The Effect of Disturbance of Menstrual Cycle on The Sleeping Cycle.

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Abstract— Background: The menstrual cycle is a cyclic change that occurs every month and causing changes in the hormones that can affect other body's systems and organs. Normally, the changes in sex hormones especially the progesterone cause an elevation in the body temperature which in turn cause a decrease in REM sleep. Also in addition to that, it acts on the progesterone-receptors agonist and this well reduces REM sleep and increase REM onset latency (ROL).

Objective: In this article we will show the normal relation between the menstrual cycle and sleep cycle, in addition, will illustrate how can a menstrual disturbance cause a sleep disturbance.

Method: Books and researchers available on the PubMed and other scientific websites such as Up to date, WebMD and Medscape were used in the preparation of this review.

Conclusion: Many studies on healthy women concluded there is an increase in non-REM sleep, stage 2 sleep, slow wave sleep (SWS), spindle frequency activity(SFA), wake after sleep onset (WASO) and microarousals/hour, while REM sleep decreased during the luteal phase. However, women who had a premenstrual syndrome have an increase in stage 2 of sleep and decrease the REM sleep, stage 3 of sleep, and SWS.

Index Terms— Menstrual cycle. Sleep cycle. Menstrual disturbance. Sleep disturbance. The effect of menstrual disturbance on the sleep cycle.

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1. INTRODUCTION:

The changes that females going into their bodies such as accelerated growth, breast budding, pubic hair, axillary hair, and menarche all are contained in the development of secondary sexual characteristics that influenced by hormonal changes. These a complex process called puberty. Puberty characterized by hormonal changes that influence physical and psychological changes [1].

Menarche means the first time of menstruation and it occurs after 2 to 2.5 years of puberty [2]. The menarcheal age in Middle Eastern Countries such as Egypt, in Cairo, was 12.59 for high-class girls, 13.09 in middle-class girls and 13.89 in rural agricultural areas. In Jordan, it was 13.79 and in Iran, was 12.5 years [3]. Shaik et al state that the average age of menarche among student girls aged between 9-16 years in Riyadh was 12.08. In the other areas of Saudi, the average menarcheal age were 15.1 years in Jeddah and 13.07 and 13.81 in Asir.

Menstrual cycle it is cyclic and ordered changes in the endometrium occurs every month. It is caused by special hormones that are secreted by the hypothalamus, pituitary gland, and ovaries. The menstrual cycle has two phases, follicular and luteal phase [4].

Also, it affects different body organs, systems, and functions. One of them is the sleep cycle.

Sleep cycle composed of two phases rapid eye movement (REM sleep) and slow wave sleep (non-REM sleep). The onset of sleep is affected by two factors the circadian rhythm and the homeostatic factor related to the length of time since previous sleep. When a person falls asleep he enters the non-REM stage during which he goes through stage 1,2 and 3 to reach stage 4. The order of this stages is reversed suddenly to reach stage 1 again. Stage 1 is followed rapidly by REM sleep and lasts few minutes and this complete a cycle of sleep. We normally spend 4-5 cycles in every time we sleep. REM stage comprises 20-25% of the cycle while non-REM comprise 75-80% of the cycle [24], [25], [26].

According to Baker and Driver, the quality of sleep is lowest during the menstrual cycle, but the time and composition of sleep remain relatively stable. Normally, there is an increase in spindle frequency activity and a minor decrease in rapid eye movement sleep in the luteal phase [5].

2. OBJECTIVE:

The aim of this review article is to understand the effect of disturbance of menstrual cycle on the sleeping cycle, so to achieve this we must be aware of:

1. The anatomy of uterus and ovaries.
2. Anatomy of the hypothalamus and pituitary gland.
3. What are the menstrual cycle, its regulation, and

disturbance?

4. What are the sleep cycle, its regulation, and disturbance?
5. The relation between sleep cycle and menstrual cycle.

3. List of abbreviation:

(GnRH)	gonadotropin-releasing hormone.
(LH)	luteinizing hormone.
(FSH)	follicle stimulating hormone.
(FP)	follicular phase.
(LP)	Luteal Phase.
(AUB)	abnormal uterine bleeding.
(DUB)	Dysfunctional uterine bleeding.
(REM sleep)	rapid eye movement.
(non-REM sleep)	slow wave sleep.
(EEG)	encephalogram.
(VLPO)	ventrolateral preoptic nucleus.
(SCN)	suprachiasmatic nucleus.
(SPZ)	subpara ventricular zone
(DMH)	dorsomedial nucleus of hypothalamus.
(RAS)	reticular activating system.
(ICSD-3)	International classification of sleep disorders-third edition.
(CRSD)	Circadian rhythm sleep–wake disorders.
(SE)	sleep efficiency.
(SOL)	sleep onset latency.
(SWS)	slow wave sleep.
(WASO)	wake after sleep onset.
(SFA)	spindle frequency activity.
(ROL)	Rapid eye movement sleep onset latency.
(PMS)	Premenstrual Syndrome.
(PMDD)	Premenstrual dysphoric disorder.

