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# Involvement of Prostaglandins in the Pathophysiology of Endometriosis

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## 1. Introduction

Prostaglandins (PGs), thromboxanes (TXs) and leukotrienes (LTs) collectively called eicosanoids, are cyclooxygenase (COX) and lipoxygenase (LOX) products. Prostanoids, PGs and TXs, are known effectors of a wide range of actions in most cells and tissues. They have been described to be involved in muscle contraction and relaxation, neurotransmitter release/unrelease, fever, sleep induction, apoptosis, cell proliferation and oncogenesis; but respecting endometriosis, what matters us mostly, is that they are central molecules involved in the reproductive system (Jabbour & Sales, 2004; Narumiya et al., 1999).

### 1.1 Prostaglandin synthesis and function

Arachidonic acid (AA) is the precursor of all eicosanoids. Phospholipase A<sub>2</sub> splits AA from plasma membrane phospholipids; once free in the cytosol it is cyclized, oxygenated and reduced to the intermediary PGH<sub>2</sub> by the COX enzymes; or to hydroperoxyeicosatetraenoic acid (HPETE) by LOX enzymes, when the LT pathway is followed.

Two COX genes are known to be highly conserved throughout the species. COX-1 gene has several splice variants: the most widely known COX-1 enzyme, the less known counterparts COX-3 and other smaller variants of the COX-1 (Chandrasekharan et al., 2002; Chandrasekharan & Simmons, 2004). COX-2 gene has, up to now, only one known protein. COX-1 is ubiquitously and constitutively expressed. It was long thought of COX-1 as the enzyme that was involved only in physiological conditions, but was proven to be upregulated in various carcinomas and to be involved in tumorigenesis (Hwang et al., 1998; Kitamura et al., 2002; Sales et al., 2002). COX-2 enzyme is physiologically induced by growth factors and cytokines; it functions when the concentrations of AA are very low (Fortier et al., 2008). Furthermore COX-2 was seen to be overexpressed in several pathological circumstances as different types of cancers, where its high expression correlates with a negative prognosis, and other inflammation related diseases, as endometriosis (Matsuzaki et al., 2004; Ota et al., 2001).

PGH<sub>2</sub> synthesized by the COXs, is used as a substrate to produce the terminal prostanoids by the PG synthases; each of them is named by their product: PGD<sub>2</sub>, PGE<sub>2</sub>, PGF<sub>2α</sub>, prostacyclin (PGI<sub>2</sub>) and thromboxane (TX). A<sub>2</sub> are produced by PGD synthase (PGDS), PGE

synthase (PGES), PGF synthase (PGFS), PGI synthase (PGIS) and TX synthase (TXS), respectively. Once synthesized prostanoids are rapidly exported by a PG transporter out of the cell and they function very close to their liberation site, in an autocrine or paracrine fashion. They exert their biological actions through G protein coupled receptors (GPCRs) and, as it happens with the synthases, each prostanoid has a distinctive receptor to which to bind to. DP, EP, FP, IP and TP are the receptors for PGD<sub>2</sub>, PGE<sub>2</sub>, PGF<sub>2α</sub>, PGI<sub>2</sub> and TXA<sub>2</sub>, respectively (Figure 1). The EP receptor has four known subtypes (EP1-EP4), each encoded by a different gene; furthermore, EP3 has eight splice variants; TP and FP have also been described to have two splice variants each (Fortier et al., 2008).

