Published in final edited form as:
*Cell Immunol*. 2008 ; 252(1-2): 7–15. doi:10.1016/j.cellimm.2007.09.009.

# Neuroendocrine Factors Alter Host Defense by Modulating Immune Function

**Cherie L. Butts** and **Estner M. Sternberg**§
*Section on Neuroendocrine Immunology & Behavior, National Institute of Mental Health/NIH; Bethesda, MD, USA*

## Abstract

An increasing body of evidence demonstrates that there is bidirectional communication between the neuroendocrine and immune systems. Interactions between these systems results in a variety of outcomes, including the well documented “sickness behavior” elicited by cytokines of the immune system that can enter the brain or activate second messengers that modify neuronal activity. Crosstalk between the neuroendocrine and immune systems can also result in production of factors by the nervous and endocrine systems that alter immune cell function and subsequent modulation of immune responses against infectious agents and other pathogens. Continued exposure to molecules produced by the neuroendocrine system has also been shown to increase susceptibility and/or severity of disease. Furthermore, neuroendocrine factors are thought to play a major role in the gender-specific difference in development of certain disorders, including autoimmune/inflammatory diseases that have a 2- to 10-fold higher incidence in females compared to males. Neuroendocrine factors can affect immune cells at the level of gene transcription but have also been shown to modify immune cell activity by interacting with intracellular signal transduction molecules, resulting in modified ability of these cells to mount a potent immune response. In this review, we will consider the various effects of the neuroendocrine system and its proteins on specific populations of immune cells and associated responses in host immunity against pathogens. We will further discuss how this modification of immune cell activity by the neuroendocrine system can contribute to susceptibility/severity of development of diseases.

### Keywords

Steroid hormones; immune system; neuroendocrine factors; innate immunity; adaptive immunity; antigen-presenting cells; lymphocytes

## 1. Introduction

A considerable number of studies have shown that the neuroendocrine and immune systems communicate with each other to promote reciprocal regulation in the host. Immune cells can sense pathogens (viruses, bacteria, fungi, tumor cells) and secrete proteins that modify cells of the neuroendocrine system, which causes sickness behavior following infection [1].

§*Corresponding author:* Dr. Esther M. Sternberg, Chief, Section on Neuroendocrine Immunology & Behavior, National Institute of Mental Health/NIH, 5625 Fishers Lane, Room 4N15, MSC 9401, Bethesda, MD 20892, Telephone: 301-496-9255, Fax: 301-496-6095, E-mail: sternbee@mail.nih.gov.

Alternatively, factors secreted by the neuroendocrine system can bring about changes in immune cell activity. The neuroendocrine system secretes steroid hormones (glucocorticoid) during the stress response but also stimulates production of other steroid hormones (estrogen, progesterone, testosterone, mineralococorticoid) under normal conditions, as occurs during the menstrual cycle of females. Classic steroid hormone actions include binding of the ligand to its receptor in the cytoplasm, formation of ligand-receptor dimers, translocation of the complex to the nucleus, and initiation of target gene transcription (identified via hormone response elements – HREs) that modify the function of the cell [2]. These transcription factors control the function of cells associated with specific physiological processes to maintain host homeostasis (Table I) but can also bring about changes in the activity of immune cells [3]. Steroid hormone receptors have also been found on the membrane of cells, and the functional relevance of membrane and cytoplasmic receptors is currently being studied [4]. In addition, studies have shown that steroid hormone-receptor complexes can act at both the genomic (transcription-dependent) and non-genomic (transcription-independent) levels to bring about changes in cellular function [5].

Initial observations showing the effects of neuroendocrine factors (steroid hormones) on the immune system were demonstrated by pathologists who discovered that hormonal alterations could influence the size of the thymus [6]. Hans Selye showed that physical (restraint) or psychological stressors caused activation of the hypothalamic-pituitary-adrenal (HPA) axis that led to shrinkage of the thymus and other lymphoid organs [7]. Several reports, including studies from our group, have demonstrated modification of immune cell function with steroid hormone treatment. Exposure to steroid hormones leads to an alteration in the ability of the cells to respond to infectious agents and other pathogens [8–10]. Understanding the specific mechanisms by which these neuroendocrine factors affect immune cell activity can help elucidate both the effects of stress on immune-mediated disease as well as some of the differences in incidence of autoimmune/inflammatory disease between males and females, which can be 2- to 10-fold higher in females [11].

## 2. Neuroendocrine Effects on Innate Immunity

Studies using *in vitro* and *in vivo* systems have confirmed that steroid hormones are able to modify innate immune responses [12]. Innate immunity is critical as it provides the initial response to a pathogen and also supplies the necessary signals to stimulate adaptive immunity. Modifications to the innate immune response can lead to a cascade of events that either allow the pathogen to thrive and damage the host or remove the organism more quickly. Immune suppression with increased steroid hormone levels, including glucocorticoids and sex hormones (testosterone, estrogen, and progesterone), has been reported in many diseases [13–16]. The effects of sex hormones have been especially studied in the context of pregnancy, in which the host is increasingly vulnerable to a variety of infectious agents compared to the non-pregnant state [17,18]. Women are thought to be especially susceptible to infections during pregnancy, including the bacterium *Listeria monocytogenes*, which poses a significant health problem [19]. Elevated levels of estrogen and progesterone that occur during pregnancy are associated with suppression of the helper T cell type I ($T_H1$) response and subsequent predisposition to infections that require these responses for clearance. One study in mice showed that levels of progesterone were lowered, with resulting fetal loss, following ligation of the $T_H1$ response-promoting CD40 receptor on antigen-presenting cells [20]. This further emphasizes the bidirectional communication between the neuroendocrine and immune systems. Physiologic concentrations of estrogen stimulate humoral and cellular immune responses, whereas higher concentrations, similar to what is produced during pregnancy, suppress immunity [21]. Although many studies have focused on how steroid hormones modify effector cell (B lymphocytes, T lymphocytes) function in disease development, other studies have appreciated the contribution of innate immune cell populations in this process.

### A. Granulocytes

Polymorphonuclear immune cells, such as granulocytes, play an important role in innate immunity. Granulocytes (basophils, eosinophils and neutrophils) have been found throughout the body, including skin, lungs, and intestines, and are among the first immune cell populations to come in contact with the external environment and pathogens. In fact, neutrophils are the first responders to be recruited after an injury (wound) [22]. These cells secrete a number of pro-inflammatory cytokines and chemokines that attract other immune cells to the site of infection. They also remove debris and foreign substances through their phagocytic activity and production of free radicals [23].

