



## The immunologic effects of estrogen on psoriasis: A comprehensive review☆☆☆

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### ABSTRACT

**Background:** Immunological changes in pregnancy are associated with improvements in some pre-existing immune-mediated skin diseases. Estrogen has been hypothesized to contribute to these changes by creating a shift from Th1 and Th17 to Th2 immunity. As this hypothesis would predict, psoriasis (a primarily Th17 mediated immune disease) tends to improve during pregnancy. However, the precise mechanism by which estrogen induces immunological change in psoriasis remains poorly understood.

**Objective:** To summarize the immunologic effects of estrogen as they relate to psoriasis during pregnancy.

**Methods:** We performed an English-language PubMed search of articles from September 2004 to September 2014 combining the key terms "psoriasis," "estrogen," "autoimmune disease," and "pregnancy."

**Results:** Estrogen appears to up-regulate Th2 cytokines and down-regulate Th1 and Th17 cytokines. This shift was initially observed in murine systems, which showed decreased mixed lymphocyte reactions of splenocytes and increased antibody production during pregnancy. Antigen stimulated splenocytes produced fewer Th1 cytokines and more Th2 cytokines in pregnant mice. IL17 producing T cells were significantly decreased in healthy pregnancies compared to non-pregnant controls.

**Limitations:** This review is limited by the paucity of studies evaluating immunological changes of psoriasis in pregnancy among human subjects.

**Conclusions:** Increased estrogen production in pregnancy is associated with decreased Th1 and Th17 cytokine production. While estrogen may be responsible for some of these immune shifts resulting in disease improvement, there remains no definitive evidence to prove the hypothesis that estrogen is responsible for such improvement.

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### Background

In pregnancy, there are a number of hormonal and immunological changes that alter the severity of pre-existing cutaneous diseases and cause new-onset cutaneous disease. Specifically, pregnancy triggers an immune shift from T-helper 1 (Th1) to T-helper 2 (Th2) immunity, which promotes fetal survival by decreasing the Th1 responses involved in rejection of the fetus as an allograft. Pregnancy also leads to a decrease in T-helper 17 (Th17) frequency (Fu et al., 2013; Nakashima et al., 2010a). As predicted, pregnancy is associated with an improvement in numerous Th1 and Th17 immune-mediated diseases, including psoriasis, rheumatoid arthritis, autoimmune encephalomyelitis, uveitis, thyroiditis, and multiple sclerosis (Abramsky, 1994; Amino et al., 1999;

Birk et al., 1988; Chiam et al., 2013; Confavreux et al., 1998; Da Silva and Spector, 1992; Damek and Shuster, 1997; Davies, 1999; Muller et al., 1999; Ostensen, 1999; Rabiah and Vitale, 2003; Runmarker and Andersen, 1995; Terry and Hague, 1998; van Walderveen et al., 1994; Whitacre et al., 1999).

Psoriasis is an immune-mediated disease that is driven by Interleukin 23 (IL23) and Th17 cells (Lowe et al., 2014), while Th1 cells may play a secondary role (Austin et al., 1999; Schlaak et al., 1994; Szabo et al., 1998; Uyemura et al., 1993). Older therapies for psoriasis have aimed to down-regulate Th1 responses. Several systemic therapies are beneficial in treating psoriasis: methotrexate, cyclosporine, acitretin, PUVA (oral psoralen and ultraviolet A light treatments), narrowband ultraviolet B (nUVB) light treatments, and hydroxyurea. An improved understanding of the immunologic mechanisms driving psoriasis has allowed for the development of various biologic therapies (Table 1) including etanercept, adalimumab, infliximab, and ustekinumab. A number of IL23 and IL17 antagonists are currently being tested in clinical trials. Each of these therapies has at least in part an anti-inflammatory mechanism of action related to immune deviation (Kang et al., 1998; Krueger, 2002).

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The purpose of this article is to review the immunologic effects of estrogen on psoriasis during pregnancy. In understanding the role of estrogen on the immune system in pregnancy, we may be better able to devise cost-effective medications like hormones with an improved safety profile over that of systemic immunosuppression to provide therapeutic alternatives for psoriasis patients.

