Review Article

Diverse Roles of Prostaglandins in Blastocyst Implantation

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Prostaglandins (PGs), derivatives of arachidonic acid, play an indispensable role in embryo implantation. PGs have been reported to participate in the increase in vascular permeability, stromal decidualization, blastocyst growth and development, leukocyte recruitment, embryo transport, trophoblast invasion, and extracellular matrix remodeling during implantation. Deranged PGs syntheses and actions will result in implantation failure. This review summarizes up-to-date literatures on the role of PGs in blastocyst implantation which could provide a broad perspective to guide further research in this field.

1. Introduction

PGs are produced from arachidonic acid which is released from the membrane phospholipids via the action of phospholipase A\(_2\) enzyme [1]. Arachidonic acid is converted into PGH\(_2\) by PG-endoperoxide synthases (PTGS), also known as cyclooxygenase (COX). COX is the key enzyme in PG biosynthesis, acting both as dioxygenase and peroxidase [2]. There are currently two identified PTGS isozymes: a constitutive PTGS1 (COX-1) and inducible PTGS2 (COX-2), which differ in their expression and tissue distribution [3]. COX dimer can be found both in the endoplasmic reticulum and nuclear membrane [2].

PGH\(_2\) is an unstable intermediate which undergoes rapid conversion into various other prostanooids by specific terminal PG synthases. The latter include PGE synthase (PGES), PGIS, PGDS, PGFS, and thromboxane synthase (TXS) that form PGE\(_2\), PGI\(_2\), PGD\(_2\), PGF\(_{2\alpha}\), and TXA\(_2\) from PGH\(_2\), respectively [4]. PGES consists of microsomal (m)PGES-1, mPGES-2, and cytosolic (c)PGES [5]. Meanwhile, alpha keto-reductase (AKR)1A1 and AKRIB1 have been identified as functional PGFS in humans [6]. PGI\(_2\), also known as prostacyclin, is non-enzymatically metabolized to a more stable form, 6-keto PGF\(_{1\alpha}\) [7]. PGF\(_2\) can be synthesized directly from PGH\(_2\), or indirectly via PGE\(_2\) while PGI\(_2\) could derive either directly from PGH\(_2\) or indirectly via PGD\(_2\) [8].

PGs act via binding to its various G-protein coupled receptor (GPCR), which include four subtypes of PGE receptor (EP) (EP1, EP2, EP3, and EP4) [9], PGF receptor (FP), PGI\(_2\) receptor (IP), and PGD\(_2\) receptor (DP) which consist of DPI and DP2 [10]. Additionally, PGI\(_2\) may act through a nuclear peroxisome proliferator-activated receptor-\(\delta\) (PPAR-\(\delta\)) [11], a ligand activated nuclear receptor. PGE\(_2\) has recently been reported to interact with PPAR-\(\delta\) [12]. The binding of PGs to its specific receptor will activate series of intracellular signaling cascade. Activation of EP1 is coupled to Ca\(^{2+}\) mobilization and EP2 and EP4 trigger while EP3 inhibits adenyl cyclase [13]. Meanwhile, FP activation is coupled to phospholipase C-inositol trisphosphate (IP\(_3\)) pathway and Ca\(^{2+}\) mobilization [14].

PGs play an indispensable role in embryo implantation. The expression of COX-1 and -2 [15], cPGES [16], mPGES-1 and -2 [17], and prostacyclin synthase [18] has been reported at the implantation site in mice, rats, and humans. PGE\(_2\)S and PGF\(_{2\alpha}\)S have been localized in the human endometrial epithelia with an increase in PGE\(_2\) and PGF\(_{2\alpha}\) concentration in the uterine fluid during the implantation window period [19]. Meanwhile, COX-1 is expressed in the luminal and glandular epithelia while COX-2 is expressed in the luminal epithelia and perivascular cells during the implantation window period in humans [20]. Female mice lacking COX-2 were infertile with specific fertilization, implantation, and decidualization defects [21]. COX-1-deficient female mice were fertile; however, they develop specific parturition defect [21]. Mice deficient of PG receptor specifically EP2 have been reported to exhibit impaired reproductive functions [22]. In rodents, PGE\(_2\) and PGF\(_{2\alpha}\) have been reported to play important role in blastocyst spacing, implantation, and...
decidualization while PGF_2α (prostacyclin) has been implicated in implantation and decidualization involving PPAR-δ [23]. PGE_2 and PGF_2α have also been reported to be involved in rodents’ myometrial circular muscle contraction which facilitates embryo transport and spacing [24].

The synthesis of PGs and its biosynthetic enzymes in the female reproductive tract can be regulated by hormones and paracrine factors. In humans, COX-1 expression in the glandular epithelia and COX-2 expression in the luminal epithelia were significantly decreased following treatment with mifepristone, a progesterone receptor antagonist, indicating that progesterone could influence COX expression [20]. In the early pregnancy in mice, uterine COX-1 gene could be regulated by the ovarian steroids, while COX-2 gene could be regulated by the implanting blastocyst [25]. Several other hormones and cytokines have also been reported to be involved in PG synthesis. Chorionic gonadotrophin (CG) was found to regulate PGE_2 production by human and primate endometrial epithelia [26]. IL-1α was reported to induce PGE_2 and PGF_2α secretion by the mouse uterine stromal cells in vitro [27]. Lyso phosphatidic acid (LPA), a bioactive lipid derivative, was reported to enhance PGE_2 synthesis and COX-2 expression in the rat uterus [28]. Activation of epithelial Na⁺ channel (ENaC) in the mouse endometrial epithelium by embryo-released serine protease, trypsin, has recently been reported to trigger Ca²⁺ influx that could lead to PGE_2 release, CREB transcription factor phosphorylation, and up-regulation of COX-2 enzyme [29].

An understanding on the role of PG in blastocyst implantation is far from complete. In view of this, we aim to summarize literatures related to PG role in implantation particularly in humans and rodents in order to provide a broad perspective to guide further research in this field.

2. Role of PGs in Increased Vascular Permeability and Angiogenesis at the Implantation Site

Increased vascular permeability and stromal edema are two of the earliest signs following blastocyst attachment [30]. In mice, increased vascular permeability could be seen at day 4.5 of the oestrus cycle, as evidence from a contrast-enhanced (CE)-MRI and fluorescence microscopic studies [31]. Changes in vascular permeability are followed by progressive increase in angiogenesis [31]. Sex steroids have been reported to exert differential effect on these changes with estrogen increases the permeability but profoundly inhibits angiogenesis in vivo, while progesterone stimulates angiogenesis however has little effect on permeability [32].

Changes in vascular permeability and angiogenesis at the time of embryo implantation were caused by differential expression of proangiogenic factor in the uterus which include the vascular endothelial growth factor (VEGF) and its receptors [33]. VEGF together with angiopoietin (Ang)-1 and Ang-2 direct angiogenesis during decidualization. Ang-1 in collaboration with VEGF induces vessel maturation and maintains vessel leakiness, whereas Ang-2 induces vessel destabilization required for further sprouting [34]. The expression of Ang-like 4 gene has been reported in the uterus at the time of decidualization in response to PPAR agonist [35] while angiomiotin (Amot-2), a vascular angiogenesis-related protein, has recently been reported to be expressed in the endometrial stroma under the progesterone influence [36].

PGs and platelet-activating factor (PAF) are important paracrine factors involved in the increase in vascular permeability at site of embryo implantation [37]. PAF receptor (PAF-R) mRNA was detected in the endometrial glands during the secretory phase of the menstrual cycle [37]. Interaction between PAF and its receptor resulted in a rapid release of nitric oxide (NO), a potent vasodilator, increased VEGF expression, and activates focal adhesion kinase, FAKp125 [38]. PAF-evoked NO release was dependent on protein kinase C (PKC) and extracellular Ca²⁺ [39].

