# Determination (IL-36γ) Levels And Study Of Its Relation With Other Cytokines In Iraqi Endometriotic Women

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## Abstract

Endometriosis, an autoimmune disease is among one of the most challenging of the 21 st century that affects women in reproductive age. The aim of the present study is to highlight the role of IL-36γ, and its relationship with other cytokines (Ang-2 and TNF-α) in the pathogenesis of endometriosis . Seventy five (75) consecutive women patient of reproductive age (25-40) years were enrolled in this study , Patients were divided into three groups , group 1 (G1) included (25) newly diagnosed endometriotic patients , that were not given any treatment related to Gynecology or anti-inflammatory medications . Second group : group 2 (G2) consists of (25) endometriotic patient who were treated with zoladex for 3 to 5 months , they received zoladex injection every 28 day in the first day after diagnosis. The third group: Group 3 (G3) involved (25) patients with recurrent endometriosis , they were post treatment of zoladex and diagnosis revealed recurrence of endometriosis. Patients groups were compared with two control groups , with matched age with patients' groups. The first control group (C) included (25) healthy women , and the second control group or pathological control group (PC) involved (25) women suffering from infertility caused by gynecological disorder unrelated to endometriosis.IL-36γ , Ang-2 and TNF-α were estimated in sera of studied groups. The results from this study revealed that IL-36γ levels were highly significant increase ($p<0.001$) and significant increase ($p<0.05$) in G1 comparing with groups C and PC respectively. While high significant decrease($p<0.001$) was found in G2 comparing with G1. Also , there are no significant differences ($p\geq0.05$) shown in G2 comparing with C group and in G3 comparing with G1.On the otherhand , Ang-2 levels were highly significant increased ($p<0.001$) and significant increase ($p<0.05$) in G1 comparing with groups C and PC respectively.

While significant decrease ($p<0.05$) was found in G2 comparing with G1. Also , there are no significant differences ($p\geq0.05$) in Ang-2 levels shown in G2 comparing with C group and in G3 comparing with G1 Our results also implied that TNF-α levels were highly significant increased ($p<0.001$) in G1 comparing with C group. While no significant differences ($p\geq0.05$) was found in G1 comparing with PC group and in G3 comparing with G1. Also there are significant differences ($p<0.05$) shown in G2 comparing with G1 and C group.

This paper is part of PhD. thesis of the third author.

Our findings for endometriotic patient groups. A high significant difference was found between Ang-2 and TNF-α levels with IL-36γ for G1 , G2 and G3. The conclusion of this study reveals that IL-36γ could be considered a novel biochemical marker in endometriotic patients. Conclusion could be drawn from the results that endometriosis may be influenced on the cytokines secretion such as IL-36γ beside Ang-2 and TNF-α in G1 and G3 , suggesting that inflammatory / immunological factors associating with angiogenesis responses play crucial roles in the pathogenesis of endometriosis. Also, the results showed the role of zoladex in alteration immune responses as shown in G2.

**keywords : IL-36γ , Ang-2 , TNF-α , endometriosis.**

# Introduction

Endometriosis is a common benign chronic – inflammatory gynecologic disorder [1,2] , defined as the presence and proliferation of functional endometrial glands (endometrial - like tissue ) outside of the normal location (uterine cavity) [1,3-5] .

Although most women experience retrograde menstruation, which may play a role in the seedling and establishment of implants, few develop endometriosis. Hence , menstrual tissue and endometrium that is refluxed into the peritoneal cavity is usually cleared by immune cells such as macrophages, natural killer (NK) cells, and lymphocytes. For this reason, immune system dysfunction is one likely mechanism for the genesis of endometriosis in the presence of retrograde menstruation[1].

Cytokines such as interleukines , growth factors and tumor necrosis factors are low molecular weight soluble glycoproteins that are secreted mainly, but not exclusively, by immunological cells such as T-cells, macrophages, and neutrophils [1,6]. Numerous cytokines, especially interleukins, have been implicated in the pathogenesis of endometriosis[1].

Interleukin-36 (IL-36) sub-family of cytokines comprises a set of provital mediators of inflammation [7]. IL-36 refers to three cytokines that are members of the IL-1 family which expressed predominantly by epithelial tissues and promote inflammatory responses. IL-36γ, a pro-inflammatory , belongs to the IL-36 subfamily [ 8,9 ] .

