storage	

(*continued on next page*)

Table 1 (*continued*)

Hormone	*Type*	*Major source*	*Molecular targets*	*Regulated by*	*Function*	*(Potential) Interest as biomarker*
Oestriol	steroid	ST	nERs, mERs		➢ ↑ Uteroplacental blood flow ➢ ↑ Myometrium contraction	uE_3 ➢ T21, T18 ↓2nd T*
HPL	polypeptide	ST, EVTs	GHR, PRLR	➢ cAMP (↑) ➢ GHRF (↑) ➢ Insulin (↑) ➢ EGF (↑) ➢ PPAR-γ/RXR-α (↑) ➢ Calcitriol (↑) ➢ Apolipoproteins (↑) ➢ IL-1, IL-6 (↑)	➢ Lipolysis, ↑ free fatty acids and ketone bodies ➢ Insulin sensitivity ➢ ↑ Fetal insulin and IGF-1 synthesis ➢ ↓ Leptin placental synthesis	
HPGH	polypeptide	ST, EVTs	GHR, PRLR	➢ cAMP (↑) ➢ Hypoglycaemia (↑) ➢ Visfatin (↑) ➢ PPAR-γ/RXR-α (↑) ➢ Insulin (↓) ➢ Leptin (↓) ➢ Cortisol (↓)	➢ Synthesis of maternal IGF-1 ➢ Lipolysis ➢ Insulin resistance, ↑ serum glucose levels ➢ ↑ Trophoblast invasion	
Leptin	Adipokine	ST, EVTs	LepRb	➢ cAMP/PKA (↑) ➢ PKC (↑) ➢ p38, ERK 1/2 (↑) ➢ RXR-α (↑) ➢ HCG (↑) ➢ oestradiol (↑) ➢ Insulin (↑) ➢ Progesterone (↓) ➢ HPL (↓) ➢ Hypoxia (↓)	➢ ↑ CT proliferation ➢ ↓ CT apoptosis ➢ ↑ Trophoblast invasion ➢ ↑ HCG and ↓ HPGH, progesterone and oestradiol placental production ➢ Angiogenesis ➢ Embryo implantation ➢ Immunomodulation ➢ Uterine quiescence ➢ ↑Pro-inflammatory cytokines and prostaglandins	➢ PE ↑1st -3rd T ➢ GDM ↑1st -2nd T

(*continued on next page*)

Table 1 (*continued*)

Hormone	*Type*	*Major source*	*Molecular targets*	*Regulated by*	*Function*	*(Potential) Interest as biomarker*
Adiponectin	adipokine	ST?	AdipoR1, AdipoR2	➢ Leptin (↓) ? ➢ TNF-α (↓)? ➢ IL-6 (↓)?	➢ ↓HCG, progesterone and HPL placental secretion ➢ ↓CT proliferation ➢ Syncytialization ➢ ↓Insulin placental signalling ➢ ↑Trophoblast invasion ➢ Modulation of angiogenesis ➢ ↑Pro-inflammatory cytokines and prostaglandins	➢ PE ↑ or ↓ 3rd T ➢ GDM ↓1st -2nd T
Resistin	adipokine	ST, EVTs		➢ Oestradiol (↓) ➢ Progesterone (↓)	➢ ↑ Trophoblast invasion? ➢ Expression of GLUT-1, ↑ glucose uptake? ➢ Angiogenesis	➢ PE ↑ or = 3rd T
Visfatin	adipokine	ST			➢ ↑ HPGH placental secretion ➢ ↑ Myometrium contraction ➢ ↑ Pro-labour cytokines	➢ IUGR ↑3rd T''
FGF21	adipokine	ST	FGFR1-4			
PAPP-A	metalloproteinase	ST, EVTs	IGFBP-4	➢ Progesterone (↑) ➢ PPAR-γ (↓) ➢ p38, ERK 1/2 (↑)	➢ IGFBP-4 cleavage and enhancement of IGFs-mediated functions ➢ ↑ Trophoblast invasion? ➢ ↑ CT proliferation? ➢ Embryo implantation?	➢ T21, T18 ↓1st T* ➢ PE ↓1st T ➢ IUGR ↓1st T ➢ GDM ↓1st T ➢ EP ↓1st T ➢ SM ↓1st T
PP13	galectin	ST		➢ Ca^{2+} influx (↑) ➢ Ischaemia (↑) ➢ p38 (↑) ➢ cAMP/PKA (↑)	➢ Immunotolerance by induction of apoptosis of maternal immune cells ➢ Regulation of blood pressure of utero-placental vasculature? ➢ Pro-inflammatory action	➢ PE ↓1st T