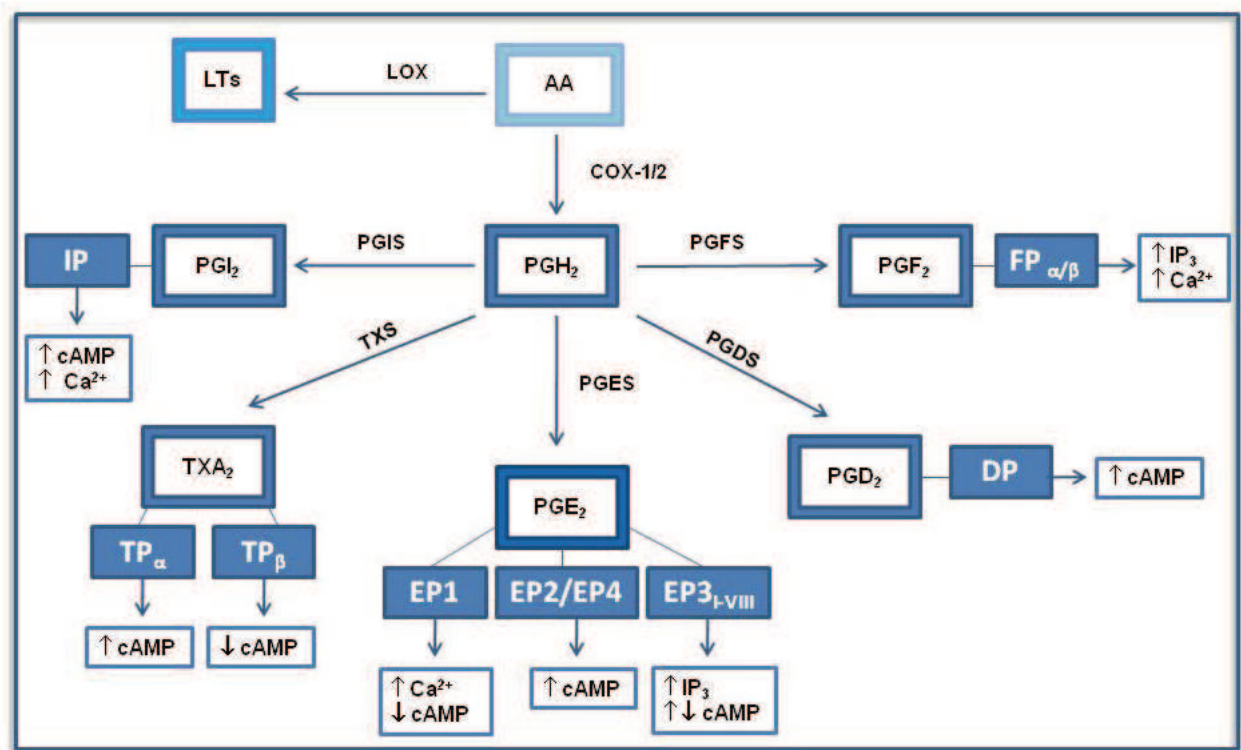
Sequence homology analysis revealed that receptors sharing a common signaling pathway are more closely related than do receptors binding the same ligand. After binding to the corresponding GPCR there is generation of soluble second messengers. Coupled to G<sub>q</sub>, DP receptor increases cyclic adenosine monophosphate (cAMP) concentration, whereas IP receptor is coupled to G<sub>s</sub> and increases not only cAMP but also mediates responses by phosphatidylinositol increasing free Ca<sup>2+</sup> concentration (Narumiya et al., 1999). Both isoforms of TP activate phospholipase C (PLC), but TP<sub>α</sub> activates adenylate cyclase while TP<sub>β</sub> inhibits it (Narumiya et al., 1999). FP receptors also act through G<sub>q</sub>, PLC and Ca<sup>2+</sup> release; while EP receptors have distinctive signaling pathways depending on the subtype binding PGE<sub>2</sub>: EP1 is coupled to G<sub>i</sub> and Ca<sup>2+</sup> channels, EP2 and EP4 share the pathway coupling to G<sub>s</sub> and increasing cAMP intracellular concentration, whereas the EP3 has specific responses depending on the splice variant, but is usually assumed as an inhibitory receptor coupled to G<sub>i</sub> (Fortier et al., 2008) (Figure 1).

## 2. Role of endometrial prostaglandins in reproduction

The uterus plays a crucial role in the implantation process of the fertilized egg. Humans and old-world primates have the particularity that they shed part of their endometrium if fertilization or implantation does not take place. Consequently, endometrium is a dynamic tissue that undergoes regulated phases of proliferation, differentiation and degradation, cyclically. PGs are known to be important actors of this process; different reports have implicated COX enzymes and PGs in several stages of reproduction (Jabbour et al., 2006).

COX-2 is physiologically expressed at different levels along the menstrual cycle. It has been shown to be expressed at its lowest level during ovulation and slightly start augmenting during the secretory phase, peaking at the late secretory and menstrual phases after which it starts decreasing again (Jones et al., 1997).

The importance of COX and PGs in reproduction has been revealed from studies of knockout mice. Even if COX-1 deficient mice were fertile, their gestation period was prolonged while parturition and viable offspring were reduced. These findings demonstrated that COX-1 is essential for normal labor in the mouse (Gross et al., 1998; Jabbour et al., 2006). On the other side, selective COX-2 ablation impairs ovulation, fertilization and implantation; and a combined approach showed that COX-2 inhibition in COX-1(-/-) mice induced complete reproductive failure, suggesting a lack of alternative sources of PG synthesis (Reese et al., 2001).



Arachidonic acid is the precursor for leukotrienes and prostaglandins. Each prostaglandin has a specific seven transmembrane G protein coupled receptor; after binding with its receptor, prostaglandins produce the up (↓) or downregulation (↑) of second messengers.

**AA:** arachidonic acid; **LTs:** leukotrienes; **LOX:** lipooxygenase; **COX-1/2:** cyclooxygenase-1 or 2; **PGH<sub>2</sub>:** prostaglandin H<sub>2</sub>; **PGIS:** prostacyclin synthase; **PGI<sub>2</sub>:** prostacyclin; **TXS:** thromboxane synthase; **TXA<sub>2</sub>:** thromboxane; **PGE<sub>2</sub>:** prostaglandin E<sub>2</sub>; **PGD<sub>2</sub>:** prostaglandin D<sub>2</sub>; **PGF<sub>2</sub>:** prostaglandin F<sub>2</sub>; **PGES:** PGE<sub>2</sub> synthase; **PGDS:** PGD<sub>2</sub> synthase; **PGFS:** PGF<sub>2α</sub> synthase; **IP, TP<sub>α/β</sub>, EP1-4, DP, FP<sub>α/β</sub>:** specific PG receptors; **cAMP:** cyclic adenosine monophosphate; **IP<sub>3</sub>:** inositol triphosphate; **Ca<sup>2+</sup>:** calcium.

