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ORIGINAL ARTICLE

Premature Ovarian Insufficiency: Challenges in Diagnosis and Management of Premature Ovarian Insufficiency

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ABSTRACT

Background: Premature Ovarian Insufficiency (POI) is a condition where normal ovarian function is lost before age 40 years which results in the formation of various clinical symptoms resulting in reduction of emotion, sexual and mental health of a patient. In a young woman, the diagnosis of failing ovarian function is complex and difficult, and if not promptly addressed, it will lead to long-term consequences.

Objective: To assess the incidence of various variables related with the diagnosis and management of premature ovarian insufficiency.

Study Design: Prospective cohort study

Place and Duration of Study: Department of Gynaecology & Obstetrics, Shaikh Zayed Hospital, Lahore from 1st April 2023 to 30th September 2023.

Methodology: One thousand females were enrolled**.** Various categorizations were considered while diagnosing the cases with premature ovarian insufficiency. These categories included family (genetic etiology) and clinical history (infectious, autoimmune etiology), symptoms (vasomotor symptoms, hot flushes, night sweats, vaginal dyspareunia and dryness, vulvovaginal atrophy, mood disturbances, loss of libido, memory problems, tiredness, insomnia, memory issues, and weight gain. Anthropometric measurements including weight, height, will be recorded. Those cases which were presenting with oligomenorrhea and clinical symptoms of POI were further placed in a separate group (Group A) than those having regular cycles and no clinical symptoms having infertility (Group B). Various tests were analyzed as the presentation may also be with sub-fertility due to the reduction in ovarian reserve, genetic disorders, autoimmune disorders, infectious, e.g. mumps/TB, deficiency of galactose-1-phosphate uridylotransferase (GALT) and iatrogenic, e.g. surgery, chemo/radiotherapy, amenorrhea (considering only skip of 3 periods) occurrence, two FSH tests which are 4 to 6 weeks apart, estrogen levels, antral follicle count (AFC), Thyroid peroxidase autoantibodies (TPA), thyroid function test (TFT) and Anti-Mullerian Hormone Test (AMH) levels. Hormone replacement therapy was regime for the females with premature ovarian insufficiency and patients were requested to keep a follow up twice a year for proper management of the premature ovarian insufficiency condition. while 5 cases had PO on diagnosis had only infertility and no clinical

Results: There were 10 females who were having oligomenorrhea (Group A) and symptoms of POI while 5 cases had PO on diagnosis had only infertility (Group B). Among the POI cases the early menarche was only reported in 3/15 females. The present study presented a significant correlation of hot flashes, mood swings, vaginal dryness, libido loss and insomnia with POI. Weight gain was observed in non-POI; group C females as well making an insignificant relation within the groups. The blood tests values presented that FSH, E2 AMH, AFC and GALT were significantly associated with disturbed levels in premature ovarian insufficiency. The levels were most significant disturbed in the oligomenorrheic females having POI.

Conclusion: A significant correlation of infertility, hot flashes, mood swings, vaginal dryness, libido loss and insomnia, and significantly disturbed levels of FSH, E2, AMH, AFC and GALT were found in POI.

Keywords: Ovaries, Syndrome, Oligomenorrhea

INTRODUCTION

Premature ovarian insufficiency (POI) is a condition where normal ovarian function is lost before age 40. This can result in symptoms such as irregular or absent menstrual periods, hot flashes, night sweats, vaginal dryness, and infertility. In a young woman, the diagnosis of failing ovarian function is complex and difficult, and if not promptly addressed, it will lead to long-term consequences.[1] The diverse clinical symptoms of POI make diagnosis challenging and symptoms may include primary amenorrhea after delayed puberty with absent breast development or secondary amenorrhea, in which a young woman initially experiences irregular menstrual cycles, followed by amenorrhea and normal pubertal development.[2]The prevalence of POI has not been formally studied. However, spontaneous POI seems to occur in 1% of women under 40 and 0.1% of those under 30.[3]

Under 40 years old, the most common experience involves a slow decrease in ovarian function. This could show up as irregular periods and the lack of menstruation at various times, along with symptoms of estrogen withdrawal.[4] The lower cut-off has been chosen by ESHRE also to encompass cases of autoimmune-mediated ovarian failure within the POI spectrum, which typically present with lower levels of FSH.[4,5] At the same time, it is important to rule out the most common causes of oligoamenorrhea (such as pregnancy, hyperprolactinemia, hypothalamic dysfunction due to weight loss, and polycystic ovarian syndrome) before considering further investigations for potential POI.[4-6]

