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REVIEW ARTICLE

Prolactin, autoimmunity, and motherhood: when should women avoid breastfeeding?

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Abstract

The sexual dimorphic prevalence of autoimmunity represents one of the most alluring observations among the mosaic of autoimmunity. Sex hormones are believed to be a mainstay of this asymmetry. The greater prevalence of autoimmunity among fertile women, disease onset/relapses during pregnancy, and postpartum are some of the points that support this theory. Undeniably, motherhood represents one of the most remarkable challenges for the immune system that not only has to allow for the conceptus but also deal with extraordinary hormonal alterations. Prolactin has a recognized immune-stimulatory effect, mainly inhibiting the negative selection of autoreactive B lymphocytes. In accordance, hyperprolactinemia has been associated with several autoimmune diseases, interfering with its pathogenesis and activity. During the pregnancy and lactation period, assorted autoimmune patients experience relapses, suggesting an active interference from increased levels of prolactin. This association was found to be significant in systemic lupus erythematosus, rheumatoid arthritis, and peripartum cardiomyopathy. Furthermore, treatment with bromocriptine has shown beneficial effects specially among systemic lupus erythematosus patients. In this review, we attempt to provide a critical overview of the link between prolactin, autoimmune diseases, and motherhood, emphasizing whether breastfeeding should be avoided among women, both with diagnosed disease or high risk for its development.

Keywords Autoimmunity · Breastfeeding · Multiple sclerosis · Prolactin · Rheumatoid arthritis · Sex hormones · Systemic lupus erythematosus · Systemic sclerosis

Introduction

Almost 30 years ago, the concept of the "mosaic of autoimmunity" was presented to the scientific community by Shoenfeld and Isenberg (1989), defining a multifactorial process in which genetic, environmental, immunological, and hormonal factors interact dynamically to engender autoimmune diseases [1]. More than 80 systemic and organ-specific autoimmune diseases have been identified so far, affecting around 5% of the Western countries population. The sexual dimorphic prevalence of autoimmunity represents one of the most alluring observations among the mosaic. Indeed, women have enhanced immune reactivity, larger antigen-presenting activity, and mitogenic responses. Besides, females present higher immunoglobulin levels, increased antibody production, and enhanced homograft rejection rate. Sex hormones are believed to be a mainstay of this asymmetry. The greater prevalence of autoimmunity among fertile women, disease onset/relapses during pregnancy, and postpartum are some of the points that support this theory. Undeniably, motherhood represents one of the most remarkable challenges for the immune system that not only has to allow the conceptus, which is likened to an allograft, but also deal with extraordinary hormonal alterations [2]. In the last two decades, growing evidence has demonstrated crucial interactions between neurologic and endocrine systems, in order to promote immunologic homeostasis. Prolactin has a recognized immune-stimulatory effect,

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mainly inhibiting the negative selection of autoreactive B lymphocytes. In accordance, hyperprolactinemia has been associated with several autoimmune diseases, interfering with its pathogenesis. In this review, we attempt to provide a critical overview of the link between prolactin, autoimmune diseases, and motherhood, emphasizing whether breastfeeding should be avoided among women, both with diagnosed disease or high risk for its development.

Motherhood, sex hormones, and the immune system

Sex hormones, such as prolactin, estrogens, and progesterone, can influence different aspects on the immune system function. Generally, estrogens and prolactin act as immune stimulants, while testosterone and progesterone play a suppressive role. Normal pregnancy is associated with extraordinary changes in the endocrine and immune signaling required to tolerate and support the development and survival of the placenta and fetus in the hostile maternal immune system environment. Maternal adaptations to pregnancy are largely mediated by the placenta, which represents a functional interface between the mother and fetus that secretes hormones and growth factors into the mother with physiological effects [3]. One of the most important immunologic adaptations is the shift, at implantation, from a Th1/Th17 pro-inflammatory response towards a Th2/Treg cell response (Fig. 1), which promotes tolerance and inhibits natural killer cell cytotoxicity [4]. Likewise, maternal circulating leukocytes, T lymphocytes, granulocytes, and monocytes increase during, while the expression of major histocompatibility complex class II by circulating monocytes is reduced, in order to prevent the maternal unwanted response against fetal antigens [5]. Close to parturition, the maternal immune system shifts to a pro-inflammatory state to promote labor [6]. Consistent with the effects of sex hormones in the immune system, alterations in the activity of several autoimmune diseases are observed during pregnancy and postpartum. In the last years, a growing interest on the immune-modulatory effects of prolactin has been seen. This molecule is an integral member of the immune-neuro-endocrinology chain and has been related with autoimmune diseases for a long time.

