Women, Estrogen, Inflammation and Autoimmune

New findings link estrogen and T cell immune response to autoimmune inflammation
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Women are more prone to the development of autoimmune diseases. The female hormone estrogen is likely to affect the immune system. A team of scientists reported new findings related to the involvement of estrogen hormone receptor in autoimmune diseases.

Women are more prone to the development of autoimmune diseases. The female hormone estrogen is likely to affect the immune system. A team of scientists from Turku Center for Biotechnology and University of Georgia reported new findings related to the involvement of estrogen hormone receptor in autoimmune diseases.

The incidence of autoimmune diseases such as MS, RA, and SLE is higher in women than in men. The estrogen hormone secreted in women may contribute to the pathogenesis of these diseases.

A research team led by Docent Zhi Chen from Turku Center for Biotechnology of the University of Turku has collaborated with researchers from the University of Georgia, United States to address the long-standing issue of hormonal effect on autoimmune diseases.

Estrogen hormone shows its action on cells mostly through estrogen receptor alpha (ERα). Researchers from Turku generated mice with ERα protein specifically deleted in T cells.

"The eureka moment of our research is that in a mouse model of human inflammatory bowel disease, transfer of naive T helper cells from ERα deficient mice did not succumb to colitis, unlike transfer from their counterparts," Docent Zhi Chen tells.

"Furthermore, using cutting-edge technique RNA sequencing approach combined with in vitro and in vivo experiments, we discovered that ERα regulates multiple aspects of T cell function, including T cell activation, proliferation and survival," Chen adds.

Regulatory T cells are group of T cells that help in preventing autoimmune diseases. The researchers found that ERα influences the function and differentiation of regulatory T cells.


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The Immune System Is a Natural Target for Estrogen Action: Opposing Effects of Estrogen in Two Prototypical Autoimmune Diseases
Deena Khan1 and S. Ansar Ahmed1,*

Analogous to other physiological systems, the immune system also demonstrates remarkable sex differences. Although the reasons for sex differences in immune responses are not precisely understood, it potentially involves differences in sex hormones (estrogens, androgens, and differential sex hormone receptor-mediated
events), X-chromosomes, microbiome, epigenetics among others. Overall, females tend to have more responsive and robust immune system compared to their male counterparts. It is therefore not surprising that females respond more aggressively to self-antigens and are more susceptible to autoimmune diseases. Female hormone (estrogen or 17β-estradiol) can potentially act on all cellular subsets of the immune system through estrogen receptor-dependent and -independent mechanisms. This minireview highlights differential expression of estrogen receptors on immune cells, major estrogen-mediated signaling pathways, and their effect on immune cells. Since estrogen has varied effects in female-predominant autoimmune diseases such as multiple sclerosis and systemic lupus erythematosus, we will mechanistically postulate the potential differential role of estrogen in these chronic debilitating diseases.

Estrogens and autoimmune diseases.
Cutolo M1, Capellino S, Sulli A, Serioli B, Secchi ME, Villaggio B, Straub RH.

Sex hormones are implicated in the immune response, with estrogens as enhancers at least of the humoral immunity and androgens and progesterone (and glucocorticoids) as natural immune-suppressors. Several physiological, pathologic, and therapeutic conditions may change the serum estrogen milieu and/or peripheral conversion rate, including the menstrual cycle, pregnancy, postpartum period, menopause, being elderly, chronic stress, altered circadian rhythms, inflammatory cytokines, and use of corticosteroids, oral contraceptives, and steroid hormonal replacements, inducing altered androgen/estrogen ratios and related effects. In particular, cortisol and melatonin circadian rhythms are altered, at least in rheumatoid arthritis (RA), and partially involve sex hormone circadian synthesis and levels as well. Abnormal regulation of aromatase activity (i.e., increased activity) by inflammatory cytokine production (i.e., TNF-alpha, IL-1, and IL-6) may partially explain the abnormalities of peripheral estrogen synthesis in RA (i.e., increased availability of 17-beta estradiol and possible metabolites in synovial fluids) and in systemic lupus erythematosus, as well as the altered serum sex-hormone levels and ratio (i.e., decreased androgens and DHEAS). In the synovial fluids of RA patients, the increased estrogen concentration is observed in both sexes and is more specifically characterized by the hydroxylated forms, in particular 16alpha-hydroxyestrone, which is a mitogenic and cell proliferative endogenous hormone. Local effects of sex hormones in autoimmune rheumatic diseases seems to consist mainly in modulation of cell proliferation and cytokine production (i.e., TNF-alpha, IL-1, IL-12). In this respect, it is interesting that male patients with RA seem to profit more from anti-TNFalpha strategies than do female patients.

