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Investigation of the Effects of Estrogen and Progesterone Hormones on Active Knee Joint Position Sense in Healthy Women in Different Phases of a Menstrual Cycle

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HIGHLIGHTS

- The proprioceptive system provides a sense of body awareness and detects and controls force and pressure.
- Menstruation is the regular, orderly shedding of the uterine wall, in response to the interactions of hormones produced by the hypothalamus, pituitary, and ovaries.
- Estrogen is a steroid hormone and involved in the female reproductive organs, as well as numerous other biological systems including the neuroendocrine, vascular, skeletal, and immune systems.

Abstract: The proprioceptive system is actually a sensory system based on an individual's knowledge of the body. The aim of this study was to investigate the effect of estrogen and progesterone hormones on understanding and to recognize the proprioceptive sense the knee joint in healthy women during the menstrual cycle. Fifteen healthy women with regular menstrual cycles participated in this study. The estrogen and progesterone levels were evaluated during a cycle in the follicular, ovulation, and luteal phases. The effect on the sense of perception and cognition of the proprioceptive knee joint in two directions (extension and flexion), by target angle reconstruction at 30° was studied. The results showed that female sex hormones affect the knee active Joint Position Sense (JPS). In the extensions, the changes of the menstrual cycle affect the JPS in constant error during the ovulation phase. In the flexion, changes in the menstrual cycle affect the JPS in constant, absolute, and variable error during the luteal phase. The findings of this study show that the menstruation phases can change the active JPS at knee joint. Since the outbreak of joint problems, especially in the knee joint, is higher in women than in men, it was predicted that hormonal changes during the menstrual

cycle affect the proprioceptive cognition of the knee joint, which in turn increases the percentage of knee injuries in women.

Keywords: Joint position sense; Estrogen; progesterone; Knee joint; Menstrual cycle.

INTRODUCTION

Nervous system and the endocrine glands control the activities of the human body. The endocrine system is mainly engaged in controlling the body's metabolic activities. But, the nervous system is involved in controlling muscle contraction, visceral and controlling the secretion of some endocrine glands [1,2]. The proprioceptive sensory system is a system that subconsciously sends information about the state of the body to the subject, based on the data receiving from joints, ligaments, and muscles. So, the brain understands when and how muscles are in rest and stretch position [2].

Controlling the movement, position and continuous flow of information depends on surrounding events. Motor responses are generally subject to three levels of motor control as follows: 1. the spinal cord for simple reflexes, 2. the lower cerebral cortex for more complex responses, and 3. the cerebral cortex for the most complex responses. Cerebellum, basal ganglia, and hippocampus are the underlying motor areas. Although the underlying areas do not directly control the activity of the motor neurons, but their presence is necessary for modulating and regulating the motor commands which issued by motor centers. Thus, proprioceptive sensory information is coded and processed in each of these centers. The highest level of regulation is in the somatosensory cortex, which processes deep sensory information to create a conscious awareness from the sense of position and joint motion. Also, proprioception sensory information is stored in the cerebellum, basal ganglia, hippocampus, and somatosensory cortex which is used in subsequent motor commands. Finally, different factors can affect the deep sensations of the joints, consisting of gender, age, anatomical and structural orientation, genetic factors, neuromuscular and hormonal factors [3-6].

Since 1991, the word "steroids" has been classified as being able to control nerve function. Subsequently, the regulatory function of progesterone, estradiol, and androgens in the central nervous system was stated in several studies. Researches indicate that the steroid hormones easily cross the blood and brain barrier and act on the brain receptors, such as the hypothalamus, hippocampus, cerebellum, basal ganglia (putamen), raphe nucleus, and cerebral cortex through the binding mechanism of ligand-phosphorylation receptor in the brain [7]. When the amount of female sex hormones is at a minimum level, the presence of estrogen and progesterone receptors on the Anterior Cruciate Ligament (ACL) of women and identifying the relationship between the neuromuscular system and the level of their sex hormones, differences in the sense of position at different times of a menstrual cycle and the amount of menopause occurs. Studies have also shown that women are more prone to ligament damage than men [8-10].

New findings indicate that the density of steroid receptors is very high in hypothalamic and hippocampal neurons. Researchers have indicated that estradiol has the ability to increase stimulation by glutamate receptors and inhibit GABA. In addition, estradiol is influential in regulating the function of NMDA (*N* -methyl-D-aspartate) receptors in the hippocampus [11,12]. Besides, ovarian steroids have protective functions on the central nervous system in addition to their hormonal role in reproductive activities [13,14].

