



## Female sex hormones and their effects on the immune system

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Cite this study: Korkmaz, T. B., & Ayaz, F. (2022). Female sex hormones and their effects on the immune system. 4<sup>th</sup> Advanced Engineering Days, 45-47

### Keywords

Sex Hormones  
Female  
Immunity  
Autoimmune Diseases  
Allergies

### Abstract

Sex hormones assign the gender features of person but it is not their only function. While doing that, those hormones also affect other functions of cells and organs. Some particular cells express sex hormone receptors and when they are exposed to those hormones, the hormone-receptor binding occurs and some specific pathways may get blocked or activated. Female sex hormone system is really complex and the hormone levels vary during menstruation cycle, in other words most of the life time of a woman witnesses constant hormonal changes. The changes in the level of female sex hormones affect the whole body during menstrual cycle as stated above. One of the most critical body systems which can be influenced by the hormonal changes is the immune system. Changes in the immune system organs, cells and their functions affect the whole body and women's life quality during some particular stages of the menstruation. Understanding the hormonal changes and their impact on the immune system may be a huge help to develop treatment methods for the autoimmune diseases, infectious diseases, hormonal allergies, healthy pregnancy and even cancer.

### Introduction

Female sex hormones such as progesterone, estrogen and estradiol are generally assumed as reproductive hormones. In reality, they are also responsible for the nervous system functions, cardiovascular functions, muscle and skeletal development, hair growth and immune system regulation [1,2]. During a lifetime of a healthy woman, level of those hormones changes regularly and the changes of those hormone levels regulate some bodily functions [1,2]. For example, during the first days of menstrual cycle, if there is no fertilization, while progesterone level decreases, estrogen level increases. With these changes, body knows that person is not pregnant and prepares body for the menstruation.

The changes in the hormone levels during the menstruation cycle, immune cells can be triggered as well. Numerous studies show that hormones such as estrogen and progesterone affect the immune system cytokines' levels such as interferons and interleukins. In particular, hematopoietic cells, thymus stromal cells, bone marrow and lymph nodes express estrogen receptors (ER); which results in the immune system regulation by the estrogen hormone [1]. Estrogen binds those receptors and triggers some of the signaling pathways related to the immune system.

Estrogen/estradiol hormone levels always change during the menstrual cycle. Its levels are high during pregnancy, whereas its low after menopause. Lymphoid tissue cells, lymphocytes, dendritic cells and macrophages express estrogen receptors and with changes in the level of the hormone, those receptors interact with estrogen differently. After interaction, those cells' numbers, functions, activities or responses change [3,4].

Progesterone hormone is produced by the placenta at high levels during pregnancy. During menstrual cycle this hormone is produced and released from the corpus luteum. Progesterone receptors are expressed by the

Natural Killer cells, T cells, Macrophages and Dendritic cells and with an interaction of those receptor and hormones, also these immune system cells functions, activity, numbers and responses change [3,4].

Androgens also occur in women in post-pubertal age. NK cells and Macrophages also express androgen receptors and when interaction happens between hormone and the receptor, those cells' functions also change [3,4].

**Table 1.** Female sex hormones and their effects on the immune system cells, molecules and regulators during the menstrual cycle. While the  $\wedge$  symbol shows the increase, the  $\vee$  symbol shows the decrease of the parameters [3]