The Complex Role of Estrogens in Inflammation
Rainer H. Straub
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There is still an unresolved paradox with respect to the immunomodulating role of estrogens. On one side, we recognize inhibition of bone resorption and suppression of inflammation in several animal models of chronic inflammatory diseases. On the other hand, we realize the immunosupportive role of estrogens in trauma/sepsis and the proinflammatory effects in some chronic autoimmune diseases in humans. This review examines possible causes for this paradox.

This review delineates how the effects of estrogens are dependent on criteria such as: 1) the immune stimulus (foreign antigens or autoantigens) and subsequent antigen-specific immune responses (e.g., T cell inhibited by estrogens vs. activation of B cell); 2) the cell types involved during different phases of the disease; 3) the target organ with its specific microenvironment; 4) timing of 17β-estradiol administration in relation to the disease course (and the reproductive status of a woman); 5) the concentration of estrogens; 6) the variability in expression of estrogen receptor α and β depending on the microenvironment and the cell type; and 7) intracellular metabolism of estrogens leading to important biologically active metabolites with quite different anti- and proinflammatory function. Also mentioned are systemic supersystems such as the hypothalamic-
p pituitary-adrenal axis, the sensory nervous system, and the sympathetic nervous system and how they are influenced by estrogens.

This review reinforces the concept that estrogens have antiinflammatory but also proinflammatory roles depending on above-mentioned criteria. It also explains that a uniform concept as to the action of estrogens cannot be found for all inflammatory diseases due to the enormous variable responses of immune and repair systems.

The Autoimmune Hormone Connection
Jolene Brighte, ND
For certain types of autoimmunity, women are affected at a rate of 10 to 1. Autoimmune disease is undeniably on the rise and who does it affect most? Us ladies! This might not come as a shock, but what might surprise you is just how much your autoimmune disease can completely wreck your hormones. Autoimmune diseases that cause hair loss, brittle nails and worse seem designed to attack our femininity. In this post we are going to explore the autoimmune hormone connection and what this means for you.

What is an autoimmune disease?
Simply put — your immune system is confused and is attacking your body rather than the stuff it should be attacking (bacteria, viruses, parasites, etc).

Under normal conditions, your immune system is out surveying the land and tagging/flagging those proteins which are not “you.” But under certain conditions immune system gets it wrong and starts tagging the proteins that are definitely you for destruction.

Before we dive into the details, I want you to know this — Autoimmune Disease is reversible and remission is possible.

Personally, I’ve been able to reverse the symptoms of my own autoimmune diseases — autoimmune thyroid and adrenal disease.

Clinically, I’ve helped thousands of patients with all types of autoimmune conditions do the same!

Now let’s dive into how autoimmune disease develops and how it can absolutely cause hormone chaos in your body.

There is a recipe for developing Autoimmune Disease
The analogy I use with my patients is a recipe for autoimmune disease. The recipe has 3 ingredients — intestinal hyperpermeability (aka leaky gut), a triggering event and the right genes.

Intestinal Hyperpermeability (aka leaky gut)
You’ve got about 70-80% of your immune system just hanging out in your gut. Well, not “just hanging out” but it’s there.

And this makes sense, right? Where is the best place to put the immune system to detect foreign invaders — the gut of course!

Since this is the place where the majority of the non-self proteins will enter, you want your immune system checking out the good, the bad and the ugly… and then handling that scene appropriately.

