Chapter

Beneficial Effect of Omega-3 Fatty Acids on Immune and Reproductive Endometrial Function

Maria A. Hidalgo, Marcelo Ratto and Rafael A. Burgos

Abstract

Omega-3 polyunsaturated fatty acids, such as docosahexaenoic acid (DHA) and eicosapentaenoic acid (EPA), are known by their anti-inflammatory effects through mechanisms such as formation of specialized pro-resolving mediators (SPM), and more recently a new mechanism dependent on the free fatty acid (FFA) receptors has been studied. DHA and EPA have shown an effect on the release of prostaglandins (PGs) E2 and F2α in endometrial cells, two PGs that have key function in fertility. In addition, other molecules such as cyclooxygenase-2, IL-1β, NF-κB, and intracellular signaling pathways are also affected by omega-3 fatty acids in endometrial cells. In this chapter, we will expose the following issues: eicosanoids in fertility and immune function in the uterus, effect of omega-3 fatty acids on endometrial function: in vivo and in vitro studies, mechanisms of action of omega-3 fatty acids in endometrial cells, and perspectives in health and diseases.

Keywords: omega-3 fatty acids, prostaglandin, endometrial cells, fertility, immune function

1. Introduction

Uterine function is key for a suitable reproductive performance and fertility. Endocrine and immune response play important roles for keeping the hormonal levels and the fetal-maternal interface. Hormones such as estrogen and progesterone are released from the ovaries; estrogen release is triggered by the hypothalamic-pituitary axis, and progesterone is secreted from the corpus luteum (CL) after ovulation. Estrogen is essential for uterine growth and cell proliferation and progesterone for endometrial receptivity and successful establishment of pregnancy [1, 2]. Estrogen and progesterone are also considered as regulators of innate immunity and inflammation in the endometrium [3]. Endometrial immune homeostasis plays an important role in the success of implantation and pregnancy, with complex interactions between the innate and adaptive immune system, through cells such as natural killer, antigen-presenting cells (macrophages and dendritic cells), and subtypes of T cells [4].

Prostaglandins (PGs), also known as prostanoids, are bioactive lipids with an important function as regulators of reproductive processes, including ovulation,

fertilization, and implantation. PGs are synthesized from arachidonic acid by different cells, and five types of PGs have been described, with specific roles and mechanism in the female reproductive system [5, 6]. Prostaglandin F2α (PGF2α) has a luteolytic effect, whereas prostaglandin E2 (PGE2) is central in ovulation, fertilization, embryo development, and implantation [7, 8]. In addition, PGE2 plays important roles in inflammatory processes, being increased at first phases of inflammation [9].

Inflammation is a complex process with two differentiated steps or conditions: acute and chronic inflammation. A number of lipid mediators act as pro-inflammatory (i.e., leukotriene and prostaglandins) or anti-inflammatory and pro-resolving (lipoxins, resolvins, maresins, and protectins) mediators. Lipid mediators derived from polyunsaturated fatty acids (PUFA) have potent anti-inflammatory effect and promote the resolution of inflammation, through specialized pro-resolving lipid mediators (SPM) [10]. Omega-3 fatty acids are a type of PUFA with known beneficial effect, which, in addition to its pro-resolving mechanism, have shown two additional anti-inflammatory mechanisms: activation of the free fatty acid (FFA)-4 receptor and inflammasome inhibition. Recent evidences have suggested an anti-inflammatory effect of docosahexaenoic acid (DHA) and eicosapentaenoic acid (EPA) in the endometrium. Furthermore, FFA4 receptor was detected in the human, mouse, and bovine uterus [11, 12]. The following sections describe the effect and potential mechanisms of omega-3 fatty acids in the immune cells and endometrium and perspectives of these fatty acids in health and disease.

2. Eicosanoids in fertility and immune function in the uterus

Eicosanoids, which include prostaglandins and leukotrienes, are members of a large family of compounds that are synthesized from arachidonic acid through the cyclooxygenase and lipoxygenase pathways [13]. PGF2α and PGE2 exert opposite actions on the corpus luteum (CL); therefore, control over their synthesis and secretion is critical either for the initiation of luteolysis or maintenance of pregnancy [7, 8].

