REVIEW

# Prostaglandin E2: A Potential Link Between NSAIDs and the Menstrual Cycle, Cofactors of Food-Dependent Anaphylaxis

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J Investig Allergol Clin Immunol 2025; Vol. 35(3): 155-169
doi: 10.18176/jiaci.1070

## Abstract

Food-induced anaphylaxis presents a significant health risk, accounting for 25% to 50% of adult allergic reactions. The variability in severity, even with identical allergen exposure (dose and allergen), suggests the involvement of other factors (cofactors) in exacerbation of allergic responses. Cofactors may function in 2 ways: by lowering the reaction threshold, ensuring patients remain asymptomatic in the absence of the cofactor and only experience symptoms when it is present; or by increasing severity, enabling patients with mild symptoms to endure a stronger reaction in the presence of the cofactor.

Two cofactors have emerged, namely, nonsteroidal anti-inflammatory drugs (NSAIDs), which are well documented, and the menstrual cycle, which has received less attention. However, their intricate interplay has not yet been elucidated. Widely used for their anti-inflammatory properties, NSAIDs disrupt gastrointestinal integrity, reduce synthesis of prostaglandin E2 (PGE2) by inhibiting the enzyme cyclooxygenase (COX), and participate in mast cell activation, thus exacerbating food allergy symptoms. Similarly, the hormonal fluctuations during the menstrual cycle affect the COX pathway, modulating mast cell activation and allergic sensitivities.

PGE2, a key mediator in immune modulation, plays a crucial role in maintaining immune homeostasis and suppressing mast cell activation. This review examines the potential role of PGE2 as a plausible link between NSAIDs and menstruation as cofactors in food allergy, suggesting a central role in modulating allergic sensitivities.

**Key words:** Cofactors. Food anaphylaxis. Prostaglandin E2 (PGE2). Menstrual cycle. Nonsteroidal anti-inflammatory drugs (NSAIDs).

## Resumen

La anafilaxia inducida por alimentos representa un riesgo significativo para la salud, suponiendo entre el 25% y el 50% de las reacciones alérgicas en adultos. La variabilidad en la gravedad de las reacciones, incluso con exposiciones idénticas al alérgeno (dosis y tipo de alérgeno), sugiere la participación de otros factores (cofactores) que exacerban las respuestas alérgicas. Los cofactores podrían actuar de dos formas: reduciendo el umbral de reacción, lo que hace que los pacientes permanezcan asintomáticos en ausencia del cofactor y experimenten síntomas solo cuando éste está presente; o aumentando la gravedad de la reacción, permitiendo que pacientes con síntomas leves sufran reacciones más graves en presencia del cofactor.

Entre los cofactores destacan los antiinflamatorios no esteroideos (AINE), bien descritos, y el ciclo menstrual, menos estudiado, aunque aún no se ha elucidado completamente su interacción. Los AINE, ampliamente utilizados por sus propiedades antiinflamatorias, alteran la integridad gastrointestinal, reducen la síntesis de prostaglandina E2 (PGE2) al inhibir las enzimas ciclooxigenasas (COX) y participan en la activación de mastocitos, exacerbando los síntomas de alergias alimentarias. De manera similar, las fluctuaciones hormonales durante el ciclo menstrual afectan la vía COX, modulando la activación de mastocitos y la sensibilidad alérgica.

La PGE2, un mediador clave en la modulación inmunológica, juega un papel crucial en el mantenimiento de la homeostasis inmunitaria y la supresión de la activación de mastocitos.

Esta revisión explora el papel potencial de la PGE2 como un vínculo plausible entre los AINE y la menstruación como cofactor en la alergia alimentaria, sugiriendo un rol central en la modulación de las sensibilidades alérgicas.

**Palabras clave:** Cofactores. Anafilaxia alimentaria. Prostaglandina E2 (PGE2). Ciclo menstrual. Antiinflamatorios no esteroideos (AINE).

## Introduction

Food allergens are the most common cause of anaphylaxis, which accounts for between 25% and 50% of adult food-induced allergic reactions [1]. Patients often experience different responses to the same exposure (ie, same dose and allergen), highlighting the random nature of severity. The influence of cofactors, ie, factors that may increase the intensity of the reaction regardless of allergen exposure, has been proposed as a typical explanation for this phenomenon [1].

Niggemann et al [2] categorized cofactors into 3 types:

1. Augmenting factors. These directly increase reaction severity through immunological mechanisms, such as physical exercise, infections, nonsteroidal anti-inflammatory drugs (NSAIDs), proton pump inhibitors, alcohol, and menstruation.
2. Concomitant diseases. These include conditions such as asthma, mastocytosis, and cardiovascular disease.
3. Nonimmunological cofactors. These do not affect the allergen–IgE-effector cell allergic reaction and include developmental stages (eg, adolescence), psychological stress, or regular medications (eg, angiotensin-converting enzyme [ACE] inhibitors) [1,3]).

However, beyond this classification, the term cofactor is generally used to describe any factor that can potentially modulate the intensity of the allergic response. Generally, cofactors can act in 2 ways: by decreasing the reaction threshold so that patients experience symptoms only in the presence of the cofactor; and by increasing the severity of the reaction [1].

NSAIDs are widely used for their analgesic, antipyretic, and anti-inflammatory properties. While they are generally safe for most people, NSAIDs can have adverse effects, including the potential to exacerbate food allergies [4].

NSAIDs exert their effects by inhibiting the activity of the enzyme cyclooxygenase (COX), thereby reducing the synthesis of prostaglandins from arachidonic acid (AA). Of relevance is the inhibition of COX-1, which is constitutively expressed and involved in maintaining physiological processes, including gastric mucosal protection and renal function. The inhibition of COX-2, which is induced by inflammation, contributes to the anti-inflammatory effects of NSAIDs by reducing the synthesis of several pro-inflammatory prostaglandins. However, this inhibition also decreases the production of prostaglandin 2 (PGE2), which has crucial modulatory functions in the immune response and mast cell homeostasis, potentially exacerbating the severity of allergic reactions in susceptible individuals [4].

Dysregulation of PGE2 synthesis can enhance allergy-induced reactions by skewing the immune response towards a more severe phenotype. Interestingly, the use of NSAIDs to treat perimenstrual symptoms has shown additive/synergistic effects in the induction of food-related anaphylaxis [5,6]. Menstruation itself is one of the cofactors described in food allergy, even if its frequency is unknown. Most reactions have been reported on premenstrual day 26 and day 7 of the menstrual cycle [7]. However, the pathogenic mechanisms underlying these reactions are not well understood [7]. Hormonal fluctuation during the menstrual cycle, mostly associated with progesterone levels, may contribute to food allergy by altering the normal regulation of AA metabolism. This would lead to decreased synthesis of modulators such as PGE2, contributing to enhanced allergy-related reactions [5-7]).

In this review, our objective is to explore common mechanisms underlying food-induced anaphylaxis by examining recent research on NSAIDs and menstruation as potential cofactors in food allergy. Specifically, we aim to determine whether PGE2 might be considered the central link between these cofactors.

## 2. Food Allergy

### *2.1 Classification of Food Allergy*

Food allergy is a global health concern, affecting individuals of all ages. It involves an abnormal immune response to food proteins, causing symptoms from mild itching to life-threatening anaphylaxis. Food allergy arises from the breakdown of immunologic and clinical tolerance, leading to 3 primary types of immune responses, as outlined by the latest guidelines of the European Academy of Allergy and Clinical Immunology on food allergy nomenclature and classification:

1. *IgE-mediated.* Food allergens bind to IgE on mast cells and basophils, causing rapid onset of symptoms (minutes to hours), such as urticaria, anaphylaxis, and respiratory distress [8].
2. *Non–IgE-mediated.* Characterized by T cell–driven inflammation, this type does not involve IgE antibodies. Symptoms typically develop over several hours to days and can include gastrointestinal disorders such as vomiting, diarrhea, and enterocolitis [9,10].
3. *Mixed IgE.* This category includes reactions where both IgE-mediated and non–IgE-mediated pathways contribute to symptoms. Immediate symptoms may include swelling or anaphylaxis, while delayed reactions could involve gastrointestinal distress, as in eosinophilic esophagitis [9,10].

