

Assessment of factors responsible for early menopause in Interior Sindh, Pakistan

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Abstract

Objective: To evaluate the factors leading to the early onset of menopause (<40 years) in the women in the interior of Sindh.

Materials and Methods: A cross-sectional study was conducted on 218 individuals among them 109 were postmenopausal women (with premature menopause) and 109 were normal menstruating females during the period of six months from November 2014 to April 2015, data was obtained from Interior Sindh, Larkana, Hyderabad, and Benazirabad. Factors considered were age, number of children, history of the obstetric process (ovarian and uterine), diseases, and premature menopause history in first-cousin marriages. The questionnaire data and blood samples were collected for hormonal assays such as LH, prolactin, and FSH. The hormone levels were analyzed by ELISA method, SPSS version 17 was used for data analysis.

Results: Out of 109 subjects the percentage of early menopause due to: anorexia nervosa was 17%, brain tumor 7%, ovarian cancer 6%, hormonal disorders 23%, hysterectomy 15%, oophorectomy 5%, Pituitary gland dysfunction 4%, Sheehan Syndrome 24%, Polycystic Ovarian Syndrome (PCOS) 8%.

Conclusion: Early menopause was found related to pathological and psychological factors including brain tumor, ovarian cancer, family history, Anorexia nervosa, and certain surgical interventions.

Keywords: Early menopause, ovarian cancer, family history, hormonal disturbance.

Introduction

The Word menopause is derived from the Greek word “meno” which means stop cease. This is an aging process due to a reduction in the ovarian hormones progesterone and estrogen.¹ The normal age of menopause is about 44-55 years, but some women suffer from menopause before 40 years of age. Menopause that occurs before 40 years of age, due to any reason, is called premature menopause. This can lead to earlier onset of chronic diseases of aging and therefore lengthen to later years as well. Menopause is a major factor for bone degeneration.¹⁻⁴

Furthermore; premature or early menopause, also known as a premature ovarian failure (POF), is an important disorder that affects a significant population of young women.⁵ Characteristics of this condition are amenorrhea, elevated gonadotropins, and decreased gonadal steroids. The effect of this condition is on both physical and psychological components, it is so because of the long term effects of the gonadotrophin depletion in the body. Furthermore, the distressing result of this condition is infertility.⁶ Proper functioning of the hypothalamus, pituitary gland, uterus, and ovaries are necessary for the normal menstrual cycle. The hypothalamus triggers the pituitary gland; the pituitary stimulates follicle-stimulating hormone (FSH) and luteinizing hormone (LH). FSH and LH trigger the ovaries to produce hormones estrogen and progesterone.⁷ Estrogens and androgens affect the skeleton during growth and skeletal homeostasis during adulthood. The decrease in estrogen concentration with menopause effects of female bone resorption.⁸ The study conducted in Jordanian women with early menopause shows that the association factor for the early menopause history in first-cousin marriages.¹ Similar studies were carried out on early menopause and risk of fracture, osteoporosis, and mortality in Swedish women aged 48 years with early menopause, later on at the age of 77, they had a risk ratio of 1.83 for osteoporosis, for fragility fracture risk ratio was 1.68 and mortality risk was 1.59.⁹

Premature menopause results in adverse effects, which include cardiovascular diseases, psychiatric diseases, mortality, neurological diseases, osteoporosis, Sheehan’s syndrome, and early death.¹⁰ Hormonal therapies have succeeded to moderate levels with some risks but many others are still under the line and faced by the patients.^{11,12}

This study was aimed to assess the factors which cause menopause at an early age and to check the prevalence

of factors which are most common along with factors having raised FSH, LH & Prolactin levels and those having low FSH, LH & Prolactin levels in the women of Interior of Sindh as compared to the women of the same age without early menopause. Also, inform the healthcare personnel about the situation so that they may consider the prevailing factors while treating the patients.

Materials and Methods

A cross-sectional study, for which participants were selected from Interior Sindh. The duration of the study was about six months. A convenient non-probability technique has been used for sampling. The sample size was 218 subjects. Females with early menopause were included in the study as case, their age is 33.3 ± 3.23 whereas women with normal menstrual cycles were included as controls for the study of age $32.67 + 3.07$ respectively. Females on medication and suffering from any disease particularly any hormonal disorder were excluded. Blood samples required for the study were collected from normal and affected individuals and written consent was obtained before the sampling. Samples were collected in 5ml gel tubes and serum was separated.

The ELISA method was used to assess the concentration of Prolactin, LH, and FSH hormones^{13,14}, in their blood by using Human diagnostic worldwide test kits with Elisa reader UVM 340. The principle is based on monoclonal antibodies and another in antibody-enzyme conjugate solution. The sample is reacted with antibodies at the same time with antibodies resulting in the sandwiching of sample molecules between the solid phase and enzyme-linked antibodies. For this 100 μ l of the conjugate is dispensed into the wells. 50 μ l of calibrator was added into the 5 wells. 50 μ l of control & samples into the wells and then the plate is covered with an adhesive sheet and incubated at 37oc for about 60 minutes. The solution is then removed from the wells and was washed with a wash solution for any unbounded antibodies. 100 μ l of the substrate was poured into the wells and was covered with aluminum foil and incubated for about 15 minutes at room temperature and stop solution (100 μ l) is added into the wells for any further color development and finally, OD is observed at 450nm in a plate reader.