Glucocorticoids, primarily produced in the adrenal glands following activation of the HPA axis during the stress response, are commonly used in the treatment of many autoimmune/ inflammatory conditions. They have been shown to inhibit cytokine release and other activity of eosinophils in asthma [24] and neutrophils in chronic obstructive pulmonary disease (COPD) [25]. Inhaled glucocorticoids have been reported to prevent histamine release by basophils in allergic disease [26]. In addition, they prevented IL-4.secretion by cultured basophils [27]. Another steroid hormone produced by adrenal glands, the mineralocorticoid aldosterone, has also been studied to determine its effects on immunity. This hormone has been associated with immune stimulation, including upregulation of major histocompatibility complex (MHC) molecules by cells [28]. However administration of elevated concentrations of aldosterone in adrenalectomized rats showed a dose-dependent reduction in the number of neutrophils in peripheral blood of these animals [29]. Studies have shown immunomodulatory effects of sex hormones on granulocyte populations in other conditions. Whereas the sex hormones testosterone and estrogen did not have an effect on cultured basophils [27], estrogens are thought to be protective in atherosclerosis and have been shown to prevent neutrophil production of free radicals [30]. A separate study showed that estrogen prevented neutrophil adhesion to porcine endothelial cells and that this inhibition was mediated through estrogen receptor – α (ER-α) [31]. Both studies utilized estrogen concentrations similar to those seen during pregnancy. Furthermore, in experiments in which the progesterone-secreting corpus luteum was removed during pregnancy by ovariectomy, the conceptus ceased to develop to full term (spontaneous abortion) and an infiltration of neutrophils was found in the endometrium [32,33]. This would indicate a regulatory role for progesterone in neutrophil recruitment during pregnancy.

### B. Monocyte/Macrophage Populations

Monocytes originate in the bone marrow from a myeloid progenitor cell also common to neutrophils [34]. They are a population of antigen-presenting cells with phagocytic properties thought to be important in the pathogenesis of atherosclerosis and insulin resistance [35,36]. Macrophages are the mature form of monocytes. They produce a variety of cytokines, such as tumor necrosis factor – α (TNF-α) and interleukin – 1β (IL-1β),to promote an inflammatory response [37], and different subsets express a variety of chemokine receptors that indicate their tissue localization and specific function [38]. At the latter stages of an inflammatory response, macrophages clear the area of injury during wound healing by phagocytosing granulocytes, which have already undergone apoptosis. [39]. Therefore, these cells can serve the function of not only attracting cells to the site of injury that increase the degree of inflammatory response but also of removal of immunological waste products.

Research has been conducted to identify the effects of steroid hormones on this population of immune cells. A recent study reported that monocytes, along with neutrophils, are the primary targets of glucocorticoids in diminishing contact hypersensitivity reactions, as evidenced by repression of their cytokine and chemokine production [40]. This is especially interesting given that this contact hypersensitivity is a T cell-dependent disease. Monocyte/macrophage

populations have also shown responsiveness to estrogen. Bacterial lipopolysaccharide (LPS)-activated macrophages isolated from mouse spleens treated with estrogen were shown to have reduced production of pro-inflammatory cytokines compared to untreated spleens [41]. Kovacs' group has conducted several studies showing gender-specific differences in response to burn injury, indicating a role for hormones. They also showed that estrogen suppressed proliferation of cultured splenocytes from mice in a macrophage-dependent manner [42].

Other hormones have also been shown to modify monocyte/macrophage function. Testosterone, considered generally immunosuppressive, induced Fas ligand (FasL)-dependent apoptosis in bone marrow-derived macrophages [43]. Another study showed that the potent testosterone metabolite dihydrotestosterone (DHT) reduced the production of nitrite and TNF-α in activated microglia, the macrophage of the central nervous system [44]. Progesterone, a steroid hormone critical for maintenance of pregnancy [45], increased expression of FasL and decreased proinflammatory cytokine (IL-12, IL-1β) production by monocytes from varicella-zoster virus (VZV)-stimulated peripheral blood mononuclear cells (PBMCs) collected from healthy subjects [46]. Progesterone was also shown to inhibit TNF-α production in uterine macrophages [47]. This inhibition was thought to occur at the level of transcription, as shown by microarray experiments that identified TNF-α as a progesterone receptor target gene [48]. Others have reported inhibition of macrophage cytokine production by progesterone and that these effects were mediated through modifying NF-κB activity [49].

### C. Dendritic Cells

Dendritic cells (DCs) are considered the most potent of the antigen-presenting cell (APC) populations and are often referred to as "professional" APCs [50]. Similar to monocyte/macrophage populations, they can recognize a pathogen using pattern recognition receptors (PRRs) and mount a potent immune response. Immature DCs are able to take up antigen using their $F_c$ receptors. When these cells receive the appropriate signal and become mature, they produce copious amounts of cytokines that stimulate other immune cells. Mature DCs also express high levels of major histocompatibility complex (MHC) and costimulatory molecules on their cell surface, which is critical for activation of naïve lymphocytes. As these cells are considered important in both innate and adaptive immunity, they are the target of many of the current vaccine efforts [51].

There are several subsets of DCs that have been identified, each of which are considered to serve distinct functions in immunity and are localized to specific locations within the body [52]. Langerhans cells, the first DC identified, and dermal DCs are known for their ability to scavenge the environment for foreign particulates. They are situated in the skin and are vital in cutaneous immune responses [53]. Interstitial DCs are found in the lamina propria and are therefore important in gut immunity [54]. Myeloid DCs, also commonly referred to as conventional DCs, are the most frequently studied type of DC and can be easily isolated from bone marrow, blood, and spleen. In addition, monocytes can be differentiated into this DC subset using granulocyte-macrophage colony-stimulating factor (GM-CFS) [55]. They are the major producers of interleukin 12 (IL-12) that stimulates interferon-γ (IFN-γ) production by T lymphocytes and cellular immune responses. Plasmacytoid DCs are important in viral immunity, secrete large amounts of type I interferons (IFN-α/β), and are significant in tolerogenic immune responses [56,57]. Recently, new DC populations have been identified [58,59]. Further investigation will be required to determine if these are distinct DC subsets from those previously reported.

