

PREMATURE AND EARLY MENOPAUSE: RISK FACTORS IN JORDANIAN WOMEN

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ABSTRACT

Objective: To identify risk factors associated with the onset of premature (<40 years) and early (40-45 years) menopause in a sample of Jordanian women.

Methods: This prospective study was undertaken at Princess Aisha Medical Complex, Amman between August 2007 and February 2008. A total of 1,000 postmenopausal women were included. Factors taken into consideration were age at menarche, age at first delivery, parity, number of miscarriages, history of gynaecological or obstetric surgeries (ovarian, tubal and/or uterine), smoking status and history of premature menopause in first-degree relatives.

Results: Out of the 1,000 women, 129 (12.9%) had had menopause before the age of 46 years: 27 (2.7%) before the age of 40 and 102 (10.2%) before the age of 46 years. In these groups, the only statistically significant factor was history of premature menopause in first-degree relatives. Interestingly, in women who had had menopause after the age of ≥ 46 years, the rate of hysterectomies was statistically higher.

Conclusion: Early and premature menopause is strongly associated with history of premature menopause in first-degree relatives. No other factors studied proved to have any statistical significance.

Key words: Early menopause, Family history, Premature menopause

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Introduction

The origin of the word menopause comes from the Greek words “*meno*” (menses, month) and “*pauses*” (stop, cease).⁽¹⁾ This normal sequelae of aging is due to reduced secretion of the ovarian hormones oestrogen and progesterone.⁽²⁾

The World Health Organization defines natural menopause as the permanent cessation of menstruation resulting from the loss of ovarian

follicular activity or follicle depletion.⁽³⁾ Natural menopause is recognized to have occurred after 12 consecutive months of amenorrhea for which there is no other obvious pathologic or physiologic cause.^(3,4) Women who have not had a spontaneous menstrual period for one year are classified as postmenopausal.^(3,4) Perimenopause includes the period immediately before menopause and the first year after the final menstrual period.^(3,4) Climacteric

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Table I. Comparison between the *premature* and *normal* groups

Criterion			Group-P (n= 27)		Group-N (n= 871)		P-value
			#	%	#	%	
S	Ovarian	Cyst	1	3.7	17	1.9	0.4258
U		LAP C	0	0	4	0.5	1.0000
R		Drilling	0	0	1	0.1	1.0000
E	Tubal	TL	3	11.1	104	11.9	1.0000
G		Ectopic	0	0	11	1.3	1.0000
R		CS	5	18.5	119	13.7	0.4054
I	Uterine	Myom	0	0	57	6.5	0.4080
E		TAH	2	7.4	105	12.1	0.7611
S		D&C	17	63.0	484	55.6	0.5562
		Never	1	3.7	135	15.5	0.1055
	Smoking	Past	1	3.7	39	4.5	1.0000
		Passive	17	63.0	552	63.4	1.0000
		Current	8	29.6	145	16.6	0.1124
	Positive family history		11	40.7	2	0.2	<0.0001
Menarche	Mean		13.3704		13.4960		0.2646
1 st pregnancy	Mean		18.3704		18.5040		0.9054
Parity	Mean		7.5926		7.5752		0.1030
Abortions	Mean		1.6296		1.5913		0.3985

Cyst= Ovarian cystectomy, LAP C= Laparoscopic ovarian cystectomy, TL= Tubal ligation, CS= Caesarean section, Myom= Myomectomy, TAH= Total abdominal hysterectomy, D&C= Dilatation and curettage

Table II. Comparison between the *early* and *normal* groups

Criterion			Group-E (n= 102)		Group-N (n= 871)		P-value
			#	%	#	%	
S	Ovarian	Cyst	3	2.9	17	1.9	0.4573
U		LAP C	1	1.0	4	0.5	0.4259
R		Drilling	1	1.0	1	0.1	0.1988
E	Tubal	TL	10	9.8	104	11.9	0.6266
G		Ectopic	2	2.0	11	1.3	0.6376
R		CS	9	8.8	119	13.7	0.2148
I	Uterine	Myom	6	5.9	57	6.5	1.0000
E		TAH	2	2.0	105	12.1	0.0007
S		D&C	48	47.1	484	55.6	0.1149
		Never	12	11.8	135	15.5	0.3814
	Smoking	Past	3	2.9	39	4.5	0.6120
		Passive	63	61.8	552	63.4	0.7460
		Current	24	23.5	145	16.6	0.0965
	Positive family history		4	3.9	2	0.2	0.0015
Menarche	Mean		13.4216		13.4960		0.9523
1 st pregnancy	Mean		17.5490		18.5040		0.2937
Parity	Mean		7.0686		7.5752		0.6474
Abortions	Mean		1.5784		1.5913		0.5287

