

## Sex Hormones and Mental Disorders

Fatma İrem Kahramanoğlu<sup>1</sup> , Ebru Yılmaz<sup>1</sup> , Oytun Erbaş<sup>1,2</sup> 

It has been proven that birth control has an important place in preventive health care, even by looking at the 45% rate of unplanned pregnancy in the USA.<sup>[1]</sup>

Contraceptives are divided into progestin-only and combined forms containing both progestin and estrogen. They are most typically offered as combined preparations.<sup>[2]</sup> Combined hormonal contraceptives (CHCs) include combined oral contraceptives (COCs), vaginal ring, and transdermal patch. CHCs, besides preventing pregnancy, regulate the menstrual cycle, suppress endometriosis, reduce dysmenorrhea, acne, and hirsutism. The standard use of COCs is 21 days parallel to the menstrual cycle starting with the 3rd day of menstrual bleeding and then after a full cycle, medication should not be used for the rest of the month, 7 remaining days.<sup>[1]</sup> The main mechanism of CHCs is based on the progestin content suppressing ovulation. Although the estrogen component also contributes to this suppression, its main function is bleeding control.<sup>[3]</sup>

Over 100 million women worldwide use oral contraceptives (OCs) to prevent pregnancy. OCs

### ABSTRACT

Mental illnesses are widespread, disabling illnesses that cause people to lose years of their lives. Furthermore, there are noticeable differences in occurrence and prognosis between male and female persons in many mental diseases, which appear to be related to sex hormones and hormonal contraceptives. This review focused on hormonal contraceptives and mental disorders, and then the relationship between them. Also reviewed were the effects of the menstrual cycle and hormonal contraceptives on mood.

**Keywords:** Brain functions, hormonal contraceptives, menstrual cycle, mental disorders, mood, oral contraceptives.

contain synthetic forms of progesterone and estrogen in different proportions and have been on the market for more than half a century.<sup>[4]</sup> Types, routes of administrations and functions of hormonal contraceptives are shown in below Table 1.<sup>[5]</sup>

### EFFECTS OF HORMONAL CONTRACEPTIVES ON PHYSIOLOGICAL HORMONE BALANCE

The menstrual cycles and hormone profiles of women using hormonal contraceptives (HCs) are completely different from women with natural cycles. Estradiol (E2) levels follow a level of approximately 30 pg/mL during HCs use.<sup>[6]</sup> Exogenous estrogen prevents ovulation by suppressing Follicle-stimulating hormone (FSH) with a negative feedback mechanism and at the same time thickens the uterus.<sup>[2,7]</sup>

Endogenous levels of progesterone and neurosteroids in the blood also differ in women using HCs.<sup>[6]</sup> The synthetic progestin which is involved in the HCs acts as progesterone and plays the role of a potent agonist of the progesterone

<sup>1</sup>ERBAS Institute of Experimental Medicine, Illinois, USA & Gebze, Turkey

<sup>2</sup>Department of Physiology, Medical Faculty of Demirođlu Bilim University, Istanbul, Turkey

**Correspondence:** Fatma İrem Kahramanođlu. Deneysel Tıp Enstitüsü, 41470 Gebze-Kocaeli, Türkiye.

**E-mail:** ikahramanoglu99@gmail.com

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**Table 1. Types and functions of hormonal contraceptives<sup>[5]</sup>**

Type of the hormonal contraception	Instance	Function
Combined hormonal contraception	Pill Patch Vaginal ring	Suppresses ovulation, thins uterine lining, thickens cervical mucus
Progestin-only hormonal contraception	Pill Injection Intrauterine device Implant	Inhibiting ovulation and making healthy normal cyclic changes in the uterine lining, thickens cervical mucus

receptor with different interactions with the androgen, glucocorticoid, and mineralocorticoid receptors.<sup>[8]</sup> Progesterone does not only suppress Luteinizing Hormone (LH) and FSH but also thickens the cervical mucus and prevents the development of the uterine lining.<sup>[9]</sup> In addition, they have roles in preventing sperm penetration into ovum.<sup>[6]</sup>

Testosterone levels in the blood decrease considerably, regardless of the dose and type of progesterone and estrogen during the HCs use. Conversely, the level of Sex hormone-binding globulin increases, and as a result, the bioavailability of testosterone and E2 further decreases.<sup>[6]</sup>