4. Literature Review:

4.1. Anatomy of the uterus and the ovaries :

Clarke and Khosla[6] state that the reproductive system of a female is a complex multi-organ system includes the hypothalamus, pituitary gland, ovaries, uterus, and vagina. (Fig. 1).

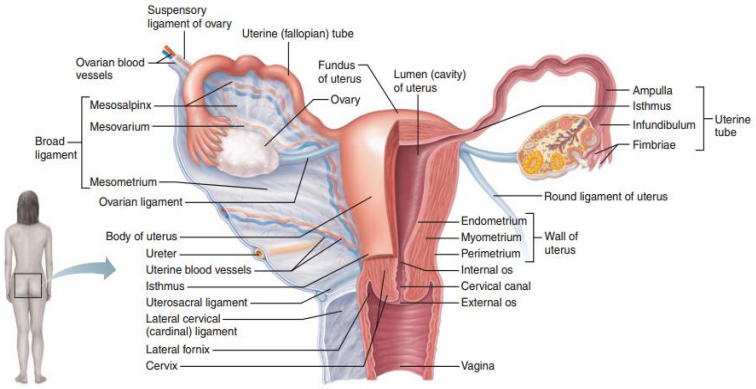

Fig. 1: Female reproductive system.

Resource: Elaine N. Marieb, Patricia Brady Wilhelm, Jon Mallatt. Human Anatomy. Sixth Edition. media update. Pearson Benjamin Cummings.2012.

The uterus is defined as a hollow, pear-shaped organ. It has a thick muscular wall which is divided into 3 layers: perimetrium (outer serosa), myometrium (middle muscular layer), and the endometrium (inner mucosa) [7], [8]. The uterus composed of the fundus that lies above the entrance of the fallopian tube, a body that lies below the entrance of the fallopian tube, and the cervix which is the narrowest part of the uterus and it penetrates the anterior wall of the vagina so is divided into supravaginal and vaginal parts. The cavity of uterine body communicates with the cervical canal through the internal os and the cervical canal, in turn, communicates with the vagina through the external os. The uterus is known as the site for the attachment and nutrition of the fertilized ovum [8].

Ovaries are paired organs that lie within the ovarian fossa against the lateral wall of the pelvis and fixed by external iliac vessels superiorly and internal iliac vessels posteriorly. The ovaries are small, oval-shaped, grayish in color and it contains the ova and releases it when it becomes mature. Also, It secretes steroidal hormones such as estrogen and progesterone. The ovaries are quite variable in position and it suspended by three ligaments which are mesovarium attach the ovary to the back of the broad ligament, suspensory ligament attaches the ovary to the lateral wall of the pelvis, and round ligament that connects the lateral margin of the uterus to the ovary [8], [9].

4.2 Anatomy of the hypothalamus and pituitary gland:

One of the complicated systems in our body is the limbic system which is located in a border zone between the cerebral cortex and the hypothalamus. It can be categorized into the limbic lobe and subcortical limbic structure. Limbic lobe composed of the subcallosal gyrus, cingulate gyrus, hippocampal formation (hippocampus, dentate gyrus, and parahippocampal gyrus), uncus, and orbitofrontal cortex. However, the subcortical limbic structures include the amygdala, Septal area, anterior nuclei of the thalamus and the hypothalamus[10], [11]. Hypothalamus and its connections with the autonomic nervous system can control

the endocrine system that influences different aspects of emotional behavior.

The hypothalamus is the ventral part of the diencephalon. It lies above the pituitary gland and below the thalamus and extends from the optic chiasma anteriorly to the mammillary body posteriorly. It forms the inferior and the lateral walls of the third ventricle. Lechan Toni [12] states that:
"hypothalamus can be divided into four surfaces: a lateral surface contiguous with the thalamus, subthalamus and internal capsule, the latter dividing the hypothalamus from the corpus striatum; a medial surface extending to the wall of the third ventricle, covered by ependymal cells; a superior surface corresponding to the hypothalamic sulcus that separates the hypothalamus from the central mass of the thalamus; and an inferior surface that is in continuity with the floor of the third ventricle."(Fig. 2)

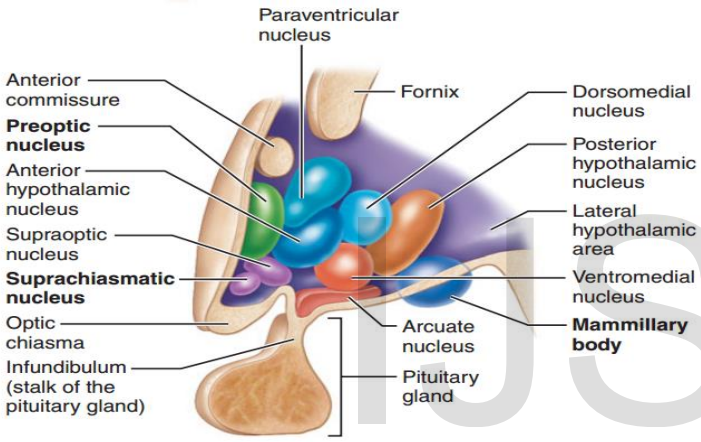

Figure 2: The nuclei of the hypothalamus.