PGE_2 was found to be more effective than prostacyclin (PGI₂), PPAR-δ, and retinoic acid (RXRA) in causing an increase in endometrial vascular permeability in rats [40]. PGE_2 mediates sex-steroid effect on VEGF and angiopoietin [34] expression which resulted in increased vascular permeability and angiogenesis during implantation and decidualization, respectively [41]. In contrast, the activity of nitric oxide synthase (NOS), an enzyme responsible for NO production which was reported to be the highest at the site of embryo implantation [42], was inhibited by PGE_2 [43], suggesting that PGE_2 could also be involved in the control of the extent of vascular permeability induced by NO. On the other hand, inducible NO itself has been reported to affect COX-2 activity and thus could affect the PG synthesis [44].

The involvement of PGF_2α in NO synthesis and blood flow to the implantation site is relatively unknown; however, PGF_2α was found to cause acute increase in blood flow to the corpus luteum by stimulating the activity of epithelial nitric oxide synthase (eNOS) [45]. Additionally, PGF_2α was also found to affect angiogenesis as reported in the endometrial adenocarcinoma tissue [46]. Prostacyclin (PGI₂), a potent vasodilator, has been reported to play important role in the increase in vascular permeability at the implantation site. The level of prostacyclin increases in early pregnancy and is the main eicosanoid produced by the endothelia of the smooth muscle arteries in parallel with the increase in the expression of PGIS [47]. Prostacyclin binds to IP in the glandular epithelial cells, resulting in rapid activation of extracellular signal regulated kinase (ERK)1/2 as well as inducing the expression of proangiogenic genes, basic fibroblast growth factor (bFGF), and Ang-1 and -2, via cross talk with the epidermal growth factor receptor (EGF-R) [48].

3. Role of PGs in Decidualization

Decidualization is the most important event attributed to PGs, which is defined as differentiation of the elongated stromal fibroblasts into secretary, epithelioid-like decidual cells. In rodents, this process is initiated by the implanting blastocyst [34] while in humans decidualization begins immediately following ovulation, reaches the peak in the mid-luteal phase of the menstrual cycle [49], in response to progesterone, and is independent of the blastocyst signal [50].
Transformation of the stromal fibroblasts into decidual cells can first be seen in the vicinity of the terminal spiral arteries which then spread throughout the endometrial compartment. The decidualized stromal cells immediately surrounding the implanting blastocyst cease proliferating and formed a primary decidual zone (PDZ) [51, 52]. Cells surrounding PDZ continue to proliferate and differentiate into polyplid decidual cells which formed secondary decidual zone (SDZ) [34]. Decidualization is associated with polyplody, that is, formation of multinucleated (mono- and binucleated) and giant cells [53, 54] due to the altered expression and functional activity of the cell cycle regulatory molecules [55] such as cyclin D1, which can be induced by heparin-binding epidermal growth factor (HB-EGF) [54].

Decidualization is characterized by enhanced production of insulin-like growth factor-binding protein-1 (IGFBP-1), prolactin (dPRL), and forkhead transcriptional factor (FOXO1) in response to hormonal stimulation [49, 56]. The expression of decidual specific genes that encode these proteins requires cAMP [57], progesterone [58], and the recently identified ERKI/2 [59] signaling. The binding of peptide hormones and prostanoids to GPCR will result in the activation of adenylyl cyclase, an enzyme involved in cAMP synthesis [60]. cAMP will then phosphorylate protein kinase A (PKA), which consist of regulatory and catalytic subunits [61]. Binding of cAMP to the regulatory subunit will result in the release and activation of the catalytic subunit which will phosphorylate target molecules in the cytoplasm or transcription factors in the nucleus [62]. Persistent rise in intracellular cAMP level is required to maintain the decidualized phenotype [63] in which cAMP withdrawal will cause the decidualized stromal cells to reacquire an undifferentiated phenotype [64].

PKA phosphorylates cAMP response element binding protein (CREB) [58] and the related cAMP response element modulator (CREM) [65]. Phosphorylation will also recruit coactivator CREB binding protein (CBP) to the promoter region of the target genes [50], facilitating DNA transcription [66]. A rise in intracellular cAMP will cause Ca<sup>2+</sup> to enter the cell via TRPC1 channel which is essential for the initiation of decidualization [67]. Decidualization process can be inhibited by several factors including transforming growth factor (TGF)-β1 [68] and Krüppel-like factor 12 transcription factor [69]. Phosphodiesterases, an enzyme that degrades cAMP into AMP which result in a decrease in cAMP level, was also found to inhibit decidualization [70].

Peptide hormones implicated in the decidualization process include relaxin [71], luteinizing hormone/human chorionic gonadotrophin (LH/hCG) [72], and corticotrophin releasing hormone (CRH) [73], while PGE₂ is the only prostanoid involved [74]. Other factors include insulin and insulin-like growth factor (IGF-I and II) [75], transforming growth factor (TGF)-β [76], epidermal growth factor (EGF), and platelet-derived growth factor (PDGF) [77]. PGE₂ has been reported to cause an increase in intracellular cAMP level and stimulates the activity of alkaline phosphatase (ALP) [78] via EP2 and EP4 receptors [79]. Meanwhile, PGE₃ and relaxin, partly via cAMP/PKA-dependent pathway, have been reported to stimulate IL-11 secretion which cause a direct increase in the cAMP level [80].

Decidual cells have been reported to synthesize and secrete PGs [81] and express PG receptors [82]. PGs can also be transported into these cells via the prostaglandin transporter (PGT). Evidences for the increase in PG synthesis include upregulation of COX-1, COX-2, cPGES, and mPGES expression in mice [16, 83], rats [18, 84], guinea pigs [85], and humans [86, 87] and upregulation of AKRIB1, a highly functioning PGF synthase responsible for PGF<sub>2α</sub> production in humans [88]. In early pregnancy in rats, COX-2 expression is increased between days 2 to 5 [89] suggesting that PGs are required in the process of stromal cells decidualization. While PGE₂ and PGF<sub>2α</sub> are the main PGs involved, prostacyclin (PGI₂) has also been implicated in decidualization in view that in mice, the expression of PGI₂ significantly increases at day 5 and gradually decreases thereafter [90]. In addition to the elevated expression of PG biosynthetic enzymes, the reported increase in the expression of EP2 and PPAR-δ in mouse decidual cells further provides evidence on the involvement of PGs in this process [91].

Progesterone is essential for decidualization in both humans and rodents. Progesterone exerts its effect via binding to the nuclear progesterone receptor-A (PR-A), which interacts with the transcription factors including CCAAT/enhancer-binding protein β (C/EBPβ) [92], forkhead proteins [93], and signal transducer and activator of transcription 5 (STAT5) [94]. Progesterone receptor (PR)-interacting protein Krüppel-like factor (KLF) 9, which expression is high in the predecidual stroma, interacts with bone morphogenetic protein 2 (BMP2) to maintain stromal cells sensitivity towards progesterone [95]. C/EBPβ is also essential for the cAMP signaling [96]. C/EBPβ mediates activation of the decidual PRL promoter, resulting in the transcription of dPRL gene [50]. In humans, a functional link between C/EBPβ and STAT3 was found to be crucial in the regulation of endometrial stromal cell differentiation [97].

In addition to dPRL, PR also participates in the transcriptional regulation of IGFBP-1 gene [98]. PR could be involved in regulating Snail, a transcription repressor which has recently been identified to play a central role in the epithelial-mesenchymal transition in which its expression has been reported to be induced by HB-EGF via EGFR-ERK-STAT3 signaling pathway [99]. HOXA-10, an abdominal-like homeobox gene reported to be involved in the decidualization process, could also be influenced by PR where loss of HOXA-10 function in mice has been reported to result in infertility [100].

