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Case Report

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Resistant Ovary Syndrome Masquerading as Premature Ovarian Insufficiency

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Abstract

Premature ovarian insufficiency (POI) is typically the end result of premature depletion of primordial follicles. However gonadotropin-resistant ovary syndrome could result in a similar clinical and laboratory picture with a more favorable outcome. A 29-year-old G0 woman with POI referred to our infertility clinic for egg donation. On ultrasound, her ovaries contained multiple resting antral follicles (AFs). Patient underwent transvaginal ultrasound-guided follicle aspiration of all visible small antral follicles. Eggs were *in vitro* matured and resulting embryos cryopreserved. Patient achieved a successful live birth with her own eggs. Gonadotropin-resistant ovary syndrome must be considered in all women diagnosed with hypergonadotropic hypogonadal POI and normal antral follicle count (AFC) and anti-Mullerian hormone (AMH). In these patients, pregnancy can be achieved with their own eggs.

Keywords: Resistant ovary syndrome; Premature ovarian insufficiency; IVF

Introduction

Primary ovarian insufficiency is the depletion or dysfunction of ovarian follicles with cessation of menses before age 40 years. It is clinically characterized by hypergonadotropic hypoestrogenic amenorrhea. The reported prevalence is 1% in women under age 40, and 0.1% of women under age 30 [1]. There is currently no consensus on criteria to identify premature ovarian insufficiency (POI) in young women. A reasonable approach to diagnosis includes: documentation of menstrual irregularity for at least 3 consecutive months, elevated follicle stimulating hormone (FSH) with low estradiol levels (confirmed with two laboratory tests at least 1 month apart), and normal prolactin and thyroid function test. Once diagnosis is confirmed, additional evaluation with karyotype, fragile X mental retardation 1 (FMR1) premutation, adrenal antibodies, and pelvic ultrasonography may be indicated to investigate possible karyotype, endocrine, or autoimmune etiologies of POI [2]. Patients will frequently be referred to reproductive endocrinology and infertility specialists to discuss available reproductive treatments; with *in vitro* fertilization using donor oocytes, often the only available treatment option.

We report a case of a patient diagnosed with hypergonadotropic hypogonadal POI who was found to have normal antral follicle count (AFC) and anti-Mullerian hormone (AMH).

Case Report

Patient MG was a 29-year-old, gravidity 0 (G0) of Hispanic origin referred to our clinic for diagnosis of POI. She experienced menarche at age 12 years with normal tanner stage development. At age 16 years she was started on Depo-Provera for contraception, which was later changed to oral contraceptive pills (oral contraceptive pills (OCPs)) until the age of 29 years. The patient had experienced amenorrhea for 6 months after stopping OCPs, and a hormone profile obtained by her gynecologist revealing an FSH level of 86.0 mIU/mL, and a luteinizing hormone (LH) level of 70.2 mIU/mL. Repeat FSH testing obtained 3 months later confirmed a persistently elevated FSH level of 65.6 mIU/mL and an estradiol of 6.6 pg/mL, with a normal karyotype. This was consistent with the diagnosis of hypergonadotropic hypogonadism. The patient's past medical, surgical, social, and family history was unremarkable. Physical exam revealed a well-developed female of normal height and weight (body mass index (BMI) = 24.2 kg/m^2). At her consultation ultrasound, the uterus appeared normal and both ovaries contained multiple resting follicles (3 - 5mm). An AMH was obtained and noted to be 5.64 ng/mL.

Patient underwent testing for a POI sequencing panel and was found to be heterozygous for the 171T variant of uncertain significance in the *NR5A1* gene.

