PREMATURE OVARIAN FAILURE

By

JAYESH J. SHETH, FRENNY J. SHETH, R. N. BANKER, BIPIN S. SHAH, R. M. NADKARNI AND N. I. SHAH

SUMMARY

The diagnosis of premature ovarian failure was made in 31 women (age 15 to 40 yrs). All these women had an elevated levels of serum FSH (123 ± 9.9 mIu/ml), serum LH (84.03 ± 8.07 mIu/ml) and low levels of serum 17B estradiol (34.05 ± 12.6 pg/ml). Five had primary amenorrhoea and 26 had secondary amenorrhoea. One patient with primary amenorrhoea had an abnormal chromosomal complement (45XO/46XX). Three of the 20 women investigated for thyroid antibody had an autoimmune thyroid disorder (thyroid antibody more than 1:1,600) and one had Addison's disease (plasma cortisol—less than 10 ng/ml). None of these women conceived after they developed ovarian failure and while on cyclic estrogen/progesterone treatment.

Introduction

The etiology of premature ovarian failure (POF) is unknown. It is probably a genetic disorder with either a reduced number of primordial follicles or an increased rate of disappearance. Endocrinologically POF is characterised by hypergonadotropic amenorrhoea before the age of 40. Though the condition is not life threatening, it has a marked emotional impact, particularly on those women who desire to conceive and raises concerns regarding the need for long term estrogen replacement.

The condition of POF may be due to a known genetic disorder associated with atresia of the follicles (Turner variants) or the destruction of germ cells by viral infection, drug or other agencies. Mild immunological deficiency may be associated with POF.

Present study was undertaken to know the etiology of POF and the relative frequency of each cause.

Material and Methods

Clinical and laboratory data of 108 women who came to our laboratory for sterility/infertility investigations were reviewed. Based on clinical findings they were divided into two groups of amenorrhoea,

1. Primary amenorrhoea (n = 8).
2. Secondary amenorrhoea (n = 100).

31 women were diagnosed as premature ovarian failure with the help of serum FSH, LH and estradiol. Out of these, 5 had primary amenorrhoea and 26

From: Unit, Medicare Centre, Ellisbridge, Ahmedabad-380 006.

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had secondary amenorrhoea. Twenty women were screened for thyroid microsomal antibody. In one patient, plasma cortisol estimation was carried out, using RIA kit of Diagnostic Products Corporation (DPC) by coat-Account method.

Hormonal investigations were carried out by radioimmunoassay using kit of DPC. In each case ^{125}I-labelled ligands served as tracers. Assay performance was monitored by control sera representing low, medium and high concentration of hormone analysed.

Results

The average age of patients with ovarian failure was 25 years ranging from 15 to 40 years. The average age of menarche was 13 years (range 11-15 years). The menstrual cycle before the onset of POF was regular in all patients except in 5 patients with primary amenorrhoea. Table I describes the hormone levels (FSH, LH, Estradiol) in 31 subjects. Of these patients, 20 were screened for autoimmune disease with the help of history and laboratory findings (thyroid microsomal antibody and hemoglobin). An associated autoimmune disease was found in 4 patients. These included 1 with Addison's disease (plasma cortisol less than 20 ng/ml) and with thyroid disease. All 3 patients with thyroid disease had strongly positive thyroidmicrosomal antibody but were clinically euthyroid (Table II). In 4 patients very low titre of thyroid microsomal antibody was found.

Though ovarian biopsy or laproscopic evaluation is not essential for the diagnosis of POF, ovarian biopsy may inentify afollicular or follicular POF. Patients with residual follicles are more likely to respond to stimulatory therapy.

In 10 of 31 patients laparoscopy was performed before hormonal investigations. Nine of them had typical atropic ovaries and 1 with primary amenorrhoea had ovarian agenesis (Mullerian tract abnormalities). Pregnancy had not occurred in any of 31 patients before onset of their premature ovarian failure.

TABLE I

Hormones Concentration in Women With Premature Ovarian Failure

Amenorrhoea		Age group in years	FSH mIu/ml	Hormones concentration LH mIu/ml	Estradiol pg/ml
Primary	Secondary				
5	26	15-40	123.5± 9.9	84.03± 8.07	34.05 ± 12.6

Values are mean ± S.D.

