REVIEW

# Role of adipokines in embryo implantation

**Davoud Jafari-Gharabaghlou[1,2], Mostafa Vaghari-Tabari[2], Hajar Oghbaei[3], Laura Lotz[4], Reza Zarezadeh[2], Yeganeh Rastgar Rezaei[5], Mahnaz Ranjkesh[6], Mohammad Nouri[2,7], Amir Fattahi[4,8], Saba Nikanfar[2,8]** and **Ralf Dittrich[4]**

[1]Student Research Committee, Tabriz University of Medical Sciences, Tabriz, Iran
[2]Department of Clinical Biochemistry and Laboratory Medicine, Faculty of Medicine, Tabriz University of Medical Sciences, Tabriz, Iran
[3]Department of Physiology, Tabriz University of Medical Sciences, Tabriz, Iran
[4]Department of Obstetrics and Gynecology, Erlangen University Hospital, Friedrich-Alexander University of Erlangen–Nürnberg, Erlangen, Germany
[5]Department of Medical Biotechnology, Faculty of Advanced Medical Sciences, Tabriz University of Medical Sciences, Tabriz, Iran
[6]Medical Radiation Science Research Group (MRSRG), Tabriz University of Medical Sciences, Tabriz, Iran
[7]Department of Reproductive Biology, Faculty of Advanced Medical Sciences, Tabriz University of Medical Sciences, Tabriz, Iran
[8]Stem Cell Research Center, Tabriz University of Medical Sciences, Tabriz, Iran

**Correspondence should be addressed to A Fattahi or S Nikanfar: amirfattahi@gmail.com or nikansaba@gmail.com**

## Abstract

Embryo implantation is a complex process in which multiple molecules acting together under strict regulation. Studies showed the production of various adipokines and their receptors in the embryo and uterus, where they can influence the maternal-fetal transmission of metabolites and embryo implantation. Therefore, these cytokines have opened a novel area of study in the field of embryo–maternal crosstalk during early pregnancy. In this respect, the involvement of adipokines has been widely reported in the regulation of both physiological and pathological aspects of the implantation process. However, the information about the role of some recently identified adipokines is limited. This review aims to highlight the role of various adipokines in embryo–maternal interactions, endometrial receptivity, and embryo implantation, as well as the underlying molecular mechanisms.

**Key Words**

- adipokine
- embryo implantation
- endometrium
- pregnancy
- trophoblast

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## Introduction

Nowadays, many advances have been achieved in the field of assisted reproductive technology (ART) and this technique could help many infertile couples to have their children. However, the main problem with this technology is the low rate of implantation after the embryo transfer (1). Statistics showed that more than 50% of embryos could not be implanted after transferring into the uterus and even in some patients the implantation failure can be seen after several transfers of good quality embryos which are described as repeated implantation failure (2).

Implantation is one of the most important steps toward pregnancy initiation, through which blastocyst invades the epithelium of the endometrium (3). To successful implantation, both embryo and endometrium should be met in a precise time and place, which is recognized as the 'implantation window' (3). During this window, the endometrium is completely ready for receiving the blastocyst. In a normal menstrual cycle, this period is from days 16 to 22; this would be approximately 5–10 days after the luteinizing hormone (LH) surge (4). The embryo implantation contains three steps, at the first stage, the blastocyst attaches with a loose connection to the implantation site in the uterine (opposition), and then trophoblasts attach to the epithelium of the endometrium (adhesion), and finally, at the last stage, the cells invade to the stromal site of the endometrium (invasion). All the steps should be precisely regulated to make the successful implantation possible (5).

Various factors are involved in the implantation process such as cytokines (e.g. IL1, IL6, and leukemia inhibitory factor), prostaglandins (e.g. PGE2), growth factors (e.g. epidermal growth factor (EGF), vascular endothelial

