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BRIEF COMMUNICATION

# Two Cases of Primary Ovarian Insufficiency Accompanied by High Serum Anti-Müllerian Hormone Levels and Preservation of Ovarian Follicles

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Primary ovarian insufficiency (POI) is defined as the presence of amenorrhea for ≥ 4 months accompanied by evidence of two serum follicle-stimulating hormone levels in the menopausal range in women aged < 40 years. Anti-Müllerian hormone (AMH) has been recognized as the most reliable marker of ovarian reserve status, and its serum level is very low or undetectable in women with POI. Here we report two cases of patients who were diagnosed with POI despite high serum AMH levels and preservation of ovarian follicles, as revealed by ultrasound. In addition, we have presented a review of the current literature regarding this condition.

**Key Words:** Anti-Müllerian hormone, Ovarian follicle, Primary ovarian insufficiency

## INTRODUCTION

Primary ovarian insufficiency (POI) is defined as the presence of amenorrhea for ≥ 4 months accompanied by two serum follicle-stimulating hormone (FSH) levels in the menopausal range for a woman < than 40 years of age [1,2]. Approximately 1% of women will develop POI before the age of 40 years [1,3]. Women with untreated POI are at increased risk of developing osteoporosis, cardiovascular disease, dementia, and Parkinsonism [4]. Although premature follicular depletion is the cause in almost all cases, additional specific evaluation is indicated to exclude conditions (e.g., chromosomal and other genetic abnormalities and autoimmune diseases) that may have potential health implications for the patient [1]. If the diagnosis of POI is confirmed, the patient should be tested for *FMR1* premutation, karyotype, and 21-hydroxylase antibody [1,2].

Anti-Müllerian hormone (AMH) is now recognized as the most reliable marker of ovarian reserve status [1,5,6]. Decreased serum AMH levels are a reflection of decreased ovarian reserve, and very low or undetectable AMH levels in women with amenorrhea strongly suggest ovarian failure [1,3,7]. In contrast, amenorrhea accompanied by AMH levels greater than 5 ng/mL is suggestive of polycystic ovary syndrome [1,8].

We report two cases of patients diagnosed with POI at separate university hospitals who showed high serum AMH levels and the preservation of ovarian follicles on ultrasound.

## CASE REPORT

### Case 1

A 33-year-old woman was referred to a university hospital for the evaluation of secondary amenorrhea for 4 months. The patient had spontaneous thelarche at age 11 years and menarche at age 13 years. She denied experiencing vasomotor symptoms. A human chorionic gonadotropin (hCG) urine test was negative. The

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results of the physical examination were as follows: height 165.0 cm, weight 60.2 kg, systolic blood pressure 132 mmHg, and diastolic blood pressure 77 mmHg. Breast development and pubic hair growth were both stage 5 according to the Tanner staging system. Basal hormonal tests revealed highly elevated serum FSH and luteinizing hormone (LH) levels (52.7 IU/L and 33.2 IU/L, respectively), a low estradiol (E2) level (17.8 pg/mL), and high AMH level (5.04 ng/mL). Serum levels of prolactin, thyroid-stimulating hormone, and free T4 were all normal. A transvaginal ultrasound revealed a normal-sized uterus with polycystic ovarian morphology (> 20 antral follicles measuring 2–9 mm) observed in the right ovary (Fig. 1A).

The patient was unmarried and wanted to preserve her fertility; therefore, she was advised to visit an infertility hospital for oocyte cryopreservation. The repeated basal hormonal tests were unchanged, and serum levels of androgens including total testosterone, free testosterone, 17α-hydroxyprogesterone, and dehydroepiandrosterone sulfate were all normal. Induction of superovulation was attempted with a starting dose of 150 IU recombinant FSH (Follitrope®; LG, Iksan, Korea) daily for oocyte cryopreservation. The dose of recombinant FSH was increased to 225 IU after one week because follicular development was not observed on ultrasound. However, follicular development was not observed despite the increase in FSH dose, and cycle cancellation was determined at that time. Further evaluation included karyotype, *FMR1* premutation, and 21-hydroxylase antibody tests. The karyotype analysis revealed 47,XXX[1]/46,XX[29]; however, it was read as a normal variant by the specialist in laboratory medicine. The *FMR1* premutation test revealed no abnormal CGG trinucleotide repeat expansion. The patient tested negative for 21-hydroxylase antibodies. In addition, anti-thyroglobulin antibodies and anti-thyroid peroxidase antibodies were negative. She was prescribed oral contraceptives (Yaz®) for hypoestrogenism associated with POI.