There are several regions in the CNS that have estrogen and progesterone receptors, including the hypothalamus, hippocampus, limbic system, and cerebral cortex. Steroid hormones protect and divide neurons in these areas of the brain. In addition, the findings indicate the role of progesterone along with a combination of estrogen called β-17 estradiol in regulating cognitive and behavioral functions. The protective effects of estrogen and progesterone against altercations in amyloid-beta-glutamate, seizure behaviors and oxidative stress have been confirmed [15,16]. The aim of this study was to investigate the effect of female sex hormones in different stages of the menstrual cycle on knee joint proprioception.

MATERIAL AND METHODS

Experimental Design

This research was conducted by semi-experimental method and available sampling. The statistical population of the research consisted of fifteen healthy women (none of the participants were excluded from the study) in the age range of 21 to 45 years. This study was conducted in a closed room with appropriate control and imaging of ventilation, temperature, light and sound with the help of Canon LXUS960-5 digital camera. The camera was mounted on a tripod perpendicular to the plane of motion of the pelvis at a distance of 80 cm from the standing position and 80 cm from the ground so that the lens was completely along the hip

joint. The digital images were connected to the computer and then the data were identified and processed through the software.

The criteria and conditions for people to enter this study have been determined, which include: no cardiovascular disease, no diabetes, no thyroid disease, no polycystic ovary syndrome, no diet or treatment, no addiction to drugs, smoking, alcohol and Caffeine, normal menstrual cycles, without drugs and even contraception, absence of neuromuscular disorders, absence of history of fracture or abnormality in the joints of both knees, lumbar spine and neck, pain and limitation in the joints of the limbs. Also, it is important that women have a normal state from three days before sampling. Subjects were controlled for avoiding drugs, smoking, caffeine, and physical activity in addition to daily life activities and non-sexual intercourse, as well as for adequate sleep and consuming a caloric diet. Subjects first filled a consent form to participate in the study and a form to collect information including demographic information. The majority of people were then identified and given the necessary training on what to do. The test was conducted in three sessions of 10 to 15 minutes.

Blood Samples

The participants had bloodletting in three cycles with having a 7-day menstrual cycle, namely the beginning of the cycle is 3-4 days (follicular time), 12-14 days (ovulation time) and 21-24 days (luteal time) in order to measure the concentration of estrogen (Monobind Inc., Germany) and progesterone (Monobind Inc., Germany) hormones. It was considered as the indicators of the peak existence of the sex hormones. All blood samples were taken before the active knee joint position sense test. Estrogen and progesterone hormones were measured by ELISA (enzyme-linked immunosorbent assay) method using the ELISA reader SLT model which is based on colorimetric methods.

Attachment of Markers

To goniometry, four markers were installed on the bony points of the long thighs and legs (Figure 1A). Each marker consists of a 2-cm square. The location of the markers from proximal to distal is:

1- The apex of the greater trochanter of the femoral bone.
2- Lateral condyle of the femoral bone.
3- Anterior region of the head of the fibula bone.
4- Lateral malleolus of the ankle.

The subject was first asked to stand upright and relaxed on the edge of the bed along with a support on it and her feet are away from the ground. The left side was placed foot on a chair and marked right side.

Active Knee Joint Position Sense Test

Using a standard goniometer, the subject was asked to extend the knee up to 30 degrees (Figure 1B) by controlling the examiner and to maintain the position for 5 seconds at the instructor's command so that the initial learning could take place. Then, a picture by the camera (in the laboratory of motor control with calibration and standardization) was recorded from the 30-degrees knee and coded into account as the reference image (Figure 1C). In all the participants, the right foot was considered the dominant foot.

