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The Effects of Hormonal Changes on Autoimmune Disease Progression

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ABSTRACT

Autoimmune diseases show gender preferences in their pathogenesis and predominantly affect females of childbearing age. This clearly demonstrates the importance of hormones in controlling the immune response and their vital role in autoimmunity. Periods of hormonal fluctuation(like pregnancy and the menstrual cycle) in levels of reproductive hormones may have a profound effect on immune processes and health.

In this review paper, I will analyze the effect of hormonal dynamics during the menstrual cycle and pregnancy on the process of regulating the immune system and the progress of autoimmune disorders such as systemic lupus erythematosus, multiple sclerosis, and rheumatoid arthritis. The relevant publications were collected with the help of PubMed and were chosen according to their relevance and timeliness.

Several studies indicate that the hormones estrogen and progesterone are necessary in regulating the immune system through dose-dependent mechanisms. In the menstrual cycle, fluctuating hormone levels can lead to inflammatory response variations, as well as increased severity of autoimmunity conditions during different cycles such as the menstruation and the late luteal phases. The pregnancy phase is immunologically distinctive due to high immune tolerance; therefore, there is low disease activity in multiple sclerosis and rheumatoid arthritis, although it is not consistent for systemic lupus erythematosus. Postpartum states often imply high disease activity due to sudden hormone reduction and immune stimulation.

To conclude, this research supports the importance of hormonal regulation on immune response and autoimmunity onset. This knowledge may facilitate better treatment and further research on hormone treatments.

INTRODUCTION

Autoimmune diseases are a major problem in a substantial percentage of the population; moreover, these diseases are more commonly observed in females of childbearing age. Diseases like systemic lupus erythematosus (SLE), rheumatoid arthritis (RA), and multiple sclerosis (MS) are more commonly observed in females compared to males. These diseases can fluctuate in severity during certain phases of the menstrual cycle when hormone production is altered. Therefore, understanding the interaction of the immune system and the reproductive system is of significant clinical importance. The menstrual cycle and pregnancy are major sources of hormonal fluctuation in females. These physiological states provide an opportunity to study how variations in hormones, including estrogen and progesterone, as well as prolactin, can either decrease or increase the severity of certain autoimmune diseases.

This area of research is meaningful in a clinical context as patients frequently report fluctuations in several autoimmune diseases during different reproductive phases as well as in the postpartum phase. There is a pronounced pattern of remission and exacerbation of these same diseases during distinct phases of the menstrual cycle and during pregnancy; therefore, understanding these phenomena is of high clinical relevance. From a broader point of view, this area of research links the endocrine, immune, and reproductive systems in ways relevant to public health and clinical medicine.

Current studies have already confirmed that male and female hormones, which include estrogen and androgens, respectively, are actively involved in controlling and regulating the immune system. Estrogen, for instance, can increase antibodies, while progesterone and androgens are known to decrease inflammatory responses in several immune cells. These are general trends, which will be discussed in more detail later, and they help explain why women are more likely to get autoimmune diseases than men. They also explain why, in many of these conditions, symptoms can change in line with hormone levels. One of the most obvious examples of hormone levels interacting with the immune system is pregnancy. When a female is pregnant, a number of changes take place, such as shifting from a protective to a tolerant system, which will allow a child to be born; this can have numerous effects on autoimmune conditions. In many women with rheumatoid arthritis or multiple sclerosis, pregnancy can result in a lessening of their symptoms, while in women with other conditions, such as lupus, pregnancy can have various effects.

Studies on the effects of hormone levels on women during their menstrual cycle have found many different effects. Individuals with SLE and Rheumatoid arthritis, for instance, see their symptoms become more severe, such as increased pain, during and before their menstruation. However, findings regarding menstrual cycle-related symptom exacerbation in SLE are not entirely consistent across studies. Some small cohort studies found worsening of symptoms in SLE patients during the menstruation and late luteal phases, while other studies have found minimal variation in disease activity. These variations are likely influenced by differences in study design, small samples, and a reliance on self-reported symptom tracking, which creates bias. These are thought to be a result of changes in estrogen and progesterone

levels, as well as fluctuations in other hormones. However, there are multiple studies, many with small sample sizes, many with inconsistent results, and many relying on self-reporting, which is not always a reliable method of determining hormone effects on autoimmune conditions.