Fig. 1. Prostaglandin synthesis and signal transduction

In addition, studies using EP and FP knockout mice have demonstrated the specific roles of PGE<sub>2</sub> and PGF<sub>2α</sub> in reproduction. It has been shown that EP2 receptors are essential for ovulation and fertilization (Kennedy et al., 1999; Ushikubi et al., 2000) and FP are indispensable for parturition (Sugimoto et al., 1998). These studies indicate not only the essential role of PGE<sub>2</sub> in the fertilization process, but also the importance of PGF<sub>2α</sub> in natural parturition.

As well, it has been described that PGs serve as endogenous ligands for nuclear receptors. In this respect, other prostanoids were identified as good peroxisome proliferator-activated receptors (PPAR) agonists with varying specificity. 15-deoxy-Δ<sup>12,14</sup> prostaglandin J<sub>2</sub> (15dPGJ<sub>2</sub>), a natural PPARγ ligand, has high affinity for PPARγ and has been proposed as a regulator of the inflammatory response (Nosjean & Boutin, 2002; Scher & Pillinger, 2009). Another PPAR ligand is PGI<sub>2</sub> that was found to play an important role via PPAR-δ nuclear receptor in implantation and decidualization (Pakrasi & Jain, 2008).

The process of implantation is considered to be analogous to pro-inflammatory responses, hence the speculation that PGs play a role in this event (Kennedy, 1979; Maybin et al., 2011; Tranguch et al., 2005). As well, several nonsteroidal anti-inflammatory drugs (NSAIDs) and

selective COX-2 inhibitors were implicated in the inhibition of endometrial vascular permeability and implantation in a variety of species (Diao et al., 2007; Sookvanichsilp & Pulbutr, 2002).

In particular in the endometrium, COXs and PGs are known to be involved in the initiation of implantation and decidualization (Kennedy et al., 2007; Tranguch et al., 2005). It is well known that endometrial vascular permeability and proliferation and differentiation of endometrial stromal cells to decidual cells are mediated by PGs (Kennedy, 1979; Kennedy & Doktorcik, 1988). The initial studies of Chakraborty and coworkers suggest an important role for PGs in the implantation process; specifically this report demonstrated that COX-2 expression during the blastocyst attachment is critical to implantation (Chakraborty et al., 1996).

In an effort to identify which PGs are involved in the implantation process, different researchers have confirmed the presence of PGE and PGF receptors in the peri-implantation endometrium (Kennedy et al., 2007). However, no single type of PG has been unequivocally associated to this event. There may be species differences and also different PGs may be involved in the implantation or decidualization processes (Kennedy et al., 2007).

### 3. PGE<sub>2</sub> and its role in the aetiopathogenesis of endometriosis

COX-2, the crucial enzyme for the production of PGs, has been described to be upregulated in different pathological inflammatory conditions. Endometriosis is characterized by the high proliferation rate of endometrial cells in an ectopic site, inflammation and pain. COX-2 is highly expressed in eutopic endometrium, both in the proliferative and secretory phases, and in ectopic lesions from endometriosis patients compared to disease free women (Ota et al., 2001). Wu and coworkers also described that COX-2 is expressed in stromal and epithelial cells derived from endometriosis patients, and is in agreement with the work from Ota and coworkers, in that this expression is higher in patients (Ota et al., 2001; Wu et al., 2002).

#### 3.1 Sources of prostaglandins

It is well known that the elevated levels of PGs found in the peritoneal fluid from patients with endometriosis are mainly produced by peritoneal macrophages and endometriotic tissues (Raiter-Tenenbaum et al., 1998; Wu et al., 2002; Wu et al., 2010). COX-2 is overexpressed in peritoneal macrophages and in ectopic and eutopic endometrial tissue derived from patients with endometriosis (Banu et al., 2008; Ota et al., 2001; Wu et al., 2002; Wu et al., 2005b). Peritoneal macrophages from endometriosis-free women express no or minimal amounts of COX-2, while the overexpression of COX-2 found in endometriosis has been associated with the elevated concentrations of PGs and the severity of the disease (Wu et al., 2002). Explicitly, induction of COX-2 expression correlated with the evidence that peritoneal macrophages from patients with endometriosis release significantly more PGE<sub>2</sub> and PGF<sub>2α</sub> compared with peritoneal macrophages from control women (Karck et al., 1996; Raiter-Tenenbaum et al., 1998). Many pro-inflammatory and pro-angiogenic factors contribute to increase PGs levels: interleukin (IL)-1β, tumor necrosis factor (TNF)-α, vascular endothelial growth factor (VEGF), macrophage migration inhibition factor (MIF) and even PGE<sub>2</sub> have been shown to induce COX-2 expression in peritoneal macrophages from women with endometriosis (Wu et al., 2002) and in endometrial and endometriotic stromal cells (Carli et al., 2009; Tamura et al., 2002; Wu et al., 2005b) (Figure 2).