Angiopoietins (Angs) are protein growth factors that promote angiogenesis [ 10-12]. It has been generally accepted that the establishment of new biomarkers as (Ang-2) played a key part in the progression of endometriosis , however this role still needs further confirmation to suggest a relation to endometriosis already proven for many pivotal factors [13] . Ang-2 participates in systemic inflammation[10-12]. It can directly activate endothelial cells and neutrophils to promote pro-inflammatory responses[10].

Tumor Necrosis Factor alpha ( TNF-α) ( a secreted pro-inflammatory cytokine ) is a non-glycosylated protein , plays a crucial role in inflammation, angiogenesis, cell proliferation , apoptosis and cell death [6,14,15]. TNF-α is widely expressed in several tissues associated with reproduction, including endometrium , where participates in several physiological inflammatory events, such as embryo implantation and menstruation., TNF produced by endometrial cells probably contributes to the adhesion process[14,15].

# Material and method

## Subjects:

Seventy five (75) consecutive women patient of reproductive age (25-40) years were enrolled in this study , who attended departments of Gynecology and Obstetrics related to the following hospitals : Baghdad Teaching Hospital / Medical City , Al-Yarmook Teaching Hospital and Kamal Al-Samarray hospital from April to October 2013. Patients were divided into three groups , Group 1 (G1) included (25) endometriotic patients that are newly diagnosed. The patients don't administrate any treatment or anti-inflammatory medications. Second group : group 2 (G2) consists of (25) endometriotic patients who were treated with zoladex for 3 to 5 months , they received zoladex injection every 28 day after the date of diagnosis. The third group: group 3 (G3) involved (25) patients with reccurent endometriosis , they were post treatment of zoladex and diagnosis revealed recurrence of endometriosis. Patients groups were compared with two control groups , with matched age with Patients' groups . The first control group (C) included (25) healthy women , and the second control group or pathological control group (PC) involved (25) women suffering from infertility caused by gynecological disorder unrelated to endometriosis.

## Blood sampling and parameters determination:

Five milliliters ( 5 mL) of venous blood were collected from the all subjects enrolled in this study , placed into plain tubes until coagulation was performed . Serum was separated from blood cells by centrifugation at 4000 r.p.m . The sera was obtained and divided into

small portions and kept frozen until analysis . The quantitative sandwich enzyme immunoassay (ELISA) technique was employed for the determination of (IL-36γ) and (Ang-2) . Also a sandwich assay DEMEDITEC TNF-α human ELISA was used for the determination of TNF-α . Chemicals were supplied as kits from Cusabio, China. The procedures were done according to the manufactured instruction as kit supplied

### Statistical analysis:

The results expressed as mean ± SEM. Students t-test was applied to compare the significance of the difference between all the studied groups. P-value ($p<0.05$) , ($p<0.001$) considered statistically significant and highly significant respectively. The correlation coefficient (r) test was used for describing the association between the different studied parameters.

## Results

Table (1) shows the sera levels of some biochemical parameters in the studied groups. The results from this study revealed that IL-36γ levels were highly significant increased ($p<0.001$) and significant increase ($p<0.05$) in G1 comparing with groups C and PC respectively. While high significant decrease($p<0.001$) was found in G2 comparing with G1. Also , there are no significant differences ($p\geq0.05$) noticed in G2 comparing with C group and in G3 comparing with G1.On the otherhand , Ang-2 levels were highly significant increased ($p<0.001$) and significant increase ($p<0.05$) in G1 comparing with groups C and PC respectively. While significant decrease ($p<0.05$) was found in G2 comparing with G1. Also , there are no significant differences ($p\geq0.05$) observed in G2 comparing with C group and in G3 comparing with G1 Our data also implied that TNF-α levels were highly significant increased ($p<0.001$) in G1 comparing with C group. While no significant differences ($p\geq0.05$) were found in PC group comparing with G1 and in G3 comparing with G1. Also there are significant differences ($p<0.05$) shown between G2 comparing with G1 and C group.

The correlation relation between all parameters is investigated. The correlation between IL36γ and Ang-2 showed highly significant positive correlation in G1 and G3 ($p<0.001$ , $r=0.054$ , $r=0.245$) , whereas a high significant negative correlation ($p<0.001$ , $r= -0.542$) was observed in G2, as shown in fig(1). On the otherhand , a highly significant positive correlation was found between IL-36γ and TNF-α in G1 and G3 ($p<0.001$ , $r=0.089$ , $r= 0.18$) , while a significant negative correlation was found in G2 ($p<0.001$ , $r= - 0.329$) as shown in fig(2).

