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Endocrine Manifestations of Systemic Lupus Erythematosus

*Ifigenia Kostoglou-Athanassiou, Lambros Athanassiou
and Panagiotis Athanassiou*

Abstract

Systemic lupus erythematosus (SLE) is a systemic autoimmune disease affecting all organ systems. It affects primarily female patients in the reproductive age. The disease has a variable course from very mild to severe and may be fatal. It is characterized by exacerbations of disease activity called flares. Estrogens seem to be involved in SLE pathogenesis as they have multiple immunomodulating properties. In SLE the autoimmune process affects the neuroendocrine axis. Stress modulates disease expression in lupus patients. The disease affects the endocrine system. Hypothyroidism occurs in SLE patients in a higher rate than that of the general population. Hyperthyroidism is also observed in SLE, however, in the rate expected for the general population. Hashimoto's thyroiditis is observed in SLE in a higher rate than that of the general population. Hyperparathyroidism is also observed in SLE, primary and secondary in the context of renal insufficiency due to lupus nephritis. Addison's disease is rare in SLE. Cushing's disease due to an adrenal adenoma has been observed, but it is rare. Ovarian function may be compromised in SLE, due to autoimmune oophoritis or drug toxicity. The recognition of endocrine disease in SLE is important as it may guide proper management and symptom amelioration.

Keywords: systemic lupus erythematosus, estrogens, neuroendocrine axis, stress, hypothyroidism, hyperthyroidism, Hashimoto's thyroiditis, hyperparathyroidism, ovarian function

1. Introduction

Systemic lupus erythematosus (SLE) is a systemic autoimmune disease affecting all organ systems [1]. It affects mainly joints, skin, blood vessels, heart, lung, kidneys, liver and the nervous system [2]. It is the prototype of systemic autoimmune diseases. In patients with SLE the immune system attacks tissues and cells leading to inflammation and damage [3]. The course of SLE is variable, and maybe either mild or severe leading sometimes to fatal damage and death [4]. The disease is characterized by periods of exacerbation, which are called flares and periods of remission [5]. SLE occurs nine times more often in the female gender mainly in the reproductive age, and it is more frequent in people of non-European descent [6]. Different types of autoantibodies are present in SLE patients [7]. The B lymphocyte is believed to play a major pathogenic role in the disease and many different autoantibodies are detected, therefore the disease is classified as a "B-cell disease" [8, 9]. However, T lymphocytes also play a role in the immunopathogenesis of SLE [10]. Because of the presence of

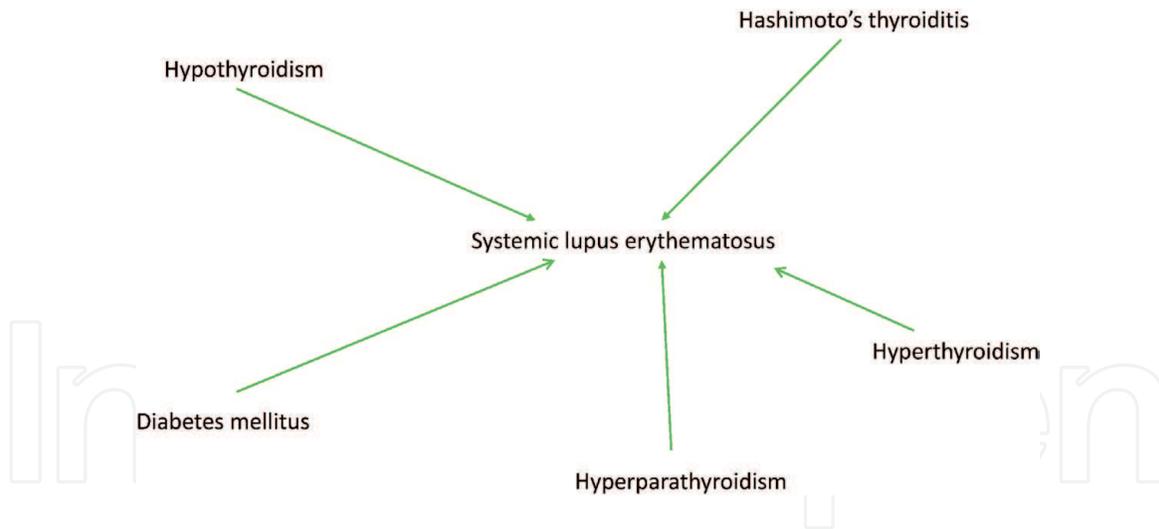


Figure 1.
Common endocrine disorders in systemic lupus erythematosus.