Prolactin, the hormone, and the cytokine

Prolactin is a peptide hormone generated in the pituitary gland, under tonic inhibition of the hypothalamus, via dopamine. Cytokines like interleukin (IL)-1, IL-2, and IL-6 stimulate its secretion, while endothelin-3 and interferon-γ play an inhibitory influence. Despite all, the pituitary gland is not the unique source of prolactin, since it can be produced in various sites including neurons, skin, ovaries, placenta, endometrium, mammary epithelium, prostate, and immune cells. When produced in extra-pituitary locations, prolactin has different molecular weight and biologic activity. Due to variations in post-translational modifications, prolactin exists in several isoforms, which have different receptor binding. The prolactin receptor is a member of the type 1 cytokine/hematopoietic

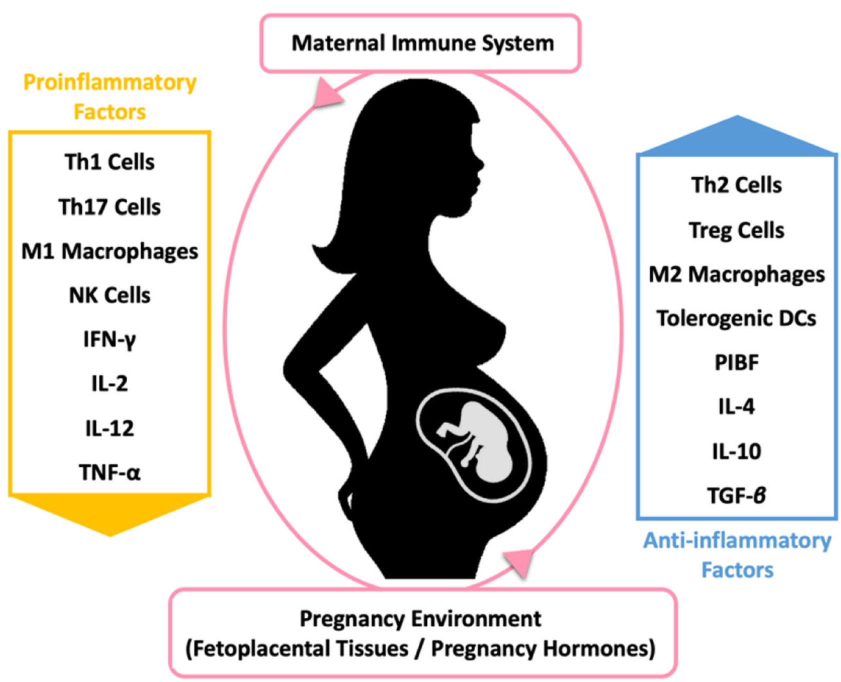

Fig. 1 Maternal immunologic adaptations during pregnancy

receptor super-family and is widely expressed through the immune system, including monocytes, lymphocytes, macrophages, natural killer cells, granulocytes, and thymic epithelial cells [7]. Binding of prolactin to its receptor activates downstream signaling pathways that will manipulate immune cell proliferation, differentiation, secretion, and survival.

Prolactin and immune modulation

Prolactin exerts a great influence on the innate and adaptive immune response, regulating the maturation of CD4-CD8-thymocytes to CD4+ CD8+ T cells, through IL-2 receptor expression. Interestingly, there is a correlation between prolactin levels and the number of B and CD4+ T lymphocytes. In addition, elevated serum levels of prolactin impair B cell clonal deletion, deregulate receptor editing, and decrease the threshold for activation of anergic B cells, promoting aberrant reactivity [8]. Prolactin also enhances immunoglobulin production and encourages the development of antigen-presenting cells expressing MHC class II and co-stimulatory molecules, including CD40, CD 80, and CD86 [9]. Likewise, prolactin changes Th1 and Th2 type cytokine production, regulates IL-6 and INF-γ production and influences IL-2 levels [10]. Moreover, a variety of auto-antibodies, such as anti-prolactin, anti-cardiolipin, anti-Ro, and anti-La, were detected in patients with hyperprolactinemia [11]. Dendritic cells are also influenced to skew antigen presentation to pro-inflammatory function phenotype, increasing interferon-α secretion.

