REVIEW ARTICLE

Chronic Urticaria in Pregnancy: Physiologic and Hormonal Background for an Immune Skin Disease

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Abstract

Chronic urticaria (CU) is a cluster of manifestations specified as recurrent pruritic erythematous wheals or angioedema (AE), lasting for more than 6 weeks and complicating 1–2% of the population. Widespread presence of CU is higher in middle-aged women than men (1.3 vs 0.8%). It is proposed that this higher prevalence in women may be linked to female sex hormones, although the precise relationship between sex hormones and immune system function remains to be fully understood. Pregnancy is a condition that impacts CU activity in susceptible individuals. Likewise, CU can have effects on pregnancy, and conversely, pregnancy may alter the presentations of CU. Studies have shown Increased number of mast cells present in skin, and elevated serum levels of autoantibodies such as IgE anti-TPO, IgE anti-dsDNA, and IgE anti-IL-24 in chronic spontaneous urticaria (CSU) patients. The role of autoimmune diseases is crucial in these patients. Based on some evidence, immunologic tolerance is outside of the placenta milieu; and some other inflammatory conditions are alleviated during pregnancy. Chronic urticaria severity, medication before pregnancy, and AE before pregnancy were compromising factors leading to intensified urticaria in pregnancy. Managing CU in pregnant women presents unique challenges. There is little evidence about the safety and efficacy of medications in pregnant women with CU, and the cost/benefit of such treatments should be evaluated. Some studies recommend H1-antihistamines. First-generation H1-antihistamines induce sleepiness and decreased attention by passing blood–brain barrier in CNS. However, second-generation H1-antihistamines have minimal CNS complication with most negligible side effects. Omalizumab, a biological monoclonal antibody against IgE molecules, is recently recommended by the guidelines as one of the therapeutic options in patients with uncontrolled CU. Cyclosporine and systemic corticosteroid are the other reserved options for the treatment of CU in pregnancy. In this review, we focused on the effect of underlying physiologic, hormonal, and immunologic changes during pregnancy over CU. Then assessed the noteworthy changes in the natural course of CU during pregnancy; the therapeutic challenges faced, and the complications associated with of CU and complications of CU during pregnancy.

Keywords: Autologous serum skin test, Chronic spontaneous urticaria, Cyclosporine, Estrogen, Leptin, Omalizumab, Progesterone, Prolactin, T regulatory.

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Introduction

Chronic spontaneous urticaria (CSU) is clinically characterized by wheals and, or angioedema (AE) lasting more than 6 weeks.[1] It affects individuals of all age groups, with a higher prevalence more often observed in females. Its prevalence has been estimated about 1–2% of the population.[1–4] Chronic urticaria (CU) is responsible for some comorbidities; at the top of them are anxiety, depression, and sleep disorders due to refractory and severe pruritus.[5,6] The immunogenic etiology of CU is not well-established, but it seems that mast cells and basophils have a central role. Chronic urticaria is classified into two main groups: chronic inducible urticaria and CSU.[7] Two main immunologic mechanisms have been recognized for the pathology of CSU:[8] first, Type I autoimmunity in CSU also known as autoallergic CSU and second, Type IIb autoimmune CSU aiCSU, in which IgG autoantibodies, and probably IgM and IgA, are responsible for direct activation of mast cells.[9] The current gold standards for the diagnosis of aiCSU include positive autologous serum skin test (ASST), basophil histamine release assay (BHRA), and immunoassay for specific IgG autoantibodies against FcεRIα/IgE.[10] Least of 8% of CSU patients have aiCSU and tend to be more severely affected, with markedly lower total IgE levels,[1] and higher rates of eosinopenia and basopenia.[7–10]

The prevalence of CU in middle-aged women is higher than in men (1.3 vs 0.8%, respectively).[5,11,12] the high prevalence of CU in women is proposed to be related to female sex hormones.[7] Although the effects of sex hormones on hereditary AE are confirmed, the role of sex hormones on CSU is uncharacterized.[7] Mast cells are from the most critical immunologic cells and the activation of these cells through their receptors induces the excretion of bioactive mediators and hypersensitivity reactions. excepting FCεR1, other mast cell receptors such as estradiol and progesterone receptors, can also activate these cells.[13–16] In females, pregnancy is a condition with strong solid and physiologic changes in many organs and systems.[17,18] Proper functioning of the immune system is necessary for a successful pregnancy. Therefore, by discerning the specific immunological pathways involved in

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the pathogenesis of urticaria, we can put forward to design novel therapeutic agents for the treatment of CU in pregnancy.

