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Estimation of Kisspeptin and Its Relationship with Some Reproductive Hormones in Different Ages of Women Menstrual Cycles

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ABSTRACT

Background: Kisspeptin, a neuropeptide, plays a crucial role in stimulating the release of gonadotropin-releasing hormone (GnRH), which is essential for triggering the luteinizing hormone (LH) surge and subsequent ovulation. Notably, kisspeptin levels increase just prior to ovulation and the LH surge, underscoring its significance in regulating the ovulatory process throughout various stages of the menstrual cycle.

Objective: To investigate how kisspeptin influences and interacts with other hormonal changes related to reproduction in both younger and older menstruating women.

Materials and methods: This study involved 30 healthy women within two different age ranges: 20-25 years and 40-45 years. They were divided into two groups, with 15 women in each group. Blood samples were collected on the eighth, sixteenth, and twenty-fourth days of the menstrual cycle to compare various parameters, including Serum Kisspeptin, Follicle-Stimulating Hormone (FSH), Luteinizing Hormone (LH), Estradiol, Progesterone, and Prolactin hormones. The comparison was made within each age group on different days and also between the two age groups on corresponding days.

Results and Conclusion: On the 16th day, there were notable increases ($p \leq 0.05$) in Kisspeptin, luteinizing hormone (LH), and prolactin levels compared to days 8 and 24 in both the first and second groups, albeit to different extents. Additionally, on the same days, the second group exhibited significant rises ($p \leq 0.05$) in Kisspeptin and prolactin when compared to the first group, although there was no significant increase in luteinizing hormone (LH). On the 8th day, there were notable increases ($p \leq 0.05$) in follicular stimulating hormone (FSH) and estradiol levels, and these changes differed between the first and second groups. Furthermore, on the same days, the second group experienced a significant rise ($p \leq 0.05$) in FSH compared to the first group, although estradiol levels did not show a significant decrease. On the 24th day, there was a significant increase ($p \leq 0.05$) in progesterone levels when compared to the 8th and 16th days, and this increase was observed in both groups. Additionally, when comparing the two groups on the same days, the second group showed a non-significant reduction in progesterone levels compared to the first group. Kisspeptin plays a crucial role in regulating the hypothalamic-pituitary-gonadal axis and collaborates with other reproductive hormones to facilitate successful ovulation in young menstruating women.

Keywords: Kisspeptin, Follicular Stimulating Hormone (FSH), Luteinizing Hormone (LH), Estradiol, Progesterone, Prolactin.

1. Introduction

Kisspeptins constitute a group of neuropeptides that play a regulatory role in various aspects of puberty, fertility, and reproduction [1]. The main regions where Kisspeptin is produced in the human body are the arcuate nucleus and the anterior ventral periventricular nucleus of the hypothalamus [2]. Additionally, Kisspeptin and its receptor (KISS1R) are present in the mammalian ovary, suggesting that Kisspeptin signals may potentially be involved in directly controlling ovarian functions such as follicle development, oocyte maturation, steroid production, and ovulation [3].Moreover, Kisspeptin besides its pivotal role in LH control, also influences prolactin secretion, its regulation of prolactin secretion may involve the concurrent reduction in dopamine activity (the main hypothalamic hormone regulating prolactin secretion), which probably facilitates prolactin secretory response [4]. Furthermore, many authors demonstrated that the serum level of Kisspeptin like steroid hormones fluctuates during the menstrual cycle and its level in the follicular phase is lower than in the pre-ovulatory phase suggesting that kisspeptin stimulates LH secretion and enhances ovulation [5,6].

On a contrasting note, Zahi et al. [6] observed that Kisspeptin levels remain low during the early follicular phase when the follicles are still in the underdeveloped stage. However, they found that Kisspeptin levels exhibit a sharp increase when the dominant follicle reaches a diameter of 1.2 cm. Additionally, Jayasena et al. [7] noted that women in the early to mid-follicular phase do not exhibit a significant LH response to Kisspeptin, but pre-ovulatory women show a considerably larger LH response to Kisspeptin. Taking these findings into consideration, the present study seeks to provide insights into the role of Kisspeptin and its relationship with various hormonal parameters during different phases of the menstrual cycle in both younger and older women.

2. Materials and Methods

The current study was conducted between 2022 and 2023, following ethical approval from the Training and Human Development Center at the Misan Health Directorate, Ministry of Health (Approval No: 132, Date: 09-03-2023). Thirty healthy women participated in this study, divided into two groups, each consisting of 15 women. The first group comprised women aged 20 to 25 years, while the second group included women aged 40 to 45 years.

