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The impact of INH-alpha (rs12720062 G/A) gene polymorphism and serum vitamin D level on risk of premature ovarian failure

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ABSTRACT

Background: The loss of ovarian function before the age of 40 is referred to as premature ovarian failure (POF). Genetic conditions and some acquired conditions may be to blame for premature ovarian failure. Vitamin D deficiency has been linked to a number of medical conditions and recent data suggest a link between premature ovarian failure and this deficiency; however, clear consensus among authors does not exist. Genetic wise, a link between premature ovarian failure and INH-alpha (rs12720062 G/A) gene polymorphism is shown by some authors.

Aim of the study: To investigate the impact of inhibin alpha gene polymorphism and serum vitamin D level to risk of premature ovarian failure.

Patients and methods: The study included forty women with signs and symptoms of POF and forty fertile and healthy women to represent the control group. Patients and control individuals were collected from three fertility units in Iraq, Um-Albaneen fertility center in Al-Imamain Al-Kadhimain Madical City - Baghdad, Higher Institute of Infertility Diagnosis and Assisted Reproductive Techniques - Baghdad, and from the infertility unit in Women's and children's hospital at Al-Diwaniyah city. Samples collection was performed during the period extended from August 2021 to Spetember 2022. Serum vitamin D level was measured by finecare and serum inhibin was measured by ELISA. Genetic study of INH-alpha (rs12720062 G/A) genotypes and alleles was done.

Results: Average vitamin D serum level of POF category was lower significantly than that of control group, 15.17 ±3.82 ng/ml versus 40.68 ±5.76 ng/ml, respectively ($p < 0.001$). In addition, mean Inhibin-Alpha of POF was significantly lower than that of group of controls, 3.27 ±1.28 (pg/ml) versus 29.13 ±9.11 (pg/ml), respectively ($p < 0.001$). Concerning INH-alpha (rs12720062 G/A) gene polymorphism, GA genotype was significantly less associated with POF in comparison with control group ($p = 0.014$); the odds ratio was 0.23; the wild homozygous GG genotype revealed significant association with POF, 34 versus 23, respectively ($p = 0.007$) and the odds ratio was 4.19. Allele G was more significantly associated with POF in comparison with control group; allele A was less significantly associated with POF in comparison with control group ($p = 0.005$).

Conclusion: Premature ovarian failure is significantly predisposed by INH-alpha (rs12720062 G/A) genotypes and alleles and it is linked pathogenetically vitamin D deficiency and low serum inhibin level.

Keywords: *Premature ovarian failure, vitamin D, INH-alpha*

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INTRODUCTION

In women under the age of 40 who have premature ovarian insufficiency, the number of ovarian follicles decreases and they stop functioning normally as endocrine and reproductive organs (Jankowska, 2017). It has the features of inadequate sex hormones of ovarian origin and diminished follicles of ovary, which hasten the menopause's onset (Wesevich et al., 2020). Due to the fact that this illness is linked to reduced level of estrogen, which results in irregular menstrual cycles and failure of pregnancies, it frequently results in subfertility or infertility (Ebrahimi and Akbari Asbagh, 2011). Hot flashes, nocturnal sweats, and sleeplessness are just a few of the menopausal symptoms brought on by the drop in estrogen secretion. Furthermore, long-term effects of early ovarian function loss raise lifetime risks of bone fragility, cardiovascular disease, and cognitive impairments (Wesevich et al., 2020).

As a result of decreased ovarian reserve and inadequate ovarian sex hormone production, premature ovarian insufficiency (POI) causes a rapid decline in functions of ovary and start of menopause at an early age (Wesevich et al., 2020). A natural physiological occurrence known as reduced ovarian reserve describes the amount and quality of older eggs in women (usually in their mid to late 30s) declining (Sharara et al., 1991). Some women develop infertility considerably sooner as a result of this illness (Aramesh et al., 2021). Since it is a steroid hormone, vitamin D is known to affect the metabolism of calcium and bones (Holick, 2007). The human AMH gene's promoter region has a functional vitamin D element (VDRE), which raise the possibility that D-vitamin may possess a direct impact on the expression of AMH (Malloy et al., 2009). Recent meta-analysis of 2700 infertile women's fertility results revealed a strong correlation between favorable outcomes with vitamin D sufficiency (Savastano et al., 2017).

Previuos studies, including those by Chapman et al. (2015) and Mutlu and Erdem (2012), which found that the INH1 G769A mutation was present in 10.5% of cases with sporadic POF as opposed to 0.005% of controls. A sample of 97 fertile controls and 70 women with early ovarian insufficiency were compared in a Brazilian study by Christofolini et al. (2017). The G769A variation manifests to be uncommon in Brazilian women having premature ovarian failure since it was only discovered in one woman in the Premature Ovarian failure category and in no controls.