Many studies using steroid hormones to study DC activity have focused on their effects in the context of pregnancy, as several autoimmune/inflammatory diseases show changes in severity during pregnancy [60–62]. In particular, helper T type I ($T_H1$)-associated autoimmune/inflammatory disease tends to be relieved, while helper T type II ($T_H2$)-associated disease can

be aggravated as a result of pregnancy. Therefore, experiments utilize pregnancy-associated concentrations of steroid hormones to determine their effects on DC function. Some groups studying the effects of steroid hormones on DC activity have focused on the reproductive tract because it is thought to be the primary site of hormone production and therefore the most appropriate site to determine immune response outcomes [63]. One group showed that progesterone administered into the female reproductive tract increased the number of Langerhans cells [64]. However, the functionality of these cells was not fully characterized.

Our group has also studied the effects of steroid hormones on this important population of immune cells. We showed that progesterone modified the ability of LPS-matured rat DCs to secrete proinflammatory (TNF-α, IL-1β) cytokines, downregulated expression of major histocompatibility complex (MHC) and costimulatory molecules, and suppressed T cell proliferative capacity by these cells. The effects on mature DC function were identified at both physiologic and pregnancy-associated concentrations of the hormone and were mediated through the progesterone receptor (PR) as the PR antagonist RU486 was able to reverse the suppressive effects [10]. We further found that progesterone modified the ability of immature DCs to take up antigenic peptide. However, this was only identified at concentrations similar to that seen during pregnancy. Other groups have shown that progesterone inhibited DC phagocytosis of *Candida albicans* [65], contributed to susceptibility to human immunodeficiency virus (HIV) in women by increasing the number of Langerhans cells available for HIV infection [66] and also increased susceptibility to *Chlamydia* infection in rats due to increased bacterial infiltrates in the uterine epithelium and vaginal secretions of these animals [67], further supporting the need to understand the role of this hormone in disease development.

There have also been reports of experiments assessing the effects of other steroid hormones on DC function. A study using androgen replacement therapy in men with type II diabetes, an autoimmune/inflammatory disease, showed a reduction in the proinflammatory cytokines (IL-1β, IL-6, TNF-α) produced by DC populations [68]. Our group examined the effects of the synthetic glucocorticoid dexamethasone on DC function [69] and showed that bone marrow-derived and splenic DCs from rats were responsive to dexamethasone treatment. This resulted in inhibition of proinflammatory cytokine secretion and downregulation of MHC and costimulatory molecules on the cell surface of DCs isolated from both organs. Unlike the results from experiments with progesterone, we found a dose-dependent effect on the antigen uptake ability of these cells and increases in IL-10 secretion with increasing dexamethasone concentrations. This would be consistent with reports from other groups reporting less potent immune suppressive effects of progesterone compared to glucocorticoids [70]. Studies analyzing the effects of steroid hormones on DCs have utilized whole DC populations. It will be important to understand the effects of steroid hormones on specific DC subsets to understand their role in immunity, as a recent study shows development of a particular DC subset from estrogen-sensitive progenitor cells [71]. Additionally, estrogen has been shown to affect DC function in development of experimental autoimmune encephalomyelitis (EAE), the experimental form of the autoimmune/inflammatory disease multiple sclerosis (22).

### E. Natural Killer Cells

Natural killer (NK) cells are the effector cells of the innate immune system, with a similar phenotype to T lymphocytes [72]. These cells have cytotoxic function, recognizing their antibody-bound target using cell-surface $F_c$ receptors and producing perforin and granzymes that break up the integrity of the plasma membrane of the target cell. They also kill using the ligand for the death receptor Fas (FasL) or TNF-related apoptosis-inducing ligand (TRAIL) to bind and stimulate apoptosis of the infected cell [73]. In addition to their cytotoxic activity, NK cells express costimulatory molecules (CD40L, OX40L) to stimulate lymphocytes and are

able to regulate immune responses by releasing cytokines and chemokines that drive specific immune responses. They secrete interferon-γ (IFN-γ) that stimulates a strong $T_H1$-type immune response or IL-5 and IL-13 that promote $T_H2$ immune responses. They make cytokines that modify activity of innate immune cell populations (TNF-α, IL-10) and chemokines (MIP-1, RANTES, IL-8) that bring immune cells to the site of cellular damage [74]. These cells are also an appropriate complement to T lymphocyte activity as they can recognize target cells that have low expression of MHC molecules on their cell surface, whereas T cells require appropriate levels of MHC molecule expression for engagement and activation.

Effects of steroid hormones on NK cell activity have also been determined. Feasibility of these studies and possible direct effects were verified by a report showing expression of steroid hormone receptors by these cells [75]. The number of uterine NK cells changes during the estrus cycle or pregnancy [76] and has been shown to only be available during reproductive age [77,78], indicating a role for hormones in their development and availability. In addition, progesterone receptor (PR)−/− mice do not have uterine NK cells [79]. NK cells transfected with an adenovirus vector expressing IL-12 showed enhanced immunity against prostate-specific tumor cells in mice. Addition of the glucocorticoid receptor-inhibiting agent mitotane to cultures of these cells enhanced NK cell cytotoxic activity [80]. Another study revealed that treatment of NK cells with estrogen and progesterone decreased their cytotoxic activity and inhibited cytokine (IL-2, IFN-γ) production [81], and administration of testosterone proved inhibitory with antibody-dependent cytotoxicity by mouse NK cells [82].

## 3. Neuroendocrine Effects on Adaptive Immunity

In addition to reports of neuroendocrine modifications of innate immune responses, there have been extensive studies showing immunomodulatory consequences of neuroendocrine factors in adaptive immunity. Adaptive immune responses are important for elimination of such pathogens as viruses and tumor cells, although they require the cells of innate immunity for appropriate activation [83]. Cells of the adaptive immune response provide antigen-specific elimination of invading pathogens and primarily involve activity of B- and T-lymphocyte populations. The majority of studies of autoimmune/inflammatory disorders have focused on adaptive immunity as these responses ultimately cause disease [84]. Steroid hormones, in particular the glucocorticoids, are commonly used as therapeutic agents to control of a number of autoimmune/inflammatory disorders, and their effects on $T_H1$-specific rheumatoid arthritis were the subject of the 1950 Nobel Prize [85]. Therefore, it is reasonable to assume that other immunosuppressive steroid hormones might be immunomodulatory in adaptive immunity.