Pregnancy and the Immune System

Among comprehensible physiologic changes experienced during pregnancy, While the implantation of allogeneic fetuses occurs during pregnancy, several immunologic cells are involved. Foreign cells can activate CD8+ cytotoxic cells and CD4+ T helper cells, but immune tolerance is supported by continuing pregnancy. Implantation of the fetus and labor phase is associated with chronic inflammatory response and a predominant TH1 cytokine formation (the first and third trimesters are proinflammatory TH1). In contrast, the second trimester represents an anti-inflammatory phase, also known as the TH2 environment.[19] It is unclear whether this inflammatory state is related to peripheral immunologic processes.[16,20] Based on some evidence, immunologic tolerance also is outside of the placenta milieu. Several inflammatory conditions, i.e., inflammatory bowel disease, rheumatoid arthritis, and multiple sclerosis, have been alleviated during pregnancy.[18–22] Results are Conflicting about the cytokine patterns in peripheral blood in trimesters of pregnancy. However, data explicate that peripheral immunologic cells in pregnant women, compared with healthy ones, show different reactions to foreign stimuli.[16,19] The relationship between sex hormones and the immunological system is complex. In the first trimester of pregnancy, measure of human chorionic gonadotropin (hCG) begins to rise. It can inhibit lymphocyte function and protect the fetus from immunologic attack. Estrogen and progesterone are necessary for the maintenance of pregnancy. Progesterone can lead to induce regulatory T-cell (T-reg) functions and reduce proinflammatory and cytotoxic responses in pregnant women. Estrogen has both effects of stimulatory and regulatory on peripheral T lymphocytes.[21,23] Estrogen is an essential factor in inducing immunologic responses in women, and estrogen receptors can lead to immunologic response deviation to TH2 polarization and induced allergic reactions. Estradiol and its receptors are capable of stimulating calcium signaling and activating mast cell release. Animal studies have shown that estradiol promotes IgE-mediated mast cell degranulation and LTC 4 synthesis in mouse models.[22]

Chronic Urticaria and Immunologic Function

It is speculated that CSU is caused by an immunological mechanism. Recent evidence confirmed significant serum levels of IgG anti-IgE and IgG anti- FcεR1 in patients with CSU.[24] So, we can see an auto-allergic reaction in these patients without external allergens. Studies have shown elevated serum levels of autoantibodies such as IgE anti-TPO, IgE anti-dsDNA, and IgE anti-IL-24 in CSU patients.[24,25] ultimately, it appears that both immunologic mechanisms are involved in inducing CSU. Increased number of mast cells are present in both involved and non-involved skin and mast cell reactivity is heightened in the cutaneous of patients with active CSU.[26,27] Eosinophil cells are other components with a significant role in CSU pathogenesis. These cells are recruited into affected skin by chemo-attractant mediators secreted by other immune cells such as mast cells.[28] Eosinophil cumulation in skin tissue can lead to mast cell degranulation and production of urticaria.[29,30] There is no perivascular cellular infiltration in cutaneous, and all the cellular components of blood are present in the skin of CSU patients. There is limited data about the role of lymphocytes, neutrophils, and eosinophils in CU. Depending on the cytokine environment, naive T cells can differentiate into TH1, TH2, TH17, and T-reg cells.[27,28] The role of autoimmunity in these patients is essential. TH17 is a main cellular component in patients with autoimmunity and can produce several cytokines, such as IL-22, IL17, IL-6, IL-8, and IL-23. IL-6 is an essential cytokine in the pathogenesis of CSU, with its elevated levels in blood and skin biopsies.[31] There are conflicting results in the serum levels of TH1 and TH2 cytokines, e.g., INF-γ and IL-4 in patients.[32] It seems that basophils are important immunologic cells in CSU. Basophil levels in the blood correlate negatively with CSU disease activity.[26,28] Studies showed that low serum IgE levels and low basophil IgE receptors play a negative prognostic role in omalizumab therapy.[28]