PGF2α is considered a pro-inflammatory molecule, and it may stimulate the synthesis of pro-inflammatory cytokines that enhance phagocytosis and lymphocyte functions [14]. PGF2α can increase IL1β, IL6, CCL2, and CXCL8 via ERK1/ERK2, PI3K, NFAT, and NF-κB pathways in the myometrial cells from term pregnant women, suggesting that PGF2α induces an inflammatory environment during the late stage of human pregnancy [15]. PGF2α in vitro enhanced neutrophil chemotaxis and the ability of neutrophils to ingest bacteria, and anti-PGF2α antibody blocked the chemotactic effects of PGF2α [16, 17]. Exogenous PGF2α increases uterine secretion of PGF2α through the activation of phospholipase A2 (PLA2) and cyclooxygenase 2 [18–20]. Also, it has been proposed that exogenous PGF2α increases luteal leukotriene B4 (LTB4) production [21]. LTB4 can stimulate chemotaxis, random migration, and antibody-independent cell-mediated cytotoxicity and may reduce the risk of uterine infections in cows [22].

Most studies about PGF2α and fertility have been performed in production animals. PGF2α and its analogs have been used to resolve uterine infections in livestock; however, its mechanism of action is not known. Moreover, it is unclear if modulation of sexual steroids levels induced by PGF2α directly alters the immune response in postpartum. Cattle are resistant to uterine infections when progesterone concentrations are basal, and they are susceptible to uterine infections when progesterone concentrations are increased [23, 24]. It has been proposed that exogenous PGF2α is an effective luteolytic factor to reduce progesterone levels

and subsequent estrus, with increased estrogen level and myometrial contractions, and would be favorable for clearance of uterine infection [25, 26]. However, other authors report that PGF2α upregulate immune functions reducing vaginal discharge, uterine inflammation, endometrium fibrosis, and infection, which could be independent of progesterone levels [27]. Also, it has been proposed that PGF2α is more effective when progesterone levels are high or a corpus luteum is palpable [28, 29]. Thus, a direct effect of PGF2α on immune system has been proposed. The in vivo effect of exogenous PGF2α suggests that immune functions do not seem entirely independent of progesterone [30]. Fenprostalene, a long-acting PGF2α analog, injected between days 7 and 10 postpartum, when progesterone concentrations are basal, reduced the incidence of endometritis in dairy cows with dystocia and/or retained fetal membranes and reduced the interval from parturition to conception [31]. The studies with cloprostenol and fenprostalene indicate that increased PGF2α during the postpartum period in dairy cattle improves uterine health [27, 31]. Indeed, jugular concentrations of 13,14-dihydro-15-keto-PGF2α, which is a metabolite that seems to reflect uterine production of PGF2α postpartum, were less in postpartum dairy cows that subsequently developed uterine infections, than in cows that did not develop uterine infections [31, 32]. Despite the above antecedents, the evidence is contradictory if exogenous PGF2α can be useful as endometritis therapy in cows [33–36].

PGE2 is the most abundant eicosanoid lipid in the inflammatory environment. Thus, PGE2 plays a pivotal role in endometriosis-associated inflammation and pain, and its production is augmented in lesions and in the peritoneal cavity [37, 38]. Exogenous PGE2 pretreatment also modulates the innate immune response, increasing the Pam3CSK4-induced inflammatory responses through Toll-like receptor (TLR)-2 signaling in bovine endometrial epithelial cells [39]. PGE2 can increase the lipopolysaccharide (LPS)-induced response on PKA, ERK1/ERK2, and IκBα phosphorylation, as well as COX-2 and IL-6 expression, and downregulate the PGE2 receptor 4 (EP4) and TLR4 in bovine endometrial cells [40]. PGE2 via EP2 and EP4 receptors can reduce the expression of CXCL8, CCL2, and granulocyte macrophage colony-stimulating factor (GM-CSF) induced by IL-1β in primary human myometrial cells [41]. In human uterine epithelial cells, misoprostol, an analog of PGE2, increases cAMP levels via EP4 and reduces the expression of antimicrobial peptides such as β-defensins [42].