### A. B Lymphocytes

Humoral immunity is driven by activity of B lymphocytes, which are the antibody-producing cells of the immune system [86]. B cells develop in bone marrow and migrate to the spleen and lymph nodes as well as other peripheral lymphoid organs, where they will encounter antigen and become activated. Upon activation, these cells form germinal centers, sites of intense B cell proliferation, and give rise to antibody-secreting plasma cells [87]. Antibodies are the antigen-specific products generated in response to B cell activation and consist of 5 different isotypes, categorized based on their heavy-chain region: immunoglobulin M (IgM, initiates classical pathway of the complement cascade); immunoglobulin D (IgD, important for elimination of self-reactive B cells); immunoglobulin G (IgG, most abundant isotype in serum and activates complement cascade); immunoglobulin A (IgA, initiates alternate pathway of the complement cascade); and immunoglobulin E (IgE, activates mast cells and granulocytes and is considered important in allergic responses). Each isotype is important in driving a variety of responses against pathogens that require humoral immunity for appropriate inactivation and elimination.

There have been several reports of the effects of steroid hormones on B cells and their development. Kincade's group showed that steroid hormones have variable effects on B lymphocyte development due to the age-dependent expression of the receptors [88,89]. They demonstrated that B cells from fetal liver were sensitive to treatment with the synthetic glucocorticoid dexamethasone but not estrogen (17β-estradiol) while those from adult bone marrow were sensitive to treatment with both agents. Reverse-transcriptase polymerase chain reaction (RT-PCR) assays showed these differences are most likely receptor-dependent because cells from fetal liver did not express estrogen receptor. Other groups have studied B cell responsiveness to steroid hormones and the outcome of disease (Table II). Estrogen has been implicated in the improper regulation of B cell development and aggravation of systemic lupus erythematosus [90,91]. Another study revealed that increasing doses of estrogen resulted in increased susceptibility to *Toxoplasma gondii* [92]. In a study designed to determine the effects of androgens on allergic rhinitis (hay fever) in phospholipase $A_2$ ($PLA_2$)-sensitized animals, castrated mice treated with testosterone were shown to have significantly lower $PLA_2$-specific IgE levels [93].

### B. T Lymphocytes

T cells are important in developing potent immune responses against viruses and tumor cells and are the primary effector cell population in the cellular arm of adaptive immunity [94]. There are a number of T cell populations that have been identified to drive a variety of immune responses, including those required for humoral, cellular, and tolerogenic responses. One of the most commonly studied T cell subsets is the $CD4^+$ T helper cell population because it promotes cellular ($T_H1$) and humoral ($T_H2$) immunity. $CD8^+$ T cells are the cytotoxic T lymphocytes that eliminate pathogens and infected cells. Similar to the previously discussed actions of NK cells, these cells are able to release molecules that injure the cellular membrane of the target cell, decrease membrane stability, and thereby eliminate invading elements. Another well-studied T cell population is the $CD4^+CD25^+$ regulatory T cell ($T_{reg}$), which is important in suppressing immunity and preventing overzealous activity by immune cells. $T_{reg}$ cells are thought to be critical in inhibition of immune responses against fetal antigens and subsequent rejection of the fetus [95]. In addition, they are presumed to play a role in preventing autoimmunity and permitting allogeneic graft tolerance [96].

Steroid hormone effects, including sex hormones, on T cell populations have been investigated. Offner's group has studied the importance of estrogen in maintaining immune suppression during pregnancy and proposed that a transient increase in the number of $T_{reg}$ cells is imperative during this process to prevent fetal rejection [97–99]. Other steroid hormones have also demonstrated immunomodulatory effects on T cell activity. Progesterone suppressed antibody production by B cells in a study using female rhesus macaques, and this was mediated by its effects on T cells [100]. Glucocorticoids have also been known to induce apoptosis of T lymphocytes and shift the cytokine response from a $T_H1$ towards a $T_H2$ pattern that reduces inflammation. These effects were mediated through the glucocorticoid receptor [101,102]. Furthermore, direct effects of testosterone on T cell activity has also been implicated based on expression of the androgen receptor in various lymphoid tissues, including thymus, bone marrow, and spleen [103].

## 4. Conclusions

Although a variety of immune factors can play a role in immunomodulation, there is much evidence of the effects of neuroendocrine factors on immunity and immune-mediated disease initiation/progression. In many conditions that exhibit differences in severity, several factors (including hormone levels, hormone receptors, or responsiveness to hormones) may play an important role in disease. This review has discussed a number of neuroendocrine factors that

contribute to immunomodulation in a variety of diseases but also under normal conditions. More studies are necessary to identify the specific mechanisms by which these factors modify immune cell activity. Understanding the interplay between neuroendocrine and immune systems can help in the development of treatments for diseases and strategies to reduce susceptibility to disease.