In summary, hormone levels are known to have a number of effects on the immune system and on autoimmune conditions, but there are still numerous unanswered questions in this area, and it remains a topic of interest due to its potential for future therapeutic interventions, which will tie in with existing knowledge in this area.

METHODS

Inclusion Criteria	**Exclusion Criteria**
Studies published between 2016-2026	Animal-only studies
Human Studies	Unrelated endocrine diseases
English studies	Non-English studies
Meta analyses, Systematic Reviews	Studies conducted prior to 2016
Pregnancy and Menstrual cycle Terminology (Ex.Immune-modulation, estrogen, progesterone, post partum period, ovulation, etc…)	Veterinary Studies
Disease-specific studies(Ex.SLE, Rheumatoid Arthritis, Multiple Sclerosis)	Environmental triggers of Autoimmune Disorders

Table 1: Inclusion vs Exclusion Criteria used for studies in the literature review

Relevant literature for this review was collected using PubMed, with searches conducted from January to March of 2026. A total of 73 articles were initially identified.

Search terms included several keywords related to hormonal changes, immune function, and autoimmune diseases, such as “estrogen immune system,” “progesterone immune modulation,” “menstrual cycle immune changes,” “pregnancy immune tolerance,” and disease-specific terms like “systemic lupus erythematosus hormones,” “multiple sclerosis pregnancy,” and “rheumatoid arthritis hormonal effects.”

Filters were applied to prioritize free full-text articles, systematic reviews, and review papers published in the past 10 years. Of the 73 articles initially identified, 25 were excluded after title and abstract screening due to a lack of relevance. The remaining 48 articles underwent full-text review, with 37 studies ultimately being included.

Articles were selected based on their relevance to endocrine-immune interactions, as well as their focus on autoimmune disorders influenced by reproductive hormonal shifts. Eligible articles went through full-text review for menstrual-cycle and pregnancy-specific content. Relevant information was then extracted and categorized into three domains: Hormonal fluctuations, Immune and endocrine system interactions, and Autoimmune disease progression.

HORMONAL CHANGES DURING THE MENSTRUAL CYCLE AND PREGNANCY

The menstrual cycle is a complex, recurring process regulated by coordinated interactions between the hypothalamus, pituitary gland, and ovaries. Its primary purpose is to regulate ovulation and prepare the uterus for potential pregnancy. The cycle is typically divided into three phases: the **follicular phase**, **ovulatory phase**, and the **luteal phase** (Leeners et al., 2017). During the early follicular phase, levels of **estrogen and progesterone are relatively low**, which triggers an increase in **follicle-stimulating hormone (FSH)** from the anterior pituitary. FSH promotes the development of ovarian follicles, each containing an oocyte, and stimulates estrogen production by granulosa cells(supporting somatic cells in the ovary that surround the developing female gamete) (Dunkel & Quinton, 2000). Rising estrogen levels during the mid-to-late follicular phase cause thickening of the endometrial lining(the innermost layer of the uterus that grows to prepare for implantation of a fertilized egg) and a negative feedback mechanism on FSH secretion (which prevents further production of FSH), while preparing the body for ovulation (Hall et al., 2005).

Ovulation is initiated by a surge in **luteinizing hormone (LH)**, typically occurring around day 14 of a 28-day cycle, which causes the dominant follicle to release its oocyte (Schmidt et al., 2002). Estrogen levels peak just prior to the LH surge, and this peak is crucial for the positive feedback that triggers ovulation. Progesterone levels begin to rise slightly after ovulation, produced by the newly formed corpus luteum (Kawamura et al., 2019). The luteal phase, which spans approximately 14 days, is dominated by progesterone secretion. Progesterone supports the endometrium, creating a receptive environment for potential embryo implantation, and also maintains low estrogen levels (Leeners et al., 2017). If fertilization does not occur, the corpus luteum regresses, leading to a sharp decline in both progesterone and estrogen, and menstruation begins, marking the start of a new cycle (Dunkel & Quinton, 2000).