## MENSTRUAL CYCLE

The menstrual cycle is a rhythmic and natural cycle that includes ovarian follicular development, ovulation, luteinization, luteolysis, and endometrium remodeling that is controlled by various autocrine, endocrine, and paracrine factors in every healthy woman. The onset of menarche is between the ages of 8.5 and 13 in women, after an average of 36 years of reproduction, menopause begins at age of 51.<sup>[10]</sup> Pubarche and axillarche follow thelarche, which is the first sign of puberty, while menarche ends puberty, all of which take about 2.3 years.<sup>[10,11]</sup> Although it has been generally accepted that a healthy woman's menstrual cycle lasts 28 days, this period is very variable in individuals, even at similar ages, it can vary from 25 to 34 days.<sup>[10,12,13]</sup>

A healthy period lasts between 3 and 7 days. Bleeding shorter than 3 days is defined as hypomenorrhea, and bleeding lasting longer than 7 days is defined as hypermenorrhea. In such a situation, it may be necessary to further investigation of depleted iron stores and anemia.<sup>[14]</sup>

## ENDOCRINOLOGY OF MENSTRUAL CYCLE

The menstrual cycle of women is regulated by the hormones and feedback mechanisms that are

secreted and carried out by the hypothalamus-pituitary-ovarian axis.<sup>[4]</sup> Gonadotropin-releasing hormone (GnRH) is secreted pulsatile from the hypothalamus every 1-1.5 hours in the follicular phase, and every 2-4 hours in the luteal phase of the cycle. The secreted GnRH stimulates the pituitary gland and causes the secretion of FSH and LH, which then stimulates the ovarian follicle. While LH affects theca cells, FSH stimulates aromatase synthesis, which converts androstenedione to E2 by affecting granulosa cells. A critical amount of E2 is secreted from the large dominant antral follicle causes GnRH secretion in the hypothalamus, stimulating an increase in LH. With this LH surge, the ovulation event occurs on the 14<sup>th</sup> day of the menstrual cycle. The ovulated follicle transforms into corpus luteum, which secretes progesterone responsible for stimulating the endometrium for implantation in a possible pregnancy.<sup>[14]</sup>

Estrogen and progesterone levels are low at the beginning of the cycle, in the early stages of the follicular phase.<sup>[4]</sup> In the continuation of the follicular phase, E2 secreted from the follicle induces the negative feedback of the hypothalamic-pituitary system.<sup>[15]</sup> Ovulation occurs as a result of the increased LH level with the rising E2 level, and in the following 12 hours, while the progesterone level starts to increase due to the luteinized follicle, the E2 levels decrease. FSH levels, which are too low in the luteal phase, inhibit the growth of a new follicle and the progesterone peak occurs towards the middle of this phase.<sup>[14]</sup> Table 2 shows the regions where sex hormones are secreted from and their functions:<sup>[14-19]</sup>

## EFFECTS OF THE MENSTRUAL CYCLE ON MOOD CHANGES AND BRAIN

Ovarian hormones are important for the cognitive function of the brain as well as for the response to environmental stimuli, and these hormones provide the neuroendocrine

**Table 2. Functions and secretion locations of sex hormones<sup>[14-19]</sup>**

Hormone	Function	Location of secretion
GnRH	GnRH neurons provide pulsatile release of GnRH by converting neural signals they receive from the brain into an endocrine output.	Hypothalamus
FSH	Follicular growth and maturation	Anterior lobe of pituitary gland
LH	Ovulation	Anterior lobe of pituitary gland
Progesterone	Reduction of uterine contractility, improvement of uteroplacental circulation,	ovaries
Estradiol	Negative feedback effect	follicle

GnRH: Gonadotropin-releasing hormone; FSH: Follicle-stimulating hormone; LH: Luteinizing Hormone.

environment that modulates the structure and function of the female brain.<sup>[5]</sup>

The main cause of the mood and mood changes in the menstrual cycle is caused by the sensitivity of the  $\gamma$  aminobutyric acid (GABA) pathway and its metabolite neurosteroids to the changes in the levels of progesterone.<sup>[6]</sup>

