# A C-634-G Polymorphism of the Interleukin-6 Gene Promoter as a Possible Risk for Idiopathic Recurrent Miscarriage

***Ayatallah A. Nassef[1], Dina R.Bahgat[1], Fouad AboHamila[2]***
Clinical and Chemical Pathology Dept.[1], Obstetric and Gynecology Dept.[2], Faculty of Medicine, Cairo University

## ABSTRACT

**Background:** Cytokines have been described to play a major role in the *pathogenesis of idiopathic recurrent miscarriage (IRM). We investigated the association between IRM and a polymorphism of the interleukin-6 (IL-6).* ***Methods:*** *In a prospective case-control study, we studied 100 women with IRM and 60 healthy controls. Peripheral venous blood sample was taken from each woman for DNA extraction and PCR was employed to genotype women for the presence of a polymorphism at position -634 in the promoter region of IL-6.* ***Results:*** *Allele frequencies among women with IRM and controls were 82.5 and 78.3% respectively for allele C (wild type); 17.5% and 21.6% respectively for allele G (mutant). No association between allele G and the occurrence of IRM was found (odds ratio 1.304; 95% confidence interval = 0.760–2.299;* P= *NS).* ***Conclusion: To our knowledge t****his is the first report on IL-6 polymorphism in IRM on Egyptian population, yet. the IL-6 polymorphism investigated was not associated with IRM in the studied group of Egyptian population.*

## INTRODUCTION

Physiologically, the maternal immune system confronts the embryo/fetus with a host-defense reaction, based on the recognition of paternally derived fetal and placental antigens[1]. To avoid rejection of the semi-allogenic embryo/fetus, the maternal immune response is selectively suppressed in physiological pregnancies[2]. While $T_H$-2 type immunity is believed to contribute to successful pregnancy, $T_H$-1 type immunity has been shown to be associated with idiopathic recurrent miscarriage (IRM)[2-4].

IL-6 is a multifunctional cytokine, produced by many different cell types, including immune cells, fibroblasts, endothelial cells, adipocytes and myocytes[5]. Secretion of IL-6 leads to a stimulation of the hypothalamic-pituitary-adrenal axis during inflammatory processes[6], promotes osteoclastogenesis and participates in the development of osteoporosis associated with estrogen withdrawal[7]. IL-6 is not constitutively expressed, but is highly inducible and produced in response to a number of inflammatory stimuli[8].

IL-6 is generally considered to be a proinflammatory cytokine. IL-6 also has anti-inflammatory properties, as

demonstrated in IL-6 gene knock-out mice[9]. The role of IL-6 expression during pregnancy, as well as its predictive value for pregnancy outcome, is unclear. In human studies, IL-6 production has been described in the decidua during early pregnancy. Also, IL-6 has been shown to induce the release of hCG from trophoblasts, leading to a subsequent cascade of progesterone production, release of $T_H2$ cytokines, e.g. IL-6, IL-4, and suppression of $T_H1$ cytokines[3,10,11]. This is compatible with an anti-inflammatory role for IL-6 in pregnancy. On the other hand, elevated levels of IL-6 and proinflammatory cytokines, e.g. IL-1, TNF-α, and IL-8 in the placenta, amniotic cells, and decidua have been demonstrated in pregnancies complicated by pre-term premature rupture of the membranes, intrauterine infection and prematurity[12,13].

The etiology of recurrent pregnancy loss remains largely unclear[14-16]. The possible immunologic etiologies of pregnancy failure have been intensively investigated[17].

A shift to type 2 T-helper ($T_H2$) cytokine production with abundant interleukin IL-6 and IL-10 is considered essential for the maintenance of normal pregnancy. There is evidence of a diminished Th2 immune response to placental antigens in women with recurrent pregnancy loss[18]. Plasma levels of IL-6, IL-8, and IL-11 have been found to be decreased in such women compared with those with normal pregnancies[19]. Additionally, IL-6 levels in maternal serum[20], amniotic fluid[21], vaginal fluid[22], and placenta[23] have been found to increase during the process of normal labor compared with the nonlabor state. One study demonstrated an increase in the frequencies of type 1 T-helper ($T_H1$) cytokine IL-1 gene promoter region variants IL-1 -511C and IL-1 –311T in women with recurrent pregnancy loss[24]. One of the $T_H2$ cytokines, IL-10 promoter region variant (-1082G→A), was not associated with recurrent pregnancy loss[25,26]. However, relationships between many diseases and IL-6 promoter gene polymorphisms, such as IL-6 -174G→C[27,28] and IL-6 -634C→G[29], were recently demonstrated. It is also, known that the former polymorphism is frequently found in Caucasians[27,28] and the latter in the Japanese[27].

