The Impact of INH-Alpha (Rs35118453 C/T) Gene Polymorphism and Serum 17-Alphahydroxylase Level on Risk of Premature Ovarian Failure

Durar Kamil Jabbar[1], Noor M. Ali[2], Hala Abdul qadir[3]
[1, 2] Al-Nahrain University/ College of Medicine, Department of Chemistry and Biochemistry, Baghdad, Iraq.
[3] Al-Nahrain University/ College of Medicine, department of Obstetrics and Gynecology/ Iraq
E-mail: durat.kamil@qu.edu.iq
E-mail: noormustafali@yahoo.com
E-mail: dr.hala1966@gmail.com

Abstract

Background: The loss of ovarian function before the age of 40 is referred to as premature ovarian failure (POF). The term describes the state in which the ovaries have lost their hormonal and germinative capacities as a result of the ovarian follicles becoming exhausted before the customary age for physiological menopause. Genetic factors such as gene polymorphism and acquired factors such as serum levels of 17-alpha hydroxylase enzyme may play a role in the pathogenesis of this condition. **Aim of the study:** To investigate the association of inhibin alpha gene polymorphism with 17-alpha hydroxylase activity in women with premature ovarian failure. **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 at 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 17-alphahydroxylase level was measured by ELISA. Genetic study of INH-alpha (rs35118453 C/T) genotypes and alleles was done. **Results:** Mean serum 17-alphahydroxylase of POF was significantly lower than that of control group, 0.03 ±0.02 (nmol/L) versus 50.69 ± 47.17 (nmol/L), respectively ($p < 0.001$). With respect to INH-alpha (rs35118453 C/T) gene polymorphism, co-dominance, dominance and recessive modes, all showed no significant association between CC, CT or TT genotypes with POF when compared to control group ($p > 0.05$) However, allelic analysis, revealed that allele C was more significantly associated with POF in comparison with control group, 72 versus 62, respectively and that allele T was less significantly associated with POF in comparison with control group ($p = 0.023$).**Conclusion:** Premature ovarian failure is significantly predisposed by INH-alpha (rs35118453 C/T) alleles.

Keywords: Premature ovarian failure, INH-alpha, 17-alphahydroxylase

1. 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 is characterized by inadequate ovarian sex hormones and diminished ovarian follicles, which hasten the menopause's onset (Wesevich et al., 2020). Due to the fact that this illness is linked to hypoestrogenism, which causes irregular menstrual cycles and pregnancy failures, 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 inadequate ovarian sex hormone production and diminished ovarian reserve, premature ovarian insufficiency (POI) causes a rapid decline in ovarian function and an early start of menopause (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).

Numerous research employed various ethnic groups and varied sample sizes, the relationship between the INHA gene polymorphisms (c.-16C > T) and POF is debatable (Shelling, 2012; Corre

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et al., 2009; Dixit et al., 2006; Harris et al., 2005; Marozzi et al., 2002; Sundblad et al., 2006; Woad et al., 2009). In actuality, two recent meta-analyses discovered no proof of a link between POI and INHA gene polymorphisms (Chand et al., 2010; Zintzaras, 2009). Actually, two research on Korean women were carried out with disparate outcomes (Yoon et al., 2012; Kim et al., 2011). Therefore the aim of the present study was to investigate the association of inhibin alpha gene polymorphism in women with premature ovarian failure.

2. 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 at 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 hormones, FSH, LH, testosterone, progesterone, prolactin, T3, T4, TSH and vitamin D were measured by finecare FIA. serum inhibin and serum 17-alphahydroxylase levels were measured by ELISA. Genetic study of INH-alpha (rs12720062 G/A) and INH-alpha (rs35118453 C/T) genotypes and alleles was done.

3. 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/m^2 versus 23.81 ±1.88 kg/m^2, respectively (p < 0.001). Comparison of mean serum 17-alphahydroxylase between premature ovarian failure group and control group is shown in table 2. Mean serum 17-alphahydroxylase of POF was significantly lower than that of control group, 0.03 ±0.02 (nmol/L) versus 50.69 ± 47.17 (nmol/L), respectively (p < 0.001).
Comparison of genotypes and alleles of INH-a (rs35118453 C/T) between premature ovarian failure and control group is shown in table 3. Co-dominance, dominance and recessive modes, all showed no significant association between CC, CT or TT genotypes with POF when compared to control group (p > 0.05) and this was further confirmed when odds ratio was estimated since the 95 % confidence interval was ranging between < 1 and > 1. However, allelic analysis, revealed that allele C was more significantly associated with POF in comparison with control group, 72 versus 62, respectively and that allele T was less significantly associated with POF in comparison with control group (p = 0.023); therefore, allele C can be considered as a risk factor for POF with an odds ratio of 2.61 and allele T as a protective factor with an odds ratio of 0.38. Comparison of mean body mass index, mean serum vitamin levels and serum hormonal levels according to INH-a (rs35118453 C/T) genotypes is shown in table 4. No significant difference was reported (p > 0.05).

