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Reproductive aspects of systemic lupus erythematosus

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ABSTRACT

Systemic lupus erythematosus (SLE) is an auto-immune systemic disease showing a strong predilection for women of reproductive age. Higher prevalance of SLE among young women are in part accounted for by the effects of estrogen hormone on immune system. The key pathophysiological features of this disease are the generation of autoantibodies and the deposition of antibody-antigen complexes in the basal membranes of the organs where they evoke inflammatory responses and injury. Young females diagnosed with SLE are more prone to developing a multitude of adverse reproductive and obstetric outcomes, especially in the presence of active disease. Our motivation in writing this review article is to outline the recent interesting findings of molecular and clinical studies showing multi-faceted roles of estrogen hormone in both normal immune function and auto-immunity and to provide an update on the ovarian function and other poor reproductive outcomes in young females with SLE.

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1. Introduction

Females generally develop stronger immune responses to antigenic stimuli than males. Perhaps, as a results of this gender difference they are more prone to developing autoimmune diseases than men. Systemic lupus erythematosus (SLE) is such an auto-immune systemic disease showing a strong predilection for women of reproductive age. The key pathophysiological features of this disease are the generation of autoantibodies and the deposition of antibody-antigen complexes in the basal membranes of the organs where they evoke inflammatory responses and injury. Higher prevalance of SLE among young women are in part accounted for by the effects of estrogen hormone on immune system. Our aim in writing this review article is to provide an update on 1) the clinical and molecular evidences showing multifaceted role of estrogen in immunity and auto-immunity, 2) the impact of SLE and its treatment regimens on reproductive function and current fertility preservation strategies in women suffering from this disease.

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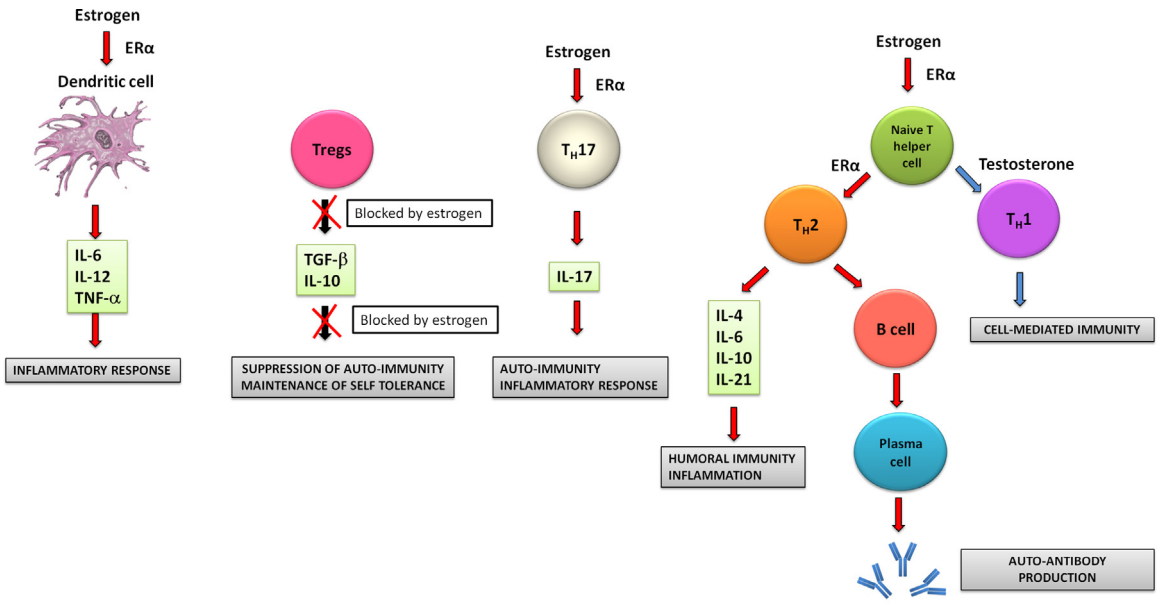

Fig. 1. The schematic illustration of how estrogen hormone induces changes in the immune system that render women more susceptible to developing SLE. Estrogen hormone promotes the differentiation of T_H2 cells and maturation of B cells into antibody producing plasma cells; activates T_H17 lymphocytes to amplify auto-immune and inflammatory responses; abrogates self-tolerance by suppressing Tregs lymphocytes; and stimulates dendritic cells to produce inflammatory cytokines. accelerated differentiation, maturation, and secretion of proinflammatory cytokines.