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growth factor (VEGF), and heparin-binding EGF), matrix-degrading enzymes (e.g. matrix metalloproteinases (MMPs)), matrix-degrading enzymes inhibitors (e.g. tissue inhibitor of metalloproteinase (TIMPs)) and molecules that have a role in cellular adhesion (e.g. integrins, selectins, and cadherins) (2, 3). It has been documented that adipose tissue-derived factors can also affect implantation (6, 7). Adipose tissue acts as an endocrine tissue and secretes hormone-like factors called adipokines. Adipokines are a kind of cytokine that contributes to energy metabolism, inflammation, immunity, and angiogenesis, as well as, reproductive maturity and fertility (6, 7, 8, 9). Regarding the latter effect, it has been well documented that obesity or excess fat can negatively influence female fertility and ovarian function such as what we see in obese women with polycystic ovary syndrome (PCOS) (10, 11). The role of adipokines has also been shown in embryo implantation (6, 7). Owing to the importance of adipokines in fertility and implantation and the lack of comprehensive study on the involvement of adipokines in embryo implantation, in this review, we aimed to address the roles of adipokines in embryo implantation and the underlying mechanisms.

## Adipokines in embryo implantation

Many studies have shown the presence of adipokines and their receptors in the woman's reproductive systems emphasizing their role in female fertility. Adipokines are also present in the uterus and placenta where they can influence implantation and pregnancy as well as maternal–fetal transmission of metabolites (6, 7). It has been demonstrated that various stages of implantation are profoundly regulated by steroids, including progesterone, estradiol, and androgens. On the other hand, the role of adipokines in the regulation of the secretion of gonadotropin-releasing hormone (GnRH), gonadotropins, and steroids suggesting their involvement in the implantation process (12). However, there is no consensus regarding the effects of adipokines on hormones which can be due to different reasons such as species differences, the dose of adipokines (13, 14), size and stage of ovarian follicles (15), and phase of the menstrual cycle (16). The association of adipokines with steroidogenesis and hormones has previously been reviewed in depth by our group (17). Interestingly, adipokines can be under the regulation of hormones. For example, the stimulatory effects of estrogen, testosterone, LH, and follicle-stimulating hormone (FSH) on resistin expression have been demonstrated in ovarian follicles (18). Moreover, it has been reported that estradiol could induce adiponectin expression (19). However, the inhibitory effects of steroids have also been reported on adipokines in ovarian follicles (19).

It has been documented that alteration of adipokine levels may result in different female reproductive issues. For example, both abnormal decreased and increased levels of adipokines have been reported in gestational diabetes mellitus, PCOS, preeclampsia, endometriosis, and intrauterine growth retardation; however, some studies did not find an association between adipokine levels and gynecological issues (12). In addition, it has been demonstrated that increased levels of adipokines can alter their functions and may cause adipokine resistance (20). Adipokines can link energy metabolism and reproduction. Implantation and pregnancy are intensely reliant on the balance of energy (21, 22), and therefore metabolic abnormalities can cause implantation failure (23). The roles of different adipokines in implantation and pregnancy have been mentioned by previous studies. In this regard, various adipokines such as leptin, adiponectin, apelin, chemerin, progranulin, retinol-binding protein 4 (RBP4), and visfatin have been investigated (7, 24, 25, 26, 27). In the following sections, we explain the adipokines and their possible role in embryo implantation. Moreover, the role of adipokines in implantation and possible underlying mechanisms are summarized in Table 1.

### Leptin

Leptin is a 16 kDa polypeptide hormone encoded by the obese (*OB*) gene and mostly produced by white adipose tissue. It acts through the leptin receptor that mainly transmits signals through the Janus kinase/signal transducer and activator of transcription signaling pathway. The main role of leptin in the body is regulation of energy balance by affecting cellular metabolism and appetite (28, 29). Interestingly, leptin can act as a pro-inflammatory cytokine due to its structural similarity with IL6. In this regard, leptin increases the expression of inflammatory cytokines such as tumor necrosis factor α (TNFα) and IL6 (30, 31). Leptin is also associated with the adaptive immune system and can enhance the proliferation and survival of T cells (30). Studies have well documented that leptin is involved in the reproductive system. For instance, this adipokine is essential for the onset of puberty, and also can affect the hypothalamus–pituitary–gonadal axis (32).