Resource: Elaine N. Marieb, Patricia Brady Wilhelm, Jon Mallatt. Human Anatomy. Sixth Edition. media update. Pearson Benjamin Cummings.2012.

The nuclei of the hypothalamus are arranged into the medial and lateral zone by imaginary parasagittal plane. Within the plane, the anterior column of the fornix and the mammillothalamic tract divide the hypothalamus into medial, lateral and periventricular regions. The medial zone contains the anterior nucleus, preoptic nucleus, suprachiasmatic nucleus, paraventricular nucleus, dorsomedial nucleus, ventromedial nucleus, arcuate nucleus and posterior nucleus. However, the lateral zone contains part of the preoptic nucleus, part of the suprachiasmatic nucleus, supraoptic nucleus, lateral nucleus, tuberomammillary nucleus and lateral tuberal nucleus [10], [12].

The pituitary gland is a pea-sized endocrine gland that lies in the sella turcica of the sphenoid bone at the base of the skull. It is the master gland of the human body because it controls the activity of the other glands, maintains homeostasis, and maintains the reproductive cycle. It has two lobes: anterior lobe (adenohypophysis) and posterior lobe (neurohypophysis). Adenohypophysis releases thyroid stimulating hormone, corticotropin, luteinizing hormone, follicle stimulating hormone, growth hormone, and prolactin directly into the blood through the sinusoids that run between the cells. It is regulated by the hypothalamus via the portal vascular system (also known as Hypothalamic Tuberoinfundibular System) that receive the releasing hormone and release-inhibitory hormones from the neurosecretory cells located in the medial zone. However, the neurohypophysis releases oxytocin and vasopressin from axon terminals that originate in cell bodies located in the hypothalamus mainly supraoptic nucleus and paraventricular nucleus. When the oxytocin and vasopressin reach to the neurohypophysis through the Hypothalamic Neurohypophysial Tract they absorbed by the fenestrated capillaries into the bloodstream. [13], [14], [15].(Fig. 3)

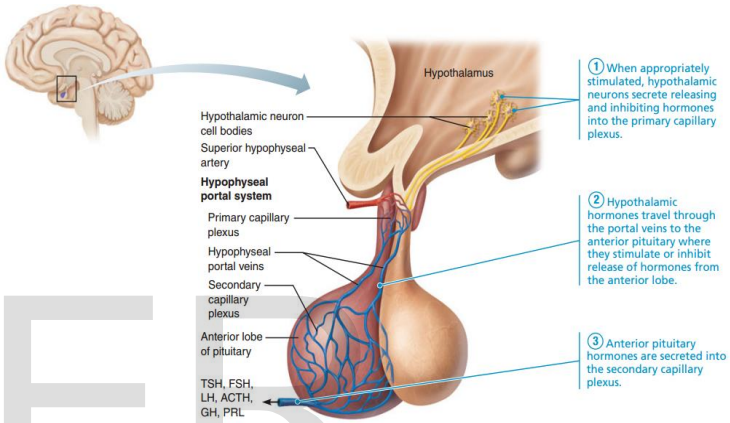

Fig. 3-A: The Hypothalamic Tuberoinfundibular System.

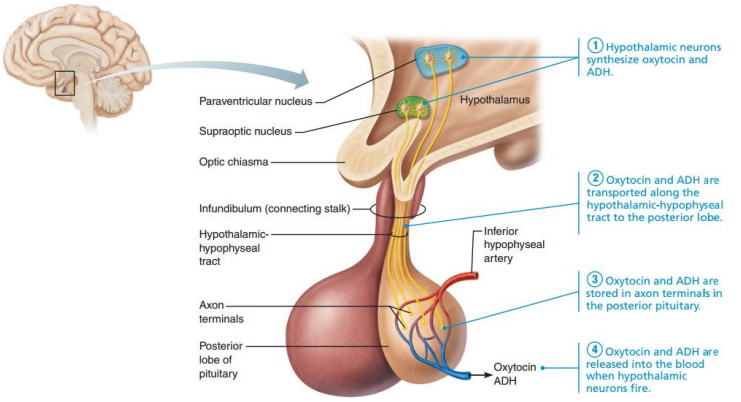

Fig. 3-B: the Hypothalamic Neurohypophysial Tract.

The figure 3-A shows the connection between the hypothalamus and anterior lobe of pituitary gland. While the figure 3-B shows the connection between the hypothalamus and posterior lobe of pituitary gland.

Resource: Elaine N. Marieb, Patricia Brady Wilhelm, Jon Mallatt. Human Anatomy. Sixth Edition. media update. Pearson Benjamin Cummings.2012.

