Would combined glucocorticoid and gonadotropin therapy improve pregnancy rates in women with primary ovarian insufficiency?

This case report involves successful ovulation induction and oocyte freezing in a 25-year-old woman with primary ovarian insufficiency (POI) and polyglandular autoimmune syndrome (PAS) type II (1). She manifested Hashimoto thyroiditis at the age of 12 years and was diagnosed with Addison disease and hypergonadotropic hypogonadism at the age of 25 years. After two failed gonadotropin stimulation cycles, 36 mature oocytes were retrieved following prednisone and gonadotropin therapy. The authors speculate that this patient had anti–FSH receptor (anti-FSHR) antibodies that were successfully treated by steroids, manifested by a lowering of serum gonadotropins and subsequent successful ovulation induction (1).

PAS consists of at least two endocrinopathies and are generally categorized as juvenile (type I) and adult (types II–IV), all of which are more common in females (2). In addition, nonendocrine autoimmune disorders may coexist, including pernicious anemia, myasthenia gravis, systemic lupus erythematosus, rheumatoid arthritis, atrophic gastritis, and autoimmune hepatitis. Juvenile PAS type I is a monogenic autosomal recessive disorder also known as autoimmune polyendocrinopathy, candidiasis, and ectodermal dystrophy (APECED). It is due to biallelic pathogenic variants in the *AIRE* gene (MIM 240300). The adult PASs are defined by specific endocrinopathies: PAS II, Addison disease plus another endocrine disorder; PAS III, type 1 diabetes and autoimmune thyroid disease; and PAS IV, heterogeneous and including other endocrinopathies not considered to be type II or III (2).

Adult PAS is much more common than the juvenile form, and it appears to be polygenic and multifactorial. Genetic variants on chromosome 6, particularly in the human leukocyte antigen (HLA) region, are associated with adult PAS, with HLA-DR3 and DR4 especially associated with PAS II. PAS defects involve both cellular and serologic autoimmunity with a breakdown in self-tolerance. Affected patients display elevated serum titers of γ-isotype autoantibodies that correlate with the severity of tissue destruction. Hypergonadotropic hypogonadism is found in 5%–10% of adult PAS, as in this patient (2).

Hypergonadotropic hypogonadism associated with the presence of multiple ovarian follicles, known as resistant ovary syndrome (ROS), has been known for many years. In fact, when homozygous pathogenic variants in the gene for FSHR (*FSHR*) were identified in Finnish women with POI (MIM 233300), the investigators realized that many had follicles present and this might be a cause of ROS and FSH resistance. This patient certainly fits into the category of ROS: She had 20 preantral follicles and an antimüllerian hormone (AMH) level of 4.3 ng/mL, which are usually good prognosticators for ovarian stimulation in eugonadal women. However, only limited success has been achieved with ovulation induction and pregnancy in hypogonadal women with POI. This patient exemplifies the poor response to standard stimulation with gonadotropins in women with ROS.

However, because of the clinical diagnosis of PAS type II and the possibility of anti-FSHR antibodies in the setting of POI, the authors treated her with relatively high doses of prednisone for 2 weeks, along with oral contraceptives, and her serum FSH dropped from menopausal levels to <10 mIU/mL (1). She continued taking prednisone and was then stimulated in a GnRH antagonist protocol with 11 days of 300 IU FSH and 80 IU hCG, and she had a remarkable response. Her peak E_2 was $\sim$1,300 pg/mL, and she had 36 metaphase II oocytes retrieved. Although only a single case, she serves as her own control, and her response suggests that perhaps the $\sim$4 weeks of steroids improved her chances for success (1).

This patient had antibodies to 21-hydroxylase, and although it was not stated, she would also be expected to possess anti–17-hydroxylase and anti–thyroid peroxidase antibodies. In this case, there were no studies of anti-FSHR antibodies, so the statement that she had anti-FSHR antibodies is only conjectural at present. Although rare, there is good evidence that anti-FSHR antibodies occur in women with POI and in men with gonadal failure. Chiauzzi et al. (3) first published a thorough characterization of anti-FSHR antibodies found in two women with POI and myasthenia gravis, but not in a regularly cycling woman with myasthenia gravis. This inhibitor was an immunoglobulin precipitated from the serum of the affected women that inhibited binding of FSH to its receptor in testes and E_2 production by granulosa cells in an in vitro bioassay. Those investigators extended their work to study patients with POI and found anti-FSHR antibodies in $\sim$9% of women (3). As the authors admit, there was some selection bias of ascertainment, so their 9% positivity rate probably exaggerates that of all women with POI. In addition, 10 of the 23 patients with ROS also had myasthenia gravis. It makes sense that patients with antibodies against one organ could generate antibodies against another organ, which occurs with PAS.

