



V64M Mutation in Leukemia Inhibitory Factor Gene in Women Infertility

***Gholamreza NIAEI¹, Bita AMIR TAGHAVI², Amir NIAEI³**

1. *Dept. of Biology, Faculty of Sciences, University of Guilan, Rasht, Iran*
2. *Dept. of Genetics, Islamic Azad University, Tehran Medical Branch, Tehran, Iran*
3. *Dept. of Internal Medicine, School of Medicine, Tebran University of Medical Sciences, Tebran, Iran*

***Corresponding Author:** Email: GolamrezaNiaci@gmail.com

(Received 10 Dec 2016; accepted 17 Jan 2017)

Dear Editor-in-Chief

Infertility is one of the major increasing gynecological problems worldwide. The incidence of infertility varies between populations mainly due their dietary, lifestyle, environmental and occupational factors, and infectious diseases. Embryonic implantation takes place on the uterine inner surface after a series of molecular and cellular interactions between the embryo and endometrium. Various different cytokines are suggested just before participating in successful implantation, including uterine natural killer cells, leukemia inhibitory factor (LIF) and interleukin 15 (IL-15) (1-3). Leukemia inhibitory factor (LIF), a pleiotropic cytokine from interleukin- (IL-) 6 families, regulates various cellular functions via binding to membrane-bound LIF receptor (LIFR) and gp130. The role of LIF in human implantation is less clear. LIF probably plays a role in endometrial function in humans and domestic species. Progesterone is a major regulator of LIF expression and coincides with progesterone dominance (3-5). The LIF gene mutation, G to A transition at position 3400 in exon 3 leading to valine to methionine exchange at codon 64 (V64M), in the AB loop region of the LIF protein (5-7). The prevalence of LIF gene mutations was investigated in a population of infertile women and found a significantly higher frequency of the functionally relevant mutation (7). The role of the LIF gene allele and the hormonal stimulation

were hypothesized, the aim of the study was to determine whether a diagnosed cause of infertility is directly related to 3400 G>A LIF gene mutation, reflected in women with various causes of infertility.

From April 2015 to October 2015, we screened 60 non-selected infertile women and 80 fertile controls with at least one live birth for LIF gene mutations in Tabriz University of Medical Science, Tabriz, Iran. Genomic DNA was extracted from human peripheral blood cells by the “salting out” technique (8). Then, single strand conformation polymorphism (SSCP) and direct sequence analysis of these aberrantly migrating bands were carried out for investigation of gene LIF V64M mutation.

In infertile women LIF gene mutations which are statistically significantly ($P<0.05$) connected to women with infertility and more frequent than in healthy women (Table 1). The 3400 G>A LIF gene Mutation may be associated with increased risk of idiopathic women infertility. Therefore, our study indicates that there is significant association between the LIF gene V64M Mutation and biological activity of LIF and cause implantation failure.

This study was limited to study of the role of only one single cytokine, LIF. It is the cumulative effect of different cytokines acting on the embryo

and the endometrium, essential for successful implantation.

Table 1: Prevalence of the 3400 G>A LIF gene mutation in patient and control groups and evaluation of their association with infertility

Polymorphism	Normal		Heterozygote		Homozygote		Pvalue
	Case (%)	Control (%)	Case (%)	Control (%)	Case (%)	Control (%)	
LIF 3400 G/A	8.1	13.8	59.9	75.5	32	10.7	0.006

Conflict of Interests

The authors declare that there is no conflict of interests.

References

1. Edwards RG (1995). Physiological and molecular aspects of human implantation. *Hum Reprod*, 10 Suppl 2:1-13.
2. Kaider AS, Kaider BD, Janowicz PB, Roussev RG (1999). Immunodiagnostic evaluation in women with reproductive failure. *Am J Reprod Immunol*, 42(6):335-46.
3. Cheung LP, Leung HY, Bongso A (2003). Effect of supplementation of leukemia inhibitory factor and epidermal growth factor on murine embryonic development in vitro, implantation, and outcome of offspring. *Fertil Steril*, 80 Suppl 2:727-35.
4. Laird SM, Tuckerman EM, Dalton CF, et al (1997). The production of leukemia inhibitory factor by human endometrium: presence in uterine flushing's and production by cells in culture. *Hum Reprod*, 12(3):569-74.
5. Giess R, Tanasescu I, Steck T, Sendtner M (1999). Leukemia inhibitory factor gene mutations in infertile women. *Mol Hum Reprod*, 5(6):581-6.
6. Novotny Z, Krizan J, Šima R, et al (2009). Leukemia inhibitory factor (LIF) gene mutations in women diagnosed with unexplained infertility and endometriosis have a negative impact on the IVF outcome. A pilot study. *Folia Biol (Praha)*, 55(3):92-7.
7. Kraličkova M, Šima R, Vaněček T, et al (2006). Leukemia inhibitory factor gene mutations in the population of infertile women are not restricted to nulligravid patients. *Eur J Obstet Gynecol Reprod Biol*, 127(2):231-5.
8. Miller SA, Dynes DD, Polesky HF (1988). A simple salting out procedure for extracting DNA from human nucleated cells. *Nucleic Acids Res*, 16(3):1215.