In the female reproductive system, it has been demonstrated that leptin receptor is present on the surface of granulosa and theca cells, and stimulates the production of the steroids in these cells (33). In supporting the role of

**Table 1** Role of adipokines in embryo implantation-related functions and their mechanism of action.

| Adipokine | Function | Mechanism of action | Ref |
|---|---|---|---|
| Leptin | Remodeling of the endometrial epithelium (human) | Stimulating proliferation and enhancing Fas ligand-induced apoptosis in EECs | (39) |
| | Repairing endometrial epithelium after embryo implantation (human) | ND | (39) |
| | Inducing blastocysts adhesion (mice) | Induction of αv and β3 integrin in EECs | (40) |
| | Stimulating trophoblast invasion (human, mouse) | Upregulating MMP expression in trophoblast cells | (123, 124) |
| | Induction of implantation-related inflammation (human) | Stimulating the production of IL6 and chemokines in EECs and ESCs | (42) |
| | Inhibition of decidualization (human) | ND | (41) |
| Adiponectin | Playing a role in maternal recognition of pregnancy and implantation (porcine) | Upregulation of basal and insulin-stimulated steroidogenic enzymes, including HSD3B, StAR, and CYP11A1 and secretion of $A_4$ and $P_4$ by the endometrium and myometrium | (51) |
| | Involving in the development of the preimplantation embryo and uterine receptivity (mouse) | Activation of autocrine and paracrine mechanisms | (56) |
| | Involving in decidualization | | |
| | Increasing uterine receptivity | Stimulation of AKT/PI3K and MAPK signaling pathways | (52) |
| | Inducing proliferation and attenuating apoptosis of uterine luminal epithelial cells (porcine) | | |
| | Involving in implantation and regulating endometrial inflammation (human) | Increasing phosphorylation of AMP-activated protein kinase in ESCs and EECs | (50) |
| | | Decreasing IL1β-induced secretion of IL6, IL8, and MCP1 from ESCs | |
| Apelin | Regulating luteal phase of the estrous cycle (pig) | Stimulating $P_4$ secretion and HSD3B activity in the middle of the luteal phase | (64) |
| | Regulating early placental development (human) | Enhancing proliferation of trophoblast cells via APJ and ERK1/2, Stat3 and AMPKα signaling | (67) |
| | Decreasing the uterine contractions and facilitating embryo implantation (human) | ND | (69, 70) |
| | Exerting hypotensive effects on blood vessels (rats) | Stimulating the phosphorylation of eNOS, activation of guanyl cyclase, and cGMP production in endothelial cells | |
| | Inducing the uterus myometrium contraction (rats) | Partially via protein kinase C pathway | |
| Chemerin | Maintaining early pregnancy and preventing embryo abortion (human) | Phosphorylation of ERK1/2 | (81) |
| | Regulating endometrial receptivity and trophoblast invasiveness (porcine) | ND | (25) |
| | Involving in maternal recognition of pregnancy (porcine) | Possibly via the conceptus-secreted substances, including uPA and E2 | (25) |
| | Decidualization and vascular remodeling during early pregnancy (human) | Accumulating NK cells at the implantation site | (83) |
| | Promoting uterine receptivity and implantation (human, mice) | Augmenting AMPKα activity | (68, 82) |
| | Increasing trophoblast invasion (human) | Production of IL8 and IP10 by NK cells | (83, 84) |
| Visfatin | Involving in implantation (mice) | Increasing PCNA expression and maintaining the balance between apoptotic and anti-apoptotic elements in the uterus | (99) |
| | Affecting uterine immune responses and morphological structure (rat) | Modulating inflammatory responses by regulating the expression of eosinophil, myeloperoxidase, and inflammatory cytokines (IL1β, IL6, and TNFα) | (97) |
| | Involving in the regulation of the placental angiogenesis (human) | ND | (100) |
| RBP4 | Increasing trophoblast proliferation and invasion (human) | Suppressing PI3K/AKT signaling pathway and upregulating MMP2 and MMP9 | (105) |

*(Continued)*

**Table 1** Continued.

| Adipokine | Function | Mechanism of action | Ref |
|---|---|---|---|
| Progranulin | Stimulating blastocyst growth and adhesion (mouse) | ND | (118) |
| | Involving in decidualization (murine) | ND | (119) |
| | Establishing placenta by involvement in hypertrophy and proliferation of the endometrial epithelium, growth and migration of cytotrophoblast, and maternal angiogenesis (mink) | ND | (26) |
| | Playing role in uterine angiogenesis and facilitating the implantation (human) | ND | (121) |
| | Involving in blastocysts hatching (mouse) | ND | (118) |