## MATERIALS & METHODS

The present case–control study was performed in Cairo, Egypt, during the years 2010–2011. We studied 100 cases aged 20–43 years with a history of recurrent pregnancy loss and 60 controls aged 21–48 years who visited the Obstetrics and Gynecology Department at Cairo University Hospital. The characteristics of the study groups are shown in Table 1. Recurrent pregnancy loss was defined as a history of two or more consecutive spontaneous abortions and stillbirths. The primary recurrent pregnancy loss group compromised 89 women with a history of two or more pregnancy losses but no live birth. The 11 women in the secondary recurrent pregnancy loss group experienced three or more pregnancy losses after one live birth. All women with recurrent pregnancy loss were

subjected to blood analyses for TORCH, antinuclear antibody, anti-DNA antibody, lupus anticoagulant, anticardiolipin antibody, anticardiolipin -2-glycoprotein I complex antibody, and activated partial thromboplastin time, d-dimer, protein S, protein C activity, and factor XII to identify patients with antiphospholipid antibody syndrome and thrombophilia.

Subjects were examined by ultrasound and hysterosalpingography for detection of anatomic abnormalities of the genital tract. All couples were also subjected to chromosome karyotypic analyses of peripheral blood. Couples with balanced type chromosomal translocation and women with recurrent pregnancy loss with uterine conformational abnormalities, such as a septate uterus, were excluded from the study, because these etiologies of recurrent pregnancy loss are known to have a close cause-and-effect relationship. Women with positive test results for autoantibodies and women with antiphospholipid antibody syndrome were included in this study, because immunologic abnormalities, including IL-6, possibly underlie the pathophysiology of recurrent pregnancy loss in these women. Of the 100 women, 13 (13.0 %) had autoimmune disease and/or antiphospholipid antibody syndrome, and 8 (8%) had hematologic abnormalities, but none had a history of thromboembolism. Control women consisted of 60 volunteers who had experienced at least two live births and no abortion and who had no history of infertility. There were no significant differences in age between cases and controls.

Participants in the study gave informed consent and the study was approved by the institutional ethical boards for human gene and genome studies at Cairo University School of Medicine. Genomic DNA was extracted from lymphocytes of peripheral blood samples by the use of standard techniques. Sequence amplification was performed with polymerase chain reaction (PCR). To analyze the -634C→G genotype, PCR amplifications were carried out as described by Ota et al.[29], with the primers 5'-GAG AGG CCT TGA AGT AAC TG-3' and 5'-AAC CAA AGA TGT TCT GAA CTG A-3' (Nanjing Bio Eng Co). The following PCR protocol was used: 95°Cfor 3 min,35 cycles of 95°C for 1 min, 59°C for 1 min, 74°Cfor 2 min,72°C for 5 min (BIO-RAD, Iapa,) After the PCR product was digested with 2 U of BsrBI endonuclease (New England Biolabs) at 37°C for 5 hours. The digested products were separated in 3.0% agarose gel electrophoresis and identified by ethidium bromide staining. The resulting products of 180-base pair (bp), a 120 and a 60-bp fragments and 180+120+60 -bp fragments represented the "CC", GG, and CG genotypes, respectively.

**QUALITY CONTROL**: 30% of samples were randomly selected to be genotyped a second time to ensure reproducibility. Genotyping was performed blinded to clinical status.

**Statistical Analysis:**

We calculated age-adjusted odds ratios (OR) and 95% confidence intervals (CI) associated with the IL-6 genotypes by unconditional logistic

regression analysis. All analyses were conducted with SPSS version13.0 software for Windows (SPSS Inc. Chicago, IL). The differences in allele frequency among groups were examined for statistical significance with chi-square test by SAS 6.12. All tests were 2-tailed and $p<0.05$ was taken to denote significance.