(*continued on next page*)

Table 1 (*continued*)

Hormone	*Type*	*Major source*	*Molecular targets*	*Regulated by*	*Function*	*(Potential) Interest as biomarker*
Activin A	dimeric glycoprotein	ST	ActRIIA, ActRIIB	➢ Oxidative stress (↑) ➢ Proinflammatory cytokines (↑) ➢ CRH (↑) ➢ Hypoxia (↓)	➢ ↑ CT proliferation ➢ ↑ Trophoblast invasion ➢ Decidualization and endometrium receptivity ➢ ↑ HCG and progesterone placental secretion ➢ ↑ Placental aromatase activity	➢ PE ↑ 1^{st}-2^{nd} T
Inhibin A	dimeric glycoprotein	ST	ActRIIA, ActRIIB	➢ HCG (↑) ➢ cAMP (↑) ➢ EGF (↑) ➢ GnRH (↑) ➢ Prostaglandins (↑) ➢ Activin (↓) ➢ Hypoxia (↓)	➢ Antagonism of activin effects	➢ T21 ↑2^{nd} T* ➢ PE ↑ 1^{st}-2^{nd} T
Kisspeptin	neuropeptide	ST	Kiss1R		➢ ↓ Trophoblast invasion ➢ ↑ Trophoblast adhesion ➢ ↓ Angiogenesis	➢ PE ↓1^{st} T ➢ SM ↓1^{st} T

↑-stimulation, ↓-inhibition; ?- inconsistent. AdipoR1 = 2- adiponectin receptor 1 or 2; cAMP = cyclic AMP; ActRIIA, B = activin receptor type II A or B; CRH = corticotrophin-releasing hormone; CT = cytotrophoblast; EGF = epidermal growth factor; EP = ectopic pregnancy; ERK 1/2 = extracellular-signal regulated kinases 1/2; EVTs = extravillous trophoblasts; FGF21 = fibroblast growth factor 21; FGFR1-4 = fibroblast growth factor receptors 1-4; GDM = gestational diabetes mellitus; GHR = growth hormone receptor; GHRF = growth hormone-releasing factor; GLUT-1 = glucose transporter 1; GnRH = gonadotropin releasing hormone; HG = hyperemesis gravidarum; HPGH = human placental growth hormone; HPL = human placental lactogen; IGF = insulin growth factor; IGFBP-4 = insulin growth factor binding protein 4; IL-1, IL-6- = interleukin 1 or 6; IUGR = intrauterine growth restriction; Kiss1R = kisspeptin receptor; LH = luteinizing hormone; mERs = membrane-associated oestrogen receptors; mPRs = membrane-associated progesterone receptors; nERs = nuclear oestrogen receptors; nPRs = nuclear progesterone receptors; PAPP-A- = pregnancy-associated plasma protein A; PE = pre-eclampsia; PKA = protein kinase A; PKC = protein kinase C; PPAR-γ = peroxisome proliferator-activated receptor gamma; PP13 = placental protein 13; PRLR = prolactin receptor; RXR-α = retinoid X receptor alpha; SM = spontaneous miscarriage; ST = syncytiotrophoblast; T = trimester; T18 = Trisomy 18; T21 = Trisomy 21; TNF-α = tumour necrosis factor alpha; uE_3 = unconjugated oestriol; uNK = uterine natural killer cells; 3β-HSD = 3beta-hydroxysteroid dehydrogenase/Δ_5-Δ_4-isomerase. *the quantification of these hormones is already included in the integrated screening test for fetal chromosomal anomalies.

18 and 13 pregnancies (Bestwick et al., 2013; Leguy et al., 2014; Nicolaides, 2011). In addition, elevated levels of inhibin A in the second trimester are associated with Down's syndrome, and the assessment of this hormone was more recently included in the quadruple screening test for fetal anomalies, in combination with the other markers (Alldred et al., 2012; Benn et al., 2003). In this way, currently, an integrated test that includes PAPP-A measurement in the first trimester and the quadruple test screen (β-HCG, unconjugated oestriol, alpha-fetoprotein and inhibin A) in the second trimester is carried out to detect fetal chromosomal anomalies. Nevertheless, it is noteworthy to mention these tests are just predictive of these pathologies and only more invasive tests, such as chorionic villus sampling, and amniocentesis, can assess the presence of chromosomal anomalies with more reliability (Chitayat et al., 2011).