many different autoantibodies, SLE is classified as a “B-cell disease.” Patients with SLE present with symptoms and inflammatory involvement that can affect virtually every organ [11]. The main features of SLE include the production of antinuclear antibodies and the deposition of immune complexes in basement membranes throughout the body where they induce an inflammatory response [12, 13]. Genetic, epigenetic, and environmental factors contribute to the development of this autoimmune process. Endocrine manifestations as expected also occur in patients with systemic lupus erythematosus [14] (**Figure 1**). Hypothyroidism has been observed in a higher rate than that expected in the general population. Hyperthyroidism has also been observed. Autoimmune Hashimoto’s thyroiditis has been observed in a higher rate than that expected in the general population. Graves’ disease has been observed in patients with SLE. Hyperparathyroidism has been observed in patients with SLE, mainly in the context of lupus nephritis. Hypoparathyroidism has also been observed. Autoimmune oophoritis leading to ovarian failure has been observed in patients with SLE. Despite the multisystem nature of the disease, it appears that it respects the adrenals, so that Addison’s disease is extremely rare in SLE.

2. The neuroendocrine axis in systemic lupus erythematosus

SLE is a systemic autoimmune disease characterized by a loss of self-tolerance [15]. The immune system is activated in the disease and pro-inflammatory cytokines are secreted [16]. The immune system and the neuroendocrine system are interconnected [17]. The two systems interact in a bidirectional manner (**Figure 2**). During the autoimmune inflammatory response cytokines released from immune cells affect the neuroendocrine axis [18, 19]. In turn the neuroendocrine system secretes hormones which modulate the immune response [20].

The main target of activation by cytokines is the hypothalamic–pituitary–adrenal (HPA) axis. Interleukin (IL) -1a and -1b, IL-6 and tumor necrosis factor (TNF)-a, which are released sequentially from macrophages upon activation, are powerful activators of the HPA axis. In vitro studies in isolated hypothalamic tissue have shown the ability of IL-1a, IL-1b, IL-6, IL-8 and TNF-a to initiate the release of corticotropin-releasing hormone (CRH) [21, 22]. In humans, a blunted HPA axis response to stimulation with hypoglycemia or CRH was shown in several autoimmune diseases, including rheumatoid arthritis, Sjogren’s syndrome, fibromyalgia and SLE [23]. However, the relationship between HPA axis reactivity

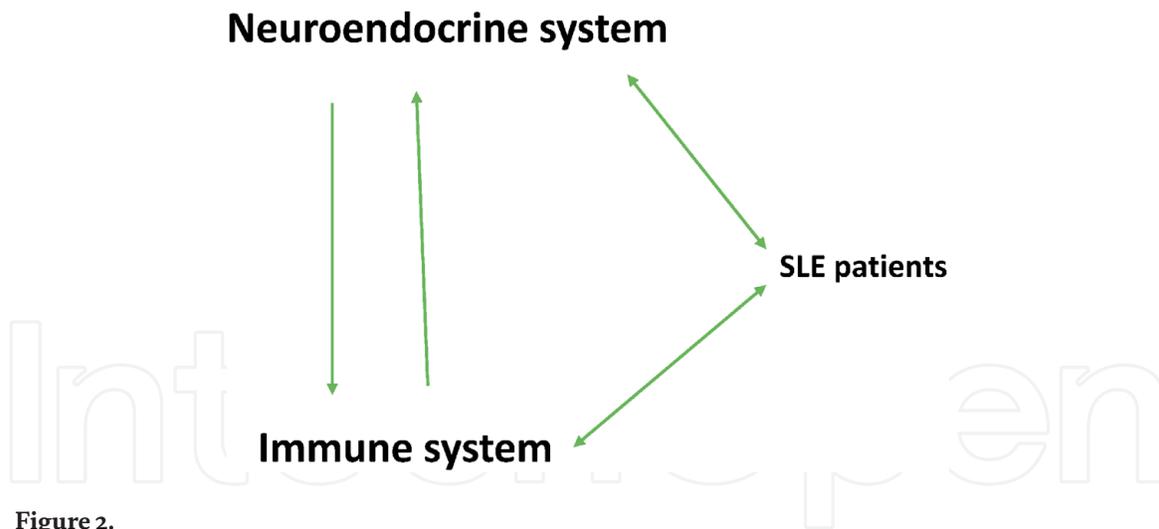


Figure 2.
The interaction between the neuroendocrine and immune systems in systemic lupus erythematosus.

and inflammatory disease was challenged by experiments which showed that in high-stress situations, rats who had a robust corticosterone-response to stress developed more severe inflammation than rats who had a less profound corticosterone response [24]. Differences in the HPA axis response to stress may discriminate patients who seem to have the same disease, but may have different responses to treatment [25]. The HPA axis is important in regulating disease severity in SLE. However, the development of the disease may alter the HPA axis response.