Specifically, food allergy can be classified depending on whether the underlying mechanism is type I hypersensitivity (IgE-mediated), type IV hypersensitivity (non–IgE-mediated), or a combination of IgE-mediated and cellular mechanisms (mixed IgE and non–IgE-mediated) [9].

### *2.2 Pathophysiology of IgE-Mediated Food Allergy*

Oral tolerance to foods involves suppression of immune responses to antigens crossing the gastrointestinal mucosa. Dendritic cells (DCs) are responsible for antigen uptake, migrate to lymph nodes, and promote food-specific regulatory T cells, which produce IL-10 and TGF-ß, inhibiting B and T cells and suppressing eosinophils, basophils, and mast cells [11].

Sensitization occurs when food-specific IgE is detectable, often owing to epithelial barrier damage. Damaged epithelial cells release cytokines such as IL-25, IL-23, and thymic stromal lymphopoietin (TSLP), activating DCs and naive T cells to develop a $T_H2$ phenotype. This leads to food antigen–specific IgE production and inflammatory signals. Sensitization can also occur via digestive pathways or exposure to antigens due

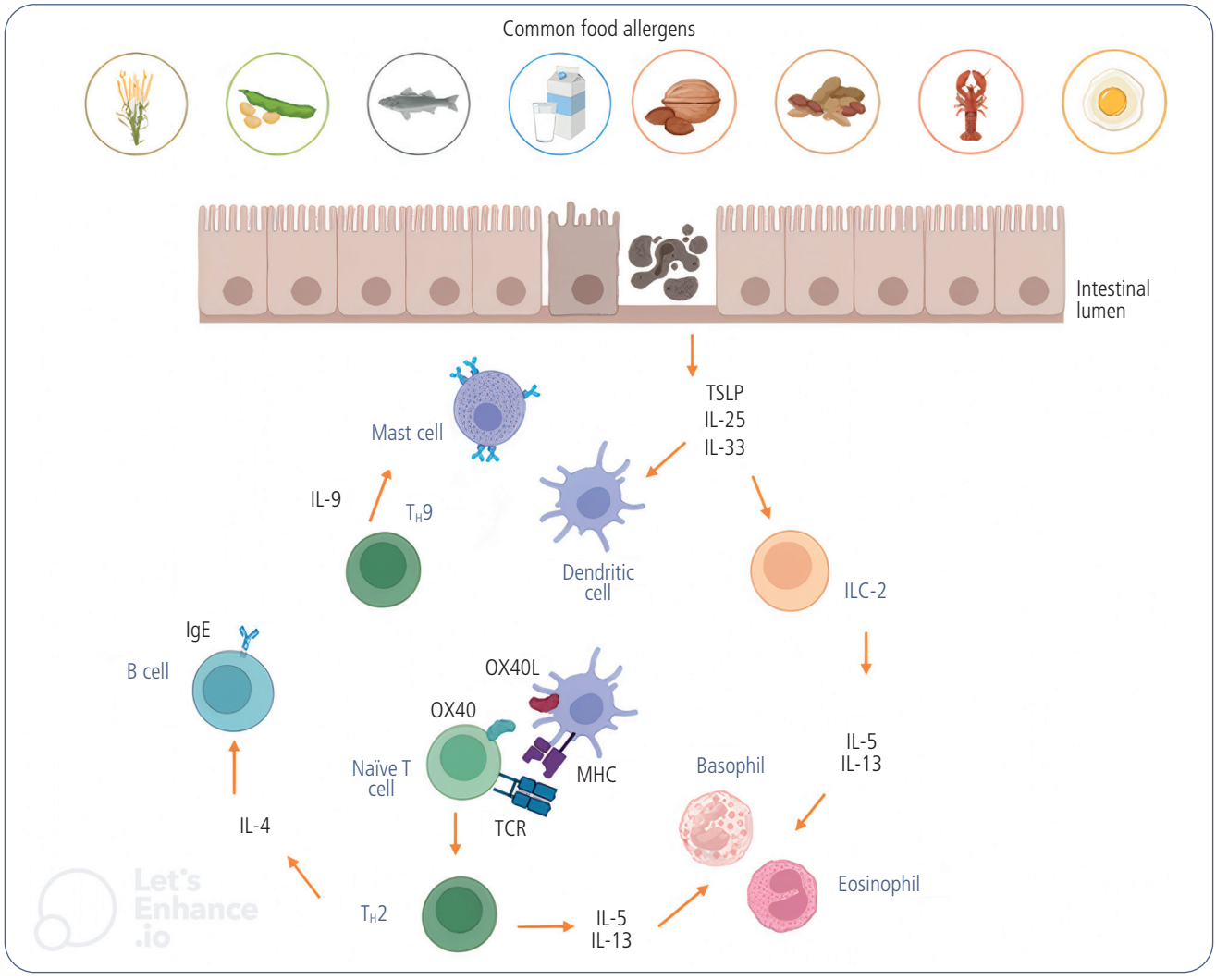


**Figure 1.** Allergic response to food antigen in the gut. Following gut epithelial damage, the proinflammatory cytokines thymic stromal lymphopoietin (TSLP), IL-33, and IL-25 promote the expansion of type 2 innate lymphoid cells (ILCs) and activate dendritic cells (DCs). Activated DCs overexpress the surface protein OX40L, which interacts with the OX40 on the naïve T cells, as well as the major histocompatibility complex (MHC) on DCs and T-cell receptor (TCR) on the naïve T cells. This interaction induces the differentiation of the naïve T cells into type 2 helper T cells ($T_H2$), which, along with ILCs produce the proinflammatory cytokines IL-5 and IL-13, recruiting eosinophils and basophils in the gut lamina propria leading to allergic sensitization. Furthermore, $T_H2$ cells secrete IL-4, which promotes IgE production by B cells. $T_H9$ cells secrete IL-9, thus promoting the recruitment of mast cells. Image edited from BioRender.

to skin barrier abnormalities [11,12]. IgE binds to basophil and mast cell receptors (FcεRI), priming them for activation. Upon re-exposure to the antigen, these cells release mediators such as histamine and tryptase, causing local and systemic symptoms [11,12].

### *2.3 Tolerance and Sensitization: Principal Components*

*Epithelial barrier.* The epithelial barrier blocks unnecessary antigen entry, maintaining tolerance by preventing inflammatory signals. Damaged epithelium releases cytokines, stimulating antigen-presenting cells and inducing an allergic response [13].

*Antigen-presenting cells and innate lymphoid cells.* Proinflammatory mediators such as TSLP, IL-25, and IL-33 enhance sensitization through development of the $T_H2$ phenotype. Activated DCs express OX40L, promoting $T_H2$ T-cell differentiation and food allergies. Type 2 innate lymphoid cells produce $T_H2$ cytokines (IL-4, IL-13) in response to TSLP, IL-25, and IL-33, enhancing mucosal mast cell activation [13] (Figure 1).

*T cells.* Damaged gut epithelium releases TSLP, IL-25, and IL-33, activating DCs to overexpress OX40L. This interaction promotes naive T-cell development into $T_H2$ cells, which release IL-5 and IL-13, recruiting basophils and eosinophils and leading to allergic sensitization. $T_H2$ cells secrete IL-4, promoting B-cell class switching and IgE production. $T_H9$ cells release IL-9, further encouraging mast cell accumulation and allergic reactions [13] (Figure 1).