The involvement of PGs in the progesterone-induced decidualization has been documented. COX-2 was reported to regulate the expression of Snail transcription repressor [99]. Dysregulation of EGF and COX-2 expression in the mouse uterus during peri-implantation period which is associated with high plasma progesterone level resulted in implantation failure [101]. Meanwhile, progesterone was also found to upregulate the expression of EP2 [102], while progesterone and HOXA-10 have been reported to upregulate the expression of EP3 and EP4 in the stroma [100]. Apart from this, other roles of PGs in these processes remain unknown.
4. Role of PGs in Extracellular Matrix Remodeling

The extracellular matrix (ECM) is composed of collagens, noncollagenous multiahesive glycoproteins, elastin, hyaluronan, proteoglycans, and glycosaminoglycans [103]. In early pregnancy, uterine ECM plays important role in decidualization, embryo attachment, trophoblast invasion, and maintenance of pregnancy [104]. ECM has been reported to undergo extensive remodeling in preparation for blastocyst adhesion, trophoblast invasion, and placentation. Changes in ECM composition are characterized by phagocytosis and enzymatic digestion of collagen fibrils, increased collagen fibril diameter, deposition of basement membrane proteins, synthesis and secretion of sulfated glycosaminoglycans, and decrease in the number of elastic fibrils surrounding the matured decidual cells [105].

Sex steroids, cytokines, PGs, and growth factors have been reported to affect endometrial ECM composition in early pregnancy [106]. Dynamic changes in ECM are evidenced from the spatiotemporal changes in the expression of matrix metalloproteinase enzyme (MMP) and tissue inhibitor of metalloproteinase (TIMP) isoforms throughout the estrus cycle and in early pregnancy. These two enzymes participate in the ECM degradation and remodelling. The expression of MMP-2 mRNA was observed in the stroma between days 3 and 5 in the secondary decidual zone on day 6, while MMP-9 mRNA was expressed in the trophoblast giant cells on day 8 of pregnancy in mice [107]. Meanwhile, the expression of TIMP-1, 2, and 3 was detected in the primary decidual zone on days 2 to 5 and in the primary and secondary decidual zone on days 6 to 8 of early pregnancy in mice [107] and rats [108, 109]. TIMPs have been proposed to regulate the extent of trophoblast invasion [110]. Human endometrial stromal cells secrete TIMP-3 which play essential role in early implantation by modulating the trophoblast invasion [111].

Progestosterone [112, 113], 17β-estradiol [114], urokinase-plasminogen activator [115], leukaemia inhibitory factor (LIF) [116], tumour necrosis factor (TNF) and interferon-γ [117], transforming growth factor beta (TGFβ), interleukin-1 and interleukin-6 (IL-1, IL-6) [118], lipopolysaccharides [119], epidermal growth factor (EGF) [120], insulin-like growth factor (IGF), and insulin-like growth factor binding protein-1 (IGFBP-1) [121] as well as trophoblast factors including hCG [122] have been reported to affect the expression and activities of MMPs and TIMPs. The effect of PGs on uterine ECM degradation and remodeling is however poorly understood. Limited observations suggested that PGE$_{2\alpha}$ might be involved in ECM turnover via affecting the expression of MMP2, cathepsin L, TIMP2 and TIMP3, plasminogen activator inhibitor1 (PAI1), tissue type plasminogen activator (tPA), urokinase plasminogen activator (uPA), endothelin 1, calponin, carboxypeptidase D and calponin acid [123]. Meanwhile, in the cervix, PGE$_2$ via EP2 and EP4 has been reported to stimulate hyaluronan synthesis in the remodeling of cervical ECM [124] while PGE$_{2\alpha}$ and IL-1α have been reported to stimulate the secretion of MMP-1 which plays important role in the degradation of extracellular collagen types I and III [125].

5. Role of PGs in Leukocyte Infiltration

A profound influx of uterine natural killer (NK) cells and macrophages is essential for successful implantation [126, 127]. In the murine decidua, NK cells are progressively inactivated by PGE$_2$ produced by the decidual cells and decidual macrophages [128]. Meanwhile, PGE$_2$ secretion by the first trimester human decidua blocks activation of the maternal decidual leukocytes with a potential antitrophoblast killer function by inhibiting *in situ* IL-2 receptor generation and IL-2 production [129]. PGE$_{2\alpha}$ may be involved in the inflammatory response by regulating neutrophil chemotaxis as reported in the endometrial adenocarcinoma tissue [130].

6. Role of PGs in Embryo Transport

The transport of gametes and embryos which involved both muscular contraction and ciliary activity is an important function of the Fallopian tube [131]. Progesterone is required for the normal embryo transport along the oviduct [132, 133]. PGs, a known mediator of muscular contractility, has long been documented to be involved in the oviductal embryo transport [134]. PGs mediate both contraction [135] and relaxation [136] of the smooth muscle. Epithelial-derived PGs activate DP, EP2, EP4, and IP receptors which cause an increase in intracellular cAMP level ([Camp])$_2$, resulting in smooth muscle relaxation [137]. On the other hand, EPI and FP activation which coupled to Ca$^{2+}$ mobilization resulted in the smooth muscle contraction [138].

Different EP isoforms that have been identified along the female reproductive tract, with their activation, can either cause increased or decreased intracellular cAMP ([Camp])$_2$, or increased intracellular Ca$^{2+}$ level though usually resulting in the smooth muscle contraction [139]. The expression of EP and FP has been reported in the human Fallopian tubes as evidence from the increased smooth muscle contraction following treatment with PGE$_{2\alpha}$ and PGE$_2$ [140]. COX-2, PGIS, and IP receptor have also been reported to be expressed in human Fallopian tubes [141] which could serve as autocrine regulator for the oviductal smooth muscle contraction [142].

7. Role of PGs in Blastocyst Growth and Development

Coordinated growth and development of the embryos from 2- to 8-cell and subsequently 8-cell into morula and blastocyst stages is a prerequisite for successful implantation [143]. During development, blastocyst expresses multiple factors and their receptors in response to sex steroids and growth factors, which in turn regulate blastocyst growth and participate in the signal exchange with the receptive endometrium. Hormones and factors expressed include the preimplantation factor (PIF) [144], chorionic gonadotrophins (cG) [145], leukemic inhibitory factor (LIF) [146], heparin-binding epidermal growth factor (HB-EGF) [147], and PGs [148].

Prostacyclin (PGI$_2$) is the most abundant PGs produced by the mouse blastocysts. In addition, the 8-cell, morula, and blastocyst stages also synthesize PGE$_2$ [149]. PGI$_2$ binds to IP
receptor and is involved in regulating embryo development [150]. Meanwhile, COX-1, COX-2, and PGIS have also been reported to be expressed in 4-cell stage embryos and beyond and in the inner cell mass and trophectoderm of the mouse blastocysts [151]. In the golden hamsters, COX-2 expression in 8-cell stage embryos through the hatched blastocysts was localized mainly in the blastocysts’ trophectoderm was critical for blastocyst hatching [152]. PGI₂ has also been reported to regulate blastocyst cells apoptosis by acting as an antiapoptotic factor [149]. Meanwhile, EP2 and FP expression which have been detected in mouse blastocysts’ trophectoderm and inner cell mass participated in embryo adhesion [19].

In addition to PGI₂, PGE₂ also plays important role in embryo development [148]. mPGES mRNA was detected at all stages during preimplantation embryo development [83] while cPGES expression has been reported in 2-cell, 4-cell, and 8-cell, morula, and blastocyst stages [16] in mice. Preimplantation mouse embryos also express PPAR-δ, which is essential for enhancing the PGI₂ effect on blastocyst hatching where impaired blastocyst formation and hatching have been reported in the PPAR-δ deficient embryos [153].

8. Role of PGs in Trophoblast Invasion

Following blastocyst adhesion, trophoblast cells differentiate and acquire the invasive phenotype [154]. The role of PGs in facilitating trophoblast invasion is largely unknown; however, several evidences indicate its involvement in this process. PGE₂ and EP2 agonist have been reported to increase the adhesiveness of human HTR-8/SVneo trophoblast cell line (human trophoblast-derived cell line) to the ECM via MEK/MAPK signaling pathway as well as upregulating the expression of cell adhesion protein such as focal adhesion kinase and intercellular adhesion molecule such as integrins [155]. Additionally, the expression of EP2 has also been reported in the trophoblast which could be stimulated by PGE₂ via autocrine signaling [155].

