



Effects of contraception pills and hormone replacement therapy on VEGF and IL-6 in per and postmenopausal women

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ABSTRACT

Contraception is a method of preventing pregnancy during the premenopausal period, whereas hormone replacement therapy (HRT) is a medical treatment used to treat menopausal issues. The purpose of this study was to look at the effects of contraception and HRT on Vascular endothelial growth factor (VEGF) and Interleukin-6 (IL-6).

One hundred (120) women were recruited: 30 with contraception, 30 with HRT, and 60 with no contraception, with HRT, and 60 with no as a control group. All women were between the ages of 31 and 70 and were categorized into four groups (31–40, 41–50, 51–60, and 61–70).

In comparison to control women (without contraception and hormonal replacement therapy), the results of this study showed a significant increase in VEGF levels in all tested women ($p < 0.05$). In comparison with the control group, there was a significant decrease ($p < 0.05$) in IL-6 levels in women taking contraception and those taking hormonal replacement therapy. Based on these findings, it is possible to conclude that the administration of contraception and hormonal reproductive therapy affects the fibrinolytic system and increases the likelihood of thrombotic events.

Keywords:

contraception, Interleukin-6, Fibrinolysis

1-1 Introduction

The contraceptive tablets always have both essentially sexual hormones of women, estrogen and progesterone, and they are offered as synthetic preparations. These synthetic preparations of hormones alter the hypothalamus-anterior pituitary-ovaries axis of fertile women in order to limit ovulation so that they can avoid conception (1).

Thrombosis, venous thromboembolism, cardiovascular events, and cerebral stroke are among the significant adverse effects that can be life-threatening to the contraceptive pill despite the proper dosage of either progesterone alone or coupled with estrogen (2, 3).

In order to maintain and control angiogenesis processes, VEGF and its receptors are essential (4). The angiogenesis process entails the production of new blood vessels from primary

blood vessels, and this mechanism is mostly in charge of blood vessel formation up until full development (5). Other growth factors, such as platelet growth factor, fibroblast growth factor, angiopoietin, and ephrin B2, can promote angiogenesis (6).

Since it has multiple functions related to host defense processes, including those involving the immune system as well as hemopoietic processes, IL-6 is regarded as a major factor or cytokine. In addition, it has a strong ability to promote the acute phase response in the body during infection. It has also been shown that excess production of IL-6 is linked to the occurrence of many chronic diseases, including osteoporosis, arthritis, and cardiovascular events. Macrophages and monocytes specialize in the synthesis and production of IL-6. The creation of IL-6 is stimulated in response to the presence of other cytokines that mediate

inflammation, such as TNFB and IL-11. During resting periods, the receptors that are specialized for IL-6 are located in the bone marrow on B-lymphocytes, hepatocytes, T-lymphocytes, and myeloid cell lines.

Material and Methods

Women of the study

The current study was carried out at the Zain al-Abiden Hospital in the province of Karbala, and it covered the months of September 2022 and April 2023. The study had 120 women, or 120 participants. Women were primarily divided into two groups based on their menstrual cycles: first, premenopausal women, whose ages varied from 31 to 50. The second group consisted of postmenopausal women aged 51 to 70. The 30 premenopausal women who had received contraceptive tablets at least two years prior were split into two age groups: 31-40 and 41-50. The thirty (30) postmenopausal women who stopped having periods around two years ago and who started taking hormone replacement treatment at least a year ago. These women were divided into two groups, 51-60 and 61-70 years old, based on their age. The remaining 60 women, who included pre- and postmenopausal women, were chosen to serve as a control group; they did not use HRT or contraceptive pills, were not pregnant, or were not nursing. All of the ladies had no chronic conditions, including diabetes, thyrotoxicosis, rheumatoid arthritis, autoimmune disease, renal and hepatic disease, or cardiovascular disease. All women were taken to hospitals and other medical facilities to have their own health conditions evaluated, and questionnaires were sent to each woman to inquire about her medical history in order to draw blood.