The mitogenic effects of estrogens are mediated by the upregulation of several growth factors and also by PGs. Specifically, aromatase and steroidogenic acute regulatory protein (StAR) are known to be regulated by PGE<sub>2</sub> in endometriotic stromal cells (Bulun et al., 2004; Noble et al., 1997; Sun et al., 2003; Tsai et al., 2001). PGE<sub>2</sub> alone via the EP2/EP4 receptor is sufficient to induce de novo synthesis of estrogen from cholesterol (Attar et al., 2009). As well, estrogen further stimulates the synthesis of PGE<sub>2</sub> in ectopic endometrial tissue (Bulun et al., 2000; Noble et al., 1997). In conclusion, estrogens, pro-inflammatory and pro-angiogenic peptides contribute to elevate the expression of COX-2 and consequently the levels of PGE<sub>2</sub> in endometriotic tissue and in peritoneal macrophages from patients with endometriosis (Figure 2).

### 3.2 Regulation of aromatase activation and estrogen production by PGE<sub>2</sub>

Aromatase is the key enzyme in the conversion of the androgens, androstenedione and testosterone, to estrone and estradiol (E<sub>2</sub>) respectively (Bulun et al., 2001). This protein was seen to be overexpressed in the eutopic endometrium of patients with endometriosis compared to controls (Noble et al., 1996) and it has been described to be expressed in the ectopic endometriotic lesion. PGE<sub>2</sub> induces not only aromatase expression but also its activity, as seen in studies conducted in endometriotic stromal cells *in vitro* (Noble et al., 1997); and its product, E<sub>2</sub>, induces COX-2 expression with the consequent synthesis of PGE<sub>2</sub> (Tamura et al., 2004). It is clear that given the way these molecules interact, a positive feedback loop is established favoring the activity of aromatase, provoking high levels of E<sub>2</sub> locally in the vicinity of the lesion (Figure 2). These high levels of E<sub>2</sub> also give the endometriotic cells a high capability of proliferating; as it has been demonstrated that, through its estrogen receptor (ER)β, E<sub>2</sub> enhances stromal cell proliferation (Trukhacheva et al., 2009).

Another mitogenic factor is fibroblast growth factor (FGF)-9. This molecule was found to be regulated by estrogen in endometriotic stromal cells in culture and, if added exogenously, cell proliferation was enhanced in a dose dependent manner. On the contrast, when cells were incubated with an aromatase or an ER inhibitor, the rate of cell proliferation diminished significantly compared to the untreated control (Wing et al., 2003). In the same study by Wing and coworkers, it was observed that not only FGF-9 is regulated by E<sub>2</sub>, but also, FGF receptors 2IIIc and 3IIIc. More recently, a study revealed that PGE<sub>2</sub>, acting through its receptor EP3 induces the expression of FGF-9 in a dose dependent manner in endometriotic cells *in vitro* (Chuang et al., 2006) (Figure 2).

### 3.3 PGE<sub>2</sub> and angiogenesis

Endometrial cells at the ectopic site are urged to establish their own irrigation network, this is essential for the further maintenance and growth of the endometriotic lesion. It is widely known that VEGF is crucial for the process of angiogenesis; this is the process by which new blood vessels can be developed from preexisting ones. It has been shown that patients with endometriosis have a higher VEGF concentration in peritoneal fluid than endometriosis free women (Mahnke et al., 2000). Moreover, it was seen that VEGF stimulates COX-2 expression (Tamura et al., 2006) and that PGE<sub>2</sub> increases VEGF production (Gately & Li, 2004; Liu et al.,

2002); as it happens with aromatase, a positive feedback loop is established in which COX-2 activity and PGE<sub>2</sub> production are favored, giving the characteristic inflammation site of endometriosis (Figure 2).