The expression of COX-2 and PGE₂ synthase was also detected in the human HTR-8/SVneo cells [156]. Co-stimulation by LIF and IL-1β induced higher amount of PGE₂ production and further migration of these cells [157]. The decidua-derived factors including PGs have been reported to increase trophoblast cell invasiveness by reducing TIMP1 and TIMP3, however up-regulate TIMP2 expression, increase the mRNA expression of integrin-5 and integrin-6, but not integrin-αV subunit, elevate the expression of MMP2, MMP3, and MMP9 mRNA and increase the activity of MMP2 and MMP9 [158]. Meanwhile, a contradicting report indicated that PGE₂ inhibits extravillous trophoblast cell functions, which could help to prevent excessive trophoblast proliferation and migration [159].

9. Conclusion

The understanding on the role of PG in blastocyst implantation and early pregnancy is far from complete. While most information was obtained from animal studies especially in rodents, more researches need to be performed in humans in order to further explore the mechanisms underlying the diverse PGs action on multiple processes of implantation.

Conflict of Interests

The author declares that there is no conflict of interests.

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References

[1] H. Satoh, K. Watanabe, M. Kawaminami, and S. Kurusu, “A comprehensive immunohistochemistry of prostaglandins F2α and E2 synthetic enzymes in rat ovary and uterus around parturition,” Prostaglandins & Other Lipid Mediators, vol. 106, pp. 23–28, 2013.

[2] W. L. Smith, Y. Urade, and P. J. Jakobsson, “Enzymes of the cyclooxygenase pathways of prostanooid biosynthesis,” Chemical Reviews, vol. 111, no. 10, pp. 5821–5865, 2011.

[3] T. Joseph, I. A. Zalenskaya, L. C. Sawyer, N. Chandra, and G. F. Doncel, “Seminal plasma induces prostaglandin-endoperoxide synthase (PTGS) 2 expression in immortalized human vaginal cells: involvement of semen prostaglandin E2 in PTGS2 upregulation,” Biology of Reproduction, vol. 88, no. 1, pp. 1–2, 2013.

[4] L. Chen, G. Yang, and T. Grosser, “Prostanoids and inflammatory pain,” Prostaglandins & Other Lipid Mediators, vol. 104-105, pp. 58–66, 2013.

[5] K. Gudis, A. Tatsuguchi, K. Wada et al., “Microsomal prostaglandin E synthase (mPGES)-1, mPGES-2 and cytosolic PGES expression in human gastritis and gastric ulcer tissue,” Laboratory Investigation, vol. 85, no. 2, pp. 225–236, 2005.

[6] N. L. Pépin and P. Chapdelaine, “Evaluation of the prostaglandin F synthase activity of human and bovine ald-keto reductases: AKR1AlcomplementAKRIBsaspotentPGFsynthases,” Prostaglandins & Other Lipid Mediators, vol. 106, pp. 124–132, 2013.

[7] J. Blanco-Rivero, V. Cachofeiro, V. Lahera et al., “Participation of prostacyclin in endothelial dysfunction induced by aldosterone in normotensive and hypertensive rats,” Hypertension, vol. 46, no. 1, pp. 107–112, 2005.

[8] R. D. Catalano, M. R. Wilson, S. C. Boddy, and H. N. Jabbour, “Comprehensive expression analysis of prostanooid enzymes and receptors in the human endometrium across the menstrual cycle,” Molecular Human Reproduction, vol. 17, no. 3, Article ID gaoq094, pp. 182–192, 2011.

[9] G. Gu, Q. Gao, X. Yuan, L. Huang, and L. Ge, “Immunolocalization of adipocytes and prostaglandin E2 and its four receptor proteins EP1, EP2, EP3, and EP4 in the caprine cervix during spontaneous term labor,” Biology of Reproduction, vol. 86, no. 5, article 159, pp. 1–10, 2012.

[10] D. E. Woodward, R. L. Jones, and S. Narumiya, “International union of basic and clinical pharmacology. LXXXIII: classification of prostanooid receptors, updating 15 years of progress,” Pharmacological Reviews, vol. 63, no. 3, pp. 471–538, 2011.

[11] H. Lim, R. A. Gupta, W-G. Ma et al., “Cyclo-oxygenase-2-derived prostacyclin mediates embryo implantation in the
mouse via PPARδ,” *Genes & Development*, vol. 13, no. 12, pp. 1561–1574, 1999.

[12] V. García-Alonso, C. López-Vicario, E. Titos et al., “Coordinate functional regulation between microsomal prostaglandin E synthase-1 (mPGES-1) and peroxisome proliferator-activated receptor γ (PPARY) in the conversion of white-to-brown adipocytes,” *Journal of Biological Chemistry*, vol. 288, no. 39, pp. 28230–28242, 2013.

[13] Y. Sugimoto and S. Narumiya, “Prostaglandin E receptors,” *Journal of Biological Chemistry*, vol. 282, no. 16, pp. 16163–16167, 2007.

[14] E. G. A. Harks, W. J. J. M. Scheenen, P. H. J. Peters, E. J. J. van Zoelen, and A. P. R. Theuvenet, “Prostaglandin F2α induces unsynchronized intracellular calcium oscillations in monolayers of gap junctionally coupled NRK fibroblasts,” *Pfugers Archiv*, vol. 447, no. 1, pp. 78–86, 2003.

[15] P. A. Scherle, W.-G. Ma, H. Lim, S. K. Dey, and J. M. Trzaskos, “Regulation of cyclooxygenase-2 induction in the mouse uterus during decidualization. An event of early pregnancy,” *Journal of Biological Chemistry*, vol. 275, no. 47, pp. 37086–37092, 2000.

[16] H. Ni, T. Sun, X.-H. Ma, and Z.-M. Yang, “Expression and regulation of cytosolic prostaglandin E synthase in mouse uterus during the peri-implantation period,” *Biology of Reproduction*, vol. 68, no. 3, pp. 744–750, 2003.

[17] S. Hara, D. Kamei, Y. Sasaki, A. Tanemoto, Y. Nakatani, and M. Murakami, “Prostaglandin E synthases: understanding their pathophysiological roles through mouse genetic models,” *Biochimie*, vol. 92, no. 6, pp. 651–659, 2010.

[18] J. Cong, H.-L. Diao, Y.-C. Zhao, H. Ni, Y.-Q. Yan, and Z.-M. Yang, “Differential expression and regulation of cyclooxygenases, prostaglandin E synthases and prostacyclin synthase in rat uterus during the peri-implantation period,” *Reproduction*, vol. 131, no. 1, pp. 139–151, 2006.

[19] F. Vilella, L. Ramirez, O. Berlanga et al., “PGE2 and PGF2α concentrations in human endometrial fluid as biomarkers for embryonic implantation,” *Journal of Clinical Endocrinology & Metabolism*, vol. 98, no. 10, pp. 4123–4132, 2013.

[20] L. Marions and K. G. Danielsson, “Expression of cyclo-oxygenase-1 and cyclo-oxygenase-2 in the human endometrium during the implantation period,” *Molecular Human Reproduction*, vol. 5, no. 10, pp. 961–965, 1999.

[21] H. Lim, B. C. Paria, S. K. Das et al., “Multiple female reproductive failures in cyclooxygenase-2-deficient mice,” *Cell*, vol. 91, no. 2, pp. 197–208, 1997.

[22] S. L. Tilley, L. P. Audoly, E. H. Hicks et al., “Reproductive failure and reduced blood pressure in mice lacking the EP2 prostaglandin E2 receptor,” *Journal of Clinical Investigation*, vol. 103, no. 11, pp. 1539–1545, 1999.

[23] H. Matsumoto, W. Ma, W. Smalley, J. Trzaskos, R. M. Breyer, and S. K. Dey, “Diversification of cyclooxygenase-2-derived prostaglandins in ovulation and implantation,” *Biology of Reproduction*, vol. 64, no. 5, pp. 1557–1565, 2001.