A4, androstenedione; AMP, adenosine monophosphate; AMPK, AMP-activated protein kinase; APJ, apelin receptor; HSD3B, 3beta-hydroxysteroid dehydrogenase; cGMP, cyclic guanosine monophosphate; CYP11A1, cytochrome P450 11A1; E2, estradiol; EEC, endometrial epithelial cells; ERK1/2, extracellular signal-regulated kinases 1 and 2; eNOS, endothelial nitric oxide synthase; ESC, endometrial stromal cells; MAPK, mitogen-activated protein kinase; MCP-1, monocyte chemoattractant protein 1; MMP, matrix metalloproteinases; ND, not defined; NK, natural killer; P4, progesterone; PCNA, proliferating cell nuclear antigen; PI3K/AKT, phosphatidyl inositol-3-kinase/ protein kinase B; StAR, steroidogenic acute regulatory protein; STAT3, signal transducer and activator of transcription 3; TNF, tumor necrosis factor; uPA, urokinase plasminogen activator .

leptin in embryo implantation, expression of its receptor (OBR) has been observed on the endometrial cells and it has been reported that decreased expression of the receptor is associated with subfertility (34). Leptin is locally produced by endometrium and blastocysts showing its importance in embryo-endometrium crosstalk during implantation (35). Findings from subsequent studies further reinforced the potential roles of leptin in the pregnancy process. In this regard, it has been shown that injecting recombinant leptin for 8 days resulted in pregnancy in leptin-deficient female mice suffering from infertility. More interestingly, pregnancy did not occur when leptin administration was stopped 0.5 or 3.5 days after mating, but it occurred when the treatment stopped 6.5 or 14.5 days after mating (36). Given that the implantation initiates 5 days after mating in mice, it seems that the most important role of leptin in pregnancy is related to the implantation stage. Another study showed that the expression of leptin receptors in the endometrium was significantly increased during the luteal phase, the phase of receptivity (37). A study also reported that the blocking of leptin receptors on the third day of pregnancy could impair embryo implantation in mice (38). Also, studies have demonstrated that leptin is involved in the proliferation and apoptosis of uterine epithelial cells, uterine receptivity, uterine immune system, and decidualization, which are necessary for implantation (39, 40, 41). On the other hand, the expression of leptin could only be detected at the blastocyst stage during the preimplantation period, the stage that can be implanted (37).

Regarding the underlying mechanisms of leptin action in implantation, it has been documented that leptin could significantly increase the adhesion rate of mice blastocysts via inducing the expression of adhesion molecules such as beta 3 integrin in endometrial epithelial cells (40) (Fig. 1). Leptin has also an association with the endometrial immune system and can induce the expression of several implantation-related inflammatory cytokines in the endometrium. In this regard, it has been indicated that leptin treatment could increase the expression of IL6, IL8, GROα, monocyte chemoattractant protein-1, and macrophage inflammatory protein-3α (MIP3α) in the endometrial epithelial and stromal cells (42). On the other hand, the essential role of inflammation in the embryo implantation process has been well-documented (43). Leptin is also involved in decidualization, a necessary step for pregnancy initiation (41). However, the effect of leptin on the decidualization is inhibitory, and therefore, extra levels of leptin as seen in the endometriosis patients can also be involved in implantation failure (41).

## Adiponectin

Adiponectin is produced by the adipose tissue, liver, bone, and placenta (44). Adiponectin acts through two receptors, AdipoR1 and AdipoR2. AdipoR1 transduces adiponectin signal through AMP-activated kinase (AMPK), whereas AdipoR1 activates peroxisome proliferator-activated receptor alpha (PPARα) (45). Adiponectin plays an important role in the regulation of energy metabolism via increasing insulin sensitivity, glucose uptake, and fatty acid oxidation, and also attenuating gluconeogenesis (46). Adiponectin is also involved in the immune system and appears to have anti-inflammatory properties via attenuating the nuclear factor-kB signaling pathway and subsequently the production of IL6 and TNFα in