4.3 The menstrual cycle:

A menstrual cycle is rhythmic changes in the rate of female hormones secretion and the corresponding changes in reproductive organs that occurs every month [15]. The female hormones include gonadotropin-releasing hormone (GnRH) that secreted in a pulsatile modality from the hypothalamus mainly from two areas: 1- the arcuate nuclei in the mediobasal area; 2-preoptic area of the anterior hypothalamus. Gonadotropic hormones also are considered as a part of female hormones which are follicle stimulating hormone (FSH) and luteinizing hormone (LH) both are secreted from the anterior pituitary gland and finally, the ovarian hormones (estrogen and progesterone) released from the ovary. The GnRH stimulates the release of FSH and LH which in turn stimulate the ovaries to secrete the estrogen and progesterone [16]. The follicular (proliferative) phase and the luteal (secretory) phase are the main phases of the menstrual cycle and the level of female hormones vary during them (see figure 4). The interval between the first day of menstrual bleeding of one cycle to the onset of menses of the next cycle is the length of the menstrual cycle and the average period is 28 days. According to Gerhard and Mark Cline et al " The ovarian cycle comprises follicular maturation during the follicular phase and ovulation and establishment of the corpus luteum during the luteal phase, followed by corpus luteum regression and menstruation" [17].

4.3a The follicular phase:

It starts from the first day of menses till the ovulation. The ovary of a female child involves primordial follicles .primordial follicle composed of ova enclosed by a single layer of granulosa cells that provide nourishment for ovum. After puberty the hypothalamus begins to release GnRH in pulsatile modality to stimulate the anterior pituitary gland to release the FSH and LH [17]. Increase level of FSH and LH help the follicles to grow. When the ova grow and additional layer of granulosa cells appear it becomes the primary follicles. The role of FSH is to accelerates the development of about 20 primary follicle each month and convert them into vesicular follicle. A follicle that grows rapidly forms a mature graffian follicle and the primary oocyte which have a diploid number of chromosomes completes the meiotic division to become with haploid number of chromosomes and converted into secondary oocyte. FSH then stimulate the hypertrophy and hyperplasia of the granulosa cells of the remaining vesicular follicle. Also, it stimulate them to convert the androgen into estrogen while the LH will stimulate the release of estrogen from the theca interna cells . This will elevate the blood level of estrogen [4],[16], [17], [18]. The increase in estrogen level enhance the endometrial epithelial and stroma cells growth accordingly the thickness of the endometrium is greatly increased to become 3-4 mm at the ovulation time [16].

4.3b Ovulation:

It occurs 14 days before the end of menstruation and it randomly occurs from one ovary on each month. LH is increased about 6-10 folds 2 days before the ovulation and this known as LH surge which stimulates luteinization of the granulosa cells. Also, it stimulates the synthesis of progesterone which is responsible for the midcycle FSH surge. The LH surge stimulates resumption of meiosis and the completion of reduction division in the oocyte with the release of the first polar body. At this phase the mature follicle releases proteolytic enzymes and prostaglandin (in response to LH and progesterone) to break down the surface of the ovary in purpose to release the ovum and its associated antral fluid pass from the follicle into the peritoneal cavity. Then the fallopian tube will pick up the released ovum [4],[16], [17], [18].

4.3c Luteal Phase:

At this phase, the follicle of released ovum is converted into corpus luteum and the granulosa cells converted into lutein cells. These changes depend mainly on LH which enhance the growth of corpus luteum. Corpus luteum secretes estrogen, progesterone and inhibition hormones for initiating negative feedback inhibition on the secretion of FSH and LH. The elevated level of the estrogen will increase the cellular proliferation in the endometrium while the elevated level of progesterone will cause obvious swelling and secretory development of the endometrium. So, at this phase the endometrium thickness is 5-6mm. The decrease level of FSH and LH cause a replacement of corpus luteum by fibrous tissues (corpus albicans). Finally, the corpus leteum will degenerates and negative feedback will disappear. So, the anterior pituitary will release FSH and LH to initiate follicles growth and the cycle start again. Before two days of the end of the cycle, the decreased level of estrogen and progesterone lead to necrosis of the endometrium, detachment of endometrium and finally the bleeding occurs. The bleeding will last about 3-5 days and the amount of blood will lost every month is month is about 20-80ml [16]. (Fig. 4)

4.4 Disturbance of menstrual cycle:

The menstrual cycle disturbance can be divided into two main categories:
1)abnormal uterine bleeding. 2)dysfunctional uterine bleeding.
The abnormal uterine bleeding (AUB) is defined by Deligeoroglou et al [20] as "excessively heavy, prolonged and/or frequent bleeding of uterine origin" include menorrhagia means the bleeding lasts more than 7 successive days or the amount of blood loss more than 80 mL, metrorrhagia in which the bleeding is not in regular interval, menometrorrhagia means irregular and heavy

bleeding, and oligomenorrhea in which the menstrual cycle interval is between 41 days and 3month [21]. Dysfunctional uterine bleeding is known as abnormal apoptosis of the endometrium when there is no structural or medical abnormality and usually the cause of it may be anovulation [19].