Prolactin (PRL) is a peptide hormone produced by the anterior pituitary. PRL can be produced by lymphocytes, which in turn express PRL receptors [26, 27]. Thus, PRL may have immunomodulatory functions [27–29]. Increased PRL levels have been observed in male and female patients with lupus [30, 31]. Furthermore, suppression of PRL secretion with bromocriptine provides beneficial effects in murine lupus and possibly in lupus patients [32]. Treatment with PRL breaks tolerance and induces a lupus like illness in autoimmune mice. PRL is in effect also a cytokine [29]. PRL receptors are distributed in the immune system [33]. Mild and moderate hyperprolactinemia has been demonstrated in 20–30% of SLE patients and was associated with active disease. Hyperprolactinemia may have a role in lupus nephritis and CNS involvement of patients who have SLE [34]. Elevated PRL levels were associated with increased disease activity in SLE and prolactin may have a pathogenic role in SLE [35]. Thus, PRL, a peptide hormone derived from the anterior pituitary gland and lymphocytes participates in the regulation of the immune response, stimulates immune cells and belongs to a network of immune endocrine interaction. Hyperprolactinemia has been found in SLE and PRL may participate in SLE activation during pregnancy [35]. High levels of prolactin may lead to the development or the exacerbation of an autoimmune disease such as SLE [36]. Prolactin is a bioactive hormone acting both as a hormone as well as a cytokine and it may act as an immunomodulator affecting the negative selection of autoreactive B lymphocytes [29].

2.1 Stress and systemic lupus erythematosus

The adrenergic nervous system runs from the CNS to lymphoid organs, namely the thymus, spleen and lymph nodes. Its effects are mediated by noradrenaline which acts through the relevant receptors [37]. Noradrenaline receptors are expressed by immune cells, namely T and B lymphocytes and macrophages [38]. Noradrenaline and adrenaline stimulate IL-10 and transforming growth factor- β production, thus enhancing Th2 immunity [39, 40]. In SLE, a disease driven by

excess IL-10, disease activity may increase during states of high catecholamine release, such as acute stress. In a prospective study of patients with SLE, disease flares were associated with emotional stress or with the number or severity of daily stressors [41, 42]. Additionally, the effect of acute psychological stress induced differential immune response in SLE patients as compared to controls [43].

The hypothalamic–pituitary–adrenal axis responds to inflammatory cytokines [44]. It has been demonstrated that inflammatory cytokines, such as IL-1a and IL-1b, IL-6 and TNF-a are powerful activators of the hypothalamic–pituitary–adrenal axis [45, 46]. In SLE patients with central nervous system involvement elevated levels of inflammatory cytokines were observed in the cerebrospinal fluid [47] suggesting an involvement of these inflammatory cytokines in disease pathogenesis.

2.2 Estrogens in the pathogenesis of systemic lupus erythematosus

SLE is a disease affecting primarily female patients in the reproductive age [48]. Evidence exists implicating estrogens in the pathogenesis of SLE [49]. An extensive cross-talk takes place between estrogen and the immune system. Estrogens are a major modulating factor of the immune response [50] (**Figure 3**). Epidemiological evidence implicates estrogens in the pathogenesis of SLE, as during childhood where estrogen secretion is minimal the female: male ratio is 3:1 as opposed to 9:1 in the reproductive age. In the postmenopausal period the ratio is 8:1 [51]. Evidence has shown that women with early menarche, or treated with oral contraceptives or hormone replacement therapy have an increased risk for SLE [52, 53]. The presence of the X chromosome appears also to be important for the pathogenesis of SLE. There appears to be a gene dose effect, as the prevalence of SLE in Klinefelter's syndrome (XXY) is 14-fold that in the general male population, whereas it is decreased in female patients with Turner's syndrome (XO) [54]. Pregnancy, in which the concentration of estrogens is extremely increased can cause a disease flare or even trigger the development of lupus [55, 56]. The puerperium is characterized by an increased risk for disease relapse [57]. Hormonal factors used for ovulation induction and in vitro fertilization may cause disease flare in SLE [52].