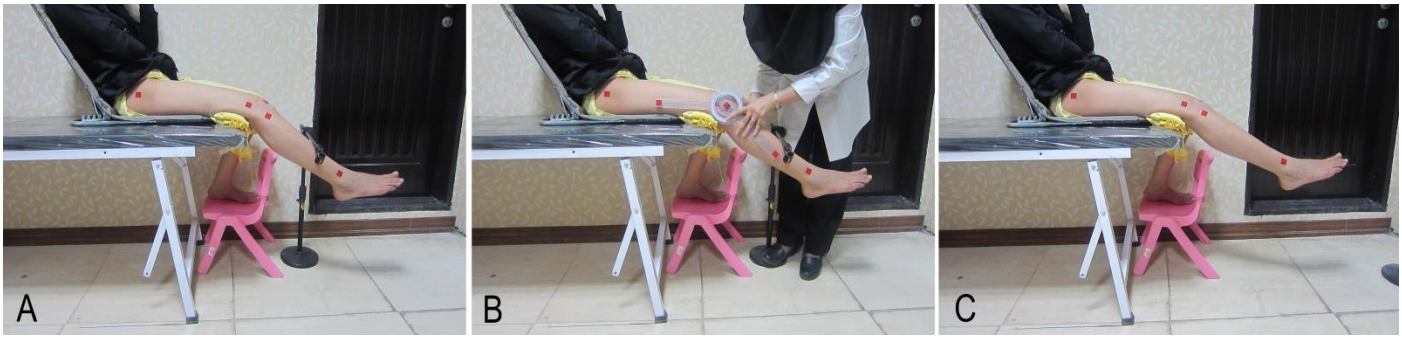

Figure 1. (A) Attachment of markers at the land mark points of the right thigh and leg. (B) Reconstruction of 30° angle. (C) Reference image of knee extension.

After recording the reference image, the subject was asked to return to the original position (90-degree knee). Then the subject's eyes were closed with blindfolds. After 5 seconds, the subject was again asked to actively bring her knee to a 30-degree angle without the examiner's control. The subject informed the examiner of reaching a 30-degree angle by pressing the light laser button in her hand (Figure 2). At this stage, a photo was taken by the camera again and coded as Repeat 1. Then the subject returns to the starting position (90-degree of knee flexion) (Figure 3). The subject performed 30-degree knee reconstruction three times with an interval of 5 seconds between each repetition, and thus, the four repetitions of the joint reconstruction with the reference amplitude were compared by the software and the error values, absolute error, constant error, and variable error of sense of position status were measured.

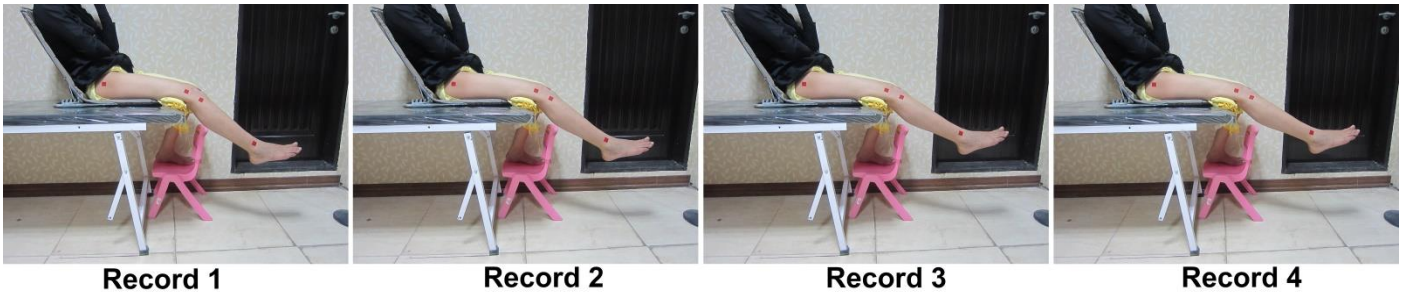

Figure 2. Imaging steps of four repetitions of knee extension to reconstruct and determine the sense and understanding of the position of the knee joint (recording 1 was the reference image).

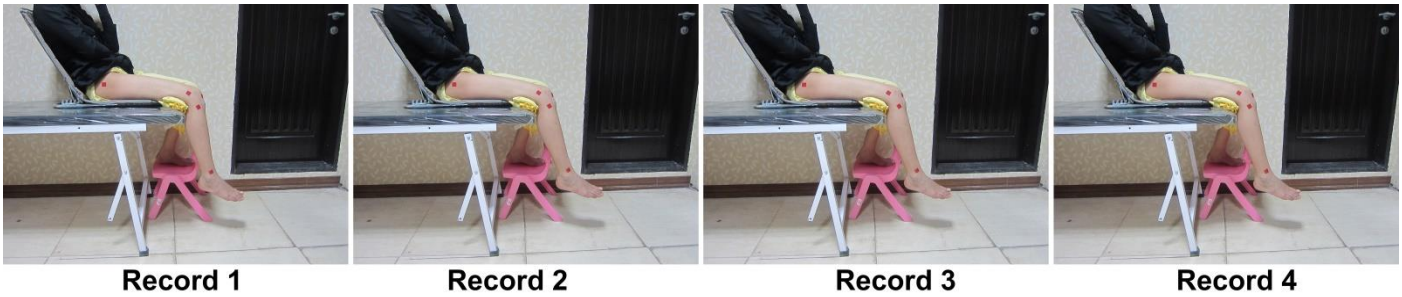

Figure 3. Imaging steps of four repetitions of knee flexion to reconstruct and determine the sense and understanding of the position of the knee joint (recording 1 was the reference image).

