Iraqi Journal of Science, 2026, Vol. 67, No. 8, pp: 4150-4160
DOI: 10.24996/ijs.2026.67.8.1

ISSN: 0067-2904

Estimation of Anti-Mullerian Hormone and Other Biochemical Parameters Levels in Iraqi Women with Psoriasis Patients Treated with Etanercept as A Biological Drug

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Received: 21/1/2025 Accepted: 10/ 11/2025 Published: 30/ 8/2026

Abstract

Psoriasis is a complex, chronic disease frequently accompanied by significant comorbidities. It adversely impacts individual physical health, social functioning, and sexual well-being. Particular exclusive concerns regarding the impact of this disease on women. The study aims to evaluate the immune state and ovarian backup in women with psoriasis disease within different age groups by evaluating the tumor necrosis factor and Anti-mullerian hormone levels, respectively. Forty-eight female patients with severe to moderate psoriasis and a control group of 50 healthy females were studied. Both groups aged between 20 and 67 years were evaluated from December 2020 to October 2021. The patients were categorized into two sub-groups (24 patients for each group), the first before treatment group and the second after treatment group (with etanercept as a biological drug). The patients that previously shown inadequate responses to other medical treatments were excluded from this study. The Anti-Mullerian Hormone, Interleukins 2&7(IL-2, IL-17) and TNF-α were evaluated in this study. The study included that the age of both groups was divided into three ranges (20-35, 36-51 and 52-67years). In patients, most psoriasis cases are 20-35 years compared to the other age ranges (36-51 and 52-67 years). TNF-α levels were increased (P<0.01) in psoriasis before care and therapy, measuring 189.5±26.0 ng/mL compared to 93.5±2.4 ng/mL in control. A notable increase ($P<0.05$) in TNF-α concentration in psoriatic patients after biological treatment in comparison to its level before treatment was noted, with a mean of 189.50±26.00 ng/mL and 223.60±41.10 ng/mL, respectively. Similarly, serum IL-2 concentration was notably increased ($P<0.05$) in psoriatic subjects before treatment with a mean of 97.50±6.60 ng/mL compared to 77.90±3.10 ng/mL in the control group, as well as differences were noted in serum IL-2 levels among psoriatic patients before and after treatment, with a mean of 97.50±6.60 ng/mL and 92.90±5.00 ng/mL, respectively. The data revealed a significant increase (P<0.05) of IL-17 cytokine level in psoriatic patients before treatment (93.80 ± 3.40 ng/ml) compared to control group (65.80 ± 2.70 ng/ml), and its level was decreased significantly (P<0.05) after treatment with a mean of 72.70 ± 4.40 ng/mL in comparison with psoriatic patients before treatment. Finally, the serum AMH level reduced statistically (P<0.05) in psoriatic patients previous to treatment assessment, where the level mean was 0.42±0.17 ng/ml, while in healthy control group was 2.5±0.16 ng/mL, and it is found a statistical increase of serum AMH concentration (P<0.05) in psoriatic patients after treatment with a mean of 2.8±0.23 ng/mL in comparison to its mean before treatment. Autoimmune syndromes may disturb

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ovarian backup regardless of immunosuppressive treatment. So, the follow-ups concerning reproductive role might be essential in women with psoriasis, especially those in reproductive periods.
Key words: anti-mullerian hormone, biological drug, psoriasis.

تقدير مستوى مضاد هرمون مولر وبعض العوامل الكيموحيوية لدى النساء العراقيات المصابات بالصدفية والمعالجات بالإيتانرسبت كعلاج بايولوجي