[24] Z.-M. Yang, S. K. Das, J. Wang, Y. Sugimoto, A. Ichikawa, and S. K. Dey, “Potential sites of prostaglandin actions in the peri-implantation mouse uterus: differential expression and regulation of prostaglandin receptor genes,” *Biology of Reproduction*, vol. 56, no. 2, pp. 368–379, 1997.

[25] I. Chakraborty, S. K. Das, J. Wang, and S. K. Dey, “Developmental expression of the cyclo-oxygenase-1 and cyclo-oxygenase-2 genes in the peri-implantation mouse uterus and their differential regulation by the blastocyst and ovarian steroids,” *Journal of Molecular Endocrinology*, vol. 16, no. 2, pp. 107–122, 1996.

[26] P. Banerjee, K. Kapru, Z. Strakova, and A. T. Fazleabas, “Chronic gonadotropin regulates prostaglandin E synthase via a phosphatidylinositol 3-kinase-extracellular regulatory kinase pathway in a human endometrial epithelial cell line: implications for endometrial responses for embryo implantation,” *Endocrinology*, vol. 150, no. 9, pp. 4326–4337, 2009.

[27] A. L. Jacobs and D. D. Carson, “Uterine epithelial cell secretion of interleukin-1α induces prostaglandin E2 (PGE2) and PGF(2α) secretion by uterine stromal cells in vitro,” *Endocrinology*, vol. 132, no. 1, pp. 300–308, 1993.

[28] M. S. Sordelli, J. S. Beltrame, M. Cella et al., “Interaction between lysophosphatidic acid, prostaglandins and the endocannabinoid system during the window of implantation in the rat uterus,” *PLoS ONE*, vol. 7, no. 9, Article ID e46059, 2012.

[29] Y. C. Ruan, J. H. Guo, X. Liu et al., “Activation of the epithelial Na+ channel triggers prostaglandin E2 release and production required for embryo implantation,” *Nature Medicine*, vol. 18, no. 7, pp. 1112–1117, 2012.

[30] J. S. Beltrame, M. S. Sordelli, M. Cella, S. P. Martinez, A. M. Franchi, and M. L. Ribeiro, “Lysophosphatidic acid increases the production of pivotal mediators of decidualization and vascularization in the rat uterus,” *Placenta*, vol. 34, no. 9, pp. 751–756, 2013.

[31] V. Plaks, V. Kalchenko, N. Dekel, and M. Neeman, “MRI analysis of angiogenesis during mouse embryo implantation,” *Magnetic Resonance in Medicine*, vol. 55, no. 3, pp. 1013–1022, 2006.

[32] W. Ma, J. Tan, H. Matsumoto et al., “Adult tissue angiogenesis: evidence for negative regulation by estrogen in the uterus,” *Molecular Endocrinology*, vol. 15, no. 11, pp. 1983–1992, 2001.

[33] M. L.-M. Rabbani and P. A. W. Rogers, “Role of vascular endothelial growth factor in endometrial vascular events before implantation in rats,” *Reproduction*, vol. 122, no. 1, pp. 85–90, 2001.

[34] S. K. Dey, H. Lim, S. K. Das et al., “Molecular cues to implantation,” *Endocrine Reviews*, vol. 25, no. 3, pp. 341–373, 2004.

[35] C. A. Scott, D. van Huyen, and B. M. Bany, “Angiopoietin-like gene expression in the mouse uterus during implantation and in response to steroids,” *Cell and Tissue Research*, vol. 348, no. 1, pp. 199–211, 2012.

[36] H. Matsumoto, E. Fukui, M. Yoshizawa, E. Sato, and T. Daikoku, “Differential expression of the motin family in the peri-implantation mouse uterus and their hormonal regulation,” *Journal of Reproduction and Development*, vol. 58, no. 6, pp. 649–653, 2012.

[37] A. Ahmed, S. Dearn, M. Shams et al., “Localization, quantification, and activation of platelet-activating factor receptor in human endometrium during the menstrual cycle: PAF stimulates NO, VEGF, and FAK (p125Fak),” *The FASEB Journal*, vol. 12, no. 10, pp. 831–843, 1998.

[38] R. Soldi, F. Sanavio, M. Aglietta et al., “Platelet-activating factor (PAF) induces the early tyrosine phosphorylation of focal adhesion kinase (p125FAK) in human endothelial cells,” *Oncogene*, vol. 13, no. 3, pp. 515–525, 1996.

[39] S. Dearn, M. Rahman, A. Lewis, Z. Ahmed, M. C. Eggo, and A. Ahmed, “Activation of platelet-activating factor (PAF) receptor stimulates nitric oxide (NO) release via protein kinase C-alpha in HEC-1B human endometrial epithelial cell line,” *Molecular Medicine*, vol. 6, no. 1, pp. 37–49, 2000.
C. Gillio-Meina, S. H. Phang, J. P. Mather, B. S. Knight, and T. G. Kennedy, “Expression patterns and role of prostaglandin-endoperoxide synthases, prostaglandin E synthases, prostacyclin synthase, prostacyclin receptor, peroxisome proliferator-activated receptor delta and retinoid X receptor alpha in rat endometrium during artificially-induced decidualization,” Reproduction, vol. 137, no. 3, pp. 537–552, 2009.

H. Matsumoto, W.-G. Ma, T. Daikoku et al., “Cyclooxygenase-2 differentially directs uterine angiogenesis during implantation in mice,” Journal of Biological Chemistry, vol. 277, no. 32, pp. 29260–29267, 2002.

M. S. Sordelli, J. S. Beltramer, J. Burdett et al., “The effect of anandamide on uterine nitric oxide synthase activity depends on the presence of the blastocyst,” PLoS ONE, vol. 6, no. 4, Article ID e18368, 2011.

M. Cella, J. Aisemberg, M. S. Sordelli et al., “Prostaglandins modulate nitric oxide synthase activity early in time in the uterus of estrogenized rat challenged with lipopolysaccharide,” European Journal of Pharmacology, vol. 534, no. 1–3, pp. 218–226, 2006.

V. Mollace, C. Muscoli, E. Masini, S. Cuzzocrea, and D. Savlemini, “Modulation of prostaglandin biosynthesis by nitric oxide and nitric oxide donors,” Pharmacological Reviews, vol. 57, no. 2, pp. 217–252, 2005.

K. Shirasuna, S. Watanabe, T. Asahi et al., “Prostaglandin F2α increases endothelial nitric oxide synthase in the periphery of the bovine corpus luteum: the possible regulation of blood flow at an early stage of luteolysis,” Reproduction, vol. 135, no. 4, pp. 527–539, 2008.

K. J. Sales, T. List, S. C. Boddy et al., “A novel angiogenic role for prostaglandin F2α-FP receptor interaction in human endometrial adenocarcinomas,” Cancer Research, vol. 65, no. 17, pp. 7707–7716, 2005.

R. R. Magness, C. R. Shideman, D. A. Habermehl, J. A. Sullivan, and I. M. Bird, “Endothelial vasodilator production by uterine and systemic arteries. V. Effects of ovariectomy, the ovarian cycle, and pregnancy on prostacyclin synthase expression,” Prostaglandins and Other Lipid Mediators, vol. 60, no. 4–6, pp. 103–118, 2000.

O. P. M. Smith, S. Batterby, K. J. Sales, H. O. D. Critchley, and H. N. Jabbour, “Prostacyclin receptor up-regulates the expression of angiogenic genes in human endometrium via cross talk with epidermal growth factor receptor and the extracellular signaling receptor kinase 1/2 pathway,” Endocrinology, vol. 147, no. 4, pp. 1697–1705, 2006.

B. Gellersen, I. A. Brosens, and J. J. Brosens, “Decidualization of the human endometrium: mechanisms, functions, and clinical perspectives,” Seminars in Reproductive Medicine, vol. 25, no. 6, pp. 445–453, 2007.