TABLE II

Thyroid Microsomal Antibody

Amenorrhoea	No. of subjects	Titre	
		Positive	Negative
Secondary amenorrhoea	20	1:1,600 (3) 1:64 (4)	13

Discussion

The clinical diagnosis of ovarian failure cannot be made unequivocally because usually these patients have normal secondary sexual characters. Women with ovarian failure may not be ammennorheic and may menstruate and ovulate sporadically (Rebar *et al*, 1982; and Szlachtar, 1979). In such conditions, detailed hormonal investigations of infertile women will help to solve the dilemma of the gynaecologist. In our study we have found that serum levels of FSH and LH that consistantly exceeded 80 mIu/ml and estradiol (less than 35 pg/ml) excluded the possibility of laboratory error for the diagnosis of POF. These findings confirm that ultimately concentrations of FSH and LH in the postmenopausal range are necessary to establish a diagnosis of ovarian failure. It is difficult to distinguish the different causes of ovarian failure with certainty. It is likely that high levels of gonadotropins are induced by a severe pathological activation of hypothalamic-pituitary negative feedback due to an insufficient or absent gonadal synthesis of steroid and to the absence of terminal follicles. Probably some nonhormonal factors take part in the etiopathogenesis of this syndrome. Among them the most important one is probably the absence of inhibin, a peptide factor produced by the gonads which regulates the hypothalamic-pituitary feedback in men and women by regulating FSH secretion. A frequent association of POF with other autoimmune disease has been reported. Michael *et al* (1985) reported an autoimmune disorder in 39% of women with POF, the majority of them had thyroid diseases. In our study, 20 of 31 patients with POF were investigated for thyroid microsomal antibody and in 3 of them we have found significant titre (1:1,600) of thyroid antibody. Addison's disease was diagnosed in 1 patient with POF. In this patient plasma cortisol level was 10 ng/ml.

Four of 5 patients with primary amenorrhoea had elevated levels of serum FSH and LH. Chromosomal study carried out elsewhere revealed an abnormal chromosomal complement (45XO/46XX) in 1 of them, while remaining had normal chromosomal pattern (46XX). Thus 3 patients had a chromosomally competent ovarian failure (CCOF syndrome) and 1 had a chromosomally incompetent ovarian failure (CIOF syndrome). Laparoscopy was not performed in any of these patients.

Several autoimmune diseases may occur concomitantly with POF. The coexistence of idiopathic hypoparathyroidism, adrenal insufficiency and gonadal failure have been noted by several authors (Duff and Bernstein, 1933; and Kleerekoper *et al*, 1974).

The large number of autoimmune disorders that are associated with POF strongly suggests that many patients develop premature menopause through an autoimmune mechanism. It is reasonable to believe that immunoglobulins interfere with the binding of gonadotropins to ovarian follicular receptors which leads to an unopposed secretion of FSH and LH from the pituitary without any action on target organ (ovary). The result is hypergonadotropic amenorrhoea in the presence of primordial follicles in the ovaries.

Further complicating the distinction between the different causes of POF is the observation that ovarian follicles of women with gonadotropin resistant ovary syndrome are refractory to FSH stimulation (Maxson and Wentz, 1983). Because the capacity to respond to FSH is a necessary step in the process of follicular

maturation, this lack of response may also result in a mild form of accelerated follicular atresia. However, there are reports of pregnancy in young women with hypergonadotropic ovarian failure (Soren, 1984). The reason is, there are two types of ovarian failures. One is the follicular form of ovarian failure when the patient may conceive after an exogenous estrogen treatment which stimulates the formation of ovarian estrogen receptors and promotes a premissive effect that allows expression of FSH action i.e. follicular maturation and ovulation. Though only a rare woman with hypergonadotropic amenorrhoea can be expected to conceive.

Pregnancy is possible also in women with autoimmune ovarian failure. Although no pregnancies have been reported. Ovulation was restored temporarily by plasmapheresis in a women with myasthenia gravis (Bateman *et al*, 1983) and by glucocorticoid therapy in a woman with a perifollicular lymphocytic infiltrate. Pregnancy in a young woman with idiopathic hypergonadotropic 'ovarian failure' has been reported by Soren (1984).

Some may argue that an ovarian biopsy is necessary to distinguish the diagnosis of follicular and afollicular form of ovarian failure. But usually this does not change the clinical management. Most women have an afollicular form of POF. Autoimmunity and gonadotropin resistance each account for approximately 11% of women with POF. Estrogen replacement therapy may result in ovulation, but this is infrequent and unpredictable while the probability of pregnancy is low. There is still a lacuna in our knowledge and understanding of the cause and management of POF. A better understanding in receptor mechanism at gonadal level is required.

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