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الخلاصة

الصدفية مرض معقد ومزمن مصحوبا في كثير من الأحيان بأمراض مصاحبة كثيرة. يؤثر سلبا على الصحة البدنية للفرد والأداء الاجتماعي والرفاهية الجنسية .وهناك مخاوف خاصة فيما يتعلق بتأثير هذا المرض على النساء. تهدف الدراسة الى تقييم الحالة المناعية ودعم المبيض لدى النساء المصابات بمرض الصدفية ضمن فئات عمرية مختلفة من خلال تقييم مستوى عامل نخر الورم (IFN-α) ومضاد هرمون مولر على التوالي. تمت دراسة ثمانية وأربعون مريضة مصابة بالصدفية الشديدة إلى المتوسطة ومجموعة ضابطة من 50 أنثى سليمة. تراوحت أعمار المجموعتين بين 20 و67 سنة وتم تقييمهما من كانون الاول 2020 إلى تشرين الاول 2021. تم تصنيف المرضى إلى مجموعتين (تضم كل منهما 24 شخصاً)، المجموعة الأولى قبل العلاج والثانية هي مجموعة ما بعد العلاج (بالإيتانرسبت كعلاج بايولوجي). في هذه الدراسة تم استبعاد المرضى الذين لم يظهروا سابقا استجابات كافية للعلاجات الطبية الأخرى. تم قياس مستويات مضاد هرمون مولر(AMH) , انتر لوكين2&7 (IL-17 & IL-2) وTNF-α في هذه الدراسة. تضمنت الدراسة تقسيم أعمار المجموعتين إلى ثلاث مديات (20-35, 36-51 ,52 -67سنة)، وكانت غالبية المصابين بالصدفية ضمن المدى من 20-35 سنة مقارنة بالمديات الأخرى (36-51 و52-67) سنة. وكانت مستويات TNF-α مرتفعة (*P>0.01*) في مرضى الصدفية قبل الرعاية والعلاج حيث بلغت 189.5 ± 26.0 نانو غرام/مل مقارنة بـ 93.5 ± 2.4 نانو غرام/مل في المجموعة الضابطة. لوحظ ارتفاع ملحوظ (*P>0.05*) في تركيز TNF-α لدى مرضى الصدفية بعد العلاج البيولوجي (223.60 ± 41.10 نانو غرام/مل) مقارنة بمستواه لدى المرضى قبل العلاج البيولوجي (189.50 ± 26.00 نانو غرام/مل). كما ارتفع مستوى IL-2 بشكل ملحوظ (*P*>0.05) في مصل مرضى الصدفية قبل العلاج وبمعدل 97.50 ± 6.60 نانو غرام / مل مقارنة بـ بمعدله لدى المجموعة الضابطة(77.90 ± 3.10 نانو غرام / مل)، كما لوحظ اختلاف بمستويات IL-2 في مصل مرضى الصدفية قبل وبعد العلاج وبمعدل 97.50 ± 6.60 نانو غرام / مل و92.90 ± 5.00 نانو غرام / مل، على التوالي. أظهرت البيانات وجود ارتفاع معنوي (*P>0.05*) في مستوى سايتو كين IL-17 في مرضى الصدفية قبل العلاج (93.80 ± 3.40 نانو غرام/مل) مقارنة بمجموعة التحكم (65.80 ± 2.70 نانو غرام/مل)، وانخفض مستواه بشكل ملحوظ (*P*>0.05) بعد العلاج وبمعدل 72,7 ± 4.4 نانو غرام/مل بالمقارنة مع مستواه لدى مرضى الصدفية قبل العلاج. وأخيراً انخفض مستوى مضاد هرمون مولر في المصل إحصائياً (*P*>0.05) في مرضى الصدفية قبل تقييم العلاج، وبلغ معدل تركيزه 0.42 ± 0.17 نانو غرام/مل بينما بلغ معدل تركيزه في المجموعة الضابطة السليمة 2.5 ± 0.16 نانو غرام/مل، كما وجد ارتفاع إحصائي (P<0.05) في تركيز مضاد هرمون مولر لدى مرضى الصدفية بعد العلاج البايلوجي وبمعدل 2,80 ± 0.23 نانو غرام/مل مقارنة بمعدله لدى المرضى قبل العلاج. قد تؤثر اعراض المناعية الذاتية على الخصوبة وصحة المبيض على الرغم من العلاج المثبط للمناعة. وبذلك تكون المتابعة المتعلقة بالدور الإنجابي ضرورية عند النساء المصابات بالصدفية وخاصة في فترات الإنجاب.

