

A Review of the Clinical and Immunologic Effects of Estrogen on Atopic Dermatitis

Mini Review

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Received: February 28, 2015 | **Published:** May 18, 2015**Abstract**

One of the most important immunologic phenomena in pregnancy is a shift from T-helper 1 (Th1) to T-helper 2 (Th2) immunity. As a result, pregnancy is associated with an exacerbation of Th2 mediated diseases such as systemic lupus erythematosus, atopic dermatitis, and forms of pemphigus such as pemphigus vulgaris. To summarize the clinical and immunologic effects of estrogen as they relate to atopic dermatitis, we performed an English-language PubMed search of articles combining key terms including "atopic dermatitis," "atopic eruption of pregnancy," "estrogen," and "pregnancy." Estrogen appears to cause Th2 polarization and subsequent increase in Th2 cytokines. Pregnant women with atopic disease have greater numbers of Th2 cells producing IL-4 and IFN-gamma cytokines, and a decrease in the Th1 chemokine ratio. Effects of estrogen on Th17 cells vary depending on cell type. Estrogen stimulates mast cell proliferation and promotes allergic sensitization. Overall, atopic dermatitis tends to worsen during pregnancy, at least in part due to the effects of estrogen on the immune system. New advances in therapies will require an increased understanding of the immunopathology of AD, some of which may be learned by studying its unique course in pregnancy.

Keywords: Atopic dermatitis; Pregnancy; Estrogen; Atopic eruption of pregnancy; Immunology

Abbreviations: Th1: T-helper 1; Th2: T-helper 2; IgE: Immunoglobulin E; Th17: T-helper 17; Th22: T-helper 22; AEP: Atopic Eruption of Pregnancy; IFN- γ : Interferon- γ ; IL-4: Interleukin-4; ROR γ t: retinoic acid-related orphan receptor γ t; ER- α : Estrogen Receptor- α

Introduction

One of the most well-known immunologic phenomena in pregnancy is a shift from T-helper 1 (Th1) to T-helper 2 (Th2) immunity in order to increase tolerance to the semi-allogenic fetus. As a result, Th2 mediated diseases such as systemic lupus erythematosus, atopic dermatitis and forms of pemphigus such as pemphigus vulgaris may worsen [1-4].

Atopic Dermatitis (AD) has been considered a chronic inflammatory disease driven by Th2 cells and characterized by elevated blood eosinophils and Immunoglobulin E (IgE) [5-8]. More recent literature has elucidated an increasingly complex pathogenesis of atopic dermatitis that involves newly identified T helper cell subsets, including T-helper 17 (Th17) and T-helper 22 (Th22) cells. Th17 cells are characterized by Interleukin 17 (IL17) and Interleukin 22 (IL22) expression, whereas Th22 cells are characterized by Interleukin 22 (IL 22) expression. Elevated levels of Th17 and Th22 cells have been identified in cutaneous lesions of AD patients, and both correlate with disease severity. However, Th 17 cells are elevated in acute AD lesions whereas Th22 cells are significantly elevated in chronic AD skin [9-11]. One explanation offered for the different roles of these T cells is that Th17 cells contribute to inflammation and injury, while Th22 cells serve to protect skin integrity [12].

One of the most common specific dermatoses of pregnancy is Atopic Eruption of Pregnancy (AEP) [13]. It is contested whether AEP is an extension of pre-existing atopic dermatitis or a separate clinical entity specific to pregnancy. However, most recently, atopic dermatitis, along with prurigo of pregnancy and pruritic folliculitis of pregnancy, have been classified together under the term AEP [14], the term utilized in this review.

The purpose of this article is to review estrogen's effects on AD clinically and immunologically. Gaining a better understanding of the relationship of AD in pregnancy, a high estrogen state, will help clarify the immune mechanisms responsible for the disease. While several other hormones of pregnancy (progesterone, leukemic inhibitory factor, estradiol, human chorionic gonadotropin and prostaglandin D2) are postulated to promote Th2 immunity [15], discussion of their effects on atopic dermatitis is outside the scope of this review.

Methods

We performed an English-language PubMed search of articles from September 1960 to September 2014 combining key terms including "atopic dermatitis" "estrogen," "atopic eruption of pregnancy," and "pregnancy." All titles and/or abstracts were screened. Full texts were obtained and content was further examined for inclusion in this narrative review.

Results

Our electronic search yielded 401 articles, which were scanned by the authors to retrieve relevant information on the immunologic and clinical effects of estrogen on atopic dermatitis (Figure 1).