The health implications associated with this life-altering diagnosis go beyond just cardiometabolic factors and also encompass psychosexual and psychosocial aspects.[5,7] The available treatment choices heavily rely on the severity of the underlying condition and the fertility potential. Nonetheless, early commencement of hormone replacement therapy will enhance genitourinary function and minimize the impact of unfavorable cardiometabolic changes.[8,9] Techniques for preserving fertility, such as ovarian cryopreservation, can be incredibly advantageous. An early diagnosis allows for the utilization of the available treatment options. Managing POI requires a comprehensive approach that includes accurate diagnosis, individualized treatment plans, addressing fertility concerns, and providing psychosocial support. The present study was designed to determine challenges in diagnosing and managing premature ovarian insufficiency.

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MATERIALS AND METHODS

This prospective cohort study was conducted at Department of Gynaecology & Obstetrics, Shaikh Zayed Hospital Lahore from from 1st April 2023 to 30th September 2023. The sample size of the study was considered as 1000 women between the ages of 11-40 years. The sample size was calculated by considering the incidence of premature ovarian insufficiency as 1% in general population. Sample size calculator software available on web was applied for calculating the samples size. A confidence interval of 95% was considered with 80% power of test and 5% margin of error. All women who visited gynecological unit within the aforementioned duration and in the inclusion, criteria were included in this study. Various categorizations were considered while diagnosing the cases with premature ovarian insufficiency. These categories included family (genetic etiology) and clinical history (infectious, autoimmune etiology), symptoms (vasomotor symptoms, hot flushes, night sweats, vaginal dyspareunia and dryness, vulvovaginal atrophy, mood disturbances, loss of libido, memory problems, tiredness, insomnia, memory issues, and weight gain. Anthropometric measurements including weight, height, was recorded. Those cases which were presenting oligomenorrhea and clinical symptoms of POI were further placed in a separate group (Group A) than those having regular cycles and no clinical symptoms but having infertility (Group B). Those females who were later not identified as premature ovarian syndrome were placed in Group C. Various tests were analyzed as The presentation may also be with sub-fertility due to the reduction in ovaries, genetic disorders, autoimmune disorders, infectious, e.g. mumps/TB, deficiency of galactose-1-phosphate uridylotransferase (GALT) and iatrogenic, e.g. surgery, chemo/radiotherapy, amenorrhea (considering only skip of 3 periods) occurrence, two FSH tests which are 4 to 6 weeks apart, estrogen levels, antral follicle count (AFC), Thyroid peroxidase autoantibodies (TPA), thyroid function test (TFT) and Anti-Mullerian Hormone Test (AMH) levels. A 5cc blood was withdrawn from each patient for blood analysis. Serum was separated and stored at 20ºC until analysis. The females having pregnancy, polycystic ovary syndrome (PCOS), hyperprolactinemia or hypothalamic dysfunction, stress or weight loss were excluded for the research. A pelvic ultrasound was taken of all the patients on the 9-11th day of their cycle. The diagnostic values were entered in a well-structured questionnaire. Patients who were diagnosed with premature ovarian insufficiency were treated for their ovarian condition up to 6 months' time and their prognosis was monitored with positive health outcomes, the bone, sexual and mental health, cardiovascular disease risks. Hormone replacement therapy was regime for the females with premature ovarian insufficiency and patients were requested to keep a follow up twice a year for proper management of the premature ovarian insufficiency condition. Data was entered and analyzed through SPSS-26.0. The analysis of comparative values and incidence s reported was interpreted by using chi square and t test. P value <0.05 was considered as significant.