The main pathophysiologic processes of SLE are the loss of self-tolerance and the production of autoantibodies with consequent inflammatory response and organ injury [15]. Estrogens are capable of inducing these alterations in the immune system. Treg cells, immunosuppressive regulatory T cells, play an important role in the maintenance of self-tolerance and the prevention of autoimmunity. SLE

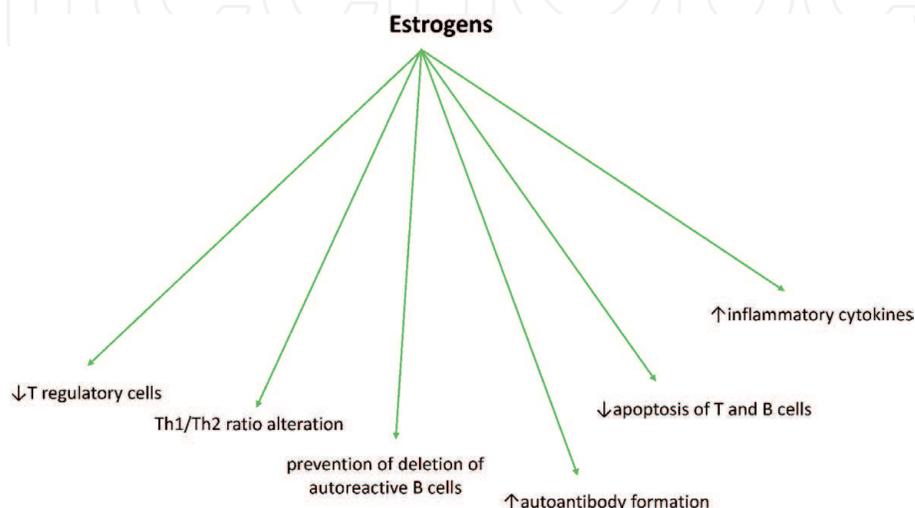


Figure 3.
The effect of estrogens on the immune system.

patients have decreased numbers of Treg cells. Estradiol diminishes Treg cells [52, 58, 59]. In SLE, there is a switch from a type 1 (Th1) to a type 2 (Th2) T cell response where serum levels of Th2 cytokines, such as interleukin 4 (IL-4), IL-6, and IL-10, are elevated and there is decreased production of Th1 cytokines, such as IL-2 and interferon γ [60–62]. Estrogens alter Th1/Th2 ratio thus altering the balance between cellular and humoral immunity. Estrogens induce the development of Th2 lymphocytes and B cell hyperactivity leading to enhanced antibody production [63]. Estrogens promote the life span of lymphocytes by decreasing apoptosis of T and B cells [64]. Thus, estrogens seem to play a key role in the development of autoimmunity. They suppress self-tolerance reducing Treg cells [65]. They alter the Th1/Th2 ratio, favoring the predominance of humoral immunity. They prevent the deletion of autoreactive B cells [66]. They induce the generation of autoantibodies and they stimulate the production of inflammatory cytokines [67].

3. Endocrine disorders in systemic lupus erythematosus

3.1 Thyroid disease in SLE

Autoimmune thyroid disease has been observed in patients with systemic lupus erythematosus, such as autoimmune Hashimoto's thyroiditis, hypothyroidism and Graves' disease.

3.1.1 Hypothyroidism

Hypothyroidism is observed in patients with SLE in a higher rate than in the normal population. In particular, Munoz and Isenberg [14] reported a rate of 5.22% hypothyroidism, i.e. 37 patients, in their cohort of 708 patients with SLE in University College of London Hospital, as compared to 1–2% in the general UK population. In this cohort the onset of hypothyroidism occurred after the onset of SLE oftener. Other reports confirmed a higher than in the general population rate of hypothyroidism in SLE. In particular, Ong and Choy [68] in a Malaysian population of SLE patients observed a prevalence of hypothyroidism of 3.7%. Antonelli et al. [69] reported a prevalence of hypothyroidism of 4.5%. In an earlier report from the University College of London Hospital SLE cohort Pyne and Isenberg [70] reported a prevalence of hypothyroidism of 5.7%.

