Low and high IgE is linked to improvement and worsening of chronic urticaria during pregnancy, respectively

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Dear Editor,

PREG-CU, the recent study on pregnancy and chronic urticaria (CU) by the Urticaria Centers of Reference and Excellence (UCAREs), showed that CU improves in half (51.1%) of patients during pregnancy, whereas 28.9% and 20% of patients, respectively, experienced worsening and no change. Low disease activity, no angioedema, and no treatment before pregnancy were risk factors for worsening during pregnancy (1).

We hypothesized that patients with chronic spontaneous urticaria (CSU) that worsens during pregnancy are more likely to have type I autoimmune CSU, also called autoallergic CSU. We also hypothesized that patients who improve during pregnancy are more likely to have type IIb autoimmune CSU (2). This hypothesis is supported by the immunological changes observed during pregnancy, i.e., decreased Th1 and Th17 immunity and a switch to a Th2-type cytokine profile (3).

To test this hypothesis, we retrieved total IgE levels of CSU patients who gave consent to be included in the PREG-CU study (1). Elevated IgE levels have been reported to be linked to autoallergic CSU, whereas low IgE is a marker of type IIb autoimmune CSU (4).

Total IgE blood levels were available for 115 of the 218 CSU patients not treated with omalizumab enrolled in PREG-CU. The median IgE level was 106 (range: 3-1664 IU/mL), more than half of patients (51.3%) had elevated IgE ([?]100 IU/mL), and 17.4% had low IgE (<40 IU/mL). Most patients with mild disease (51%) or moderate disease (61%), but only one in four patients with severe disease (26%) had elevated IgE levels ([?]100 IU/mL). IgE levels were lower in patients with severe disease (68 IU/mL) vs mild (112 IU/mL; p=0.009) or moderate disease (128 IU/mL; p=0.018), and low IgE levels (<40 IU/mL) were more frequent in patients with severe than mild disease (36.8 vs 11.6%; p=0.034).

CSU patients who got worse during pregnancy had higher IgE levels (154 vs. 82.2 IU/mL; p=0.033) and numerically higher rates of elevated IgE (57.5 vs. 46%) compared to patients who got better during pregnancy. In contrast, patients who improved during pregnancy more often had low IgE levels than patients who deteriorated (22 vs. 12.5%), but this was not statistically significant. One in three of our patients (34.9%) had elevated anti-TPO, another marker of type IIb autoimmune CSU, but this was not linked to improvement during pregnancy.

Worsening of CSU during pregnancy in patients with high IgE levels may be explained, in part, by the role that IgE and Th2 immunity play in the pathogenesis of their CSU. High IgE, in CSU, has been linked, in some studies, to autoallergy, characterized by the presence of IgE autoantibodies (5). Pregnancy skews

immunity towards Th2 responses and patients with Th2-driven diseases, including allergies, often experience worsening of their disease during pregnancy (3). Improvement of CSU during pregnancy in patients with low IgE may point to a role of Th1 and Th17 cytokines in the pathogenesis of their disease. Low IgE is a type IIb autoimmune CSU marker, which is linked to Th1 and Th17 autoimmunity (6). Pregnancy decreases Th1/Th17 immunity, and patients with TH1/TH17-driven autoimmune diseases often experience improvement during pregnancy (3). Our finding that elevated IgG-anti-TPO, another marker of type IIb autoimmune CSU, is not linked to CSU improvement during pregnancy remains unexplained. Many CSU patients with IgG-anti-TPO also have IgE-anti-TPO and vice versa, which could point to both autoallergic and autoimmune drivers of their CSU. Better biomarkers are needed to identify which patients have autoallergic CSU, autoimmune CSU, both or none of these.

Our findings support the notion that CSU is a heterogeneous disease, with at least two endotypes, i.e., autoallergic and autoimmune. Further studies are needed to better characterize the course of disease during and after pregnancy, in patients with autoallergic CSU and with autoimmune CSU. IgE levels may help to predict which CSU patients get worse and which improve when they get pregnant.

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