It seems reasonable to consider using glucocorticoids in patients with POI because of the strong association of autoimmune disorders. If this worked, you would think these studies would have already been done. In fact, a randomized controlled trial was published by Badawy et al. in 2007 (4). They randomized 58 women with POI to 28 days of 6 mg/day dexamethasone or placebo, and then all of the women received GnRH agonist/300 IU gonadotropin stimulation. The treatment group had a statistically higher family history of POI, but ovulation occurred in $\sim$20% of the steroid group vs. 10% of the control group. Only one follicle $\geq$18 mm in size was observed in all subjects, and only two pregnancies occurred, both in the steroid group. No mention was made regarding autoimmune conditions or family members with autoimmune disorders. However, this suggests that glucocorticoids could be beneficial in some women with POI. Perhaps women with PAS and POI are the ideal group (if medically stable) to treat with glucocorticoids and gonadotropins, which would be important to determine before treating a large

number of patients with this therapy. The prednisone could have had an effect if she had antibodies to 17-hydroxylase, another unidentified immunogen, antibodies against FSH, or nonspecific inhibition of FSH binding to its receptor. Therefore, whether there are antibodies against FSHR can only be presumptive at this time and should be proved.

Receptor antibodies could either impair function, as with the described FSHR antibodies, or mimic the normal hormone, as with antibodies to thyroid-stimulating hormone receptor in Graves disease. Therefore, it leads one to speculate if FSHR antibodies resulting in activation could produce spontaneous ovarian hyperstimulation syndrome (sOHSS). It is well known that activating, heterozygous, germline *FSHR* variants cause some cases of sOHSS (MIM 608115), and that it can be inherited in an autosomal dominant fashion. Perhaps some FSHR antibodies could activate the FSHR resulting in sOHSS?

Close surveillance of this patient for worsening symptoms and the development of other autoimmune disorders will need to be done. It will be interesting to see the function of these oocytes, i.e., how many fertilize and develop into blastocysts with resultant pregnancy. Based on her response, we would expect a good outcome, but right now this is not known. Another consideration is the risk of transmitting PAS II on to a child. Vertical transmission suggesting autosomal dominant inheritance with incomplete penetrance has been reported in PAS II, so appropriate genetic counseling with up to a 50% risk with each pregnancy becomes an important component of patient management. It is possible that her mother with Graves disease could have PAS II, but with reduced penetrance for other endocrinopathies such that she has not been given the specific diagnosis. It is also important not to forget that this patient has a family history of breast, ovarian, and thyroid cancer, so appropriate counseling and testing for autosomal dominant cancer syndromes needs to be considered.

In summary, this is an interesting case that should provoke additional studies. It is probably not a good idea right now to give prednisone to all women with POI until we have better data. Perhaps patients with PAS who have POI with antral follicles and a reasonably normal AMH could be studied first, or at least women with POI who have one other autoimmune disorder. They could be randomized to treatment with or without prednisone and the response could be evaluated. Further studies on this patient would also help better characterize her autoimmune status and the potential reason for her favorable response. It seems that there might be more optimism for women with POI seeking fertility treatment than when I last commented about autoantibodies for FSHR (5).

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REFERENCES

1. Riestenberg C, Ahern S, Shamonki M. Follicle-stimulating hormone receptor autoantibody associated primary ovarian insufficiency successfully treated with corticosteroids: a case report. F S Rep 2020;1:206–8.
2. Kahaly GJ, Frommer L. Polyglandular autoimmune syndromes. J Endocrinol Invest 2018;41:98.
3. Chiauzzi VA, Bussmann L, Calvo JC, Sundblad V, Charreau EH. Circulating immunoglobulins that inhibit the binding of follicle-stimulating hormone to its receptor: a putative diagnostic role in resistant ovary syndrome? Clin Endocrinol 2004;61:46–54.
4. Badawy A, Goda H, Ragab A. Induction of ovulation in idiopathic premature ovarian failure: a randomized double-blind trial. Reprod Biomed Online 2007;15:215–9.
5. Layman LC. Autoantibodies against the FSH receptor: association or causation? Clin Endocrinol 2004;61:414–5.