Variable error (*VE*) is the root mean square of the difference between the reconstructed joint angle and the set angle minus the square of the constant error. According to the following formula, B is the values of the placement of the joint marker on the x and y coordinate in the spatial reconstruction of the joint. A is the placement values of the marker in the selected conventional domain and K is the number of times the test is conducted; in addition, CE is a constant error. $VE=\sqrt{}= [\Sigma (B-A)^2/K]-(CE)^2$.

Thus, the four repetitions of the detailed reconstruction with the reference range were calculated and compared by the software; in addition, the error values were calculated.

Absolute error (AE) is the mean absolute value of the difference between the reconstructed joint angle and the specified angle. According to the following formula, B is the values of the placement of the joint marker on the x and *y* coordinate axis. In general, it is the spatial reconstruction of the joint. A is the placement values of the marker in the selected conventional domain. K is the number of times the test is conducted. $AE = \Sigma(B-A)/K$

Constant error (CE) is the mean difference between the reconstructed joint angles and set angle. According to the following formula, B is the values of the placement of the joint marker on the x and y coordinate axis; in general, it is also the spatial reconstruction of the joint. *A* is the placement values of the marker in the selected conventional domain. *K* is the number of times the test is conducted. $CE=\Sigma(B-A)/K$.

Statistical Analysis

The data were analyzed by SPSS software version 21 and the normal distribution of the variables was evaluated by Smirnov-Kolmogorov test. Descriptive statistics calculations consist of determining the mean and standard deviation. A comparison test was performed with repeated measurements between three

stages of the menstrual cycle; additionally, hormone changes, the absolute values, constant, and variable errors were evaluated.

RESULTS

The anthropometric data are according to table 1. There are no significant differences in demographic data. Research variables were measured in three states, namely follicular (before the cycle) ovulation (during the cycle) and luteal (after the cycle).

Table 1. Demographic information of test participants (n= 15).

Variables	Mean	SD	Minimum	Maximum
Age (year)	34.46	3.42	25	45
Height (cm)	161.3	4.99	150	179
BMI (Kg/m^2)	25.4	2.93	17.1	34.2

After the assessment of the normal distribution (KS), it was shown that all the variables (constant, absolute and variable errors) distribution between normal and multiple tests measurements were compared in three phases of the menstrual cycle (Table 2). There was no significant difference in the angles of the knee extension (opening) as a reference for assessing the joint perception error. This indicated the test's accuracy and the level (P = 0.482).

Table 2. Comparison between the menstrual cycle phases on the reconstructed state in constant, absolute, and variable errors of the perception of the knee extension state reference (n=15).

Multivariate Tests						
Effect Refrence	Value	F	Hypothesis df	Error df	P Value	Partial Eta Squared
Hotelling's Trace	0.119	0.772	2.000	13.000	0.482	0.106

The data in Table 3 is illustrated the comparison of three conditions before, during and after the menstrual cycle. A significant difference was observed in the constant error of the sense of knee extension at different stages of the menstrual cycle (p = 0.007).

Table 3. Multivariate Tests for the knee extensions, constant joint position sense error (n=15).

Effect	Value	*F*	Hypothesis *df*	Error df	*P* Value	Partial Eta Squared
Hotelling's Trace	1.145	7.445	2.000	13.000	**0.007**	0.534

Based on the data in Table 4, Postoperative test of constant error knee extension of the sense of position was observed, the constant error during ovulation is much greater than before (follicular) and after (luteal). In fact, the error changes are greater at this stage and the average of these changes is close to zero. The lowest error of changes was seen in the follicular stage (P =0.001).

Table 4. Knee extension post hoc test comparison between three phases for constant joint position sense error in the knee extension movement (n=15).

		Mean difference	Standard deviation	*P* Value	Low limit	Upper limit
Follicular phase	Ovulation phase	-7.144	1.791	**0.001**	-10.985	-3.303
	Luteal phase	-3.596	2.386	0.154	-8.713	1.521
Ovulation phase	Luteal phase	3.548	2.529	0.182	-1.876	8.972

Based on the data in Tables 5 and 6, no significant difference was observed in absolute error and variable sense of knee extension at different stages of the menstrual cycle (Figure 4A).

Table 5. Multivariate Tests for the knee extensions, absolute joint position sense error (n=15).