Pregnancy acts as a maintained luteal phase, beginning with fertilization and implantation. Following conception, the **blastocyst produces human chorionic gonadotropin (hCG),** which acts in a similar function to LH, which maintains the corpus luteum and stimulates continued production of progesterone and estrogen during the first trimester (Butt et al., 2022). Early hormone levels are essential for maintaining the lining of the uterus and facilitating the development of the embryo. There is an increased level of progesterone, which peaks during the second trimester, and estrogen, whose levels continuously increase until term, at which point their concentration can be as high as 30 times greater than pre-pregnancy levels (Leeners et al., 2017; Brar et al., 2023). Estrogen and progesterone are mostly involved in uteroplacental circulation, uterine quiescence(inactivity and relaxation of uterus smooth muscle that lasts throughout pregnancy), and breast preparation for breastfeeding (Brar et al., 2023; Leeners et al., 2017).

Besides progesterone and estrogen, there are many other hormones that support pregnancy. Prolactin secretion increases throughout the pregnancy to aid in the preparation of the mammary glands for lactation (Glynn et al., 2006). Relaxin, which is secreted by both the corpus luteum and the placenta, facilitates connective tissue remodeling as well as the softening of the cervix (Cirillo et al., 2018). The placental growth hormone, which replaces the pituitary growth hormone, manages maternal metabolism to support nutrient availability in the fetus. (Butt et al., 2022). These hormones, together, make up a coordinated system that functions to support fetal growth, while simultaneously altering external physiology of other organ systems (Brar et al., 2023; Leeners et al., 2017).

The hormonal concentrations in the process of pregnancy change with each trimester. In the first trimester, hCG becomes the primary hormone that promotes the synthesis of progesterone and helps to support the development of placenta through thickening of the uterus wall (Butt et al., 2022). At this stage, progesterone remains dominating while the level of estrogen rises. During the second trimester, the concentration of both hormones grows significantly and helps to accelerate the processes of rapid growth of the uterus and the fetus as well as stabilize the condition of the maternal cardiovascular system (Leeners et al., 2017; Cirillo et al., 2018). Finally, at the third trimester, the amount of estrogen becomes high while progesterone ensures uterine quiescence up until the beginning of childbirth (Glynn et al., 2006; Brar et al., 2023). After delivery, the postpartum period begins with the withdrawal of estrogen and progesterone, and the onset of lactation to help the reproductive tract recover.

Menstrual and pregnancy cycles have immense systemic effects aside from their reproductive purposes. Estrogen and progesterone affect metabolic rate, heart performance, bone mass, and brain function (Leeners et al., 2017; Kawamura et al., 2019). For example, high estrogen levels during the follicular phase enhance lipid metabolism and vasodilation (which is why females typically have better cholesterol levels than men), while progesterone dominance in the luteal phase can contribute to mild fluid retention and thermoregulation changes (Schmidt et al., 2002; Leeners et al., 2017). During pregnancy, the progressive increase in estrogen and progesterone helps maintain maternal hemodynamic stability (a normal blood pressure) despite the expanding blood volume and supports insulin sensitivity adaptations necessary for fetal nutrient supply, like lowering insulin sensitivity to increase glucose levels for the mother and fetus (Brar et al., 2023; Cirillo et al., 2018).

Overall, the menstrual cycle and pregnancy represent two of the most notable natural periods of hormonal fluctuation in human females. The cyclical rise and fall of estrogen, progesterone, and other reproductive hormones coordinate ovulation, endometrial preparation, implantation, and fetal development. These hormonal fluctuations have far-reaching effects on maternal physiology and establish the context for later interactions between endocrine and immune systems, which are explored in Subtopic 2. Understanding these detailed hormonal patterns is crucial for interpreting female-specific disease processes and for clinical management of reproductive health (Leeners et al., 2017; Butt et al., 2022; Brar et al., 2023).