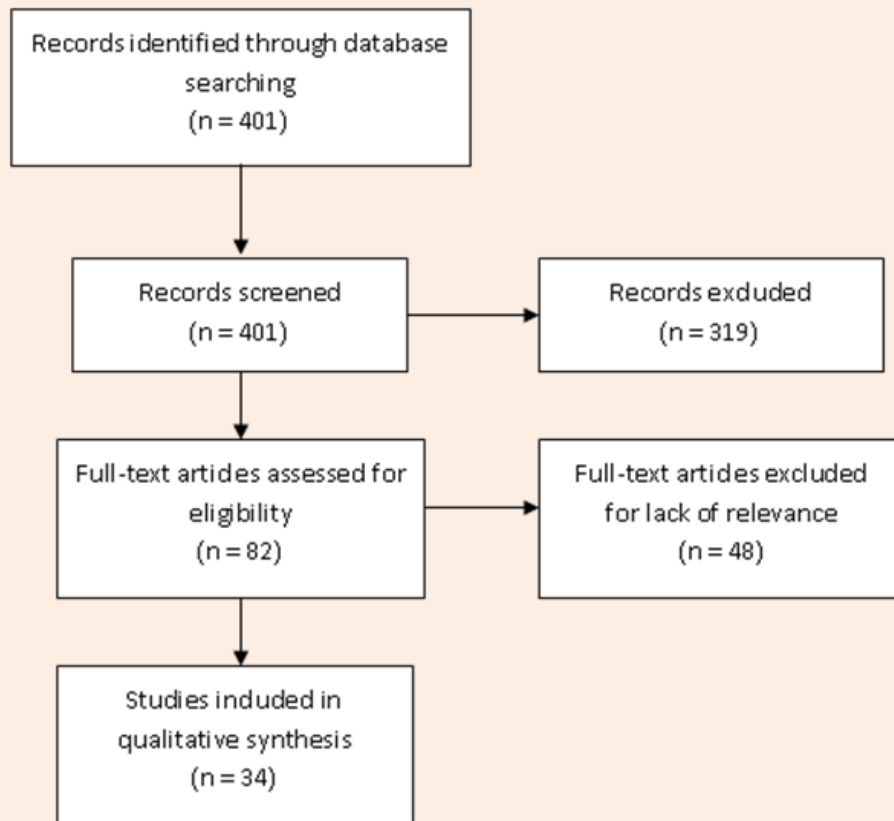


Figure 1: Methods used for Literature Search.

Atopic dermatitis in pregnancy

Atopic Eruption of Pregnancy is the most common dermatosis of pregnancy, accounting for one third to one half of all cases. Only 20-40% of these patients have a pre-existing history of eczema, while the rest develop symptoms for the first time in pregnancy [14,16]. In a study that interviewed 23 female patients with pre-existing atopic dermatitis who experienced pregnancy, 14 (61%) noticed a deterioration of their clinical symptoms during pregnancy [17]. Similarly, Kemmet et al. [18] reported that more than 50% of patients experience deterioration of atopic dermatitis in pregnancy [18].

AEP most commonly starts before the third trimester of pregnancy, and tends to recur in subsequent pregnancies [16]. The clinical presentation of AEP is divided into two clinical subtypes: E-type (eczematous changes) with severely dry skin and eczematous changes usually affecting face, neck, and flexural surfaces or P-type (papular changes) with excoriated papules, predominantly on extensor surfaces [19].

The effects of estrogen on atopic dermatitis are evidenced by fluctuating disease severity with menstruation and menopause. Of 97 patients surveyed on the association of atopic dermatitis to their menstrual cycle, 31 (32%) noticed a deterioration of their AD related to their menstrual cycle. The exacerbation of AD was more likely to be premenstrual, within 10 days before menstruation, when estrogen levels are at their highest [17]. Additionally, a greater

reduction in estrogen secretion was observed in postmenopausal asthmatic women as compared to postmenopausal healthy women [20]. Estrogen dermatitis, a condition describing cyclical skin eruptions (papulovesicular lesions, urticaria, eczema, or pruritus) that worsen premenstrually, has also been described [21]. Successful treatments for estrogen dermatitis include withdrawing exogenous sex hormones, tamoxifen therapy, and oophorectomy [22,23]. Finally, estrogen receptors discovered on keratinocytes cause changes in skin hydration collagen content, and glycosaminoglycan concentrations as levels of estrogen fluctuate [24]. These changes in skin composition may contribute to the barrier dysfunction associated with AD. Altogether, these findings suggest that estrogen may play a role in the exacerbation of disease.

