Follicle-stimulating hormone receptor autoantibody associated primary ovarian insufficiency successfully treated with corticosteroids: a case report

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Objective: To report a case of successful controlled ovarian stimulation (COH) for oocyte cryopreservation in a patient with autoimmune primary ovarian insufficiency (POI) and polyglandular autoimmune syndrome (PGAS) type 2.
Design: Case report.
Setting: Private in vitro fertilization clinic.
Patient(s): 25-Year-old woman, G0, with autoimmune POI and PGAS type 2.
Intervention(s): Diagnosis of autoimmune interference with FSH signaling, with subsequent high-dose corticosteroid immune suppression and successful oocyte cryopreservation.
Main Outcomes Measure(s): Successful stimulation with exogenous gonadotropins, oocyte retrieval, and cryopreservation.
Result(s): Retrieval and cryopreservation of 36 metaphase-II (MII) oocytes.
Conclusion(s): Scrutiny of POI cases will facilitate identification of a subset of patients in whom immune suppression with short-term, high-dose corticosteroids may enable successful COH. (Fertil Steril Rep® 2020;1:206–8. ©2020 by American Society for Reproductive Medicine.)
Key Words: Primary ovarian insufficiency, autoimmunity, corticosteroids, resistant ovary syndrome, FSH receptor IgG

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Primary ovarian insufficiency (POI) is diagnosed in the setting of amenorrhea and hypergonadotropic hypogonadism before the age of 40 and has a prevalence of approximately 1% in the general population (1). POI is a heterogeneous disease with causes including chromosomal and genetic abnormalities, autoimmune disorders, chemotherapy, radiation, infections, and prior pelvic surgery; however, the majority of POI cases are idiopathic. Data supporting the use of treatments aimed at increasing ovulation and pregnancy rates (eg. estrogen supplementation, corticosteroids) in POI patients are lacking, and these patients consistently respond poorly to stimulation with exogenous gonadotropins (2–4). Oocyte donation is therefore the established treatment option.

In 1969, Jones and de Moraes-Ruehsen (5) coined the phrase "resistant ovary syndrome" to describe the presentation of three patients with hypergonadotropic hypogonadism and resistance to exogenous gonadotropins in the setting of numerous antral follicles. Although early follicular depletion is the most common mechanism of POI, it is now recognized that a subset of patients experience functional ovarian failure as a result of aberrant signaling along the hypothalamic—pituitary—ovarian (HPO) axis due to steroidogenic enzyme defects, paracrine regulators, and inactivating mutations and autoantibodies to the gonadotropins and their receptors. Identification of such cases may enable tailored treatment with improved outcomes compared to those in the POI population in general.

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Polyglandular autoimmune syndrome (PGAS) type 2 is a rare autoimmune disorder that has a prevalence of approximately 5 in 100,000 persons in the United States and that is diagnosed when autoimmune adrenal insufficiency is present in conjunction with either autoimmune thyroid disease and/or type 1 autoimmune diabetes mellitus. Less commonly, PGAS type 2 patients develop additional autoimmune disease including myasthenia gravis, celiac disease, and autoimmune primary ovarian insufficiency. The cause of PGAS type 2 is unknown, though the increased prevalence of autoimmune disease in PGAS patients' family members supports a genetic component. Similar to other autoimmune disorders, PGAS type 2 is more common in women than men, with a ratio of 3:1. Treatment for the component disorders primarily involves hormone replacement therapy and is principally the same as when these disorders occur in isolation.

We report a case of a 25-year-old woman, G0, with POI and PGAS type 2 presenting after two failed oocyte cryopreservation cycles who was treated with corticosteroid suppression and underwent successful oocyte retrieval of 36 MII oocytes. Institutional review board approval for this case report was obtained from the University of California–Los Angeles.

MATERIALS AND METHODS

A 25-year-old woman, G0, with POI and PGAS type 2 presented to an in vitro fertilization (IVF) clinic desiring oocyte cryopreservation. Menarche was at 11 years of age, with irregular menstrual cycles thereafter. The patient had been diagnosed with Hashimoto's thyroiditis at 12 years of age and was subsequently diagnosed with Addison's disease with +21-hydroxylase antibodies at age 25 years after presenting with secondary amenorrhea and chronic near-syncope. POI was diagnosed based on 1.5 years of amenorrhea and persistently elevated gonadotropins (follicle-stimulating hormone [FSH] 40–60s mIU/mL, luteinizing hormone 30–40s mIU/mL, estradiol undetectable). Family history was notable for Grave's disease in the patient's mother, as well as breast, thyroid, and ovarian cancer on her father's side. Surgical history included open appendectomy and laparoscopic cholecystectomy. Current medications included hydrocortisone, fludrocortisone, and levothyroxine.

The patient had recently undergone two cycles of controlled ovarian hyperstimulation (COH) for oocyte cryopreservation at another IVF clinic which were both cancelled due to lack of response (no increase in serum estradiol and no follicular development). The first cycle was human menopausal gonadotropin (hMG) 150 IU daily with concurrent oral estrogen supplementation. The second cycle was gonadotropin-releasing hormone (GnRH) antagonist protocol (Ganirelix Acetate; Organon USA Inc., Roseland, NJ) with recombinant FSH (rFSH) 300IU (Follistim^{T}; Organon Incl) + hMG 150 IU daily with oral estrogen and testosterone therapy.