Blood samples were collected on the eighth, sixteenth, and twenty-fourth days of the menstrual cycle in both young and older menstruating women. The aim was to compare various parameters among these different days within each group and to compare these parameters between the two age groups on corresponding days. It's important to note that the individuals in the sample were healthy women with regular menstrual cycles who had undergone medical evaluation by specialist physicians.

Serum kisspeptin levels were determined using enzyme-linked immunosorbent assay (ELISA) system kits, while serum levels of FSH, LH, estradiol, progesterone, and prolactin were measured using Vidas system kits. Statistical analysis was carried out using one-way Analysis of Variance (ANOVA), followed by Duncan's test, and t-tests were used to assess differences between groups, with a significance level set at $p \leq 0.05$ [8].

3. Results

Kisspeptin levels showed a significant increase ($p \leq 0.05$) on the 16th day when compared to the 8th and 24th days for the first group, while there was no significant increase in the second group, as illustrated in Figure 1. Furthermore, in Figure 2, it's evident that, except for the 24th day, there was a significant increase ($p \leq 0.05$) in kisspeptin levels in the second group compared to the first group on the corresponding days.Follicular stimulating hormone (FSH)

In Figure 3, we can observe that follicle-stimulating hormone (FSH) levels had a significant increase ($p \leq 0.05$) on the 8th day, except for the 16th day in the first group, when compared to the 16th day in the second group and the 24th day in both groups. Additionally, as demonstrated in Figure 4, there was a significant increase ($p \leq 0.05$) in FSH levels in the second group compared to the first group on the corresponding days, except for the 16th day.Luteinizing hormone (LH) The levels of LH exhibited a notable and statistically significant increase ($p \leq 0.05$) on the 16th day when compared to both the 8th and 24th days in both groups, as depicted in Figure 5. Furthermore, when comparing the two groups for the same days, there was an increase in LH levels in the second group compared to the first group, although this increase did not reach statistical significance, as illustrated in Figure 6. Estradiol Estradiol levels showed a non-significant increase on the 8th day when compared to the 16th day, but there was a significant ($p \leq 0.05$) increase when compared to the 24th day in both groups, as illustrated in Figure 7. Additionally, when comparing the two groups for the same days, Estradiol levels displayed a non-significant decrease in the second group compared to the first group, as depicted in Figure 8. Progesterone levels exhibited a statistically significant increase ($p \leq 0.05$) on the 24th day when compared to both the 8th and 16th days in both groups, as depicted in Figure 9. Furthermore, when comparing the two groups for the same days, Progesterone levels displayed a non-significant decrease in the second group compared to the first group, as shown in Figure 10. Prolactin levels showed a notable and statistically significant increase ($p \leq 0.05$) on the 16th day when compared to the 8th day, and there was no significant difference when compared to the 24th day in both groups, as illustrated in Figure 11. Furthermore, when comparing the two groups for the same days, Prolactin levels exhibited a significant increase ($p \leq 0.05$) in the second group compared to the first group, as demonstrated in Figure 12.

