

# Genetic evaluation of rs36513 SNP of UIMC1 and Biochemical Parameters in Early Menopause in Babylon City, Iraq

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## Abstract

Premature menopause or Early menopause (POF) is a condition characterized by amenorrhea, hypoestrogenism, and elevated serum gonadotrophin level in women younger than 40 years old. This work aimed to evaluate the association of candidate genetic polymorphism in called trans membrane protein 150 B (TMEM150B ) and ubiquitin interaction motif containing 1 (UIMC1) also the hormonal changes with POF in one district of Iraq (province of Babylon) by enrolling Arab ancestors. The genetic variants that would be studied in this project were carefully selected according to the recent findings in this field, and by employed several specialized databases . The selected variant are transmembrane protein 150B (TMEM150B ) and ubiquitin interaction motif containing 1 (UIMC1) and their relation with premature ovarian failure. This study include (200) females , their ages between (35-40 years) and body mass index in normal and overweight, (50) of them were with amenorrhea for 6 months, and the other (150) apparently healthy as control group. Concerning rs365132, the genetic association with POF showed that there was no significant allelic or genotypic association recorded ( $P > 0.2$ ), except that the patients group was significantly deviated from Hardy-Weinberg equilibrium exact test ( $P=0.023$ ). For rs11668344, the genetic association with POF showed that there was no significant allelic or genotypic association recorded ( $P > 0.2$ ), except that the patients group was significantly deviated from Hardy-Weinberg equilibrium exact test ( $P=0.023$ ). The hormonal results of the present study showed significant increase in FSH in patients compared with controls group. ( $P < 0.0001$ ) and this study showed significant decrease ( $p \leq 0.001$ ) in EST in patients compared with controls group. As a conclusion , the study conclude that rs365132 and rs11668344 genes variants do not represent genetic factors which can modulate the development of POF in Arab population from Babylon province .

**Keywords:** *Trans membrane protein, Early menopause, ubiquitin interaction motif.*

## Introduction

The menopause was considered a natural biologic event that affects every woman. For most women, the menopause transition coincides with the midlife years and was characterized as a time of multiple physiological, psychological and social changes that

can impact a women's health<sup>(1)</sup>. Premature menopause (PM) refers to menopause that occurs before age 40 years, and early menopause refers to menopause that occurs at or before age 45 years<sup>(2)</sup>. Premature menopause and early menopause, whether spontaneous or induced, were associated with long-term health risks which may include premature death, cardiovascular disease, neurologic disease, osteoporosis, psychosexual dysfunction, and mood disorders. Estrogen mitigates some but not all of these consequences<sup>(3)</sup>. Fogle in 2017 was searched in different types of premature menopause or early menopause result in different long-term health

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consequences remains unknown. Their hormonal milieu differ because the postmenopausal ovary was hormonally active, producing small amounts of estradiol and estrone, as well as androgens including testosterone, androstenedione, and dehydroepiandrosterone <sup>(4)</sup>. Following bilateral oophorectomy in premenopausal women, estradiol levels drop, testosterone levels drop by 40–50%, and follicle-stimulating hormone levels rise abruptly. Women undergoing bilateral oophorectomy continue to have lower levels of androgens than naturally menopausal women even beyond 65 years of age <sup>(5)</sup>. Concern about the risks of hormone therapy following publication of results from the Women's Health Initiative clinical trials may be inappropriate if applied to women with premature menopause or early menopause who typically need estrogen in adequate replacement doses for a duration of time long enough to reduce the consequences of prolonged estrogen deficiency. It was important that clinicians not withhold health-promoting estrogen replacement for these women <sup>(6)</sup>. Many mutations causing POI were in genes involved with hormone function. Missense mutations in the AMH gene had been identified that result in mutant AMH with loss of AMH-receptor activation. Mutations in INHA, inhibin alpha chain, had also been found in POI. As well as mutations in FSHB (discussed above), several mutations with functional effects had been identified in FSHR, the follicle stimulating hormone receptor. In-frame, frameshift and missense mutations had been identified in NR5A1, a transcriptional regulator of genes tangled in hormone regulation by hypothalamic-pituitary-gonadal and adrenal axis <sup>(7)</sup>. Genetic impacts regulate the dimensions of the primordial follicle pool, have an effect on the frequency of vesicle abnormal condition, and are a main determinant of climacteric age. Genetic causes for POI can account for about 20% to 25% of cases with the start of more refined genetic screening technologies <sup>(8)</sup>. The amount of genes had

been identified both from studies of POI and GWAS that were involved in homologous recombination; MCM8, MSH5 and DMC1. A common variant in MCM8, a DNA helicase involved in DNA repair, Three sisters with amenorrhea and hypergonadotropic hypogonadism are related with a decrease in menopause age by up to one year, whereas a homozygous mutation in this gene resulted in a deficiency of double strand break reparation. Common variants near MSH5, which was involved in meiotic recombination, had been found to reduce age at menopause by 0.16 years, And this gene also identified a heterozygous missense mutation causing POI <sup>(9)</sup>.