1. Introduction

One of the long-lasting skin disorders driven by the immune system is psoriasis, marked by widespread pro-inflammatory activity, influenced by environmental and genetic factors [1, 2]. The illness typically begins between the ages of 20 and 40, affecting individuals of all genders [3]. Psoriasis can differ significantly between regions because of various external and inherited factors [4]. A comprehensive global review indicates that this frequency among adults is between 0.5% and 11.4% [5]. The condition is characterized by well-defined red plaques covered with white scales that often spread across the body. It results from an initial dysfunction of keratinocyte combined with an abnormal immune response involving type I interferon (IFN-α) and T cells [6]. The exact cause of keratinocyte damage remains unclear. Environmental, genetic, and immunological factors contribute to the condition [7]. Elevated levels of TNF-α have been observed in blood and affected skin in individuals with active skin syndrome [8]. TNF-α is a potent cytokine that promotes inflammation. Diversity impacts different cell types and is crucial the advancement. Persistent inflammation conditions like psoriasis are generated in various cellular elements, including cells have immune function, such as B cells, T cells, basophils, eosinophils, dendritic cells, neutrophils, mast cells, and non-immune units (including astrocytes, fibroblasts, glial cells, granuloma cells, and keratinocytes). Natural activity of TNF- α is activated through attaching to one or more different types of receptors: Tumor necrosis factor receptor I (TNFRI, also known as p55) and type II (TNFRII, or p75) are key components in the immune response [9,10]. The Etanercept (ETN) is one of the TNF inhibitors authorized to treat psoriasis and is marketed under the brand Enbrel. ETN is a soluble protein that consists of the ligand-binding outside the cell portion of the receptor of TNF and the Fc region of IgG1. It effectively neutralizes both soluble and transmembrane TNF [11]. The soluble tumor necrosis factor (sTNF) receptor protein exhibits a reversible binding affinity for tumor necrosis factor, thereby influencing the migration of neutrophils and trafficking of dendritic cells and T-cells. Consequently, this interaction decreases the synthesis of pro-inflammatory cytokines at both local and systemic levels, along with their related effects [12,13]. According to current evidence, women with chronic inflammatory disorders have a lower ovarian reserve. Ovarian reserve measures of a woman's remaining follicular pool in her reproductive years. The anti-mullerian hormone (AMH) is the most specific physiological marker for detecting ovarian reserve. It is a glycoprotein that has a140 - kDa linked by disulfide bonds [14]. In adult females, AMH is secreted by the follicular cells of the ovary; its primary biological function appears to be the suppression of follicular development during the initial phases [15]. Increasing evidence shows that the feminine hormonal state through gestation influences the course of psoriasis, and that psoriasis, in turn, influences pregnancy outcomes. Despite the evidence linking psoriasis to pregnancy, ovarian reserve and functioning in psoriatic individuals have yet to be investigated by measuring AMH serum concentration before and after therapy in women of various ages. This study aimed to assess the influence of ETN, administered outside its established medical indications, on female reproductive function in eumenorrheic women. [15].

2. Materials and methods

Forty-eight female individuals who recruited from the Dermatology and Venereology including the moderate to severe psoriasis clinic Department at Baghdad Teaching Hospital between December 2020 and October 2021. The patient group was divided into two sub-groups with 24 patients each; Measurements were taken at two time points: pre-treatment (baseline) and post-treatment. Fifty healthy females were considered the control group; both

groups were 20-67 years old. The medical treatment was stopped and changed to biological therapy (ETN) in the present research.

2.1 Blood sampling

Blood samples were collected at 5 milliliters from both patient and control groups. The samples were then centrifuged at 1510xg for 10 minutes to facilitate serum separation. The TNF-α, IL-2, IL-17, and AMH were measured using the human ELISA Kit from Demeditec, Germany. Data analysis was conducted utilizing the Statistical Analysis System. (SAS) software. Chi-square -$\chi 2$ test, mean ± SE, and ANOVA Table to P value <0.05 was considered statistically significant (SAS, 2004).

3. Results and Discussion

3.1 Age data

Table 1 presents the age distribution of the studied groups, categorized into three ranges: 20-35, 36-51, and 52-67 years. The majority of patients with psoriasis fall within the 20–35 years age group, compared to the other ranges (36-51 & 52-67 years).

Table 1: Percentage age of the studied groups

Group		Age range (years)			Total	Mean age (years)±SEM
		20-35	36-51	52-67		
Psoriasis patients	No.	25	14	9	48	42.8±2.0
	%	52.08%	29.17%	18.75%	100	
control	N0.	16	23	11	50	36.6±2.2
	%	32%	46%	22%	100	

The findings were consistent with those of [16,17], who proposed that although psoriasis may strike anyone at any age, more psoriatic patients are between 15 and 30 years. The incidence of psoriasis rises with advanced age [18]. One's geographic location influences the chance of developing psoriasis; disease prevalence increases as one moves further away from the equator.