Methods

Collection of blood samples

Blood samples were taken from 8 to 10 in the morning. The women were required to sit on a chair for at least 10 minutes before collection. The left hand's antecubital vein was more refined. To increase blood circulation, massage therapy was applied to the selected arm. A tourniquet was tightened around the arm about 7 cm above the collection site to cause the vein to protrude more.

Measurement of estradiol hormone concentration (pg/ml) (VEGF),:-

The basic measurements were made using an ELISA kit supplied by the Chinese business Elabscience. According to the supplier company's instructions, this approach relies on the binding of antibodies to antigens on the outermost layer of wells in a plate.

Statistical analysis:-

Data from the current study were collected, displayed as means and standard deviation (SD), and then analyzed using a computer application called SPSS. P 0.05 was regarded as the lower limit of significance for differences between research groups (Daniel, 1999).
The Outcomes

The Results

(1): Levels of vascular endothelial growth factor (VEGF pg/ml) in women with contraceptives therapy and control women :-

In the primary and secondary age groups (41-50, 51-60 years old, respectively) of women administered contraceptive therapy in comparison to those without contraceptives (13.2+4.6, 18.9+6.9pg/ml, respectively), there was a significant heightening (p0.05) in the levels of VEGF (48+9.4, 62.2+16.7pg/ml).

Figure(1)

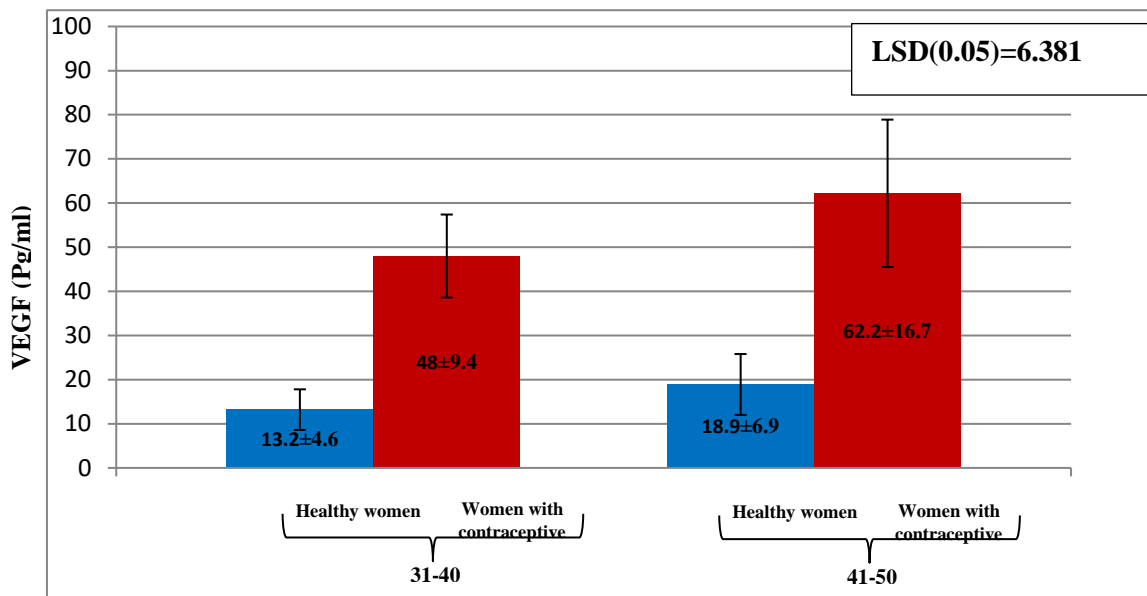


Figure (1): Results of VEGF (Pg/ml) in women.

Figure(1) . Levels of vascular endothelial growth factor (VEGF pg/ml) in women with contraceptives and control groups .

Results were means ±SD.