Effect	Value	F	Hypothesis df	Error df	P Value	Partial Eta Squared
Hotelling's Trace	0.289	1.881	2.000	13.000	0.192	0.224

Table 6. Multivariate Tests for the knee extensions, variable joint position sense error (n=15).

Effect	Value	F	Hypothesis df	Error df	P Value	Partial Eta Squared
Hotelling's Trace	0.234	1.520	2.000	13.000	0.255	0.190

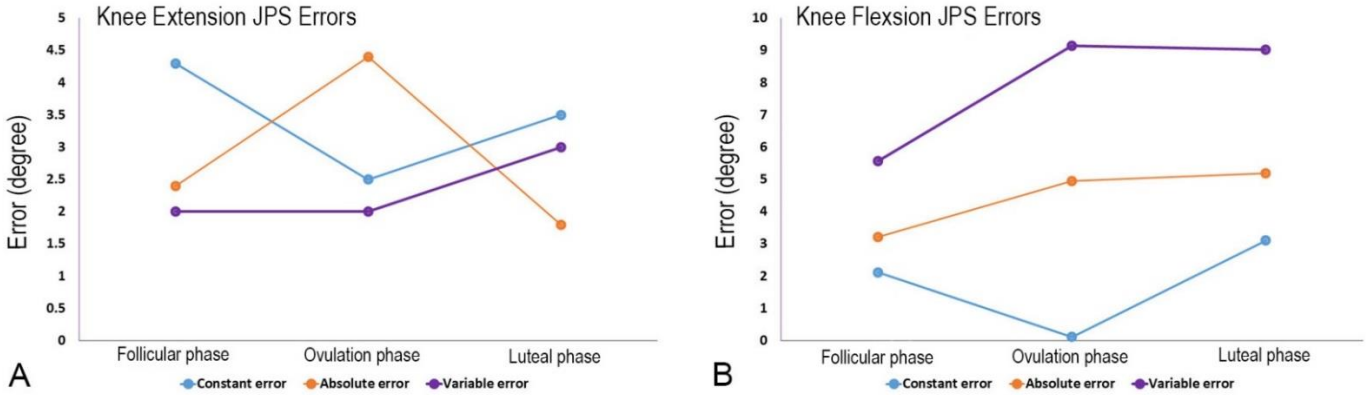

Figure 4. (A) Knee extension, constant error, Absolut error, variable error (n=15). (B) Knee flexion, constant error, Absolut error, variable error (n=15).

General Findings Extension JPS KNEE Proprioceptive:

Constant Error: Ovulation

Absolut Error: -

Variable Error: -

Based on the data in Table 7, there is no significant difference in the angles of flexion of the knee in comparison to reference for evaluating the error of joint perception. This indicates the accuracy and the level of the test (P = 0.370).

Table 7. Knee flexion at reference angle (n = 15).

Multivariate Tests						
Effect Refrence	Value	F	Hypothesis df	Error df	P Value	Partial Eta Squared
Hotelling's Trace	0.165	1.075	2.000	13.000	0.370	0.142

Based on the data in Table 8, a significant difference was observed in the constant error of the sense of knee flexion at different stages of the menstrual cycle. The constant error of continuation test the sense of knee flexion status in Table 9 shows that the most error is in the luteal stage, the error occurs in one direction.

Table 8. Multivariate Tests for the knee flexion, constant joint position sense error (n=15).

Effect	Value	F	Hypothesis df	Error df	P Value	Partial Eta Squared
Hotelling's Trace	0.846	5.501	2.000	13.000	**0.019**	0.458

Table 9. Comparison between three phases for constant joint position sense error in the knee flexion movement (n=15).

		Mean difference	Standard deviation	P Value	Low limit	Upper limit
Follicular phase	Ovulation phase	2.004	0.653	**0.008**	0.603	3.405
	Luteal phase	-0.995	1.78	0.587	-4.827	2.838
Ovulation phase	Luteal phase	-2.99	1.706	0.101	-6.65	0.661

Based on the data in Table 10, a significant difference was observed in the absolute error of the sense of knee flexion at different stages of the menstrual cycle. The Absolute error of continuation test the sense of knee flexion in Table 11 shows that the most error is in the luteal stage.

Table 10. Multivariate Tests for the knee flexion, absolute joint position sense error **(**n=15).

Effect	Value	F	Hypothesis df	Error df	P Value	Partial Eta Squared
Hotelling's Trace	0.761	4.949	2.000	13.000	**0.025**	0.432

Table 11. Comparison between three phases for absolute joint position sense error in the knee flexion movement (n=15).