Psoriasis prevalence varied from 0.5 to 11.4 percent in adults and 0 to 1.4 percent in children[15].

3.2 Tumor Necrosis Factor-α (TNF-α) concentration

Figure 1 shows that TNF-α levels were significantly higher ($P<0.01$) in the group before biological treatment, with a mean value of 189.50±26.00 ng/ml, compared to the control group, which had a mean of 93.50±2.40 ng/mL. Furthermore, there was a notable reduction ($P<0.05$) in the variation of TNF-α levels among psoriatic patients before and following treatment, with values of 189.50±26.00 ng/mL and 223.60±41.10 ng/mL, respectively. The majority of studies support these findings [19, 20], and recent research has further confirmed the crucial role of TNF-α in various physiological processes [21,22]. However, investigations by Tigalonova et al. [23] and Sabri et al. suggest that TNF-α levels do not show significant differences between psoriasis patients and healthy individuals [24].

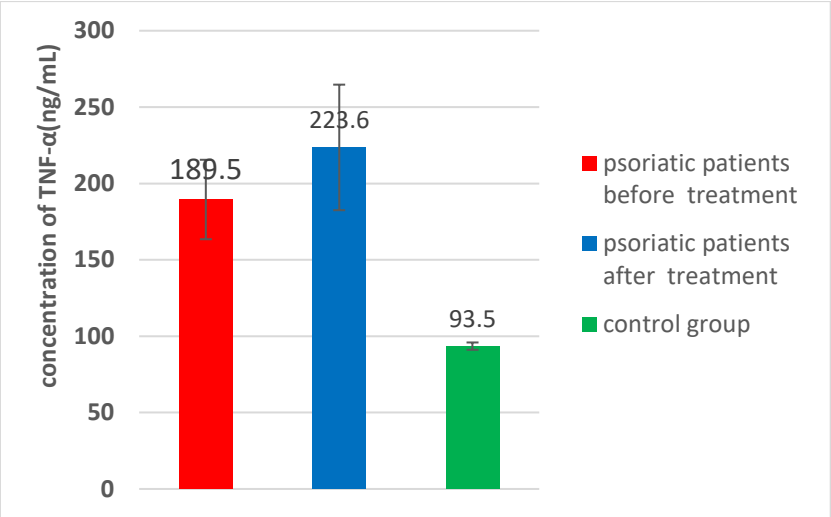

Figure 1: Average of TNF-α in a prior and later biological treatment group compared to a control.

Monocytes and macrophages are the primary contributors to the synthesis of TNF-α; however, other cells, including natural killer (NK) cells, basophils, neutrophils, eosinophils, and lymphocytes can also produce this cytokine [25] Additionally, non-immune cells such as astrocytes, glial cells, neurons, osteoblasts, melanocytes, smooth muscle cells, spermatogenic, and tumor cells, contribute to its production. In the skin, keratinocytes, Langerhans cells, various dendritic cells, activated T cells, macrophages, fibroblasts, and endothelial cells also contribute [26]. Inflammatory factors are produced in the psoriatic skin lesions, where TNF-α plays a significant role as a pro-inflammatory cytokine, promoting the inflammatory response through multiple pathways. Promoting the infiltration of inflammatory cells into dermal injuries is among these factors. By enhancing the expression of molecules that have adhesion properties on vascular endothelial cells, it also stimulates the activation of supplementary pro-inflammatory mediators [27]

Although the etiology of psoriasis remains blurred, some evidence shows that individuals suffering from active skin conditions demonstrate increased concentrations of TNF-α in their bloodstream as well as in the lesions of the affected skin. These results indicate that serum TNF-α levels can fluctuate due to various factors, such as its production, localization within tissues, degradation processes, and clearance mechanisms. The biological compartments responsible for elevated circulating TNF-α in psoriasis have not been fully characterized. A considerable quantity of free cytokines is required to reach concentrations capable of eliciting biological responses in remote skin lesions. It is possible that there are additional sources contributing to cytokine production, which could provide insights into the mechanisms underlying psoriasis and its associated comorbidities [28].
The concentration of TNF-α was remarkably high in psoriasis patients administered with ETN compared to patients before treatment. These data revealed that ETN increases the level of TNF-α [29].