All data obtained were put into SPSS version 17 for analysis of results.

Ethical Consideration: The questionnaire was anonymously administered to the women/girls, with

the permission of the ethical review committee of the Department of Physiology. Written consents were taken from the control and subject groups before managing the questionnaires. The present study will be used for the research purpose.

Results

In this study, 109 cases and 109 healthy controls were studied. From cases, 104 were housewives, and 5 were office workers. The mean age of the cases involved in this study was 33.3 ± 3.23 while controls 32.67 ± 3.07 . The mean FSH, LH, and PROLACTIN were higher in study cases than controls. The mean BMI value of controls was (24.14 ± 3.78) and that of study cases was (23.78 ± 4.56) .

In the case of Anorexia Nervosa (17%), the mean FSH level was lower in cases than in controls, similarly, the mean LH level of cases was lower than in controls. Whereas, the mean Prolactin level was higher in subjects than in controls. The results were significant as shown in table-1.

In subjects of Brain Tumor (7%), the mean FSH level was higher than in the control; similarly, the mean LH levels were also higher in study subjects than in controls. The mean Prolactin level was also elevated in subjects as compared to controls. Women undergoing Ovarian Cancer (6%) have a mean FSH level, mean LH level, and mean Prolactin level increased than controls.

In the case of Hormonal disorders (23%), the mean FSH level was greater in study subjects than controls, similarly the mean LH level and mean Prolactin level were also notable than controls.

Post Hysterectomy (15%) cases had a high level of FSH, LH, and Prolactin as compared to the controls. In cases of Oophorectomy (5%) the mean FSH level, mean LH level and mean Prolactin level was higher than controls which herald early menopause.

In the case of Pituitary Dysfunction (4%) the study subjects had a higher mean FSH level than in controls, similarly, the mean LH level of subjects was also higher than in controls and the mean Prolactin level was also at an elevated level in subjects than in controls.

Similarly, in the case of Sheehan Syndrome, the cases had a greater mean FSH level mean LH level, and mean Prolactin level than controls. Women undergoing Polycystic Ovarian Syndrome (8%) had raised levels of mean FSH, LH, and Prolactin than normal women.

Table 1: Differences in FSH, LH, and Prolactin level in control & cases of early menopause in different conditions

Different conditions	Hormones	CASE	CONTROL	T-VALUE	P-VALUE
ANOREXIA NERVOSA	FSH	7.79 ± 1.95	10.8 ± 1.66	4.85	<0.001
	LH	13.5 ± 3.17	20.30 ± 1.75	8.86	<0.001
	PRL	22.01 ± 2.13	11.34 ± 1.94	15.71	<0.001
BRAIN TUMOR	FSH	14.04 ± 3.88	10.94 ± 1.85	1.972	0.09
	LH	21.54 ± 5.21	21.05 ± 1.55	0.235	0.82
	PRL	27.41 ± 4.70	10.54 ± 1.88	9.631	<0.001
OVARIAN CANCER	FSH	40.4 ± 4.70	11.86 ± 1.04	13.60	<0.001
	LH	60.9 ± 5.93	21.1 ± 2.35	15.63	<0.001
	PRL	40.2 ± 10.07	13.25 ± 2.98	6.22	0.002
HORMONAL DISORDER	FSH	36.20 ± 6.97	10.21 ± 2.12	17	<0.001
	LH	45.82 ± 8.80	20.38 ± 3.18	15.63	<0.001
	PRL	33.62 ± 6.04	13.12 ± 2.33	16.9	<0.001
HYSTERECTOMY	FSH	32.74 ± 5.4	10.38 ± 2.38	13.9	<0.001
	LH	42.07 ± 6.73	20.41 ± 3.73	9.64	<0.001

OOPHORECTOMY	PRL	30.54 ± 5.29	15.80 ± 4.33	6.87	<0.001
	FSH	34.48 ± 4.25	7.46 ± 1.08	13.21	<0.001
	LH	49.14 ± 9.77	17.26 ± 4.08	9.803	0.001
PITUITARY DYSFUNCTION	PRL	26.48 ± 5.59	11.64 ± 1.54	6.904	0.002
	FSH	46.00 ± 2.25	10.30 ± 2.34	35.94	<0.001
	LH	65.22 ± 4.25	20.92 ± 2.19	14.727	0.001
SHEEHAN SYNDROME	PRL	40.95 ± 9.03	14.92 ± 3.31	6.643	0.007
	FSH	38.40 ± 9.29	10.39 ± 2.30	14.284	<0.001
	LH	54.27 ± 8.90	20.38 ± 3.28	18.801	<0.001
POLYCYSTIC OVARIAN SYNDROME	PRL	38.49 ± 9.78	13.22 ± 4.36	10.511	<0.001
	FSH	42.82 ± 3.37	10.81 ± 2.22	18.051	<0.001
	LH	57.42 ± 6.26	21.08 ± 2.69	19.019	<0.001
ALL CASES	PRL	41.87 ± 6.28	12.98 ± 2.80	12.832	<0.001
	FSH	31.35 ± 13.4	10.4 ± 2.13	15.780	<0.001
	LH	43.12 ± 17.3	20.39 ± 2.96	13.754	<0.001
	PRL	32.9 ± 9.26	13.08 ± 3.4	21.47	<0.001