		Mean difference	Standard deviation	P Value	Low limit	Upper limit
Follicular phase	Ovulation phase	-1.73	0.722	0.31	-3.278	-0.182
	Luteal phase	-1.983	1.23	0.131	-4.636	-4.636
Ovulation phase	Luteal phase	-0.253	1.57	0.874	-3.621	3.115

Based on the data in Table 12, a significant difference was observed in the error of the variable sense of knee flexion at different stages of the menstrual cycle. The variable sense of continuation test of the sense knee flexion status in Table 13 shows that the most error is in the luteal stage (Figure 4B).

Table 12. Multivariate Tests for the knee flexion, variable joint position sense error (n=15).

Effect	Value	F	Hypothesis df	Error df	P Value	Partial Eta Squared
Hotelling's Trace	1.073	6.976a	2.000	13.000	**0.009**	0.518

Table 13. Comparison between three phases for variable joint position sense error in the knee flexion movement (n=15).

		Mean difference	Standard deviation	P Value	Low limit	Upper limit
Follicular phase	Ovulation phase	-3.567	1.204	**0.010**	-6.149	-.984
	Luteal phase	-3.437	2.129	0.129	-8.003	1.128
Ovulation phase	Luteal phase	0.129	2.712	0.963	-5.687	5.945

General Findings Flexion JPS KNEE Proprioceptive:

Constant Error: Luteal
Absolut Error: Luteal
Variable Error: Luteal

Based on the data in Tables 14 and 15, no significant difference was observed in estrogen and progesterone levels at different menstrual cycle phases (P = 0.431 and P = 0.064, respectively). This indicates the accuracy of measuring the estrogen and progesterone levels at different menstrual cycle phases.

Table 14. Multivariate Tests for the estrogen level at different phases of the menstrual cycle **(**n=15).

Effect		Value	F	Hypothesis df	Error df	Sig.	Partial Eta Squared
Est	Hotelling's Trace	0.146	0.946	2.000	13.000	0.413	0.127

Est: estrogen.

Table 15. Multivariate Tests for progesterone level at different phases of the menstrual cycle **(**n=15).

Effect		Value	F	Hypothesis df	Error df	Sig.	Partial Eta Squared
Prog	Hotelling's Trace	0.525	3.414	000	13.000	0.064	0.344

Prog: progesterone.

DISCUSSION

Numerous factors can affect the proprioceptive sense of the joints. These factors include gender, age, anatomical and structural orientation, genetic factors, neuromuscular factors, and hormonal factors. This project was aimed to investigate the effects of estrogen and progesterone in different phases of the menstrual cycle (follicular, ovulation, luteal) of healthy women on the sense of perception and cognition of the proprioceptive sense of the knee and hip joints. Studies have shown that steroid receptors in the hypothalamus and limbic system of the hippocampus and cerebral cortex not only increase neuronal excitability but also protect and divide neurons in these areas [15,16]. Evidence has shown that high concentrations of estrogen in the hippocampus causes interferences. Acetylcholine is said to play a crucial role in the brain synaptic transmission. α7- and α4β2-nicotinic acetylcholine receptors are two receptors which are abundant in the brain hippocampus. These receptors play an essential role in supportive and learning functions. One of the causes of Alzheimer's is binding of amyloid plaques to α7 receptors, which causes memory loss. Today, hormone therapy is used to cure Alzheimer's by injecting estrogen into the hippocampus. This causes acetylcholine to bind to the α7 receptor in the competition between amyloid plaques and acetylcholine for binding to the α7 receptor, thereby it increases synaptic transmissions. Therefore, it can be predicted that high concentrations of estrogen increase acetylcholine-dependent synaptic transmissions, and this will increase the probability of a failure in synaptic transmissions [17].

Estrogen can inhibit the stimulatory activity of glutamate in the brain in two ways: The first is the effect on NMDA receptors, and the second is the effect on glutamate transporter receptors (EAATS) [18]**.** Following stroke, the release of the neurotransmitter glutamate increases exponentially. Today, one of the most important treatments to reduce the effects of stroke is the infusions of estrogen into the hippocampus. Injectable estrogen binds to NMDA receptors, and as a result it reduces the activity of these receptors and prevents the excitatory activity of glutamate in the cell [19].