4. Discussion

The levels of Kisspeptin exhibited a significant increase ($p \leq 0.05$) on the 16th day compared to other days in both groups. This notable increase suggests a potential role for Kisspeptin in the ovulatory process, given its known influence on the upregulation of GnRH secretion and its pivotal role in triggering the LH surge. This is particularly noteworthy because LH levels also increased on the 16th day, as shown in Figure 5. Additionally, it's worth mentioning that ovarian steroids such as estradiol and progesterone may exert both positive and negative feedback effects on the sites where Kisspeptin is produced. Interestingly, in the current study, estradiol decreased significantly while progesterone increased significantly on the same day of the cycle (16th day), as depicted in Figure 7 and Figure 9. Kisspeptin, as a neuropeptide, is known to enhance GnRH secretion and plays a crucial role in the LH surge and ovulation. Its expression typically rises just prior to ovulation and the LH surge [9, 10, 2]. Moreover, as discovered by [11], Kisspeptin plays a pivotal role in the menstrual cycle by acting upstream of GnRH. It is produced by the hypothalamus and influences the secretion of both FSH and LH directly through GnRH neurons in the anterior pituitary gland. This is significant because the LH surge, which occurs in the middle of the menstrual cycle, is responsible for initiating the process of ovulation [12]. Additionally, estrogen has a dual impact on kisspeptinergic neurons. It utilizes the ER α receptor to stimulate the secretion of Kisspeptin, contributing to the LH surge, and at the same time, it exerts a negative feedback mechanism to suppress Kisspeptin secretion towards the end of the follicular phase, coinciding with the decrease in FSH levels [13].On the other hand, the present Kisspeptin increased significantly ($p \leq 0.05$) in all days of the second group in comparison with the similar days of the first group. The current deficiency of estradiol and progesterone levels associated with progressive age (second group), as shown in figure 8 and figure 10, may be behind the high levels of Kisspeptin in this group by their positive and negative feedback mechanism on the Kisspeptin production, leading to high levels of GnRH secretion and more gonadotropins, as the present results pointed out a high level of FSH and LH in second group as shown in figure 4 and figure 6. Furthermore, premenopausal women (second group) are characterized by high and low levels of gonadotropins and sex steroid hormones, respectively as shown in Figure 8 and Figure 10. There is an initial decrease in ovarian steroids [14] and an increase in kisspeptin levels [10] during progressive age, this increase may occur due to the lack of estrogen-negative feedback [15]. In addition, Ibrahim *et al*. [16] showed that Kisspeptin serum levels increase with age, whereas its higher in women above 35 years than those less than 24 years, whereas, alteration in estrogen levels at late and end reproductive age may participate in elevating the Kisspeptin level. The present FSH showed an increased tendency on the 8^{th} day of the cycle for the first and the second groups. This increase may be explained by the influence of the ovarian steroids feedback (positive and or negative) mechanisms on the hypothalamus and anterior pituitary and a subsequent release of GnRH and FSH, particularly, the current findings indicated that estradiol and progesterone hormones increased and decreased respectively at the 8th day in comparison with other days in both groups as shown in Figure 7 and Figure 9. Marraudino *et al*. [17] showed that the secretion of gonadotropins is under ovarian control via a feedback mechanism. In addition, the ovarian steroids exert critical suppressive and stimulatory actions upon the brain to control GnRH release that drives the menstrual cycle, whereas the activity of the “GnRH surge generator” is primed by the rising follicular phase levels to generate the preovulatory surge [18]. Since the hypothalamus plays a pivotal role in the hierarchical control of the HPG axis, the circulating levels of estrogen serve as a messenger for transmitting the maturity status of ovarian follicles to the hypothalamus. This estrogen action is referred to as "the negative feedback action of estrogen" on GnRH pulses [19]. On the other hand, the present results revealed that FSH levels increased significantly ($p \leq 0.05$) in all days of the second group in comparison with the similar days of the first group. This increase may be explained via the high levels of Kisspeptin that enhance GnRH and gonadotropin secretion as the present Kisspeptin levels increased significantly in the second group in comparison with the first group Figure 2. Moreover, premenopausal women and those who inside the menopausal transition are characterized by a poor ovarian response to high secretion of gonadotropin which leads to low levels of ovarian steroids as Figure 8 and Figure 10 mention that estradiol and progesterone reduced during these ages (second group). The LH levels significantly increased ($p \leq 0.05$) on the 16th day in both groups, a time closely associated with the ovulatory period. This surge in LH is essential during ovulation, where a greater amount of this hormone is needed. As indicated in Figure 1, the present results corroborate the idea that Kisspeptin levels are higher during the ovulatory period. Kisspeptin plays a role in up-regulating the secretion of GnRH and LH. Moreover, this LH surge likely contributes to the development and maintenance of the new corpus luteum, concurrently with the involvement of prolactin (a luteotropic hormone) and estradiol in promoting increased progesterone secretion. Notably, in the current study, both progesterone and prolactin levels increased on the 16th day of the menstrual cycle, as depicted in Figure 9 and Figure 11. Hoskova et al. [20] demonstrated that

Kisspeptin, a hypothalamic neuropeptide, strongly stimulates GnRH secretion, which, in turn, triggers LH pulses. LH plays a critical role in processes like ovulation, luteal development, progesterone production, and the maintenance of a healthy corpus luteum, underscoring its importance as a luteotropic hormone [21]. On the other hand, the present results revealed that LH levels increased (not significantly) in all days in the second group in comparison with the similar days in the first group. Although this slight elevation, it's worth mentioning that the ending of women's reproductive age may be the possible cause of the high levels of gonadotropins, in addition, the synergistic action of the present high levels of Kisspeptin and prolactin perhaps beyond LH elevation as shown in figure 2 and figure 12, moreover, the present low levels of estradiol during these age (menopausal transition) as shown in figure 8 may be losses or attenuates the control of LH release via its feedback mechanism, thereby, unlimited amount of LH be secreted. Talaulikar *et al.* [22] showed that the menopausal transition is characterized by highly variable patterns of gonadotropin and sex steroid output, as women progress through the transition, follicle failure appears to occur and sex steroid production wanes dramatically but intermittently. Furthermore, Vural *et al*. [23] showed that in the poor responder group (< 45 years) FSH and LH levels were higher, but estradiol levels and the number of oocytes were lower in comparison with other younger groups.