Phase	Estrogen	Progesterone	Immune Characteristics	Clinical relevance
Early Follicular	Low	Low	Mildly pro-inflammatory environment	Starts thickening of endometrium
Ovulation	High	Low	Humoral immunity activation	Most fertile time for pregnancy to occur
Luteal	Moderate	High	High immune tolerance, very low inflammation	Prepares endometrium for potential pregnancy
Menstruation	Very low	Very Low	Low immune tolerance, high inflammation	Endometrial breakdown
First Trimester	Rising/moderate	High	Controlled high inflammatory state	Early pregnancy support
Second Trimester	High	High	Greater immune tolerance/ anti inflammatory	Reduced autoimmune responses in some diseases
Third Trimester	Very high	High	Anti-inflammatory	Often lowest MS/RA activity
Postpartum period	Rapid decline/ low	Rapid decline/low	Immune rebound/reactivation	Increased risk of clinical worsening in some diseases

Table 2: Hormonal and immune changes across menstrual cycle and pregnancy phases

PHYSIOLOGICAL INTERACTIONS BETWEEN THE ENDOCRINE AND IMMUNE SYSTEM AND THEIR REPRODUCTIVE IMPLICATIONS

The endocrine and immune systems have significant interconnections, continuously communicating through common mediators, receptors, and feedback mechanisms. Reproductive hormones including estrogen, progesterone, human chorionic gonadotropin, and prolactin act not only as reproductive hormones but also as immune system regulators that affect differentiation, maturation, and functions of immune cells and cytokine release (Straub, 2014; vom Steeg and Klein, 2016). Hormone receptors are

present on the surface of immune cells, making it possible for circulating levels of hormones to adjust according to reproductive requirements. In particular, such an interaction is especially relevant to reproductive events like menstruation and pregnancy that involve major changes in hormonal levels and limitations for the functioning of the immune system (Moulton, 2018; Klein and Flanagan, 2016).

Estrogen is important in regulating the immune system, where its actions vary in response to different concentrations and affect both the innate and adaptive immune systems. Immune cells such as T and B lymphocytes, macrophages, dendritic cells, and natural killer cells contain estrogen receptors that facilitate both the genomic and non-genomic signal transduction pathways (Klein and Flanagan, 2016). Estrogen usually favors activation of the immune system through increased production of antibodies, pro-inflammatory cytokines, and survival of B cells at low concentrations, but at high concentrations, as seen during pregnancy, estrogen has an anti-inflammatory effect on the immune system (Straub, 2014; Bereshchenko et al., 2018). These effects help explain why immune-mediated diseases often fluctuate with estrogen levels.

Estrogen-induced changes in immune function are phase-dependent and correspond to a body's attempts to balance its necessity for protection from pathogens with its requirements for reproductive competence (The immune system requires protection from pathogens whereas the reproductive system requires that non-self objects must be preserved). Increased estrogen concentrations within the follicular phase result in immune surveillance intensification at the level of the female reproductive tract, which is achieved via enhancing the recruitment of white blood cells and increased immune system activity in mucosa (Wira et al., 2020). Immune priming within the reproductive tract occurs before ovulation as a way of ensuring its protection against any infections, while still preserving tissue integrity (Gourdy et al., 2018). Post-ovulation, however, progesterone concentration begins to increase, inducing a partial dampening of immune system activity, and preparing for a potential embryo's attachment by lowering inflammation and promoting immune tolerance (Moulton, 2018).