D. F. Wang, H. Minoura, T. Sugiyama et al., “Analysis on the promoter region of human decidual prolactin gene in the progesterone-induced decidualization and CAMP-induced decidualization of human endometrial stromal cells,” Molecular and Celluar Biochemistry, vol. 300, no. 1–2, pp. 239–247, 2007.

B. C. Paria, X. Zhao, S. K. Das, S. K. Dey, and K. Yoshinaga, “Zona occludens-1 and E-cadherin are coordinately expressed in the mouse uterus with the initiation of implantation and decidualization,” Developmental Biology, vol. 208, no. 2, pp. 488–501, 1999.

S. K. Das, “Cell cycle regulatory control for uterine stromal cell decidualization in implantation,” Reproduction, vol. 137, no. 6, pp. 889–899, 2009.
by both SMAD-dependent and SMAD-independent pathways,” *PloS ONE*, vol. 5, no. 9, Article ID e12970, 2010.

[69] X. Shen, Y. Hu, Y. Jiang et al., “Krüppel-like factor 12 negatively regulates human endometrial stromal cell decidualization,” *Biochemical and Biophysical Research Communications*, vol. 433, no. 1, pp. 11–17, 2013.

[70] O. Bartsch, B. Bartlick, and R. Ivell, “Phosphodiesterase 4 inhibition synergizes with relaxin signaling to promote decidualization of human endometrial stromal cells,” *Journal of Clinical Endocrinology & Metabolism*, vol. 89, no. 1, pp. 324–334, 2004.

[71] M. R. Campitiello, P. de Franciscis, D. Mele et al., “Endometrial LGR7 expression during menstrual cycle,” *Fertility and Sterility*, vol. 95, no. 8, pp. 2511–2514, 2011.

[72] P. J. Bonnamy, A. Benhaim, and P. Leymarie, “Uterine luteinizing hormone/human chorionic gonadotropin-binding sites in the early pregnant rat uterus: evidence for total occupancy in the periimplantation period,” *Endocrinology*, vol. 132, no. 3, pp. 1240–1246, 1993.

[73] N. Vitoratos, D. C. Papaiothodorou, S. N. Kalantaridou, and G. Mastorakos, “‘Reproductive’ corticotropin-releasing hormone,” *Annals of the New York Academy of Sciences*, vol. 1092, pp. 310–318, 2006.

[74] G. R. Frank, A. K. Brar, M. I. Cedars, and S. Handwerger, “Prostaglandin E2 enhances human endometrial stromal cell differentiation,” *Endocrinology*, vol. 134, no. 1, pp. 258–263, 1994.

[75] C. Ganeff, G. Chatel, C. Munaut, F. Frankenne, J.-M. Foidart, N. Vitoratos, D. C. Papatheodorou, S. N. Kalantaridou, and G. Mastorakos, “Regulation of human endometrial stromal cell decidualization,” *Molecular Human Reproduction*, vol. 15, no. 1, pp. 27–38, 2009.

[76] H. J. Chang, J. H. Lee, K. J. Hwang et al., “Transforming growth factor (TGF)-β1-induced human endometrial stromal cell decidualization through extracellular signal-regulated kinase and Smad activation in vitro: peroxisome proliferator-activated receptor gamma acts as a negative regulator of TGF-β1,” *Fertility and Sterility*, vol. 90, supplement 4, pp. 1357–1365, 2008.

[77] N. Chegini, M. J. Rossi, and B. J. Masterson, “Platelet-derived growth factor (PDGF), epidermal growth factor (EGF), and EGF and PDGF β-receptors in human endometrial tissue: localization and in vitro action,” *Endocrinology*, vol. 130, no. 4, pp. 2373–2385, 1992.

[78] G. M. Yee and T. G. Kennedy, “Prostaglandin E2, cAMP and cAMP-dependent protein kinase isozymes during decidualization of rat endometrial stromal cells in vitro,” *Prostaglandins*, vol. 46, no. 2, pp. 117–138, 1993.

[79] S. A. Milne, G. B. Perchick, S. C. Boddy, and H. N. Jabbour, “Expression, localization, and signaling of PGE2 and EP2/EP4 receptors in human nonpregnant endometrium across the menstrual cycle,” *Journal of Clinical Endocrinology & Metabolism*, vol. 86, no. 9, pp. 4435–4459, 2001.

[80] E. Dimitriadis, C. Stoikos, M. Baca, W. D. Fairlie, J. E. McCoubrie, and L. A. Salamonson, “Relaxin and prostaglandin E2 regulate interleukin 11 during human endometrial stromal cell decidualization,” *Journal of Clinical Endocrinology & Metabolism*, vol. 90, no. 6, pp. 3458–3463, 2005.

[81] J. Kang, P. Chapdelaine, P. Y. Laberge, and M. A. Fortier, “Functional characterization of prostaglandin transporter and terminal prostaglandin synthases during decidualization of human endometrial stromal cells,” *Human Reproduction*, vol. 21, no. 3, pp. 592–599, 2006.

[82] J. A. Arosh, S. K. Banu, P. Chapdelaine et al., “Molecular cloning and characterization of bovine prostaglandin E2 receptors EP2 and EP4: expression and regulation in endometrium and myometrium during the estrous cycle and early pregnancy,” *Endocrinology*, vol. 144, no. 7, pp. 3076–3091, 2003.

[83] H. Ni, T. Sun, N.-Z. Ding, X.-H. Ma, and Z.-M. Yang, “Differential expression of microsomal prostaglandin E synthase at implantation sites and in decidual cells of mouse uterus,” *Biology of Reproduction*, vol. 67, no. 1, pp. 351–358, 2002.

[84] A. Arslan and H. H. Zingg, “Regulation of COX-2 gene expression in rat uterus in vivo and in vitro,” *Prostaglandins*, vol. 52, no. 6, pp. 463–481, 1996.

[85] K. E. Bracken, W. Elger, I. Jantke, A. Nanninga, and B. Gellersen, “Cloning of guinea pig cyclooxygenase-2 and 15-hydroxyprostaglandin dehydrogenase complementary deoxyribonucleic acids: steroid-modulated gene expression correlates to prostaglandin F(2α) secretion in cultured endometrial cells,” *Endocrinology*, vol. 138, no. 1, pp. 237–247, 1997.

[86] K. J. Shaw, C. Ng, and B. W. Kovacs, “Cyclooxygenase gene expression in human endometrium and decidua,” *Prostaglandins Leukotrienes and Essential Fatty Acids*, vol. 50, no. 5, pp. 239–243, 1994.

[87] N. Alfaidy, M. Sun, J. R. G. Challis, and W. Gibb, “Expression of membrane prostaglandin E synthase in human placenta and fetal membranes and effect of labor,” *Endocrine*, vol. 20, no. 3, pp. 219–225, 2003.

[88] E. Bresson, S. Boucher-Kovalik, P. Chapdelaine et al., “The human aldose reductase AKR1B1 qualifies as the primary prostaglandin F synthase in the endometrium,” *Journal of Clinical Endocrinology & Metabolism*, vol. 96, no. 1, pp. 210–219, 2011.

[89] I. St.-Louis, M. Singh, K. Brasseur, V. Leblanc, S. Parent, and E. Asselin, “Expression of COX-1 and COX-2 in the endometrium of cyclic, pregnant and in a model of pseudopregnant rats and their regulation by sex steroids,” *Reproductive Biology and Endocrinology*, vol. 8, article 103, 2010.

[90] J. H. C. Kengni, I. St.-Louis, S. Parent, V. Leblanc, C. Shooner, and E. Asselin, “Regulation of prostaglandin D synthase and prostacyclin synthase in the endometrium of cyclic, pregnant, and pseudopregnant rats and their regulation by sex steroids,” *Journal of Endocrinology*, vol. 195, no. 2, pp. 301–311, 2007.