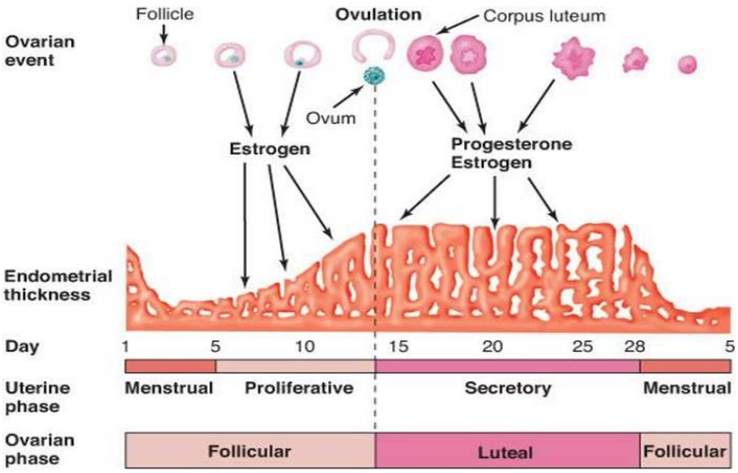

Figure 4: Here we can see the hormonal changes and their associated changes in the follicles and the endometrium.

Resource: Vander's Human Physiology: The Mechanisms of Body Function, 11th ed. McGraw-Hill, 2008.

4.4a Dysfunctional uterine bleeding pathophysiology:

It is not fully understood but it is thought to be due to a problem with the feedback of estradiol to the LH that make the menstrual cycle monophasic and anovulation.
According to Creatsas et al:
"DUB is occurs due to the absence of midcycle LH surge follicle atresia occurs and become cystic, producing only estrogens but not progesterone. During these anovulatory cycles, unopposed estrogens, which are products of ovarian follicles and of the extragonadal aromatization of androstenedione, induce endometrial proliferation. The lack of progestogenic stabilization effect, results in abnormal shedding of the endometrium. Furthermore, the imbalance of prostaglandins (PGs) seems to play a role in ovulatory DUB. During menstruation there is a balance between the vasoconstriction effect of PGF2a and vasodilation of PGE2 and PGI2 (Prostacyclin). Circulating steroid levels have a great influence in endometrial PG release. An increase in total PG release and disproportional rise in PGE2 have been demonstrated in ovulatory DUB" [19].

4.4b Abnormal uterine bleeding pathophysiology:

The pathophysiology of menorrhagia can be either organic, anatomic, and endocrinologic. Julia et al state that if there is no sign of etiological cause of the menorrhagia then it said to be as a result of DUB in which there is absence of midcycle LH surge. When LH surge is lost then the corpus luteum does not form so there is no progesterone secretion while the estrogen will increase the endometrium thickening . The endometrium growing fast so its blood supply will not be enough for it. So, it will degenerate at different levels of the endometrial lining. organic causes maybe infections in the genitourinary origin or coagulation disorder. The endocrine cause may be hyperthyroidism, hypothyroidism, or hypogonadism that occurs due to Prolactin-producing pituitary tumors which affect GnRH release leading to decrease level of LH and FSH. Anatomic causes maybe fibroids and polyps presence, or Endometrial hyperplasia [21].

4.4c Premenstrual Syndrome:

It is a cyclic disorder occurs during the luteal phase due to a change happens in the neurohormones and neurotransmitters regulation. Premenstrual Syndrome is characterized by physical and emotional symptoms. When the symptoms are severe it is considered as premenstrual dysphoric disorder. The symptoms differ from one woman to another and they can manifest with a wide variety of symptoms, including depression, mood liability, abdominal pain, breast tenderness, headache, fatigue, insomnia, and dreamful sleep. PMS is thought to be due to the hormonal changes that happen during the menstrual cycle. Changes in the mRNA expression of central monoamine neurotransmitter and central steroidal hormones receptors, in the limbic system can affect their function and further lead to abnormities in the expression of the key protein(s) in the signal pathways regulated by these receptors [22], [23].

4.5 sleep cycle:

The sleep is defined as temporal unconsciousness during which the person who is in state of sleep is not consciously aware of the external environment but he can be aroused by sensory stimuli or any other stimuli. People spend about one third of their life asleep. Sleep has a circadian rhythm controlled by the biological clock function of suprachiasmatic nucleus. The circadian rhythm coincide with light-dark cycles. It has two types that alternate with each other 1-rapid eye movement (REM sleep);2- slow wave sleep (non-REM sleep). During the sleep this two stages alternate cyclically with each other and absence one of these stages result in the sleep disorders. The encephalogram (EEG) is a graphic record of the spontaneous vibration of brain's electrical activity. The recorded waves are divided in four waves that are generated in different sleep stages and each one of them has its own characteristics [24], [25], [26]. (Fig. 5).

4.5a Slow wave (Non-REM) sleep:

It is the restful stage of sleep that the person experience during the first hour of sleep. When the sleep begins it starts with non-REM sleep and it occupies 75-80% of the sleep cycle. It divided into four stages 1,2,3,4. Stage 1 lasts from 1

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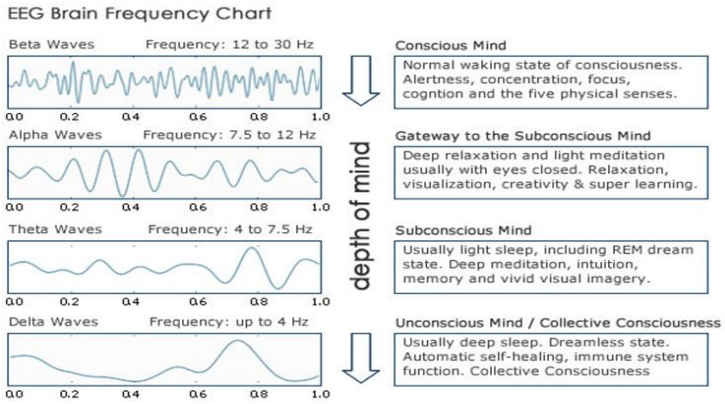

Fig. 5: It shows the changes that occur in the brain electricity during different stages of sleep.