However, progesterone is critical for the maintenance of immune tolerance during pregnancy and for the regulation of inflammation through pregnancy. There are progesterone receptors on several immune cells, including T cells, macrophages, and dendritic cells, enabling progesterone to reduce pro-inflammatory cytokine secretion and support regulatory immune processes (Areia et al., 2021). Progesterone has a substantial impact on immunology through its ability to produce regulatory T cells that play a crucial role in preventing maternal rejection of the fetus (Zenclussen, 2013). Progesterone reduces the cytotoxicity of natural killer cells and moves helper T cell responses from pro-inflammatory Th1 responses to Th2/humoral immune responses, which favor the fetus. The Th1 response is inflammatory and fights intracellular infections such as cancer and viruses. Th2 immunity is anti-inflammatory and relies on antibodies produced adaptively to protect against extracellular bacteria and parasites. Th2 immunity is necessary for fetal development as it reduces inflammation and protects the fetus from immune rejection (Arck and Hecher, 2013).

Pregnancy is a special immunological state that exhibits a sufficient balance in immune responses, but not immune suppression in general. This occurs via endocrine control mechanisms throughout each trimester that respond to physiological needs (Mor et al., 2017). In early pregnancy, immune response activity is

precisely controlled to facilitate implantation, but also maintain inflammatory signaling needed for placental formation (Aghaeepour et al., 2017). During later stages of pregnancy, the increasing concentrations of hormones including estrogen, progesterone, and human chorionic gonadotropin induce further immune suppression through regulatory T cell expansion and cytotoxicity inhibition (Wira et al., 2020). These hormonal effects protect the fetus, while promoting effective defense against pathogens.

Human chorionic gonadotropin is involved in the regulation of immune response during early pregnancy via the manipulation of immune cell migration (process that refers to the movement of leukocytes into tissues from the circulatory system as a means of fighting infections and inflammations) and cytokine secretion. The studies have revealed the capacity of hCG to stimulate regulatory T cell proliferation as well as regulate uterine natural killer cell activity in favor of successful placentation and fetal survival (Schumacher et al., 2018). Apart from its endocrine action, hCG influences immune responses and vascular transformation at the maternal-fetal interface (Bereshchenko et al., 2018).

Additionally, prolactin is known to participate in endocrine-immune interaction processes especially during pregnancy and lactation. The presence of prolactin receptors has been identified in lymphocytes and macrophages, where signaling pathways of prolactin have been demonstrated to stimulate lymphocyte proliferation and the secretion of cytokines under specific circumstances (Gala, 1991; Shelly et al., 2012). Although prolactin promotes immune stimulation, its actions are largely determined by its interactions with other hormones such as estrogen and progesterone (Moulton, 2018).

The fact that the relationship is bidirectional makes understanding the endocrine-immune relationship even more challenging. Immune cell-derived cytokines have been found to impact both the production of hormones and their receptors, leading to a relationship with feedback mechanisms between the immune system and endocrine glands (Straub, 2014). Inflammatory cytokines, for example, may affect the signaling process between the hypothalamus and the pituitary gland, thus impacting the levels of reproductive hormones and the regulation of the menstrual cycle (Bereshchenko et al., 2018). This type of interaction becomes especially important in the case of chronic inflammatory disorders or autoimmune diseases, as immune dysregulation will impact the hormonal signaling process.

Cyclic fluctuations in female hormonal levels, that are characteristic of the female reproductive cycle physiology, result in continual changes in immune regulatory systems, thus creating conditions conducive to developing immune dysregulation. Enhancement of the Th2-type immune response due to the estrogenic effect, as well as increased immune responsiveness, is beneficial for the development of antibodies-based immune response, though under some circumstances makes the organism more vulnerable to immune dysregulation (Klein and Flanagan, 2016). These differences may be exacerbated or diminished depending on the hormonal changes occurring in particular life stages, such as puberty, pregnancy, and menopause, when immune regulation must rapidly adapt to changing endocrine environments (vom Steeg and Klein, 2016).

Notably, the effects of reproductive endocrine immune interactions extend beyond the reproductive stage and menstruation. Chronic stimulation by immune-modulating hormones throughout reproductive life stages may affect immune memory, inflammatory thresholds, and the risk of disease in later life (Moulton,

2018). Knowledge about hormonal effects on immune systems during such life stages is essential in explaining the dynamics of disease development in autoimmune and inflammatory diseases.