PATIENTS AND METHODS

The study included forty (40) women with signs and symptoms of POF and forty (40) fertile and healthy women to represent the control group. Patients and control individuals were collected from three fertility units in Iraq, Um-Albaneen fertility center in Al-Imamain Al-Kadhimain Madical City - Baghdad, Higher Institute of Infertility Diagnosis and Assisted Reproductive Techniques - Baghdad, and from the infertility unit in Women’s and children’s Hospital - Al-Diwaniyah city. Samples collection was performed during the period extended from August 2021 to Spetember 2022. Patients consent was obtained from all participating women. Data about age and body mass index were collected. Serum vitamin D level was measured by finecare FIA and serum inhibin was measured by ELISA. Genetic study of INH-alpha (rs12720062 G/A) genotypes and alleles was done.

RESULTS

Comparison of demographic characteristics between premature ovarian failure group and control group is shown in table 1. There was no significant difference in mean age between patients with premature ovarian failure and control groups, 32.93 ±4.26 years versus 32.08 ±5.37 years, respectively ($p = 0.435$). The mean body mass index (BMI) of patients with premature ovarian failure was significantly more than that of control group, 27.14 ±1.96 kg/m2 versus 23.81 ±1.88 kg/m2, respectively ($p < 0.001$).

Comparison of vitamin D between premature ovarian failure group and control group is shown in table 2. Mean serum vitamin D of POF group was significantly lower than that of control group, 15.17 ±3.82 ng/ml versus 40.68 ±5.76 ng/ml, respectively ($p < 0.001$).

In addition, POF group included 4 (10.0 %) women with sub-optimal level (20-29 ng/ml), 36 (90.0 %) had vitamin D deficiency (<20 ng/ml) and no one had normal level of (≥ 30 ng/ml). On the other hand control group included 40 (100.0 %) women with normal level of (≥ 30 ng/ml) and the difference was significant ($p < 0.001$).

Comparison of mean serum Inhibin-Alpha between premature ovarian failure group and control group is shown in table 3. Mean Inhibin-Alpha of POF was significantly lower than that of control group, 3.27 ±1.28 (pg/ml) versus 29.13 ±9.11 (pg/ml), respectively ($p < 0.001$).

Comparison of genotypes and alleles of INH-a rs12720062 G/A between premature ovarian failure and control group is shown in table 4. According to co-dominance mode and considering the wild GG genotype as a reference , the following was found: GA genotype was significantly less associated with POF in comparison with control group, 4 versus 12, respectively and the difference was significant ($p = 0.014$); the odds ratio was 0.23 indicating that GA genotype is a protective factor against POF, on the other hand, genotype AA was less associated with POF in comparison with control group, 2 versus 5, respectively, but the difference was not significant ($p = 0.118$), thus, genotypes AA in the codominance mode is neither a protective factor nor a risk factor and this was further confirmed when odds ratio was estimated since the 95 % confidence interval was ranging between < 1 and > 1.

With respect to dominance mode, comparing the wild homozygous GG genotype to other genotypes, revealed significant association with POF, 34 versus 23, respectively ($p = 0.007$) and the odds ratio was 4.19 indicating that women carrying GG genotype are about 4 times more liable to have POF in comparison with women carrying GA or AA genotypes. However, recessive mode analysis revealed no significant association between AA genotype and POF ($p = 0.235$) and this was further confirmed when odds ratio was estimated since the 95 % confidence interval was ranging between < 1 and > 1.

Allele analysis revealed that allele G was more significantly associated with POF in comparison with control group, 72 versus 58, respectively and that allele A was less significantly associated with POF in comparison with control group ($p = 0.005$); therefore, allele G can be considered as a risk factor for POF with an odds ratio of 3.41 and allele A as a protective factor with an odds ratio of 0.29.

TABLE 1: Comparison of demographic characteristics between premature ovarian failure group and control group

Characteristic	Premature ovarian failure n = 40	Control n = 40	p
Age (years)			
Mean ±SD	32.93 ±4.26	32.08 ±5.37	0.435 I
Range	20 -39	21 -39	NS
BMI (kg/m2)			
Mean ±SD	27.14 ±1.96	23.81 ±1.88	<0.001 I
Range	23.83 -30.82	20.83 -27.77	***

n: number of cases; SD: standard deviation; BMI: body mass index; I: independent samples t-test; C: chi-square test; NS: not significant; ***: significant at $p \leq 0.001$

TABLE 2: Comparison of vitamin D between premature ovarian failure group and control group