Immuno Component	Effect of the Hormones		
	Estradiol	Progesterone	Androgens
Toll Like Receptors	TLR4, TLR7, TLR9 $\wedge$	TLR3, TLR7 $\vee$	TLR4 $\vee$
Macrophages	TLR4 $\wedge$	Inducible Nitric Oxide Synthase, Nitric Oxidev FIZZ1, YM1 $\wedge$	Inducible Nitric Oxide Synthase, Nitric Oxidev TNF $\vee$
Nuclear Factor- $\kappa$ B	Activity $\vee$	Activity $\vee$	Activity $\vee$
Dendritic Cells	Activity $\wedge$ TLR7, TLR9 $\wedge$ CC-Chemokine Ligand2 $\wedge$ CXC-Chemokine Ligand10 $\vee$ IFN $\alpha$ $\vee$	CD40, CD80, CD86 $\vee$ CD110 $\wedge$ IL-18, IL-10 $\wedge$	Not Defined
Neutrophils	Numbers $\wedge$ Degranulation $\wedge$ Elastase release $\wedge$	Not Defined	Numbers $\wedge$ Kinases and leukotriene formation $\vee$
Natural Killer Cells	IFN $\gamma$ $\wedge$ Granzyme B $\wedge$ FASLigand $\vee$	Numbers $\wedge$ Caspase dependent apoptosis $\wedge$	Not Defined
Eosinophils	Numbers $\vee$ Mobilization $\vee$	Numbers $\wedge$	Not Defined
Inflammatory Cytokines	/ Low estrogen / IL-1beta, IL-6, TNF $\wedge$ / High estrogen / IL-1 $\beta$ , IL-6, TNF $\vee$	TNF, IFN $\gamma$ $\vee$ IL-6 $\wedge$	IL-1 $\beta$ , IL-2 $\wedge$ TNF $\vee$
Suppressive Cytokines	IL-4, IL-10, TGF $\beta$ $\wedge$	IL-4, IL-5, TGF $\beta$ $\wedge$	IL-10, TGF $\beta$ $\wedge$
Chemokines	CC-Chemokine Ligand2 $\vee$ CXC-Chemokine Ligand1 $\wedge$	CXC-Chemokine Ligand2 $\vee$	CC-Chemokine Ligand3 $\vee$
T <sub>H</sub> 1 cells	/ Low estradiol / Activity $\wedge$	Activity $\vee$	IFN $\gamma$ $\vee$
T <sub>H</sub> 2 cells	/ High estradiol / Activity $\wedge$	Activity $\wedge$	IL-4, IL-5 $\vee$ GATA3 $\vee$
T <sub>H</sub> 17 cells	Numbers $\vee$ IL-17 $\vee$	Percentages $\vee$	IL-17 $\wedge$
Treg cells	Numbers $\wedge$	Percentages $\wedge$	Numbers $\wedge$
CD8 <sup>+</sup> T cells	Response $\wedge$	Response $\vee$	Numbers $\vee$ Activity $\vee$
B cells	IgG, IgM $\wedge$	CD80, CD86 $\vee$	Not Defined
Antibody response	Response $\wedge$	Total antibody $\wedge$ Autoantibodies $\vee$	Response $\vee$

## Results

The female immunity mainly depends on the effects of the sex hormones on the immune system cells and other target organs. Sex hormones regulate the innate immune system and adaptive immune system mechanisms. Especially estrogen mostly triggers molecular mechanisms of the immune-mediated diseases. While estrogen has protective effect for MS (Multiple Sclerosis) and RA; for SLE, it has pathogenic effect [5,6]. For the treatment, blocking estrogen receptors may provide better outcomes but still more research about this topic should be conducted. Leptin hormone also has a role as immune-stimulatory, so treatment may include targeting this hormone as well. On the other hand, progesterone and androgens have immune-protective role and they can be considered as immunotherapy candidates [5].

Allergies are also another case related to the sex hormones in females. Studies showed that estrogen may trigger allergic reactivity. Generally, under hormone therapies, when estrogen level increases, estrogen binds estrogen receptors on mast cells and causes histamine release. Because of that, during pregnancy or menstruation, allergic reactions may peak. For the treatment of these type of hormone allergies immunotherapy may be the safest one. The other ones may require birth control practices like surgery or IUD. For immunotherapy, bioidentical hormones which are obtained from the natural sources are diluted with different chemicals. Concentration may

differ from patient to patient. This type of treatment may not end the allergy but it can relieve or stop the allergy symptoms [7].

A study showed that women were more likely to have autoimmune diseases than men. Sjogren syndrome, thyroid diseases, scleroderma, myasthenia gravis and systemic lupus erythematosus diseases are more common in women. Developing immunotherapy methods which are specialized for women can be the solution for these autoimmune diseases. Also, women have more dramatic immune response for the infectious diseases. At the first glance, it may seem like an advantage but in reality, during the infection, women can show increased symptoms and they may be severe in some cases [8].

## Discussion and Conclusion

Immune system plays an important role in the healthy cell functions, auto-immune diseases, tumor progression and cancer [6]. Female sex hormones affect the immune system differently so disease progression in females differ from those in the males. Understanding the female sex hormones and their interactions with the body during the certain phases of the menstruation is the key point for the treatment of the immune system related diseases. Some of the available treatment methods can cause damage to the patient over time, and are not specific enough. Also, research about this area is very limited, despite the knowledge of menstrual cycle being the key of mammalian life. In conclusion, focusing on this topic can improve female life quality in general.

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