In summary, the interaction of the physiology of the endocrine and immune system is the key to understanding the impact of hormonal variations on immunity. These interactions have not developed incidentally but through biological adaptation, balancing reproduction and immune defense. These immune adaptations and responses provide a mechanistic basis for why certain autoimmune diseases fluctuate in severity during important reproductive phases and hormonal transitions. Through describing these interactions as hormone-mediated immune regulation, we can build a base and examine how such processes lead to autoimmune pathology and manifestations in future sections.

HORMONAL INFLUENCES ON AUTOIMMUNE DISEASE

Evidence suggests a marked sexual bias in autoimmune diseases, with hormonal fluctuations linked to symptom changes during reproductive periods. The discussion above in the preceding paragraphs has already highlighted the relationship between hormones and immunity; thus, the explanation as to how certain autoimmune disorders like systemic lupus erythematosus, multiple sclerosis, and rheumatoid arthritis experience varying disease activity during times of major hormonal fluctuations can be explained using the information presented above about hormones and immunity.

Systemic Lupus Erythematosus (SLE)

Systemic lupus erythematosus is one of the autoimmune disorders with higher hormone sensitivity and it disproportionally affects females. Estrogen acts as an important factor in lupus pathogenesis through promotion of B cell activation, autoantibody production, and survival of autoreactive cells, mechanisms that may explain variation of SLE disease activity(Cunningham et al., 2022, Li et al., 2023).

Fluctuations in symptoms due to menstrual cycles have been documented in individuals suffering from SLE. Several researchers have noted an increase in the symptoms like fatigue and joint pain and even exacerbation of the disease during periods of hormonal withdrawal for estrogens and progesterone (Baker et al., 2021). This is especially true during the late luteal and early menstrual cycles, where there is a decrease in the levels of both hormones.

There is a particular change in the activity pattern of SLE during pregnancy, resulting from activation of the immune tolerance system. Although previously deemed as a period prone to SLE intensification, recent studies reveal that pregnant women often have stable or even decreased disease activity (Lateef and Petri, 2017; Buyon et al., 2023). Although this pattern is frequently reported, most evidence is from cohort studies that are influenced by confounding variables such as medication adjustments, and selection bias towards healthier pregnancies. This reflects the endocrine-immune mechanisms outlined in Subtopic 2 (Zenclussen, 2013). Conversely, the postpartum period is known to be accompanied by a heightened susceptibility to flare-ups because of abrupt hormonal withdrawal and lack of immune tolerance

established during pregnancy (Li et al., 2023). However, the magnitude of clinical relapse varies between studies, as underlying mechanisms remain incompletely understood, and interactions of environmental factors affect hormonal withdrawal.

The influence of hormones on lupus is also relevant to treatment options. The knowledge gained from the effects of estrogen on the immune system has made doctors cautious about using estrogen hormones, such as in contraceptive pills, for individuals with an active condition (Cunningham et al., 2022).

Multiple Sclerosis (MS)

Pregnancy and its effect on autoimmune disease via hormone changes is exemplified most clearly in multiple sclerosis. MS is an autoimmune disease wherein the destruction of myelin occurs due to the autoimmune attack by inflammatory cytokines and T cells in the central nervous system. Studies have indicated that estrogen and progesterone possess neuroprotective effects against MS (Voskuhl, 2020).

There is an indication that pregnant patients with MS tend to have fewer relapses, especially those in their third trimester, where there is an increase in the level of estrogens and progesterones (Hellwig et al., 2023). Elevated reproductive hormone levels during pregnancy may reduce inflammatory activity, and support nervous system protection in MS through mechanisms discussed previously(Gold et al., 2021, Schumacher et al., 2019).

In contrast, the postpartum period is a period when the risk of contracting diseases increases for patients with multiple sclerosis. The rapid drop in the level of reproductive hormones following childbirth is linked to immune reactivation and increased inflammatory activity, resulting in more frequent relapses occurring typically within three to six months after birth (Dobson and Giovannoni, 2019). Changes in symptoms associated with the menstrual cycle have also been noted in MS, where women develop increased symptoms of fatigue, weakness, or sensory complaints during their menstrual period (Gold et al., 2021). This may be an indication of the transient nature of inflammation, due to the withdrawal of estrogen, in a manner similar to that seen in SLE.