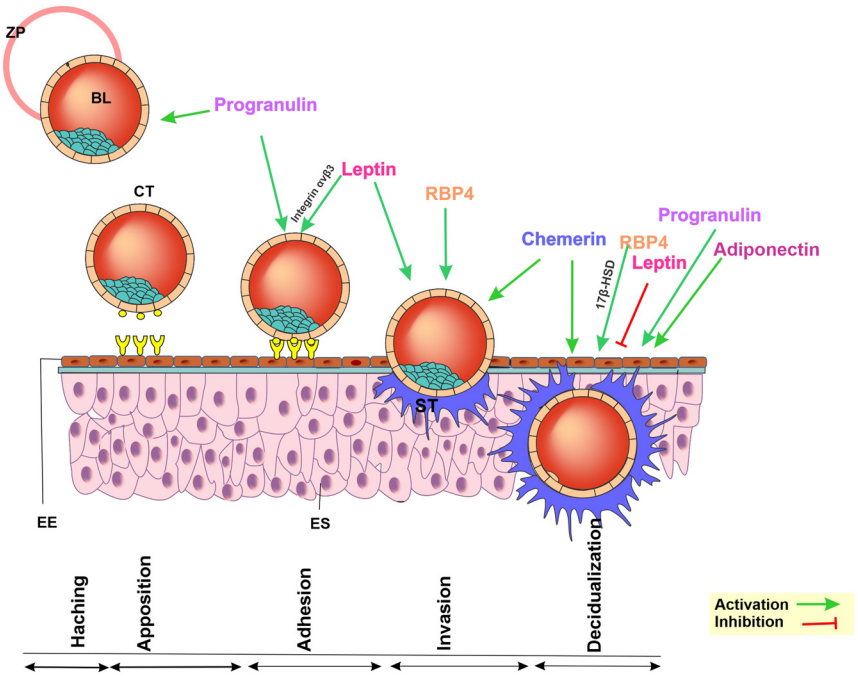


**Figure 1**
Schematic diagram demonstrating the involvement of adipokines during different stages of the blastocyst implantation in the endometrium. ZP, zona pellucida; BL, blastocyst; CT, cytotrophoblast; ST, syncytiotrophoblast; ES, endometrial stroma; EE, endometrial epithelium.

macrophages. Roles of adiponectin in the reproductive system have also been indicated. Adiponectin attenuates LH secretion from the pituitary gland and regulates GnRH receptor expression (47). A study reported that mice lacking adiponectin showed folliculogenesis issues and impaired fertility potential (48). It has also been demonstrated that the serum levels of adiponectin were directly correlated with the number of retrieved oocytes in women who underwent in vitro fertilization (49).

The expression of adiponectin receptors in the endometrium and the involvement of adiponectin in the embryo implantation-related processes encouraged scientists to investigate the potential roles of this adipokine in embryo implantation. In this respect, it has been found that *ADIPOR1* and *ADIPOR2* were expressed in epithelial and stromal cells of the endometrium and their expression was markedly increased during the mid-luteal phase, the time of embryo implantation (50). Low expression of adiponectin receptors has also been reported in the endometrium of women with unexplained recurrent implantation failure (7). The production of steroids is important for appropriate embryo implantation and it has been shown that adiponectin enhances the expression of steroidogenic enzymes such as 3β-hydroxysteroid dehydrogenase and steroidogenic acute regulatory protein (51). Furthermore, adiponectin induces proliferation and attenuates apoptosis of uterine luminal epithelial cells, and subsequently increases uterine receptivity. These effects are mediated by the stimulatory effect of adiponectin on phosphatidylinositol-3-kinase/protein kinase B (AKT/PI3K) and MAPK signaling pathways (52). Adiponectin can also induce endometrium receptivity via reducing IL6 secretion by endometrial epithelial cells (50, 53). Adiponectin can decrease nitric oxide (NO) levels in the endometrium. Given that in the pre- and peri-implantation stages the expression of inducible nitric oxide synthase (iNOS) is increased in the endometrium, it can be postulated that adiponectin plays a regulatory role in NO-related processes during the implantation (54, 55). However, further studies are needed to clarify how adiponectin acts in favor of implantation by reducing NO synthesis, a factor that is required for implantation. Interestingly, the expression of adiponectin receptors is increased during decidualization, suggesting the potential role of this adipokine in decidualization (56). To sum up, adiponectin is involved in embryo implantation via affecting steroidogenesis, the proliferation of uterine epithelial cells, regulating endometrial inflammation, NO synthesis, and endometrium receptivity, and decidualization; however, future studies are likely to reveal further insight into the role of adiponectin in embryo implantation.