The present estradiol increased significantly ($p \leq 0.05$) in the 8^{th} day (except the 16^{th} in both groups) in comparison with other days in both groups. Estradiol hormone and its relationship with hypothalamic pituitary gonads (HPG) axis may be an indicator for the ovarian follicle's maturation, therefore, the follicular phase of the cycle (including 8^{th} day) characterized with these presents high levels of FSH and estradiol hormones as shown in figure 3, that act simultaneously on the ovarian follicle's growth and maturation. As ovarian follicles expand and mature in response to GnRH, circulating estrogen fine-tunes the pulsatile release to maintain adequate circulating levels of GnRH and gonadotropins; this estrogen action is known as "the negative feedback action" on GnRH pulses [21]. Moreover, many researchers pointed that an elevation of estradiol hormone during the first few days of the follicular phase resulted from granulosa cells of the follicle stimulating by circulating levels of FSH rise to secrete estradiol, whereas estradiol levels continuing to rise as follicles mature [24,25]. on the other hand, the present results revealed that estradiol levels decreased not significantly in all days in the second group in comparison with the similar days in the first group. However, with this slight present reduction in ovarian estradiol, the premenopausal and menopausal transition women (second group) have a poor ovarian response with the present high levels of gonadotropins (FSH, LH) as shown in figure 4 and figure 6 stimulation. Kawamura *et al*. [26] showed that women aged 30 to 45 years with a poor ovarian response had elevated serum FSH levels as well as low serum estradiol levels. Furthermore, in premenopausal women, Ovarian follicle depletion and resistance to gonadotropins, leading to decreased estrogen synthesis, explain the lower estrogen concentrations observed recently compared to those recorded in years past [27].

The present progesterone increased significantly ($p \leq 0.05$) in the 24^{th} day in comparison with other days in both groups. The luteal phase of the cycle (including the 24^{th} day) is characterized by the presence of a corpus luteum that secretes the current high levels of progesterone and some estradiol, furthermore, the deficiency in the present Kisspeptin and gonadotropins levels (during the 24^{th} day) as shown in figure 1, figure 2 and figure 3 may reflect the current high level of progesterone. In addition, Szeliga *et al*. [28] showed that the progesterone receptor (PR) on KNDY neurons mediates the inhibitory actions of progesterone, which leads to a decrease in LH pulse frequency during the luteal phase.

Conversely, the current findings revealed a consistent decrease in progesterone levels throughout the menstrual cycle for the second group when compared to the corresponding days in the first group. This subtle reduction in ovarian progesterone levels can be attributed to the fact that women in the premenopausal and menopausal transition phase (second group) experience a diminishing number of follicles along with elevated levels of gonadotropins (FSH, LH), as illustrated in Figure 4 and Figure 6. Furthermore, they exhibit lower levels of estradiol, as indicated in Figure 8. Similar patterns have been observed in previous research where serum progesterone tended to be lower in older individuals [5], and the ovarian reserve was found to decline with age [29].Furthermore, Santoro *et al*. [30] found that the number of antral follicles in the ovaries has been reported to be significantly decreased in women over an age range of 22–42 years old and deviations in reproductive hormone patterns associated with reproductive aging, shortened follicular phases, elevated follicular phase estrogen, and decreased luteal phase progesterone. Prolactin levels exhibited a significant increase ($p \leq 0.05$) on the 16th day compared to the 8th day in both groups, except for the 24th day. The 16th day of the menstrual cycle likely signifies the ovulatory period and the surrounding timeframe. The rise in prolactin during this period is associated with higher levels of both Kisspeptin (which promotes LH release and acts as a dopamine antagonist) and LH (an agent involved in ovulation), as depicted in Figure 1 and Figure 3. Additionally, it's worth noting that prolactin and LH originate from the same release source and are considered luteotropic hormones, which means they act along a similar pathway.Aguino *et al*. [4] showed that Kisspeptin besides its pivotal role in LH control, is also influencing prolactin secretion, Its regulation of prolactin secretion may involve the concurrent reduction in dopamine activity which probably facilitates prolactin secretory response. On the other hand, the slight elevation of the present prolactin in the second group in comparison with the first group may be explained by its correlation with the current high levels of Kisspeptin (dopamine's inhibition) during menopause transition (second group) as shown in figure 2, furthermore, the current prolactin may be associated with the present decline in estradiol levels as shown in figure 8 (via disturbing the ovarian function) and with the current decline in progesterone levels as shown in figure 10 (via the early corpus luteum premature regression). It is worth mentioning that the menopause transition is characterized by hormonal heterogeneity, thereby, it is not easy to clarify an integrated hormonal picture in these premenopausal women. Serum prolactin levels increased concurrently as long as Kisspeptin increased during aging [10], Previous research has demonstrated that Kisspeptin stimulates prolactin production by blocking the activity of TIDA neurons [31]. Furthermore, it was observed that prolactin levels increased as rats aged. Additionally, the connections between TIDA neurons and Kisspeptin neurons remained intact even after the reproductive aging process [32]. Moreover, research by Auriemma et al. [33] demonstrated that elevated prolactin levels have detrimental effects on ovarian functions due to their direct inhibitory impact on the ovaries. This inhibition results in a reduced synthesis of estrogen and progesterone.