3.1.2 Hyperthyroidism

Hyperthyroidism is observed in patients with SLE. In their cohort of 708 patients with SLE Munoz and Isenberg [14] observed a prevalence of hyperthyroidism of 1.41% (10/708 SLE patients), similar to that in the general population [71]. Watad *et al* [72] and Ong *et al* [68] reported a prevalence of hyperthyroidism in SLE patients of 2.59% and 2.6%, respectively. Chan *et al* [73] observed a prevalence of 5.8% of hyperthyroidism in a study of 69 SLE patients. However, only 2.9% had a clinical hyperthyroidism.

3.1.3 Autoimmune Hashimoto's thyroiditis

Autoimmune Hashimoto's thyroiditis is frequently observed in patients with SLE. The prevalence of Hashimoto's thyroiditis in patients with SLE as opposed to control subjects was investigated in a study [74]. The association of Hashimoto's thyroiditis and anti-thyroid antibodies to the clinical, serological

profile and disease activity as well as cumulative organ damage in this group was also investigated. In a group of 301 SLE patients and 141 controls TSH levels, T4 levels, antiTg antibodies and antiTPO antibodies were measured by chemiluminescence and immunometric methods. The serological and clinical profile of the patients was reviewed. SLE disease activity was measured using the SLEDAI index. The prevalence of Hashimoto's thyroiditis was 12.6% in SLE as opposed to 5.6% in controls, the difference being statistically significant. A lower prevalence of malar rash and a higher prevalence of anti-Sm was noted in lupus patients with Hashimoto's thyroiditis. No association was noted between Hashimoto's thyroiditis and disease activity or cumulative organ damage. In conclusion, a two-fold increased risk of Hashimoto's thyroiditis was noted in lupus patients. In a study performed in China 63 cases of lupus patients who also had Hashimoto's thyroiditis were studied [75]. Lupus patients were classified in four groups, those in remission, those with low disease activity, those with moderate and those with high disease activity. Free T3 levels were found to be negatively correlated with disease activity. In an effort to find a way to treat effectively Hashimoto's thyroiditis and SLE a group of scientists [76] injected human amniotic epithelial cells in murine models of Hashimoto's thyroiditis and SLE. They observed that levels of antiTg, antiTPO antibodies and TSH levels decreased as well as evidence of tissue destruction within the thyroid decreased. Additionally, the injection of human amniotic epithelial cells induced the disappearance of anti-dsDNA antibodies and ANA in mice with SLE and improved immunoglobulin profiles. It downregulated the ratio of Th17/Treg cells in both Hashimoto thyroiditis and SLE mice and upregulated the proportion of B10 cells. Human epithelial amniotic cells suppressed the levels of pro-inflammatory cytokines, IL-17A and IFN- γ and enhanced TGF- β in the murine models of Hashimoto's thyroiditis and SLE, thus suggesting a common pathogenic substrate in both diseases.

3.1.4 Graves' disease

Graves' disease is a systemic autoimmune disease with multiple manifestations, affecting the thyroid, the eyes and the skin [77]. Cases of Graves' disease have been described in patients with SLE [78]. The case of a patient with Graves' disease who later developed SLE has been described in the literature [79].

3.2 Pancreatic dysfunction in SLE pathogenesis and form

3.2.1 Diabetes mellitus 1

Cases of diabetes mellitus 1 have been described in SLE. In a cohort of SLE patients in the UK the prevalence of diabetes mellitus 1 was investigated [80]. The coexistence of diabetes mellitus 1, SLE and celiac disease has been described in a young female patient [81]. It appears that diabetes mellitus 1 is rare among SLE patients. However, the risk of developing renal disease, retinal disease and peripheral neuropathy requires careful follow up of the patients. It is also important for the physician to decide which complication is due to lupus or diabetes as the management is different.

3.2.2 Diabetes mellitus 2

Diabetes mellitus type 2 is reported with increasing frequency nowadays [82]. Hence, diabetes mellitus 2 has been reported in patients with SLE. In their cohort of 485 SLE patients Cortes et al. [80] reported 4 patients with diabetes mellitus 2

and two considered to have steroid induced diabetes mellitus. Thus, it appears that diabetes mellitus 2 is infrequent within lupus patients. This may be due to the fact, that lupus develops in a younger age than diabetes mellitus 2 [14]. The relationship between SLE and gestational diabetes has been studied in a meta-analysis [83]. It was found that SLE does not seem to increase the risk of gestational diabetes. However, steroid use in SLE may increase the risk of gestational diabetes.