Prolactin, pregnancy, and breastfeeding

Prolactin plays a major role on pregnancy-stimulated neurogenesis of the mother brain, regulating behavior and promoting maternal adaptation to offspring. The PRL-GH family is one of the main families of hormones secreted by the placenta. The family members share structural similarity to one another and may bind, with varying affinity to prolactin and growth hormone receptors, which are widely expressed in the human body. Interestingly, on the human fetal membranes, prolactin plays a selective immuno-modulatory effect upon pro-inflammatory response, downregulating secretion of TNF-α and IL-1β simultaneously on the maternal-fetal interface, while maintains levels of IL-10 unmodified [12]. Maternal serum levels slightly increase during pregnancy and reach peak values on delivery, probably, due to growing serum concentrations of estradiol. Besides, the inhibitive effect of placental steroid hormones on prolactin disappears shortly after the separation of the placenta, thereby triggering the onset of milk synthesis [13]. During the lactation period, plasma levels of prolactin are markedly increased. Suckling stimulates the nerve endings in the nipple-areolar complex and strongly promote hormone release. Stuebe et al. (2015) performed a large study to evaluate prolactin levels in women who exclusively breastfed their infants. The authors successfully demonstrated a wide changing baseline values for prolactin (from 9 ng/dl before breastfeeding and 74 ng/dl 10 min after), depending on the feeding frequency [14]. In addition, stress of any kind has been proven to raise serum levels of prolactin, which are more evident among women, presumably due to higher estradiol levels on the lactotrophic cells. Interestingly, prolactin receptors have been found in the choroid plexus of the sub-ventricular zone, one of the neurogenic areas of the adult forebrain, and its believed to play a crucial role in parental neurogenesis, contributing to adaptive behaviors observed while expecting.

Hyperprolactinemia and autoimmune diseases

The prolactin gene is located on the short arm of chromosome 6, near the HLA-DRB1 region. Genetic studies have demonstrated the strong association between HLA-DRB1 polymorphisms and several autoimmune diseases, such as systemic lupus erythematosus, rheumatoid arthritis, and Sjögren syndrome [15]. Likewise, studies have risen the possibility that extended haplotypes encoding for HLA-DRB1 and high prolactin production might enhance the susceptibility of developing autoimmune diseases. The expected rate of hyperprolactinemia among healthy population is up to 3%. The highest levels occur physiologically during lactation, but also as result of several diseases, including prolactinoma, hypothyroidism, and adrenal insufficiency. In addition, high prolactin levels have been documented in several autoimmune diseases, frequently influencing disease development and perpetuation [16]. During pregnancy and postpartum, women with diagnosed autoimmune diseases or high susceptibility to develop them face a great challenge to maintain the equilibrium among assorted pieces of the mosaic (Table 1). Nonetheless, the growing scientific development seen in the past few decades has allowed to reachprogressively better outcomes in young women affected by autoimmune disorders [26, 27].

Prolactin and systemic lupus erythematosus

Systemic lupus erythematosus is an autoimmune disease primarily affecting young women at reproductive age, with a ratio of 9:1 when compared to men. High levels of prolactin have been detected in 15–33% of systemic lupus erythematosus patients, from both genders. The association between hormone titers and disease activity or organ involvement remains controversial, probably due to different bioactivity displayed by the prolactin isoforms [28]. Despite all, more recent studies support a significant association between prolactin levels and the disease clinical and serological activity [29].

Table 1 Influence of prolactin on autoimmune diseases and breastfeeding considerations

Disease	Relation between prolactin and disease activity	Breastfeeding	Comments
Systemic lupus erythematosus	Significant	Avoid	Prolactin is correlated with neurological, hematological, renal involvement, serositis, low complement and high anti-double-stranded DNA antibodies, lupus anticoagulant, and poor outcomes during pregnancy [17, 18, 19].
Anti-phospholipid syndrome	No association	To be further investigated	Prolactin is correlated with the presence of lupus anticoagulants, intrauterine growth retardation, and miscarriages [20].
Rheumatoid arthritis	Controversial	Avoid	The risk of developing rheumatoid arthritis is increased in women who breastfeed after the first pregnancy and around 90% will flare within the first 3 months postpartum [21, 22].
Systemic sclerosis	Controversial	To be further investigated	The pregnancy per se does not exacerbate the disease [23, 24].
Multiple sclerosis	No association	Encouraged	Prolonged lactational amenorrhea was associated with a fourfold decreased risk of postpartum relapses [25].
Peripartum cardiomyopathy	Significant	Avoid	Increased oxidative stress and subsequent generation of prolactin impairs the cardiac vasculature and metabolism, leading to systolic heart failure [26].