RESULTS

There were 10 females who were having oligomenorrhea (Group A) and symptoms of POI while 5 cases were presenting POI on diagnosis with no significant clinical symptoms or presence of irregularity in menstruation (Group B). There were 985/1000 females which were not suffering from POI (Group C). The early menarche at age of 11-14 years was reported in the 43.85% females in group C while 56.1%. Among the POI cases the early menarche was only reported in 3/15 females (Table 1)

The familial and clinical history of each group as well as the infection, autoimmune related history, smoking and marital status was compared within groups. It was observed that there was no significant relation of POI with autoimmunity, infections, smoking or presence of marital status. However, a very few autoimmune cases were presented in the POI group (Table 2)

The present study presented a significant correlation of hot flashes, mood swings, vaginal dryness, libido loss and insomnia with POI. Weight gain was observed in non-POI; group C females as well making an insignificant relation within the groups (Table 3). The blood tests values presented that FSH, E2 AMH, AFC and GALT were significantly associated with disturbed levels in premature ovarian insufficiency. The levels were most significant disturbed in the oligomenorrheic females having POI (Table 4). The ultrasonography of the one of the patients suffering from POI with a history of early menarche presented with smaller ovaries with no prominent follicle (<3mm) presented (Fig. 1).

The females having POI diagnosed were further placed on hormone replacement therapy in the below mentioned regime. Each patient was monitored for the outcome until 6 months of time with a follow up values of blood tests as well as clinical symptoms (Table 4)

Table 1: Distribution of age among enrolled females

Variable	Group A N=10	Group B N=5	Group C N=985
Age (years)			
11-14	--	--	200 (20.3%)
15-20	--	--	232 (23.5%)
21–25	1 (10%)	1 (0.2%)	120 (12.1%)
26–30	1 (10%)	--	75 (7.61%)
31–35	1 (10%)	--	153 (15.5%)
36–40	7 (70%)	4 (0.8%)	205 (20.8%)
Early menarche age (years)			
11-14	2 (20%)	1 (20%)	432 (43.85%)
15-20	--	--	553 (56.1%)

Table 2: Comparison of family, clinical history, smoking, marital status among groups

Variable	Group A N=10	Group B N=5	Group C N=985	P value
Family History				
Yes	2 (20%)	1 (20%)	5 (0.5%)	0.456
No	8 (80%)	4 (80%)	980 (99.5%)	0.000
Clinical History				
Infection (Mumps/TB)	1 (10%)	--	420 (42.6%)	-
Autoimmune Disorder	1 (10%)	--	20 (2.03%)	-
Single	4 (40%)	1 (20%)	250 (25.3%)	<0.005
Married	6 (60%)	3 (60%)	700 (71.06%)	0.000
Widow/divorced	1 (10%)	--	35 (3.55%)	-
Smoking	1 (10%)	--	20 (2.03%)	-

Table 3: Comparison of clinical symptoms within groups

Clinical symptoms	Group A N=10	Group B N=5	Group C N=985	P value
Hot flashes	20%	-	20%	0.513
Insomnia	60%	-	10%	0.275
Night sweats	20%	-	20%	--
Vaginal dyspareunia	40%	-	5%	0.546
Vaginal dryness	50%	-	5.80%	0.432
Vulvovaginal atrophy	50%	-	1.20%	0.003
Mood swing	70%	-	7%	0.002
Libido loss	60%	-	13.10%	0.010
Memory loss	60%	-	10%	0.412
Weight gain	50%	-	55.80%	0.991
Infertility	57%	100%	4%	

Table 4: Comparison of blood test within various groups

Blood Tests	Group A N=10	Group B N=5	Group C N=985	P value
FSH IU/L	31.73±4.2	14.91±4.3	6.8±1.17	0.021
E2 pg/ml	16.1±4.5	30.2±3.3	103.2±25.1	0.012
TSH mIU/L	0.4±1.1	0.6±1.1	1.2±1.8	0.787
AMH ng/ml	0.078±0.071	0.424±1.0	2.52±2.7	0.045
AFC	0.5±0.1	4±3.3	21±3.5	0.032
BMI kg/m^2	23.3. ±3.6	22.83±3.1	22.80±2.8	0.765
Age in Menarche	14.25±2.0	14.08±1.8	14.07±1.3	0.987
GALT mg/dl	1.3±0.2	0.9±0.1	0.8±0.1	0.028

Normal Ranges: FSH: Before puberty: 0 to 4.0 mIU/mL (0 to 4.0 IU/L) During puberty: 0.3 to 10.0 mIU/mL (0.3 to 10.0 IU/L) Women who are still menstruating: 4.7 to 21.5 mIU/mL (4.5 to 21.5 IU/L) After menopause: 25.8 to 134.8 mIU/mL (25.8 to 134.8 IU/L), E2: 30 to 400 pg/mL for premenopausal women. 0 to 30 pg/mL for postmenopausal women. TSH: 0.5 to 5.0 mIU/L, AFC: between 10-20 follicles, in her late 30s around 8-15 follicles, and by her 40s,AMH: 2–6.8 ng/ml, GALT: <1 mg/dL