## Apelin

Apelin is encoded by the *APLN* gene as a preproprotein and following the post-translational modifications, several active forms of apelin are produced, including apelin 36,

apelin 17, and apelin13, among which apelin13 has the highest biological activity. It acts through a G protein receptor named APJ (57, 58, 59). Apelin is involved in many biological functions, including angiogenesis, blood pressure regulation, heart contraction, water intake, and anti-inflammatory processes (57, 60). Apelin also has direct and indirect roles in the reproductive system. In this regard, it has been reported that apelin 13 could attenuate the secretion of LH, FSH, and prolactin from the pituitary gland (61). Apelin and its receptor are expressed in oocytes and follicles and their expression has a positive correlation with ovarian follicle growth (62, 63). These findings support the important role of apelin in female fertility.

Apelin can be involved in the embryo implantation process via enhancing the basal steroid secretion in ovarian cells and inhibiting FSH-induced steroid secretion. Moreover, apelin stimulates progesterone secretion in the middle of the luteal phase and also stimulates hydroxysteroid dehydrogenase (HSD) activity (64). There is emerging evidence that the expression level of apelin increases during the estrous cycle and decreases following corpus luteum degeneration (65). Apelin is also expressed by endometrial tissue and its expression is more pronounced during the secretory phase of the menstrual cycle, confirming the possible role of apelin in endometrial receptivity and implantation (66). In this respect, it has been seen that apelin induces some of the important implantation-related signaling pathways, especially MAPK signaling (67). It seems that the association of apelin with different signaling pathways and their effect on implantation is an interesting issue that deserves further study. For example, apelin has recently been shown to enhance the proliferation of trophoblast cells by phosphorylation of extracellular signal-regulated kinase (ERK1/2), Stat3, and AMPKα (67). On the other hand, it has been shown that the ablation of the *Prkaa1* and *Prkaa2* genes which are involved in encoding the catalytic domains α1 and α2 of AMPKα, could impair embryo implantation in mice (68). Therefore, apelin may play an important role in implantation by affecting AMPKα signaling. Moreover, apelin can weaken uterine contractions and consequently facilitate embryo implantation in the human myometrium (69). In contrast, in a study on rats, it has been reported that apelin induced uterus contraction partially via the protein kinase C pathway (70). Additionally, apelin has antioxidant properties and could increase catalase activity and attenuate reactive oxygen species production (71, 72). Since oxidative stress could have detrimental effects on embryo implantation (73, 74, 75), the apelin-induced antioxidant defenses could support successful implantation. Given the role of apelin in modulating the immune system and inflammation, and on the other hand, the importance of these events in embryo implantation, it is likely that apelin has further roles in the implantation process. However, few studies have been performed on the association of apelin with implantation and further investigations are required to clarify the underlying mechanisms.

## Chemerin

Chemerin is highly expressed in white adipose tissue, liver, and lung. Moreover, its receptor, chemokine-like receptor 1 (CMKLR1), is abundantly found in immune cells (76). This adipokine is involved in the differentiation of adipose cells, chemotaxis of immune cells, angiogenesis, and production of cytokines such as IL6 (76, 77). Chemerin exerts an inhibitory effect on ovarian follicular development and can induce arresting of follicle growth and apoptosis of granulosa cells (78). In addition, studies have shown that chemerin attenuated FSH-induced follicular steroidogenesis which raised the possibility of involvement in PCOS (79).