## RESULTS

The characteristics of the study groups are shown in Table1. The frequency of the --634C→G genotype in 100 cases with recurrent pregnancy loss were compared with those in 60 controls among an Egyptian population (Table 2). There was no significant difference in the-634C→G genotype frequency (CC vs. CG/GG) between the women with recurrent pregnancy loss and the controls. The risk of recurrent pregnancy loss was the same in the carriers of the G allele and in women with the wild type (CC) (OR 0.737; 95% CI - 0.737–2.735).

We next evaluated the -634C→G genotype in both subgroups of women with three or more pregnancy losses and women with two pregnancy losses (Table 3). We found that the allele frequencies as well as the distribution of genotypes were not significantly different between the study and the control groups. Allele frequencies among women with IRM and controls were 82.5 and 78.3 % respectively for allele C (wild type), and 17.5 and 21.6% respectively for allele G (mutant). No association between allele G and the occurrence of IRM was found (odds ratio 1.304; 95% confidence interval = 0. 760–2.299; *P* = NS).

**Table1:** Characteristics of 100 cases with recurrent pregnancy loss and 60 controls in an Egyptian population.

| Characteristics | Cases | | Controls | |
|---|---|---|---|---|
| | No | % | No | % |
| Age (years) | | | | |
| 20-29 | 35 | 35 | 19 | 31.66 |
| 30-39 | 62 | 62 | 32 | 53.33 |
| >40 | 3 | 3 | 9 | 15 |
| Number of previous pregnancy losses | | | | |
| 2 | 42 | 42 | ---------- | |
| 3 | 40 | 40 | ---------- | |
| >4 | 18 | 18 | ---------- | |

**Table 2:** Distribution of IL-6 genotypes among 100 cases with recurrent pregnancy loss and 60 controls

| IL-6 genotype | Cases | | Controls | | OR (95%CI) | P value |
|---|---|---|---|---|---|---|
| | No | % | No | % | | |
| -634C→G | | | | | | |
| CC | 65 | 65 | 34 | 56.6 | 1 | 0.189 |
| CG | 35 | 35 | 26 | 43.3 | 1.420(0.737-2.735) | |

**Table 3:** Distribution of IL-6 genotypes among cases with 3 or more pregnancy loss and 2 pregnancy losses and controls

| | Cases | | Controls | | OR (95%CI) | P value |
|---|---|---|---|---|---|---|
| | No | % | No | % | | |
| 3 or more pregnancy losses | | | | | | |
| CC | 35 | 62.5% | 34 | 56.6 | 1 | 0.326 |
| CG/GG | 21 | 37.5% | 26 | 43. | 1.275 (0.606-2.682 | |
| 2 pregnancy losses | | | | | | 0.574 |
| CC | 25 | 56.8% | 34 | 56.6 | 1 | |
| CG/GG | 19 | 40.2% | 26 | 43. | 1.006(0.459-2.206) | |

**Table 4:** IL-6 G634C allele polymorphism: allele frequencies among women with recurrent pregnancy losses and controls

| Allele | Women with IRM | | Controls | | Odds ratio (95%) | P value |
|---|---|---|---|---|---|---|
| | No | % | No | % | | |
| C (wild) | 165 | 82.5 | 94 | 78.33 | 1 | |
| G(mutant) | 35 | 17.5 | 26 | 21.66 | 1.304(0.760-2.299) | 0.219 |

## DISCUSSION

Many investigators have assessed possible associations between etiologies of recurrent pregnancy loss and gene polymorphisms, including a family of enzymes responsible for metabolism of environmental toxins, glutathione S-transferase (GST)[30-33], and associations between etiologies of recurrent pregnancy loss and the GSTP1[31] and GSTM1 polymorphisms[33] have been demonstrated. Others sought etiologies in gene polymorphisms susceptible to infection in women with recurrent pregnancy loss; these cytokine genes included tumor necrosis factor-α[26,33,34], interferon-α[26], IL-1β[34,35], and anti-inflammatory cytokine IL-10[25,26]. Among these studies, however, only one demonstrated an increase in the frequencies of IL-1α promoter region variants IL-1 α 511C and IL-1 α -311T in women with recurrent pregnancy loss; a IL-1 α 511C variant was found to be associated with $T_H1$ overimmunity to trophoblast antigens[24].