-Results marked with different letters were significantly different (p<0.05) .

(2):-Values of interleukin -6 (IL-6pg/ml) of women intake contraceptives therapy and control women .

It was discovered that the first group of women (31–40 years old) who use contraceptives had significantly higher levels of IL-6 (30.1–9.2 pg/ml; p 0.05) than the control

group (19.1±5.6 pg/ml). Contrarily, the results of IL-6 were non-significantly lower (p>0.05) in the second age group (41-50 years old) of premenopausal women who use contraceptives (29.9±6.3) compared to those who do not (31.9±6.9 pg/ml) (figure 2).

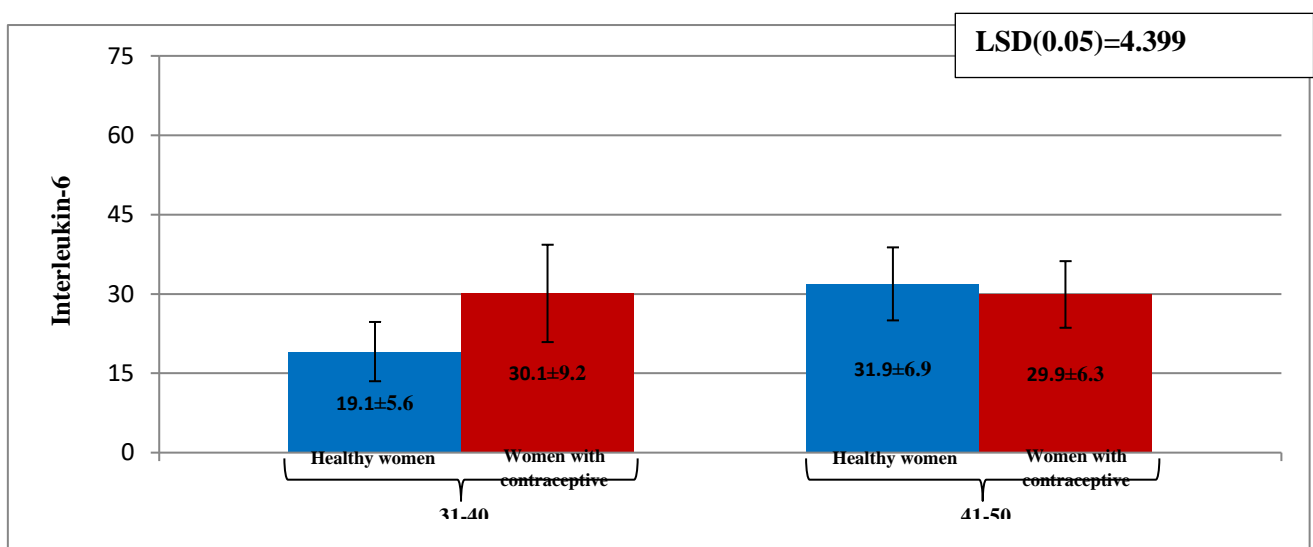


Figure (2): Results of interleukin-6 in women.