3.3 Parathyroid disease in SLE

3.3.1 Hyperparathyroidism

Primary hyperparathyroidism is frequently recognized nowadays due to the routine measurement of serum calcium levels. Primary hyperparathyroidism has been reported in patients with lupus. However, there are just a few case reports in the literature of patients with SLE and primary hyperparathyroidism. Primary hyperparathyroidism due to the presence of a parathyroid adenoma in a 47-year old female patient with SLE has been described [84]. Hypercalcemia resolved in this patient after removal of the adenoma. Primary hyperparathyroidism due to a cystic parathyroid adenoma has also been described in a 62-year old female patient with SLE [85]. In their cohort of 708 lupus patients Munoz and Isenberg [14] also identified 5 (0.70%) patients with hyperparathyroidism, 1 with primary hyperparathyroidism and 4 patients with secondary hyperparathyroidism in the context of chronic renal failure due to lupus nephritis. Hyperparathyroidism presented after lupus in all cases described.

3.4 Adrenal disease in SLE

3.4.1 Addison's disease

Addison's disease has been reported in patients with SLE. However, there are only a few case reports of Addison's disease in patients with SLE. The case of a 29-year old female patient who presented with Addisonian crisis in the presence of SLE and responded therapeutically to corticosteroids, both as far as Addison's and lupus is concerned has been described [86]. In their cohort of lupus patients Munoz and Isenberg [14] did not identify any patient with Addison's disease. It appears that Addison's disease is a rare occurrence in lupus patients.

3.4.2 Cushing's syndrome

The occurrence of Cushing's syndrome due to an adrenal adenoma in patients with SLE is rare. The case of an 18-year old female patient with subclinical Cushing's syndrome who developed lupus has been described [87]. The patient was successfully treated by surgical removal of the adrenal adenoma. A case of a 51-year old woman with SLE who developed Cushing's syndrome and was found to have a left adrenal adenoma has been described [88]. The patient was successfully managed by laparoscopic left adrenalectomy.

4. Ovarian function

Reproductive function of young female patients with SLE is commonly perturbed by various pathophysiologic mechanisms [89]. Ovarian reserve is diminished even in the presence of mild lupus suggesting a direct effect of the disease

itself on ovarian function [90, 91] (**Figure 4**). It is possible that the underlying process is autoimmune oophoritis [92–94]. The clinical manifestations of these abnormalities are menstrual irregularity, amenorrhea, or premature ovarian failure. Menstrual irregularities are frequently observed in patients with SLE, and many of them are associated with the activity of the disease [95]. SLE itself induces dysfunction in the hypothalamic–pituitary–ovarian axis and elevates serum prolactin [35, 96, 97]. A study compared the levels of anti–müllerian hormone (AMH) as a marker of ovarian reserve between SLE patients and control subjects and found that SLE patients had significantly lower AMH levels than did the control subjects. No correlation was observed between disease activity and AMH levels [91]. Female SLE patients may have subfertility issues due to active disease, the use of immunosuppressive medications and delayed childbearing [98]. These findings show that SLE itself has a negative influence on ovarian reserve and function.

SLE patients presenting with severe manifestations of the disease are treated with the alkylating agent cyclophosphamide [99, 100]. Cyclophosphamide is toxic to the ovaries [101–103]. SLE patients exposed to cyclophosphamide have a much higher risk of developing premature ovarian failure and infertility as compared to those receiving less toxic agents [91, 95, 104]. Cyclophosphamide leads to a decrease in reproductive life span and possibly premature ovarian failure. If the loss of ovarian function develops during or shortly after the completion of therapy, it is termed acute ovarian failure. For those who retain ovarian function after the completion of chemotherapy, a subset will go on to develop premature menopause before the age of 40 [105]. The clinical manifestations of ovarian damage in women at reproductive age vary from temporary irregular menses to amenorrhea, infertility, and premature ovarian failure depending on the magnitude of the damage. The probability of developing permanent ovarian failure depends on the following factors: patient’s age and the type, dose, and duration of the treatment. If the patient is older and her ovarian reserve is low, they are less likely to retain or regain menstrual function than younger ones. Studies have documented that cyclophosphamide administration is the most significant risk factor for ovarian failure and that AMH is a sensitive and reliable marker of ovarian reserve and damage after exposure to cyclophosphamide in female patients with SLE [106–108]. In the case of cyclophosphamide administration in lupus patients fertility preservation may be attempted [108]. Currently, embryo or oocyte freezing are the established methods used for fertility preservation in patients receiving gonadotoxic treatment [109–111]. Other