The other placental-related hormones, leptin (Hedley and Christiansen, 2008; Rizos et al., 2002) and PP13 (Akolekar et al., 2010; Koster et al., 2009) are not altered in Down's syndrome, and one study reported that the latter is decreased in the first trimester of trisomy 18 and 13 gestations (Akolekar et al., 2010).

Intrauterine growth restriction

Intrauterine growth restriction (IUGR) is characterized by a deficient uterine fetal growth (fetal weight <10th percentile) and is the leading cause of perinatal morbidity and mortality. It implies a pathological condition that may be caused by several factors, including insufficient uteroplacental vasculature, poor nutrition, vascular disease, smoking, fetal anomalies or congenital infections. For these reasons, IUGR differs from small for gestational age (SGA), a fetus that is simply below of 10th percentile, which grew in a healthy intrauterine environment and is associated with low perinatal morbidity (Lausman et al., 2012; Sankaran and Kyle, 2009). Currently, no accurate predictive tests are available for IUGR; therefore the search for reliable biomarkers to diagnose and predict this pregnancy-related complication is relevant to use in combination with other screening techniques, including uterine artery Doppler ultrasonography. Several publications reported the levels of placental-related hormones as different in this condition, although different reports are often contradictory. Indeed, in the first trimester of women that give birth to SGA or IUGR newborns, β-HCG levels are low (Abdel Moety et al., 2015; Pihl et al., 2008) or not altered (De Leon et al., 2004; Spencer et al., 2005). In the second trimester, HCG serum concentration is increased (Androutsopoulos et al., 2013; Audibert et al., 2005). In this way, the ability of HCG serum levels to predict IUGR is inefficient. Concerning PAPP-A levels, many studies have reported that lower concentrations of this hormone in the first trimester of women are associated with a higher prevalence of IUGR and SGA (Abdel Moety et al., 2015; Kirkegaard et al., 2011; Montanari et al., 2009; Spencer et al., 2005). In addition, low PAPP-A levels are related to an abnormal morphometry in the placenta at delivery in pregnancies with IUGR (Odibo et al., 2011).

Robust evidence about changes in maternal blood levels of other placental hormones and IUGR are scarce. In the first trimester of IUGR gestations, PP13 maternal blood levels were reported as low (Chafetz et al., 2007) or not altered (Cowans et al., 2008). Regarding adipokines, a study reported that low adiponectin and high leptin levels are registered at term in gestations diagnosed with IUGR (Kyriakakou et al., 2008). Another report showed leptin levels are increased in the second trimester of early onset IUGR, but no alterations were registered in leptin an adiponectin levels of women that subsequently develop IUGR (Savvidou et al., 2008). Nevertheless, another study reported that adiponectin levels were not altered in the third trimester of women diagnosed with IUGR, whereas visfatin levels were increased (Fasshauer et al., 2007), which is in agreement with alterations in visfatin levels at term in IUGR (Malamitsi-Puchner et al., 2007) and SGA pregnancies (Mazaki-Tovi et al., 2010). Therefore, evidence linking adipokine and IUGR are still very weak.

Gestational diabetes mellitus

Gestational diabetes mellitus (GDM) affects about 6% of gestations and manifest after the 24th week of gestation. It is characterized by insulin resistance and fasting glycaemia levels higher than 92 mg per ml (Garrison, 2015). Because of the recent redefinition of GDM's diagnostic criteria, only the studies diagnosing this pathology according to these novel criteria will be addressed in this section. The levels of some adipokines are altered in the first and second trimester of women that later develop GDM. In fact, increased serum levels of leptin and decreased levels of adiponectin are registered in these women (Bao et al., 2015). Regarding other adipokines, in the second trimester of GDM women, visfastin levels were higher (Coskun et al., 2010; Gok et al., 2011), lower (Park et al., 2013; Rezvan et al., 2012) or unchanged (Karatas et al., 2014), compared with the control group. The FGF21 levels in one study were significantly higher in women with GDM at term (Tan et al., 2013), but other studies reported that no alterations were observed between GDM and control group (Dekker Nitert et al., 2014; Stein et al., 2010). Similarly, the evidence about resistin levels in this gestational complication are contradictory (Lobo et al., 2013). On the other hand, PAPP-A levels are also decreased in the first trimester of women that are later diagnosed with GDM (Beneventi et al., 2014; Lovati et al., 2013), and a recent study showed that PP13 levels are decreased in the third trimester of women with GDM (Unverdorben et al., 2015).