2. SECTION-1: estrogen in auto-immunity and lupus: emerging evidence from clinical and molecular studies

The effects of estrogen are not confined to reproduction but also extend to the immune system as recent studies revealed an extensive interaction between estrogen and immune cells. There is a female predominance of SLE and other autoimmune diseases during the reproductive age, when the systemic effects of estrogen predominate. A number of observational studies support the potential role of estrogen in predisposing to SLE. For instance, one study compared the female-to-male ratio of SLE in different age groups to analyze the effect of estrogen on immune system. Their results showed that the female/male ratio is 3:1 in pre-pubertal children whereas the ratio increases up to 15:1 in adults, then drops to 8:1 after menopause (Lahita, 1999). The Nurse's Health Study demonstrated that early menarche and the use of estrogen containing regimens increases the risk for SLE in women (hazard ratios of 1.5–2.1) (Buyon et al., 2005; Costenbader et al., 2007). In a similar manner, the use of gonadotropins for ovulation induction increases the rate of SLE flares compared to clomiphene (27% vs. 6% of the cycles) (Huong et al., 2002). Immune cells (B cells, T cells, monocytes, dendritic macrophages) express cognate estrogen receptors ERα and ERβ (nuclear isoforms and/or membrane receptors) (Lee and Chiang 2012). By binding to these receptors and activating several signaling pathways, estrogen plays important roles in both immunity and in the female predominance of auto-immunity. Estrogen-induced changes in the immune system are illustrated in the Fig. 1. There is a switch from a type 1 (T_H1) to a type 2 (T_H2) T helper subset in SLE (Liblau et al., 1995; Constant and Bottomly 1997). The resultant imbalance between T_H1 and T_H2 cytokine production may contribute to the pathogenesis of SLE Estrogen may support the development of T helper 2 subset lymphocytes, B cell hyperactivity and more antibody production, while testosterone may have the opposite effects, promoting T helper 1 activity (Lee and Chiang 2012) (Fig. 2). Estrogen also fosters the differentiation of B cell into antibody-producing plasma cells by stimulating the expression of IL-21, which is a critical mediator of this transformation and found at higher levels in serum, peripheral blood mononuclear cells (PBMCs), and T helper cells of SLE

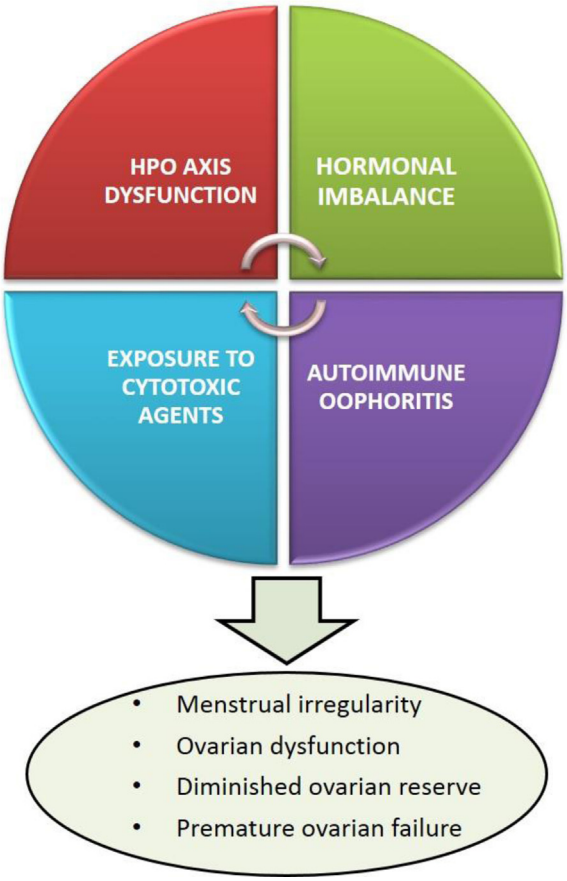

Fig. 2. Contributory factors causing menstrual irregularity, ovarian failure and infertility in women with systemic lupus erythematosus.
SLE involves many organ systems. The ovarian function can be compromised both autoimmune oophorotis; and by gonadotoxic effects of cyclophosphamide. In addition, hormonal imbalances and altered hypothalamic pituitary ovarian axis can further contribute to ovarian dysfunction culminating in menstrual irregularity, infertility and ovarian failure.