Evidence has shown that estrogen increases the expression of glutamate transporters and receptors, which are the most abundant transporters in the hippocampus. These receptors reduce the accumulation of glutamate in the synaptic space [20]. Based on the above-mentioned data, it can be predicted that in the ovulation phase it decreases due to high estrogen concentration or glutamate receptor activity or it affects the proprioception due to the increased expression of glutamate receptors in the hippocampus. This causes failure in the proprioception of the knee joints. GABA is the most important neurotransmitter in the brain. The d GABA receptor density in different areas of the brain, especially in the hippocampus, is very high. Previous studies have shown that GABA receptors are affected by sex hormones. Therefore, the hormone estrogen increases the inhibitory activity of GABA [21]. Based on these data, it can be predicted that in the ovulation phase, high concentrations of estrogen increase the inhibitory activity of GABA in the hippocampus. This can be one of the reasons for the failure in the proprioceptive senses during the ovulation phase. Recently, It has been determined that the high level of estrogen in women during ovulation is directly involved in slowing down and their concentration problems. In fact, high levels of estrogen have also been shown to interfere with women's ability to concentrate. This article states that high concentrations of estrogen definitely inhibit the ability of cognitive concentration in female mice [22].

Estrogen and progesterone sometimes work in opposite ways to modulate each other's activity. The contrasting effects between estrogen and progesterone have been demonstrated by the fact that progesterone can inhibit increased ridges density in the hippocampus. Progesterone reduces the increase in estrogen-induced spatial memory in female rodents whose ovaries have been removed. Recent results reveal that progesterone inhibits the protective effects of estrogen on hippocampal neurons. In fact, progesterone inhibits estrogen signaling in the cell [23]. Studies on progesterone show that this hormone reduces neural stem cells and dentate gyrus in the hippocampus. In general, the neurosteroid metabolite of progesterone is

important for neurogenesis in cells, hippocampal neurons, and stem cells of the cerebral cortex [24,25]**.** Increased progesterone levels during the luteal phase of the menstrual cycle are considered to be partly responsible for negative mood changes. Although ovarian steroids are needed to initiate premenstrual symptoms, they are thought to have different sensitivities to GABAergic receptors. Evidence has shown the association of progesterone with the adverse mood symptoms of postmenopausal women, indicating that postmenopausal women are exposed to high concentrations of allopregnanolone. The concentration of progesterone in the amygdala, cerebellum and hypothalamus in fertile women in the luteal phase of menstruation is significantly higher after menopause. These data suggest that the pattern of steroid secretion during certain menstrual cycles branches out from certain tissues of the brain [26].

Electron microscopy studies showed the presence of non-nuclear progesterone receptors in the glia and dendritic ridges. Progesterone can also act directly on GABAergic receptors to enhance GABA inhibition, thereby countering the effects of estrogen [27]. Studies have also shown that most progesterone-A receptors are present in the hippocampus and frontal cortex of female rats. Findings in female rats show that the expression of progesterone-A receptors specifically increased by estrogens in the cerebellum. In the hippocampus and olfactory bulb of rats, estrogen increases the expression of type A receptors. The findings also indicate the role of progesterone along with a combination of 17β-estradiol in regulation function and behavior [28]. A large body of evidence from basic science studies about the body shows that progesterone is effective in reducing the neurological effects of brain injuries. Recent studies have shown that in people with brain damage, injecting progesterone into the hippocampus improves cognitive status. Progesterone also inhibits inflammation and apoptosis [29].

According to the information listed, it can be inferred that the effects of progesterone on the hippocampus are enormous. Since the hippocampus is one of the most affected areas in the proprioception, it can be said that it is possible that the hormone progesterone, through binding to the A receptor on the hippocampus, can affect proprioceptive sense at high concentrations [30]. In addition, Studies have also shown that postmenopausal women are more vulnerable to cognitive impairment than young women [31]. Moreover, in studies conducted on anterior cruciate ligament (ACL) injury, it has been found that the amount of ACL injury in women is much higher than men. In addition, the most injuries were observed in female athletes on days 9, 14 and 28 of menstruation. These are the days when the highest concentration of estrogen is experienced during the cycle [4].

According to the results of this project, based on statistical data, the largest proprioceptive error in knee flexion was observed in the luteal stage. These results may be evidence of the effects of high concentrations of progesterone on proprioceptive senses. Although the exact mechanism of the effects of progesterone on proprioception is still unknown, further studies are required to study on the impact of changes in progesterone concentrations during the menstrual cycle in women. In addition, no scientific study has been done regarding the impacts of this hormone on proprioception. However, based on past studies on the impacts of this hormone on the hippocampus, several possible suggestions for proprioception failures due to high concentrations of progesterone can be made:

1. Increased progesterone reduces dendritic ridges in the hippocampus [32]. This results in a decrease in proprioceptive senses and as a result increases the error in this sense.