## Discussion

IL-36γ level increased in (G1) compared with control group (C) and pathological control (PC) . IL-36 plays significant roles in immune responses [16]. Endometriosis is an autoimmune disease[ 1] and the role of the immunological system in endometriosis with several abnormalities indicated [16] . Previous study reported that dendritic cells (DCs), the initiators of immune responses, respond strongly to IL-36 which plays significant roles in immune responses[17]. Our results also agreed with other study that indicates IL36γ as a novel direct target of T-cells action in myeloid cells and contributes to T-cells functions in immunopathology and influence the differentiation of native T-cells in the human system. [17,18]

Other studies revealed that the biology properties of IL-1 family ligands ( including IL-36γ) are typically pro-inflammatory. Since endometriosis involve inflammatory disorders , as [1,2]. Inflammatory stimuli increase IL-36γ gene expression in primary human keratinocytes[18].

Infertile women generally suffer from gynecological disorders implicate immunological/inflammatory responses. [19]. Previous studies revealed that the induction of proinflammatory cytokines may be unrecognized cause of idiopathic infertility. Several macrophages-derived cytokines are present in the follicular fluids of infertile women [20,21].

Zoladex ( gonadotropin releasing hormones) (GnRH) has been proved for relieving pain in endometriotic patients [22] , this concept has been explained as its role in regression of the inflammatory nature responsible for adhesions , the main cause of pain . On the other hand , a strong inflammatory reaction in endometriosis reported to be associated with the detrimental effect on fertility [23] . IL-36γ is decreased in G2 ( after treatment with zoladex) compared with G1 ( newly diagnosed patients , without any treatment). GnRH are able to markedly reduce the inflammatory reaction [23]. Accumulating evidence suggests that GnRH, apart from regulating the hypothalamo- pituitary-gonadal axis, also exerts potent effects on the immune system [24].

Our findings of decreased inflammatory reaction among GnRH users are in agreement with other results which indicate that GnRH can control the development and functioning of the immune system via the hypothalamus-pituitary axis and is involved in an autocrine or paracrine regulation of the immune response during postnatal life [25]. There are several possible mechanisms of GnRH action on the immune system: it can interact with specific receptors on thymic epithelial cells that synthesize peptides participating in T-cell maturation, as well as directly interact with such receptors on lymphocytes. In addition , these biological effects of GnRH at the tissue level were not influenced by different treatment periods [23].

Taken together , these findings indicate that IL-36γ exerts marked stimulatory effects on DC and may therefore play a critical role in early immune and inflammatory responses related to tissue damage and pathogens of endometriosis.

In the present study the non-significant differences between (G1) and (G3) agreed with other studies indicate that endometriosis is a recurrent disease [26,27] because immunological and inflammatory responses have appeared again.

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The proximity of peritoneal fluid to endometriotic lesions shows the milieu in which the immune mediators are associated with the local inflammation of endometriosis [28].

(Ang-2) levels elevated in Group 1 (G1) compared with control group (C) and pathological control Group (PC). Previous suggested that angiopoietins may be considered acute pro-inflammatory mediators , which may contribute to initial steps of pathogenic angiogenesis [10].

Current knowledge has reported that angiopoietin-2 (Ang-2) participates in the inflammatory process [11] .

During inflammatory processes, newly formed vessels supply the inflamed tissues with nutrients and oxygen allowing the transport of inflammatory cells. Among these, neutrophils are the first cells recruited in the angiogenic bed and provide cytokines together contribute to regulate angiogenesis [10] .

On the otherhand , it has reported that angiogenesis enables endometrial cells to proliferate. [29]

Macrophage-derived cytokines in the follicular fluids of women with infertility due to immunological causes [21] .

In contrast , Ang-2 level decreases in sera of Group 2 (G2) patients ( after treatment with zoladex) compared to (G1) ( newly diagnosed patients , without any treatment) , Our data are in agreement with previous results , which support zoladex role in regression of the inflammatory nature responsible for adhesions. Furthermore , GnRH ( involving zoladex) are able to markedly reduce the inflammatory reaction. Further experiments relating to the

expression of GnRH receptors in vascular endothelial cells and the effect of GnRH on these cells may clarify the anti-angiogenic response of GnRH [22,23].

The non- significant difference between (G1) and (G3) , indicates the recurrence of endometriosis as revealed by previous studies , suggesting that inflammatory mediators have been shown again[26,27].