[91] P. L. Pakrasi and A. K. Jain, “Cyclooxygenase-2 derived PGE2 and PG12 play an important role via EP2 and PPARα receptors in early steps of ovid induced decidualization in mice,” *Placenta*, vol. 29, no. 6, pp. 523–530, 2008.

[92] B. M. Jacobsen and K. B. Horowitz, “Progestosterone receptors, their isoforms and progesterone regulated transcription,” *Molecular and Cellular Endocrinology*, vol. 357, no. 1-2, pp. 18–29, 2012.

[93] M. Christian, X. Zhang, T. Schneider-Merck et al., “Cyclic AMP- induced forkhead transcription factor, FKHR, cooperates with CCAAT-enhancer-binding protein β in differentiating human endometrial stromal cells,” *Journal of Biological Chemistry*, vol. 277, no. 23, pp. 20825–20832, 2002.

[94] I. Y. H. Mak, J. J. Brosens, M. Christian et al., “Regulated expression of signal transducer and activator of transcription, Stat5, and its enhancement of PRL expression in human endometrial stromal cells in vitro,” *Journal of Clinical Endocrinology & Metabolism*, vol. 87, no. 6, pp. 2581–2588, 2002.

[95] J. M. P. Pabona, Z. Zeng, F. A. Simmen, and R. C. M. Simmen, “Functional differentiation of uterine stromal cells involves cross-regulation between bone morphogenetic protein 2 and Krüppel-like factor (KLF) family members KLF9 and KLF13,” *Endocrinology*, vol. 151, no. 7, pp. 3396–3406, 2010.

[96] V. P. Kocidea, S. Adhikary, F. Emig, J.-H. Yen, M. G. Toscano, and D. Ganea, “Prostaglandin E2-induced IL-23p19 subunit is
regulated by cAMP-responsive element-binding protein and C/AATT enhancer-binding protein β in bone marrow-derived dendritic cells," *Journal of Biological Chemistry*, vol. 287, no. 44, pp. 36922–36935, 2012.

[97] W. Wang, R. N. Taylor, I. C. Bagchi, and M. K. Bagchi, "Regulation of human endometrial stromal proliferation and differentiation by C/EBPβ involves cyclin E-cdk2 and STAT3," *Molecular Endocrinology*, vol. 26, no. 12, pp. 2016–2030, 2012.

[98] H. Matsumoto, K. Sakai, and M. Iwashita, "Insulin-like growth factor binding protein-1 induces decidualization of human endometrial stromal cells via α5β1 integrin," *Molecular Human Reproduction*, vol. 14, no. 8, pp. 485–489, 2008.

[99] X.-H. Zhang, X. Liang, T.-S. Wang et al., "Heparin-binding epidermal growth factor-like growth factor (HB-EGF) induction on Snail expression during mouse decidualization," *Molecular and Cellular Endocrinology*, vol. 381, no. 1-2, pp. 272–279, 2013.

[100] H. Lim, L. Ma, W.-G. Ma, R. L. Maas, and S. K. Dey, "Hoxa-10 regulates uterine stromal cell responsiveness to progesterone during implantation and decidualization in the mouse," *Molecular Endocrinology*, vol. 13, no. 6, pp. 1005–1017, 1999.

[101] H. Song, H. Lim, S. K. Das, B. C. Paria, and S. K. Dey, "Dysregulation of EGF family of growth factors and COX-2 in the uterus during the preattachment and attachment phases of the blastocyst with the luminal epithelium correlates with implantation failure in LIF-deficient mice," *Molecular Endocrinology*, vol. 14, no. 8, pp. 1147–1161, 2000.

[102] A. K. Brar, G. R. Frank, C. A. Kessler, M. I. Cedars, and S. Handwerger, "Progesterone-dependent decidualization of the human endometrium is mediated by CAMP," *Endocrine*, vol. 6, no. 3, pp. 301–307, 1997.

[103] J. Huxley-Jones, D. L. Robertson, and R. P. Boot-Handford, "On the origins of the extracellular matrix in vertebrates," *Matrix Biology*, vol. 26, no. 1, pp. 2–11, 2007.

[104] H. Diao, J. D. Aplin, S. Xiao et al., "Altered spatiotemporal expression of collagen types I, III, IV, and VI in Lpar3-deficient peri-implantation mouse uterus," *Biology of Reproduction*, vol. 84, no. 2, pp. 255–265, 2011.

[105] P. A. Abrahamsohn and T. M. Zorn, "Implantation and decidualization in rodents," *Journal of Experimental Zoology*, vol. 266, no. 6, pp. 603–628, 1993.

[106] R. Salgado, A. Covarrubias, R. Favarо, C. Serrano-Nascimento, M. Nunes, and T. T. Zorn, "Estradiol induces transcriptional and posttranscriptional modifications in versican expression in the mouse uterus," *Journal of Molecular Histology*, vol. 44, no. 2, pp. 221–229, 2013.

[107] S. K. Das, S. Yano, J. Wang, D. R. Edwards, H. Nagase, and S. K. Dey, "Expression of matrix metalloproteinases and tissue inhibitors of metalloproteinases in the mouse uterus during the peri-implantation period," *Developmental Genetics*, vol. 21, no. 1, pp. 44–54, 1997.

[108] Y.-G. Zhao, A.-Z. Xiao, X.-M. Cao, and C. Zhu, "Expression of matrix metalloproteinase-2, -9 and tissue inhibitors of metalloproteinase-1, -2, -3 mRNAs in rat uterus during early pregnancy," *Molecular Reproduction and Development*, vol. 62, no. 2, pp. 149–158, 2002.

[109] P. R. Hurst and R. D. Palmay, "Matrix metalloproteinases and their endogenous inhibitors during the implantation period in the rat uterus," *Reproduction, Fertility and Development*, vol. 11, no. 7-8, pp. 395–402, 2000.

[110] J. Y. Zhu, Z. J. Pang, and Y. H. Yu, "Regulation of trophoblast invasion: the role of matrix metalloproteinases," *Reviews in Obstetrics and Gynecology*, no. 3-4, pp. e137–e143, 2012.

[111] H. Fluhr, S. Krenzer, and M. Zygmunt, "Different regulation of tissue inhibitors of metalloproteinases-1, -2 and -3 in human endometrial stromal cells during decidualization in vitro," *Reproductive Medicine and Biology*, vol. 7, no. 4, pp. 169–175, 2008.

[112] Y. Dang, W. Li, V. Tran, and R. A. Khalil, "EMMPRIN-mediated induction of uterine and vascular matrix metalloproteinases during pregnancy and in response to estrogen and progesterone," *Biochemical Pharmacology*, vol. 86, no. 6, pp. 734–747, 2013.

[113] H. Itoh, A. H. Kishore, A. Lindqvist, D. E. Rogers, and R. A. Word, "Transforming growth factor β1 (TGFβ1) and progesterone regulate matrix metalloproteinases (MMP) in human endometrial stromal cells," *Journal of Clinical Endocrinology & Metabolism*, vol. 97, no. 6, pp. E888–E897, 2012.

[114] L. A. Russo, B. J. Peano, S. P. Trivedi et al., "Regulated expression of matrix metalloproteinases, inflammatory mediators, and endometrial matrix remodeling by 17beta-estradiol in the immature rat uterus," *Reproductive Biology and Endocrinology*, vol. 7, article 124, 2009.

[115] M. G. Martinez-Hernández, L. A. Baiza-Gutman, A. Castillo-Trápala, and D. R. Arment, "Regulation of proteases during mouse peri-implantation development: urokinase-type plasminogen activator expression and cross talk with matrix metalloproteinase 9," *Reproduction*, vol. 141, no. 2, pp. 227–239, 2011.

[116] A. Tapia, L. A. Salamonsen, U. Manuelpillai, and E. Dimitriadis, "Leukemia inhibitory factor promotes human first trimester extravillous trophoblast adhesion to extracellular matrix and secretion of tissue inhibitor of metalloproteinases-1 and -2," *Human Reproduction*, vol. 23, no. 8, pp. 1724–1732, 2008.