Resource:
https://www.lifeimproving.com/wpcontent/uploads/2014/02/brainwaves_chart.jpg

to 7 minutes and it comprise 2-5%. EEG move from alpha waves to low-voltage, mixed-frequency waves. The EEG wave in this stage is alpha wave which associate with wakeful relaxation state. Stage 2 lasts from 10 to 25 minutes in the initial cycle and prolonged with each successive cycle. It comprise 45-50% of the sleep cycle. EEG shows relatively low-voltage, mixed-frequency activity associated with sleep spindles and K-complexes. Stage 3ans 4 both are referred to slow-wave sleep. Stage 3 last about few minutes and comprise 3-8% of sleep. The EEG shows increased high-voltage, slow-wave activity. Stage 4 lasts 20-40 minutes and comprise 10-15% of sleep.

Also, the stage 4 is the deepest stage of sleep and the person is difficult to aroused by normal stimuli. There is an increased amounts of high-voltage, slow-wave activity on the EEG. There will be a mild reduction in blood pressure (ABP), heart rate, respiratory rate (RR), muscle tone, regional cerebral oxygen consumption, and regional cerebral blood flow [16], [25], [26], [27], [28].

4.5b REM Sleep:

This stage of sleep is associated with the dreams and the brain is quite active. It is not restful occurs at episodes every 90 minutes and last 5-30 minutes. It comprises 20-25% of the sleep cycle. EEG waves at REM sleep are identical to the waves of wakefulness state which are low-voltage, mixed-frequency waves. During REM sleep there are a decrease in muscle tone, irregular heart rate, respiratory rate, and blood pressure, increase in brain metabolism and the brain will be highly activated. Also, there is an irregular muscle movement and rapid eye movement. This stage is important for memory consolidation [16], [25], [26], [27], [28].

4.6 Sleep cycle Regulation:

There are two process that regulate the sleep-wake cycle the first one is Process S (sleep-dependent homeostatic process) and the second one is process C (sleep-independent circadian process). Process S is homeostatic dependent on the interval of the prior sleep and waking. It is induced by the accumulation of sleep-promoting substance such as adenosine. The adenosine acts as homeostatic regulator on the basal forebrain. When the glycogen(which store the body's energy) is exhausted, it breaks down into extracellular adenosine that accumulates at basal forebrain. In the basal forebrain it will inhibit arousal system and excite the ventrolateral preoptic nucleus (VLPO) by inhibiting GABAergic inputs to induce sleep [26], [27], [28]. Process C is independent on the interval of the prior sleep and waking. The circadian rhythm is controlled by suprachiasmatic nucleus (SCN) of the hypothalamus. The SCN is known as "master clock" and it is dependent on the light input during the daytime and the melatonin secretion during the dark cycle to coordinates tissue-specific rhythms [30]. The outputs from SCN are guided to the subparaventricular zone (SPZ) and to the dorsomedial nucleus of hypothalamus (DMH). However, the outputs to VLPO is less. SPZ transmit the inputs from SCN to the DMH and preoptic region to increase the circadian response. DMH has important role in conveying signals from SCN to sleep-regulatory system. Also, It send GABAergic projections to the VLPO nucleus and to glutamate-thyrotropin-releasing hormone afferents to the excitatory lateral hypothalamic area [30]. So, the SCN, SPZ, and DMH play important role in the regulation of circadian sleep behavior (Fig. 6).

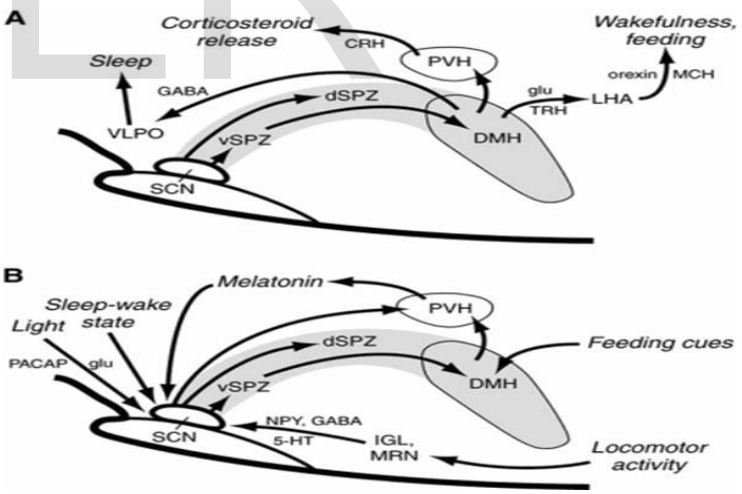

Fig. 6.