*Basophils and mast cells.* These cells are crucial in allergies, with B cells producing IgA antibodies for maintenance of

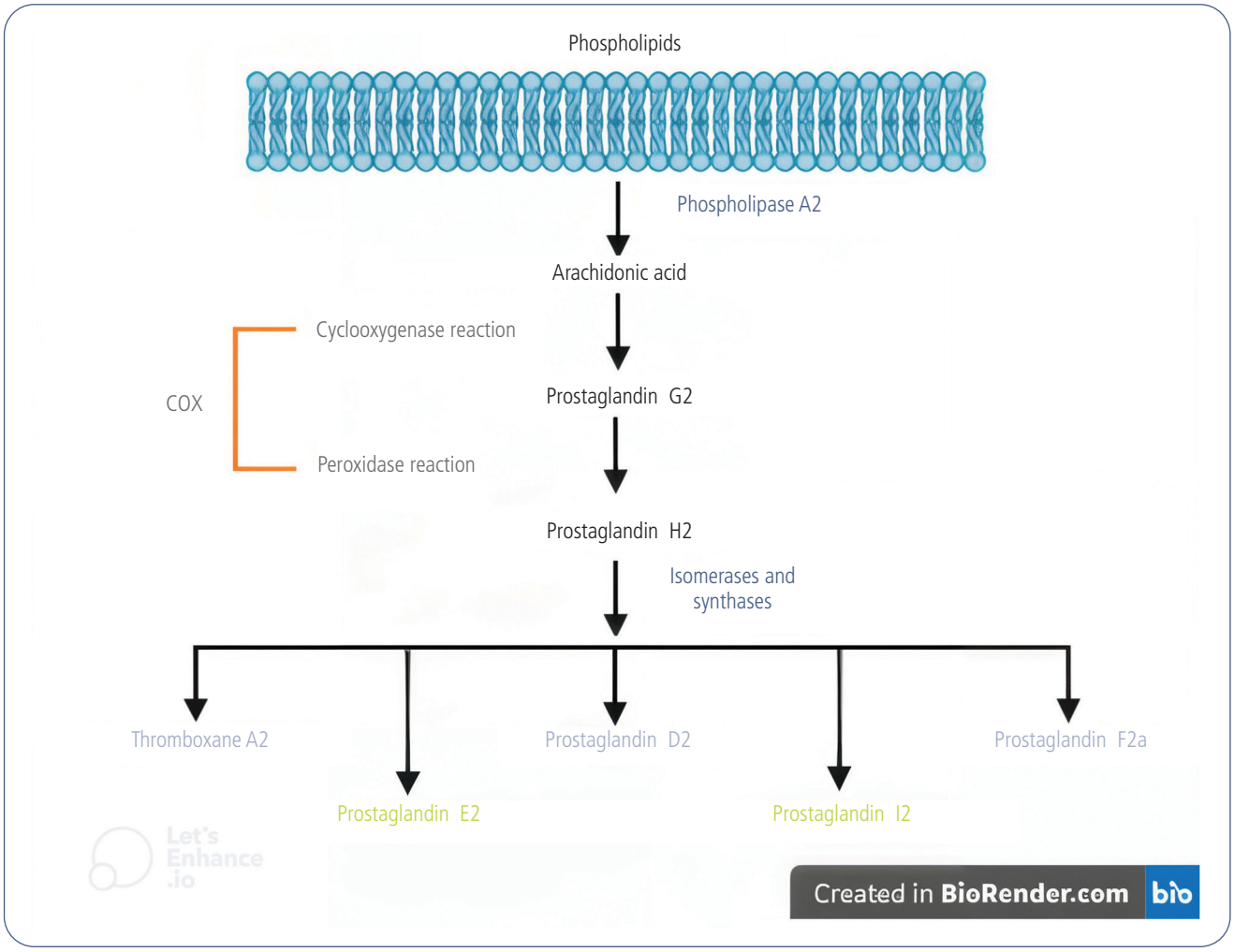


**Figure 2.** Biosynthesis of prostanoids.

tolerance. IL-4 influences B-cell class switching and food-specific IgE production. Antigen-bound IgE interacts with FcεRI receptors on basophils and mast cells, releasing mediators upon antigen exposure and causing anaphylaxis. Histamine, tryptase, platelet-activating factor, prostaglandins, and leukotrienes contribute to allergic reactions. The immune system components (epithelium, innate immune cells, T cells, B cells, effector cells) can either induce sensitization or promote tolerance. Environmental and genetic factors shape immune responses, potentially altering the pathophysiology of IgE-mediated food allergies [13] (Figure 1).

## 3. NSAIDs, Food Allergy, and Anaphylaxis

### *3.1 Cyclooxygenase Pathway, Prostaglandin E2, and Anaphylaxis*

The therapeutic target of NSAIDs, the COX enzyme, was first identified in 1971 by Vane [14]. The COX pathway is a crucial biochemical pathway involved in the synthesis of prostanoids, including prostaglandins and thromboxanes. It comprises 3 steps:

1. Mobilization of AA, from membrane phospholipids through the action of a phospholipase A2.
2. Biotransformation by COX of AA in PGG2 in a cyclooxygenase reaction and the immediate conversion of PGG2 to PGH2 in a peroxidase reaction.
3. Conversion of PGH2 to different prostanoids by the activity of specific isomerases and synthases [5] (Figure 2).

There are 2 main isoforms of COX: COX-1, which is constitutively expressed in most tissues and engaged in homeostatic processes, and COX-2, which is activated by inflammatory stimuli and is essential for producing prostanoids during inflammation [5].

The lipid bilayer of the intracellular phospholipid membranes of the nuclear envelope and the endoplasmic reticulum contains both isoforms, which are integral membrane proteins. However, the nuclear envelope has a higher concentration of COX-2 [15].

PGE2 can be defined as the most versatile and pleiotropic eicosanoid mediator [15,16]. In recent decades, many studies have suggested a protective role of PGE2 in the precipitation of allergic symptoms [17,18] and in maintaining immune homeostasis by regulating the balance between

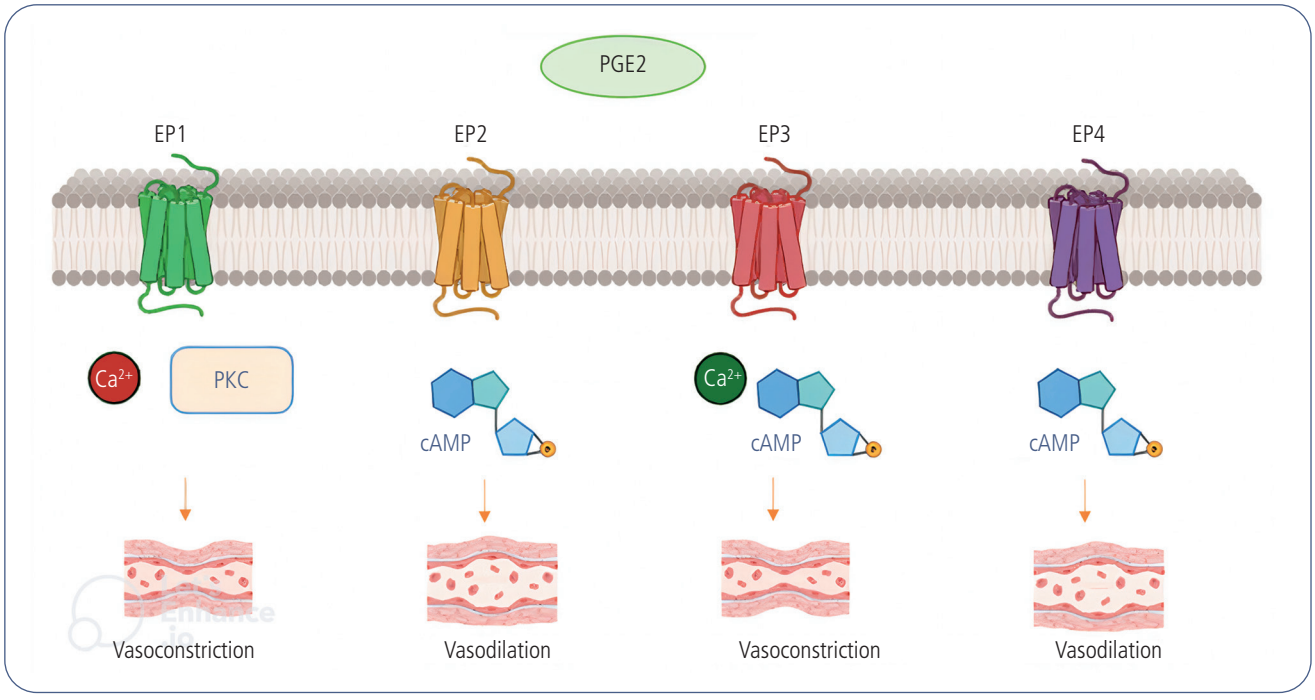


**Figure 3.** Prostaglandin E2 receptors (EPs). EP1, EP2, EP3, and EP4 receptor and are distinguished by amino acid identities, specific ligand binding profiles and different signal transduction properties. PGE2 indicates prostaglandin E2; PKC, protein kinase C; cAMP, cyclic adenosine monophosphate.

proinflammatory and anti-inflammatory responses [6]. PGE2 has been shown to suppress mast cell activation, inhibit T-cell proliferation, and promote regulatory T-cell function, thereby modulating allergic sensitivity [18].