## Case 2

A 25-year-old woman visited the primary gynecologic clinic because of amenorrhea for 6 months. She had frequently experienced hot flashes, night sweats, and insomnia. She experienced thelarche at age 12 years and menarche at age 14 years. Her menstruation had been irregular since menarche. A hCG urine test was negative. Basal endocrine testing revealed highly elevated serum FSH and LH levels (29.4 IU/L and 43.5 IU/L, respectively), a low E2 level (25.5 pg/mL), and normal prolactin level (14.10 ng/mL). Tests were repeated after 7 weeks and revealed serum FSH and E2 levels of 52.6 IU/L and 41.0 pg/mL, respectively, and an AMH level of 10.88 ng/mL. The patient was referred to a university hospital for further evaluation.

The initial physical examination at the university hospital revealed the following: height 156.8 cm, weight 66.9 kg, systolic blood pressure 120 mmHg, diastolic blood pressure 80 mmHg, pulse rate 20/min, respiratory rate 80/min, and body temperature 36.4°C. Breast development and pubic hair growth were both stage 5 according to the Tanner classification system. A transrectal ultrasound revealed a normal-sized uterus with polycystic ovarian morphology (35 antral follicles measuring 2–9 mm in the right ovary [Fig. 1B] and 26 in the left ovary). The repeated serum FSH, LH, E2, and AMH levels acquired in the university hospital were unchanged. Elevated thyroid stimulating hormone (TSH; 6.63 mIU/L) and normal free T4 (1.07 ng/dL) levels were observed, and all anti-thyroid antibody tests showed above normal blood levels of antibodies (anti-

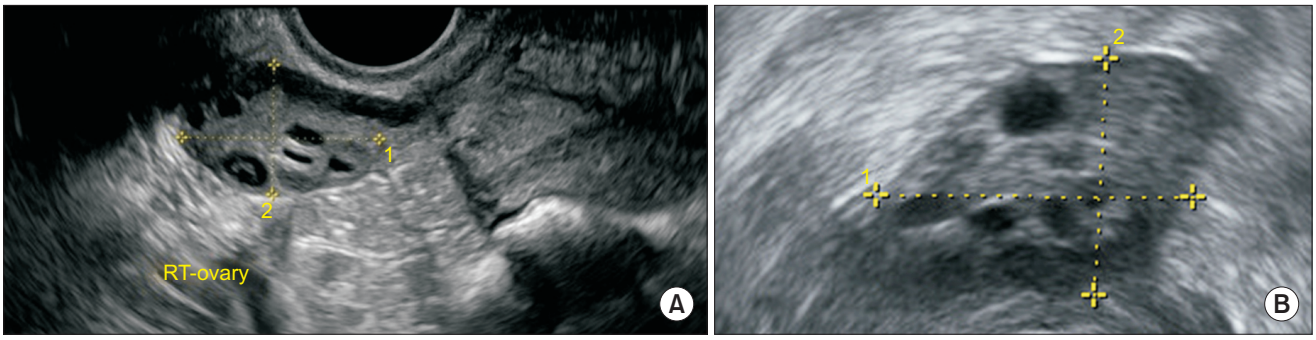


Fig. 1. Ultrasound findings of right (RT) ovary in: (A) Case 1; (B) Case 2.

thyroglobulin antibody 234.6 IU/mL and anti-thyroid peroxidase antibody 845.1 IU/mL). Serum androgen levels were normal. A karyotype analysis revealed a normal female karyotype. The *FMR1* premutation test was normal, and the 21-hydroxylase antibody test was negative. She was prescribed conjugated estrogens (Premina®) 0.625 mg/d in combination with cyclic micronized progestogen (Utrogestan®) 200 mg daily for 14 days per month.

## DISCUSSION

Women with amenorrhea younger than 40 years of age with an evidence of persisting hypergonadotropic hypogonadism are diagnosed with POI [1]. Diagnosis should be confirmed by an elevated FSH level greater than 40 IU/L and an E2 level below 50 pmol/L in the absence of bilateral oophorectomy [4].