In the present study, we attempted to establish an association between a polymorphism in the promoter region of the IL-6 gene, known to alter IL-6 protein expression, and the occurrence of IRM. Our hypothesis to test the IL-6 gene as a candidate gene for IRM was based on existing evidence that immunological processes are involved in the pathogenesis of this condition[4].

There are now several well documented instances where nucleotide polymorphisms occur

within the regulatory region of cytokine genes, and some of these are associated with an altered rate of gene expression (8 In addition, women with IRM have been found to carry a polymorphic allele of the IL-1 receptor antagonist gene (IL-1 RN*2) more often than women without a compromised reproductive history[36].

Recently, von Wolff and colleagues found an abnormal expression of IL-6 and IL-1 β- mRNA in endometrium during the mid-secretory phase in women with IRM[37]. Others, reported significantly higher serum concentrations of the $T_H2$ cytokines IL-6 and lL-10 at normal delivery than in women with IRM[38]. Furthermore, higher IL-6 levels were found in women with IRM who had a successful pregnancy as compared with women with IRM who had another abortion[38]. Thus, the dominance of $T_H2$ cytokines seems to be of importance in maintaining pregnancy. Our study, however, falls short of determining a significant effect of the IL-6 genotype on IRM.

Saijo and colleagues[39] have demonstrated an association between recurrent pregnancy loss and the 634 C to G genotype of the IL-6 gene. They also found that recurrent pregnancy loss risk in the carriers of the G allele was lower than that in the wild type (OR=46). Also, **Ota et al.,**[29] reported frequencies of the IL-6 -634C-G allele in a sample of Japanese women: gene frequencies of the C and G alleles were 0.814 and 0.186, respectively.

During pregnancy, IL-6 serum levels are detectable and increase significantly at the time of delivery[38,40]. In those patients with intra-amniotic infection, high intra-amniotic IL-6 levels are detectable[12]. Thus, based upon these and our findings, a model of the role of IL-6 during pregnancy can be proposed. In normal pregnancy, IL-6 may be regarded as part of an antiinflammatory mechanism aimed at maintaining pregnancy. Based on our data, there seems to be no effect of IL-6 on IRM. At the time of acute inflammatory responses such as in intra-amniotic infection, IL-6 seems to act as an inducer of acute phase reactions and an important player in the elicitation of cellular immune responses.

## CONCLUSION

Multiple cytokine polymorphisms were reported to be associated with RSA. However, a majority of studies were not confirmed by other investigators or refuted by others. Inconsistent study results might be related to: (i) the production of these cytokines is partly under genetic controls and other factors affect cytokine levels; (ii) ethnic background, environmental factors, and selection criteria for study populations are different and (iii) the possibilities exist that multiple cytokine gene polymorphisms or other genes in linkage disequilibrium may play a role in RSA

In summary, this is the first report of a genetic variant of the IL-6 C634→G promoter gene among Egyptian women with IRM. We could demonstrate that the polymorphism at position –634 in the promoter region of IL-6 is not associated with altered risk of IRM in a sample of Egyptian

population. Based on our data, IL-6 seems not to be a candidate gene for that condition.