Estrogen's effects on atopic dermatitis

Several studies have implicated estrogens as enhancers of Th2 mediated humoral immunity and antibody synthesis [25]. Tamasi et al. [26] showed significantly greater numbers of Interferon- γ (IFN- γ) and Interleukin-4 (IL-4) cytokine producing T cells among pregnant asthmatic women when compared to asthmatic non-pregnant women [26]. Longitudinal Th2 polarization over the course of pregnancy showed a significant decline in Th1 chemokine ratio (IP10/eotaxin). The decrease in the chemokine ratio was associated with more frequent asthma symptoms in pregnancy [27].

Whereas estrogen uniformly enhances Th2 mediated humoral immunity, it exerts variable effects on Th17 across cell types. Khan et al showed that, in murine splenocytes, estrogen upregulated levels of both IL17 and IL17-specific transcription factor retinoic acid-related orphan receptor gamma t (ROR gamma t) [28]. Similarly, in the lung tissue of mice with cystic fibrosis, exogenous estrogen led to increased mRNA levels of IL-17 [29]. However, in murine bone marrow cells, estrogen suppresses IL-17 mediated osteoclast differentiation—a phenomenon that has been postulated to play an important role in post-menopausal bone loss [30]. The effects of estrogen on Th 17 immunity in dermal cells remain unknown, as do its effects on Th22 immunity.

The role of estrogens on the immune response is, in part, exerted by activation of the NFκB complex pathway, which stimulates cell proliferation of macrophages and fibroblasts [31]. Mast cells display a high affinity estrogen receptor (Estrogen Receptor-α; ER-α) which, upon stimulation with estrogen, causes a rapid, dose-related release of preformed granular protein B-hexosaminidase from mast cells and enhanced IgE mediated release [32]. Physiological concentrations of estradiol added to two mast cells/basophil lines (RBL-2H3 and HMC-1), and primary cultures of bone marrow derived mast cells, all of which naturally express ER-α, induce the partial release of B-hexosaminidase. Estradiol also enhances IgE-induced degranulation and potentiates leukotriene C4 production in RBL-2H3 [33]. A single subcutaneous estrogen injection was shown to partially negate the natural tolerance process of IgE formation, and promote allergic sensitization in rodent models [34]. In contrast, tamoxifen, an estrogen receptor antagonist, has been shown to inhibit mast cell secretion [35]. Additionally, progesterone has been shown to inhibit secretion of rat peritoneal mast cells that had previously been stimulated [35].

Disease treatment during pregnancy

There are no adverse effects on maternal or fetal outcome as a result of AEP [14,19,36]. Thus, the goal of treatment is symptom relief. Treatment may be divided into topical therapy, phototherapy, and systemic therapy. Topical therapies employed for AED include those involved in the management of all eczema patients, and should be considered first line therapy. These include emollients, tepid baths, and mid-low potency corticosteroids [37]. Phototherapy, in the form of ultraviolet B phototherapy, may be used in cases of unresponsive, severe AEP [38]. Systemic medications must be used with additional caution. While first generation antihistamines, such as chlorpheniramine and diphenhydramine are considered safe for itch relief in AEP (Pregnancy category B), one study found that the use of systemic antihistamines in the final two weeks of pregnancy increases the risk of retrolental fibroplasia in premature infants by 7.5% [39]. Alternative systemic medications for recalcitrant, severe AEP include a short course of prednisone or prednisolone, or cyclosporine for the shortest duration possible with regular monitoring of blood counts, blood pressure and renal function [37,40].

Conclusion

Atopic dermatitis tends to worsen during pregnancy, likely in part to the effects of estrogen on the immune system. Specifically, this involves the shift towards Th2 immunity and increased

production of Th2 cytokines. Estrogen's effects on Th17 and Th 22 may also play a role in the exacerbation of disease in pregnancy. Additionally, the high estrogen state of pregnancy stimulates mast cell activation and allergic desensitization.

There remains great need for further research to advance our understanding of the immunological basis of AD. Currently there are no targeted therapies for AD, despite a prevalence of 10-20% in children and 1-3% in adults. New advances in therapies will require an increased understanding of the immunopathology of AD, some of which may be learned by studying its unique course in pregnancy.

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