[117] H. A. Otun, G. E. Lash, B. A. Innes et al., "Effect of tumour necrosis factor-α in combination with interferon-γ on first trimester extravillous trophoblast invasion," *Journal of Reproductive Immunology*, vol. 88, no. 1, pp. 1–11, 2011.

[118] P. Paiva, L. A. Salamonsen, U. Manuelpillai, and E. Dimitriadis, "Interleukin 11 inhibits human trophoblast invasion indicating a likely role in the decidual restraint of trophoblast invasion during placentation," *Biology of Reproduction*, vol. 80, no. 2, pp. 302–310, 2009.

[119] L. Anton, A. G. Brown, S. Parry, and M. A. Elovitz, "Lipo-polysaccharide induces cytokine production and decreases extravillous trophoblast invasion through a mitogen-activated protein kinase-mediated pathway: possible mechanisms of first trimester placental dysfunction," *Human Reproduction*, vol. 27, no. 1, pp. 61–72, 2012.

[120] K. Biadasiewicz, S. Sonderegger, P. Haslinger et al., "Transcription factor AP-2α promotes EGF-dependent invasion of human trophoblast," *Endocrinology*, vol. 152, no. 4, pp. 1458–1469, 2011.

[121] U. Hiden, E. Glitzner, M. Hartmann, and G. Desoye, "Insulin and the IGF system in the human placenta of normal and diabetic pregnancies," *Journal of Anatomy*, vol. 215, no. 1, pp. 60–68, 2009.

[122] J. Prast, L. Saleh, H. Husslein, S. Sonderegger, H. Helmer, and M. Kößler, "Human chorionic gonadotropin stimulates trophoblast invasion through extracellularly regulated kinase and AKT signaling," *Endocrinology*, vol. 149, no. 3, pp. 979–987, 2008.

[123] E. A. Callegari, S. Ferguson-Gottschall, and G. Gibori, "PGF2α induced differential expression of genes involved in turnover of extracellular matrix in rat decidual cells," *Reproductive Biology and Endocrinology*, vol. 3, article 3, 2005.
[124] C. M. Kershaw-Young, M. Khalid, M. R. McGowan, A. A. Pittsillides, and R. J. Scaramuzzi, “The mRNA expression of prostaglandin E receptors EP2 and EP4 and the changes in glycosaminoglycans in the sheep cervix during the estrous cycle,” *Theriogenology*, vol. 72, no. 2, pp. 251–261, 2009.

[125] M. Yoshida, N. Sagawa, H. Itoh et al., “Prostaglandin F2α, cytokines and cyclic mechanical stretch augment matrix metalloproteinase-1 secretion from cultured human uterine cervical fibroblast cells,” *Molecular Human Reproduction*, vol. 8, no. 7, pp. 681–687, 2002.

[126] A. Takashima, F. Ishikawa, T. Kuwabara et al., “Uterine natural killer cells severely decrease in number at gestation day 6 in mice,” *Reproductive Biology*, vol. 89, no. 4, article 101, 2013.

[127] J. Y. Lee, M. Lee, and S. K. Lee, “Role of endometrial immune cells in implantation,” *Clinical and Experimental Reproductive Medicine*, vol. 38, no. 3, pp. 119–125, 2011.

[128] J. M. Scodras, R. S. Parhar, T. G. Kennedy, and P. K. Lala, “Prostaglandin-mediated inactivation of natural killer cells in the murine decidua,” *Cellular Immunology*, vol. 127, no. 2, pp. 352–367, 1990.

[129] R. S. Parhar, S. Yagel, and P. K. Lala, “PGE2-mediated immunosuppression by first trimester human decidual cells blocks activation of maternal leukocytes in the decidua with potential anti-trophoblast activity,” *Cellular Immunology*, vol. 120, no. 1, pp. 61–74, 1989.

[130] A. E. Wallace, K. J. Sales, R. D. Catalano et al., “Prostaglandin F2α/F-prostanoid receptor signaling promotes neutrophil chemotaxis via chemokine (C-X-C motif) ligand 1 in endometrial adenocarcinoma,” *Cancer Research*, vol. 69, no. 14, pp. 5726–5733, 2009.

[131] A. Bylander, K. Lind, M. Goksor, H. Billig, and D. J. Larsson, “The classical progestosterone receptor mediates the rapid reduction of fallopian tube ciliary beat frequency by progestosterone,” *Reproductive Biology and Endocrinology*, vol. 11, article 33, 2013.

[132] L. S. Roblero and A. C. Garavagno, “Effect of oestradiol-17β and progesterone on oviducal transport and early development of mouse embryos,” *Journal of Reproduction and Fertility*, vol. 57, no. 1, pp. 91–95, 1979.

[133] E. W. Overstrom, R. M. Bigsby, and D. L. Black, “Effects of physiological levels of estradiol-17β and progesterone on oviduct edema and ovum transport in the rabbit,” *Biology of Reproduction*, vol. 23, no. 1, pp. 100–110, 1980.

[134] C. H. Spilman and M. J. K. Harper, “Effects of prostaglandins on oviducal motility and egg transport,” *Gynecologic Investigation*, vol. 6, no. 3–4, pp. 186–205, 1975.

[135] K. Yamaji, T. Yoshitomi, H. Ishikawa, and S. Usui, “Prostaglandins E1 and E2, but not F 2α or lanaprost, inhibit monkey ciliary muscle contraction,” *Current Eye Research*, vol. 30, no. 8, pp. 661–665, 2005.

[136] R. L. Jones, W. A. N. Wan Ahmad, D. F. Woodward, and J. Wang, “Nature of the slow relaxation of smooth muscle induced by a EP2 receptor agonist with a non-prostanoid structure,” *Prostaglandins, Leukotrienes, and Essential Fatty Acids*, vol. 88, no. 4, pp. 321–330, 2013.

[137] D. M. Slater, S. Astle, N. Woodcock et al., “Anti-inflammatory and relaxatory effects of prostaglandin E2 in myometrial smooth muscle,” *Molecular Human Reproduction*, vol. 12, no. 2, pp. 89–97, 2006.

[138] G. Chiossi, M. M. Costantine, E. Bytautiene et al., “The effects of prostaglandin E1 and prostaglandin E2 on in vitro myometrial contractility and uterine structure,” *American Journal of Perinatology*, vol. 29, no. 8, pp. 615–622, 2012.
[155] A. Waclawik, P. Kaczynski, and H. N. Jabbour, “Autocrine and paracrine mechanisms of prostaglandin E2 action on trophoblast/conceptus cells through the prostaglandin E2 receptor (PTGER2) during implantation,” *Endocrinology*, vol. 154, no. 10, pp. 3864–3876, 2013.

[156] P. Dominguez-Lopez, L. Diaz-Cueto, A. Olivares, A. Ulloa-Aguirre, and F. Arechavaleta-Velasco, “Differential effect of DDT, DDE, and DDD on COX-2 expression in the human trophoblast derived HTR-8/SVneo cells,” *Journal of Biochemical and Molecular Toxicology*, vol. 26, no. 11, pp. 454–460, 2012.

[157] H. Horita, E. Kuroda, T. Hachisuga, M. Kashimura, and U. Yamashita, “Induction of prostaglandin E2 production by leukemia inhibitory factor promotes migration of first trimester extravillous trophoblast cell line, HTR-8/SVneo,” *Human Reproduction*, vol. 22, no. 7, pp. 1801–1809, 2007.

[158] G. Godbole, P. Suman, S. K. Gupta, and D. Modi, “Decidualized endometrial stromal cell derived factors promote trophoblast invasion,” *Fertility and Sterility*, vol. 95, no. 4, pp. 1278–1283, 2011.

[159] C. Biondi, M. E. Ferretti, B. Pavan et al., “Prostaglandin E2 inhibits proliferation and migration of HTR-8/SVneo cells, a human trophoblast-derived cell line,” *Placenta*, vol. 27, no. 6-7, pp. 592–601, 2006.