Characteristic	Premature ovarian failure n = 40	Control n = 40	p
Vitamin D3 (ng/ml)			
Mean ±SD	15.17 ±3.82	40.68 ±5.76	<0.001 I ***
Range	7.95 -24.12	30.2 -53.9	
Normal (≥ 30 ng/ml)	0 (0.0 %)	40 (100.0 %)	<0.001 C ***
Sub-optimal level (20-29 ng/ml)	4 (10.0 %)	0 (0.0 %)	
Deficiency (<20 ng/ml)	36 (90.0 %)	0 (0.0 %)	

n: number of cases; SD: standard deviation; I: independent samples t-test; C: Chi-square test; ***: significant at $p \leq 0.001$

TABLE 3: Comparison of serum 17-alphahydroxylase and Inhibin-Alpha between premature ovarian failure group and control group

Characteristic	Premature ovarian failure n = 40	Control n = 40	p
Inhibin-Alpha (pg/ml)			
Mean ±SD	3.27 ±1.28	29.13 ±9.11	<0.001 I ***
Range	1 -5	15.4 -45.9	

n: number of cases; SD: standard deviation; I: independent samples t-test; ***: significant at $p \leq 0.001$

TABLE 4: Comparison of genotypes and alleles of INH-a rs12720062 G/A between premature ovarian failure and control group

Mode	INH-a rs12720062 G/A	Premature ovarian failure	Control	p	OR	95% CI
	Genotypes	n = 40	n = 40			
Co-dominance	GG	34	23	Reference		
	GA	4	12	0.014 C *	0.23	0.06 -0.79
	AA	2	5	0.118 C NS	0.27	0.05 -1.52
Dominance	GG	34	23	0.007 C **	4.19	1.44 - 12.22
	GA+AA	6	17	Reference		
Recessive mode	GG+GA	38	35	Reference		
	AA	2	5	0.235 C NS	0.37	0.07 -2.02
Allele	G	72	58	0.005 C **	3.41	1.42 -8.23
	A	8	22		0.29	0.12 -0.71

INH: inhibin; n: number of cases; OR: odds ratio; CI: confidence interval; C: chi-square test; NS: not significant; *: significant at $p \leq 0.05$; **: significant at $p \leq 0.01$

DISCUSSION

In the present study, average vitamin D serum level of POF category was lower significantly than that of group of controls and most of women within the group of POF were complaining of deficiency of vitamin D. Kebapcilar et al. (2013) performed a study on 35 women with POF and 28 women who were healthy controls and found that serum vitamin D of POF group was significantly lower than that of control group; therefore we agree with the results of Kebapcilar et al. In the study of Ersoy et al. (2016), forty-eight women diagnosed with POF, and 82 women recruited as controls and the results indicated lack of significant difference in mean serum vitamin D between patients and control group in clear controversy to our results.

The role of vitamin D in relation to ovary physiology has been documented (Irani and Merhi, 2014). Changes in the level of steroidogenesis and in the level of AMH have been linked to vitamin D deficiency (Merhi et al., 2014, 23). Experimental studies have shown that vitamin D can affect gene expression for receptors of AMH and FSH in granulosa cells (Merhi et al., 2014). In addition, clinical study showed a positive correlation between serum vitamin D level and serum AMH level (Dennis et al., 2012). Moreover, a negative significant correlation has been found between serum FSH and serum vitamin D level (Kebapcilar et al., 2013). All above data suppose the existence of a link between vitamin D deficiency and POF.

Deficiency of Vitamin D has been linked to a variety of autoimmune diseases (Murdaca et al., 2019). On the other hand, POF has been considered to be related to an autoimmune pathogenesis but the exact mechanism is not well understood (Kebapcilar et al., 2013). Therefore, we can suggest according to our observation that vitamin D insufficiency in patients with POF, seen in our study, plays a significant participation in the etiology of POF through an autoimmune mechanism since we found in addition, an association with thyroid abnormality which can be linked to POF by a shared autoimmune predisposition.

In the current study, mean serum levels of Inhibin-Alpha of POF were significantly lower than that of control group. Lower level of serum inhibin in association with POF has been observed in several previous reports (Munz et al., 2004; Chapman et al., 2015). Indeed, it is suggested that the low level of inhibin is part of the pathogenesis of the disease because it will lead to increased activity of activin hormone that will stimulate FSH and leads to increased rate of folliculogenesis and premature exhaustion of ovarian follicles and thereby early menopause (Chand et al., 2010; Christofolini et al., 2017). The low serum level of inhibin-alpha has been linked to genetic variations in the genes that encode inhibin and the suggestion that such genetic variation will cause reduction in the production and secretion of this hormone with resulted augmented activin hormone effect (Christofolini et al., 2017).

Our findings revealed that concerning the INH-alpha (rs12720062 G/A) SNP, GG is the most frequent genotype in both controls and POF patients and that AA genotype is the least frequent. Similarly, allele G was the more frequent than Allele A in both groups. In patients with POF, there was significant deviation from Hardy Weinberg equilibrium indicating that the SNP may play a role in the etiology of POF at least partially. In addition, we found that genotype GG and allele G were risk factors, genotypes GA and allele A were protective factors against POF; whereas, genotype AA plays no significant role.