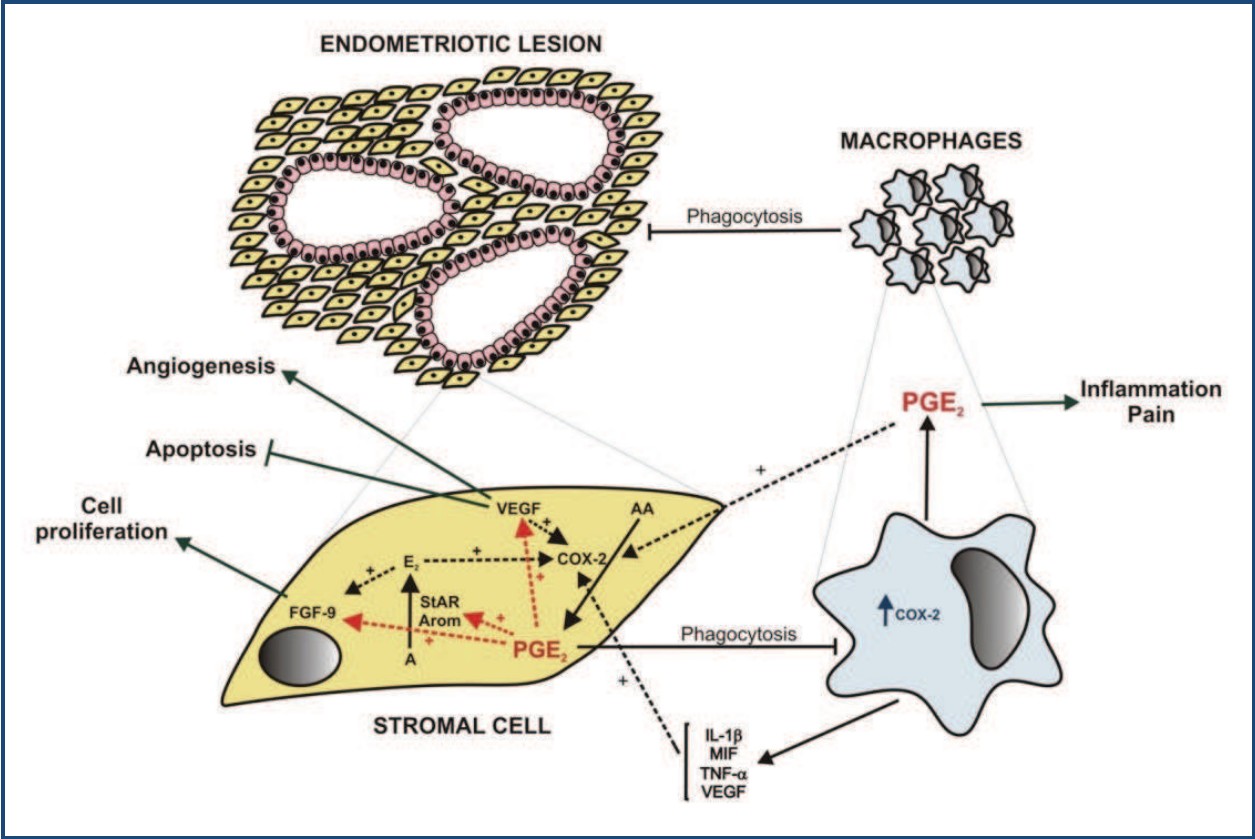
### 3.4 Prostaglandins as immune and inflammatory mediators in endometriosis

Immune dysfunction has been proposed to play an important role in endometriosis (Dmowski W.P. & Braun, 2004; Vinatier et al., 1996). Peritoneal macrophages may play a key role in this respect, and may control the function of other immune cells. One of the altered mechanisms involved in the implantation and propagation of endometrial tissues ectopically is the decrease of the phagocytic ability of peritoneal macrophages (Chuang et al., 2009).

In their earlier studies, Braun and coworkers reported that the decrease in peritoneal macrophages cytotoxic function is controlled by PG synthesis (Braun et al., 1992) (Figure 2). To elucidate the molecular mechanism implicated in the reduced phagocytic ability of peritoneal macrophages in endometriosis, recent *in vitro* and *in vivo* studies demonstrated that PGE<sub>2</sub>, via the EP2 receptor-dependent signaling pathway, inhibits the expression of the scavenger receptor CD36 in peritoneal macrophages. Reduced expression of any one of the scavenger receptors may result in loss of phagocytic ability of macrophages (Chuang et al., 2010). Another work suggests that the expression and the enzymatic activity of MMP-9, a metalloproteinase that plays important roles in the scavenger activity of macrophages, is reduced by PGE<sub>2</sub> in peritoneal macrophages derived from endometriosis patients compared to controls (Wu et al., 2005a). Wu and coworkers also reported that this inhibitory effect of PGE<sub>2</sub> may be mediated via the EP2/EP4-dependent PKA pathway (Wu et al., 2005a). These data allow us to explain some of the disruptions observed in the endometriotic macrophage functions and provide a functional link between COX-2 overexpression and endometriosis development (Ota et al., 2001; Tamura et al., 2002; Wu et al., 2005b).

There is abundant evidence demonstrating that endometriosis is accompanied by inflammatory reactions in the peritoneum, resulting in abnormal levels of a variety of cytokines, chemokines and pro-inflammatory factors in the peritoneal fluid (Gazvani & Templeton, 2002; Lousse et al., 2010). It is also well known, that the number of macrophages is increased in the peritoneal fluid of endometriosis patients and that they are in a hyperactive state (Halme & Surrey, 1990; Raiter-Tenenbaum et al., 1998). Production of inflammatory cytokines by these macrophages such as monocyte chemoattractant protein (MCP)-1, IL-1 $\beta$ , TNF- $\alpha$  and IL-6 is also increased in peritoneal fluid (Wu et al., 2007). As well, we found that the release of PGE<sub>2</sub> by peritoneal macrophages was 100-fold higher in advanced endometriosis patients than in controls (Raiter-Tenenbaum et al., 1998).