3. Effect of omega-3 fatty acids on endometrial function: in vivo and in vitro studies

Several studies have suggested that supplementation of omega-3 fatty acids during pregnancy is beneficial for establishment and maintenance of pregnancy, maintains gestation length and fetal growth, prevents preterm birth, and decreases the rate of gestational diabetes [43]. These effects of omega-3 fatty acids have been mainly studied in animals such as bovine and ovine; however, some recent studies have begun to be performed to demonstrate the beneficial effect of these fatty acids in humans and mice. Consumption of omega-3 fatty acids has been associated with a reduction of the symptoms and lower risk of developing endometriosis in women, a hormone-dependent chronic inflammatory condition [44, 45]. In wild-type mice, the administration of EPA reduced the number of endometriotic lesions, similarly as was observed in a transgenic mouse model with high levels of omega-3 fatty acids [46]. In a rat model of endometriosis, the EPA supplementation reduced the endometriotic lesions and expression of pro-inflammatory gene, suggesting that the EPA supplementation might be a strategy for the treatment of endometriosis [47].

Some studies in vitro have evidenced that the supplementation of mice with omega-3 fatty acids increased implantation markers such as laminin and leukemia inhibitory factor in endometrial epithelium and stroma, which would encourage the endometrium for a favorable environment of implantation [48]. Through an abortion mouse model and human stromal cells, it was suggested that omega-3 fatty acids activate the signaling pathways ERK1/ERK2 and AMPK, which increase FOXO1 and GLUT 1 expression, and the increased glucose uptake would be important for the maintenance of pregnancy [11].

Several studies in bovines have proposed that omega-3-rich diet improve the reproductive performance. It has been described that incorporation of fatty acids of omega-3, and also omega-6, in the bovine diet influences some of the reproductive process involved in the follicular development [49] and progesterone and PGF2α production [50, 51] regulating embryo survival and implantation.

It has been shown that high intake of omega-6 fatty acid induces a change in membrane phospholipids, increasing the proportion of arachidonic acid, which would favor the synthesis of PG of the series 2, and eicosanoid, so it would turn into a pro-inflammatory environment [52]. By contrast, the dietary increase of the omega-3 fatty acid especially EPA and DHA would increase the proportion of these phospholipids in the cell membranes, which would ultimately result in the decrease of the synthesis of the PG series 2, whereby they would act as an anti-inflammatory mechanism [52]. Based on the effect of fatty acids on PG secretion, several studies conducted in dairy cattle have been addressed to attenuate the endometrium secretion of PG at the time of the embryo-maternal recognition of pregnancy in order to improve embryo survival and pregnancy rate [53–55]. Dairy cows supplemented with conjugated linoleic acid (CLA) have higher pregnancy rates than their non-supplemented control group, and the probability of pregnancy increases by up to 26% and that the interval of first postpartum ovulation was reduced by 8 days [56].

Also, the supplementation of dairy cows with polyunsaturated omega-3 fatty acids as EPA can inhibit the synthesis of PGF2α through competition with arachidonic acid by COX-1 and COX-2 enzymes or in the case of DHA competing with arachidonic acid with the phospholipase A2 enzymes [57]. For this reason, fish meal included in the bovine diet could reduce PGF2α and delay regression of the CL, improving embryonic survival and female fertility [51]. The supplementation of cows with omega-3 fatty acid from the fish meal not only reduces the endometrial concentration of arachidonic acid but also increases the concentration of both EPA and omega-3 fatty acids in the endometrium [58]. When fish meal was included in the diet in a study conducted with beef cows (Angus), an increase in EPA and DHA in luteal tissue and a reduction of arachidonic acid in the endometrium resulting in an increase in the fertility of cows were observed [59]. However, in addition to its effect on PG secretion, some studies have concluded that diets rich in EPA and DHA can have a direct effect on the growth of the conceptus per se [60]. Others speculate that the delay on CL regression would allow not well-developed embryos to reach their competent size to initiate a maternal dialog before the luteolytic secretion of PG [50, 61].

The roles of omega-3 and omega-6 fatty acids on prostaglandin secretion have been well documented in in vitro and in vivo studies. The production of PGF2 α was suppressed in an endometrial cell culture when the culture medium was supplemented with omega-3 fatty acids [62]. However, when the medium was supplemented with omega-6 fatty acids, the increase in the ratio of omega-6 to omega-3 produced an increase of PGF2α [63]. Similarly, in studies conducted with dairy cows, the supplementation with different ratio of fatty acids from omega-6 to omega-3 altered the secretion on PGF2 α induced by either oxytocin [64] or spontaneous [49]. The production of PGE2 induced by LPS also was inhibited in the cellular line of bovine endometrium BEND treated with DHA [12].

