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Role of COX-2 for Successful Embryo Implantation Process: A Mini-review

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Abstract

The endometrium undergoes a dynamic proliferation of cells and vascular tissue under the influence of ovarian steroid hormones. Implantation is an essential process in the development of pregnancy, where there is close contact between embryo and uterus, including supposition, adhesion, and invasion. The changes occur in the human endometrium, including endometrial secretion changes, blood vessels, and immune response, leading to the uterine receptivity period. Cyclooxygenase (COX) is an enzyme that plays a role in the metabolic conversion of arachidonic acid to prostaglandins (PG). It is known that Cyclooxygenase-2 (COX-2) plays a key role in the endometrium. COX-2 is essential for blastocyst implantation and decidualization. The deficiency of COX-2, but not COX-1, results in multiple female reproductive failures (including implantation defects). We reviewed the literature on COX-2 and embryonal implantation in the endometrium and its potential mechanisms that lead to physiological implantation. This review aims to identify the essential roles of COX-2 in the successful implantation process, especially in decidualization, implantation, and embryo growth. The regulation of COX-2 expression in endometrial cells is controlled by ovarian steroid hormones (progesterone and estrogen) through the ENaC pathway to regulate the phosphorylation CREB transcription factor. The presentation of COX-2 varies throughout the stage of embryo development.

Introduction

The endometrial tissue consists of the functional and basal layers. The functional layer is a thin layer that enters the uterine cavity directly, whereas the basal layer is a thicker layer that is permanently linked to the myometrium. The luminal epithelium, stroma, and superficial glands comprise the functional layer (glandular epithelium). The functional layer, which fluctuates during the menstrual cycle depending on the action of steroid hormones, determines the tissue thickness. 17-estradiol (estrogen) and progesterone are the primary components in this endometrial preparation for pregnancy, and their concentrations fluctuate in a predictable pattern during the menstrual cycle [1].

Proliferation, differentiation, shedding, and regeneration are just a few distinct processes that occur in the endometrium throughout a woman's lifetime. The proliferative phase of the endometrium develops in reaction to estrogen, beginning within the basal layer and remaining after the feminine cycle. Ovulation determines the transition from proliferative to secretory phase. It is controlled by estrogen and progesterone directly and indirectly, and it encourages intervention by secondary autocrine complexes, paracrine components, cytokines, chemokines, their receptors, and second messengers [2]. The proliferative phase of the menstrual cycle occurs between days 0 and 13, and the ovulation process is at day 14, while the secretory phase is at 15–28 days of the menstrual cycle. Estrogen affects the proliferative phase, resulting in the rapid construction of the functional layer of the endometrium, extensive repair of tissues previously damaged by menstruation, suppressed innate immunity, and growth factor molecules causing cell proliferation. The secretory phase occurs after the proliferative and ovulation phases; the pituitary hormones and ovarian progesterone take over the role of estrogen in the functional layer through differentiation toward decidualization. Decidualized endometrium is ready to provide an optimal environment for blastocyst implantation and early embryonic growth, known as endometrial receptivity [2], [3], [4].

Implantation is an essential process in the development of pregnancy, where there is close contact between embryo and uterus, including supposition, adhesion, and invasion. The changes occur in the human endometrium, including endometrial secretion

changes, blood vessels, and immune response, leading to the uterine receptivity period. This process occurs 5–7 days after ovulation and remains receptive for ~4 days (20–24 days menstrual cycle) and is called a window of implantation. Successful implantation requires coordinated vascular development and maintenance within the mother-embryonic interface to provide an adequate environment to support embryonic development. Sufficient uterine vascularization and regulatory cells or factors are critical during implantation. At the same time, inappropriate endometrial angiogenesis and the resulting immune reaction can lead to reproductive failure (infertility), particularly recurrent miscarriage and repeated implantation failure [4], [5].