Resource: Schwartz JR., Roth T. Neurophysiology of Sleep and Wakefulness: Basic Science and Clinical Implications. Current Neuropharmacology.2008;6(4):367-378. doi:10.2174/157015908787386050.

SCN receive information via the retinohypothalamic fibers to be activated. Then the SCN reduce the activity of paraventricular nucleus during which axons descends to the preganglionic sympathetic neurons of the lateral horn in the spinal cord. The lateral horn cells excite the superior cervical ganglia that project to pineal gland and that will lead to a decrease in the secretion of the melatonin. When the sun sets

the effect of the inhibiting connections decrease to allow the increase of the excitatory connection and that will increase the melatonin secretion. The norepinephrine is released and enhance the second messenger which is the cyclic AMP. Cyclic AMP contribute to the production of melatonin [29]. The initiation of non-REM sleep occurs by active inhibition of the thalamus and cerebral cortex by preoptic nucleus. Preoptic nucleus release GABA-ergic projection to 1- histaminergic neurons in posterior area of the hypothalamus and inhibits their excitatory; 2- facilitatory neurons in the brainstem (Adrenergic neurons in locus locus coeruleus, serotonergic neurons in raphe nuclei, and Cholinergic neurons in the pons) which activate the thalamus and cerebral cortex in a wakefulness state. However, the REM sleep begins by increase the activity of the cholinergic neurons in the dorsolateral area of pons. These cholinergic neurons send excitatory axons to the reticular activating system (RAS) and thalamus leading to activation of the cerebral cortex. REM sleep terminated by increasing the activity of noradrenergic neurons in locus coeruleus and serotonergic neurons in the raphe nucleus. Both of them send inhibitory projections to the reticular activating system (RAS) [26].

4.7 Sleep disturbance:

The sleep disorders are classified into 6 major categories according to the last updated ICSD-3 (International classification of sleep disorders-third edition):

1. Insomnia.
2. Sleep-related breathing disorders.
3. Central disorders of hypersomnolence.
4. Circadian rhythm sleep-wake disorders(CRSD).
5. Parasomnias.
6. Sleep-related movement disorders.

Also, they make another category named by other sleep disorder to put a condition of sleep disorder that not fit in the categories above [32].

Insomnia defined by ICSD-3 [32] "a repeated difficulty with sleep initiation, duration, consolidation, or quality that occurs despite adequate opportunity and circumstances for sleep, and results in some form of daytime impairment." It occurs as a result of hyperarousal experience throughout the day and night and it explained by both cognitive and physiological models. According to the cognitive model worry and excessive thinking of stressful life, events can lead to acute episodes of insomnia especially in initiating sleep and returning back to sleep after waking. When the person experience sleep disturbance in addition to the stressors he had before he starts to develop a concern about not getting enough sleep [33]. However, increase alertness during the day and night make the sleep difficult and there will be an elevated level of all metabolic rate, cerebral glucose metabolism [34]. Sleep disturbance combined with lack or effort of breathing is known as sleep-related breathing disorders. It is divided into four division they are obstructive sleep apnea disorders, central sleep apnea syndrome, sleep-related hypoventilation/ hypoxemia disorders, undefined/non-specific sleep disorders [33], [34]. The ICSD-3 definition of Central disorders of hypersomnolence as " the primary complaint is daytime sleepiness not caused by disturbed nocturnal sleep or misaligned circadian rhythms." It is subdivided into eight categories:

1) Narcolepsy type 1.
2) Narcolepsy type 2.
3) Idiopathic hypersomnia.
4) Kleine-Levin syndrome.
5) Hypersomnia due to a medical disorder.
6) Hypersomnia due to a medication or substance.
7) Hypersomnia associated with a psychiatric disorder.
8) Insufficient sleep syndrome.

The cause of central disorders of hypersomnolence is thought to be as a result of decreased hypocretin that is produced in the lateral hypothalamus and it has an important role in the regulation of the sleep-wake cycle because it enhances the histaminergic, nonadrenergic, serotonergic, and cholinergic systems [36]. CRSDs arise from a" chronic pattern of sleep and wake disturbance that is due to dysfunction of the circadian clock system, or misalignment between the timing of the endogenous circadian rhythm and externally imposed social and work cycles, that result in clinically significant functional impairments" [37]. It is divided into :

1) Alteration of the circadian rhythm itself.
   a) Delayed sleep phase disorder.
   b) Advanced sleep phase disorder.
   c) Irregular sleep-wake rhythm.
   d) Free-running disorder.
2) Jet lag and shift work disorder during which the external environment and/or social circumstances are altered relative to the endogenous circadian clock.