The elevated levels of TNF-α levels in sera of Group 1 (G1) compared to control group (C) reflects the importance of TNF-α in pathological inflammation related to autoimmune diseases.

TNF –α has diverse and critical roles in the pathogenic progression of a number of chronic inflammatory disorders. TNF is a key signalling protein in the immune system. As a regulatory cytokine, TNF orchestrates communication between immune cells and controls many of their functions[6,30].

Endometriosis is associated with chronic inflammatory process with defects in immune system. Particularly , the development of endometriosis seems to be associated with increased number of macrophages that secrets inflammatory products including TNF-α [26]. The reason for non-significant variation between Group1 (G1) and pathological control group (PC) may be due to deregulated or excessive production of TNF-α has been implicated in the pathogenesis of not only endometriosis but also several debilitating inflammatory conditions [31].

Other studies [31,32] supported the role of TNF-α or its receptors were reported to affect certain phases of the immune process, including innate immune activation or DC maturation/recruitment, T cell priming , T cell function , or pathogen clearance.

In fact , TNF belongs to a super family of ligand/receptor proteins called the TNF/TNF receptor (TNF/TNFR) superfamily proteins. TNFRs are either constitutively expressed (TNFR) or inducible (TNFR2). TNF-α/TNFR2 signals on T cells were critically required for effective priming, proliferation, and recruitment of tumor-specific T cells [31].

TNF-α facilitates the proliferation of immune cell clones, especially of T cells, to counter a pathological infection or invasion. They also allow the differentiation and recruitment of naive immune cells to continue waging the battle, as well as the destruction of superfluous immune cell clones to limit internal inflammation and tissue damage once the infection or invasion has resolved [33] .

In contrast , TNF-α levels are depressed in sera of G2 patients compared to G1 patients , this depression reflects the zoladex action on immunity, which was indicated in a previous study that zoladex ( as GnRH) is involved in the modulation of T helper cytokine balance. GnRH administration is associated with an increase in T cell proliferation and natural killer cell activity , and can reverse thymic involution in aging mice and increase the helper T cells during immunodeficiency [24].

At last , the reason for non-significant difference in TNF-α between G1 and G3 is the recurrence of endometriosis, thus immunodeficient features have appeared again [26,27].

Conclusion could be drawn from the results that endometriosis may be influence on the cytokines secretion such as IL-36γ beside Ang-2 and TNF-α in G1 and G3 , suggesting that inflammatory / immunological factors associating with angiogenesis responses play crucial roles in the pathogenesis of endometriosis. Also, the results showed the role of zoladex in alteration immune responses as shown in G2.

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**Table No. (1): Levels of IL-36γ , Angiopoitein -2 , Tumor necrosis factor-α in sera of the studied groups.**

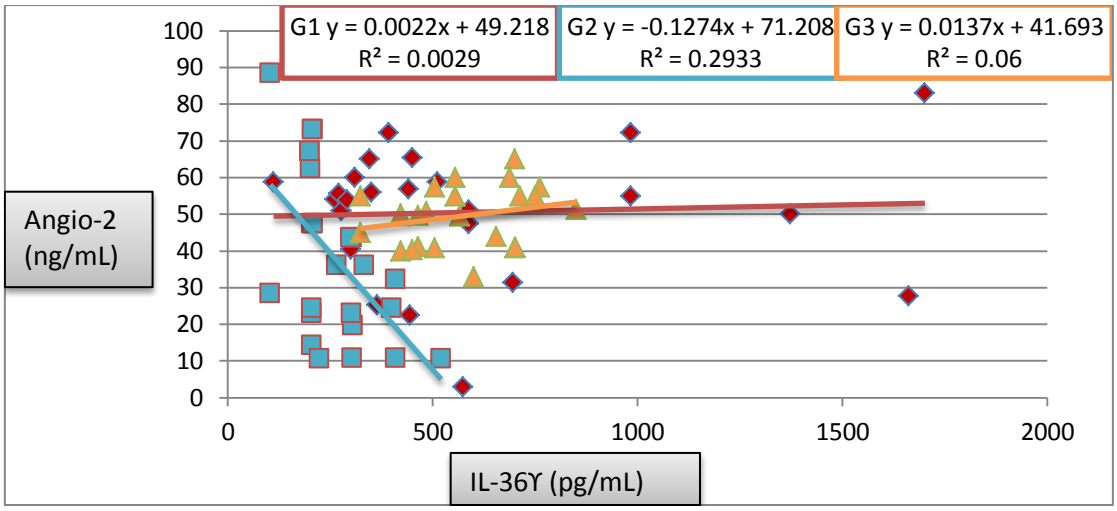
| Parameter | Mean ±SEM C | Mean ±SEM BC | Mean ±SEM G1 | Mean ±SEM G2 | Mean ±SEM G3 | C vs G1 T.Test | BC vsG1 T.Test | G1 vs G2 T.Test | C vs G2 T.Test | G1vs G3 T.Test |
|---|---|---|---|---|---|---|---|---|---|---|
| IL-36γ | 246.1 ±22.2 ( Pg / mL) | 332.4 ±17.0 ( Pg / mL) | 587.8 ±89.2 ( Pg / mL) | 258.4 ±19.2 ( Pg / mL) | 547.9 ±28.9 ( Pg / mL) | H.S | S | H.S | N.S | N.S |
| Angio-2 | 28.6 ±3.4 ( ng / mL) | 38.8 ±3.8 ( ng / mL) | 49.4 ±3.6 ( ng / mL) | 36.9 ±4.5 ( ng / mL) | 47.6 ±1.7 ( ng / mL) | H.S | S | S | N.S | N.S |
| TNF-α | 5.5 ±0.1 ( Pg / mL) | 7.6 ±0.3 ( Pg / mL) | 7.5 ±0.5 ( Pg / mL) | 6.3 ±0.2 ( Pg / mL) | 8.0 ±0.9 ( Pg / mL) | H.S | N.S | S | S | N.S |