Hyperprolactinemia was correlated with neurological, hematological, and renal involvement, serositis, low complement, and high anti-double-stranded DNA antibodies [18]. Interestingly, high levels of prolactin and IL-6 were found to be present in the cerebrospinal fluid from patients with neuropsychiatric lupus. In animal models, prolactin was capable to induce the development of lupus-like phenotype in non-prone mice and exacerbate the disease in a lupus murine experimental study [30]. On the other hand, the presence of anti-prolactin antibodies was inversely correlated with lupus activity and correlates with better outcomes in pregnant lupus patients [31]. During pregnancy, hormones like estrogen and prolactin have crucial interactions with the immune system, amplifying the inflammatory effect that characterizes disease flairs. Hyperprolactinemia during the second and third trimester of pregnancy was associated with lupus anticoagulant, disease activity, and poor outcomes for mother and fetus [19]. The treatment of pregnant women with bromocriptine was shown to prevent disease relapses, improve outcomes, and reduce the doses of concomitant steroidal therapy [32]. A clinical trial performed by Jara et al. (2007) explored the role of bromocriptine during pregnancy of women with systemic lupus erythematosus. The patients were separated in two groups, one treated with prednisolone and the other treated with prednisolone plus bromocriptine. The prolactin levels were determined at 25, 30, and 35 weeks of gestation. The authors successfully demonstrated a significant decrease in prolactin levels among the group treated with bromocriptine. Also, those patients did not suffer disease relapse and had better outcomes [33]. In accordance, the treatment with bromocriptine for 2 weeks in postpartum patients with lupus showed benefits concerning to the protection against disease flairs and allowed lower steroid and immunosuppressant doses [32]. In conclusion, the evidence strongly supports the role of prolactin in the pathogenesis and activity of systemic lupus erythematosus. Therefore, breastfeeding should be avoided in order to prevent disease relapses. The treatment with bromocriptine during pregnancy and puerperium has shown clinical and serological benefits, improving maternal-fetal outcomes.

Prolactin and anti-phospholipid syndrome

Anti-phospholipid syndrome is a systemic autoimmune condition, characterized by thrombotic events and/or pregnancy morbidity in the presence of anti-phospholipid antibodies. Praprotnik et al. (2010) analyzed a large cohort, aiming to evaluate the impact of prolactin in the anti-phospholipid syndrome. When compared to healthy controls, subjects with anti-phospholipid syndrome presented significantly higher levels of prolactin. Hyperprolactinemia was detected in 12% of the patients, with no differences among genders or disease subtypes (primary or secondary). In addition, high levels of prolactin were shown to be correlated with the presence of lupus anticoagulants, intrauterine growth retardation, and miscarriages. Interestingly, no significant correlation with thrombotic events was found [20]. In the last years, several studies emerged reporting prolactin as a novel risk factor for thrombotic events, since it acts as a potent platelet aggregation co-activator [34]. Blank et al. (1995) explored the effect of bromocriptine in the development of experimental systemic lupus erythematosus and anti-phospholipid syndrome in animal models. The treatment had a suppressive effect on both diseases, probably downregulating autoimmune phenomena through induction of natural nonspecific CD8 suppressor cells. Since then, bromocriptine has been thought to be a promising treatment for this disease, although, evidence in human models is still scarce in the literature.