**Methods**

We performed an English-language PubMed search of articles in September 2014 for articles dated from September 2004 to September 2014 combining key terms including "psoriasis," "estrogen," "autoimmune disease," 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 404 articles, which were scanned by the authors to retrieve relevant information on the immunologic effects of estrogen on psoriasis. (Fig. 1)

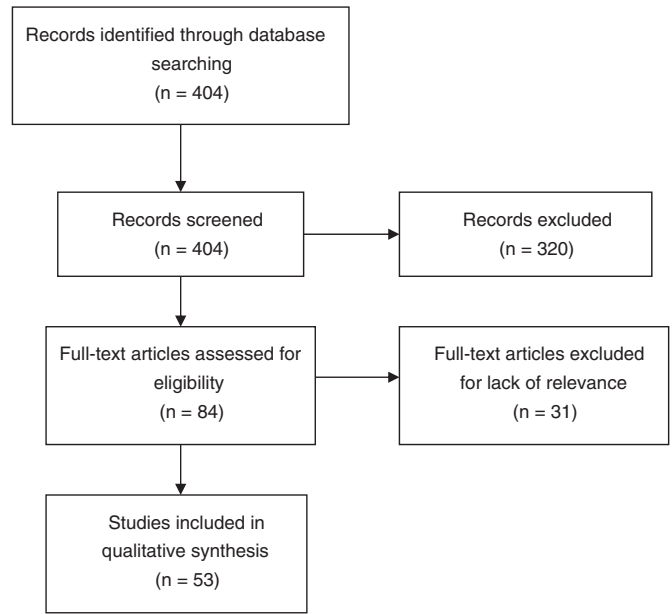


Fig. 1. Methods used for literature search.

*Psoriasis in Pregnancy*

Data suggest that psoriasis tends to improve with high estrogen states. Retrospective studies examining psoriatic change in pregnancy have shown that approximately half of patients improve during pregnancy, and up to 70% experience a postpartum flare (Boyd et al., 1996; Dunna and Finlay, 1989; Farber and Nall, 1974; Farber et al., 1968; McHugh and Laurent, 1989; McNeill, 1988; Mowad et al., 1998; Park and Youn, 1998). Murase et al performed the first study that examined body surface area (BSA) in pregnancy and the postpartum period, comparing 47 pregnant psoriasis patients with 27 non-pregnant psoriasis patients (Murase et al., 2005). During pregnancy, 55% of patients reported improvement, 21% reported no change, and 23% reported worsening. However, among postpartum patients, only 9% reported improvement, 26% reported no change, and 65% reported worsening. Psoriatic BSA decreased significantly from 10 to 20 weeks' gestation (P < 0.001) compared with controls, whereas BSA increased significantly by 6 weeks postpartum (P = 0.001) compared with controls. In patients with 10% or greater psoriatic BSA who reported improvement, lesions decreased by 83.8% during pregnancy. There were significant or near significant correlations between improvement in BSA and estradiol levels (P = .009, r = 0.648), estriol (P = .06, r = 0.491), and the ratio of estrogen to progesterone (P = .006, r = 0.671).

Patients treated with high dose estrogen oral contraceptives experience improvement of their psoriasis (Mowad et al., 1998) and psoriatic arthritis (McHugh and Laurent, 1989). In contrast, psoriasis worsens when estrogen levels drop postpartum (Boyd et al., 1996; Dunna and Finlay, 1989; McNeill, 1988; Mowad et al., 1998), prior to menses (Mowad et al., 1998), and at menopause (Mowad et al., 1998).

Exogenous estrogen treatment in a prospective clinical trial has never been done in psoriasis.

*The Immunology of Psoriasis*

Initially, evidence supporting the immunopathogenicity of Th1 cells in psoriatic lesions came from data demonstrating that Interferon-γ (IFNγ), Tumor Necrosis Factor-α (TNFα) and IL12 were detected by RT-PCR in lesions, while levels of IL4, IL5 and IL10 were low to undetectable. This pattern of cytokine expression was also observed using flow cytometry of cells derived from lesions (Austin et al., 1999; Schlaak et al., 1994; Szabo et al., 1998; Uyemura et al., 1993). TNFα immunoreactivity and bioactivity were consistently higher in lesions, as compared with uninvolved (clinically normal) skin samples (Etehadhi et al., 1994).