As shown in Table: 1; the serum FSH, LH, and Prolactin level is significantly higher in menopausal women (in Brain tumor, Ovarian cancer, hysterectomy, Oophorectomy, Polycystic ovarian syndrome and in pituitary disorders) as compared to normal menstruating females.

Table 2: Differences in BMI in control & cases of early menopause in different conditions

BMI	CASE	CONTROL	T-VALUE	P-VALUE
ANOREXIA NERVOSA	25.94 ± 3.47	25.64 ± 3.92	1.000	0.332
BRAIN TUMOR	23.42 ± 4.27	23.3 ± 4.24	0.711	0.515
OVARIAN CANCER	23.0 ± 3.6	23.00 ± 3.68	1.147	0.289
HORMONAL DISORDER	25.43 ± 3.23	23.47 ± 3.95	0.2801	0.01
HYSTERECTOMY	25.3 ± 3.65	24.9 ± 3.78	1.000	0.334
OOPHORECTOMY	23.2 ± 2.28	23.1 ± 2.18	0.670	0.47
PITUITARY DYSFUNCTION	24.0 ± 2.82	22.50 ± 4.12	1.000	0.391
SHEEHAN SYNDROME	25.79 ± 3.10	23.66 ± 3.88	2.797	0.01
POLYCYSTIC OVARIAN SYNDROME	27.12 ± 2.79	24.62 ± 3.96	1.01	0.34
ALL CASES	23.7 ± 4.56	24.14 ± 3.78	0.688	0.493

As illustrated in table no.2 BMI was slightly fluctuating in both case and control groups however not reaching the significance level. BMI is not a factor causing the onset of early menopause.

Discussion

Early menopause is linked with long term multiple health consequences including diabetes¹⁵ cardiac problems, psychiatric disturbances, neurological disorders, osteoporosis along with increased mortality.^{16,17}

However, the adverse effects could be minimizing by giving estrogen therapy but it is not much beneficial in treating all these health issues.¹⁶

This study is in conformation with reflective study¹⁸ where the trends of hysterectomy were studied in the rural tertiary level teaching hospitals in Northern India. It was concluded that early menopause is either impulsive or driven. Women suffering from menopause, because of bilateral hysterectomy, oophorectomy, or cancer treatment.^{19,20} This is all associated with early menopause. In contrast to this study, women with brain cancer had increased prolactin. The chances of infertility increase as a result of oncological treatment. It is postulated that chemotherapy and radiations used in cancer treatments lead to earlier menopause presented with much severe symptoms.²¹ In this study women who have undergone surgeries like hysterectomy and oophorectomy are nearly at increased risk of early menopause. Furthermore, a study conducted in USA²² also established that women undergoing surgeries have more risk for having early menopause.^{23,24} also conducted a similar study in women with and without hysterectomy. She also concluded that surgeries are related to earlier onset of menopause.

Also the study on the Jordanian Women, 2010 shows that the women who suffered from early menopause were having a history of premature menopause in their parents, siblings or child¹ furthermore it is reported that inheritance/genetic accounts for about 25-30% in the onset of premature menopause cases.²⁵ Apart from the above-mentioned reasons one of the abnormalities of early menopause is the osteoporosis, estrogen depletion is linked with increased loss in bone mass and density, which results in approximately 9 million cases of bone fractures per year all around the globe.^{26,27} conducted a study that reveals that early menopause was associated with low (BMI) which is also in confirmation with this study that both low and high BMI are causes of early menopause. Anorexia is also a sign of early menopause. The loss of weight is a ubiquitous feature of amenorrhea. It is reported that being underweight may speedup menopause.²⁸ Likewise a study also demonstrated the Anorexia

Nervosa is one of the causes of amenorrhea leading to early onset of menopause.²⁹

There are certainly other contributing factors that result in early menopause, females with low parity or null parity are highly prevalent to premature/early menopause, likewise, females who experience early menarche are also at greater risk.^{30,31} Study conducted in the UK reported that twin females at higher risk of early menopause.³² Apart from genetics and physiological factors many social and lifestyle factors are also linked with early and immature menopause-like cigarette smoking^{33,34} childhood malnutrition, emotional stress, and cognitive function during childhood greatly influence timings of menopause.³⁵

Study Limitations

The study was conducted on a small population due to fewer resources, big sample size could portray a clearer picture of the story.

Conclusion

In the Interior of Sindh, women have symptoms of early menopause. Results of the study revealed that there are many underlying causes of early menopause but the common factors observed were certain pathological conditions, poor diet, surgeries, and cancer.

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