The biological impact of TNF-α is initiated through its attachment to one or more different receptors: TNF-α receptor type I (TNFRI), also known as p55 or CD120a, and TNF-α receptor type II (TNFRII), also known as p75 or CD120b [9,30]. The TNFRI and TNFRII are expressed in all cell types except red blood cells. Upon binding to these receptors, both TNF-α forms promote apoptosis, cell proliferation, and cytokine production. Each receptor consists of two subunits [30,31].

Etanercept has the extracellular domain of human TNFRII molecules linked to the Fc portion (CH2 and CH3 domains) of human IgG1. It is believed that ETN can form a 1:1 complex with the TNF-α trimer. In contrast to INF and the antidrug antibody(AD) , which creates stable complexes with TNF-α, ETN tends to form fairly unstable complexes. ETN binds to free TNF-α and effectively inhibits the formation of TNF-α trimers *in vivo* [32].
TNF-α prompts cells to briefly express TNF-α on their plasma membranes (referred to as tTNF) [30,31]. INF, ADA, and ETN interact with transmembrane TNF-α, but their binding affinities are weaker than those for soluble TNF-α [30]. The INF and ADA, which are IgG1 antibodies essential for targeting tTNF, can fix complement and may also cause damage to TNF-α-expressing cells through antibody-dependent cell cytotoxicity (ADCC) [31]. The ETN contains the Fc region of IgG1, which can also trigger ADCC [32].

This study demonstrated that treatment of psoriasis with the biological agent ETN leads to increased concentrations of TNF-α in the bloodstream. This effect occurs because ETN blocks TNF-α receptors and inhibits TNF-α's action. ETN effectively reduces inflammation, which is beneficial for managing autoimmune diseases. However, unlike naturally occurring soluble TNF-α receptors, ETN is a fusion protein with a significantly longer half-life in circulation. As a result, it exerts a more profound and sustained biological effect [33].

3.3 Interleukin-2 (IL-2) levels among sera of the studied groups
IL-2 plays a crucial role in the immune system by influencing T cells [34,35]. It also promotes the proliferation of keratinocytes [36]. In this study, the serum levels of IL-2 were significantly elevated ($P>0.05$) in psoriatic patients before treatment with a mean of 97.50±6.60 ng/mL compared to the healthy control group with a mean of 77.90±3.10 ng/mL, there were no significant differences ($P>0.05$) observed in serum IL-2 levels in patients before and following treatment, with values recorded at 97.50±6.60 ng/ml and 2.90±5.00ng/mL, respectively, as illustrated in Figure 2.

The serum concentrations of IL-2 were elevated in moderate and severe cases of psoriasis compared with the control group; IL-2 was increased in psoriatic patients, which is in agreement with previous studies [37,38].

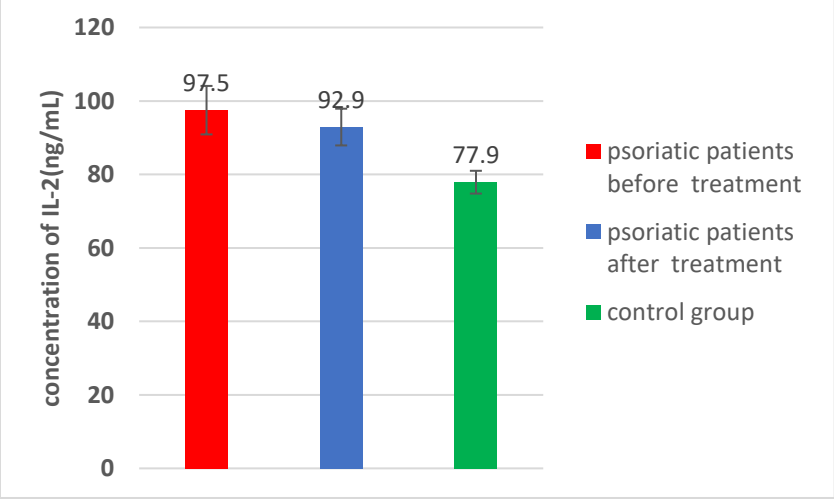

Figure 2: The levels of IL-2 in psoriatic patients prior to and following treatment compared to a control group.