The endometrium is a complex multicellular steroid target that disintegrates monthly without pregnancy and recovers rapidly. Endometrium will undergo several changes in maintaining the pregnancy when there is implantation and will decay when there is no pregnancy [1], [4]. In the early proliferative phase of the menstrual cycle, the endocrine environment is controlled by estradiol (E2) within the early proliferative phase of the menstrual cycle. The endometrium is characterized by the expansion of vascular tissue and endometrial cells. Progesterone is secreted by an ovulated follicle, namely corpus luteum (an ovulated follicle). Progesterone is required for the foundation and maintenance of pregnancy within the endometrium but it must be already prepared by estradiol [1].

The endometrium is composed of simple columnar epithelial cells and multicellular stroma. The stroma has the cellular components of connective tissue with a fibroblast-like stromal and contains a few tubular organs adjoining the luminal surface, spiral arteries, and mediates the fluctuating traffic of recruited innate immune cells [1]. Stromal cells undergo decidualization in the secretory phase, and epithelial cells develop into specialized structures known as pinopodes and secrete cell adhesion molecules [2].

Cyclooxygenase (COX) is an enzyme that plays a role in the metabolic conversion of arachidonic acid to prostaglandins (PG) that consists of two isoforms: COX-1 and COX-2. Although both enzymes' structure and enzymatic activity are very similar, COX-1 and COX-2 perform different roles, allowing for different localization and regulation. COX-1 is expressed in all tissues in specific cell types and produces prostaglandins and thromboxane needed to maintain physiological functions such as regulating blood flow, platelet aggregation, and mucus production in the stomach. On the other hand, COX-2 is induced by pathologic stimuli, such as tissue damage such as trauma, ischemia, infection, or inflammation conditions which can increase mitogens, growth factors, and cytokines [6], [7], [8].

It is known that Cyclooxygenase-2 (COX-2) plays a key role in the endometrium [6]. COX-2 is essential for blastocyst implantation and decidualization, and COX 2-derived prostacyclin (PGI2) is the crucial PG for these two processes. The previous studies have shown that female mice lacking COX-2 but not COX-1 will undergo regenerative failure and implantation defects [9]. This literature review aims to explore the essential roles of COX-2 and embryonal implantation in the endometrium, its potential components that lead to physiological implantation, and distinguish the variables that impact the effective and successful implantation through COX-2 role in decidualization, implantation, trophoblast invasion, and embryo growth.

Methods

We comprehensively reviewed the literature on COX-2 in the endometrium, the influences of COX-2 on endometrial function, and the potential mechanisms that lead to impaired implantation. PubMed and Google Scholar websites were used to identify relevant articles with several search terms such as "COX-2" or "cyclooxygenase-2," and "endometrium" were used in combination with "implantation." References from this article are used to identify additional sources. Only reports written in English in the last 20 years are included in this review. We described and expanded on what is currently known about the relationship between COX-2 and the endometrium regarding the implantation process.

COX-2 expression and regulation in the endometrium

The uterus' endometrium or mucosal lining is unique and essential for fertility and reproduction. It is a monthly cycle of angiogenesis, proliferation, exuviation, and remodeling under the effect of sex hormones. The particular tissue consists of epithelium, glandular, and stromal cells, and its dynamic support for implantation [7]. Prostaglandins (PGs) are one of the bioactive lipid compounds, also essential for embryo implantation. Research showed that a lack of phospholipase A2 and cyclooxygenase-2 (COX-2), which catalyze PG synthesis, results in implantation failure. A previous study showed that taking non-steroid anti-inflammatory drugs which block PG synthesis during pregnancy significantly increases the risk of miscarriage. Repeated implantation failure in IVF trials is correlated with impaired endometrial PG synthesis. Prostaglandin E2 (PGE2), mainly produced by COX-2-driven synthesis, is suggested to become one of the essential PGs to initiate decidualization, a differentiation of endometrial stromal cells process required for embryo implantation. It was previously demonstrated that the