S:- significant variation , ( $p<0.05$).
H.S:- high significant, ( $p<0.001$).
N.S:- non significant , ($p\geq0.05$).

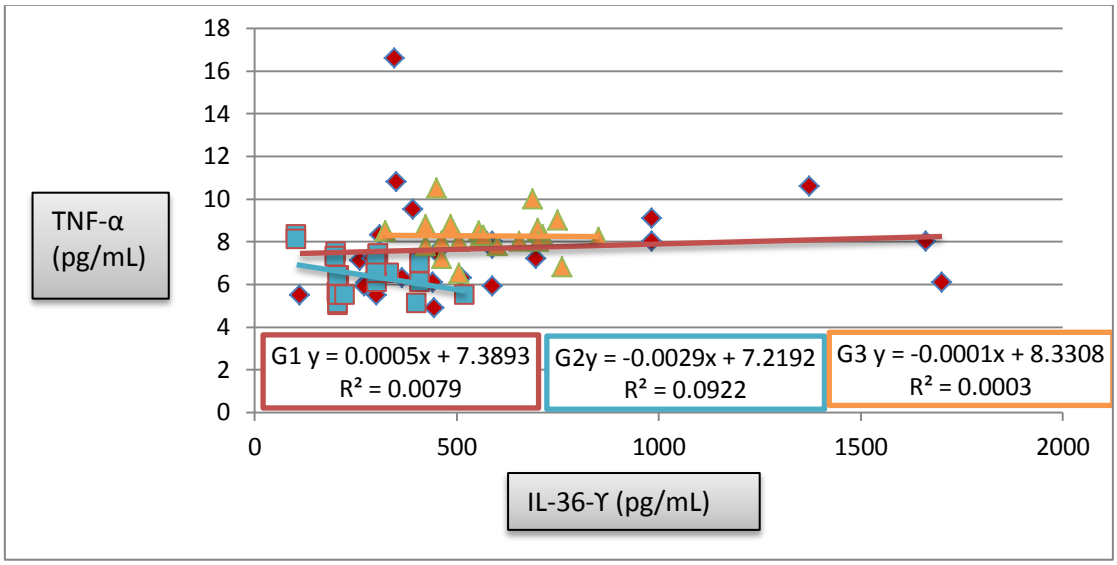
**TableNo, (2) : Student t.test (p) and Correlation coefficient (r) for IL-36γ verse( Ang-2 and TNF-α) for patients groups.**

| Correlated Parameters | G1 | G2 | G3 |
|---|---|---|---|
| IL-36γ vs Angio-2 | P<0.001 | P<0.001 | P<0.001 |
| | r=0.054 | r= -0.542 | r= 0.245 |
| IL-36γ vs TNF-α | P<0.001 | P<0.001 | P<0.001 |
| | r=0.089 | r= -0.329 | r= 0.018 |

P values< 0.001 considered high significant (HS).




