Original Article

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Premature Ovarian Failure: An Association with Autoimmune Diseases

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Introduction: Premature Ovarian Failure (POF) is the cessation of ovarian function before the age of 40 years. POF is reported to be associated with autoimmune diseases in 20-30% of cases.

Aim: Patients presenting with idiopathic POF were screened for the presence of autoimmune disorders.

Materials and Methods: Twenty patients with idiopathic POF were included in the study. Baseline investigation in all subjects included fasting serum FSH, LH, E2, progesterone, free T3, free T4, Thyroid-Stimulating Hormone (TSH) and Anti-Thyroperoxidase (anti-TPO) antibodies, testosterone and Dehydroepiandrosterone (DHEAS) levels. Fasting and post-glucose (2 hours after 75g of oral glucose) serum calcium and phosphate were estimated using appropriate assays in biochemistry laboratory.

Results: Seven patients (35%), who presented with secondary amenorrhea, had thyroid disorders and were already on thyroxine replacement therapy. One patient also had vitiligo. There was no history of adrenal disorder. Anti-TPO levels were elevated in two (10%) patients of secondary amenorrhea group. The levels of serum testosterone were low in three patients. Serum DHEAS levels were low in 13 patients. Blood sugar levels (fasting and 2 hour post 75g glucose load) and fasting insulin levels were normal. Serum calcium and phosphate levels were normal in all the patients.

Conclusion: Thyroid autoimmunity is the most common autoimmune disease associated with POF. The finding of low DHEAS in a large percentage of patients (65%), suggests possibility of adrenal dysfunction. This requires further testing for adrenal reserve and adrenal autoantibodies.

Keywords: Amenorrhea, Autoimmunity, Thyroid autoantibodies

INTRODUCTION

Premature Ovarian Failure (POF) is the syndrome consisting of primary or secondary amenorrhea, hypergonadotropism and hypoestrogenemia in women below 40 years of age. It is diagnosed on the basis of two levels of serum FSH ≥40mIU/mL taken 6 weeks apart. It affects one in 10,000 women by age 20, one in 1,000 women by age 30 and one in 100 women by age 40 [1]. Ovarian failure manifests itself between 30-39years in 82.5% cases [2]. POF accounts for 5-10% cases of secondary amenorrhea [3,4] and 10-28% cases of primary amenorrhea [2].

Most of the cases of POF are idiopathic, accounting for 60-80% of total cases [1,5,6]. Other causes of POF include genetic, autoimmune, iatrogenic and those resulting from environmental insults. POF is reported to be associated with autoimmune diseases in 20-30% of cases. Most common are the thyroid disorders, which are seen in 30-40% of cases of POF [7-11]. Adrenal autoimmunity is second most common autoimmune disease associated with POF [12,13]. Diabetes mellitus is seen in 2.5% of the cases [12]. Autoimmune Polyglandular Syndromes (APS) are a rare group of disorders characterized by autoimmune activity against more than one endocrine organ; non-endocrine organs can also be affected. APS type I is an autosomal recessive disorder, characterized by autoimmune dysfunction of parathyroid gland (hypocalcemeia) and adrenal gland (Addison's disease). POF is seen in 41- 72% of patients with APS Type I [12,13]. APS Type II is a more common disorder associated with Addison's disease, primary hypothyroididsm and Grave's disease. Primary hypogonadism is less common in this group. The prevalence of ovarian failure in APS-II is 10-25% [13]. Various toxins (smoking) and viruses (Mumps) have been implicated in the occurrence of POF [5,9,14]. Iatrogenic causes include surgery, chemotherapy and radiotherapy, which account for a small proportion of cases.

In the present study, patients presenting with idiopathic POF were screened for the presence of autoimmune disorders like thyroid and adrenal disease.

MATERIALS AND METHODS

An observational study was conducted at Maulana Azad Medical College and Lok Nayak hospital, New Delhi, India, between April 2009-to March 2010. Twenty consecutive patients with idiopathic POF of >1 year duration attending the Gynae-endocrinology clinic during 1 year period were recruited for the study after obtaining their consent. Approval from ethical committee was taken for the study.

Inclusion Criteria: Age 18-39 years, Amenorrhea of > 1 year duration with serum Follicle Stimulating Hormone (FSH) ≥ 40m IU/mL on 2 occasions 4-6weeks apart.

Exclusion criteria: Age>40 years, abnormal karyotype, Iatrogenic POF (post surgery).

A detailed history (including age, duration of amenorrhea, pattern of preceding menstrual cycles, past pregnancies, symptoms like hot flushes, smoking, any pelvic surgery) was taken from all the patients. History of thyroid disorder or any other autoimmune disease was asked. Family history of POF or early menopause was noted. A general physical, systemic and pelvic examination was done.