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 INS
Range	20 -39	21 -39	
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 ≤ 0.001

Table 2: Comparison of serum 17-alphahydroxylase between premature ovarian failure group and control group

Characteristic	Premature ovarian failure *n* = 40	Control *n* = 40	*p*
17-alphahydroxylase (nmol/L)			
Mean ±SD	0.03 ±0.02	50.69 ± 47.17	<0.001 I ***
Range	0.01 -0.06	0.08 -150.9	

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

Table 3: Comparison of genotypes and alleles of INH-a (rs35118453 C/T) between premature ovarian failure and control group						
Mode	INH-a rs35118453 C/T Genotypes	Premature ovarian failure n = 40	Control n = 40	p	OR	95% CI
Co-dominance	CC	33	26	Reference		
	CT	6	10	0.191 C NS	0.47	0.15 -1.47
	TT	1	4	0.122 C NS	0.20	0.02 -1.87
Dominance	CC	33	26	0.075 C NS		
	CT+TT	7	14	Reference		
Recessive mode	CC+CT	39	36	Reference		
	TT	1	4	0.166 C NS	2.54	0.89 -7.20
Allele	C	72	62	0.032 C *	2.61	1.06 -6.42
	T	8	18		0.38	0.16 -0.94
INH: inhibin; ***n***: number of cases; **OR**: odds ratio; **CI**: confidence interval; **C**: chi-square test; **NS**: not significant; *: significant at $p \leq 0.05$						

Table 4: Comparison of mean body mass index, mean serum vitamin levels and serum hormonal levels according to INH-a (rs35118453 C/T) genotypes				
Characteristic	CC *n* = 33	CT *n* = 6	TT *n* = 1	*p*
BMI	27.11 ±1.96	27.54 ±2.14	25.71 ±	0.658 K NS
17alphahydroxylase	0.03 ±0.02	0.03 ±0.02	0.05±	0.644 K NS
INH: inhibin; n: number of cases; BMI: body mass index; K: Kruskal Wallis test; NS: not significant				

4. Discussion

The mean body mass index (BMI) of patients with premature ovarian failure was significantly more than that of control group indicating that obesity and overweight are among features associated with premature ovarian failure in addition, most of women with premature ovarian failure enrolled in our study where either overweight or obese, further augmenting the evidence of the association between obesity and premature ovarian failure. Previous data have shown conflicting results with respect to association between body mass index and premature ovarian failure; the linkage between weight and menopause time appears to be nonlinear, as both overweight and underweight females may undergo early menopause (Rostami Dovom et al., 2021).

These two possibilities could help explain some of the relationship between obesity and early ovarian failure: (1) Hyperinsulinemia, insulin resistance, and a decrease in steroid hormone binding globulin (SHBG) are all linked to obesity in the general population, which raises testosterone, dihydrotestosterone, and androstenediol levels (Brewer and Balen, 2010). Increasing insulin, glucose, triglycerides, and C-reactive protein, an inflammatory marker in follicular fluid, are associated with decreasing SHBG (Robker et al., 2009). Age, on the other hand, raises insulin resistance and the risk of type 2 diabetes in general. Hyperinsulinemia is closely related to insulin resistance (Weyer et al, 2001). Additionally, it has been documented that antimullerian hormone (AMH), a crucial indicator of ovarian reserve, has a negative correlation with homeostatic model assessment for insulin resistance (HOMA-IR) levels (Park et al., 2010). The reduction of ANM in obese/overweight women may be explained by taking these connections into account (2). Poor oocyte quality has been seen in obese adults as a result of ototoxicity of inflammatory substances released by adipose tissue (Robker, 2008; Cardozo et al., 2011; Purcell SH, Moley, 2011).