Conclusion

In summary, the menstrual cycle is a complex physiological process that influences various aspects of the body, acting collectively and independently in its different phases. Kisspeptin plays a central role in regulating the hypothalamic-pituitary-gonadal axis and collaborates with other reproductive hormones to facilitate successful ovulation in menstruating women. Understanding these interactions enhances our knowledge of reproductive physiology and offers insights into improving fertility and reproductive health.

Conflicts of Interest

There are no conflicts of interest.

Acknowledgment

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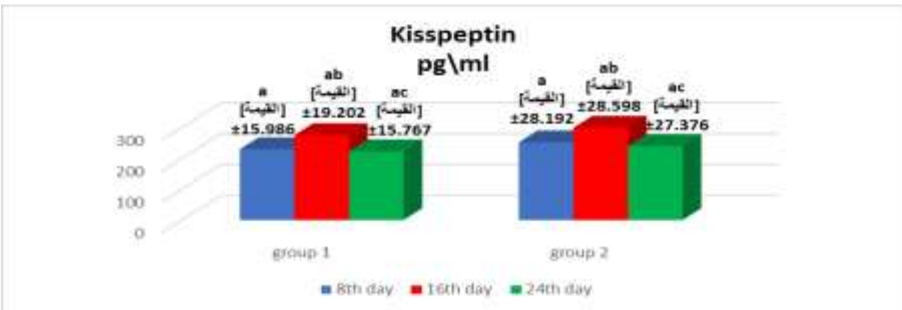

Figure 1 Changes of Kisspeptin levels during different phases of menstrual cycle in both group

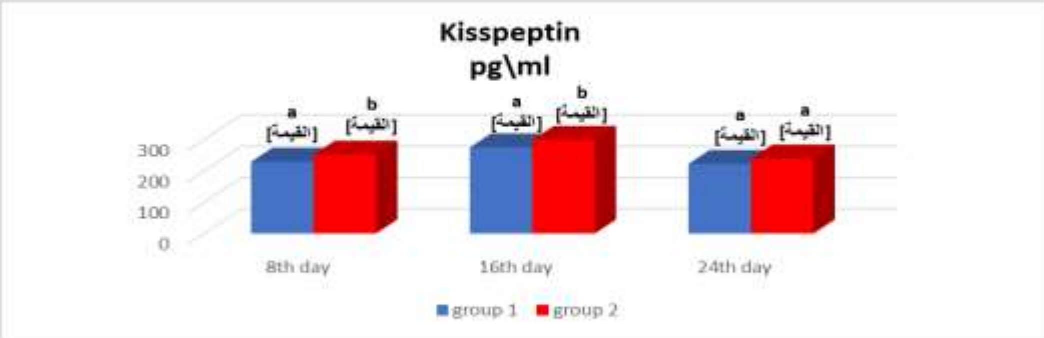

Figure 2 Changes of Kisspeptin levels in similar days during different phases of menstrual cycle in both group

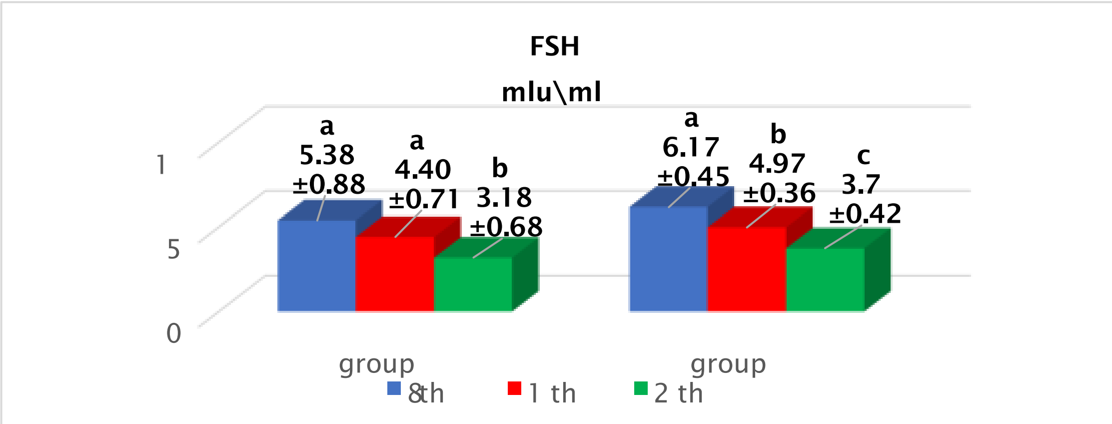

Figure 3 Changes of FSH levels during different phases of menstrual cycle in both group