Baseline investigations were carried out at presentation. The baseline investigation in all subjects included fasting serum FSH, Luteinzing hormone (LH), Estradiol (E2), progesterone, free T3, free T4, thyroid-stimulating hormone (TSH) and Anti-Thyroperoxidase (anti-TPO) antibodies, testosterone and Dehydroepiandrosterone (DHEAS) levels. Fasting and post-glucose (2 hours after 75g of oral glucose), fasting insulin levels, serum calcium and phosphate were estimated using appropriate assays in biochemistry laboratory.

STATISTICAL ANALYSIS

Data was analysed by statistical software SPSS 16.0. Descriptive statistics were presented in terms of minimum, maximum, mean ± standard deviation for continuous variables and categorical data are presented by counts (percentage). Significance of correlation between continuous and categorical variables was calculated by Student's t-test. The statistical significance was taken as $p \leq 0.05$.

RESULTS

Out of 20 patients, four presented with primary amenorrhea and 16 patients had secondary amenorrhea. The mean age of primary amenorrhea group was 19.5 ± 1 year and of secondary amenorrhea group was 34.5 ± 4.14 years. Associated symptoms such as irregular cycles, hot flushes, dyspareunia and genitourinary complaints were seen in 10 patients (50%) and all these patients presented with secondary amenorrhea. Only one patient with POF had family history suggestive of POF in the form of history of early menopause in her family [Table/Fig-1].

Baseline hormonal profile of patients with primary and secondary amenorrhea is summarized in [Table/Fig-2]. Difference between mean serum FSH, LH, estradiol and progesterone levels in patients of primary amenorrhea and secondary amenorrhea group were not statistically different.

In present study, seven patients (35%), who presented with secondary amenorrhea, had thyroid disorders and were already on thyroxine replacement therapy [Table/Fig-3]. In 65% of cases, there was no endocrine disorder.

Demographic data	Primary Amenorrhea (n=4)	Secondary Amenorrhea (n=16)	Total (n=20)
Age			
<25yrs	4	1	5(25%)
26-30yrs	0	1	1(5%)
31-35yrs	0	5	5(25%)
36-40yrs	0	9	9(45%)
Associated symptoms(hot flushes, genitourinary complaints)		10	10(50%)
Onset of disease			
Sudden onset		6	6(37.5%)
Irregular cycles		10	10(62.5%)
Parity			
P_0		5	5(38.4%)
P_1		2	2(15.3%)
$\geq P_2$		6	6(46.3%)
Family history of POF		1	1(5%)

[Table/Fig-1]: Demographic data of POF patients.

Hormones	Primary amenorrhea (n=4)	Secondary amenorrhea (n=16)	p-value
Mean serum FSH ± SD (mIU/mL)	92.37 ± 40.0	112.3 ± 35.04	0.334
Mean serum LH ± SD (mIU/mL)	42.03 ± 14.51	59.48 ± 15.73	0.059
Mean serum estradiol ± SD (pg/ml)	15.51 ± 21.03	8.49 ± 5.15	0.219
Mean serum progesterone ± SD (ng/ml)	0.39 ± 0.17	0.34 ± 0.19	0.638

[Table/Fig-2]: Baseline hormonal profile in patients with POF.

Autoimmune association	Primary amenorrhea (n=4)	Secondary amenorrhea (n=16)	Total number of patients (n=20)
Positive history of endocrine disease	0	7	7 (35%)
Raised Anti TPO levels (< 34 IU/mL)	0	2	2(10%)
Low serum DHEAS (<98.8µg/dl)	2	11	13(65%)

[Table/Fig-3]: Association with endocrine disorder.

Serum TSH levels were found to be in normal range (0.5-4.7mIU/L) in 80% of patients. In three patients (15%), the levels were high and in one patient (5%) the level was low. In one patient with high serum TSH, serum T4 was low and in other two patients the levels were normal. The patient with low serum TSH value had high levels of serum T4. In 18 patients (90%) patients the T4 levels were normal (12-22 pmol/L). Serum T3 levels were normal in all the patients.

Anti-TPO levels were normal in 18 patients and elevated in two (10%) patients of secondary amenorrhea group suggesting autoimmune pathology.

All the patients with abnormal thyroid function tests and raised anti TPO levels were known cases of thyroid disorder and were on treatment.

Mean serum testosterone levels ± SD in patients with primary amenorrhea were 0.09 ± 0.05 ng/ml and in those with secondary amenorrhea were 0.13 ± 0.08 ng/ml. The normal range is 0.06-0.82 ng/ml.

The mean DHEAS levels ± SD in primary amenorrhea group were 122.27 ± 67.18 µg/dl and in secondary amenorrhea group was 92.32 ± 43.51µg/dl. The normal range is 98.8-340µg/dl.

The levels of serum testosterone were low in one patient of primary amenorrhea and two patients of secondary amenorrhea group. Serum DHEAS levels were low in two patients with primary amenorrhea and 11 patients with secondary amenorrhea. The finding of low DHEAS in a large percentage of patients (65%), suggests possibility of adrenal dysfunction and adrenal autoimmunity which needs to be studied further.