Allopregnanolone is a neurosteroid with anticonvulsant and anxiolytic effects, which changes according to the varying progesterone levels in the menstrual cycle, and is affected by progestins in different ways. Although these changes have yet to be explained precisely and clearly, it is important to recognize groups in which such mood disorders are more likely to occur, such as women using oral contraceptives and adolescents.<sup>[6]</sup>

Despite depression and anxiety being more common in women than men, such symptoms are more common in certain periods of life (premenstrual, pregnancy, etc.).<sup>[6,20]</sup> One of the most important organs where the receptors of sex hormones such as estrogen receptor- $\alpha$  and estrogen receptor-, progesterone receptor A and B, and the androgen receptor are the brain, which can help explain sex differences in brain structure. In addition, sex hormones have an effect on the development and plasticity of the brain throughout

life in women.<sup>[6,21]</sup> The effects of some sex hormones on the brain are shown in Table 3.

One of the most prominent effects of menstrual cycle hormones on the brain is the changes in the gray matter volumes of the hippocampus, amygdala, and temporal and parietal lobes.<sup>[31]</sup> These changes can be assumed to be the basis of cyclical behavior changes.

Steroids also affect the brain connection. Although sex hormones were first observed in the hypothalamus,<sup>[32]</sup> it was found that they were also expressed in the limbic system.<sup>[33,34]</sup> Sex steroids stimulate the brain in a variety of cognitive and emotional aspects by affecting receptors.<sup>[5,35]</sup> Progesterone increases luteal excess amygdala reactivity and functional pairing of the amygdala and prefrontal cortex. Conversely, testosterone reduces this pairing.<sup>[6,36]</sup> These effects show how sex hormones cause gender differences across the brain. Today, it is known that many neurosteroids affect different cognitive and emotional processes. While the activated GABAergic system has anti-anxiety and antidepressant effects in humans, the decreased activity of the GABAergic system has been found to be associated with depression and anxiety.<sup>[37]</sup> In addition, the regulation of the release of glutamate,  $\gamma$  aminobutyric acid (GABA), acetylcholine,

**Table 3. Effects of sex hormones on the brain**

Sex Hormone	Hormone receptor locations	Effects on brain
Estrogen	Limbic system, hypothalamus, thalamus, pituitary, basal ganglia, and cerebral cortex <sup>[22-24]</sup>	Reduces cell loss, increases neurogenesis, neuroplasticity, synaptic density, and transmission <sup>[24-26]</sup>
Progesterone	Frontal cortex, hypothalamus, thalamus, hippocampus, amygdala, cerebellum <sup>[24,27]</sup>	Protects against neuronal inflammation and apoptosis, enhances neurogenesis, neuronal regeneration, synaptic transmission, and neuroplasticity <sup>[24,27,28]</sup>
Testosterone	Hypothalamus, hippocampus, frontal cortex, and amygdala <sup>[24,29,30]</sup>	Regulates hippocampal neuroplasticity, neurotrophin expression increases neurogenesis and neuroregeneration <sup>[24,29,30]</sup>

**Table 4. Mental disorders and their clinical presentations**

Anxiety disorders	Individuals with anxiety disorders are fearful and anxious which are excessive, persistent, and associated with impairments in life. These feelings can lead to physical symptoms such as headaches, stomach aches, increased heart rate, and shaking. <sup>[42]</sup>
<b>Mood disorders</b>	
Major depressive disorders	Major depressive disorder is characterized by depressive mood, sleep changes, loss of interest and pleasure, lack of energy, reduced concentration, change in appetite, psychomotor changes, and suicidal thoughts. <sup>[41]</sup>
Bipolar disorders	Bipolar disorder is a lifelong and episodic illness characterized by striking and persistent mood swings between elevated mood and depression. If an individual with elevated mood behaves or feels abnormally energetic, happy, or irritable it is called mania, if clinical presentation is less severe it is called hypomania. This disorder is mostly diagnosed in young adulthood. <sup>[43,44]</sup>
Premenstrual dysphoric disorder	Emotional and physical symptoms such as depression, anxiety, irritability, social withdrawal, headache, abdominal bloating, breast tenderness that occur a week before the onset of menses, in most of the menstrual cycles. <sup>[45]</sup>
Psychotic disorders	Delusions, hallucinations, disorganized thinking, and speech, grossly disorganized or abnormal motor behavior are key features to define psychotic disorders. Individuals with psychotic disorders lose their touch with reality. <sup>[41]</sup>
Neurodevelopmental disorders	Caused by a group of conditions in developmental period and deficits mostly begin early in development. Signs of these disorders vary from specific limitations of learning to global impairments of social skills or intelligence. <sup>[41]</sup>

norepinephrine, dopamine, and serotonin, which interacts with the brain's neurotransmitter systems, is carried out by progesterone, estrogens, and androgens.<sup>[38]</sup>