epithelial sodium channel (ENaC) in the endometrial epithelial cells could be activated by embryo-derived protease, which triggers a sequence of events, such as Ca2+ ion increase, phosphorylation of CREB (Ca2+/cAMP responsive element binding protein), downregulation of miR101 and miR199a, upregulation of COX-2 and eventually PGE2 production, and releases to the stroma, leading to decidualization and embryo implantation. Nevertheless, it must be considered that the permeability of plasma membrane to PGE2 is low due to its negative charges, and how PGE2 is released from the endometrial epithelial cells for induction of stromal decidualization required for embryo implantation remains unclear [4].

At the implantation window period in humans, COX-1 is expressed in the luminal and glandular epithelium, while COX-2 is expressed in the luminal epithelium and perivascular cells. COX-1 expression in the glandular epithelium and COX-2 expression in the luminal epithelium was essentially diminished after the treatment with a progesterone receptor antagonist, suggesting progesterone may impact COX expression. Female mice lacking COX-2 were infertile with particular fertilization, implantation, and decidualization defects. In mice's early pregnancy, the uterine COX-1 gene could be directed by the ovarian steroids, while the embedding blastocyst could produce the COX-2 gene [10].

A previous study observed the expression and regulation of COX-1, COX-2, and prostaglandin levels during pregnancy in pseudopregnancy and estrous cycle rat models. The study indicates that COX-2 expression can be detected on days 2–5 of pregnancy which is the pre-implantation period. COX-2 reaches peak levels on day 12 of pregnancy when decidual regression occurs, undetected from day 18 to day 21. COX-2 was induced on days 21 and 22 during the parturition. A previous study investigated that COX protein in the endometrium is regulated by sex steroid hormones such as 17b-estradiol and progesterone during pregnancy in pseudo pregnant rats model. It was found that in the pseudo pregnant rats model, COX-1 expression was increased significantly on day 5 (decidualization occurred). At the same time, COX-2 was not detected on day 5, but its levels would increase gradually until reaching a peak on day 9 before the decidual regression process. These observations suggest that sex steroid hormones can regulate COX-1 and COX-2 expression through different factors. Several other hormones and cytokines have also been reported to be involved in PG synthesis. Chorionic gonadotrophin (CG) was found to regulate the production of PGE2 in human and primate endometrial epithelia. Lysophosphatidic acid (LPA), a bioactive lipid derivative, enhanced PGE2 synthesis and COX-2 expression in the rat uterus [10].

It is known that COX-2 expression is highest during the estrus phase compared to the other phase during the estrous cycle. The COX-2 signal was recognized weakly at days 5.5 and 20 of pregnancy, while on 10 and 22 days of gestation, the most robust COX-2 expression was recognized. Immunofluorescence analysis was performed to determine the localization of COX-2 expression at the endometrium of pregnant rats. It is mainly found in the luminal region and glandular endometrial epithelial cells and less in endometrial stromal cells [10].

COX-2 is expressed in both eutopic and ectopic endometrium, even though its mRNA is higher in ectopic endometrium. In a previous study, celecoxib encompasses a stimulatory development impact on epithelial and endothelial cells (angiogenesis), and it can be utilized to improve endometrial thickness in ART (Assisted Reproductive Technology). Even though the angiogenic impact of lower celecoxib dosages in some studies contrasts with the anti-angiogenic has implications for a COX-2 inhibitor [7].