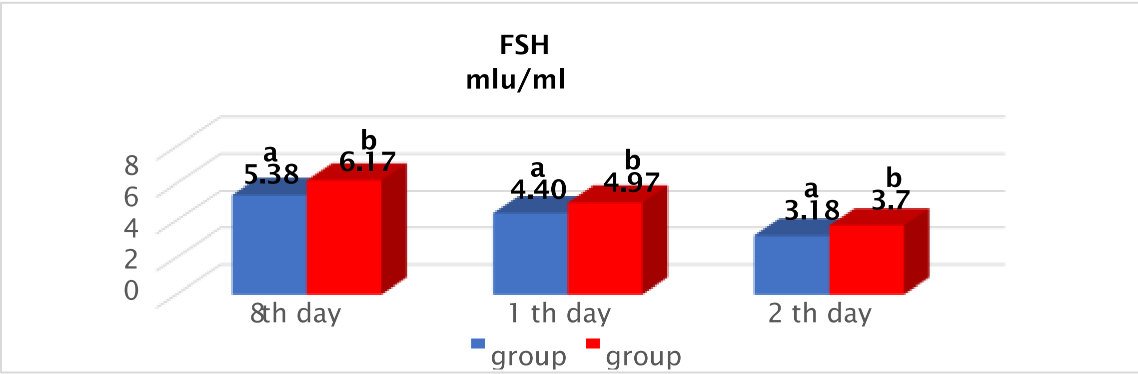

Figure 4 Changes of FSH levels during different phases of menstrual cycle in both group

Figure 5 Changes of LH levels during different phases of menstrual cycle in both group

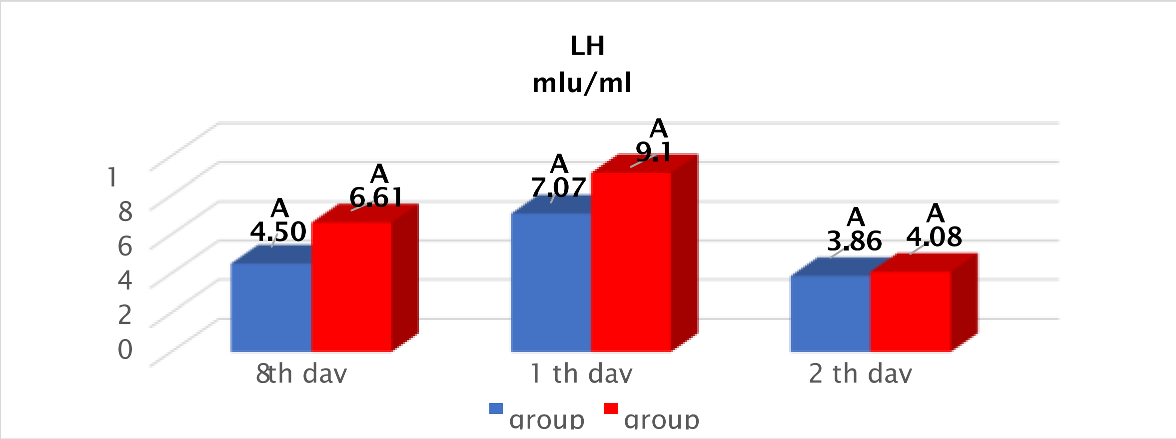

Figure 6 Changes of LH levels in similar days during different phases of menstrual cycle in both groups.

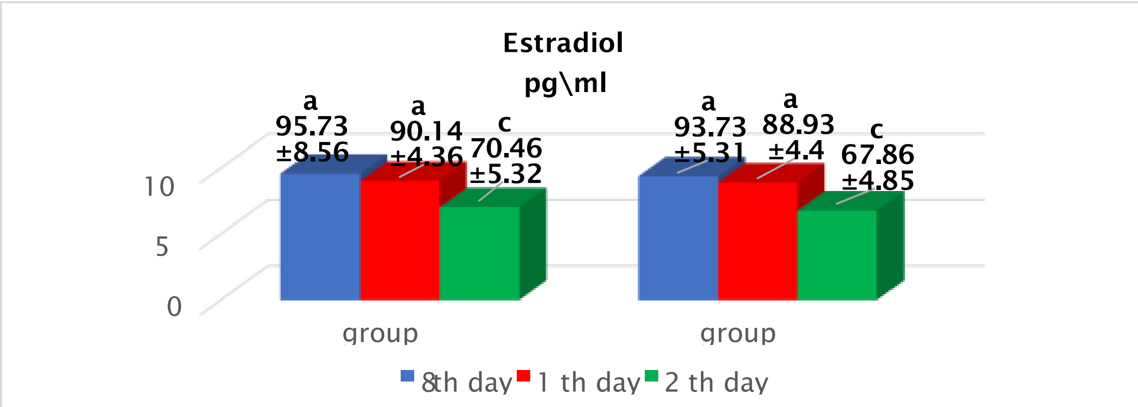

Figure 7 Changes of estradiol levels during different phases of menstrual cycle in both group