Figure (2) :- Results of interleukin-6 (IL-6pg/ml) in premenopausal women

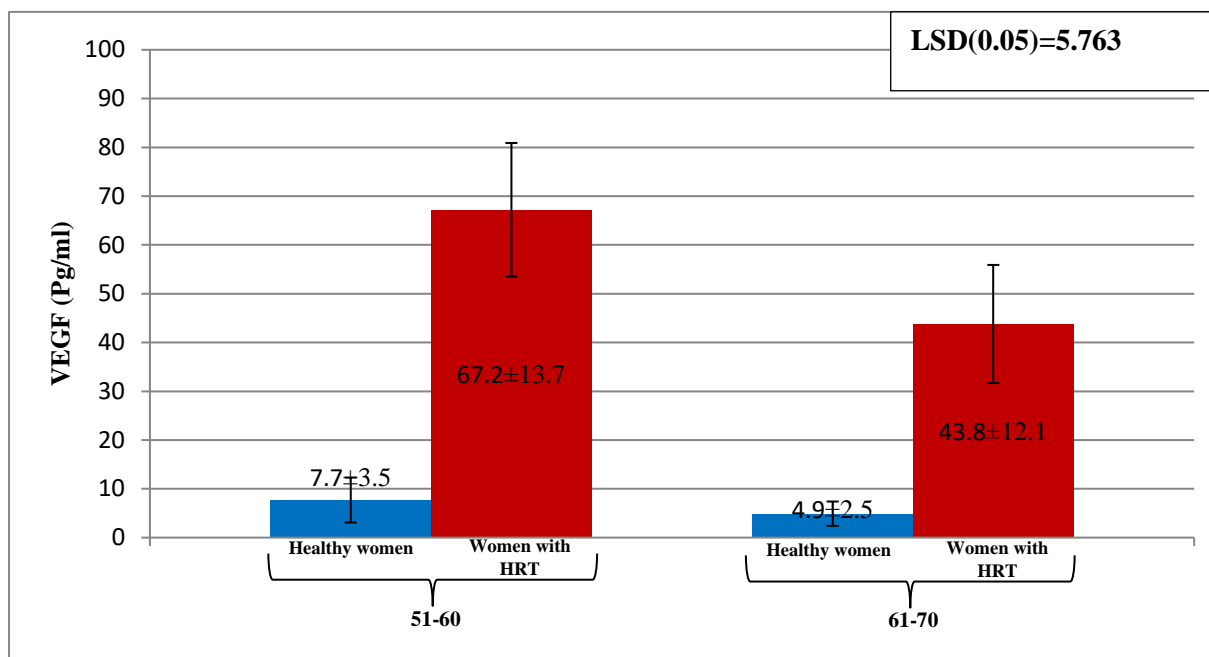
Results were presented as means SD.

-means with various letters differed significantly at p 0.05.

(3):-Vascular endothelial growth factor (VEGF) pg/ml levels in postmenopausal women receiving HRT:-

Findings shown in the accompanying figure (3) showed that postmenopausal women on

HRT had significantly higher levels of VEGF (67.2±13.7, 43.8±12.1) as compared to control women (7.7±3.5, 4.9±2.5 pg/ml) in both the first and second groups of age (51-60, 61-70 years old).



(3)_:- Vascular endothelial growth factor (VEGF) ng/ml levels in postmenopausal women on HRT and control women.

Figure (3): Results of VEGF (Pg/ml) in women.

-Results were means ±SD.

-Results with different were significantly different (p<0.05).

(4):-Values of interleukin -6(IL-6pg/ml) in postmenopausal women treated with hormone replacement (HRT) :-