The endometrium, placenta, trophoblasts, and conceptuses express members of the chemerin system which may reflect the role of this adipokine in embryo–maternal interactions (80). Furthermore, it has been shown that local factors in the uterus could affect the protein expression of the chemerin system during early gestation (25). It has been indicated that this adipokine can prevent embryo abortion via regulating ERK1/2 phosphorylation, an important signaling pathway in embryo implantation (25, 81). In this respect, an upregulation of CMKLR1 in the decidua and a reduction of chemerin in plasma have been reported in women who had spontaneous abortions (81). In a study on pigs, it has been seen that the protein expression of chemerin and CCRL2 (C-C motif chemokine receptor-like 2; a chemerin receptor) in the endometrium was in the highest levels during implantation (25). Moreover, this group demonstrated that the levels of GPR1 (protein-coupled receptor 1c; a chemerin receptor) were significantly increased in the endometrium during embryo migration. An enhanced expression of chemerin and its receptors (CMKLR1, CCRL2, and GPR1) was also observed in the myometrium of pigs during embryo implantation (25). An elevated expression of chemerin has been found in the stromal cells during decidualization (81). Chemerin can augment AMPKα activity which is involved in uterine receptivity and implantation (68, 82). This adipokine also plays a key

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role in the accumulation of natural killer (NK) cells at the implantation site (83); the NK cells induce trophoblast invasion by producing different cytokines such as IL8 and IFNγ-inducible protein 10 (84). Moreover, chemerin takes part in vascular remodeling and angiogenesis across early pregnancy (83).

The clinical evidence has shown that elevated proinflammatory factors such as MIP1β, TNFα, and dendritic cells (DCs) following endometrial biopsy could increase the rate of successful implantation (85). Chemerin is involved in the regulation of inflammatory processes (86). Chemerin is also able to enhance the accumulation of DCs at the site of inflammation (87). Moreover, a correlation has been reported between serum levels of chemerin and TNFα (88). Interestingly, Gnainsky *et al.* (89) found a positive association between levels of TNFα in the endometrium and successful implantation. Nevertheless, chemerin also has anti-inflammatory and pro-oxidating effects (82, 90) that may influence embryo implantation; so further studies are needed to clarify the exact role of chemerin in implantation.

## Visfatin

Visfatin or nicotinamide phosphoribosyltransferase (NAMPT) functionally acts as an enzyme restricting the conversion of nicotinamide to nicotinamide mononucleotide (NMN) which subsequently activates the synthesis of nicotinamide adenine dinucleotide (NAD+) and thus plays a regulatory role in the energy metabolism (91, 92). Visfatin is also involved in inflammatory responses (secretion of IL1β, IL6, and TNFα), prevention of neutrophils apoptosis, and maturation of B cells (93, 94). Moreover, recent studies have shown that visfatin could bind and activate the Toll-like receptor 4 (95) and also due to its insulin-mimetic activity, can bind the insulin receptor and cause insulin resistance and consequently regulate glucose levels (96).

Based on the immunohistochemical findings, visfatin is expressed in the myometrium, perimetrium, and especially the endometrium, showing the potential role of this adipokine in functions of the uterus (97). Interestingly, the expression of this adipokine is under the control of steroids as estrogen increases visfatin levels and progesterone has an inhibitory effect on its expression (98). Annie *et al.* (99) have reported that visfatin can be involved in implantation through increasing proliferating cell nuclear antigen expression and maintaining the balance between apoptotic and anti-apoptotic elements in the mice uterus. As another mechanism, Yang *et al.* (97) have shown that visfatin modulates inflammatory responses by regulating the expression of eosinophil, myeloperoxidase, and inflammatory cytokines and therefore plays a vital role in the uterine immune responses. In line with this study, Kim *et al.* (100) have also demonstrated that visfatin is involved in the regulation of the placental inflammatory response and angiogenesis. Although the information regarding the role and the molecular mechanism of visfatin in embryo implantation is not adequate, the findings of several studies elucidate its involvement in early pregnancy (101).