COX-2 and decidualization

COX-1 expression was found to be elevated during implantation and parturition. However, the levels of COX-1 decreased during decidualization periods [10]. On the other hand, COX-2 expression increases on days 2–5 of pregnancy in mice, indicating the involvement of PGs in the decidualization process of endometrial stromal cells [10], [11]. Progesterone has a key role in the decidualization process by initiating its action by binding to receptors in the nucleus (progesterone receptor-A/PR-A) and subsequently interacting with various transcription factors [12]. Other studies mention the involvement of PGs in the decidualization process induced by progesterone. COX-2 is known to regulate the expression of Snail, one of the transcriptional repressors involved in the mesenchymal-epithelial transition process during decidualization, which is highly expressed in the subluminal stroma at the implantation site [13], [14]. Dysregulation of COX-2 expression related to high progesterone plasma levels in mouse uteri during peri-implantation is one of the causes of implantation failure [15].

Mechanical stimulation is known to promote decidualization. A serine protease is expressed at the endometrial blastocyst interface and can activate ENaC. These gating properties of ENaC localize at apical and luminal epithelium and are most expressed at implantation, leading to the fact that ENaC is responsible for decidualized signals from embryo implantation and downstream events leading to decidualization [16]. Activation of epithelial Na+ channel (ENaC) in the mouse endometrial epithelium by an embryo-released serine protease, trypsin, has recently been reported to trigger Ca2+ influx that could lead to PGE2 release, CREB transcription factor phosphorylation, and upregulation of COX-2 enzyme [10].

COX-2 in embryo transport, blastocyst growth, and development

The patency of the fallopian tube is required in the gametes and embryos transports, which involves muscular contraction and ciliary activity. PGs are known to have a role in embryo transport in the oviduct by acting as a mediator in smooth muscle contraction and relaxation [17], [18], [19]. Another study reported that the COX-2 receptor is expressed in the human fallopian tube and plays a regulatory function in the smooth muscle contraction process in the oviduct [20], [21].

During development, the blastocyst expresses multiple factors and receptors in response to sex steroids and growth factors. They act to regulate blastocyst growth and participate in the signal exchange with the receptive endometrium [11]. The growth and development of an embryo from two, four, and eight cells into morula and blastocyst is a complex and essential process for successful implantation [22]. Previous studies using bovine embryos at the morula and blastocyst stages showed that PGE2 biosynthesis involves the COX-2/mPGES-1 signaling pathway. COX-2 and mPGES-1 expression have been identified in various mechanisms involving PGE2, such as inflammation and tissue repair in the female reproductive system [23]. In human embryos, COX-1 is expressed earlier in the embryogenesis process at the zygote and 2-cell stage, whereas COX-2 is detected in the 8-cell, morula, and blastocyst stages [24]. COX-1, COX-2, and PGIS have also been expressed in 4-cell stage embryos and beyond and in the mouse blastocysts' inner cell mass and trophectoderm. 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. Mouse blastocysts primarily produce prostacyclin (PGI2). The 8-cell (morula) and blastocyst stages also synthesize PGE2. PGI2 binds to IP receptors and is involved in regulating embryo development. PGI2 has also been reported to regulate blastocyst cell apoptosis by acting as an antiapoptotic factor [11].

COX-2 in trophoblast invasion and embryo implantation

Endometrial receptivity lasts for only a constrained time. Thus embryos must relocate effectively into the receptive uterus at this constrained time. An increase in stromal vascular permeability has a vital role in sites of blastocyst adhesion. Successful mammalian pregnancy is determined by blastocyst implantation into the maternal uterus. COX-2 is mainly expressed in the luminal epithelium and stroma around the implantation embryos. Failure of embryo implantation and decidualization is caused by COX-2 insufficiency, which marks that the blastocysts were in a formative delay state after being transplanted into oviducts. It appeared that the advancement arrange of embryos did not influence the implantation rate, and early-stage of embryos was advantageous to pregnancy during embryo transfer [25].