Circulating levels of AMH are now recognized as a more reliable marker of ovarian reserve status compared to FSH, inhibin B, and the antral follicle count [1,5,6]. AMH levels have been alleged to be very low or undetectable in women with POI [3,5,7]. However, in the present two cases, both POI patients had high serum AMH levels (> 5 ng/mL).

One possible explanation is that the cause of POI in the present case reports is steroidogenic autoimmunity. Approximately 4% of women with POI were noted to have steroidogenic cell autoimmunity (SCA) with lymphocytic oophoritis (autoimmune oophoritis) as the mechanism for follicular dysfunction [1,2,9]. Some studies noted that women with POI due to SCA (SCA-POI) had normal serum AMH levels [3,7,10,11]. La Marca et al. [11] reported that AMH concentrations were significantly higher in women with SCA-POI than in women with idiopathic POI or postmenopausal women, and two thirds of women with recent-onset (< 5 years) SCA-POI had normal serum AMH levels. Normal serum AMH levels in SCA-POI suggest that the pool of growing follicles in autoimmune POI is initially preserved [7,12]. Ovarian antibody testing is not clinically reliable for diagnosing autoimmune oophoritis because some women with biopsy-proven autoimmune oophoritis may have a negative test for ovarian antibodies [2]. However, women with autoimmune lymphocytic oophoritis appear to reliably test positive for adrenal antibodies, and the most readily available antibody is 21-hydroxylase. In our cases, both patients tested negative for the 21-hydroxylase antibody; thus, autoimmune oophoritis is hardly considered as a strong causative factor.

Several other autoimmune disorders have also been associated with POI; hypothyroidism is the most common disorder [13], but there are no direct evidences of relationship between hypothyroidism and its effect against POI [1]. In addition to testing for the 21-hydroxylase antibody, women who are suspected of having POI should be screened for anti-thyroid antibodies (antithyroid peroxidase and antithyroglobulin antibodies) [1,2]. In case 2, all anti-thyroid antibodies were positive along with the elevation of serum TSH levels; however, the presence of thyroid autoantibodies does not prove autoimmune ovarian failure [2].

Another possible (and seemingly more attractive) explanation concerning our cases is that a FSH receptor mutation or FSH-resistant ovaries (FSHRO) induced POI in our patients. Disproportionately elevated FSH levels can be observed despite the presence of ovarian follicles in cases of inactivating mutations involving the FSH or LH receptors [1]. Kallio et al. [10] previously identified a recessively inherited inactivating mutation in the FSH receptor gene, which results in a dramatic reduction in signal transduction and FSHRO. Additionally, they reported that serum levels of AMH in women with FSHRO were not significantly different from those in normal control women and significantly higher than levels in women with primary or secondary amenorrhea of unknown etiology [10].

Gonadotropin-resistant ovary syndrome (gonadotropin-ROS) or ROS, first described by Jones and De Moraes-Ruehsen [14] in 1969, is known to be one of the causes of ovarian failure leading to primary or secondary amenorrhea. The presence of a normal amount of antral follicles is a criterion that distinguishes ROS from the classical POI [14,15]. Besides an age-compatible number of small antral follicles, additional cardinal clinical features of ROS are normal chromosome, elevated gonadotropin levels of menopausal range, and unresponsiveness to gonadotropin stimulation [15], all of which are consistent with our cases. If the diagnosis of our cases is correct for ROS, in vitro maturation (IVM) of oocytes may be a feasible option of treatment for infertility in our cases because some authors reported successful live births in women with ROS following IVM using their own oocytes [15,16].

In case 2, the chromosomal karyotyping test revealed 47,XXX[1]/46,XX[29]; however, this result was read as a normal variant because 1%–2% of 47,XXX cells

could be found in normal women [17]. Women with a 47,XXX karyotype may develop ovarian failure [2], and even low-level X-mosaicism (between 6%–10% of aneuploid cells) might be associated with the development of POI [17].

AMH is an undoubtedly useful marker for the assessment of ovarian reserve, and it also may be a feasible marker for the diagnosis of POI. However, in rare situations, normal or high serum AMH levels may occur in patients who are diagnosed with POI. Further studies are needed to clarify the utility of serum AMH levels in women suspected of having POI.

## CONFLICT OF INTEREST

No potential conflict of interest relevant to this article was reported.

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