Chronic Urticaria and Pregnancy

Women with CSU at their reproductive age ask their physicians about the effects of pregnancy on urticaria. Unfortunately, the response to this question is lacking in many kinds of literature.[1] Lack of proper shreds of evidence raises questions about the efficacy and safety of therapeutic regimens in pregnant women with urticaria.[33] Chronic urticaria can affect pregnancy, and conversely, pregnancy may change the disease presentations.[34] In clinical experience, we can see changes in CU activity and severity across the menopausal period, menstrual phase, and consumption periods of oral contraceptives. In pregnancy, several hormones and mediators are released with proinflammatory properties. For example, prolactin levels increase slightly during pregnancy and suddenly find increased concentration during and after delivery. Prolactin stimulates the immune system, and it can cause autoimmune disorders. The placenta is the second source of leptin. Leptin levels rise in the pregnancy period and can activate the proinflammatory cytokines. Proinflammatory (IL-6, IL-1, INF-γ, and TNF-α) and anti-inflammatory (TGF-β and IL-10) cytokines are necessary for fetal implantation, delivery, and fetal rejection, respectively.[34–36] Some studies have found a correlation between leptin levels and the pathogenesis of CSU and its severity.[37–39] Prolactin may be significantly higher for the disease severity in ASST positive CSU patients. Still, the functional role of this hormone in CSU is controversial.[40,41] In one study, the effects of pregnancy on CU were assessed in 288 cases.[2] They found that 124 patients experienced worsened urticaria during pregnancy. Most exacerbations occur during the third (27.6%) or first (22.8%) trimesters; and 19% have CU throughout their entire pregnancy. Stress was a common trigger factor for exacerbations in pregnancy. Chronic urticaria severity, medication before pregnancy, and angioedema before pregnancy were compromising factors leading to intensified urticaria in pregnancy.[1] Conversely, CU activity and its treatments with medications such as first-generation antihistamines, may put burden on pregnant women and their fetuses.[1,42–44] Pregnant women with CU have an impaired quality of life and may suffer from anxiety and depression.[45–47] Several skin eruptions in pregnancy must be differentiated from the diagnosis of CSU. Gestational pemphigoid, known as a rare disease with sudden onset, presents with popular urticaria and generalized blisters. Biopsy shows perivascular infiltrations with lymphocytes and eosinophils in the subepidermal area. Prurigo of pregnancy is another disorder that manifests after 20 weeks of gestation identified by pruritic papular and nodular eruptions on extensor surfaces. Skin biopsy is not specific, and lesions are usually resolved after delivery. Pruritic urticarial papule and plaque of pregnancy (PUPPP) is an urticarial plaque with severe itching on abdominal striae, but the face, handsand soles are spare. It

usually resolves 2 weeks after delivery and repeats for further pregnancies.[31,42–44]

Antihistamine Therapy in Pregnancy

Antihistamines are the primary therapeutic options for allergic disorders. Histamine and antihistamines interact with histamine receptors. Histamine receptors belong to the G-protein-coupled receptors superfamily. Histamine receptors act as a cellular switch in an equilibrium state. These receptors will be on when histamine molecules cross-link the third and fifth transmembrane domains. Inversely, antihistamines can inactive histamine receptors by cross-linking of fourth and sixth transmembrane domains.[48,49] Four histamine receptors are found in the central nervous system: B cells, gastric mucosa, mast cells, and basophils.[46] Histamine is a crucial neurological mediator in the human brain involved in the circadian rhythm of sleep and wakefulness. First-generation H1-antihistamines can pass through the blood–brain barrier and induce sleepiness and decreased attention. However, second-generation H1-antihistamines have minimal CNS complication with most negligible cholinergic side effects.[47] Medical therapeutic options should be considered in pregnant women. Approximately, 10–15% of pregnant women use antihistamines for the management of hyperemesis gravidarum, allergic rhinitis, asthma, indigestion, and urticaria during pregnancy. Although, based on some studies the administration of antihistamine aimed at the treatment of allergic rhinitis and urticaria is well tolerated; information about the safety and fetal complications remains inconclusive.[50]