The pathophysiology is not well understood but there are several mechanisms involve long endogenous circadian period that alters the relationship between sleep onset or offset with the timing of other endogenous circadian rhythms, alteration in entrainment mechanisms such as hypersensitivity of melatonin suppression to light at night, altered homeostatic process indicated by sleep deprivation that causes alternation in slow-wave activity and sleep propensity and the last mechanism is the behavioral factors facilitate CRSD [37] . Parasomnia emerges from or associated with sleep. It classified by the state of sleep into NREM parasomnia and REM parasomnia. NREM parasomnias appear to be due to comorbid conditions that stimulate repeated arousal or promote sleep inertia and it includes confusional arousals, sleep walking disorder, and sleep terrors and sleep related eating disorder. REM parasomnia involves sleep behavior disorder and isolated sleep paralysis. REM parasomnia is due to dysfunction of the neurons in the pons that is related to REM sleep so that it sometimes be predictable for neurodegenerative disease [38]. Sleep-related movement disorders are defined as stereotyped movements that occur during sleep or at its onset. It includes:

1) Clinical conditions for example:

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a) Restless legs syndrome.
b) Periodic limb movement disorder.
c) Sleep-related leg cramps.
d) Sleep-related bruxism.
e) Sleep-related rhythmic movement disorder.

2) Physiological movement:
   a) Alternating leg muscle activation.
   b) Excessive hypnic fragmentary myoclonus [39].

4.8 The relation between sleep cycle and menstrual cycle:

There is a number of studies which discussed sleep-wake patterns across the menstrual cycle in healthy women. They found that there is a change in sleep architecture while there is no change in sleep homeostasis and quality. Also, they found that some women report that they have a disturbed sleep during the late luteal phase (LP) and premenstrual days. A systematic study of sleep EEG across the menstrual cycle in healthy women, they record sleep every night through a complete mensural cycle. The result of this study showed no menstrual cycle-related change in sleep efficiency (SE), sleep onset latency (SOL), slow wave sleep (SWS) and wake after sleep onset (WASO). Non-REM (NREM) sleep and stage 2 sleep significantly increased in the LP, while REM sleep significantly decreased in the LP. Also, there are a number of studies compared sleep at different phases across the menstrual cycle (mid-FP versus mid-LP, mid-FP versus late-LP, mid-FP versus mid-LP versus menses). They found significant decrease of REM sleep during mid-LP compared to the mid-FP, latency to stage 3 sleep also decreased during the mid-LP compared to menses, and there is no change for stage 2 sleep and SWS. Sleep comparison at the mid-FP and mid-LP, one study found no significant differences between any sleep parameters (including SE, SOL, REM sleep and SWS), whereas another study showed a significant decrease in REM sleep and significant increase in SWS at the mid-LP compared to the mid-FP [44]. Baker et al state that the healthy women had an increase of WASO and microarousals/hour at late-LP compared to the mid-FP and no other change between menstrual phases [40]. Studies showed that the effect of menstrual cycle on the EEG revealed that there is a decrease on the spindle frequency activity (SFA) during the FP and it increased during late-LP. Boivin and Shechter summarized these findings and they said "the most common sleep findings across the menstrual cycle include decreases in REM sleep, increases in stage 2 sleep and SFA, and no changes in sleep propensity and quality (SOL and SE, resp.) during the LP compared to the FP. Most studies agree with the absence of changes in homeostatic sleep mechanisms (i.e., SWS and SWA) at different menstrual cycle phases, although some inconsistencies remain". Changes that occurs in the LP is thought to be as a result of change in sex hormone profile mainly the progesterone that is secreted from the corpus luteum which cause an elevation in the body temperature that causes a decrease in REM sleep or by acting on progesterone-receptor agonist that reduced REM sleep while lengthening ROL. The increase in the SFA during the LP is due to the neuroactive metabolites of progesterone acting as an agonistic modulators of central nervous system GABAA –receptors in a benzodiazepine-like manner [41].

4.9 The effect of disturbance of menstrual cycle on the sleeping cycle:

A study was done on six healthy controls and three women complain of PMS failed to find a significant difference in any sleep parameter. Another study was done on 18 controls and 23 women complain of PMDD find no difference. They found in both groups increased in ROL while there is a decrease in REM sleep and stage 3 in the LP compared to FP. However, one study compared PMS patient with control group showed that the PMS group had a long stage 2 sleep and less REM sleep also the stage 3 of sleep and intermittent awakenings varied across the menstrual cycle [42]. Lynne et al compare healthy women to a PMS patient and found there is a decrease in SWS and REM sleep. Also, they found an increase in stage 2 sleep during the LP in the two groups [42]. The studies done to show the EEG during the PMS showed no difference in the results from the EEG done on healthy women [41]. So, women with PMS and PMDD have a poor sleep. Poor sleep involves bedtime, sleep quality, sleep onset latency, sleep maintenance and wake time. Women who had PMDD have a poor response to melatonin in their LP compared to FP [43].

5. CONCLUSION:

Sleep cycle normally can be affected by the menstrual cycle during the luteal phase, especially in the late luteal phase. There is an increase in non-REM sleep, stage 2 sleep, SWS, spindle frequency activity, WASO and microarousals/hour, while REM sleep decreased during the luteal phase.

Also, the premenstrual syndrome can affect the sleeping cycle. It can affect the sleep quality and sleep onset latency and there will be a difficulty to maintain sleep and wake time. It causes an increase in stage 2 of sleep, and decrease the REM sleep, stage 3 of sleep, and SWS.

6. CONFLICT OF INTEREST:

The authors have no conflict of interest to declare.

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