Blood sugar fasting (<95mg%) and post 75g of oral glucose levels (<140mg%) were normal in all the patients. In the present study mean fasting insulin ± SD levels were 6.97 ± 3.20 µIU/ml. The levels were normal in all the patients. Maximum insulin level was 16.33 µIU/ml and minimum insulin level was 2.58 µIU/ml.

Serum calcium levels (9-11mg/dl) and phosphate levels (3.5-5.5mg/dl) were found to normal in all the patients. Abnormal levels would be suggestive of parathyroid disorders.

DISCUSSION

POF is associated with autoimmune diseases and endocrinopathies in 20-30% of cases. POF is reported in patients with Addisons disease (20%), thyroid diseases (9%), polyglandular syndromes (2%), rheumatoid disease (1%) and in less than 1% cases of systemic lupus erythmatoses, vitiligo, myasthenia gravis, insulin dependent diabetes mellitus and Crohn's disease [15]. Histological finding of lymphocytic and plasma cell infiltrates in proximity to the follicles, and to theca cells and increased binding of gamma globulins to the ovarian tissues is seen in patients of POF [15,16]. Some studies have reported decreased T-cells and natural killer cells in cases of POF, which results in increase of B-cell activity and production of antibodies [15,17]. Circulating autoantibodies to ovarian tissue has been demonstrated in women with POF [16]. Remission was in POF patients, who were successfully treated for co-existent immune diseases with cortisol or plasmapheresis [15,18].

Conway et al., studied 135 women with POF [19]. Clinically evident autoimmune disease was present in 10% cases. Ten patients had hypothyroidism and two had Addison's disease and one patient had insulin dependent diabetes mellitus. Full autoimmune screen showed 34% of women with POF had at least one antibody screen positive, most common being antithyroid antibodies. The autoimmune group however was indistinguishable from those with negative autoimmune screen with regards to age of onset, prevalence of primary amenorrhea, endocrine, ultrasound and bone mineral density measurements. Thirty percent of patients who experienced return of menstruation had positive antibody screen.

In India Goswami et al., studied prevalence of thyroid autoimmunity in 58 patients of POF [7]. These patients were screened for T3, T4, TSH and anti TPO antibodies. Anti-TPO positivity (> 34 IU/ML) was seen in 24.1% patients with POF. In a study (n=37), conducted in North India, Shah et al., reported endocrine abnormalities in 49% of the patients [8]. Eight (22%) had abnormal thyroid function tests and 12 of 29 (41%) patients showed impaired response of plasma cortisol to adrenocorticotropic hormone stimulation. However, no patients had overt thyroid or adrenocortical disease.

Alper et al., studied 33 patients of idiopathic POF [4,20]. An associated autoimmune disease was found in 39% (13/33) patients. Eleven had thyroid disease, one had Addison's disease and one patient had vitiligo. Positive family history of autoimmune disease was found in 18% of cases with autoimmune disease. Rebar et al., studied clinical and endocrinological characteristics in 26 women with POF [21]. In all these women, adrenal function as tested using ACTH hormone revealed adequate adrenal reserves. Thyroid function tests, antimicrosomal antibodies and serum calcium and phosphorus levels were normal in all, except in three (11%) patients who had evidence of thyroiditis, as evident by raised thyroid antibody titers. Betterie et al., studied the association of clinical and latent autoimmune diseases in 50 patients with POF [22]. In patients with POF Addison's disease was present in 18% cases and other autoimmune diseases (Hashimoto's, Grave's disease, Hashimoto's disease and IDDM, Hashimoto's disease and alopecia areata and SLE) were found in 20% cases. Steroid producing Cell Antibodies (SCA) was positive in 78% of cases with adrenal disease and in 10% of cases with other autoimmune disease. SCA was positive in 3% of cases with no autoimmune disease. Bachelot et al., studied 357 women with idiopathic POF [23]. Around 10.1% of the patients had personal history of autoimmune disease most common being the thyroid disorders and 14% of the patients had anti TPO antibodies.

The results of our study matched the finding of the previous studies. Thyroid disorders were the most common associated endocrinopathy. Anti-TOP antibodies were positive in 10% of the cases suggesting possible autoimmune pathology.

LIMITATION

Screening for ovarian autoantibodies and tests for adrenal reserve would confirm adrenal gland involvement in our patients. However, these tests could not be conducted due limitation of resources.

CONCLUSION

POF is complex disorder associated with variety of causes like autoimmunity, iatrogenic causes and environmental insults. Autoimmune destruction of ovarian tissue occurs due to leucocytes and auto-antibodies. In the present study, involvement of other endocrine glands was seen in 20-30% of cases, thyroid and adrenal glands being the most common ones. The results from our study are consistent with available data. Thus, routine screening of patients with idiopathic POF must include tests for thyroid, adrenal and ovarian autoantibodies.

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