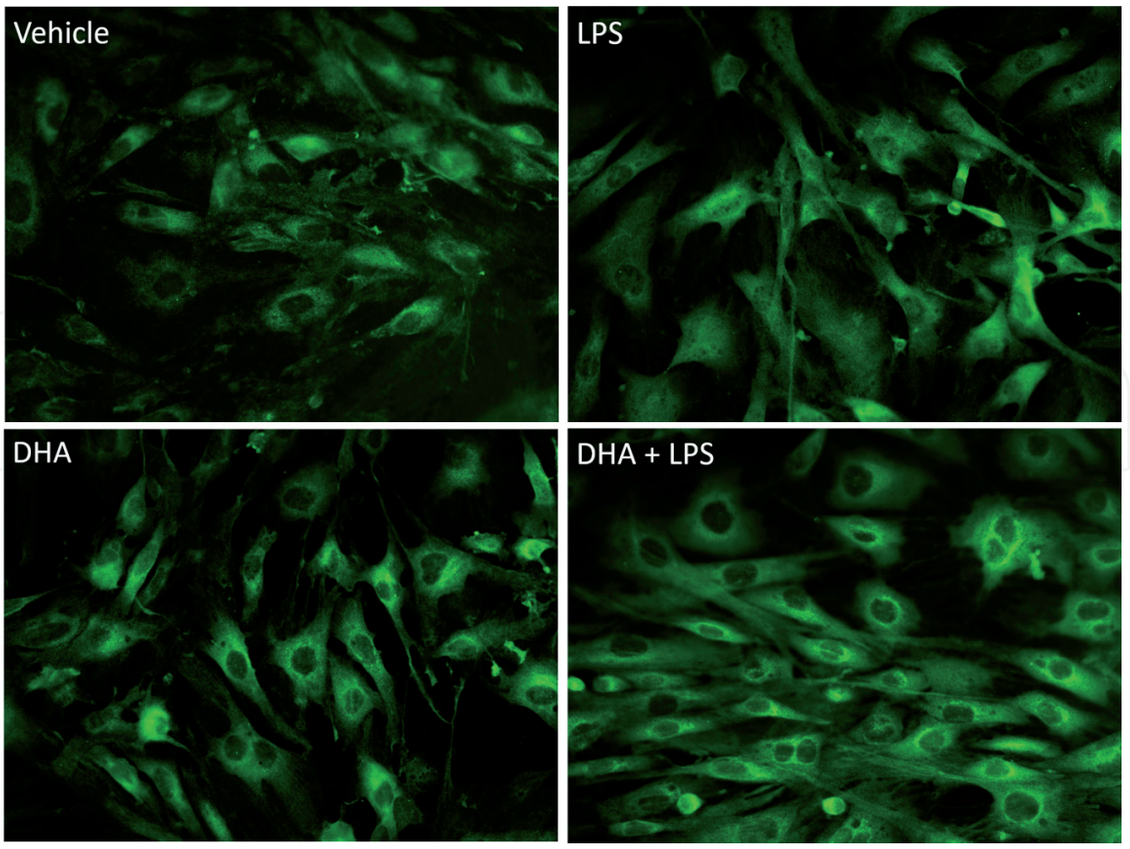

Figure 1.
Localization of NF-κB in BEND cells treated with DHA and stimulated with LPS. BEND cells were treated with 50 μM DHA for 15 min, and then 1 μg/ml LPS was added and incubated for 30 min. NF-κB was detected by immunocytochemistry and epifluorescence microscopy. Magnification 40X [65].

Additionally, recent evidences show an inhibition of the translocation of the transcription factor NF-κB induced by LPS in BEND cells treated with DHA (**Figure 1**; unpublished data).

4. Mechanisms of action of omega-3 fatty acids in endometrial cells

The first known anti-inflammatory mechanism of omega-3 fatty acids was the formation of specialized pro-resolving mediators (SPMs) derived from DHA. The enzymatic oxygenation of DHA via 12–/15-lipoxygenase (LOX) and 5-LOX leads to the formation of the D-series resolvins (RvD1, RvD2, RvD3, RvD4, RvD5, and RvD6), neuroprotectins/protectins, and maresins in different cells [10, 66], and resolvins have a potent effect on leukocyte migration and also reduce production of pro-inflammatory cytokines [67]. All those evidences have been obtained in different cellular types, but in the uterus or endometrial cells, there are not yet studies about formation of SPM.