Rastogi et al [19] showed that patients who are prone to anaphylaxis have a compromised PGE2 system. They found that patients with Hymenoptera sting anaphylaxis showed significantly lower levels of PGE2 in sera than healthy controls. Moreover, the PGE2 levels were inversely correlated with the severity of anaphylaxis. In a murine model, the authors also showed that the severity of anaphylaxis was reduced by an increase in PGE2 caused by the prostaglandin itself or an inhibitor of the PGE2-degrading enzyme. In addition, the agonists of the PGE2 receptors EP2 and EP4 protected mice against anaphylaxis [19]. Interestingly, the study demonstrated that PGE2 interfered with the phosphorylation of 2 proteins, phospholipase C $\gamma$-1 and extracellular signal–regulated kinase, which are involved in mast cell activation. Thus, the evidence shows that in humans and in mice, relative PGE2 deficit increases the risk of anaphylaxis, whereas PGE2 stability defends against allergic responses [19].

Of note, Muñoz-Cano et al [20] found no differences in baseline plasma PGE2 levels when comparing food-allergic patients with anaphylaxis and healthy volunteers [20]. However, this discrepancy may be explained by differences in methodology, etiology of anaphylaxis, and the samples collected.

### *3.2 Prostaglandin E2 Receptors*

PGE2 can bind to 4 types of G protein-coupled receptors, known as EP1, EP2, EP3, and EP4 [16,21]. Prostaglandins produced by the COX pathway can regulate the balance between proinflammatory and anti-inflammatory signals in the gastrointestinal tract, where the interactions with ingested food antigens are initiated. PGE2 receptors are involved in diverse types of intracellular signaling and can be expressed differently in tissues. The EP1 receptor exerts mostly constrictive functions and signals via $Ca^{2+}$ mobilization with slight phosphatidylinositol activity. The distribution of the E1 receptor has been described in pulmonary veins, the myometrium, colonic longitudinal muscle, mast cells, and keratinocytes [21,22]. The EP2 and EP4 receptors are widely distributed and involved in bronchodilation and anti-inflammatory processes. They function by increasing intracellular cyclic adenosine monophosphate (cAMP) through the activation of adenyl cyclase [22] (Figure 3). EP3 exerts mainly contractile functions, such as the constriction of the pulmonary artery in the lung and is widely distributed in almost all tissues [23]. In general, EP2 and EP4 receptor signaling promotes the accumulation of cAMP, which is associated with the inhibition of cell function, whereas EP1 and EP3 receptors induce an increase in intracellular calcium, which is associated with cellular activation [21] (Figure 3).

Muñoz-Cano et al [20] recruited 10 healthy volunteers and 25 patients with a clinical history of anaphylaxis elicited by peach and sensitized to Pru p 3. They analyzed EP receptor gene expression in isolated basophils using q-RT-PCR and found that EP3 was significantly increased and EP4 decreased in anaphylaxis patients [20]. These results agree with the evidence reported for respiratory and other allergic diseases, in which the members of the PGE2 receptor family play crucial roles in modulating inflammatory responses. The authors demonstrated that receptors with known proinflammatory activity (EP3) and

anti-inflammatory activity (EP4) were significantly up- and down-expressed, respectively, suggesting a proinflammatory effect of PGE2 on affected patients. Moreover, PGE2 has been reported to reduce basophil reactivity via both the IgE/FcεRI and fMLP pathways in food-allergic patients and in healthy controls [20].

### *3.3 NSAIDs as a Cofactor in Food-Dependent Anaphylaxis*

NSAIDs have emerged as significant cofactors in food allergy and anaphylaxis, acting through both immunological and nonimmunological mechanisms. While food anaphylaxis is primarily IgE-mediated, NSAIDs can amplify these reactions by increasing gastrointestinal permeability, enabling allergens to access systemic circulation and enhancing mast cell degranulation. Additionally, NSAID cross-hypersensitivity, a nonimmunological mechanism, contributes to this association through COX-1 inhibition, which reduces prostaglandin levels, exacerbating inflammation and disrupting the gastrointestinal barrier. Studies indicate that NSAIDs are implicated in up to 25% of cases of food-dependent NSAID-induced anaphylaxis (FDNIA), presenting a notable risk factor with an OR higher than 11 [24]. Cardona et al [25] analyzed 74 cases of severe allergic reactions triggered by food in combination with cofactors such as NSAIDs, exercise, and alcohol, finding that anaphylaxis was the most common clinical manifestation (85.1%), with NSAIDs present in 58% of cases and exercise in 52.7%. The responsible foods were mainly plant-derived, with lipid transfer proteins being the most frequently involved allergen. The study emphasizes the importance of considering these cofactors in the diagnosis and management of allergic reactions, suggesting that NSAID consumption before ingesting food to which one is sensitized can significantly increase the severity of allergic reactions.

Prostaglandins play a crucial role in maintaining the integrity of the gastrointestinal barrier, mucosal homeostasis, and defense mechanisms against luminal insults. These bioactive molecules exert diverse physiological effects, including regulation of mucosal blood flow, epithelial cell proliferation, and mucus secretion. Preserving epithelial tight junctions is one of the prostaglandins' main roles in the gastrointestinal tract [26]. These junctions are essential for controlling paracellular permeability and obstructing the passage of potentially dangerous substances into the blood. Prostaglandins accomplish this by influencing production and localization of tight junction proteins, which are crucial elements of intercellular junctional complexes and include occludins and claudins [26]. Additionally, prostaglandins exhibit anti-inflammatory properties by inhibiting leukocyte adhesion and cytokine production, thereby attenuating inflammation-induced disruption of the gastrointestinal barrier [26].

By blocking prostaglandin production, NSAIDs disrupt the delicate balance of mucosal homeostasis in the gastrointestinal tract, potentially increasing the permeability of the gastrointestinal barrier and enabling larger molecules, including food allergens, to penetrate the bloodstream. This increased permeability and inflammation create an environment conducive to the development of food allergies. Additionally, NSAIDs can directly damage the intestinal lining, leading to erosion and ulceration, which can further exacerbate barrier dysfunction and increase the likelihood of allergen penetration. Furthermore, NSAIDs cause damage to the mitochondria, which results in impaired intestinal epithelial cells and increased intestinal permeability [26-28]. In 2006, Nakamura et al [29] reported the first case of wheat allergy dramatically enhanced by aspirin in a dose-dependent manner. A 68-year-old man experienced recurrent urticaria after consuming wheat-containing foods for several years. Skin prick tests and serum specific IgE confirmed wheat allergy. Challenge tests involving wheat ingestion, aspirin intake, exercise, and combinations of these factors revealed that aspirin administered before wheat ingestion notably exacerbated symptoms. Serum histamine release induced by gluten was enhanced by aspirin in a dose-dependent manner. Sánchez-López et al [30] analyzed a sample of 328 patients referred for suspected NSAID hypersensitivity (NSAIDH); of these, 16% were diagnosed with food-dependent NSAID-induced hypersensitivity (FDNIH). Patients with FDNIH were significantly younger and had a higher prevalence of rhinitis,

**Table 1.** Principal Characteristics of Estrogen and Progesterone in the Immune Response.

| Aspect | Estrogen | Progesterone |
|---|---|---|
| Source | Fluctuates during the menstrual cycle, influencing the pre- and postmenopause immune response, and pregnancy [41]. | Secreted by the corpus luteum and placenta during pregnancy [42]. |
| Receptors | ERα and ERß are expressed in various immune cells, including mast cells, thus affecting immune responses [43,45]. | PR-A and PR-B are present in immune cells such as NK cells, macrophages, dendritic cells, and T cells [44]. |
| Effects | Enhances allergic sensitization by increasing IgE production [45].<br>Promotes $T_H1$ responses under low estrogen conditions and $T_H2$ responses under high estrogen conditions [43].<br>Increases mast cell degranulation and histamine release via Erα [49].<br>Female mice showed more pronounced anaphylactic responses than males; severity was linked to estradiol-mediated effects [50]. | Inhibits IgE-mediated histamine secretion from mast cells [46,47].<br>Inhibits NF-κB activation, reducing the synthesis of proinflammatory cytokines [48,49].<br>Acts as a bronchial smooth muscle relaxant, potentially affecting asthma exacerbations [51]. |

Abbreviations: ER, estrogen receptor; NK, natural killer; PR, progesterone receptor; $T_H$, helper T cell.