And it does this wonderfully. That is until the intestinal lining becomes compromised and the space between the cells of your intestine lose their integrity and start allowing large particles through.
Chronic stress, food sensitivities/ allergies, bacterial infections, parasites, viral infections, antibiotics, and some drugs (including NSAIDs) can cause a breakdown of your gut’s integrity at the cellular level.

This is how food sensitivities develop and is at the heart of autoimmune disease.

Food particles and infectious proteins from bacteria, yeast, viruses, and parasites begin entering the bloodstream and as you can imagine, your immune system is not happy about this. So it fights back.

The Triggering Event
Food particles escaping into the bloodstream alone can be enough to trigger an autoimmune disease.

Consider gluten as one example. When the gluten molecule enters, your immune system tags it with an antibody and signals for its destruction. This alone can increase inflammation, but it can also be the beginning of an autoimmune condition.

Gluten contains a protein called gliadin and that protein just happens to have an amino acid sequence that is close enough to your own thyroid gland. Yikes!

Your immune system sets out with good intentions to get rid of this non-self protein, but as it sets out to do its job (your immune system is very diligent) and destroy the tagged protein, it gets confused and also attacks your thyroid.

This process is known as molecular mimicry and is a big reason why you should definitely ditch gluten if you have an autoimmune thyroid condition and really, any autoimmune condition.

Bacteria, Viruses, Yeast and Parasites
Infections are a definite culprit and often precede the onset of autoimmune disease.

Under normal conditions, your immune system would take these bad bugs down. Unfortunately, these infections are pretty smart and evading detection.

The immune system can once again get confused and begin attacking your body as it tries to clear the infection.

Stress
It’s a common trigger for many chronic disease, with autoimmune disease being no exception.

When stress is high, it is triggers a cascade of hormones that result in immune dysregulation. The alteration in immune system dysfunction is thought to ultimately lead to autoimmune disease and the rise in inflammation.

While we can’t definitively point to stress as “the cause” of autoimmune disease, one study in the Autoimmunity Reviews stated, “[..] many retrospective studies found that a high proportion (up to 80%) of patients reported uncommon emotional stress before disease onset.”

The autoimmune hormone connection is greatly impacted by stress hormones. We’ll explore more about stress, stress hormones and autoimmune disease below.

Childbirth
Approximately 1 in 12 women will develop an autoimmune thyroid condition after giving birth. Other autoimmune disease can also be triggered by childbirth, but thyroid disease is by far the most common.

Why is childbirth particularly special?
Because the immune system shifts to accommodate baby. Once baby is born, the immune system shifts again, during a time when there is little sleep and stress is high.

Read more about postpartum thyroid disease.

What your mama gave ya!
The genes… this is where a lot of people get hung up in health. Think of your genes more like a roadmap — they can determine which direction you go, but they aren’t in control of how you get there.

If you’ve got the genes for autoimmune disease or maybe you don’t know if you have the genes, but you have a family history of… let’s say rheumatoid arthritis for this example then here is how it might go.

So you have the genes for rheumatoid arthritis, but that doesn’t seal your fate. It tells us what might be coming down the pipeline and what you are risk for, but without the other 2 ingredients (trigger and leaky gut), you may never develop this disease.

Conversely, if you don’t have the genes for this disease, you aren’t likely to develop rheumatoid arthritis.

How Do Hormones Affect Autoimmune Disease?
The collection of glands that produce hormones is known as the endocrine system and it can be a prime target of autoimmune disease.

Your thyroid, adrenal, ovaries, testes, pancreas, pituitary and other glands and the hormones they make can be direct targets of the immune system.

Here are some of the common ways this can show up:

- Insulin Dependent Diabetes
- Pre-Diabetes
- Hypothyroidism (Hashimoto’s Thyroiditis)
- Hyperthyroidism (Grave’s Disease)
- Estrogen Dominance
- Progesterone Deficiency
- Infertility
- Miscarriage
- Addison’s Disease (The adrenal disease President Kennedy had)
- Alopecia areata (yes, autoimmune diseases that cause hair loss are common)
- Carpal Tunnel
- Fibromyalgia
- Fatigue
- Anxiety/Depression
- And more…

Estrogen may enhance the inflammatory process of the immune system, making autoimmune symptoms worse.