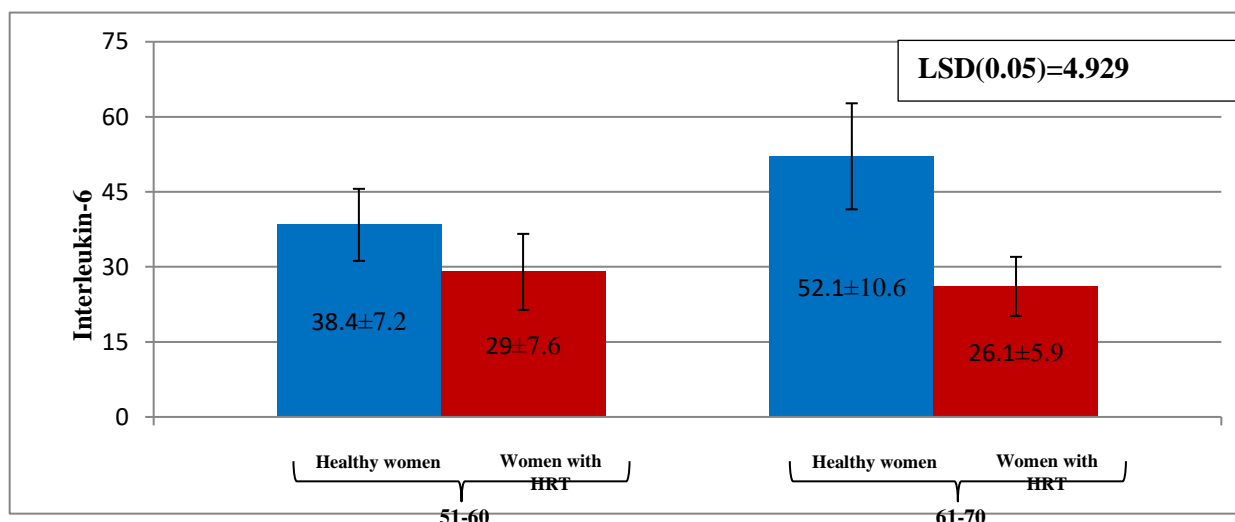


Figure (4): Results of interleukin-6 in women.

Results were presented as means SD.

Results from several experiments differed considerably (p 0.05).

Discussion and Conclusion

Data from the current investigation showed that, when compared to control women, both women using contraception and those using HRT had significantly higher levels of VEGF (p 0.05). The current study supported the following facts. The endometrial glands tend to secrete a significant amount of vascular endothelial factor (VEGF), which has been linked to numerous bleeding issues of the endometrial lining in women who have taken contraceptive pills. Additionally, the increase of VEGF was found to be associated with a significant decrease in progesterone receptor activity.

When ovarian cells begin to promote follicles, angiogenic factors play a major role in initiating and regressing the vasculature. One such angiogenic factor is VEGF, which has the ability to increase the number of endothelial cells and their permeability by binding to its receptor, called VEGF2, which emerges on the outer layer of endothelial cells (10). More explanations were attained to explain the effect of hormone replacement therapy (HRT) as a contributing agent to the incidence of irregular endometrial bleeding when women discontinue HRT intake. Women who receive HRT experience modulation in two crucial angiogenic factors, such as VEGF and thrombospondin-1 (TSP-1), and it was well discovered that 17 beta-estradiol elevates VEGF concentrations in the glands of the endometrial epithelium (called Ishikawa cells).

The findings of this study (4-) verified a substantial increase in IL-6 in the first group (p 0.05) along with a non-significant difference in the second group, while the levels of IL-6 in the third and fourth groups both significantly decreased (p 0.05) when compared to the control group. confirmed that women who had been administered contraceptive drugs complained of 75 types of inflammation and hemorrhage in periodontal tissues, and these variations were linked to increased levels of IL-6(12). This suggests that contraceptive pills

have the ability to affect menstrual hormones and ultimately prevent ovulation. It is not surprising that IL-6 plays a role in the body's inflammatory processes since it is a cytokine that mediates a variety of inflammatory and anti-inflammatory activities in many parts of the body. According to a prior study (13), an increase in the quantity of female sexual hormones (estrogen and progesterone) serves to decrease circulating IL-6 before inflammation occurs. Studies on the long-term use of oral contraceptives have shown that these medications are associated with an increased risk of blood clotting and an incidence of disturbance in inflammatory components of chronic immunological disease (14).

conducted an experiment on female Wister rats treated with a combination of oral contraceptives (Duofem) at doses of 0.6 mg/kg/Bw intragastrical at various intervals (36, 48, 60, and 7 days)(15). They found that serum levels of IL-6 and fibrinogen were significantly lower at the end of the experiment and came to the conclusion that IL-6 and inflammatory cytokines were crucial in controlling fibrinogen synthesis. In contrast to androgens, which restrict immunological activity, estrogens have the ability to activate the immune system, which allows them to boost the expression of IL-6 (16).

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