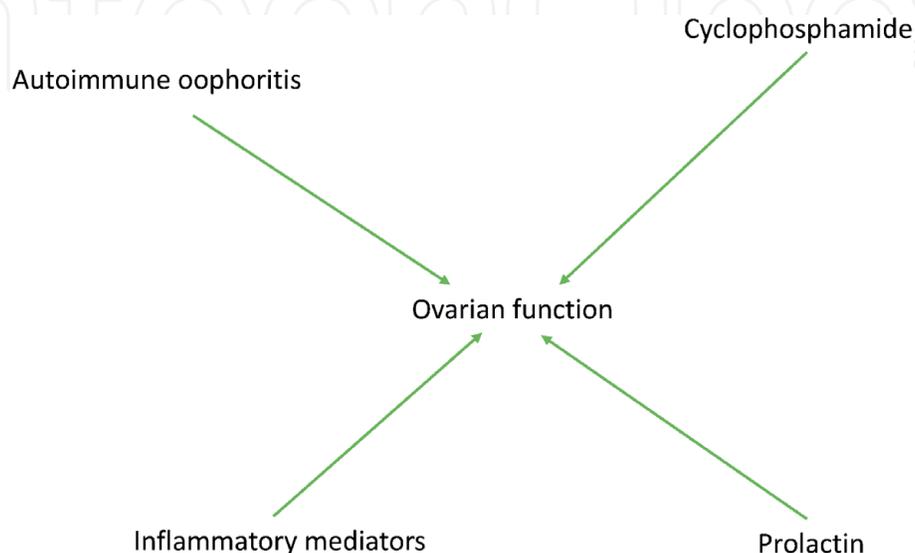


Figure 4.
Factors adversely affecting ovarian function in systemic lupus erythematosus.

options are ovarian tissue freezing and the use of gonadotropin-releasing (GnRH) hormone agonist treatment concurrently with chemotherapy [112, 113].

In conclusion, the reproductive function of female SLE patients can be adversely affected by various mechanisms such as, the chronic inflammatory state, autoimmune ovarian disease in the form of autoimmune oophoritis, lupus flares associated with hyperprolactinemia, which may interfere with ovulation and may modulate immune activity and temporary or even permanent premature ovarian failure as a result of the administration of cytotoxic agents such as cyclophosphamide.

5. Conclusion

SLE is a systemic autoimmune disease which affects all organ systems and occurs frequently in female patients in the reproductive period. Estrogens appear to modulate the immune response, induce loss of self-tolerance, alter the Th1/Th2 balance in favor of the Th2 process, induce the survival of T and B lymphocytes and the production of autoantibodies. Estrogens appear to be involved in the pathogenesis of SLE. In SLE neuroendocrine system function is affected by the autoimmune process, the neuroendocrine system affecting in turn the disease process. Stress appears to affect disease expression in lupus patients. In SLE hypothyroidism occurs oftener than in the general population, hyperthyroidism occurs in the same rate as in the general population and Hashimoto's thyroiditis is present oftener than in a control population. Diabetes mellitus 1 occurs sometimes, diabetes mellitus 2 occurs less frequently than in the general population. Hyperparathyroidism has been observed in lupus patients. Addison's disease is extremely rare in lupus patients. Cushing's disease occurs infrequently in lupus patients. The ovarian function is affected in female SLE patients. Primary ovarian failure may occur due to autoimmune oophoritis. Cyclophosphamide in SLE is used and its use may be accompanied by the development of premature ovarian failure. The recognition of endocrine disease is important in SLE as symptoms may be similar to those of lupus, however management may be different. The recognition and treatment of an endocrine problem in SLE may guide treatment and lead to symptom amelioration and proper patient management.

Author details

Ifigenia Kostoglou-Athanassiou^{1*}, Lambros Athanassiou²
and Panagiotis Athanassiou³

1 Department of Endocrinology, Asclepeion Hospital, Voula, Athens, Greece

2 Department of Rheumatology, Asclepeion Hospital, Voula, Athens, Greece

3 Department of Rheumatology, St. Paul's Hospital, Thessaloniki, Greece

*Address all correspondence to: ikostoglouathanassiou@yahoo.gr

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