Cytokines are important mediators and modulators of local and systemic inflammation and are involved in many cutaneous inflammatory disorders. The first clinical observation

concerning psoriasis and interleukins was by [39] who reported that administration of IL-2 in patients have a past medical history of this disease, suffering from renal carcinoma metastasis, led to the appearance and clinical exacerbation of psoriasis. Some studies showed that after three months' treatment of psoriatic patients with ETN, the concentration of IL-2 remains at the same levels.

3.4 Interleukin-17 (IL-17) levels in sera of the studied groups

IL-17 levels were significantly elevated in untreated psoriatic patients (93.8 ± 3.4 ng/mL) compared to healthy controls (65.8 ± 2.7 ng/mL; $P<0.05$). Following treatment, levels decreased significantly (72.7 ± 4.4 ng/mL; $P<0.05$) relative to pre-treatment values (Figure 3).

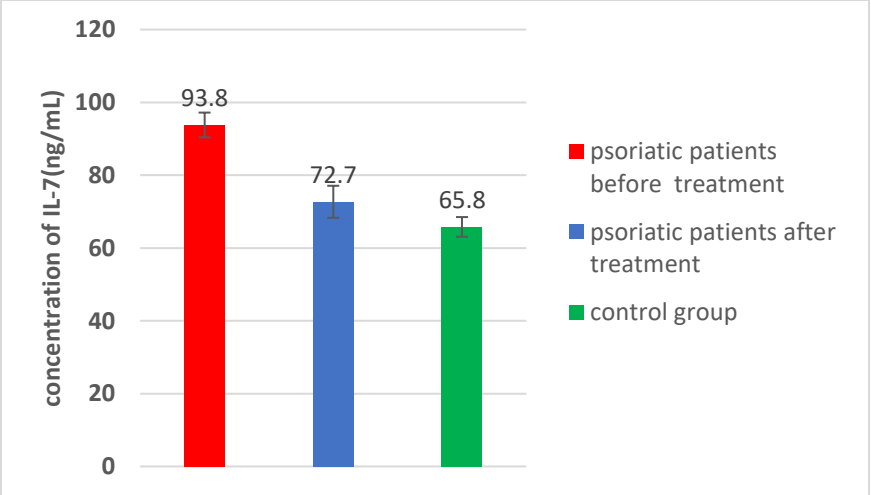

Figure 3: IL-17 concentration in psoriatic patients before and after treatment groups compared to the control group

IL-17 is essential in the progression of several autoimmune inflammatory conditions. Cells that produce IL-17, including T cells, natural killer cells, and innate lymphoid cells, play a significant role in this process. Prior studies have indicated that individuals with psoriasis exhibit high levels of serum concentrations of IL-17 before treatment, studies indicating that these concentrations are higher in psoriatic patients compared to healthy controls.

Psoriasis involves dysregulated immune system interactions within the skin's epithelial and connective tissues [40]. Dendritic cells (DCs) serve as crucial immune system defenders, facilitating the adaptive immune response in psoriasis. Their presence is significantly increased in psoriatic plaques, where they can initiate the auto-proliferation of T-cells upon activation [41]. Triggered DCs serve as antigen-presenting cells; they produce cytokine intermediaries such as IL-12 and IL-23, crucial for the diversity of T-cells into Th-1 and Th-17 cells, respectively. Th-17 cells are crucial in their function in epithelial immune surveillance. They secrete cytokines that activate innate immune cells, initiating a cascade of pro-inflammatory cytokines like IL-1 and IL-6, TNF-α, and IFN-γ. Activated Th-17 Cells generate cytokines such as IL-17A and IL-17F and IL-22, leading to elevated levels of IL-17. Consequently, Th-17 cells and their related cytokines have increased levels in skin injuries caused by psoriasis [42].

The present study displayed that the levels of IL-17 in psoriasis after treatment significantly decreased compared with those in psoriatic patients before treatment. These effects indicate that serum levels of IL-17 decreased in treatment with ETN [43].

3.5 AMH levels in sera of the studied groups

The present data indicated a significant decrease in AMH levels in psoriatic patients before treatment, recorded at 0.420±1.70 ng/mL, compared to the control group, which exhibited levels of 2.50±1.60 ng/mL ($P<0.05$). Furthermore, a significant alteration ($P<0.05$) in AMH levels was observed in psoriatic patients when comparing pre-treatment and post-treatment values, which were 0.420±1.70 ng/mL and 2.80±2.30 ng/mL, respectively, as shown in Figure 4.