## References


1. Sternberg EM. Neural-immune interactions in health and disease. J Clin Invest 1997;100(11):2641–2647. [PubMed: 9389725]
2. Webster JI, Tonelli L, Sternberg EM. Neuroendocrine regulation of immunity. Annu Rev Immunol 2002;20:125–163. [PubMed: 11861600]
3. Sternberg EM. Does stress make you sick and belief make you well? The science connecting body and mind. Ann N Y Acad Sci 2000;917:1–3. [PubMed: 11268334]
4. Thomas P, Pang Y, Dong J, Groenen P, Kelder J, de Vlieg J, Zhu Y, Tubbs C. Steroid and G protein binding characteristics of the seatrout and human progestin membrane receptor alpha subtypes and their evolutionary origins. Endocrinology 2007;148(2):705–718. [PubMed: 17082257]
5. Song IH, Buttgereit F. Non-genomic glucocorticoid effects to provide the basis for new drug developments. Mol Cell Endocrinol 2006;246(1–2):142–146. [PubMed: 16388891]
6. Selye H. Variations in organ size caused by chronic treatment with adrenal cortical compounds: An example of a dissociated adaptation to a hormone. J Anat 1941;76(Pt 1):94–99. [PubMed: 17104883]
7. Selye H, Fortier C. Adaptive reactions to stress. Res Publ Assoc Res Nerv Ment Dis 1949;29:3–18. [PubMed: 14854281]
8. Webster EL, Barrientos RM, Contoreggi C, Isaac MG, Ligier S, Gabry KE, Chrousos GP, McCarthy EF, Rice KC, Gold PW, et al. Corticotropin releasing hormone (CRH) antagonist attenuates adjuvant induced arthritis: role of CRH in peripheral inflammation. J Rheumatol 2002;29(6):1252–1261. [PubMed: 12064844]
9. Wilder RL, Elenkov IJ. Hormonal regulation of tumor necrosis factor-alpha, interleukin-12 and interleukin-10 production by activated macrophages. A disease-modifying mechanism in rheumatoid arthritis and systemic lupus erythematosus? Ann N Y Acad Sci 1999;876:14–31. [PubMed: 10415590]
10. Butts CL, Shukair SA, Duncan KM, Bowers E, Horn C, Belyavskaya E, Tonelli L, Sternberg EM. Progesterone inhibits mature rat dendritic cells in a receptor-mediated fashion. Int Immunol 2007;19(3):287–296. [PubMed: 17289656]
11. Butts C, Sternberg E. Different approaches to understanding autoimmune rheumatic diseases: the neuroimmunoendocrine system. Best Pract Res Clin Rheumatol 2004;18(2):125–139. [PubMed: 15121035]
12. Sternberg EM. Neural regulation of innate immunity: a coordinated nonspecific host response to pathogens. Nat Rev Immunol 2006;6(4):318–328. [PubMed: 16557263]
13. Nalbandian G, Kovats S. Understanding sex biases in immunity: effects of estrogen on the differentiation and function of antigen-presenting cells. Immunol Res 2005;31(2):91–106. [PubMed: 15778508]
14. Medina KL, Kincade PW. Pregnancy-related steroids are potential negative regulators of B lymphopoiesis. Proc Natl Acad Sci U S A 1994;91(12):5382–5386. [PubMed: 8202495]
15. Fukuzuka K, Edwards CK 3rd, Clare-Salzer M, Copeland EM 3rd, Moldawer LL, Mozingo DW. Glucocorticoid and Fas ligand induced mucosal lymphocyte apoptosis after burn injury. J Trauma 2000;49(4):710–716. [PubMed: 11038090]
16. Fukuzuka K, Edwards CK 3rd, Clare-Salzler M, Copeland EM 3rd, Moldawer LL, Mozingo DW. Glucocorticoid-induced, caspase-dependent organ apoptosis early after burn injury. Am J Physiol Regul Integr Comp Physiol 2000;278(4):R1005–R1018. [PubMed: 10749790]
17. Piccinni MP. Role of immune cells in pregnancy. Autoimmunity 2003;36(1):1–4. [PubMed: 12765464]
18. Verthelyi D. Sex hormones as immunomodulators in health and disease. Int Immunopharmacol 2001;1(6):983–993. [PubMed: 11407317]

19. Bakardjiev AI, Theriot JA, Portnoy DA. Listeria monocytogenes traffics from maternal organs to the placenta and back. PLoS Pathog 2006;2(6):e66. [PubMed: 16846254]
20. Erlebacher A, Zhang D, Parlow AF, Glimcher LH. Ovarian insufficiency and early pregnancy loss induced by activation of the innate immune system. J Clin Invest 2004;114(1):39–48. [PubMed: 15232610]
21. Paavonen T. Hormonal regulation of immune responses. Ann Med 1994;26(4):255–258. [PubMed: 7946244]
22. Fahey TJ 3rd, Sherry B, Tracey KJ, van Deventer S, Jones WG 2nd, Minei JP, Morgello S, Shires GT, Cerami A. Cytokine production in a model of wound healing: the appearance of MIP-1, MIP-2, cachectin/TNF and IL-1. Cytokine 1990;2(2):92–99. [PubMed: 2104219]
23. Singer AJ, Clark RA. Cutaneous wound healing. N Engl J Med 1999;341(10):738–746. [PubMed: 10471461]
24. Kay AB. The role of eosinophils in the pathogenesis of asthma. Trends Mol Med 2005;11(4):148–152. [PubMed: 15823751]
25. Jeffery P. Anti-inflammatory effects of inhaled corticosteroids in chronic obstructive pulmonary disease: similarities and differences to asthma. Expert Opin Investig Drugs 2005;14(5):619–632.
26. Schleimer RP, Lichtenstein LM, Gillespie E. Inhibition of basophil histamine release by anti-inflammatory steroids. Nature 1981;292(5822):454–455. [PubMed: 6166866]
27. Schroeder JT, MacGlashan DW Jr, MacDonald SM, Kagey-Sobotka A, Lichtenstein LM. Regulation of IgE-dependent IL-4 generation by human basophils treated with glucocorticoids. J Immunol 1997;158(11):5448–5454. [PubMed: 9164967]
28. Weber KT. The neuroendocrine-immune interface gone awry in aldosteronism. Cardiovasc Res 2004;64(3):381–383. [PubMed: 15537489]
29. Miller AH, Spencer RL, hassett J, Kim C, Rhee R, Ciurea D, Dhabhar F, McEwen B, Stein M. Effects of selective type I and II adrenal steroid agonists on immune cell distribution. Endocrinology 1994;135(5):1934–1944. [PubMed: 7956914]
30. Buyon JP, Korchak HM, Rutherford LE, Ganguly M, Weissmann G. Female hormones reduce neutrophil responsiveness in vitro. Arthritis Rheum 1984;27(6):623–630. [PubMed: 6329234]
31. Geraldes P, Gagnon S, Hadjadj S, Merhi Y, Sirois MG, Cloutier I, Tanguay JF. Estradiol blocks the induction of CD40 and CD40L expression on endothelial cells and prevents neutrophil adhesion: an ERalpha-mediated pathway. Cardiovasc Res 2006;71(3):566–573. [PubMed: 16797503]
32. Staples LD, Heap RB, Wooding FB, King GJ. Migration of leucocytes into the uterus after acute removal of ovarian progesterone during early pregnancy in the sheep. Placenta 1983;4(4):339–349. [PubMed: 6634664]
33. Gottshall SL, Hansen PJ. Regulation of leucocyte subpopulations in the sheep endometrium by progesterone. Immunology 1992;76(4):636–641. [PubMed: 1398753]
34. Volkman A, Gowans JL. The Origin Of Macrophages From Bone Marrow In The Rat. Br J Exp Pathol 1965;46:62–70. [PubMed: 14295560]
35. Hansson GK. Inflammation, atherosclerosis, and coronary artery disease. N Engl J Med 2005;352 (16):1685–1695. [PubMed: 15843671]
36. Shoelson SE, Lee J, Goldfine AB. Inflammation and insulin resistance. J Clin Invest 2006;116(7): 1793–1801. [PubMed: 16823477]
37. Gordon S, Taylor PR. Monocyte and macrophage heterogeneity. Nat Rev Immunol 2005;5(12):953–964. [PubMed: 16322748]
38. Weber C, Belge KU, von Hundelshausen P, Draude G, Steppich B, Mack M, Frankenberger M, Weber KS, Ziegler-Heitbrock HW. Differential chemokine receptor expression and function in human monocyte subpopulations. J Leukoc Biol 2000;67(5):699–704. [PubMed: 10811011]
39. Martin P, Leibovich SJ. Inflammatory cells during wound repair: the good, the bad and the ugly. Trends Cell Biol 2005;15(11):599–607. [PubMed: 16202600]
40. Tuckermann JP, Kleiman A, Moriggl R, Spanbroek R, Neumann A, Illing A, Clausen BE, Stride B, Forster I, Habenicht AJ, et al. Macrophages and neutrophils are the targets for immune suppression by glucocorticoids in contact allergy. J Clin Invest 2007;117(5):1381–1390. [PubMed: 17446934]