It has also been demonstrated that the overexpression of COX-2 is markedly induced by IL-1 $\beta$ , TNF- $\alpha$  and MIF and that these pro-inflammatory agents strongly stimulate the production of PGE<sub>2</sub> (Carli et al., 2009; Wu et al., 2002) (Figure 2). However, not only the overexpression of COX-2 increases the production of PGE<sub>2</sub>, but also a decrease in the deactivating enzyme 15-PGDH was found, showing an imbalance between eicosanoid biosynthesis and degradation in endometriosis patients compared with controls (Lousse et al., 2010). As a result, the concentration of PGE<sub>2</sub> in the peritoneal fluid is elevated in patients with endometriosis, which leads to a more severe pathological process.



Macrophages synthesize and liberate PGE<sub>2</sub>, VEGF, MIF, IL-1 $\beta$ , TNF- $\alpha$ ; all of these factors stimulate the expression and/or activity of COX-2 producing higher concentrations of PGE<sub>2</sub>. The high levels of PGE<sub>2</sub> stimulate the expression of the angiogenic factor VEGF and the steroidogenic capacity of endometriotic cells by the upregulation of StAR and aromatase, which augments the biosynthesis of estrogen. E<sub>2</sub> and PGE<sub>2</sub> further induce FGF-9 expression to stimulate endometriotic cell proliferation. As a result, angiogenesis and cell proliferation are augmented while apoptosis is inhibited. Moreover, PGE<sub>2</sub> suppresses the phagocytic ability of macrophages, which fail to phagocytose the retrograde endometrial tissue and allow the implantation and proliferation of endometriotic lesion.

**A:** androstenedione; **AA:** arachidonic acid; **Arom:** aromatase P450; **COX-2:** cyclooxygenase-2; **E<sub>2</sub>:** estradiol; **IL-1 $\beta$ :** interleukin 1 $\beta$ ; **MIF:** macrophage migration inhibitory factor; **PGE<sub>2</sub>:** prostaglandin E<sub>2</sub>; **StAR:** steroidogenic acute regulatory protein; **TNF- $\alpha$ :** tumor necrosis factor  $\alpha$ ; **VEGF:** vascular endothelial growth factor; **FGF-9:** fibroblast growth factor-9.

Fig. 2. Peritoneal environment in endometriosis

4. Prostaglandins and pelvic pain

Endometriosis has been traditionally included among the most important causes of pelvic pain in women of reproductive age. A recent case-control study described that 73% of women with endometriosis reported experiencing abdominopelvic pain, dysmenorrhea, or menorrhagia compared with only a 20% of the controls (Ballard et al., 2008).

The role of PGs has been examined in women suffering from heavy menstrual bleeding and dysmenorrhea (Maybin et al., 2011). Dysmenorrhea is defined as the excessive pain during menstruation; and menorrhagia or heavy menstrual bleeding is the excessive menstrual blood loss during the menstrual periods. These may be primary disorders or secondary to endometrial pathology such as endometriosis (Maybin et al., 2011; Tietjen et al., 2006).



The pelvic pain of dysmenorrhea has been demonstrated to be mediated through the action of PGE<sub>2</sub> and a direct relationship between the severity of dysmenorrhea and the production of PGs has been observed in endometriosis (Coco, 1999; Koike et al., 1992; Nasir & Bope, 2004). As well, analysis of menstrual fluid from women suffering from dysmenorrhea revealed augmented levels of PGE<sub>2</sub> and PGF<sub>2α</sub> (Dawood & Khan-Dawood, 2007a, 2007b; Lumsden et al., 1983).

Increased synthesis of PGE<sub>2</sub> and PGF<sub>2α</sub> in the endometrium has important implications for menstruation (Baird et al., 1996). PGE<sub>2</sub> is a potent vasodilator leading to increased oedema and contributing to pain at time of menstruation. Increased COX-2 and enhanced PGE<sub>2</sub>-EP-induced cAMP production has been found by Smith and coworkers in the endometrium of women with objective heavy menstrual bleeding. These authors suggest that the increased expression of the rate-limiting COX enzymes in the endometrium of women with heavy menstrual blood loss will lead to an increase in PG production and to a magnified inflammation (Smith et al., 2007).

In addition, there is well reported evidence for the hyperalgesic properties of PGs; and EP receptors have been shown elevated in sensory neurons that lead to increased pain perception (Bley et al., 1998; Levine & Taiwo, 1990). Wienecke and coworkers also demonstrated that PGE<sub>2</sub> induces headache in healthy subjects by sensitization of cranial perivascular sensory afferents (Wienecke et al., 2009). Therefore, PG inhibition usually resolves the pain and many studies have demonstrated the efficacy of NSAIDs and specific COX-2 inhibitors in relieving dysmenorrheic pain (Coco, 1999; Hayes & Rock, 2002). Suprofen, ibuprofen and acetaminophen were shown to be efficient not only for pain relief but for menstrual fluid PGs suppression as well (Dawood & Khan-Dawood, 2007a, 2007b).