COX-2 was identified amid early pregnancy from day 2 to 5, expanded amid decidual regression, and expressed at the time of parturition. COX-2 protein expression increased at the estrus phase of the rat's estrus cycle. It is found that COX-2 is modulated in the endometrium of pseudo-pregnant rats, proposing that they are controlled by 17beta-estradiol and progesterone. PGE2 (Prostaglandin E2) metabolite levels were found on days 10, 12, and 14 of pregnancy. PGF2-alpha (Prostaglandin F2-alpha) metabolite levels increment was observed on day 14. The concentration of this both metabolites changed during pseudo-pregnancy, and the highest levels were observed on day 7. A critical increment in PGE2 metabolite was observed in the proestrus phase. On the other hand, PGF2-alpha metabolite was significantly increased in the proestrus and metestrus phases. Estradiol in cultured endometrial stromal cells regulates the COX-2 protein [10].

The mRNA and protein expression of COX-1 and COX-2 were illustrated in the developing rodent placenta, with expanding expression observed toward parturition. COX-2 exhibited more prominent expression than COX-1 after mid-gestation and had a corresponding shift in spatial expression from the labyrinthine to the junctional zone at term. COX-1 and -2 were also expressed in the human term placenta. The results demonstrate that COX-1 and COX-2 are described in the rodent and human placentas. The differential COX-2 expression designs in rodent placenta imply that there may be gestational changes within the biosynthesis of PGs and other potential bioactive essential fatty acids metabolites. Functional and physiological significance of COX-1 and COX-2 in the placenta, particularly influencing normal pregnancy and fetal development, and also provide insights into therapeutic utilization of COX inhibitors in pregnancy can be explored with COX establishment isoforms expression [26].

Cells in cultured unstimulated trophoblasts expressed overwhelmingly either mPGES-1 or COX-2, even though there were cells coexpressing both enzymes. mPGES-1 and COX-2 became more consistently co-localized with IL-1b treatment. mPGES-1 was not transcriptionally co-induced with COX-2 by the cytokine treatment. It showed that mPGES-1 is not involved in the inducible COX-2 mediated pathway for PGE2 biosynthesis at the transcriptional level. However, treating IL-1b results in better coordination of the mPGES-1 and COX-2 protein immunolocalization, eliciting PGE2 synthesis [27].

The association of PGs in the trophoblast invasion process is still unclear, but several studies propose the possible action of PGs in the trophoblast

invasion process. A previous study showed that the adhesion ability of the human trophoblast cell line to the extracellular matrix through the MEK/MAPK signaling pathway could be modulated by PGs and EP2 agonists. PGs and EP2 agonists also upregulate the expression of proteins that play a part in the cell adhesion process, such as integrins [28].

Embryo implantation includes the interaction between an implantation-competent blastocyst and receptive uterus. During the embryo implantation process, uterine stromal cells surrounding the implanting embryo undergo the decidualization process. The stromal cells undergo extensive proliferation and subsequent differentiation into polyploid decidual cells. Proper decidualization is fundamental for embryonic development within the uterus and accomplishing successful pregnancy. Diminishing decidualization can lead to miscarriage or pathological pregnancy such as preeclampsia or intrauterine growth retardation. COX-2 is a prerequisite enzyme for prostaglandin biosynthesis and exerts influence on decidualization. COX-2 inhibitors will cause a deficiency of PGE2, which is essential for decidualization. It is also found that a lack of COX-2 can cause a decrease in VEGF mRNA levels, where VEGF is a crucial angiogenesis promoter for decidualization [29].

Discussion

Endometrium layers consist of epithelial and stromal cells, which are unique and dynamic under the effects of the ovarian steroid hormone, estrogen, and progesterone. The dynamic changes of the endometrium support the implantation, which is essential for fertility and reproduction. Prostaglandin E2 (PGE2) is among the most PGs in the endometrium, where its synthesis is driven by COX-2, an enzyme that converts arachidonic acid to PGs. Successful embryo implantation needs a decidualization process and differentiation of endometrial stromal cells to become polygonal and multi-nuclei cells. Progesterone has an essential role in the decidualization process by binding to the receptors in the nucleus of epithelial cells (progesterone receptor-A/PR-A) and interacting with some transcription factors. One of the transcription factors is CREB (Ca+/cAMP responsive element binding protein). Phosphorylation of CREB is triggered by the epithelial sodium channel (EnaC) in endometrial epithelial cells. EnaC in endometrial epithelial cells can be activated by embryo-derived protease (trypsin), which leads to some events, such as Ca2+ ion increase and phosphorylation of CREB, the transcription factor known to regulate COX-2. That event will lead to upregulation of COX-2 and eventually PGE2 synthesis. PGE2 is released to the endometrial stromal cells, leading to decidualization and embryo implantation (Figure 1) [4], [10], [12], [15], [16].