41. Deshpande R, Khalili H, Pergolizzi RG, Michael SD, Chang MD. Estradiol down-regulates LPS-induced cytokine production and NFkB activation in murine macrophages. Am J Reprod Immunol 1997;38(1):46–54. [PubMed: 9266010]

42. Gregory MS, Duffner LA, Faunce DE, Kovacs EJ. Estrogen mediates the sex difference in post-burn immunosuppression. J Endocrinol 2000;164(2):129–138. [PubMed: 10657848]

43. Jin L, Ai X, Liu L, Wang Z, Cheng Y, Qiao Z. Testosterone induces apoptosis via Fas/FasL-dependent pathway in bone marrow-derived macrophages. Methods Find Exp Clin Pharmacol 2006;28(5):283–293. [PubMed: 16845445]

44. Brown CM, Xu Q, Okhubo N, Vitek MP, Colton CA. Androgen-mediated immune function is altered by the apolipoprotein E gene. Endocrinology 2007;148(7):3383–3390. [PubMed: 17395708]

45. Stites DP, Siiteri PK. Steroids as immunosuppressants in pregnancy. Immunol Rev 1983;75:117–138. [PubMed: 6226589]

46. Enomoto LM, Kloberdanz KJ, Mack DG, Elizabeth D, Weinberg A. Ex vivo effect of estrogen and progesterone compared with dexamethasone on cell-mediated immunity of HIV-infected and uninfected subjects. J Acquir Immune Defic Syndr 2007;45(2):137–143. [PubMed: 17356463]

47. Tibbetts TA, Conneely OM, O'Malley BW. Progesterone via its receptor antagonizes the pro-inflammatory activity of estrogen in the mouse uterus. Biol Reprod 1999;60(5):1158–1165. [PubMed: 10208978]

48. Lydon JP, DeMayo FJ, Funk CR, Mani SK, Hughes AR, Montgomery CA Jr, Shyamala G, Conneely OM, O'Malley BW. Mice lacking progesterone receptor exhibit pleiotropic reproductive abnormalities. Genes Dev 1995;9(18):2266–2278. [PubMed: 7557380]

49. McKay LI, Cidlowski JA. Molecular control of immune/inflammatory responses: interactions between nuclear factor-kappa B and steroid receptor-signaling pathways. Endocr Rev 1999;20(4):435–459. [PubMed: 10453354]

50. Banchereau J, Steinman RM. Dendritic cells and the control of immunity. Nature 1998;392(6673):245–252. [PubMed: 9521319]

51. Mosca PJ, Lyerly HK, Clay TM, Morse MA, Lyerly HK. Dendritic cell vaccines. Front Biosci 2007;12:4050–4060. [PubMed: 17485358]

52. Mellman I, Steinman RM. Dendritic cells: specialized and regulated antigen processing machines. Cell 2001;106(3):255–258. [PubMed: 11509172]

53. Anjuere F, Martin P, Ferrero I, Fraga ML, del Hoyo GM, Wright N, Ardavin C. Definition of dendritic cell subpopulations present in the spleen, Peyer's patches, lymph nodes, and skin of the mouse. Blood 1999;93(2):590–598. [PubMed: 9885220]

54. Iwasaki A. Mucosal dendritic cells. Annu Rev Immunol 2007;25:381–418. [PubMed: 17378762]

55. Talmor M, Mirza A, Turley S, Mellman I, Hoffman LA, Steinman RM. Generation or large numbers of immature and mature dendritic cells from rat bone marrow cultures. Eur J Immunol 1998;28(3):811–817. [PubMed: 9541575]

56. Gilliet M, Boonstra A, Paturel C, Antonenko S, Xu XL, Trinchieri G, O'Garra A, Liu YJ. The development of murine plasmacytoid dendritic cell precursors is differentially regulated by FLT3-ligand and granulocyte/macrophage colony-stimulating factor. J Exp Med 2002;195(7):953–958. [PubMed: 11927638]

57. Steinman RM, Hawiger D, Nussenzweig MC. Tolerogenic dendritic cells. Annu Rev Immunol 2003;21:685–711. [PubMed: 12615891]

58. Taieb J, Chaput N, Menard C, Apetoh L, Ullrich E, Bonmort M, Pequignot M, Casares N, Terme M, Flament C, et al. A novel dendritic cell subset involved in tumor immunosurveillance. Nat Med 2006;12(2):214–219. [PubMed: 16444265]

59. Chan CW, Crafton E, Fan HN, Flook J, Yoshimura K, Skarica M, Brockstedt D, Dubensky TW, Stins MF, Lanier LL, et al. Interferon-producing killer dendritic cells provide a link between innate and adaptive immunity. Nat Med 2006;12(2):207–213. [PubMed: 16444266]

60. Steinman L. Elaborate interactions between the immune and nervous systems. Nat Immunol 2004;5(6):575–581. [PubMed: 15164017]

61. Elenkov IJ, Wilder RL, Bakalov VK, Link AA, Dimitrov MA, Fisher S, Crane M, Kanik KS, Chrousos GP. IL-12, TNF-alpha, and hormonal changes during late pregnancy and early postpartum:

implications for autoimmune disease activity during these times. J Clin Endocrinol Metab 2001;86 (10):4933–4938. [PubMed: 11600565]