However, more recent evidence indicates that psoriasis is driven by IL17 producing T cells (Th17 cells), rather than Th1 cells. In 2004, Lee et al showed that lesional skin had an increase in IL23 (Lee et al., 2004), a cytokine secreted by dermal dendritic cells and monocytes (Fuentes-Duculan et al., 2010). Furthermore, studies have documented an abundance of IL17 producing cells in psoriasis (Kryczek et al., 2008; Lowes et al., 2008; Ortega et al., 2009). These two cytokines, IL17 and IL23, are closely linked: IL23 is required for the expansion of Th17 cells (Lowes et al., 2014). Overall, it appears that Th1 and Th17 cells collaborate to contribute to the immuno-pathogenicity of psoriasis (Kryczek et al., 2008; Ortega et al., 2009).

Many treatments for psoriasis act at least in part through therapeutic immune deviation (Kang et al., 1998; Krueger, 2002). Particular emphasis has been placed on the pathogenic role of TNFα and the protective role of IL10. Three of the currently used biologics for psoriasis (Infliximab, Adalimumab, and Etanercept) are anti-TNFα therapies. Also, trials of systemic treatment with IL10 demonstrated efficacy,

**Table 1**  
Selected biologics tested in psoriasis

Drug	Target	Currently FDA approved for plaque psoriasis
<b>Ustekinumab (Stelara)</b>	IL-12 and IL-23 shared p40 subunit	Yes
<b>Briakinumab</b>	IL-12 and IL-23 shared p40 subunit	No
<b>LY2525623 SCH 900222, CNTO 1959, AMG 139</b>	Anti-IL-23 p19 subunit monoclonal antibody	No
<b>Etanercept</b>	TNFα Receptor fusion protein	Yes
<b>Infliximab, adalimumab</b>	Anti-TNF monoclonal antibody	Yes
<b>Secukinumab,</b>	IL-17	Yes
<b>Ixekizumab, brodalumab</b>	IL-17	No

Created with information from Lowes et al. (2014)

with limitation due to problems of long term administration and the risk of developing neutralizing antibodies (Asadullah et al., 1998, 1999, 2000, 2001; Friedrich et al., 2002). Ustekinumab, a highly effective biologic medication, induces its effects via antagonism of IL23, which in turn, inhibits Th17 cell proliferation. Several medications that block IL17 (Secukinumab, Ixekizumab, Brodalumab) show great promise thus far in Phase 2 clinical trials (Brown et al., 2015). Thus, previous studies provide evidence that a systemic treatment with the ability to decrease IL23, IL17, TNF $\alpha$  and/or increase IL10 would be beneficial in psoriasis patients.

### The Immunology of Pregnancy

In both mice and man, failure to shift from Th1 to Th2 mediated immunity in pregnancy results in an increase in spontaneous abortion (Hill et al., 1995; Krishnan et al., 1996a; Lin et al., 1993). This shift in immune response from Th1 to Th2 occurs both locally at the maternal fetal interface (Lin et al., 1993; Sacks et al., 2001; Wegmann et al., 1993) as well as systemically (Dudley et al., 1993; Elenkov et al., 2001; Fabris et al., 1977; Hill et al., 1995; Krishnan et al., 1996b; Marzi et al., 1996). The systemic shift away from Th1 and toward Th2 was initially shown in murine systems by a decrease in mixed lymphocyte reactions of splenocytes and an increase in antibody production during pregnancy (Fabris et al., 1977). Antigen stimulated splenocytes produce fewer Th1 cytokines and more Th2 cytokines when derived from pregnant mice (Dudley et al., 1993; Krishnan et al., 1996a). In humans, peripheral blood mononuclear cells (PBMC) in women with successful pregnancies produced IL-10, but no IFN $\gamma$ , upon stimulation with trophoblast antigens (Hill et al., 1995). In another study, antigen- and mitogen-stimulated PBMC derived from patients with normal pregnancies demonstrated a decrease in the production of IL-2 and IFN $\gamma$  and an increase in production of IL-4 and IL-10, with the lowest quantities of IL-2 and IFN $\gamma$  and the highest quantities of IL-4 and IL-10 present in the third trimester of pregnancy (Marzi et al., 1996). During the third trimester of pregnancy, ex vivo monocytic IL-12 production was also found to be about three-fold and TNF $\alpha$  production was approximately 40% lower than postpartum values (Elenkov et al., 2001).