Cyst= Ovarian cystectomy, LAP C= Laparoscopic ovarian cystectomy, TL= Tubal ligation, CS= Caesarean section, Myom= Myomectomy, TAH= Total abdominal hysterectomy, D&C= Dilatation and curettage

is the transition from the reproductive to the non-reproductive state.^(3,4) Clinically, menopause is defined as the cessation of ovarian function.^(2,3,4) The impact of the menopause on quality of life is not limited to middle age. The sequelae may also contribute to the chronic diseases of aging and thus extend to the later years as well.⁽⁴⁾ Menopause has been implicated in bone loss and susceptibility to fractures, decline in cognitive function, reduced

physical functioning, changes in body mass and fat distribution, glucose intolerance and diabetes, the development of cardiovascular risk factors, carotid atherosclerosis, and coronary disease.⁽⁵⁾ However, late natural menopause is correlated with an increased risk of breast cancer.⁽⁴⁾

This study was undertaken to identify risk factors associated with early and premature menopause in a sample of Jordanian women.

Table III. Comparison between the *premature* and *early* groups

Criterion			Group-P (n= 27)		Group-E (n= 102)		P-value
			#	%	#	%	
S	Ovarian	Cyst	1	3.7	3	2.9	1.0000
U		LAP C	0	0	1	1.0	1.0000
R		Drilling	0	0	1	1.0	1.0000
E	Tubal	TL	3	11.1	10	9.8	0.7344
G		Ectopic	0	0	2	2.0	1.0000
R		CS	5	18.5	9	8.8	0.1687
I	Uterine	Myom	0	0	6	5.9	0.3424
E		TAH	2	7.4	2	2.0	0.1929
S		D&C	17	63.0	48	47.1	0.1940
	Smoking	Never	1	3.7	12	11.8	0.2990
		Past	1	3.7	3	2.9	1.0000
		Passive	17	63.0	63	61.8	1.0000
		Current	8	29.6	24	23.5	0.6167
	Positive family history		11	40.7	4	3.9	<0.0001
Menarche	Mean		13.3704		13.4216		0.6999
1 st pregnancy	Mean		18.3704		17.5490		0.4740
Parity	Mean		7.5926		7.0686		0.9609
Abortions	Mean		1.6296		1.5784		0.4293

Cyst= Ovarian cystectomy, LAP C= Laparoscopic ovarian cystectomy, TL= Tubal ligation, CS= Caesarean section, Myom= Myomectomy, TAH= Total abdominal hysterectomy, D&C= Dilatation and curettage

Methods

This study was started in August 2007 at Princess Aisha Medical Complex, Amman. The aim was to collect information about the time of menopause from 1,000 women, to identify the fraction who had had premature or early menopause, and to detect any responsible factors.

Many women were excluded; exclusion criteria included hysterectomy and/or bilateral oophorectomy before the onset of natural menopause, history of radio- and/or chemotherapy, and history of primary amenorrhoea.

All the clinics of the medical centre helped in gathering the data. The ladies were questioned regarding age at menarche, menopause, first delivery, and parity, number of miscarriages, ovarian, tubal and/or uterine surgeries, history of smoking and family history of premature menopause in first-degree relatives (parents, offspring and siblings). Since most of the answers given were from memory, recall bias proved to be the most significant limitation.

The women were divided into three groups: Group-P (*premature*), Group-E (*early*), and Group-N (*normal*).

Statistical analysis was done using GraphPad® Instat software. The data was analysed using a contingency table which determined the chi-square and the p-value, where $p < 0.05$ was considered

statistically significant.

Results

Table I compares the *premature* and *normal* groups. No statistically significant differences were noted with regard to age at menarche, age at first pregnancy, parity and miscarriages. Nevertheless, a positive family history of premature menopause in first-degree relatives proved to be statistically significant.