Table 4: Management of POI cases with Hormone replacement therapy

Estrogens		Progestogens (in case of intact uterus)	
Name	Dosage	Name	Dosage
Oral 17β-E2	2-4mg	Oral Dihydro-progesterone	10–20 mg orally
Oral CEE	0.625–1.25 mg	Oral Norethisterone	1–5 mg orally
Transdermal, 17β-E2	50–100 µg	Transdermal Norethisterone	0.25 mg
Topical		Natural Progesterone	200 mg cyclically or 100 mg continuously

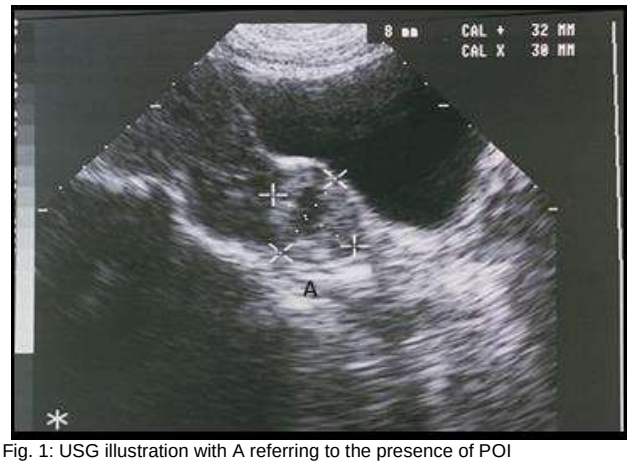

Fig. 1: USG illustration with A referring to the presence of POI

DISCUSSION

Premature ovarian insufficiency (POI) refers to the loss in the ovarian activity which further results in amenorrhea earlier than the age of 40 years. The diagnosis of the POI especially in cases of young women becomes a critical challenge. However, it is highly important for the POI diagnosis to be performed on time for earlier intervention and management of the condition. A delay in the diagnosis may affect negatively the POI health outcomes.[4] There are various steps which need to follow in term of correct and timely diagnosis of POI. The regularity of menstrual cycle as well as age of menarche is very significant factors related to women health. Early menarche may be related with various ovarian conditions such as premature ovarian insufficiency.

The literature has supported the statements that POI is associated with primary or secondary amenorrhea as well as oligomenorrhea in females.[10] The similar was observed in the present study result wherein even with the diagnosed 15 cases of POI there were 3 cases having a history of early menarche. Even though oligomenorrhea is identified as absence of menstrual cycle for at least 6 months however in the present study the absence of 3 months was considered for oligomenorrheic term. The same pattern has been followed in other studies as well which has stated in their article that 3-4 months absence of menstruation can be commenced as oligomenorrhea.[11]

It is evidently proven the fact that various clinical symptoms are associated with the POI condition and may play a major role in the diagnosis of the disease. In the current research as well the estrogen deficiency as well as follicle stimulating hormone elevated abnormal levels were significantly associated with the POI females.[12] The typical menopausal symptoms were observed in the POI cases with vaginal dryness, insomnia and heat flash. Studies elsewhere has also proven the similar facts and described a high correlation with aforesaid clinical symptoms in conditions of POI.[13-15]

The significance of the family history, AMH, AFC and an incidence of genetic predisposition for the POI is demonstrated as 10-15% in first degree relatives. In the present study family history was found in 3/15 cases. The pelvic USG is considered as a routine diagnostic step in majority of gynecological conditions including POI. Useful related information in context to follicular visibility, or absence is illustrated through the ultrasonography.[16-18]

The POI cases are managed through the administration of hormone replacement therapy, which has proven its efficient results in condition of POI. It has been proven that hormone replacement therapy can improve the fat body consumptions and reduce the insulin sensitivity.[19-21] Further it assists in improving the quality life of patients with between emotional and physical health outcomes. The current study patients suffering from POI were also administered with HRT and positive health outcomes were observed within the follow up time.

CONCLUSION

Early menarche was not significantly associated with POI. A significant correlation of hot flashes, mood swings, vaginal dryness, libido loss and insomnia was found with POI. Within the blood tests values presented that FSH, E2 and results of AMH, AFC and GALT were significantly associated with disturbed levels in premature ovarian insufficiency

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