## REFERENCES


1. **Beer, A.E. (1983)**: Immunopathologic factors contributing to recurrent spontaneous abortions in humans. Am. J. Reprod. Immunol., 4(4): 182–184.
2. **Wegmann, T.G., Lin, H., Guilbert, L. and Mosmann, T.R. (1993):** Bidirectional cytokine interaction in maternal-fetal relationship: is successful pregnancy a TH2 Phenomenon? Immunol. Today 14(7): 353–356.
3. **Hill, J.A (1992):** Cytokines considered critical in pregnancy. Am. J. Reprod. Immunol., 28 (3-4) :123–126
4. **Jenkins, C., Roberts, J., Wilson, R., MacLean, M.A., Shilito, J. and Walker, J.J. (2000):** Evidence of a TH1 type response associated with recurrent miscarriage. Fertil. Steril., 73(6): 1206–1208.
5. **Papanicolaou, D.A., Wilder, R.L., Manolagas, S.C. and Chrousos, G.P. (1998):** The pathophysiologic roles of interleukin-6 in human disease. Ann. Intern. Med., 128(2): 127–137.
6. **Mastorakos, G., Chrousos, G.P. and Weber, J.S. (1993):** Recombinant interleukin-6 activates the hypothalamic-pituitary-adrenal axis in humans. J. Clin. Endocrinol. Metab., 77(6): 1690–1694.
7. **Manolagas, S.C. and Jilka, R.L. (1995):** Bone marrow, cytokines, and bone remodeling: Emerging insights into the pathophysiology of osteoporosis. N. Engl. J. Med., 332(6): 305–311.
8. **Wilson, M., Blum, R., Dandona, P. and Mousa S. (2001):** Effects in humans of intravenously administered endotoxin on soluble cell-adhesion molecule and inflammatory markers: a model of human diseases. Clin. Exp. Pharmacol. Physiol., 28(5-6): 376–380.
9. **Xing, Z., Gauldie, J., Cox, G., Baumann, H., Jordana, M., Lei, X.F. and Achong, M.K. (1998):** IL-6 is an antiinflammatory cytokine required for controlling local or systemic acute inflammatory. J. Clin. Invest., 101(2): 311–320.
10. **Siiteri, P.K., Febres, F., Clemens, L.E., Chang, R.J., Gondos, B. and Stites, D. (1977):** Progesterone and maintenance of pregnancy: is progesterone nature's immunosuppressant ? Ann. N. Y. Acad. Sci., 286: 384–397.
11. **Nishino, E., Matsuzaki, N., Masuhiro, K., Kameda, T., Taniguchi, T., Takagi, T., Saji, F. and Tanizawa, O. (1990):** Trophoblast-derived interleukin-6 (IL-6) regulates human chorionic gonadotropin release through IL-6 receptor on human trophoblasts. J. Clin. Endocrinol. Metab., 71(2): 436–441.
12. **Romero, R., Avila, C., Santhanam, U. and Sehgal, P.B. (1990):** Amniotic fluid interleukin 6 in preterm labor.

Association with infection. J. Clin. Invest., 85(5): 1392–1400.

13. **Fukuda, H., Masuzaki, H. and Ishimaru, T. (2002):** Interleukin-6 and interleukin-1 receptor antagonist in amniotic fluid and cord blood in patients with pre-term, premature rupture of the membranes. Int. J. Gynaecol. Obstet., 77(2): 123–129.
14. **Stirrat GM (1990):** Recurrent abortion. II. Clinical associations, causes, and management. Lancet 336:728–33.
15. **Parazzini F, Bocciolone L, Fedele L, Negri E, La Vecchia C, Acaia B. (1991):** Risk factors for spontaneous abortion. Int. J. Epidemiol., 20(2): 157–61.
16. **Cramer DW, Wise LA.(2000):** The epidemiology of recurrent pregnancy loss. Semin. Reprod. Med., 18(4) :331–9.
17. **Clark DA, Arck PC, Chaouat G (1999):** Why did your mother reject you? Immunogenetic determinants of the response to environmental selective pressure expressed at the uterine level. Am. J. Reprod. Immunol., 41(1) :5–22.
18. **Raghupathy R, Makhseed M, Azizieh F, Hassan N, Al-Azemi M, Al-Shamali E.(1999)**: Maternal Th1- and Th2-type reactivity to placental antigens in normal human pregnancy and unexplained recurrent spontaneous abortions. Cell Immunol., 196(1): 122–30.
19. **Koumantaki Y, Matalliotakis I, Sifakis S, Kyriakou D, Neonaki M, Goymenou A, et al.(2001):** Detection of interleukin-6, interleukin-8, and interleukin-11 in plasma from women with spontaneous abortion. Eur. J. Obstet. Gynecol. Reprod. Biol., 98(1):66–71.
20. **Arntzen KJ, Lien E, Austgulen R (1997):** Maternal serum levels of interleukin-6 and clinical characteristics of normal delivery at term. Acta Obstet. Gynecol. Scand., 76(1):55–60.
21. Olah KS, Vince GS, Neilson JP, Deniz G, Johnson PM. **(1996):** Interleukin-6, interferon-gamma, interleukin-8, and granulocyte-macrophage colony stimulating factor levels in human amniotic fluid at term. J. Reprod. Immunol., 32(1):89–98.
22. **Imseis HM, Greig PC, Livengood CH 3rd, Shunior E, Durda P, Erikson M**. **(1997):** Characterization of the inflammatory cytokines in the vagina during pregnancy and labor and with bacterial vaginosis. J. Soc. Gynecol. Investig., 4(2):90–4.
23. **Steinborn A, Gunes H, Roddiger S, Halberstadt E. (1996):** Elevated placental cytokine release, a process associated with preterm labor in the absence of intrauterine infection. Obstet. Gynecol., 88(4 Pt 1):534–9.
24. **Wang ZC, Yunis EJ, De los Santos MJ, Xiao L, Anderson DJ, Hill JA. (2002):** T helper 1-type immunity to trophoblast antigens in women with a history of recurrent pregnancy loss is associated with polymorphism of the IL1B promoter region. Genes Immun., 3(1):38–42.