Table II, compares the *early* and *normal* groups. This proved to be similar to the *premature* group where a positive family history of premature menopause in first-degree relatives was statistically significant. An interesting finding was that women with normal-onset menopause (≥ 46 years) had a statistically significant increase in the rate of hysterectomies that were performed. The percentage of women who smoked was higher in the *early* group when compared to the rest (23.5% versus 16.6%), but this did not prove to be statistically significant ($p=0.0965$).

Table III compares the *premature* and the *early* groups. Here, we also note that there were no statistically significant differences with regard to age at menarche, age at first pregnancy, parity and miscarriages, however, a positive family history of premature menopause in first-degree relatives also proved to be statistically significant.

Discussion

Normal menopause generally occurs after the age of ≥ 46 years with an average age of 51.3 years.⁽¹⁾ In contrast, menopause is regarded as premature when it begins before the age of 40 years.⁽⁶⁾

Early menopause describes women who develop menopause between 40-45 years of age. This happens in approximately 10% of women.^(1,7)

Premature menopause generally describes a syndrome consisting of amenorrhea (three or more months' duration), elevated gonadotrophin levels and decreased oestrogen levels typical of those found in postmenopausal women.⁽⁶⁾ It affects 1% of women by the age of 40 years and 0.1% by the age of 30 years.⁽⁸⁾ Previously, follicle-stimulating hormone levels in the menopausal range were regarded as evidence of depletion of ovarian follicles, resulting in irreversible and permanent cessation of ovarian function. It is now clear, however, that approximately 50% of women with apparent premature menopause may have intermittent and unpredictable ovarian function; 25% may ovulate, and 6% to 10% may conceive after the diagnosis is made.^(6,9)

In women who present with 46 XX spontaneous premature ovarian failure as their primary concern there is a clear association between serum adrenal cortex autoantibodies and the presence of histologically confirmed autoimmune oophoritis.⁽¹⁰⁾

Fragile X mental retardation 1 (FMR1) gene is the gene responsible for fragile X syndrome, the most common hereditary cause of mental impairment and developmental delay. Practice guidelines from the American College of Obstetricians and Gynecologists Committee on Genetics recommend FMR1 carrier testing for women with premature ovarian insufficiency, particularly if they have a family history of fragile X, or family members with premature ovarian insufficiency, unexplained mental impairment, developmental delay, dementia, or a tremor/ataxia syndrome.⁽¹¹⁾

In our study, a total of 1,000 women were questioned regarding the time of their menopause and 129 women had had menopause before the age of 46 years. Out of this group, 27 (2.7%) had had premature menopause, leaving 102 women (10.2%) with early-onset menopause. This agrees with Margaret-Mary Wilson as the accepted percentage of women with early menopause.⁽¹⁾ In these ladies, there was a positive family history of premature menopause in first-degree relatives.

Premature menopause, however, is a different story. Our results are much higher than figures mentioned by Kalantaridou *et al.*⁽⁸⁾ which states that approximately 1% of women will experience premature menopause. This may be secondary to social aspects in our community where inter-familial marriages are common. Needless to say, there was a statistically significant association of a positive family history of premature menopause in first-degree relatives in women who had had premature menopause themselves when compared to the rest.

Although cigarette smoking is often mentioned as a risk factor to premature and early menopause, it was not so in our study. The percentage of women who had had premature and early menopause, and who were current smokers was high but this did not reach statistical significance. This is in contrast to the findings of Mikkelsen *et al.*⁽¹²⁾ and Parazzini *et al.*⁽¹³⁾ who concluded that current cigarette smoking is associated with lower age menopause.

Although we excluded women who had had premenopausal hysterectomy from our study, we asked all women whether they underwent this operation after having the menopause. An interesting finding that we had was that the number of women who underwent hysterectomy was significantly higher in women who had normal-onset menopause when compared to the women with early and premature menopause. This was just a finding with no reasonable explanation. Perhaps if the number of women was higher, we would not have had this result.

Conclusion

Early and premature menopause was strongly associated with history of premature menopause in first-degree relatives. No other factors studied proved to have any statistical significance.

More studies with larger numbers of women need to be undertaken in order to determine factors responsible for early and premature menopause.

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