A recent study suggests that the major modality to substantially alleviate pain in endometriosis is suppression of ovarian function and induction of a steady hormonal condition, anovulation and, eventually, amenorrhea (Vercellini et al., 2011). Hormonal manipulation and surgery have been found to be efficient in the management of pelvic pain associated to endometriosis (Vercellini et al., 2011). Oral contraceptives, GnRH agonists, danazol and progestins have been shown to reduce the production of PGs, which are responsible in large part for pelvic pain (Crosignani et al., 2006; Venturini et al., 1997).

Given that, further investigations should focus on how to inhibit the production of PGs in endometriosis to control the pain and the development of the pathology.

## 5. Endometriosis and its therapies

As an estrogen-dependent disease, endometriosis treatment has aimed at reducing estrogen concentrations with reversible therapies, using oral contraceptives in a cyclical or continuous fashion as well as with GnRH analogues as first line medical treatments. Progestins, aromatase inhibitors (AIs) and, less frequently, androgens are also used. Removing lesions in a conservative surgery, or even having a radical intervention when the extent of the disease is major, is the surgical approach nowadays available. The most ordinary way of treating endometriosis is attacking from both flanks, with the surgical intervention and dealing with the symptoms with the drug therapy. In any case, the disease is likely to reappear after cessation of therapy; in fact, recurrence rate for endometriosis is between 4-25% (Meuleman et al., 2011).

### 5.1 PGE<sub>2</sub> synthesis inhibition and pain treatment

One of the most inhabilitating symptoms of endometriosis for carrying a normal life is the elevated pelvic pain patients experience. It includes pain before and during periods, during sexual intercourse, while urinating or defecating and during menstruation. It has been of great importance to provide the patient with a better quality of life ameliorating pain symptoms. Elevated concentrations of PGE<sub>2</sub> in peritoneal fluid from endometriosis patients is the major cause thought to be involved in pain and inflammation processes (Wu et al., 2002).

There have been done a large number of studies focusing on the inhibition of COXs activity. Whether it is blocking simultaneously COX-1 and COX-2 or with selective COX-2 inhibitors, the ultimate goal is to lower the concentrations of PGE<sub>2</sub>.

NSAIDs, among them: ibuprofen, naproxen, diclofenac or aspirin; are used primarily for pain treatment, from a headache to menstrual cramps, from a backache to treating an inflammation due to a sprain. These NSAIDs are non-selective COX inhibitors; this means that they prevent the synthesis of PGs from both COXs. Of course, as a constitutively and ubiquitously expressed enzyme, COX-1 inhibition has side effects that should be avoided. Gastrointestinal ulcer is not a rare effect after long term inhibition of COX-1 (Wadman, 2007); this is why COX-2 selective inhibitors have been developed.

Celecoxib belongs to the family of NSAIDs with high selectivity for COX-2 inhibition. Other coxibs have been developed too (rofecoxib, valdecoxib) but were withdrawn from the market in the mid 2000s by the Federal Drug and Food Administration (FDA) of the United States of America because they were proven to have serious cardiovascular adverse events. Coxibs were and are mostly used in arthritis; the one still available for purchase, celecoxib, is prescribed in familial adenomatous polyposis and as an adjuvant in breast cancer (Basu et al., 2006; Falandry et al., 2009; Iwama, 2009; Jankowski & Hunt, 2008; Lynch et al., 2010). Celecoxib has not been approved yet for the treatment of endometriosis. There is one study that evaluated the effectiveness of a COX-2 specific inhibitor on relieving pain symptoms associated to endometriosis after a conservative surgery. Cobellis and coworkers demonstrated in their study that rofecoxib was effective for the management of pain and no recurrence occurred during the six months of treatment (Cobellis et al., 2004).

Ferrero and coworkers, recently published a review where they compiled information on the use of AIs and how they contributed to diminish endometriosis related pain. This systematic study shows that the AIs, letrozole and anastrozole, are effective in treating pain symptoms; when withdrawn symptoms reappear, but they cannot be used for a long term therapy because of the adverse effects these compounds have on bone density (Ferrero et al., 2011). Endometriosis patients need chronic treatment, and this could be achieved combining AIs with a hormonal therapy to reduce the loss of bone density (Ferrero et al., 2011).

### 5.2 PGE<sub>2</sub> synthesis inhibition and the control over endometriosis development

There have been conducted several studies in which AIs were used and the progression of endometriosis was evaluated. When letrozole or anastrozole were added to endometrial epithelial cells from endometriosis patients in culture, cell proliferation was inhibited and apoptosis augmented (Meresman et al., 2005). When the same two compounds were used for the treatment of surgically induced endometriosis in mice, not only cell proliferation was diminished and apoptosis increased within the endometriotic like lesion, but PGE was also

decreased in the peritoneal fluid of mice treated with letrozole but not with anastrozole (Bilotas et al., 2010).