25. **Karhukorpi J, Laitinen T, Karttunen R, Tiilikainen AS. (2001):** The functionally important IL-10 promoter polymorphism (-1082G3A) is not a major genetic regulator in recurrent spontaneous abortions. Mol. Hum. Reprod., 7(1):201–3.
26. **Babbage SJ, Arkwright PD, Vince GS, Perrey C, Pravica V, Quenby S, et al. (2001):** Cytokine promoter gene polymorphisms and idiopathic recurrent pregnancy loss. J. Reprod. Immunol.,51(1):21–7.
27. **Fernandez-Real JM, Broch M, Vendrell J, Gutierrez C, Casamitjana R, Pugeat M, et al. (2000):** Interleukin-6 gene polymorphism and lipid abnormalities in healthy subjects. J. Clin. Endocrinol. Metab., 85(3):1334–9.
28. **Fishman D, Faulds G, Jeffery R, Mohamed-Ali V, Yudkin JS, Humphries S, et al. (1998):** The effect of novel polymorphisms in the interleukin-6 (IL-6) gene on IL-6 transcription and plasma IL-6 levels, and an association with systemic-onset juvenile chronic arthritis. J. Clin. Invest., 102(7):1369–76.
29. **Ota N, Nakajima T, Nakazawa I, Suzuki T, Hosoi T, Orimo H, et al. (2001):** A nucleotide variant in the promoter region of the interleukin-6 gene associated with decreased bone mineral density. J. Hum. Genet., 46(5):267–72.
30. **Hirvonen A, Taylor JA, Wilcox A, Berkowitz G, Schachter B, Chaparro C, et al. (1996):** Xenobiotic metabolism genes and the risk of recurrent spontaneous abortion. Epidemiology 7(2):206–8.
31. **Zusterzeel PL, Nelen WL, Roelofs HM, Peters WH, Blom HJ, Steegers EA. (2000):** Polymorphisms in biotransformation enzymes and the risk for recurrent early pregnancy loss. Mol. Hum. Reprod., 6(5):474–8.
32. **Mendola P, Moysich KB, Freudenheim J, Shields PG, Schisterman EF, Graham S, et al. (1998):** Risk of recurrent spontaneous abortion, cigarette smoking, and genetic polymorphisms in NAT2 and GSTM1. Epidemiology 9(6):666–8.
33. **Sata F, Yamada H, Kondo T, Gong Y, Tozaki S, Kobashi G, et al. (2003):** Glutathione S-transferase M1 and T1 polymorphisms and the risk of recurrent pregnancy loss. Mol. Hum. Reprod., 9(11):165–9.
34. **Reid JG, Simpson NA, Walker RG, Economidou O, Shillito J, Gooi HC, et al. (2001):** The carriage of pro-inflammatory cytokine gene polymorphisms in recurrent pregnancy loss. Am J. Reprod. Immunol., 45(1):35–40.
35. **Baxter N, Sumiya M, Cheng S, Erlich H, Regan L, Simons A, et al. (2001):**Recurrent miscarriage and variant alleles of mannose binding lectin, tumor necrosis factor and lymphotoxin alpha genes. Clin. Exp. Immunol., 126(1):529–34.
36. **Unfried, G., Tempfer, C., Schneeberger, C., Widmar, B., Nagele, F. and Huber, J.C.**

**(2001):** Interleukin 1 receptor antagonist polymorphism in women with idiopathic recurrent miscarriage. Fertil. Steril., 75(4): 683–687.