Rheumatoid Arthritis (RA)

Rheumatoid arthritis is a condition marked by joint inflammation and tissue destruction due to an immune reaction against the body's own tissues. This condition, like SLE and MS, usually remits during pregnancy and hence serves as a typical case of pregnancy-related immune modification. There are well-established reports of a reduction in joint pain, joint stiffness, and inflammatory indicators among pregnant patients suffering from rheumatoid arthritis; however, some studies report a negligible effect on symptoms during pregnancy (de Man et al., 2008; Förger & Villiger, 2020).

Improvement during pregnancy reflects immune tolerance and reduced inflammatory signaling, associated with elevated reproductive hormone levels(El-Gabalawy et al., 2022). Moreover, an increase in regulatory T cells during pregnancy leads to lower joint inflammation (Zenclussen, 2013). The above

findings are consistent with the interaction between endocrine and immunity systems discussed in Subtopic 2.

Although the condition improves during pregnancy, people with rheumatoid arthritis may suffer disease exacerbation after delivery. This is attributed to abrupt postpartum hormone withdrawal and associated inflammatory reactivation of the immune system(Förger and Villiger, 2020). It is important to note, however, that while postpartum disease intensification is commonly reported, many analyses do not account for stress related factors following birth, or medications used during pregnancy. Changes in menstrual symptoms have also been observed, with some people suffering from joint pain and inflammation during the menstrual period and the late luteal stage, owing to the inflammatory effect caused by hormonal withdrawal (El-Gabalawy et al., 2022).

The impact of hormones on RA is useful for the treatment of the condition. Changes must be made in the treatment plan depending on whether a woman is pregnant, nursing, or has gone through menopause to ensure that her RA does not worsen during these stages.

Disease	Menstruation Phase effects	Pregnancy effects	Postpartum period effects	Mechanism
SLE	Increased fatigue, joint pain, symptom variability in some patients	Variable response; may remain stable or improve depending on baseline disease activity	Elevated risk of disease activity most patients, some responses vary across studies	Estrogen-mediated B-cell activation, autoantibody production
Multiple Sclerosis	Increased fatigue or sensory symptoms reported in some patients	Reduced relapse rates, especially third trimester	Symptoms worsen, and relapse risk increases within 3-6 months	Reduced Th1 inflammation, higher immune tolerance
Rheumatoid Arthritis	Increased pain/stiffness in some patients during menstruation	Frequently reduced disease activity and symptoms	Increased likelihood of symptom exacerbation	Increased regulatory/helper T-cells, Cytokine suppression

Table 3: Comparative effects of hormonal changes on autoimmune diseases

INTEGRATION ACROSS DISEASES

Although all three disorders demonstrate association between hormonal effects and disease activity, the magnitude of these effects differ substantially by disease-specific mechanisms and baseline disease conditions that can vary person to person. Elevated levels of progesterone and estrogen during pregnancy and certain phases of the menstrual cycle are often associated with reduced disease activity in conditions such as Multiple Sclerosis and Rheumatoid Arthritis; however, there are more variable responses in Systemic Lupus Erythematosus that may depend on baseline activity of the disease, or a person's genetics . Conversely, hormone withdrawal during the postpartum period and the menstruation phase has been associated with increased risk and worsening of symptoms, but this relationship varies between studies and different conditions. This specific disease process stems from the endocrine/immune system interaction that has been mentioned previously, including cytokine modulation, and regulatory T cell action.