Much research has been done evaluating the effects of inhibiting COXs activity regarding the development of endometriosis with *in vivo* and *in vitro* approaches. Celecoxib has been shown to have anti-proliferative and pro-apoptotic effects over endometrial epithelial cells in culture obtained from biopsies of women with and without endometriosis; it was also effective in diminishing COX-2 expression, reducing the synthesis of VEGF and PGE<sub>2</sub> (Olivares et al., 2008). Similar results had previously been achieved in various cancer models (Basu et al., 2005; Chun & Surh, 2004). Given that the endometrial cells at the ectopic site have a very similar behaviour to neoplastic cells; it is not surprising that treatments aim at the same targets.

There is one very complete work from Efstathiou and coworkers where they compared seven different selective (rofecoxib and celecoxib) and non-selective (aspirin, ibuprofen, indomethacin, naproxen and sulindac) NSAIDs on the establishment and development of endometriosis in a mouse model (Efstathiou et al., 2005). In this work, celecoxib given orally twice daily and indomethacin administered subcutaneously daily for four weeks, were both effective in significantly diminishing the percentage of established lesions compared to the control group. All the NSAIDs evaluated in the same study, except for aspirin, significantly inhibited the growth of the established lesions compared to the control group (Efstathiou et al., 2005). A study in a rat model of endometriosis, evaluated the effect of parecoxib, another selective COX-2 inhibitor, and showed not only a significant reduction in lesion size, but also, a significant inhibition on the expression of VEGF, its receptor Flk-1 and COX-2 compared to the untreated group with endometriosis (Machado et al., 2010). Machado and coworkers also observed a significant reduction of the levels of PGE<sub>2</sub> in endometriotic homogenized tissue treated with parecoxib compared to the untreated group (Machado et al., 2010).

More recently a new approach targeting more than one molecule to prevent the development of the disease has gained importance. Promising results were achieved firstly in cancer models, which targeted COX-2 and PPAR $\gamma$ . This combinational therapy resulted in the inhibition of cell proliferation and apoptosis enhancement *in vitro* and increased overall survival rate *in vivo* (Mustafa & Kruger, 2008; Sun et al., 2009). When celecoxib was combined with rosiglitazone, a PPAR $\gamma$  agonist, for the treatment of surgically induced endometriosis in a mouse model, a reduced number of established lesions was observed as well as the volume of established ones; also induction of apoptosis and reduction of the cell proliferation rate and vascularization was achieved (Olivares et al., 2011).

Reducing PGE<sub>2</sub> concentration in the peritoneal environment would not only be relieving the pain caused by the disease but would also be affecting its development. This is one of the main goals of endometriosis treatments; now it is time to decide whether the drugs used to achieve these results are the appropriate ones to manage with this disease.

## 6. Conclusion

In conclusion, PGs play a substantial role in the physiological and pathological processes in the reproductive system. PGs are known to be involved in the initiation of the physiological implantation and decidualization. Also, COX-2 and PGE<sub>2</sub> were seen to be

overexpressed in several pathological circumstances as different types of cancers and other inflammation related diseases.

There is no doubt that PGE<sub>2</sub> is implicated in the aetiopathogenesis of endometriosis and contributes to the development and maintenance of the disease. The elevated levels of PGs found in the peritoneal fluid from patients with endometriosis are mainly produced by peritoneal macrophages and endometriotic tissues. As well, the peritoneal estrogens, pro-inflammatory and pro-angiogenic molecules contribute to elevate the expression of COX-2 and consequently the levels of PGE<sub>2</sub> in endometriosis patients. The pelvic pain associated to endometriosis has also been demonstrated to be mediated through the action of PGE<sub>2</sub> and inhibition of PG production usually resolves the pain.

Given these data, further investigations should focus on how to inhibit the production of PGs in endometriosis, to control the pain and the development of the pathology.

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## 8. References

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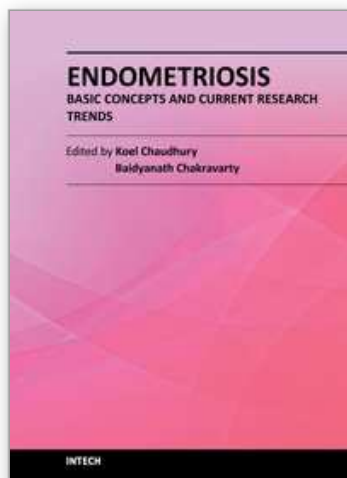
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## **Endometriosis - Basic Concepts and Current Research Trends**

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This book provides an insight into the emerging trends in pathogenesis, diagnosis and management of endometriosis. Key features of the book include overviews of endometriosis; endometrial angiogenesis, stem cells involvement, immunological and hormonal aspects related to the disease pathogenesis; recent research reports on infertility, endometrial receptivity, ovarian cancer and altered gene expression associated with endometriosis; various predictive markers, and imaging modalities including MRI and ultrasound for efficient diagnosis; as well as current non-hormonal and hormonal treatment strategies. This book is expected to be a valuable resource for clinicians, scientists and students who would like to have an improved understanding of endometriosis and also appreciate recent research trends associated with this disease.

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