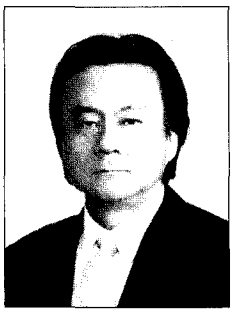
S 3

Bunpei Ishizuka

Department of Obstetrics and Gynecology
St. Marianna University School of Medicine



2000-present	Professor and Chair
	Dept. Ob/Gyn, St. Marianna University School of Medicine
1993	Associate Professor
	Dept. Ob/Gyn, St. Marianna University School of Medicine
1979-1981	Research Fellow
	Dept. Reproductive Medicine, University of California, San Diego, U.S.A.
1979	Doctor of Medical Science: Keio University
1971	M.D.: Showa University School of Medicine

Premature Ovarian Failure: An Update

Bunpei Ishizuka, M.D.

St. Marianna University School of Medicine, Japan

Premature ovarian failure (POF), which occurs in 1% of all women, is defined as hypergonadotropic amenorrhea under 40 years of age. It is diagnosed when serum FSH levels exceed 40mIU/ml in 2 consecutive blood samples taken 7-10 days apart.

POF was considered to be a rare and irreversible condition. However, with the advent of RIA and recent ovulation induction methods, cases of successful ovulation induction and pregnancy have been reported. In addition, there have been reports of cases with spontaneous remission of POF, demonstrating that this condition is not always irreversible. Also, recent reports on patients with infertility, regular menses and elevated serum FSH levels, who are poor responders to controlled ovarian stimulation (COH), suggest that POF may be a progressive disorder.

Reported causes of spontaneous POF include: a) Genetic abnormality, which could involve chromosomal aberrations largely involving the X chromosome. A large number of genes have been screened as candidates for causing POF; however few clear causal mutations have been identified. b) Autoimmune ovarian damage, as suggested by the observed association of POF with other autoimmune disorders. Anti-ovarian antibodies are reported in POF by several studies, but their specificity and pathogenic role are questionable. c) Iatrogenic causes include ovarian damage following surgical, radiotherapeutic or chemotherapeutic interventions as in malignancies.

Screening for associated autoimmune disorders and karyotyping constitute part of a diagnostic work-up. There is no role of ovarian biopsy or ultrasound in making diagnosis.

By analyzing 105 consecutive, spontaneous POF patients, we found that 16% of those patients showed chromosomal abnormality and about 50% of the patients demonstrated circulating auto-antibodies. About 25% of the patients who had auto-antibodies were diagnosed as having clinical autoimmune diseases. Among 55 normokaryotypic patients tested, 3(3.4%) demonstrated FMR-1 premutation. Thus, in about 25% of the spontaneous POF patients, possible etiological factors can be identified.

The difference among the natural courses of the disease was investigated according to the different etiology among POF patients.

Ovulation induction in cases with established POF is rarely successful, however, occasionally follicle maturation is obtainable in cases with a relatively short history of amenorrea. The basis of ovulation induction in POF patients is exogenous estrogen administration, which acts by sensitizing the granulose cells to the effect of FSH, leading to ovulation and conception. Oral contraceptives

may act similarly by down-regulating the LH and FSHRs. Down-regulation of gonadotropin secretion using GnRH analogues occasionally reverses POF for a short while, but is usually not effective. Also, HMG or rFSH administration is not usually effective in inducing ovulation, however, adjuvant administration of an NO donor, e.g. L-arginine or glucocorticoid may increase the success rate.

Thus, management essentially involves hormone replacement and infertility treatment, the only proven means for the latter being conception with donated oocytes. Embryo cryopreservation, ovarian tissue cryopreservation and oocyte cryopreservation hold promise in cases where ovarian failure is foresseable, as in women undergoing cancer treatment.