Prolactin and rheumatoid arthritis

Rheumatoid arthritis is a chronic autoimmune disease, which is characterized by pain, swelling, and stiffness of the joints due to synovial inflammation that if untreated leads to progressive and irreversible destruction of cartilage and bone. The relationship between prolactin and rheumatoid arthritis was denoted due to the location of the human prolactin gene on chromosome 6 close to the HLA region [35, 36]. Previous clinical trials have demonstrated high levels of prolactin, both in serum and synovial fluid of patients with rheumatoid arthritis, probably due to an enhanced systemic secretion or increased prolactin production by immune cells, such as macrophages, suggesting a correlation with disease activity [37]. In contrast, some studies fail to confirm such association. While expecting, about 65% of rheumatoid arthritis patients experience disease improvement, likely due to a transient period of hypercortisolism. In the postpartum period, disease relapses are often seen. The risk of developing rheumatoid arthritis is increased in women who breastfeed after the first pregnancy, suggesting an immune stimulation from prolactin. Almost 90% will flare within the first 3 months postpartum and nearly all patients will flare by 9 months. Jorgensen et al. (1996) performed a large study to evaluate the impact of pregnancy and breastfeeding in women with rheumatoid arthritis, and successfully found that parity, duration of breastfeeding, and number of breast-fed children were significantly increased in women with severe disease. Indeed, those with more than 3 children had a 4.8-fold increased risk of developing severe disease, and those with more than 3 breastfed children had a 3.7-fold increased risk for poor disease prognosis. In addition, 46% of patients with severe disease had a history of breastfeeding for a duration greater than 6 months before disease onset, compared with 26% of patients with mild rheumatoid arthritis ($p < 0.008$) [38]. Furthermore, in animal models, bromocriptine was able to suppress postpartum exacerbation of collagen-induced arthritis [39]. In humans, the treatment with bromocriptine obtained controversial results, probably because this medication does not affect lymphocyte-derived prolactin secretion. Current literature is scarce and not conclusive when relating prolactin and rheumatoid arthritis. Systemic secreted and locally produced prolactin may offer distinct contributions to inflammatory arthritis. In addition, the use of bromocriptine has not been reported in pregnant patients with rheumatoid arthritis. Despite all, the association between breastfeeding and disease onset and relapses has been reported in several studies; therefore, women with recognized susceptibility or diagnosed disease might benefit from avoiding nursing.

Prolactin and systemic sclerosis

Systemic sclerosis is a connective tissue disease characterized by alterations of the microvasculature, disturbances of the immune system, and massive deposition of collagen and other matrix substances in the skin and internal organs. Hyperprolactinemia has been described in 13–59% of patients with systemic sclerosis. In addition, there is significant correlation between the hormone levels and the severity of skin sclerosis, cardiovascular, and lung involvement [40]. The sources of hyperprolactinemia in systemic sclerosis patients include increased dopaminergic tone, lymphocyte secretion, and drugs. Women with systemic sclerosis can achieve successful pregnancies, although they have higher risk of fetal complications, mainly due to skin fibrosis. Patients with disease duration of less than 4 years, with diffuse cutaneous subtype, presence of anti-RNA polymerase III, or anti-topoisomerase I antibodies are at higher risk for obstetric complications and should delay pregnancy until the disease is quiescent. The pregnancy per se does not exacerbate the disease, even though women with organ insufficiency mainly pulmonary hypertension should avoid pregnancy due to an elevated risk of hemodynamic complications. In conclusion, prolactin was found to be correlated with disease activity and severity. Despite all, there is no data available advancing prolactin as a promising target in the treatment of this disease, nor discussing whereas women should avoid breastfeeding.

Prolactin and multiple sclerosis

Multiple sclerosis is a chronic inflammatory disorder of the central nervous system characterized by the presence of multifocal areas of immune cell infiltration, demyelination, and axonal damage mainly located in the white matter. In animal models, it is represented by experimental autoimmune encephalomyelitis, believed to be an inflammatory response against oligodendrocytes that form myelin sheath surrounding neuronal axon driven by myelin-reactive CD4+ Th1/Th17 cells [41]. In 1983, Nagy et al. revealed a clinical improvement of experimental autoimmune encephalomyelitis following treatment with bromocriptine [42]. Since then, various studies support the benefits of bromocriptine on animal models. Despite all, controversial results have been obtained while exploring hyperprolactinemia and multiple sclerosis in humans. Indeed, the source of high prolactin levels among those patients is unclear, albeit observations suggest it may be part of a nonspecific hypothalamic–pituitary–adrenal axis dysregulation, due to demyelination and/or neurodegeneration. Assorted trials have demonstrated a positive correlation between hyperprolactinemia and disease onset, recurrence, and with the number of anti-myelin oligodendrocyte glycoprotein antibody secreting cells [43], although treatment with bromocriptine showed no efficacy in reducing disease activity. Historically, it was believed that pregnancies could be harmful to women with multiple sclerosis by causing severe postpartum exacerbations or increasing the risk of long disability. Nowadays, it is known that the risk of relapse significantly declines during pregnancy, particularly during the third trimester, only to increase threefold in the first 3–4 months postpartum. A recent meta-analysis reported that women who breastfed were almost half as likely to experience a postpartum disease relapse, even though the use of disease modification therapies represents a strong confounder [44]. Further, Hellwig et al. (2015) performed a large, prospective cohort study of pregnant women with multiple sclerosis who intended to breastfeed their newborns. The authors reported that an earlier return of menses was associated with a higher risk of relapse in the first 6 months postpartum, which suggests that exclusive breastfeeding acts like a treatment with a natural end date [45]. In accordance, biological studies in healthy women have demonstrated that high frequency and intense sucking maintain hyperprolactinemia and low luteinizing hormone levels. Prolonged lactational amenorrhea was associated with a fourfold decreased risk of postpartum relapses [25]. No studies have examined the long-term effect of breastfeeding, particularly exclusive breastfeeding. Taken together, these findings suggest that it is plausible that exclusive breastfeeding could lead to decreased disease activity, although it is unknown if it is due to prolactin levels or the influence of amenorrhea in cytokine production. Definitely, the protective impact of breastfeeding behavior on multiple sclerosis deserves further investigations.