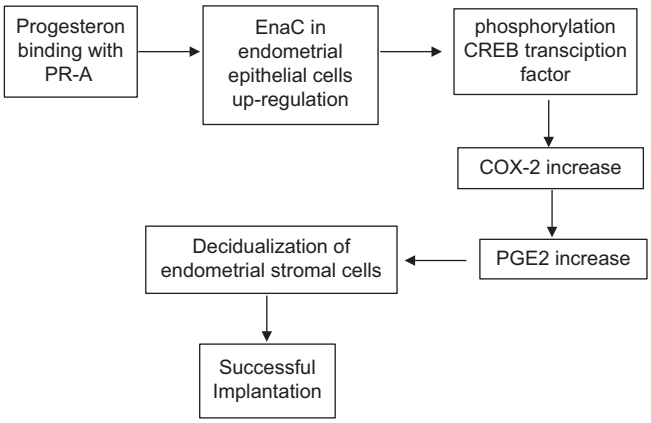

Figure 1: Regulation of COX-2 in endometrial cells for successful implantation through the ENaC pathway [4], [10], [12], [15], [16].

The previous research by Chen *et al*. (2017) shows that blocking PG synthesis by non-steroid anti-inflammatory drugs suggests a higher risk of miscarriage. IVF trials show that impaired endometrial PG synthesis leads to implantation failure. It is also supported by another research by S.J. Li *et al*. (2015) that COX-2 deficiency will cause the loss of implantation and decidualization, which causes the development of blastocyst delay after they are transplanted into oviducts. Besides the role of COX-2 in implantation described above, some functions of cyclooxygenase support the pregnancy [4], [25] (Table 1).

Table 1: Cyclooxygenase-2 expression in implantation and embryo development

Stage/location	Expression of cyclooxygenase and functions	References
Day 2–5 pregnancy	COX-2 increase, COX-1 decrease Decidualization	[10], [11], [13], [14], [15], [16], [17], [18], [19]
Oviducts (embryo transport)	COX-2 increase Contraction of the smooth muscle of oviducts	[17], [18], [19], [20], [21]
Zygote and two cells stage embryo	COX-1 dominant	[11], [22], [23], [24]
Four cells stage embryo	COX-1, COX-2	[11], [22], [24]
Eight cells stage embryo, morula, and blastocyst	COX-2 dominant	[11], [22], [24]

COX: Cyclooxygenase.

Conclusion

From this review, we can understand mechanisms of COX-2 expression and regulation in the endometrium and the role of COX-2 in decidualization, embryo implantation, and embryo development. The principle of COX-2 expression in endometrial cells is influenced by ovarian steroid hormones (progesterone and estrogen) through the ENaC pathway to regulate phosphorylation of CREB transcription factor and control prostaglandin production. Further research about the mechanism of COX-2 is needed to explore to identify the factors that influence COX-2 expression

in the implantation and could be applied in reproduction technology.

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Disclosure Statement

All authors declare that there are no conflicts of interest that could be perceived as prejudicing the impartiality of the research reported.

Author Contribution Statements

RDP and DMR conceived of the presented idea. RDP wrote the manuscript with support from DMR, RAS, and IPS. RAS and IPS helped supervise the project. All authors discussed the results and contributed to the final manuscript.

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