Your body can make antibodies directly against estrogen and progesterone too. When this occurs, women experience delayed ovulation or don’t ovulate. Their uterine lining may not develop during their cycle making pregnancy difficult to achieve, periods erratic or short and cycles may be extremely short or long.

And as you can imagine, insufficient hormones can lead to mood swings, increased irritability, feeling like anything will make you cry, experiencing depression or anxiety, and make you feel susceptible to stress.
As women, we are experience autoimmune disease at a higher rate than men. Gender alone puts us at higher risk. But why?

The Estrogen Autoimmune Connection
Current research is trying to answer this very question and understand why autoimmune disease seems to have a preference for women.

One current hypothesis is that the estrogen may actually enhance the inflammatory process of the immune system, meaning it could increase the number of antibodies attacking our tissues.

This is especially a concern in women who are experiencing estrogen dominance or excess estrogen.

Research has shown that a woman’s immune system is more robust during reproductive years—when estrogen is its highest. As a woman transitions into menopause, estrogen declines and a woman’s immune system is more comparable to a man’s. For this reason, some women see a decline in their autoimmune symptoms post-menopause.

And it is the spikes and dips of estrogen that can drive autoimmune disease wild in peri-menopause. Before the ovaries have called it quits to producing hormones, there are often many ups and downs in estrogen production. Most women experience these as hot flashes.

But for autoimmune women, these can be experienced as a flare in symptoms—sudden joint pain, hair loss, fatigue, changes in skin, and other symptoms.

Estrogen isn’t all bad, however. While the decline in estrogen accompanies a decline in immune function, there is also a level of immune dysfunction that can arise. This may be one of the reasons we see a rise in heart disease (which has a strong autoimmune component) in postmenopausal women.

So it would seem that it’s a bit of a Goldilocks situation — not too much, not too little, but just the right amount of estrogen is necessary for appropriate immune system regulation. For this reason, bioidentical hormone therapy should be considered on an individualized basis.

The Cortisol Autoimmune Connection
Your adrenal glands play a big role in immune health by modulating inflammation and regulating the immune cells via the hormone called cortisol.

Chronic stress, whether it be mental, physical or emotional, can disrupt the way your brain and adrenal glands talk. The Hypothalamic-Pituitary-Adrenal axis (HPA axis) is the mechanism by which your body regulates your cortisol output.

Disruption to the HPA axis has been shown to influence the rise in inflammation and autoimmune disease, including autoimmune thyroid disease (Hashimoto’s and Grave’s), multiple sclerosis, Sjogren’s syndrome, alopecia areata (hair loss), inflammatory bowel disease (Crohn’s and Ulcerative Colitis), and many more.

Downregulation of the HPA axis can result in lower cortisol output, but it is also possible to develop Chronic stress can lead to glucocorticoid receptor resistance (GCR), a state in which the body becomes resistant to cortisol hormone. This is also commonly known as cortisol resistance.
In the early stages, there will be higher levels of circulating cortisol as the body fails to dampen the inflammatory response. The inflammation is allowed to progress, as is the autoimmune disease and cortisol levels plummet and the inflammation continues to climb.

There have been multiple studies linking stress, HPA axis dysregulation (commonly called adrenal fatigue) and autoimmune disease. Rheumatoid arthritis, which primarily affects the joints, multiple sclerosis, autoimmune thyroid disease, and autoimmune diabetes are but a handful of the autoimmune conditions linked to stress.

The Cortisol Estrogen Connection
As we’ve already discussed, elevations in estrogen may drive inflammation and autoimmunity. But it doesn’t need to be a frank elevation of estrogen, it can be a relative state of estrogen dominance that contributes to immune dysregulation and many unwanted hormone symptoms.

Cortisol and progesterone share a common precursor hormone called pregnenolone. When stress, inflammation, or immune dysregulation is high, your body will preferentially make cortisol to try to dampen the inflammation. The result is elevated cortisol at the expense of progesterone.