**Table 2.** Sex Differences in Allergic Diseases.

| |
|---|
| **Immune response** |
| Females generally have more reactive immune systems, which protect better against infections but also increase susceptibility to allergies [52,53]. |
| **Prevalence and presentation of allergic diseases** |
| Males are more affected by allergies in childhood, while females show higher prevalence in adulthood, particularly in urticaria, anaphylaxis, and food allergies [54-57].<br>The prevalence of food allergy is higher in women, with sex differences in sensitization to specific allergens such as peanut [58-60]. |
| **Severity and phenotype of allergic reactions** |
| Women tend to experience more severe allergic reactions, such as anaphylaxis, and report reactions to more foods than men [61,62]. |
| **Impact of sex hormones** |
| Hormonal changes affect the prevalence of food allergy, with studies suggesting increased female predominance in adulthood and fluctuating patterns around puberty and menopause [49,53,62-65]. |

previous food allergies, and sensitization to pollens and foods. This study highlights that using 4 key variables (sensitization to Pru p 3, sensitization to Tri a 19, anaphylaxis, and any NSAID other than pyrazolones involved in the reaction), we can accurately distinguish FDNIH from general NSAIDH, with a sensitivity of 92% and specificity of 96%. Romano et al [31] expanded on this by investigating hypersensitivity reactions to NSAIDs, specifically focusing on 2 types of food-related hypersensitivity: NSAID-exacerbated food allergy (NEFA) and NSAID-induced food allergy (NIFA). In a prospective study of 414 patients, the authors found that NEFA and NIFA accounted for 18% of suspected NSAIDH. Key diagnostic criteria for these conditions included mild reactions or tolerance to foods without NSAIDs, followed by cutaneous or anaphylactic reactions when foods and NSAIDs were combined, positive food allergy tests, and negative drug challenges with NSAIDs. In most cases of NEFA/NIFA (89%), Pru p 3 was the implicated food allergen. Consistent with Sánchez-López et al, the authors

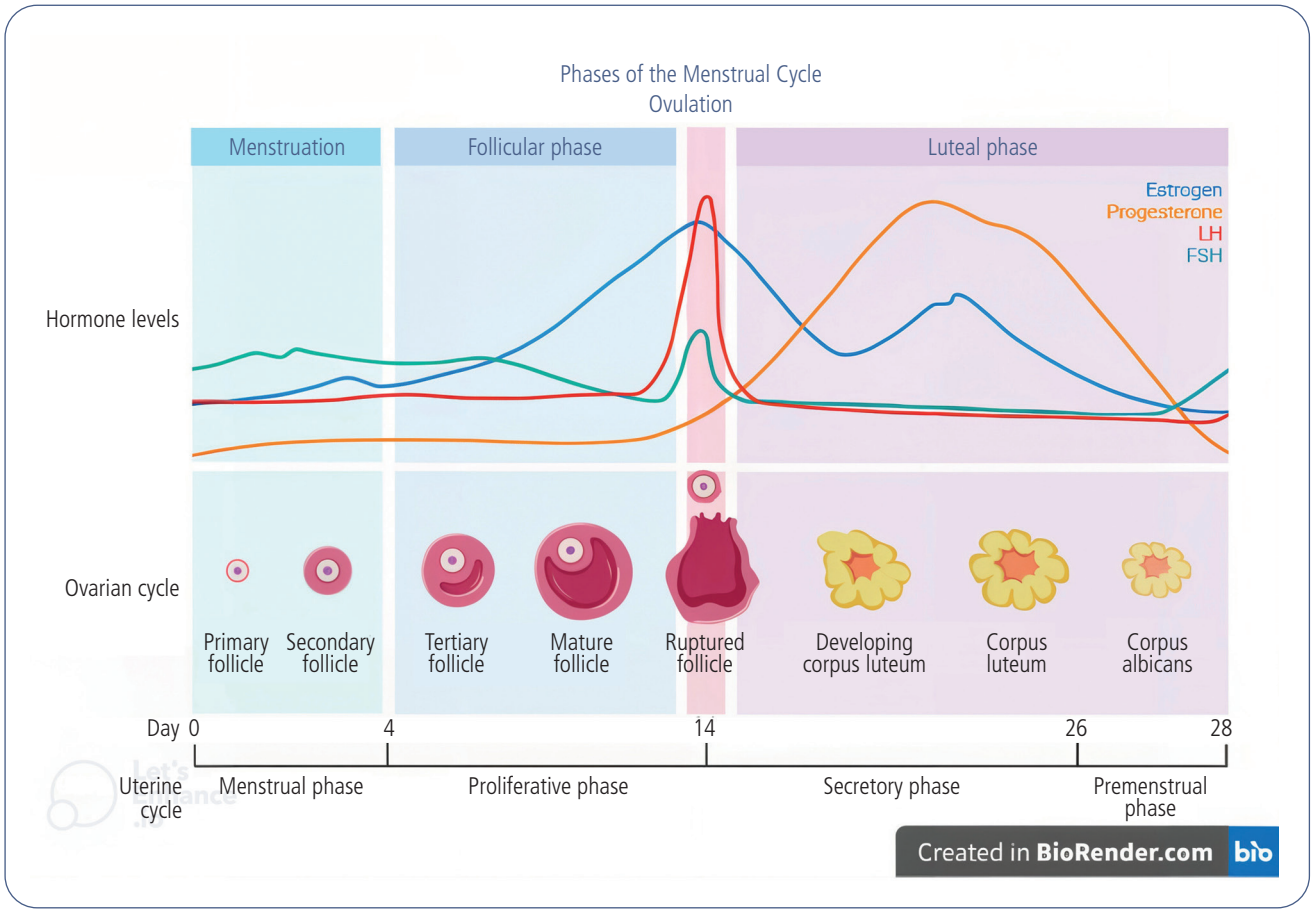


**Figure 4.** Phases of the menstrual cycle and hormonal fluctuations. Image by BioRender.

emphasized the importance of questioning patients about foods ingested near NSAID exposure and suggested that targeted food allergy tests and NSAID drug challenges should be part of the diagnostic evaluation for these reactions [31]. Doña et al [32] provided an updated algorithm for diagnosing and managing hypersensitivity reactions to NSAIDs, with a focus on multiorgan reactions and the new category of NSAID-induced urticaria/angioedema/anaphylaxis (NIUAA). The algorithm also highlights the role of NEFA/NIFA, which should be considered in patients who experience urticaria or anaphylaxis after taking NSAIDs [32].

The effects of NSAIDs on serum allergen levels after wheat ingestion were addressed in a study where the authors investigated whether aspirin, diclofenac, loxoprofen, and meloxicam affected the absorption of gliadin, an allergen present in wheat, in healthy individuals. The results showed that the administration of conventional-dose and low-dose aspirin, as well as diclofenac and loxoprofen, increased serum gliadin levels after wheat ingestion in most cases. However, meloxicam, a selective COX-2 inhibitor, had no significant effect on serum gliadin levels. The study results reported that aspirin, diclofenac, and loxoprofen facilitated the absorption of gliadin from the gastrointestinal tract into the bloodstream, indicating that NSAID-related gastrointestinal hyperpermeability may accelerate the development of symptoms in patients with gliadin/wheat allergy [33].

In addition, NSAIDs can directly affect IgE-mediated activation of mast cells and basophils, increasing both their activation and degranulation [34].

Concretely, Steinke et al [35] demonstrated that aspirin could induce mast cell activation by measuring calcium influx and PGD2 release. However, they could not find differences in outcome for controls or for patients with NSAID-exacerbated respiratory disease.