Other pregnancy-related conditions

Ectopic pregnancy affects about 1–2% of gestations and is generally diagnosed by transvaginal pelvic sonography and physical examination (Barash et al., 2014). This approach, however, may be inconclusive, and unknown location pregnancies need to be followed until its diagnosis is made. In this way, β-HCG discriminatory level (value above which an intrauterine pregnancy [IUP] should be visualized by ultrasonography) is evaluated (Barash et al., 2014), as the levels of this hormone are usually decreased in ectopic pregnancy (Mueller et al., 2004; Seeber et al., 2006). In some cases, serial β-HCG measurements are monitored every 48 h, and the profile and slope of β-HCG curves are evaluated. In IUP, β-HCG value usually

doubles in 48 h, whereas failure to increase at this rate indicates ectopic pregnancy or non-viable pregnancy (Barash et al., 2014). Nevertheless, it has been reported that there is no unique pattern in HCG curves of women with ectopic pregnancy, so the challenge of distinguishing ectopic pregnancy from other conditions of symptomatic early pregnancy (IUP and spontaneous abortions) still remains (Dillon et al., 2012). Furthermore, decreased levels of progesterone (Martinez-Ruiz et al., 2014; Mueller et al., 2004) and PAPP-A (Mueller et al., 2004; Sjoberg, 1987) are also observed in this pathology.

Hyperemesis gravidarum is a condition characterized by a rare and severe form of nausea and vomiting during pregnancy, which generally occurs between the fourth and 10th weeks and disappears by the 20th week of pregnancy. It affects 0.3–2% of pregnancies, and is the most frequent cause of hospitalization during the first half of gestation (Verberg et al., 2005). The most probable cause of hyperemesis gravidarum is HCG, as the higher incidence of this pathology coincides with the HCG peak in serum, and HCG levels are increased in this condition (Derbent et al., 2011; Niemeijer et al., 2014).

Additionally, in women who later undergo spontaneous abortion, serum levels of progesterone (Hahlin et al., 1990; Phipps et al., 2000), PAPP-A (Santolaya-Forgas et al., 2004; Tong et al., 2012) and kisspeptins (Jayasena et al., 2014) are reduced.

Conclusion

Pregnancy is a physiological state characterized by drastic changes in the hormonal profile. In fact, during this period, placenta synthesises and secretes several hormones that are crucial for the regulation of distinct pregnancy stages, such as decidualization and implantation and labour, and also for the maternal metabolic adaptation and preparation for breastfeeding. Nevertheless, the direct involvement of each placental hormone in these processes was not demonstrated in most of the cases, as each of these hormones is tightly regulated in space and time by several factors, including by other placental hormones. Therefore, future work should focus to unveil which hormones are the major controllers of these pregnancy-related events and influence the action of other hormones.

On the other hand, altered levels of placenta hormones may negatively affect different pregnancy processes, and are associated with poor gestational outcome. The deficient production of these hormones may also contribute to the altered placental development observed in these conditions. Indeed, abnormal levels of these hormones are detected in several pregnancy-related diseases, so their potential as biomarkers to predict and enable early diagnosis these conditions has been studied. As the same hormonal fluctuations are registered in different pathologies, however, it is a challenge to establish a link between endocrine alterations and a specific pregnancy-related pathology. In this way, the combination of measurements of different hormones, analysed with other clinical examinations and risk factors, have been exploited to improve the detection rate and decrease the number of false-positives, in attempting to find reliable biomarkers.

In conclusion, the endocrine function of the human placenta is critical for the success of distinct pregnancy events and fetal development, as an abnormal production of placental hormones has been associated with anomalies in these processes and poor gestational outcome. Moreover, these endocrine alterations may be helpful in predicting and diagnosing pregnancy-related conditions, providing an early planning of the best clinical strategies to manage these conditions.

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