Several mechanistic patterns can be seen when comparing these specific autoimmune diseases through their respective immune pathways. Diseases like SLE are more strongly associated with B-cell activation and antibody-mediated responses, and, therefore, may respond differently to hormonal fluctuations than diseases like multiple Sclerosis and rheumatoid arthritis which involve T-cell inflammatory mechanisms. Estrogen-mediated enhancement of antibody-driven humoral immunity may contribute to increased autoreactive B-cell survival in SLE(which could potentially worsen symptoms or increase risk of disease), whereas progesterone-related regulatory T-cell expansion and suppression of inflammatory cytokines may explain the reduction of symptoms and disease activity in MS and rheumatoid arthritis during pregnancy. This broader context helps connect endocrine physiological responses with clinical-study variability across several autoimmune disorders.

Overall, although there is a distinct association between reproductive hormone fluctuations, and autoimmune disease activity, current literature is based on observational studies with varying methodologies. Inconsistencies across findings could be created through sample size differences, disease severity, and treatment processes. As a result, while many important general trends can be identified, caution should be exercised when interpreting disease-specific responses to hormonal fluctuations.

FUTURE RESEARCH

Although great strides have been made in researching the association between hormones and immunity, there still exist many areas that need further research. For instance, one particular field where research has lagged significantly is the use of longitudinal designs to follow immune markers and disease activity across many menstrual cycles and pregnancies. Current research mainly depends on cross-sectional designs, and this makes it extremely difficult to establish any temporal relationship between hormonal changes and changes in immune parameters. Future studies should use longitudinal designs that track

hormonal fluctuations alongside immune markers. This would allow researchers to examine how endocrine changes affect immune cells and the feedback mechanisms that govern hormone levels

There is also much left to explore about variations in response to hormones. Not all individuals affected by autoimmune diseases show variations in symptoms during their menstrual cycle or pregnancy. This could be due to genetics, hormone receptors, and previous exposure of the body to other pathogens. Exploring these variations among individuals can lead us to identify a subset of individuals whose conditions are more prone to variation in hormones and could benefit from targeted therapeutic strategies.

The postpartum phase requires more consideration as well, since it is frequently identified as being a high-risk phase for clinical worsening within several autoimmune diseases. Although hormonal withdrawal is frequently mentioned as being one of the causes for this increased vulnerability, the specific immune processes involved remain poorly characterized. For example, it is unknown which inflammatory cytokines have a greater presence in the post partum or menstruation periods.

Lastly, there is also the necessity for further research into the interaction between exogenous hormones and autoimmunity. Evidence is inconsistent, and specific to certain diseases, which makes it difficult to create clinical recommendations. Studies that explore the effects of various hormones on the immune system can help healthcare providers offer better counseling and management advice for their patients, as a targeted way to control autoimmune diseases.

CONCLUSION

The link between the influence of hormonal changes associated with the menstrual cycle and pregnancy on the development of autoimmune diseases constitutes an important juncture between endocrinology and immunology. Autoimmune diseases are more prevalent in females from birth and commonly develop or experience shifts in intensity at reproductive ages. This highlights the need to examine the effects that reproductive hormones (like estrogen and progesterone) have on the functioning of the immune system, as illustrated by the examples presented throughout this review.

In the synthesis of information from physiologic literature and specific diseases, there are clear trends. High exposure to hormones like estrogen and progesterone, especially during pregnancy, tends to correlate with tolerance and low disease activity in diseases like multiple sclerosis and rheumatoid arthritis, whereas systemic lupus erythematosus demonstrates more inconsistent responses based on baseline disease control. In contrast, hormone withdrawal during the menstruation phase, late luteal phase, and postpartum period have been associated with symptom exacerbation. However, it is important to note that included studies were observational or retrospective, limiting causal conclusions, and increasing confounding factor susceptibility.

Together, these findings suggest that reproductive hormonal levels and changes may influence autoimmune disease progression through disease-specific modulation of immune system pathways, rather

than a constant mechanism. Clinically, these results highlight the importance of anticipating hormone-associated periods of disease vulnerability . Understanding these patterns may improve clinical management during high risk periods, such as immune rebound(reversal of immune system's suppression during pregnancy to an active pro-inflammatory state during the postpartum period) after giving birth. In future therapies, there could be more use of timed interventions to identify endocrine states clarify how immune cell dysfunction contributes to increased disease activity.

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