Some studies recommend first-generation antihistamines. Among the first generation of antihistamines, chlorpheniramine, dimenhydrinate, cyproheptadine, tripelennamine, and dexchlorpheniramine are the FDA-approved and categorized in group B rating (no sufficient study in humans and no fatal outcome in animal studies). Hydroxyzine, diphenhydramine, and clemastine are in group C rating (no adequate study in humans but proved risk in animal studies). Other studies have known first-generation antihistamines responsible for the increased risk of fetal malformation; and second generations are preferred for use. Diphenhydramine had been associated with cleft palate if used in the first gestational trimester. Recent data discourage the use of first-generation antihistamines in the first trimester due to a potential increased risk of dementia.[42,51,52] According to the EAACI/GA^{2}LEN/EDF/WAO guideline,[44] the safety of antihistamine therapy in pregnant women with CU has not been systematically studied. First generation antihistamines are contraindicated in pregnancy. No documented report about birth defects is published via the use of second-generation antihistamines in pregnancy; but there are small studies with low sample sizes about cetirizine and loratadine.[45,46] Cetirizine is an active metabolite of hydroxyzine. It is a second-generation antihistamine administered for pregnant women. Studies showed that taking cetirizine in pregnancy does not accompany fetal and mother complications.[49] The H2 blockers are another medication that may be prescribed in patients with CU. These drugs are used for gastroesophageal reflux in pregnancy. Studies have shown no association between the administration of famotidine, cimetidine, ranitidine, and pregnancy outcome and complication.[53,54]

Monoclonal Anti-IgE Antibody

This group of medications is referred to biological drugs. Omalizumab is a monoclonal antibody against IgE molecules and it suppresses the interaction between IgE molecules and its receptors; represented by FcεR1 on mast cells and basophils, and FcεR2 on B cells and antigen-presenting cells. Recently, EAACI guideline recommends omalizumab as one of the therapeutic options in patients with uncontrolled CSU.[55,56] Animal studies on cynomolgus monkeys showed no maternal toxicity, teratogenicity, or embryotoxicity after omalizumab administration during the pregnancy period. Data on omalizumab administration in pregnant women is still insufficient. This drug can cross into the placenta, especially in the second and third trimesters.[57,58] The FDA has approved omalizumab for use in the group B medication in pregnancy. No adverse reaction was seen in the mother and fetus after the administration of omalizumab in 11 pregnancies, and data support omalizumab to be considered safe in pregnant women.[59–62]

Cyclosporine

Cyclosporine A is a calcineurin inhibitor with immunomodulatory effects. It can suppress T-cells selectively. It moderately regulates mast cell function and inhibits mediator release. It may be used in refractory atopic dermatitis, CSU, and other dermatological disorders. Cyclosporine has a better risk-benefit ratio in long-term administration than corticosteroids.[44,63] Cyclosporine is not shown to be teratogen in animals and humans. It may lead to increase blood pressure in mother, So its administration in pregnancy should remain as magic bullet for severe recalcitrant cases.[59] Finally, the administration of cyclosporine in pregnant women should remain a second choice based on the risk-benefit ratio.[43]

Systemic Corticosteroids

Administration of topical steroids is not recommended. Because of significant side effects, corticosteroid routine use should be avoided in patients with CU for the long time. In urticaria exacerbations, we can use corticosteroids in short-time and low doses. Despite the fact, this group of drugs causes many adverse effects, they may have some benefits during pregnancy. For example, they are administered during early pregnancy to prevent miscarriage or in mid-late pregnancy for fetal lung maturation. Contradictory data exist about the teratogenicity of synthetic corticosteroids in early pregnancy. Furthermore, it is necessary to consider the risk-benefit ratio in pregnant women.[52,63]

Conclusion

Among several skin eruptions that can occur in the pregnancy period, CSU is a challenging condition. There are dramatic changes in sex hormones during the pregnancy period that may alter the process of disease in pregnant women. Although finding the aggravating factors is impossible in most patients, some underlying conditions may affect the severity and duration of the disease. Drugs, autoimmunity, infections, emotional stresses, and rarely food allergies can influence the typical course of CU. The goal of treatment is complete remission of disease and normalization of quality of life. So, pharmacological treatment should be considered with maximum advisable effect and minimum dose, especially in the first trimester.

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