On the other hand, women with lower BMIs (18.5 kg/m2) have limited fat storage, which could result in poor ovarian follicle quality (Akahoshi et al., 2002; Hardy et al., 2008; Zhu et al., 2018). Contrary to popular belief, slender women's lower BMI is not associated with a drop in the manufacture of the hormone estrogen in their adipose tissue because the initiation of estrogen synthesis in peripheral fat occurs after menopause (Tao et al., 2015).

In the current study, mean serum levels of 17-alphahydroxylase of POF were significantly lower than that of control group. The low level of serum levels of 17-alphahydroxylase in our study may reflect it's under production by the failing ovary. We unforunatley failed to find a prior study that measured serum level of 17-alphahydroxylase in women with POF in comparison with a control group. Summarization of our findings revealed that concerning the INH-alpha (rs35118453 C/T) SNP, CC is the most frequent genotype in both controls and POF patients and that TT genotype is the least frequent. Similarly, allele C was the more frequent than Allele T in both groups. In patients with POF, there was no significant deviation from Hardy Weinberg equilibrium indicating that the SNP may play a minimal role in the causation of POF. In addition, we found that genotypes CC, CT and TT were not associated significantly with POF, thus none of them can be regarded as a risk factor for POF; however, allelic analysis revealed that allele C is a significant risk factor and allele T is a significant protective factor for POF.

In an Egyptian study, the case-control study design was used to assess the relationship between the INH-alpha (rs35118453 C/T) SNP and POF (n = 50 for POF and n = 50 for controls). According to Egyptian research, the frequencies of the homozygous genotypes CC, CT, and TT of the INHa-16C>T

polymorphism in women with POF were 70% (35/50), 24% (12/50), and 6% (3/50), respectively. This finding is more or less similar to our finding in that CC is the more frequent genotype and TT is the least frequent genotype. They also discovered that, similar to our findings, the T allele was present in 12% of patients with POF and 27% of the control group, whereas the C allele was present in 82% of patients with POF and 73% of the control group. Although their findings are consistent with ours regarding INH-alpha (rs35118453 C/T) gene polymorphisms and POF in Egyptian women, we disagree with their findings about allelic analysis.

Rah et al. (2014) used 136 Korean women with POF and 225 control women to study the association between INH-alpha (rs35118453 C/T) SNP and POF. They discovered that there is no significant association between INH-alpha (rs35118453 C/T) SNP and POF based on genotype or allele analysis. These results partially support our findings with regard to genotype analysis, but they are in opposition to them with regard to allele analysis.

Because numerous research employed various ethnic groups and varied sample sizes, the relationship between the INHA gene polymorphisms (c.-16C > T) and POF is debatable (Shelling, 2012; Corre et al., 2009; Dixit et al., 2006; Harris et al., 2005; Marozzi et al., 2002; Sundblad et al., 2006; Woad et al., 2009). In actuality, two recent meta-analyses discovered no proof of a link between POI and INHA gene polymorphisms (Chand et al., 2010; Zintzaras, 2009). Actually, two research on Korean women were carried out with disparate outcomes (Yoon et al., 2012; Kim et al., 2011). Yoon et alfindings .'s imply no connection between the INHA gene polymorphism (c.-16C > T) and risk of idiopathic POI, however Kim et alfindings .'s confirm the association (Yoon et al., 2012; Kim et al., 2011). According to Kim et al., POI patients had a lower frequency of the two individual polymorphisms (C allele of the c.- 16C > T and G allele of the c.- 124A > G) than did controls (Kim et al., 2011).

According to a new genome-wide association analysis, POI may have overlapping polygenic rather than monogenic etiologies (Panay N, Kalu, 2009; Perry et al., 2013; Pyun et al., 2012). In order to detect a relationship, a large sample size may be needed because the impact of a single genetic variant on the onset of disease may be modest. Differences between earlier INHA association studies (Shelling, 2012; Dixit et al., 2006; Sundblad et al., 2006; Woad et al., 2009; (Yoon et al., 2012; Kim et al., 2011; Dixit et al., 2004). According to prior meta-analysis findings for the c.-16C > T polymorphism using 1398 controls and 936 cases, and the c.-124A > G polymorphism using 1446 controls and 938 cases (Zintzaras, 2009). It is believed that the polymorphisms c.-16C > T and c.-124A > G in the INHA promoter may contribute to lower inhibin levels in POI patients (Shelling, 2012; Kim et al., 2011).

In order to clarify the precise significance of INHA gene polymorphisms and haplotypes in POI pathogenesis, additional research that employ more comparable analysis methodologies and/or that pool raw data are required.

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