Two more recent mechanisms have been described in macrophages and endothelial cells: (1) binding of DHA to FFA4 receptor/β-arrestin and inhibition of TAK1/NF-κB, thus reducing synthesis of pro-inflammatory factors, and (2) inhibition of NLRP3 inflammasome. FFA4 receptor is a G-protein-coupled receptor with high affinity by DHA described first in the intestine and macrophages. Recent studies evidenced the presence of FFA4 receptor in the human, mouse, and bovine endometrium [11, 12]. After ligand binding, FFA4 receptor couples to β-arrestin2, which is followed by receptor endocytosis and inhibition of TAB1-mediated activation of TAK1, a protein activated after inflammatory stimuli such as LPS, which

induce signaling through the NF-κB pathway, thus reducing TNF-α, IL-6, and MCP-1 [68, 69]. Other studies have proposed omega-3 fatty acids to reduce the NLRP3 inflammasome activation [70–73]. The first evidence proposed two mechanisms dependent on FFA4 receptor to the reduction of inflammasome activation: first, DHA stimulation caused FFA4 receptor internalization through β-arrestin2, which reduced the initial inflammasome priming step by suppressing the nuclear translocation of NF-κB, and second, DHA enhanced autophagy, thereby reducing inflammasome complex formation or presenting inflammasome components for destruction [73]. Then, it was demonstrated that DHA reduced NLRP3 inflammasome expression in hepatocytes [70].

In the endometrium, only two lines of evidences about potential mechanisms of action of omega-3 have been studied. In human stromal cells, FFA4 receptor promoted decidualization through the upregulation of the GLUT1-mediated glucose uptake and glucose-6-phosphate dehydrogenase-mediated pentose-phosphate pathway [11]. In mice, FFA4 receptor protects LPS or RU486-induced abortion [11]. In summary, omega-3 fatty acids via FFA4 receptor increase ERK1/ERK2 and AMPK signaling and upregulate FOXO1 and GLUT1 expression, which increases glucose uptake and activates the pentose-phosphate pathway, promoting decidualization and maintenance of pregnancy. In addition, it was also shown that FFA4 receptor upregulates the expression of chemokines and cytokines such as CXCL12, TGFβ, and IL-15 [11]. In bovine endometrial cells, it was evidenced the presence of mRNA and protein of FFA4 receptor as well as an increase of intracellular calcium mobilization induced by DHA or a synthetic agonist (TUG891) of FFA4 receptor, which was inhibited by AH7614, a FFA4 receptor antagonist [12]. Also, DHA reduced NF-κB activation and PGE2 production induced by LPS; however, AH7614 did not modify these effects, suggesting that other mechanisms would be involved in the anti-inflammatory effect of DHA, which should be studied [12].

5. Perspectives in health and diseases

Until now, omega-3 fatty acids have been only used as dietary supplements, or DHA-rich diet has been recommended by their beneficial effects for health. However, although the mechanism of action of DHA has begun to be elucidated, it has not been recommended yet as an anti-inflammatory drug. The recent studies have described several possible anti-inflammatory mechanisms and propose omega-3 fatty acids as potential treatment for spontaneous abortion for its effect on decidualization and the maintenance of pregnancy [11]. Also, omega-3 fatty acids would be useful for the prevention and treatment of endometriosis because this disorder is characterized by a chronic inflammation [44, 46, 47]. In veterinary medicine, omega-3 fatty acids have potential use in fertility of dairy cows. Omega-3- rich supplements have been associated with improved reproductive performance, and the recent evidence of the presence of FFA4 receptor in the endometrium [12] could contribute to understand the mechanism as omega-3 fatty acids exert its effects, and open new possibilities for the prevention and treatment of the endometrial inflammation associated with infectious diseases, such as metritis or endometritis.

6. Conclusions

Omega-3 fatty acids have anti-inflammatory effects through different mechanisms, described in macrophages and endothelial cells: formation of SPMs, activation of the FFA4 receptor, inhibition of TAK1/NF-κB activation, and inflammasome

inhibition. These mechanisms have not yet been demonstrated in the endometrium, but the presence of the FFA4 receptor and the inhibition of NF-κB, PGE2, and PGF2α suggest that similar anti-inflammatory mechanism could occur in the endometrium. Furthermore, omega-3 fatty acids could be useful for the treatment of disorders such as endometriosis or metritis/endometritis, as well as the prevention of spontaneous abortion and improvement of fertility.

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Conflict of interest

The authors declare no conflict of interest.

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