62. Huck B, Steck T, Habersack M, Dietl J, Kammerer U. Pregnancy associated hormones modulate the cytokine production but not the phenotype of PBMC-derived human dendritic cells. Eur J Obstet Gynecol Reprod Biol 2005;122(1):85–94. [PubMed: 16154043]
63. Wira CR, Fahey JV. The innate immune system: gatekeeper to the female reproductive tract. Immunology 2004;111(1):13–15. [PubMed: 14678193]
64. Wieser F, Hosmann J, Tschugguel W, Czerwenka K, Sedivy R, Huber JC. Progesterone increases the number of Langerhans cells in human vaginal epithelium. Fertil Steril 2001;75(6):1234–1235. [PubMed: 11384659]
65. Pepe M, Jirillo E, Covelli V. In vitro infection of human monocyte-derived dendritic cells with Candida albicans: receptorial involvement and therapeutic implications. Curr Pharm Des 2006;12 (32):4263–4269. [PubMed: 17100628]
66. Mingjia L, Short R. How oestrogen or progesterone might change a woman's susceptibility to HIV-1 infection. Aust N Z J Obstet Gynaecol 2002;42(5):472–475. [PubMed: 12495087]
67. Kaushic C, Zhou F, Murdin AD, Wira CR. Effects of estradiol and progesterone on susceptibility and early immune responses to Chlamydia trachomatis infection in the female reproductive tract. Infect Immun 2000;68(7):4207–4216. [PubMed: 10858238]
68. Corrales JJ, Almeida M, Burgo R, Mories MT, Miralles JM, Orfao A. Androgen-replacement therapy depresses the ex vivo production of inflammatory cytokines by circulating antigen-presenting cells in aging type-2 diabetic men with partial androgen deficiency. J Endocrinol 2006;189(3):595–604. [PubMed: 16731790]
69. Butts CL, Shukair SA, Duncan KM, Harris CW, Belyavskaya E, Sternberg EM. Effects of dexamethasone on rat dendritic cell function. Horm Metab Res 2007;39(6):404–412. [PubMed: 17578756]
70. Law WY, Chen WH, Song YL, Dufour S, Chang CF. Differential in vitro suppressive effects of steroids on leukocyte phagocytosis in two teleosts, tilapia and common carp. Gen Comp Endocrinol 2001;121(2):163–172. [PubMed: 11178882]
71. Welner RS, Pelayo R, Garrett KP, Chen X, Perry SS, Sun XH, Kee BL, Kincade PW. Interferon-producing killer dendritic cells (IKDCs) arise via a unique differentiation pathway from primitive c-kitHiCD62L+ lymphoid progenitors. Blood 2007;109(11):4825–4931. [PubMed: 17317852]
72. Cooper MA, Fehniger TA, Caligiuri MA. The biology of human natural killer-cell subsets. Trends Immunol 2001;22(11):633–640. [PubMed: 11698225]
73. Screpanti V, Wallin RP, Grandien A, Ljunggren HG. Impact of FASL-induced apoptosis in the elimination of tumor cells by NK cells. Mol Immunol 2005;42(4):495–499. [PubMed: 15607805]
74. Zanoni I, Granucci F, Foti M, Ricciardi-Castagnoli P. Self-tolerance, dendritic cell (DC)-mediated activation and tissue distribution of natural killer (NK) cells. Immunol Lett 2007;110(1):6–17. [PubMed: 17451813]
75. Henderson TA, Saunders PT, Moffett-King A, Groome NP, Critchley HO. Steroid receptor expression in uterine natural killer cells. J Clin Endocrinol Metab 2003;88(1):440–449. [PubMed: 12519888]
76. Tayade C, Black GP, Fang Y, Croy BA. Differential gene expression in endometrium, endometrial lymphocytes, and trophoblasts during successful and abortive embryo implantation. J Immunol 2006;176(1):148–156. [PubMed: 16365405]
77. Koopman LA, Kopcow HD, Rybalov B, Boyson JE, Orange JS, Schatz F, Masch R, Lockwood CJ, Schachter AD, Park PJ, et al. Human decidual natural killer cells are a unique NK cell subset with immunomodulatory potential. J Exp Med 2003;198(8):1201–1212. [PubMed: 14568979]
78. Hickey M, Crewe J, Goodridge JP, Witt CS, Fraser IS, Doherty D, Christiansen FT, Salamonsen LA. Menopausal hormone therapy and irregular endometrial bleeding: a potential role for uterine natural killer cells? J Clin Endocrinol Metab 2005;90(10):5528–5535. [PubMed: 16046584]
79. Mulac-Jericevic B, Mullinax RA, DeMayo FJ, Lydon JP, Conneely OM. Subgroup of reproductive functions of progesterone mediated by progesterone receptor-B isoform. Science 2000;289(5485): 1751–1754. [PubMed: 10976068]
80. Raja Gabaglia C, Diaz de Durana Y, Graham FL, Gauldie J, Sercarz EE, Braciak TA. Attenuation of the glucocorticoid response during Ad5IL-12 adenovirus vector treatment enhances natural killer

cell-mediated killing of MHC class I-negative LNCaP prostate tumors. Cancer Res 2007;67(5):2290–2297. [PubMed: 17332360]