37. **von Wolff, M., Thaler, C.J., Strowitzki, T., Broome, J., Stolz, W. and Tabibzadeh, S. (2000)** : Regulated expression of cytokines in human endometrium throughout the menstrual cycle: dysregulation in habitual abortion. Mol. Hum. Reprod., 6(6)627–634
38. **Makhseed, M., Raghupathy, R., Azizieh, F., Farhat, R., Hassan, N. and Bandar, A. (2000):** Circulating cytokines and CD30 in normal human pregnancy and recurrent spontaneous abortions. Hum. Reprod., 15(9): 2011–2017.
39. **Saijo Y, Sata F, Yamada H, Kondo T, Kato EH, Kishi R.(2004):** Single nucleotide polymorphisms in the promoter region of the interleukin-6 gene and the risk of recurrent pregnancy loss in Japanese women. Fertil Steril., 81(2):374-8.
40. **Austgulen, R., Lien, E., Liabakk, N.B., Jacobsen, G. and Arntzen, K.J. (1994):** Increased levels of cytokines and cytokine activity modifiers in normal pregnancy. Eur. J. Obstet. Gynecol. Reprod. Biol., 57(3): 149–155.

## الملخص العربى

***آية الله امير ناصف[1] ـ دينا محمد رشيد بعجت[1] ـ فؤاد ابو هميله[2]***

قسمي الباثولوجيا الأكلينيكيه و الكيمائيه[1] ـ والتوليد وأمراض النساء[2] ـ كلية الطب ـ جامعة القاهره

وصفت السيتوكينات بأنها تلعب دورا رئيسيا في التسبب في فقدان الحمل المتكرر مجهول السبب. ولذا تهدف هذه الدراسة استقصاء مدى علاقة التعدد الشكلي لجين انترلوكين ٦ وفقدان الحمل المتكرر مجهول السبب.

تم إجراء هذه الدراسة في قسمي الباثولوجيا الأكنينيكيه و الكيمائيه ، والتوليد وأمراض النساء بكلية الطب جامعة القاهره ، وقد شملت الدراسة ١٠٠ مريضه بفقدان الحمل المتكرر مجهول السبب ومجموعة ضابطة شملت ٦٠ أصحاء لا يعانون من أمراض ولا يتعاطون أدوية تتعارض مع الدراسة وقد تم اخذ عينة دم من كل من شاركت في البحث ، تم استخلاص الحمض الدي اوكسي ربيوزي منها ، واستخدم جهاز التفاعل التسلسلي عديد البلمرة للكشف عن التعدد الشكلي في موقف ـ٦٣٤ في منطقة المروج من انترلوكن-٦. وكانت ترددات أليل C (البري النوع) بين النساء من عانوا فقدان الحمل المتكرر مجهول السبب ، والمجموعة الضابطة ٨٢.٥ ، ٧٨.٣ ٪ على التوالي ، و ١٧.٥ و ٢١.٦ ٪ على التوالي لمجموعة الأليل G(المسخ). ولم يوجد أي ارتباط بين G أليل وحدوث فقدان الحمل المتكرر مجهول السبب (نسبة الأرجحية ٤١.٣٠٤؛ فاصل الثقة ٩٥ ٪ = ٧٦ و٠ ـ٢،٢٩٩، P= NS).

**الاستنتاج :** هذا هو التقرير الأول على تعدد الشكل الجيني انترلوكين ٦ في فقدان الحمل المتكرر مجهول السبب في مصر. وقد أظهرعدم ترافق مع فقدان الحمل المتكرر مجهول السبب في مجموعة السيدات المدروسه من السكان في مصر.