The Th1/Th2 paradigm has recently been expanded to include a third population of T cells: Th17 cells. Santner-Nanan showed that the percentage of Th17 cells is significantly decreased in healthy pregnancies compared to non-pregnant controls (Santner-Nanan et al., 2009). However, the number of circulating Th17 cells does not change during normal pregnancy (Nakashima et al., 2010a). In patients with unexplained recurrent spontaneous abortions (URSA), the proportion of Th17 cells was significantly higher in the peripheral blood and decidua compared to the proportion in early, normal pregnant women (Wang et al., 2010). Specifically, Th17 cells may play a role in the induction of inflammation in the late stage of abortion (Nakashima et al., 2010b). Conversely, the frequency of T-regulatory (Treg) cells was significantly lower in the patients with URSA (Wang et al., 2010). Also, amniotic IL17 levels are elevated in patients with chorioamnionitis associated with pre-term labor, and plasma IL17 levels are elevated in patients with unexplained infertility (Ito et al., 2010). Altogether, these studies indicate that normal pregnancy induces a shift away from Th17 immunity, and that increased plasma IL17 levels have a negative impact on fertility.

A significant decrease in the Th1 response, the delayed type hypersensitivity (DTH) response to the recall antigen tetanus, has been documented during pregnancy and during treatment with estradiol (Holland et al., 1984; Jansson et al., 1990; Manyonda et al., 1992). This was supported by changes in PBMC cytokine production when an estrogen was administered *in vitro* to treat human T cell lines (Correale et al., 1998; Gilmore et al., 1997; Zang et al., 2002). Estrogen also appears to suppress murine IL17 production, as seen in Th17 mediated diseases such as autoimmune encephalomyelitis and collagen-induced arthritis (Bebo et al., 2001; Jansson et al., 1994; Tyagi et al., 2012). Finally,

there have been previous reports that the state of pregnancy can alter subpopulations of circulating immune cells, but there is no clear consensus regarding consistent changes at each trimester in humans (Mahmoud et al., 2001; Makrydimas et al., 1994; Matthiesen et al., 1996; Tallon et al., 1984; Watanabe et al., 1997).

### Discussion

Pregnancy is associated with diminished Th1 and Th17 immunity. Both T-helper cells are postulated to play a role in the pathogenesis of psoriasis, and the dampening of their respective cytokines by targeted biologic therapy leads to disease improvement. Associations provided by the literature suggest that the high estrogen state of pregnancy is perhaps one factor for these immune shifts, and thus disease improvement. However, there is no definitive evidence to demonstrate the hypothesis that estrogen improves psoriasis in pregnancy. Without further studies showing that the absence of estrogen (e.g. an estrogen knockout or anti-estrogen antibody) could block such improvement, this hypothesis remains speculative.

Our review is not without limitations. First, our report is limited by the paucity of studies evaluating immunological changes of psoriasis in pregnancy among human subjects. As a substitute, we have used murine models to understand some of the immunologic effects during pregnancy. However, there is a much clearer dichotomy between murine immune responses as either Th1 or Th2 than in humans (Kidd, 2003). As a result, the role of estrogen on the murine immune system may not lend itself as well to extrapolation in the pregnant woman. Also (related to our first limitation), we included non-randomized studies in this review, which may introduce some selection bias. However, because we are studying psoriasis in pregnant women, most of the data in humans is from non-randomized studies rather than randomized studies (due to ethical considerations).

There remains great need for further research to advance our understanding about the effects of estrogen on psoriasis. We recommend further murine studies that evaluate the specific role of estrogen in disease improvement. Perhaps in the future, studies may be performed using estrogen as the primary treatment modality for patients who have psoriasis. Specifically we recommend studying the experimental use of estradiol, which is an estrogen unique to pregnancy that is associated with fewer adverse effects than estradiol (Follingstad, 1978; Lauritzen, 1987). We believe this research would be an essential first step in advancing our understanding of the immunologic effects of estrogen on psoriasis and, even more importantly, the development of an inexpensive topical or oral treatment for psoriasis which could potentially have an improved safety profile over systemic immunosuppressants for women of childbearing age.

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