Progesterone naturally opposes estrogen, or in other words, protects you from the harmful effects of estrogen. When progesterone dips estrogen is left unopposed and you experience what is called a relative estrogen dominance.

Now there is lots of cortisol trying to dampen inflammation and lots of estrogen trying to ramp it up. And to make matters worse, you might be resistant to that cortisol. The result? Inflammation climbs and autoimmune disease goes wild!

Is Autoimmune Disease Causing Your Hormone Imbalance?
If you are experiencing symptoms any of the following symptoms, I recommend getting advanced lab testing and the help of an experienced hormone and autoimmune disease expert.

Common Symptoms of Hormone Imbalance
- Heavy, painful periods
- Infrequent periods
- Hot flashes
- Insomnia
- Fatigue
- Anxiety
- Depression
- Tender breasts
- Hair loss
- Irritability, mood swings
- Infertility or miscarriage
- Dry skin, brittle nails and hair
- Temperature intolerances
- Feeling “wired and tired”
- Sugar/ salt cravings

Lab Testing to Understand the Autoimmune Hormone Connection
In my clinic, we use the Dutch hormone testing method, as it is the most advanced hormone testing available. The Dutch test offers the most extensive information of sex and adrenal hormones and helps us understand how your body is processing these hormones.

We also explore what your individual root cause may be through functional diagnostic testing, including:
Comprehensive Stool Analysis: Evaluate the overall health of the digestive tract, including parasites, candida, inflammation, and other digestive issues.

4 point Salivary Cortisol Test: Measures the health and functional of the adrenal glands and determine degree of dysfunction (commonly called “adrenal fatigue”).

Complete Nutritional Assessment Test: A comprehensive look into what nutrients your body specifically needs to operate at your best.

Proprietary Blood Work: Complete thyroid panel, sex hormones, autoimmune screening, nutrient deficiencies, metabolic and immune function, allergens, molds, advanced cardiovascular screening, heavy metals.

Predictive Antibody Screening: Measure predictive antibodies, some of which can appear up to ten years before the clinical onset of autoimmune disease. Learn more about predictive antibody testing.

Food Sensitivity Testing: Evaluate IgG and IgA antibodies to investigate food sensitivities.

If you are wanting to take a deeper look into how your hormones may be influencing your autoimmune disease or understand your risk for autoimmunity, I encourage you to contact my office today and learn more about our patient discount for Dutch testing.

Estrogen Dominance and What to Do About It
Amy Myers, MD

Are you struggling with infertility, PMS, mood swings, weight gain, or low libido? If so, you could be dealing with a hormone imbalance. Having too much estrogen—known as estrogen dominance—is not only linked to a set of frustrating and uncomfortable symptoms; it also puts you at risk for a whole host of chronic issues. From fatigue and irritability to autoimmune conditions, thyroid dysfunction, and cancer, estrogen can wreak havoc on your body if it’s not in proper balance with your other reproductive hormones, such as progesterone.

And here’s the hard truth—estrogen dominance is at an all-time high. We’re seeing the rates spike across the board, in both women and men, across age ranges. And the rates of cancers and chronic illnesses linked with estrogen dominance are on the rise right along with it.

That’s because we are being constantly bombarded by xenoestrogens (industrial chemicals that mimic the behavior of estrogens) in our modern environment. They’re everywhere—in our food, personal care products, furniture and clothes. From the water we drink to the food we eat, you encounter a shocking number of these endocrine-disrupting xenoestrogens in the course of a day, without even knowing it.

It scares me when I think about how toxic our world has become, especially since I am a mother to a little girl. That’s why I’m even more passionate about arming you with the knowledge you need to make smart choices for yourself and your family.

In this article, I’ll walk you through what estrogen dominance is, how you’re being exposed to xenoestrogens, and simple, diet and lifestyle changes you can make to minimize your risk, naturally clear estrogen from your system, and maintain an optimal hormonal balance.