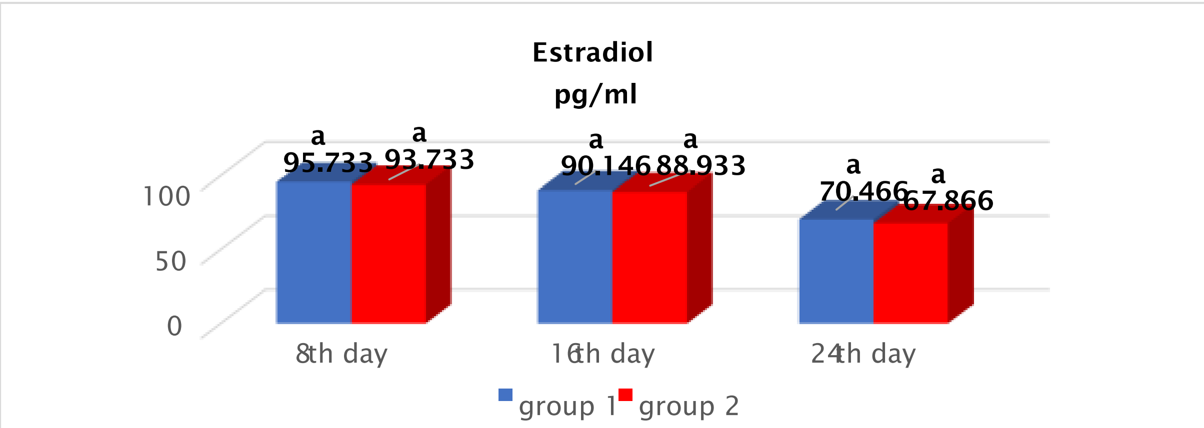

Figure 8 Changes of estradiol levels in similar days during different phases of menstrual cycle in both group

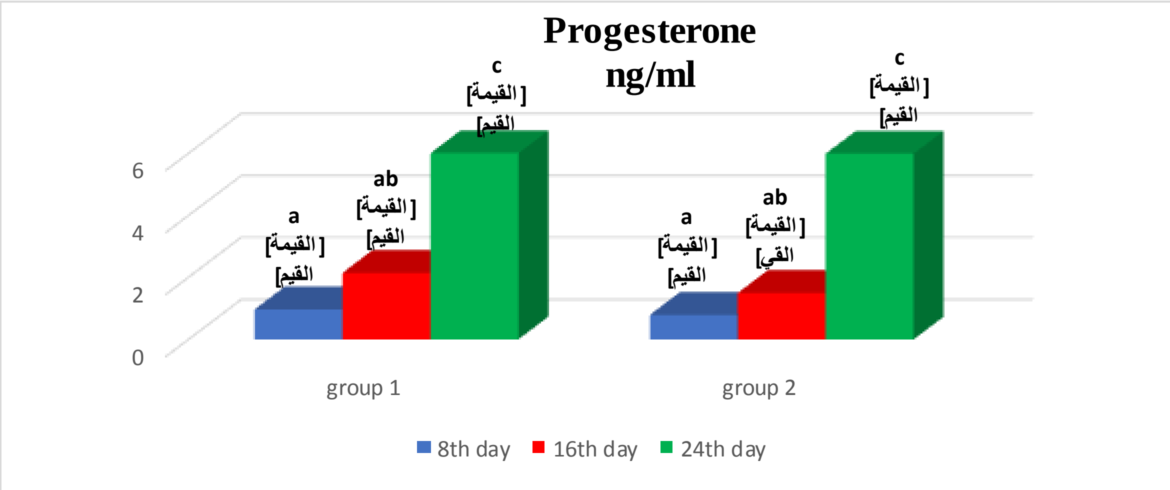

Figure 9 Changes of progesterone levels during different phases of menstrual cycle in both group