2. The effect of progesterone on GABA receptors in the hippocampus. As mentioned earlier, progesterone modulates GABA inhibitory activity. The result is increased inhibitory activity in the hippocampus. This can affect GABA receptors in the hippocampus at high concentrations of progesterone [33]. As a result, because of increased GABA inhibitory activity, the proprioceptive sensory system is less able to perform its cognitive functions. This causes errors in the sense of proprioception.

3. Previous studies have shown that increasing progesterone concentrations affect glutamate release and reduce the secretion of this neurotransmitter in the hippocampus. This reduces the excitability of neurons. As mentioned before, epilepsy is more common in men than women. Perhaps one of the reasons for this is that there is less progesterone in men than in women. In a form of epilepsy called menstrual epilepsy, patients usually develop epileptic seizures in the menopausal phase, which are mainly due to decreased progesterone levels. Today, one of the most effective hormone therapy methods for epilepsy is the infusion of progesterone into the hippocampus. Due to the inhibitory effects of this hormone, excessive secretion of glutamate is prevented [34,35].

There is not enough evidence to suggest how this mechanism works. However, some findings suggest that progesterone inhibits the production of the neurotransmitter glutamate by affecting the enzyme glutamate syntheses [36]. Based on this information, it can be predicted that increasing the concentration of progesterone in the luteal phase reduces the release of glutamate-stimulating neurotransmitter [35]. This can reduce the responsiveness and irritability of the proprioceptive sense systems in the hippocampus and result in an error in processing the senses of the condition transmitted from the knee joints.

Astrocytes have been proved to be vital for normal CNS function [37]. Evidence also demonstrated that one of the causes of cognitive impairment in patients with diabetes has been due to increased GFAP expression. In diabetes, there is a change in the function of astrocytes that results in metabolic and oxidative disorders in glial cells, which is followed by an increase in GFAP. Studies have also revealed that in people with diabetes the sense of proprioception has drastically decreased. This may be due to excessive presence of GAFP in the central nervous system. On the other hand, new findings have shown that progesterone increases GFAP in the central nervous system [38].

Research also shows that during the stress cycle, dentate gyrus in the hippocampus expresses a variable amount of this protein. This is accompanied by different sizes of astrocytes [39,40]. Based on this information, it can be predicted that as the concentration of progesterone in the luteal phase increases, glial fibrillary acidic protein (GFAP) reduces. This can reduce the responsiveness and irritability of the proprioceptive sense systems in the hippocampus. This result in an error in processing the proprioceptive sense transmitted from the knee joints. Few studies have been performed on the acute effects of progesterone on synaptic flexibility.

CONCLUSION

Knee extension, the most constant error of the position sense can be seen in the ovulation phase. Absolute error and variable error have not been observed in the three phases of the menstrual cycle. However, constant error becomes significant when absolute error and variable error makes sense. This is because this error indicates the dominance of the error in one direction and after the error is identified, it becomes absolute and variable. Therefore, in knee extension no error was reported in three phases. Knee flexion was significantly different in the luteal phase in all three absolute constant and variable errors. Therefore, knee injuries are more likely to occur in flexion movements than in extensions. It can be predicted that the concentration of sex hormones, especially progesterone, reduces the sense of recognition of the knee. This happens as these it affects their receptors on the hippocampus, and, as a result, it impairs the reconstruction of the target angle. Therefore, according to the results of this study, it is possible that the increase in the concentration of female sex hormones in the ovulation and luteal phases compared to the follicular phase affects the hippocampus and this causes impaired movement control and increased joint stiffness.

It is possible that the increase in error is considered a reduction in the degree of freedom in the central control system on the joints and flexibility is reduced as we are doing sports or as we are in competitions. The joint is very stable and does not interact with external forces and lose the ability to absorb incoming forces and gets hurt. This increase in error along with an increase in the concentration of sex hormones during the late follicular phase (Day 9) and the ovulation phase (Day 14) and the luteal phase (Day 28) causes changes in joint control and joint rigidity and injury in athletes. However, the exact mechanism of the effects of sex hormones on proprioceptive sense is still unknown, and the study of the effects of changes in sex hormone concentrations during the menstrual cycle in women requires further studies. In this study, brain structures affected by high concentrations of sex hormones were not studied. However, this study paves the way for future studies to determine the exact mechanism of the effects of estrogen and progesterone in determining the mechanisms involved in the proprioceptive sense changes associated with different concentrations of these steroid hormones.

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