Autoimmune Disease

In some autoimmune conditions, high levels of estrogen can enhance the inflammatory response of the immune system, increasing the antibodies that attack your body’s own tissues. Although it’s entirely a clear cut issue. Estrogen is actually protective for some autoimmune conditions, such as multiple sclerosis (MS). It seems to be the sharp fluctuations in estrogen levels (such as those that happen around childbirth and menopause) that contribute to autoimmunity. It also has to do with the types of estrogens in your system, and whether they are your natural hormones or the synthetic xenoestrogens that exist in our environment.

Because women tend to be more susceptible to estrogen dominance, this helps explain why autoimmune conditions are so much more common among women.
Hormones and Inflammation

Research into the interplay between inflammation and hormones is still in its infancy. In particular, the sex hormones such as estrogens and progesterone appear to have important, but complex effects on the body’s inflammatory response. For example, many observers have wondered if the increase in inflammatory diseases that coincide with menopause, such as arthritis, might be related to shifts in the balance of progesterone and estrogens.

The complexity of hormonal effects on inflammation is evident in the scientific literature. For example, a literature review examining the role of estrogens in inflammation concluded that estrogens can either inflame or dampen inflammation, depending on a variety of factors, including the amount and composition of estrogens, the type of immune stimulus, the types of cells becoming inflamed, the presence of other hormones, and the presence of hormone receptors. A 2007 article published in Endocrine Reviews concurs that estrogens have both anti-inflammatory and pro-inflammatory roles, and that estrogens do not function in the same manner in all inflammatory diseases, due to “the enormous variable responses of immune and repair systems.”

A 2003 study published in the Journal of the American College of Cardiology suggested two possible keys to this puzzle regarding estrogens’ effects on inflammation:

the type of estrogen
the route of administration.

This study of 26 women, which compared the administration of two different types of estrogen, showed that oral conjugated equine estrogen pills (Premarin®) doubled CRP levels and lowered levels of an anti-inflammatory growth factor (insulin-like growth factor-1 or IGF-1). Conversely, estradiol (Climara®) delivered via a transdermal patch did not increase markers for inflammation. “Because CRP is a powerful predictor of an adverse prognosis in otherwise healthy postmenopausal women,” the authors concluded, “the route of administration may be an important consideration in minimizing the adverse effects of ET [estrogen therapy] on cardiovascular outcomes.”

A depletion of cortisol, the “stress” hormone, is also often implicated in furthering a pro-inflammatory state. Like insulin, cortisol is required for energy metabolism. It is also produced in large amounts in response to an acute short-term stress, such as an infection. Thus, cortisol response must be adequate to handle short-term inflammation. After the stress and inflammation passes, the body’s “fight or flight” hormones quickly return to normal.

The problem with cortisol occurs when inflammation doesn’t stop. “Constant stress means constant secretion of cortisol,” Dr. Sears says. “As your body adapts to chronic stress, you become hyperinsulinemic, thereby creating more visceral fat. This fuels a new round of cortisol secretion, and the end result is you get fatter and wind up with chronic silent inflammation.”

Unfortunately, the body’s hormonal balance favors excess cortisol as we age, and counterbalancing levels of estrogens and testosterone drop. The resulting chronically high cortisol levels take a heavy toll on the body, from insulin resistance to reduced immune system function.

Excess cortisol is also associated with a low level of thyroid hormone, which typically results in difficulty losing weight, chronic infections, fatigue, and a wide variety of other conditions that may further compound the effects of inflammation.

Future research may unlock a clinical role for the adrenal hormone pregnenolone, the precursor to all steroid hormones in the body. Prior to the use of prescription cortisone in the 1950s, pregnenolone was used to treat
arthritis after it was shown to be effective against joint swelling and inflammation. A study done in 1951 noted that those who responded to pregnenolone found the greatest benefit in recent lesions with the most visible inflammation. In his book, Pregnenolone: Nature’s Feel Good Hormone, Ray Sahelian, MD, wrote, “It remains to be seen how Preg[nenolone] can be effectively used in combination with other prescribed medicines and to alleviate the pain and other symptoms of rheumatoid arthritis.” He also noted that positive findings would permit lowering doses of non-steroidal anti-inflammatory drugs (NSAIDS), which cause serious side effects.