Several studies have demonstrated that inhibition of COX-1 causes activation of inflammatory cells (mast cells, basophils), with subsequent generation of proinflammatory mediators. In contrast, selective COX-2 inhibition is generally well tolerated because of the continuing function of COX-1 [36-38]. Pascal et al [39] studied the effect of a nonselective COX inhibitor (L-ASA) and a selective COX-2 inhibitor (valdecoxib) on basophils activated by peach lipid transfer protein (Pru p 3) in patients with food anaphylaxis. The authors demonstrated that patients with cofactor-independent food-induced anaphylaxis differed from those with FDNIA in terms of the higher reactivity and sensitivity of their basophils to Pru p 3. However, it is notable that, although the phenotypes were different, L-ASA increased the basophil activation induced by Pru p 3 in both groups of patients. Interestingly, valdecoxib showed a mild protective effect on Pru p 3–induced basophil activation in FDNIA patients.

To better understand the determinants of NSAID-dependent and NSAID-independent food anaphylaxis, Muñoz-Cano et al [40] examined the transcriptional profiles associated with both cases. Analyses of next-generation sequencing from whole-blood samples from lipid transfer protein–allergic patients at baseline revealed distinct transcriptional profiles, namely, associations with gastrointestinal diseases and aberrations in genes and pathways related to gut epithelial

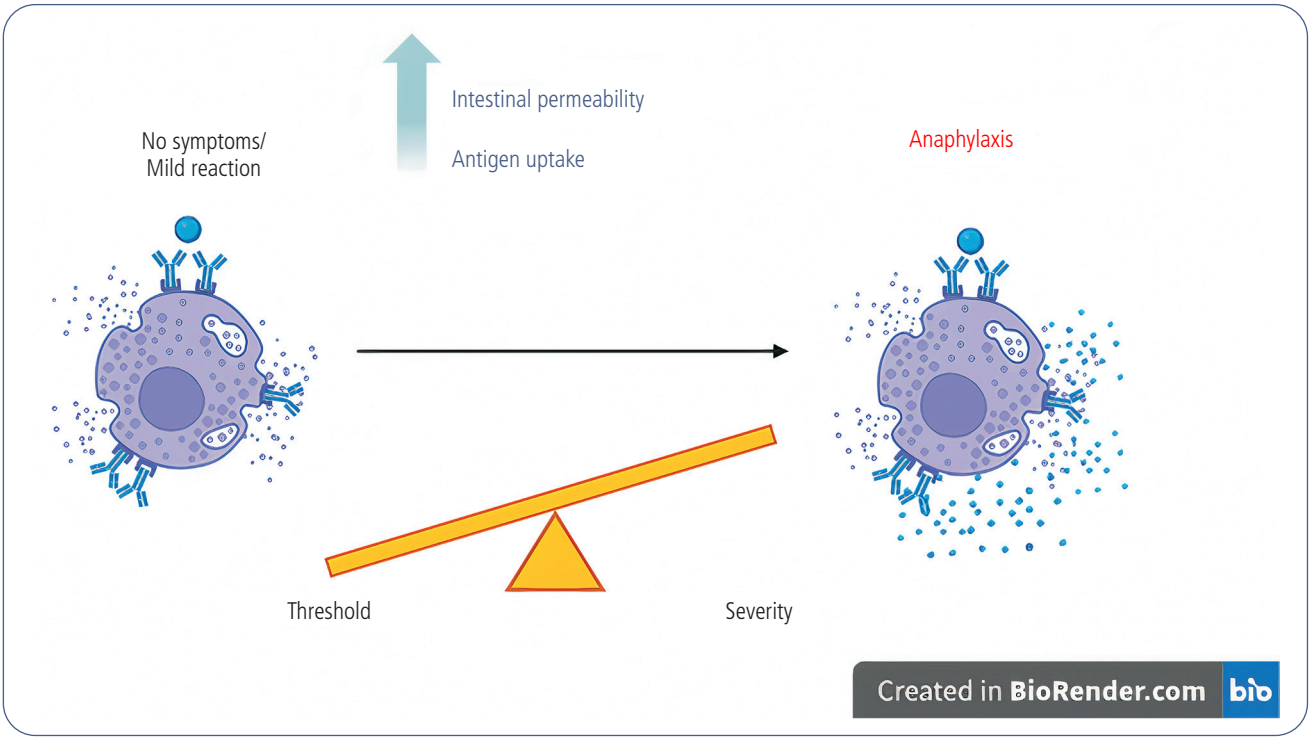


**Figure 5.** Nonsteroidal anti-inflammatory drugs (NSAIDs) and menstruation act as cofactors in food allergy. NSAIDs and menstruation decrease the threshold of allergen and increase the severity of the reaction.

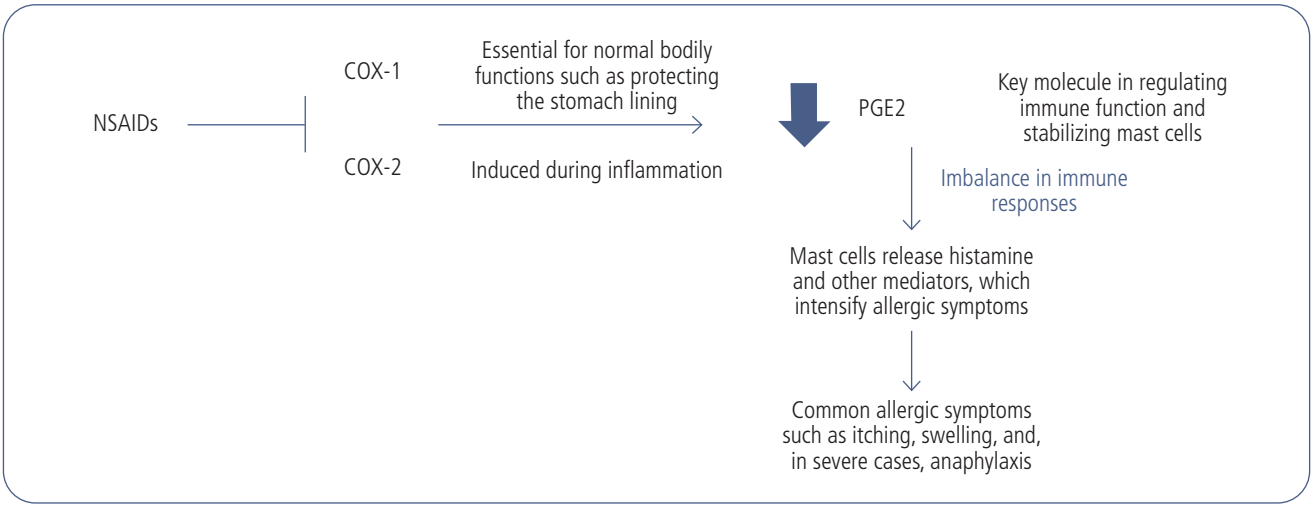


**Figure 6.** COX inhibition, role of PGE2, and mast cell activation. COX indicates cyclooxygenase; PG, prostaglandin.

turnover, which may predispose individuals to food allergies and intestinal inflammation. The authors reported that the 2 groups presented differential regulation of the IFN-γ pathway, IgG receptors, and adenosine metabolism, with overexpression of ADORA3, which potentially provides the pathogenic basis of their distinct responses.

## 4. Menstruation, Sex Hormones, and Allergy

The menstrual cycle is characterized by hormonal fluctuations, particularly of estrogen and progesterone, which influence the immune response (Figure 4). Estrogen has been shown to enhance the immune response, potentially increasing allergic sensitivity, while progesterone may exert immunomodulatory effects, influencing the severity of allergic reactions (Tables 1 and 2). In addition to the well-established process of mast cell activation and subsequent degranulation through the IgE receptor, there is growing recognition of the involvement of female sex hormones in mast cell activation [65-68].

