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Commentary

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Pregnancy Outcome in Poly-Autoimmune Disorders: The Case of APECED Syndrome

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Abbreviations: APECED, autoimmune polyendocrinopathy-candidiasis–ectodermal dysplasia; Treg, regulatory T cell.

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Autoimmune polyendocrinopathy-candidiasis–ectodermal dysplasia (APECED) or PAS I is a rare monogenic disorder affecting 10 people/million characterized by different loss-of-function mutations on the *AIRE* gene (1). The *AIRE* gene encodes a protein representing a nonconventional transcription factor, predominantly expressed in the thymus, which localizes to chromatin encompassing the target genes and activates, through histones binding, the complexes involved in the initiation of gene transcription (2). It induces ectopic expression of self-antigens in thymus cells that are otherwise silenced and restricted to other tissues. Ultimately, the *AIRE* gene determines the central tolerance through the deletion of autoreactive thymocytes and modulates the peripheral tolerance through the positive selection of regulatory T cells (Tregs) (1). Its loss of function seems to enable the escape of autoreactive T clones from the thymus to circulation, where poorly efficient Tregs may not ensure peripheral tolerance (3). Almost all developmental tissues are expressed in the thymus under the control of *AIRE* (3), and therefore pregnancy represents a primary event for human immune system. It was previously thought that a constant suppression of the maternal immune system may characterize a successful pregnancy. However, more recent data pointed out that finely modulated immune response guides implantation and placentation, fetal growth, and initiation of labor. Therefore, one could expect, beside the reduction of fertility (4), an increased rate of miscarriage in patients with APECED syndrome, due to the overwhelming role of *AIRE*. While a large body of studies have been dedicated to pregnancy complications in women with the most frequent autoimmune disorders, the few studies focused on pregnancy outcome of APECED patients were carried out in a broader context examining phenotypic presentations of Finnish and Russian cohorts of patients, without describing deeply the pregnancies' course (5). The paper by Laakso and colleagues (5) represents the sole multicentric study on the pregnancy outcome in patients with APECED. In this study, they describe that 43 out of 240 potentially fertile women with APECED became pregnant, with a cumulative number of 83 pregnancies. The low number of pregnancies in the whole group of potentially fertile components of this cohort was partly expected since up to 60% of patients with APECED have primary ovarian failure at a young age but with a large variability in different cohorts (4). In murine models, however, the effect of *AIRE* mutations on fertility is not restricted to ovarian T-lymphocyte infiltration and progressive follicle depletion but also delayed embryonic development and impaired decidualization (6). In humans,

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a 3-fold higher proportion of Treg cells in decidua has been described as compared to the peripheral blood and this concentration is significantly reduced in pregnancies with adverse outcomes (3). Owing to the retrospective nature of this study, it would be difficult to state whether APECED patients experienced implantation failure that, because of its early occurrence without clinical signs, may remain hidden or mistaken with a normal period. This might have reduced the measurable prevalence of pregnancy, which is, in fact, between 13% and 26% in the different cohort encompassed in this study.

The novelty of these results are also related to the low frequency of pregnancy complications such as gestational hypertension and preeclampsia (respectively 8% and 7% of pregnancies) and gestational diabetes (2%), comparable to or even lower than the ones observed in the general population. Noticeably, the clinical course of the APECED-encompassed disorders seemed not to be negatively influenced by pregnancy status, despite the needed adjustments of individual treatments. Offspring birth characteristics were in the normal range in 84% of children. Single or multiple miscarriages have been observed in 14 pregnancies (17%), data not dissimilar to those observed in the general population (5). Neither maternal age nor specific clinical picture of patients was significantly associated with the pregnancy loss. The authors themselves partially explained this result highlighting that most of the women with successful pregnancies showed fewer than 4 APECED manifestations, indicating that the milder phenotype would be related to a more favorable pregnancy outcome. This is in keeping with the finding that 2 out of the 4 women who had pregnancy ending only in miscarriage or ectopic pregnancies showed at least 6 syndrome manifestations. The observed percentage of repeated pregnancy losses in this cohort was even similar to the one observed in a recent paper evaluating patients with thyroid autoimmunity associated with nonendocrine autoimmune disorders (7). The pregnancy loss in these women was independent from the associated autoimmune disorder, suggesting that the immunologic derangement per se might be responsible for recurrent pregnancy loss (7). These poly-autoimmune syndromes, however, are polygenic and multifactorial in nature and apparently have nothing to do with *AIRE* mutations (1). On the other hand, the 2 thymus-derived regulatory T cells, Treg and natural killer T cells, are substantially unaffected in the absence of *AIRE* in murine models (8), empowering the hypothesis that different genetic and environmental factors are involved in the phenotypic expression of this syndrome. In human pregnancy, the actual characterization of the whole immunological imbalance in patients with APECED represents a difficult task: The genetic alterations in patients may differ, leading to the development of different phenotypes. Moreover, in patients bearing the same *AIRE* mutation, substantially different phenotypes have been described (5).

The findings of this paper indicate that most women with APECED have a pregnancy outcome and a rate of complications not dissimilar from the general population. However, the low number of pregnancies among the women in the cohorts studied suggests that the women with APECED who become pregnant may represent a selected cluster, characterized by a milder phenotype. This hypothesis is in keeping with the remnant ability of these women to overcome the immune imbalance that may characterize the women bearing a more severe phenotype.

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Additional Information

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