## RBP4

Vitamin A is indispensable for the function of the immune system, epithelial tissue maintenance, and differentiation. Besides, it plays an undeniable role in the reproductive system including ovarian follicle development and endometrial receptivity (102, 103). RBP4, a component of adipokines (104), acts as a specific carrier of vitamin A from the liver to the peripheral tissues and is involved in the regulation of cell differentiation and invasion (105, 106). There are different types of RBP (1 to 4) that have diverse functions in the various tissues; RBP4 is the most abundant type in the serum. Interestingly, in addition to the liver, this protein is produced by the endometrium (107). It has been demonstrated that the plasma concentration of RBP4 is regulated by progesterone and it reaches the maximum level at the mid to late phases of a menstrual cycle to provide vitamin A for the uterus (108, 109). Given the importance of vitamin A in uterine functions, the availability of this vitamin in the uterus is contingent on the concentration of RBP4. The immunocytochemistry analysis has verified the secretion of RBP4 by the uterus (107), which infers the importance of RBP4 in uterine functions. More interestingly, studies have indicated that the expression of RBP4 is increased on days 7 and 13 of a cycle, which are two important checkpoints for preimplantation (110). The HSD17B is involved in the regulation of estrogen and androgen levels and also plays an important role in decidualization. Studies on human endometrial stromal cells have shown that RBP4 could induce 17β-HSD expression in the epithelial cells (111, 112). Elevated levels of RBP4 during the decidualization can confirm that RBP4 is involved in decidualization via inducing HSD17B expression. Also, RBP4 can induce the secretion of VEGF, an essential factor for angiogenesis and implantation (113). A study by Li *et al.* (105) showed that overexpression of RBP4 could increase trophoblastic

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proliferation and invasion via suppressing the PI3K/AKT signaling pathway and upregulating the matrix-degrading enzymes (MMP2 and MMP9), which are important in the implantation and decidualization processes.

### Progranulin

Progranulin (PGRN) structurally acts as a precursor of granulin, epithelin, and PC cell-derived growth factor (26, 114). In the intact form, PGRN has anti-inflammatory effects but it acts as a proinflammatory factor when it is cleaved into granulin (115). PGRN is expressed in almost all tissues but it can abundantly be found in rapidly dividing tissues such as keratinocyte, enterocyte, gastrointestinal tract, and uterine epithelium. PGRN is highly expressed in the uterine epithelium during implantation (116). Furthermore, the expression of PGRN has been reported in preimplantation embryos with the highest levels in the blastocyst stage (117). In addition to blastocyst outgrowth, PGRN can promote the adhesion of blastocyst (118). The maternal and embryonic expression of PGRN suggests its role in the implantation and placentation process. Moreover, the involvement of PGRN in endometrial decidualization has been demonstrated (119). In mink, the association of PGRN expression with hypertrophy and proliferation of endometrial epithelium as well as growth and migration of cytotrophoblast suggests its role in embryo implantation and placentation (26). Given the anti-inflammatory properties of PGRN and its role in the growth of epithelial cells and also the presence of this adipokine in all stages before the implantation, it can be postulated that PGRN is involved in embryo implantation. It has been shown that the expression of PGRN dramatically drops following implantation (120). Perez *et al.* (121) showed that PGRN could play an effective role in uterine angiogenesis and facilitating implantation in humans. It has also been documented that the expression of PGRN is increased during human embryo implantation, and dysregulated PGRN expression is associated with pregnancy-related diseases such as abnormal placental angiogenesis (122). Qin *et al.* (118) have indicated that PGRN is secreted from the mammalian blastocysts into the surrounding medium and it is involved in the preparation of the blastocyst for hatching and implantation. In this regard, they reported that adding exogenous PGRN to the culture medium could considerably increase blastocyst hatching, an essential process for implantation (118). Overall, according to the results of studies, PGRN might be an effective factor for embryo implantation, however, to clarify the exact role of this adipokine in implantation further studies are required.

## Conclusion

Adipokines and their receptors are present in embryonic and uterine components suggesting their significant roles in fetal–maternal crosstalk during implantation. The involvement of adipokines has been demonstrated in the regulation of peri-implantation embryo development, trophoblast activity, endometrial receptivity, decidualization, and implantation. Moreover, abnormal alterations in the levels of adipokines may result in pregnancy complications, including implantation failure and recurrent spontaneous abortions (7, 41). These alterations might be either as a consequence of disturbances in the upstream factors, such as hormones or as a causative factor in affecting downstream implantation-related pathways, for example, steroidogenesis. However, the exact underlying mechanisms by which adipokines are involved in implantation are not thoroughly understood and merits further investigation. Furthermore, additional comprehensive studies are required to determine whether the measurement of adipokine system components in uterine fluid during early pregnancy can provide valuable data regarding the prediction of successful implantation.

**Declaration of interest**
The authors declare that there is no conflict of interest that could be perceived as prejudicing the impartiality of this review.

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