## **Materials and Methods**

This work was planned as case-control study conducted in conjunction with the Babel gynaecology Hospital within the Branch of organic chemistry at the faculty of drugs, University of city. The topics enrolled in this study was 200, these topics are classified as follows: A group of patients (50) diagnosed with misperiod for at least 4 months in female under the age of 40 are collectively required to diagnose POI. With 35-40 years of age. Control group comprises 150 subjects of healthy volunteers and subjects set up within normal ranges as suggested by doctor consultants during their visit to the doctor, 35-40 years of age. There are 4 index of body mass groups <sup>(10)</sup>. Elimination conditions were diabetes mellitus patient, hypertension, contraceptives (estrogens), and obesity BMI > 30. Inclusion criteria was diagnosis requires miss period for at least 4 months in female younger than 40 years of age.

## **Results**

Analysis of demographic characteristics of study subjects showed that there were significant differences in FSH, EST, MOH, PRO, and LH between patients and control group, as shown in Table 1.

**Table 1: FSH, EST, PRO, MOH, and LH levels (ng/ml) in study groups**

	Group	N	Mean	Std. D	Std. E
FSH	Case	50	50.5400	17.63254	2.49362
	Control	150	19.0000	3.48920	.28489
EST	Case	50	50.5400	17.63254	2.49362
	Control	150	19.0000	3.48920	.28489
AMH	Case	50	1.6320	.32729	.04629
	Control	150	2.8767	.60738	.04959
PRO	Case	50	14.5200	3.62666	.51289
	Control	150	10.8800	3.07822	.25134
LH	Case	50	8.9200	2.46477	.34857
	Control	150	7.8800	2.31980	.18941

Analysis of demographic characteristics of study subjects showed that there were significant differences in EST in correlation with rs36513 SNPs of UIMC1 between group of patients and control group as shown in Table 2.

**Table 2: Correlation of EST with rs36513 SNPs of UIMC1**

	N	Mean	Std. Deviation	Std. Error	95% Confidence Interval for Mean		Min	Max
					Lower Bound	Upper Bound		
G/G	29	56.2069	28.36796	5.26780	45.4163	66.9975	10.00	110.00
A/A	44	67.0455	27.02966	4.07487	58.8277	75.2632	20.00	110.00
A/G	127	68.0315	26.75697	2.37430	63.3328	72.7302	15.00	110.00
Total	200	66.1000	27.22584	1.92516	62.3037	69.8963	10.00	110.00

(I) BSO	(J) BSO	Mean Difference (I-J)	Std. Error	Sig.	95% Confidence Interval	
					Lower Bound	Upper Bound
G/G	A/A	-10.83856-	6.47024	.095	-23.5984-	1.9213
	A/G	-11.82460-*	5.56731	.035	-22.8038-	-.8454-
A/A	G/G	10.83856	6.47024	.095	-1.9213-	23.5984
	A/G	-.98604-	4.73210	.835	-10.3181-	8.3460
A/G	G/G	11.82460*	5.56731	.035	.8454	22.8038
	A/A	.98604	4.73210	.835	-8.3460-	10.3181

\*. The mean difference is significant at the 0.05 level.

Analysis of demographic characteristics of study subjects showed that there were differences in LH in correlation with UIMC1 between group of patients and control group as shown in Table 3:

**Table 3: Correlation of LH with rs36513 SNP of UIMC1**

	N	Mean	Std. Deviation	Std. Error	95% Confidence Interval for Mean		Minimum	Maximum
					Lower Bound	Upper Bound		
G/G	29	7.3103	2.36195	.43860	6.4119	8.2088	4.00	12.00
A/A	44	8.0909	2.18683	.32968	7.4261	8.7558	4.00	12.00
A/G	127	8.3465	2.44423	.21689	7.9172	8.7757	4.00	15.00
Total	200	8.1400	2.39354	.16925	7.8062	8.4738	4.00	15.00

Analysis of demographic characteristics of study subjects showed that there were differences in AMH in correlation with UIMC1 between group of patients and control group, as shown in Table 4:

**Table 4: Correlation of AMH with rs36513 SNP of UIMC1**

	N	Mean	Std. Deviation	Std. Error	95% Confidence Interval for Mean		Minimum	Maximum
					Lower Bound	Upper Bound		
G/G	29	2.2621	.84152	.15627	1.9420	2.5822	1.00	3.50
A/A	44	2.7273	.74095	.11170	2.5020	2.9525	1.50	3.50
A/G	127	2.5787	.75083	.06663	2.4469	2.7106	1.00	3.50
Total	200	2.5655	.77106	.05452	2.4580	2.6730	1.00	3.50

Analysis of demographic characteristics of study subjects showed that there were differences in LH in correlation with TMEM between group of patients and control group as shown in Table 5

**Table 5: Correlation of LH with rs897798 TMEM SNPs**

	N	Mean	Std. Deviation	Std. Error	95% Confidence Interval for Mean		Minimum	Maximum
					Lower Bound	Upper Bound		
G/G	41	8.0541	2.22294	.36545	7.3129	8.7952	4.00	15.00
A/A	73	7.7534	2.34391	.27433	7.2066	8.3003	4.00	12.00
A/G	86	8.5233	2.49577	.26913	7.9882	9.0583	4.00	15.00
Total	200	8.1480	2.40375	.17170	7.8093	8.4866	4.00	15.00

## Discussion

The searched for the premature or early menopause was the first step in a chain of causality leading to tissue or organ dysfunctions and lesions via hormonal mechanisms<sup>(12)</sup> With POF, follicle-stimulating hormone levels are elevated and estradiol levels are low, but sporadic increases in estradiol may occur<sup>(13)</sup> Ovarian androgens remain age-appropriate in these women<sup>(14)</sup>. Luteinizing hormone “hyperactivity” appears to have no effect in women. However, in the present study, we observed a strong relation between the variant LH and POF that was not caused by hormonally resistant ovaries. , abnormal LH secretion can induce anovulation, luteal insufficiency, and premature oocyte maturation, leading to menstrual disorders, PCOS, recurrent spontaneous abortions, and infertility<sup>(15)</sup>. Abnormal LH and/or LH receptors have been linked with endometriosis-associated infertility<sup>(16)</sup>. Menopausal symptoms in patients with POI are consequent to the premature decline in ovarian follicle number and a dysfunction of the residual follicles with resulting hypoestrogenemia and, to a lesser extent, a decline in ovarian testosterone. Adequate systemic estrogen replacement is critical for symptom control, whereas local estrogen may be required for addressing focal symptoms such as genitourinary symptoms<sup>(17)</sup>. AMH is considered a good and reliable parameter in the assessment of ovarian reserve<sup>(18)</sup>. Its reduced levels may indicate reduced ovarian reserve, even if the woman has regular menstrual cycles and the levels of FSH and E<sub>2</sub> are still normal. A good correlation has been found between AMH levels and age and also between AMH levels and the number of antral follicles. The diversity of results depending on the type of laboratory test used and the absence of a universal calculation method to facilitate the comparison of results obtained via different tests is a significant limitation associated with the use of AMH as a test for ovarian reserve. Clinical signs of PCOS include elevated luteinizing hormone (LH) and gonadotropin-releasing hormone (GnRH) levels, whereas follicular-stimulating hormone (FSH) levels are muted or unchanged. As a result of the increase in GnRH, stimulation of the ovarian thecal cells, in turn, produces more androgens<sup>(19)</sup>. Follicular arrest can be corrected by elevating endogenous FSH levels or by providing exogenous FSH. Some studies suggest that PCOS is a primary defect in young girls who are entering puberty and who have a

family history of the disorder. Approximately 25% of patients with PCOS have elevated prolactin levels<sup>(20)</sup>. In the first GWAS of menstrual cycle length we found a strong association between an FSH lowering, likely functional, variant in the FSHB promoter and longer cycles<sup>(21)</sup>. This locus has been previously robustly associated with age at menopause in the ReproGen GWAS of menopause timing and the allele associated with longer cycle length is associated with later age at menopause<sup>(22)</sup>. We not observe associations for the majority of age at menopause GWAS signals with length of menstrual cycle, including the four signals with effects of over one-third of a year per allele on menopause timing, implying that the association is specific to FSHB: Either FSHB has independent effects on both cycle length and menopause, or changes in cycle length are causally influencing menopause timing.

**Acknowledgments:** The authors thanks all women participated in this study

**Ethical Clearance:** The Research Ethical Committee at scientific research by ethical approval of both environmental and health and higher education and scientific research ministries in Iraq

**Conflict of Interest:** The authors declare that they have no conflict of interest.

**Funding:** Self-funding

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