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Case Report

Gonadotropin-Resistant Ovary Syndrome Presented with Secondary Amenorrhea and Infertility: A Case Report

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Abstract

Resistant ovary syndrome (ROS) is a presentation of hypergonadotrophic hypogonadism condition with very low incidence. Infertility is one of the most common complaints of women with this syndrome. We herein present a case of a 27-year-old woman with all features of secondary amenorrhea and secondary sexual characteristics. In 2018, the patient was referred to the Hazret-e-Zeinab Infertility Center affiliated to Shiraz University of Medical Sciences, Shiraz, Iran. She was diagnosed with secondary amenorrhea and increased gonadotropin secretion after menopause. However, the patient had a normal antral follicle count, anti-Müllerian hormone level, 46, XX karyotype, and thyroid function. After taking oral contraceptives her menstruation started, but she showed no response to high doses of exogenous gonadotropins. She was advised to have an embryo derived from *in vitro* maturation. By using patients' own oocyte maturation, this technique could be a better treatment for infertile women with ROS. This case report is particularly interesting due to the rarity of its prevalence and similarity with primary ovarian insufficiency.

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Keywords ● Primary ovarian insufficiency ● Ovarian reserve ● Infertility ● Amenorrhea

What's Known

- Resistant ovary syndrome is one of the disease lead to ovarian failure and secondary amenorrhea.
- Diagnosis of this disease is based on having a normal 46, XX karyotype, normal secondary sexual characteristics, elevated follicle-stimulating and luteinizing hormone, and normal anti-Müllerian hormone.

What's New

- A case of a patient with all features of secondary amenorrhea and secondary sexual characteristics is described.
- Live birth is possible in patients with gonadotropin-resistant ovary syndrome.

Introduction

Resistant ovary syndrome (ROS) is a presentation of hypergonadotrophic hypogonadism condition with very low incidence. Infertility is one of the most common complaints of women with this syndrome. Previous studies have associated ROS with primary or secondary amenorrhea, normal secondary sexual characteristics, normal chromosome level, elevated gonadotropin levels of menopausal range, unresponsiveness to gonadotropin stimulation, and an acceptable number of small antral follicles.[1] Due to certain similarities, ROS could be incorrectly diagnosed as primary ovarian insufficiency (POI); the differentiating factor is the number of antral follicles.[2] The main features of ROS are endogenous hypergonadotropinemia, the presence of a normal amount of ovarian follicles, and hyporeceptivity of the ovaries to an excessive stimulation with exogenous human gonadotropin. Several studies have described patients with one or two of these features. However, only a few cases of patients with all three features have been reported.[3] We herein present a case of a 27-year-old woman with all features of secondary amenorrhea and secondary sexual characteristics.

Case Presentation

In December 2018, a 27-year-old nulligravida woman was referred to Hazret-e-Zeinab Infertility Center affiliated to Shiraz University of Medical Sciences, Shiraz, Iran. The patient experienced seven years of secondary amenorrhea and five years of infertility. Preliminary investigations showed that the patient had a normal male factor and normal hysterosalpingography. Since her menarche at the age of 11, she had a normal menstrual cycle. At the age of 20, as a result of cyclic progesterone therapy, which only lasted 3-4 months, she developed secondary amenorrhea and was treated for regular withdrawal bleeding. However, bleeding occurred only with sequential estrogen and progesterone. During this period, she did not report having had any hot flushes. She was prescribed medication for the induction of ovulation without a positive response.

The general physical examination of the patient was normal and her body mass index was 19.8 kg/m^2. She had a normal female body hair pattern, breasts, and external and internal genitalia. Six years earlier, at the age of 21, the results of her first hormonal assay were thyroid-stimulating hormone (TSH): 1.9 mU/L (0.4-6.21), follicle-stimulating hormone (FSH): 79.8 IU/L (menopausal value >35), luteinizing hormone (LH): 63.7 IU/L (menopausal value>14), prolactin: 12.8 ng/ml (0-20), and anti-Müllerian hormone (AMH): 6.5 ng/ml (normal range>1). A chromosomal study reported 46, XX compatible with a normal female pattern. At the age of 23, the adrenal cortex function test showed normal results; adrenocorticotropic hormone (ACTH): 23.4 pg/ml (8.3-57.8), urine free cortisol: 22.6 mcg/dl (10-100), insulin-like growth factor 1 (IGF1): 192 ng/ml (116-341), and cortisol 8 AM: 20.6 mcg/dl (5.49-28.7). FSH was again elevated beyond menopausal values; FSH: 98.42 IU/l (35.6), LH: 82.5 IU/l (73.3), AMH: 3.87 ng/ml (normal range>1), prolactin 48 ng/ml (1.2-37). The patient was treated with cabergoline 0.5 mg twice weekly for two years, after which her brain MRI was normal. In 2017, at the age of 26, the results of her hormonal assay were AMH: 2.46 ng/ml (normal range>1), FSH: 29.5 IU/l (25.8- 134.8 post-menopausal range), and prolactin: 18 ng/ml (4.79-23.3).

After gynecological and endocrinological investigations, the patient was treated with a high-dose (450 IU/day) of exogenous gonadotropin (Menopur 75 IU; Ferring GmbH, Kiel, Germany) for 10 days without any response or follicle growth. Transvaginal ultrasonography for follicle counts was done monthly on the second day of withdrawal bleeding after the estrogen and progesterone treatment. All antral follicles measuring up to 11 mm on both ovaries were counted.

After consultations, the patient and her partner opted for the *in vitro* maturation (IVM) approach. She began a cycle, but the oocytes retrieved by ovum pick-up did not qualify for IVM. Written informed consent was obtained from the patient for the publication of the present rare case report.

Discussion

The case of a 27-year-old woman with secondary amenorrhea and secondary sexual characteristics is reported. The present case report is particularly interesting due to the rarity of its prevalence and similarity to POI.

In the past, invasive methods such as ovarian biopsies have been used to identify primordial and immature follicles. Upon histological examination of a full-thickness ovarian biopsy, the absence of follicles would differentiate POI from the more infrequent ROS. Nowadays, non-invasive approaches are used to detect the presence of antral follicles.[3] Hormone biomarkers such as inhibin B and AMH are also good diagnostic indicators of ROS. However, an increase in the diameter of small antral follicles reduces AMH concentrations, while it increases inhibin B levels.[4] Therefore, AMH levels can better reflect on the quality of antral follicle and ovarian reserve in order to distinguish ROS from POI.[5] For a better evaluation of the ovarian reserve in female patients, multiple hormonal assays (FSH, AMH, and AFC) are required. In case of inconsistency between clinical manifestations, biomarkers, and ultrasonography (as in our case report), one should consider the presence of ROS.

Li and colleagues reported a case of ROS with secondary amenorrhea and infertility in a multiparous woman. After being diagnosed with ROS, their patient had a live birth after IVM treatment.[6] Some previous studies on ROS only focused on patients features and the pathogenesis of the disease.[7, 8] However, since 2016, there are only three case reports of patients who underwent IVM using their own premature oocytes that resulted in healthy babies at term.[6, 9, 10] Despite the unsuccessful IVM treatment in our patient, this new technique should be offered by infertility centers to help such patients to have children using their own oocytes.

Conclusion

ROS should be considered when a patient has POI symptoms but presents normal AMH levels

and antral follicle count. As an alternative to the use of donated eggs, the IVM technique should be proposed to such patients to facilitate pregnancy using their own oocytes.

Conflict of Interest: None declared.

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