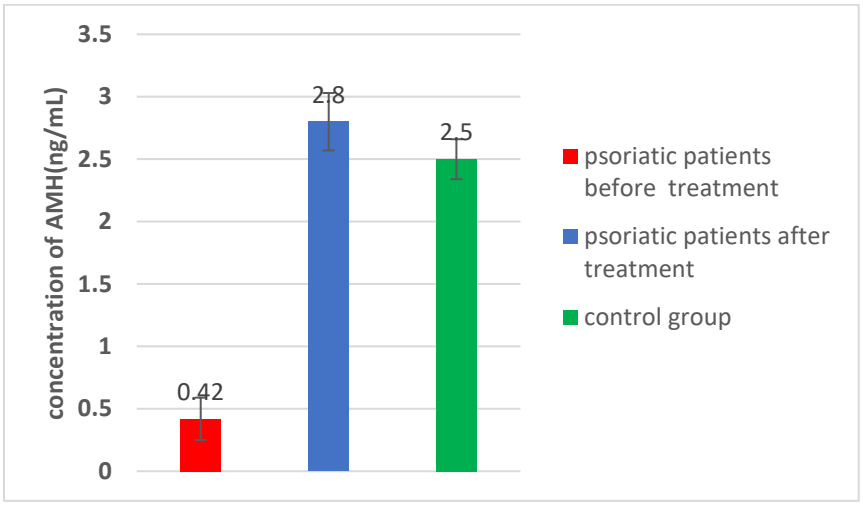

Figure 4: Levels of AMH in psoriatic patients before and after treatment and the healthy control group.

Tumor necrosis factor-alpha is a cytokine with a molecular weight of 26 kDa, integral to advancing endometriosis. Stimulated macrophages produce it and facilitate the synthesis and secretion of other cytokines. This particular cytokine can be found in human follicles, cumulus cells, and the corpus luteum, as well as in follicular fluid. *In vitro* studies suggest that TNF-α may inhibit FSH-induced estradiol production, affecting ovarian steroidogenesis [44]. It has been confirmed that low doses of TNF-α monoclonal antibodies (mAb) could potentially be used to manage endometriosis in non-human primates. The pathway of action of anti-TNF-α monoclonal antibodies appears to be associated with the induction of apoptosis in peripheral mononuclear cells (PMC) and the inhibition of critical cytokines and growth factors, such as granulocyte-macrophage colony-stimulating factor (GM-CSF) and interleukin-15 (IL-15) [45]. Studies conducted on mouse testes have demonstrated the inhibitory role of AMH concerning follicular maturation induced by FSH, indicating that gonadotropins and androgens control AMH expression. The findings highlight a significant influence of TNF-α on AMH levels in the serum of patients. Consequently, it has been concluded that the drug has a beneficial effect on the fertility of women treated with ETN [46]. The current study recommends further investigation into other immunological and hormonal factors to assist patients experiencing infertility.

Conclusion:

This study demonstrates that etanercept is an effective therapeutic option for patients with moderate-to-severe plaque psoriasis. Biological treatments for psoriasis utilize targeted agents that obstruct particular molecular pathways essential to the progression of the disease, and they now include several well-established, licensed treatment options for patients with severe disease. The immunological analysis was near control level after treatment. Autoimmune diseases can impact ovarian reserve, even in patients receiving immunosuppressive therapy. The study's findings indicate that females diagnosed with psoriasis may have a reduced reserve of ovarian oocytes. Nevertheless, findings suggest that the administration of

Etanercept may positively influence ovarian function, potentially reducing various reproductive issues in females. Further research is required to validate the ovarian backup in patients diagnosed with psoriasis vulgaris at different phases of the disease, encompassing larger sample sizes.

Acknowledgment

We are grateful to the Assts. Prof.Dr. Basmann Medhat Fadheel, Department of Dermatology, College of Medicine, University of Baghdad, for his work in diagnosing the clinical cases in the Dermatology and Venereology Department in Baghdad Teaching Hospital, used in this work, and all thanks to all patients who contributed to this research with the hope cure.

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