Baseline ultrasound showed an antral follicle count of 20 and antimüllerian hormone (AMH) was 4.3 ng/mL. Based on the patient's normal ovarian reserve testing and paradoxically elevated gonadotropins in the setting of autoimmune disease and prior resistance to exogenous gonadotropins, the assessment was that the patient likely had an FSH receptor abnormality, possibly secondary to FSH receptor autoantibodies. With this hypothesis in mind, a plan of high-dose steroid therapy leading into an ovarian stimulation with the goal of temporary suppression of immune function was proposed, and the patient consented. The patient's hydrocortisone was stopped and was replaced with high-dose prednisone, given its greater glucocorticoid relative to mineralocorticoid properties. The patient was placed on oral contraceptive pills (OCPs) × 14 days and prednisone 40 mg daily. On the fourth day off of OCPs, her gonadotropins had normalized (FSH 7.9 mIU/mL, E2 45 pg/mL), and she was started on a GnRH antagonist protocol, with FSH 300 IU + hCG 80 IU daily. She remained on prednisone 40 mg daily throughout her stimulation. She had 11 days of stimulation with a peak E2 of 1299 pg/mL and was triggered with hCG 5000 IU SQ (Novarel; Ferring Pharmaceuticals). Oocyte retrieval was performed 36 hours later, with 36 metaphase II oocytes retrieved and cryopreserved. Prednisone was discontinued after oocyte retrieval, and she resumed her baseline hydrocortisone. Informed consent for publication of clinical details and/or clinical images was obtained from the patient.

DISCUSSION

Inactivating autoantibodies to the FSH receptor (Ig-FSHR) have been investigated as a potential cause of primary ovarian insufficiency, particularly in the setting of concomitant autoimmune disease (6–12). However, only one group has definitively documented the presence of Ig-FSHR in patients presenting with POI (13–15). Escobar et al. (13) and Chiauzzi et al. (15) first demonstrated the presence of an FSHR inhibitory factor in the serum of two patients with myasthenia gravis and POI. Through immunoprecipitation, FSH binding studies with rat testis homogenates, radioligand competition studies, and in vitro bioassays, Chiauzzi et al. (15) provided strong evidence that this inhibitory factor was in fact Ig-FSHR. In a subsequent publication, Chiauzzi et al. (14) reported on a cohort of women 14 to 38 years of age who were diagnosed with POI and 46, XX karyotypes and were tested for Ig-FSHR between 1982 and 2001. Of the 247 women in the cohort, 23 (just over 9%) tested positive for Ig-FSHR. All 23 Ig-FSHR–positive patients had previously been diagnosed with resistant ovary syndrome, by either ovarian biopsy (n = 20) or ultrasonography (n = 3). Patients with Ig-FSHR–positive POI had a high rate of autoimmune diagnoses (autoimmune thyroiditis 22.7%, rheumatoid arthritis 2.8%, systemic lupus erythematosus 0.8%, and vitiligo 0.8%). The authors acknowledge that the ~9% prevalence seen in their cohort is likely an overestimation compared to that in the POI population in general, because for the first 10 years of their study the laboratory was specifically focused on resistant ovary syndrome cases. Of note, the clinical management and reproductive outcomes of these or other such resistant ovarian syndrome patients has not been reported.

Although the use of corticosteroids for suppression of aberrant autoimmune antibodies seems intuitive, success in the general autoimmune POI population is lacking and

therefore it is not routinely recommended (1). We report a case of successful COH and oocyte cryopreservation with the use of short-term, high-dose prednisone for temporary immune suppression in a patient with presumptive Ig-FSHR–associated POI who was initially resistant to stimulation with maximal dosing of gonadotropins.

In theory, aberrant FSH signaling due to autoimmunity could be caused by antibodies against FSH, its receptor, or downstream effectors, and immune suppression with corticosteroids would be expected to allow normal stimulation in either case. However, in the setting of antibodies directed at FSH itself, cross-reactivity of those immunoglobulins would be expected to result in a falsely low FSH measurement by immunoassay, which was not seen in this case. In addition, in a study of 135 women undergoing IVF in Estonia, Ig-FSH was positive in a high percentage of the infertile patients and the control subjects, and not was associated with elevated FSH levels (average 8.73 ± 4.69 IU/L) (16). Therefore, we conclude that the mechanism responsible in the case presented here is most likely anti-FSHR immunoglobulin.

CONCLUSION

Recognition of discordant ovarian reserve testing and response to ovarian stimulation enabled successful COH and oocyte cryopreservation in this patient with a diagnosis of primary ovarian insufficiency. The heterogeneous nature of POI requires that we approach each clinical scenario with scrutiny. The association of preexisting autoimmune disease with the presence of Ig-FSHR, as seen in the Chiauzzi et al. (14) cohort of POI patients, suggests that FSHR autoimmunity should be on the differential, particularly in this subset of patients. This case provides evidence that a small subset of POI patients may benefit from immune suppression with a short course of high-dose corticosteroids, potentially enabling fertility preservation for family building with the patient's own genetic offspring.

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