**Figare No. (1): Correlation between Interleukin-36 γ and Angiopoitein-2.**




**Figare No. (2) : Correlation between Interleukin-36 γ and TNF-α.**

# تقدير مستويات الإنترلوكين 36 كاما ودراسة علاقته مع سايتوكينات أخرى مع الأنجيوبويتين لمريضات عراقيات بهجرة بطانة الرحم

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## الخلاصة

يعد مرض هجرة بطانة الرحم من أحد التحديات الخطيرة في القرن الحادي والعشرين التي تواجه النساء في سن الإنجاب. إن هدف هذه الدراسة هو تسليط الضوء على دور الIL-36γ وعلاقته بالسايتوكينات الأخرى ( Ang-2 و TNF-α) في نشوء هذا المرض. أخذت (75) مريضة ضمن سن الإنجاب( 20-45) سنة وقسم المرضى على ثلاث مجاميع ، إذ تضمنت المجموعة الأولى G1 (25) مريضة تم تشخيصهن حديثا ، ولم يعطن أي علاج نسائي أو مضادا للإلتهاب ، في حين تألفت المجموعة الثانية G2 من (25) مريضة تم تشخيصهن منذ (3-5) أشهر ويتلقين العلاج (حقن الزولادكس) كل 28 يوما إعتبارا من اليوم الأول لتشخيص المرض. أما المجموعة الثالثة G3 فقد تضمنت (25) مريضة أشار تشخيصهن تكرار نشوء المرض بعد إكتمال الجرع العلاجية اللازمة. تمت مقارنة المجاميع المرضية بمجموعتين ضابطة بالمدى العمري نفسه . تضمنت المجموعة الضابطة الأولى C (25) إمرأة لاتعاني من أي مرض مزمن ، في حين تضمنت المجموعة الضابطة الثانية PC (25) إمرأة تعاني من العقم بسبب إضطراب نسائي غير مرتبط بهجرة بطانة الرحم. تضمن البحث تقدير مستويات ال الIL-36γ وال Ang-2 والTNF-α في مصل دم المجاميع المرضية والضابطة. أثبتت نتائج هذه الدراسة أن مستويات الIL-36γ قد ارتفعت بشكل معنوي عال($p<0.001$) و معنوي ($p<0.05$) في G1 مقارنة مع C و PC على التوالي ، بينما وجد انخفاض معنوي عال ($p<0.001$) في G2 مقارنة مع G1 . وجد إختلاف غير معنوي ($p\geq0.05$) في G2 أيضا مقارنة مع C وكذلك في G3 مقارنة مع G1 ، ومن ناحية أخرى وجد أن مستويات الAng-2 قد ارتفعت بشكل معنوي عال ($p<0.001$) و معنوي ($p<0.05$) في G1 مقارنة مع C و PC على التوالي ، بينما وجد انخفاض معنوي عال ($p<0.001$) في G2 مقارنة مع G1 . لوحظ اختلاف غير معنوي ($p\geq0.05$) لل Ang-2 في G2 أيضا مقارنة مع C وكذلك في G3 مقارنة مع G1 . إن نتائجنا أوحت أن مستويات ال TNF-α قد ارتفعت بشكل معنوي عالي ($p<0.001$) في G1 مقارنة مع C ، بينما وجد اختلاف غير معنوي ($p\geq0.05$) في G1 مقارنة PC وكذلك في G3 مقارنة مع G1 كما لوحظ إختلاف معنوي ($p<0.05$) لG2 بالمقارنة مع G1 و C.

كما أشارت نتائجنا إلى وجود تناسب مابين مستويات الAng-2 والTNF-α من جهة ومستوى ال IL-36γ من جهة أخرى للمجاميع المرضية ، إذ لوحظ فرق معنوي عال في مستويات الAng-2 وال TNF-α مقارنة مع مستوى الIL-36γ لمجاميع G1 و G2 و G3 . إن النتائج تؤكد أن مرض هجرة بطانة الرحم قد يؤثر في إفراز السايتوكينات ، على سبيل المثال IL-36γ و Ang-2 و TNF-α ، مما يشير إلى أن العوامل الإلتهابية المناعية المترافقة مع الإستجابات الخاصة بالأوعية الدموية تؤدي دورا حاسما في نشوء مرض هجرة بطانة الرحم ، فضلا عن دور الزولادكس في تحسين الإستجابة المناعية كما هو الحال في G2.

**الكلمات المفتاحية : اللإنترلوكين 36 كاما ، الانجيوبويتين ، عامل النخر الورمي ، هجرة بطانة الرحم**