Female sex steroid hormones function mainly through their receptors: progesterone acts through the progesterone receptor PR-A or PR-B, while estrogen acts through the estrogen receptor ERα or Erβ [69]. Essentially, steroid receptors are best characterized by nuclear receptors that function as transcription factors in gene expression. Over the last 10 years, evidence has emerged indicating the presence of additional binding sites located on the plasma membrane. These sites are commonly activated during the fast-acting effects of steroids, which can last for minutes or even seconds [70]. To date, many authors have demonstrated the expression of estrogen and progesterone receptors in human, mouse, and rat mast cells [67,71,72]. Additionally, it has been reported that tamoxifen, a tissue-specific ER antagonist, inhibits the fast stimulation of mast cell degranulation generated by estrogen, demonstrating that estrogen can induce mast cell degranulation through one of its receptors [73].

Furthermore, Jensen et al [74] were able to demonstrate that mast cell maturation was marked by a considerable increase in the synthesis of β-tryptase when the human mast cell line (HMC-1) was treated in vitro with physiological concentrations of estrogen and progesterone. In addition, this treatment led to HMC-1–induced degranulation. It has long been hypothesized that female sex hormones may have an impact on mast cell functioning and, consequently, on the symptoms of related illnesses. Studies generally report that the prevalence of asthma is higher in women than in men, with sex differences becoming more pronounced during adolescence and the reproductive years. However, the exact ratio can vary depending on factors such as age, hormonal changes, and environmental influences, as well as the study population being analyzed [75]. Zierau et al [72] demonstrated that sex hormones play a significant role in modulating the activity of mast cells, finding that estrogen and progesterone directly affect mast cell maturation, degranulation, and the number of mast cells in various tissues, including the airways. Additionally, they reported that the clinical features of asthma in women are correlated with serum levels of estradiol and progesterone, with many women experiencing worsened asthma symptoms during the perimenstrual phase. This hormonal influence is supported by the finding that ovariectomized rats showed reduced airway inflammation, which was restored upon estrogen replacement.

From this perspective, it is interesting to note that in the last 30 years, there has been a significant rise in the prevalence and impact of asthma and other allergic diseases, particularly in developing countries. The increase may be linked to the growing presence of environmental compounds that mimic estrogen, known as xenoestrogens. These compounds, found mainly in water and food, have been shown to activate and exacerbate allergic reactions, potentially explaining, at least in part, the surge in allergic diseases observed in developing countries [76]. Moreover, it is of interest that mast cells are present in the uterus of different species, including humans [72,77-79]. It has already been demonstrated that the number of mast cells in the uterus fluctuated during the estrous cycle, suggesting that their presence was related to female

**Table 3.** Summary of Studies on Eicosanoids and Their Effects on Reproductive Physiology and Asthma.

| Aspect | Details | Conclusion |
|---|---|---|
| Effects of estradiol on COX-2 and PGE2 | Estradiol (E2) upregulates COX-2 and PGE2 synthesis in HUMECs, effects blocked by COX-2 inhibitors [96]. | E2 influences COX-2 and PGE2, with potential implications for treating endometriosis and cancer. |
| Physiological functions of eicosanoids | Eicosanoids regulate menstrual bleeding, ovulation, implantation, and pregnancy maintenance [97-99]. | PGE2 is vital in reproductive processes and fertility. |
| Role of PGE2 and EP receptors | PGE2 binds EP1-4 receptors; receptor expression varies during the menstrual cycle [100] | EP receptors are crucial for reproductive events, offering therapeutic potential. |
| Disorders and dysregulation | PGE2 dysregulation linked to endometriosis, PCOS, recurrent miscarriage, and gestational diabetes [98,99] | Targeted therapies for eicosanoid pathways could address reproductive disorders. |
| PMA | PMA linked to hormonal changes, increase in IL-5/IL-8, and aspirin-exacerbated respiratory disease [104-107] | Hormonal fluctuations worsen asthma, suggesting targets for management of PMA. |

Abbreviations: COX, cyclooxygenase; HUMEC, human uterine microvascular endothelial cell; PCOS, polycystic ovary syndrome; PG, prostaglandin; PMA, perimenstrual asthma.

sex hormones. Ovariectomized mice presented a smaller number of uterine mast cells compared to nonovariectomized control mice. In this way, when mice underwent hormone replacement—estradiol alone or in combination with progesterone—the number of mast cells was restored [74].

Kalogeromitros et al [80] studied the potential influence of the phases of the menstrual cycle on dermal reactivity to skin-prick testing. They studied 15 atopic women with seasonal rhinoconjunctivitis and/or asthma with known sensitivity to olive and wall pellitory pollen and 15 nonatopic, healthy, female controls. Skin-prick tests with histamine, morphine, and in the atopic group with wall pellitory and/or olive pollen, were performed 3 times during the same menstrual cycle, corresponding to bleeding (days 1-4), midcycle (days 12-16), and the late progesterone phase (days 24-28). In both atopic and nonatopic women, the wheal-and-flare size to histamine, morphine, and pollen increased on days 12-16 of the cycle, corresponding to ovulation and peak estrogen levels. These results suggest a potentially higher risk of symptoms worsening depending on the phase of the menstrual cycle. These data have been confirmed in later studies in 42 female patients with seasonal allergic rhinoconjunctivitis [81]. Alongside SPTs, serum levels of estradiol, progesterone, luteinizing hormone, and follicle-stimulating hormone were measured. The findings revealed that the most significantly positive findings were reported when SPTs were performed at mid-cycle and serum levels of estradiol and luteinizing hormone exhibited a positive correlation with SPT results [81].

Menstruation is considered a cofactor in food allergy, although its prevalence is still unknown. Clinical evidence suggests that the days before and during menstruation would be the most associated with menstruation-dependent food anaphylaxis [82].

Perimenstrual asthma (PMA) is yet another menstruation-related entity that may resemble catamenial food anaphylaxis, since it is defined as cyclical exacerbation of asthma symptoms during the luteal phase and/or during the first days of the menstrual cycle [83]. Several studies demonstrated that 30%-40% of women with asthma experience worse symptoms during the perimenstrual phase of the cycle, when sex hormone fluctuations are highest [84-86]. However, it is important to highlight that other studies have reported both protective and deteriorating effects of sex hormones on lung function and airway inflammation. Specifically, estrogen has been shown to have protective effects on airway responsiveness in females, as in the study by Matsubara et al [87], where endogenous estrogen negatively regulated airway responsiveness in female mice. On the other hand, the effects of sex hormones may be context-dependent, as discussed by Leffler et al [88], who highlighted the complex role of sex hormones in modulating immune responses and IgE-mediated sensitization, with males typically showing higher IgE-mediated sensitization before puberty and females exhibiting increased allergic responses after puberty. This inconsistency may be explained by the lack of uniform methodologies between studies focused on the role of sex hormones.

Progesterone hypersensitivity is a rare and overlooked disorder in the setting of hypersensitivity to either endogenous or exogenous progestogen hormones and is not necessarily associated with food allergy [89]. It can occur with symptoms ranging from mild dermatitis, urticaria, and asthma to angioedema and anaphylactic shock, usually during the luteal phase of the menstrual cycle [89].

Bauer et al [7] reported one of the largest series of catamenial anaphylaxis (8 patients). Onset of reactions was at a median age of 34 years, with an average of 10 perimenstrual anaphylactic episodes per patient. Reactions occurred between day 26 (premenstrual) and 7 of the menstrual cycle. Interestingly, skin test results for progesterone were negative in all but 1 patient, and no improvement was observed after various treatment regimens, including high-dose systemic corticosteroids, ketotifen, celecoxib, antihistamines, and oral contraceptives. However, some patients did improve with leuprolide (a luteinizing hormone releasing hormone analog), medroxyprogesterone, or salpingo-oophorectomy. Only 1 patient had food allergy [7]. The authors propose an additional mechanism to explain catamenial anaphylaxis, which may involve a vasoactive component of menstrual fluid prostaglandins. This hypothesis is supported by the observation that prostaglandin F2α plays a crucial role in modulating mediator release in mast cells, while prostaglandin I2 (prostacyclin) acts as a potent vasodilator and could potentially trigger systemic reactions in susceptible individuals [90-95] (Figures 5 and 6).