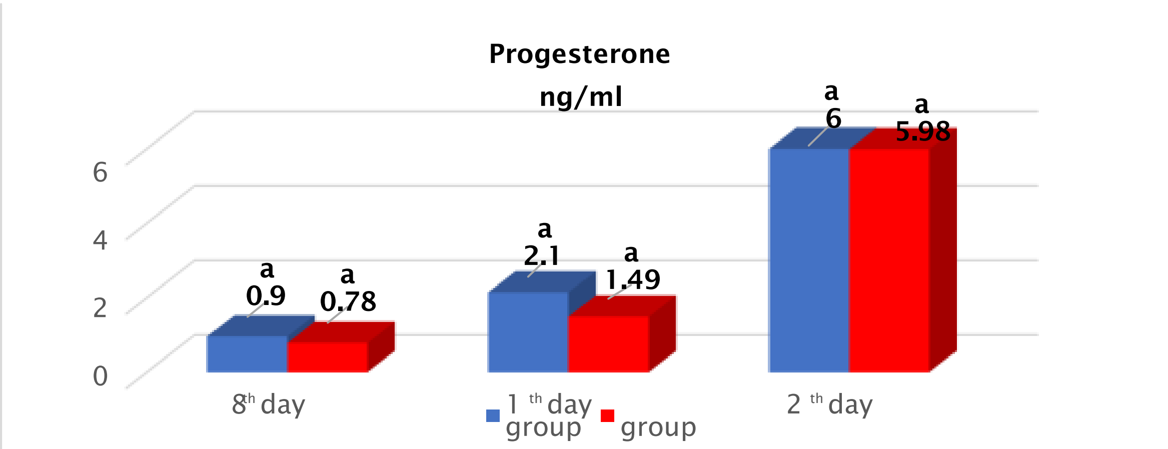

Figure 10 Changes of progesterone levels in similar days during different phases of menstrual cycle in both group

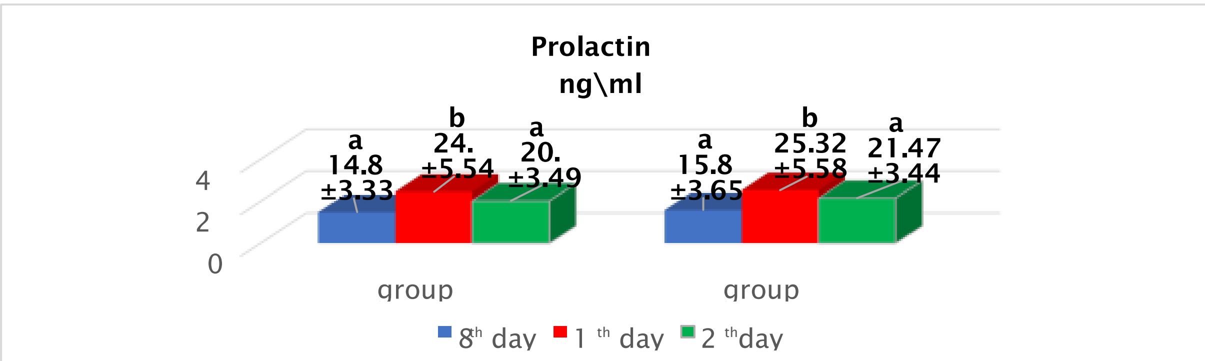

Figure 11 Changes of prolactin levels during different phases of menstrual cycle in both group

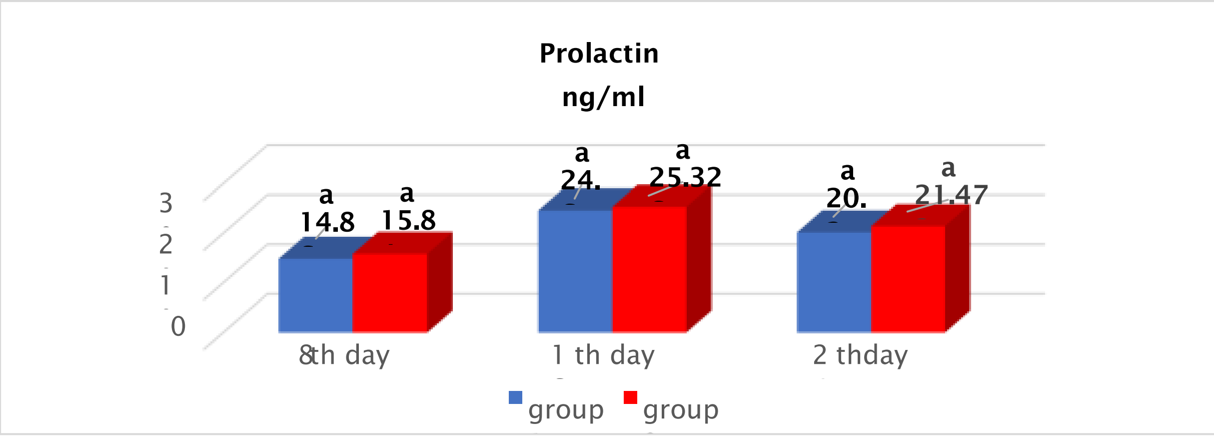

Figure 12 Changes of prolactin levels in similar days during different phases of menstrual cycle in both group

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