Prolactin and peripartum cardiomyopathy

Peripartum cardiomyopathy is a life-threatening disease defined by heart failure towards the end of pregnancy or in the months following delivery, affecting previously healthy women. The etiology of this disease is unknown, although putative mechanisms have been proposed, such as viral infections, low selenium level, stress-activated cytokines, inflammation and autoimmune reactions, and a pathological response to hemodynamic stress [46]. Several studies successfully demonstrated an active role of prolactin in the pathophysiology of peripartum cardiomyopathy. Increased oxidative stress and subsequent generation of 16 kDa prolactin impair the cardiac vasculature and its metabolism, finally culminating in systolic heart failure [47]. Recently, Haghikia et al. (2015) identified the presence of auto-antibodies against troponin I and sarcomeric myosin in the serum of patients with peripartum myocardiopathy, supporting the possibility of an underlying autoimmune disorder. Furthermore, the presence of these antibodies was positively correlated with the severity of left ventricle dysfunction and lower rate of full cardiac recovery on follow-up [48]. In addition, patients demonstrated a heightened level of fetal microchimerism, an abnormal cytokine profile (increased levels of TNF, IL-6, and soluble Fas receptors), decreased levels of CD4+ CD25lo regulatory T cells, and a significant reduction in the plasma levels of progesterone, estradiol, and relaxin, contributing to aberrant immunologic activities and the inflammatory process. In the last years, several studies emerged using dopamine agonists in the treatment of this disease, with great results so far [49, 50]. The 2010 European position statement advises against breastfeeding based on the concern for propagating the pathogenic prolactin pathway by continual stimulation of prolactin release.

Conclusions

The great asymmetry between genders in autoimmune diseases is believed to rely on sex hormones. Prolactin has a recognized immune-stimulatory effect, promoting autoreactivity and it was found to be implicated in the pathogenesis of several autoimmune diseases. Interestingly, it has also been associated with disease relapses during pregnancy and lactation period, mainly among systemic lupus erythematosus, rheumatoid arthritis, and peripartum cardiomyopathy patients. Immunological studies of pregnant and postpartum women with autoimmune diseases offer a biologically rich opportunity to improve our understanding of the hormonal impact on the disease relapse pathophysiology. Improving our understanding on the intricate relationship between prolactin and autoimmunity during pregnancy and breastfeeding could allow new strategies for the management of these patients.

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Compliance with ethical standards

Disclosures None.

Abbreviations HLA, Human leukocyte antigen; IL, Interleukin; IFN, Interferon; MHC, Major histocompatibility complex; PIBF, Progesterone-induced blocking factor; PRL-GH, Prolactin-growth hormone; RNA, Ribonucleic acid; Th, T helper cells; TGF, Transforming growth factor; TNF, Tumor necrosis factor; Treg, T regulatory cells

Highlights

a) Sex hormones, such as prolactin, are believed to be a mainstay of the genders asymmetry in autoimmune diseases.

b) Prolactin has a recognized immune-stimulatory effect, mainly inhibiting the negative selection of autoreactive B lymphocytes, promoting autoimmunity.

c) During the pregnancy and lactation period, assorted autoimmune patients experience disease relapse, suggesting an active influence of prolactin.

d) A significant association between prolactin and disease flairs was found in systemic lupus erythematosus, rheumatoid arthritis, and peripartum cardiomyopathy patients; therefore, breastfeeding should not be encouraged.

e) Exclusive breastfeeding could lead to decreased disease activity among multiple sclerosis patients.

f) Bromocriptine acts as an immunosuppressant of autoimmune phenomena via induction of natural nonspecific CD8 suppressor T cells and has shown beneficial effects specially among systemic lupus erythematosus patients.

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