## 5. Regulation of Sex Hormones and Role of the Cyclooxygenase Pathway in Asthma, Reproductive Health, and Disease

Tamura et al [96] investigated the effects of 17-estradiol (E2) on COX-2 expression and PGE2 synthesis in human uterine microvascular endothelial cells (HUMECs). E2 treatment was found to increase COX-2 mRNA levels by 2.3- to 2.4-fold in HUMECs in a time-dependent manner. This increase was accompanied by an increase in COX-2 protein levels and PGE2 synthesis in culture media compared with untreated cells (controls). Pretreatment of HUMECs with NS-398, a selective COX-2 inhibitor, abolished E2-induced PGE2 synthesis, suggesting that E2 specifically induced up-regulation of COX-2 activity. Moreover, E2 completely reversed the activation of COX-2 mRNA and protein levels, as well as generation of PGE2 by the estrogen receptor antagonist ICI 182780. Furthermore, HUMECs were found to predominantly express estrogen receptor α, while estrogen receptor β was barely detected. Of note, E2 did not modify COX-2 expression in human dermal microvascular endothelial cells (HDMECs). This difference may be because the HDMEC line does not contain estrogen receptors. These findings have important implications for reproductive physiology, inflammation, and oncogenesis and could lead to new therapeutic strategies to treat diseases such as endometriosis and cancer by regulating the COX-2/PGE2 pathway [96]. Manipulation of sex hormone levels or receptor activity as a therapeutic approach could reduce the severity of hormone-related allergic and inflammatory diseases.

Eicosanoids have diverse physiological functions in the reproductive system, controlling menstrual bleeding and maintaining the corpus luteum [97]. Studies in animal models, particularly mice, provide valuable insights into the specific roles of EP receptors in reproductive events. For instance, EP2 deficiency in mice leads to impaired ovulation and fertilization, highlighting the importance of this receptor in oocyte maturation and cumulus cell function [98,99]. In humans, the expression of EP receptors fluctuates throughout the menstrual cycle, suggesting their involvement in mediating processes such as implantation. However, discrepancies regarding the precise expression patterns of EP receptors across different phases of the menstrual cycle have been reported [100]. The role of PGE2 and EP receptors extends to processes such as trophoblast invasion, embryo implantation, and extracellular matrix remodeling during early pregnancy [100]. Dysregulation of PGE2 and EP receptors is implicated in the pathogenesis of various reproductive disorders, namely, endometriosis, polycystic ovary syndrome, recurrent miscarriage, fetal growth restriction, and gestational diabetes mellitus, all of which affect pregnancy outcomes [100] (Table 3).

In the case of endometriosis, endometriotic lesions are characterized by high COX-2 and PGE2 biosynthesis compared with the healthy endometrium [101,102]. The regulation of COX-2 expression involves various factors implicated in endometriosis. In particular, local estrogen production in ectopic and eutopic endometrial tissues stimulates COX-2 activity, leading to increased prostaglandin synthesis and inflammation. Estrogen enhances COX-2–derived PGE2 synthesis, contributing to development of endometriosis. Moreover, cytokines such as IL-1β overexpress COX-2 in ectopic endometrial cells, activating MAPK-dependent signaling pathways. Nerve growth factor also increases COX-2 expression, potentially via high-affinity Trk receptors. Targeting COX-2 may offer several benefits, including pain relief, inhibition of lesion growth, and prevention of recurrence [102]. PGE2 and PGF2α levels in uterine tissue peak during menstruation, then decrease and fluctuate, reaching minimum levels in relation to the increase in progesterone from day 21 of the menstrual cycle [103]. In fact, while estrogens seem to be related to an increase in the production of PGE2, progesterone has a proven inhibitory effect [96]. In the case of the proinflammatory mediator PGD2, maximum levels are associated with the peak of progesterone during the luteal phase (day 21) [101]. Finally, an increase in leukotriene levels occurs in the days before ovulation (day 14). These modifications in the levels of eicosanoid mediators are also related to a change in the tissue expression of their receptors. Thus, the EP2, EP3, and EP4 receptors for PGE2 are more highly expressed during the luteal phase, whereas those of the receptors for PGD2 are more highly expressed during the premenstrual phase. Finally, the highest levels of COX-2 expression are observed during menstruation [103].

The role of sex hormones has also been studied in the case of the PMA phenotype. Orzech et al [104] conducted an intriguing study analyzing the influence of serum sex hormone concentrations on lower airway inflammation. The authors found that during the luteal phase of the cycle in PMA patients, serum estradiol levels increased, as did the estradiol-to-progesterone ratio and sputum concentrations of IL-5 and IL-8 compared to non-PMA asthma patients. Additionally, serum testosterone levels were decreased, and the total number of sputum inflammatory cells was higher in PMA patients in both the follicular and luteal phases than in non-PMA asthma patients [104].

A Spanish multicenter study of 44 reproductive age women with near-fatal asthma exacerbations revealed that 25% of exacerbations occurred on the first day of menstruation, with more frequent use of rescue medication during the previous 7 days and a trend toward greater severity of asthma and of the near-fatal asthma attacks. These findings suggest that menstruation may contribute to the instability of asthma. Moreover, the authors highlighted the need for specific recommendations in management plans for women with PMA [105].

Interestingly a large-scale study of women with severe asthma found that PMA was common (17%) and independently associated with poorly controlled disease and aspirin sensitivity, suggesting the potential contribution of prostaglandins to this phenotype [60]. A recent study evaluated the prevalence and characteristics of PMA among a cohort of patients with aspirin-exacerbated respiratory disease (AERD). PMA was identified in 24% and was associated with earlier development of each clinical feature of AERD than in the non-PMA group. PMA patients required more emergency department visits and hospitalizations than AERD patients without PMA, indicating a more severe phenotype. Notably, this study first reported that

PMA patients also experienced perimenstrual worsening of nasal symptoms (84% vs 9% of non-PMA) [106]. Therefore, dysregulation of PGE2 signaling followed by mast cell activation and cysteinyl leukotriene and PGD2 production is part of the underlying mechanism of AERD [107]. There is an evident clinical association between PMA and AERD, and several authors have suggested a possible common mechanistic pathway [106,107] (Table 3).

## 6. Conclusion

Food allergies and anaphylaxis are complex immune-mediated disorders influenced by several factors, including NSAIDs and menstruation. NSAIDs, commonly used for their anti-inflammatory properties, can exacerbate food allergy symptoms by disrupting gastrointestinal barrier integrity and directly affecting mast cell activation. Furthermore, the interaction between NSAIDs and food allergens underscores the need for cautious management in patients with known allergies.

Menstruation emerges as an intriguing cofactor in food allergy, with hormonal fluctuations impacting mast cell activation and allergic sensitivities. Catamenial anaphylaxis, occurring predominantly during the luteal phase of the menstrual cycle, highlights the role of progesterone in modulating allergic responses. Understanding the interplay between sex hormones and allergic reactions during menstruation provides insights into potential therapeutic strategies for managing food allergy.

PGE2 emerges as a pivotal mediator with a dual role in food allergy. While reduced PGE2 levels correlate with increased risk and severity of anaphylaxis, the stability of this mediator defends against allergic responses. The intricate regulation of PGE2 synthesis and its impact on mast cell activation highlights its potential as a therapeutic target for managing allergic disorders.

However, it is important to acknowledge that several confounding variables, such as hormonal fluctuations, concurrent medications, and environmental factors, may influence outcomes in studies on NSAIDs, menstruation, and food allergies. Confounders can complicate the interpretation of results, suggesting that future research should focus on better controlling for these variables. By incorporating more rigorous study designs and addressing confounders, researchers will be able to provide more reliable insights into the mechanisms underlying these complex interactions.

In conclusion, the intricate nature of food allergy necessitates a comprehensive understanding of its cofactors, including NSAIDs and menstruation. By elucidating the mechanisms underlying these interactions, clinicians and researchers could develop targeted interventions to better manage and prevent allergic reactions, ultimately improving the quality of life for individuals living with food allergies and anaphylaxis.

### *Funding*

This research was supported by grants from the Instituto de Salud Carlos III (PI22/00920) and FEDER Thematic Networks and Cooperative Research Centers RICORS Red de Enfermedades Inflamatorias (REI), Madrid, Spain and from the Catalan Society of Allergy and Clinical Immunology (SCAIC).

### *Conflicts of Interest*

The authors declare that they have no conflicts of interest.

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*Manuscript received September 18, 2024; accepted for publication January 28, 2025.*

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