We attempted estrogen-priming followed by controlled ovarian hyperstimulation using menotropins, resulting in no ovarian response after 15 days of stimulation with follicles remaining < 5 mm. After informed counseling we proceeded with retrieval of immature eggs for *in vitro* maturation (IVM). Patient was given 10,000 IU of human chorionic gonadotropin (HCG) to prime the ovaries. Transvaginal ultrasound-guided follicle aspiration of all visible follicles was performed 35.5 h following HCG administration. A total of 12 eggs were re-

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trieved. All 12 eggs were co-cultured, unstripped, in our IVM media for 24 h. Our IVM media was prepared using SAGE™ In-Vitro Maturation Media from Origio® supplemented with 75 mIU of Menopur®. The following day the eggs were stripped and evaluated: 10 eggs were germinal vesicles (GV), one immature (MI), and one atretic. The eggs were all cultured in the same media for a second night. Evaluation on day 2 now revealed seven mature (MII) eggs, four remained as GVs, and one atretic egg. All seven MII eggs were fertilized by intracytoplasmic sperm injection on day 2 and all resulting embryos were cryopreserved in the cleavage stage.

The patient underwent a standard medicated frozen embryo transfer cycle (oral Estrace followed by intramuscular progesterone) 2 months later, with three frozen-thawed cleavage stage embryos. The patient's initial HCG test was 144 mIU/mL that appropriately rose to 353 mIU/mL. An ultrasound performed at 6 weeks of gestation revealed a viable singleton intrauterine pregnancy. First trimester cell-free deoxyribonucleic acid (DNA) testing reported a female fetus with low risk for chromosomal abnormality. Patient went on to have an uncomplicated full-term vaginal delivery of a healthy baby girl weighing 3.88 kg.

Discussion

We present a case of a woman diagnosed with POI who in fact had gonadotropin-resistant ovary syndrome due to an FSH receptor (*FSHR*) mutation. This rare form of ovarian dysfunction results from FSH resistance rather than follicular depletion [3, 4]. Resistant ovary syndrome is rare, and is found in less than 1% of POI patients [5].

In a recent study, histologic evaluation from an ovarian biopsy of a patient with *FSHR* mutation showed many small follicles in primordial, primary, and secondary stages of development [6]. However, *corpora lutea* and mature Graafian follicles were absent suggesting that the primary amenorrhea was due to a block in follicular maturation and not depletion of ovarian follicles. During folliculogenesis, the primordial follicles do not express FSHR [7]. FSHR, along with LH, estrogen and androgen receptors, begins to be expressed by the granulosa cells and thecal cells as the follicles progress from the primary to the secondary (pre-antral) stage [8]. In patients with FSH resistance, follicular maturation starts but then is impaired, with follicular arrest at the small antral stage which appear as 3 - 5mm follicles on transvaginal ultrasound [9].

AMH is expressed in the granulosa cells of preantral and small antral follicles and serves as a molecular biomarker for the relative size of the ovarian reserve [10]. Previous studies have shown that patients with FSH resistance have low to normal AMH values, while women with POI (due to follicular depletion) have very low to undetectable AMH [11]. In our patient, follicles were able to reach the early antral follicle stage as noted by her baseline ultrasound and age appropriate AMH.

There have been sparse case reports of successful live births in women with resistant ovary syndrome following *in vitro* maturation. IVM is still considered experimental and optimal protocols have not been established [12]. However the limited data on live births following IVM/ *in vitro* fertilization (IVF) show no increase in adverse obstetric and perinatal outcomes [13].

In conclusion, initial workup for POI should include an AMH level and a detailed pelvic ultrasound to evaluate for antral follicles. In patients with true POI, the FSH, AMH and AFC should be concordant. Discordant test results should prompt further evaluation. Gonadotropin-resistant ovary syndrome must be considered in all women diagnosed with hypergonadotropic hypogonadal POI. Successful pregnancy may be achieved with IVM in such cases.

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Conflict of Interest

No part of this work was presented at the Annual Clinical Meeting of the American College of Obstetricians and Gynecologist or at any other organizational meeting. All authors have no conflict of interest to declare.

Informed Consent

Signed informed consent from the patient to present her care as a case report was obtained.

Author Contributions

The authors performed all of the manuscript preparation, writing, and editorial assistance.

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