In an Iraqi study by Al-Sabbagh et al. (2020), The results of the RFLP used to investigate the variant in this gene revealed that all of the controls and the majority of patients were homozygous for the wild-type G allele. The frequency of the G allele was 92.8 percent in the patient group and 100 percent in the control group, compared to 7.2 percent in the POF patient group and 0 percent in the control group. The frequency of the GG genotype was found to be (100%) in the control group and (85.7%) in POF, whereas the GA genotype was found to be (14.3%) and (0%), respectively, in patients and controls. These results are consistent with observation regarding the order of frequencies of genotypes GG, GA and AA, but, they are inconsistent with our observation to which genotype is a risk factor for POF, they claimed GA genotype, whereas, we claimed the GG genotype. A heterozygous alteration was discovered in a New Zealand population that was strongly linked with the syndrome (7% in POF, n = 38, compared with 0.07% in controls, n = 150; P = 0.011) (Shelling et al., 2000). In another meta-analysis of these data, the Asian Indian populations had a significant odds ratio of 8.10 (95% CI 1.27-51.6) and a cumulative odds ratio of 1.38 (95% CI 0.48-3.94) (Zintzara, 2009). The Asian Indian population has a greater frequency of INHA gene mutations (Dixit et al., 2004, 2006; Prakash et al., 2009). 10.5% of the sporadic POF cases (n = 133), as opposed to 0.005% of the controls, had the INHA G769A mutation, according to Dixit and colleagues (Dixit et al., 2004, 2006). One patient in this group had a homozygous mutation. With three different readings of 100, 88, and 85 IU/l, this patient had the highest circulating FSH levels ever observed in the group under investigation.

At age 24, this patient underwent menopause. Six carriers (10%) were detected out of the 60 women with primary amenorrhoea who were individually screened for the inhibin subunit mutation. One mutation carrier was reported to develop primary amenorrhea by Shelling et al. in 2000.

The results of this investigation were compared to those of other studies, including those by Chapman et al. (2015) and Mutlu and Erdem (2012), which found that the INH1 G769A mutation was present in 10.5% of cases with sporadic POF as opposed to 0.005% of controls. A sample of 97 fertile controls and 70 women with early ovarian insufficiency were compared in a Brazilian study by Christofolini et al. (2017). The G769A variation manifests to be uncommon in Brazilian women with premature ovarian failure since it was only discovered in one woman in the Premature Ovarian failure category and in no controls. Women with POI had high levels of inhibin A that are comparable to those found in postmenopausal women. Elevated FSH concentrations, which are indicative of aging function of reproduction, are thought to be caused by decreasing levels of inhibin in perimenopausal women and concurrently elevated levels of activin A. Despite that the reduced ratio of inhibin/activin seen after menopause is likely caused by altered inhibin synthesis, it is possible that ovarian failure is caused by mutations in the gene of INHA, which could result in reduced inhibin level and, as a result, higher levels of FSH (Christofolini et al., 2017). There is a SNP in INHA G769A (rs12720062) that changes the amino acid from alanine to threonine. A decrease in the amount of bioactive inhibin may result from a functional mutation in any one of the three inhibin genes. This loss could stop the pituitary's negative feedback loop, raise FSH levels, hasten the follicles' early depletion, and hence lead to POF. Given that the INHA G769A mutation is frequently a heterozygous mutation, any effects this modification may have on the biological activity of inhibin are probably not going to result in a total loss of function. It is hypothesized that 50% less inhibin action in mutation carriers will affect two stages of development: I fetal gonadal development; and (ii) the control of proper folliculogenesis and ovulation. A decline in inhibin biological potency might prevent the fetal ovary from developing normally, which would impact ovarian function after delivery. Ovarian dysregulation, particularly at the follicular development stage, may be brought on by an increase in circulating FSH levels brought on by a reduction in the endocrine impact of inhibin. A reduction in inhibin bioactivity may be a factor in abnormal folliculogenesis, maturation, and atresia since inhibin has significant paracrine effects on the actions of activin, GDF9, and BMP15 within the follicles (Chand et al., 2010). It has been hypothesized that the alteration interferes with inhibin's ability to bind to its potential receptor (Makanji et al., 2014). Alternative explanations for the functional impact of this transition mutation include dimer formation, decreased glycosylation, and prevention of cleavage of the mature peptide. Due to this, the subsequent signal transduction pathway cannot be activated, and the FSH level cannot be deregulated by negative feedback (Fallahian et al., 2009; Mutlu and Erdem, 2012). To better understand the connection between the genetic variations in the inhibin alpha subunit and POF, larger cohort studies with suitable controls are needed.

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