81. Stopinska-Gluszak U, Waligora J, Grzela T, Gluszak M, Jozwiak J, Radomski D, Roszkowski PI, Malejczyk J. Effect of estrogen/progesterone hormone replacement therapy on natural killer cell cytotoxicity and immunoregulatory cytokine release by peripheral blood mononuclear cells of postmenopausal women. J Reprod Immunol 2006;69(1):65–75. [PubMed: 16236362]
82. Hou J, Zheng WF. Effect of sex hormones on NK and ADCC activity of mice. Int J Immunopharmacol 1988;10(1):15–22. [PubMed: 3366506]
83. Kelsall BL, Biron CA, Sharma O, Kaye PM. Dendritic cells at the host-pathogen interface. Nat Immunol 2002;3(8):699–702. [PubMed: 12145651]
84. Sternberg EM, Chrousos GP, Wilder RL, Gold PW. The stress response and the regulation of inflammatory disease. Ann Intern Med 1992;117(10):854–866. [PubMed: 1416562]
85. Kirwan JR, Balint G, Szebenyi B. Anniversary: 50 years of glucocorticoid treatment in rheumatoid arthritis. Rheumatology (Oxford) 1999;38(2):100–102. [PubMed: 10342620]
86. Lipsky PE. Systemic lupus erythematosus: an autoimmune disease of B cell hyperactivity. Nat Immunol 2001;2(9):764–766. [PubMed: 11526379]
87. Nutt SL, Kee BL. The transcriptional regulation of B cell lineage commitment. Immunity 2007;26(6):715–725. [PubMed: 17582344]
88. Medina KL, Garrett KP, Thompson LF, Rossi MI, Payne KJ, Kincade PW. Identification of very early lymphoid precursors in bone marrow and their regulation by estrogen. Nat Immunol 2001;2(8):718–724. [PubMed: 11477408]
89. Igarashi H, Kouro T, Yokota T, Comp PC, Kincade PW. Age and stage dependency of estrogen receptor expression by lymphocyte precursors. Proc Natl Acad Sci U S A 2001;98(26):15131–15136. [PubMed: 11752459]
90. Grimaldi CM, Hill L, Xu X, Peeva E, Diamond B. Hormonal modulation of B cell development and repertoire selection. Mol Immunol 2005;42(7):811–820. [PubMed: 15829269]
91. Grimaldi CM, Cleary J, Dagtas AS, Moussai D, Diamond B. Estrogen alters thresholds for B cell apoptosis and activation. J Clin Invest 2002;109(12):1625–1633. [PubMed: 12070310]
92. Pung OJ, Luster MI. Toxoplasma gondii: decreased resistance to infection in mice due to estrogen. Exp Parasitol 1986;61(1):48–56. [PubMed: 3943592]
93. Yamatomo T, Okano M, Ono T, Nakayama E, Yoshino T, Satoskar AR, Harn DA Jr, Nishizaki K. Sex-related differences in the initiation of allergic rhinitis in mice. Allergy 2001;56(6):525–531. [PubMed: 11421897]
94. Lanzavecchia A, Sallusto F. Lead and follow: the dance of the dendritic cell and T cell. Nat Immunol 2004;5(12):1201–1202. [PubMed: 15549117]
95. Zenclussen AC, Schumacher A, Zenclussen ML, Wafula P, Volk HD. Immunology of pregnancy: cellular mechanisms allowing fetal survival within the maternal uterus. Expert Rev Mol Med 2007;9(10):1–14. [PubMed: 17462112]
96. Kingsley CI, Karim M, Bushell AR, Wood KJ. CD25+CD4+ regulatory T cells prevent graft rejection: CTLA-4- and IL-10-dependent immunoregulation of alloresponses. J Immunol 2002;168(3):1080–1086. [PubMed: 11801641]
97. Polanczyk MJ, Hopke C, Huan J, Vandenbark AA, Offner H. Enhanced FoxP3 expression and Treg cell function in pregnant and estrogen-treated mice. J Neuroimmunol 2005;170(1–2):85–92. [PubMed: 16253347]
98. Polanczyk MJ, Hopke C, Vandenbark AA, Offner H. Estrogen-mediated immunomodulation involves reduced activation of effector T cells, potentiation of Treg cells, and enhanced expression of the PD-1 costimulatory pathway. J Neurosci Res 2006;84(2):370–378. [PubMed: 16676326]
99. Polanczyk MJ, Hopke C, Vandenbark AA, Offner H. Treg suppressive activity involves estrogen-dependent expression of programmed death-1 (PD-1). Int Immunol 2007;19(3):337–343. [PubMed: 17267414]
100. Lu FX, Abel K, Ma Z, Rourke T, Lu D, Torten J, McChesney M, Miller CJ. The strength of B cell immunity in female rhesus macaques is controlled by CD8+ T cells under the influence of ovarian steroid hormones. Clin Exp Immunol 2002;128(1):10–20. [PubMed: 11982585]

101. Evans-Storms RB, Cidlowski JA. Regulation of apoptosis by steroid hormones. J Steroid Biochem Mol Biol 1995;53(1–6):1–8. [PubMed: 7626441]

102. Schaaf MJ, Lewis-Tuffin LJ, Cidlowski JA. Ligand-selective targeting of the glucocorticoid receptor to nuclear subdomains is associated with decreased receptor mobility. Mol Endocrinol 2005;19(6): 1501–1515. [PubMed: 15705660]

103. Wunderlich F, Benten WP, Lieberherr M, Guo Z, Stamm O, Wrehlke C, Sekeris CE, Mossmann H. Testosterone signaling in T cells and macrophages. Steroids 2002;67(6):535–538. [PubMed: 11960632]

## Table I

**Effects of neuroendocrine factors (steroid hormones) on immune and non-immune processes in the host**

As estrogens and mineralocorticoids have been shown to have immunostimulatory effects at lower concentrations, the referenced actions on immune cell activity include experiments using elevated concentrations of the hormone.

| Steroid Hormone | Example | Function (Non-Immune) | Function (Immune) |
|---|---|---|---|
| Androgens | Testosterone, Dihydrotestosterone | Development of 2$^{nd}$ sexual characteristics (male) | Apoptosis of monocyte populations (Ref. 34) |
| Estrogens | 17β-estradiol, Estriol | Development of 2$^{nd}$ sexual characteristics (female) | Suppression of neutrophil activity (Ref. 22) |
| Glucocorticoids | Cortisol, Cortisone | Glucose metabolism, maturation of lung during fetal development | Proinflammatory cytokine inhibition, immune cell apoptosis (Ref. 56) |
| Mineralocorticoids | Androstenedione | Maintenance of salt-water balance | Reduction of peripheral blood neutrophils (Ref. 19) |
| Progestins | Progesterone | Embryo implantation, maintenance of pregnancy | Obstruction of neutrophil recruitment (Ref. 25) |

## Table II

**Outcomes of disease in experiments modifying steroid hormone availability**

Studies show immunomodulatory effects by steroid hormones in various diseases. The data in this table identifies the specific steroid hormone thought to have the greatest impact on disease development based on the results.

| Disease | Experimental Procedure | Steroid Hormone Modified by Procedure | Results |
|---|---|---|---|
| Diabetes, Type II | Castration | Testosterone | Worsened disease |
| Experimental Autoimmune Encephalitis (Mult Sclerosis) | Pregnancy | Estrogen, Progesterone | Disease remission |
| Infection (*Brugia malayi*) | Gonadectomy | Estrogen | Increased resistance |
| Rheumatoid Arthritis | Adrenalectomy | Glucocorticoid | Worsened disease |
| Systemic Lupus Erythematosis | Pregnancy | Estrogen, Progesterone | Worsened disease |
| Wound Healing | Topical Administration | Estrogen | Accelerated repair, decreased wound size |