Neurosteroids can affect GABA receptor A in both potentiating and inhibitory ways. Progesterone is considered to be the precursor of enhancers of deoxycorticosterone GABA receptor A. Progesterone turns into allopregnanolone, an important neurosteroid that enhances GABA through various metabolic pathways. GABA, strengthened by the effects of neurosteroids, thus supports the reduction of depression, sedation, hypnosis, and anxiety. As a result of the unbalanced production of these neurosteroids, the risk of premenstrual dysphoric disorder (PMDD), panic disorder, depression, and other mental health problems increases.<sup>[39]</sup> Finally, progesterone and its metabolites reduce depression and increase sleep.<sup>[40]</sup> In addition, serum and intracerebral allopregnanolone (ALLO) levels and enhancers were found at lower levels in women diagnosed with depression.

#### *Mental disorders*

Mental disorders are psychological, biological, or developmental dysfunctions in an individual's cognition, emotion regulation, or behavior.<sup>[41]</sup> These disorders may be occasional, long-lasting, or recurring. Mental disorders are mostly characterized by abnormalities of thoughts, perceptions, emotions, behaviors, and relationships with others.

There are many types of mental disorders, either connected to sex hormones or another pathogenesis, some of which are described according to their clinical presentations in Table 4.

Several biological and psychosocial risk factors have been associated with mental disorders such as but not limited to genetic vulnerability, history of head trauma, maternal age, disturbed family environment, social dysfunction, and substance abuse.<sup>[46,47]</sup>

The burden of mental disorders is present in childhood as idiopathic intellectual disability and autism spectrum disorders (ASD) and continue into older ages with depressive disorders, anxiety disorders, and schizophrenia.<sup>(48)</sup> Starting at age 10, females experience a higher year lived with disability (YLD) rate due to mental and neurological disorders.<sup>[48,49]</sup> When mental disorders are examined in terms of mortality, substance use disorders and anorexia nervosa are the ones with the highest ratios, besides borderline personality disorder, depression, bipolar disorder, opioid use, and schizophrenia has more than 10 times suicide mortality rate compared with the general population.<sup>[49]</sup>

#### *Oral contraceptive and sex hormone related neuropsychiatric disorders*

Sex differences are common in disorders affecting CNS (central nervous system) such as headache disorders, especially migraine, stroke,

**Table 5. Classified risk factors of migraine<sup>[58]</sup>**

Genes	>38 migraine-related gene polymorphisms
Hormones	Menstrual cycle Pregnancy
Environment	Barometric pressure Stress
Metabolism	Diet Neuroendocrine function
Drugs	Exacerbating medications

schizophrenia, bipolar disorder (BD), post-traumatic stress disorder (PTSD), major depressive disorder, multiple sclerosis (MS), and Parkinson's disease.<sup>[50-54]</sup>

### *Migraine*

Migraine is a common primary headache disorder characterized by several neurological, gastrointestinal, and autonomic symptoms. This condition is best described as moderate to severe headache, lasting 4-72 hours. According to the Global Burden of Diseases, Injuries, and Risk Factors Study migraine is one of the leading causes of disability.<sup>[55,56]</sup>

### **Migraine has two main subtypes**

*Migraine without aura:* Unilateral headache that is moderate to severe intensity and also associated with photophobia, phonophobia, and nausea.<sup>[56]</sup>

*Migraine with aura:* Recurrent attacks with unilateral fully reversible CNS symptoms called "migraine aura" as: visual, sensory, motor, retinal, speech/language, and brainstem.<sup>[56]</sup> Up to a third of migraineurs experience CNS symptoms.<sup>[57]</sup> The classified risk factors for migraine are described in Table 5.

The condition underlying sex differences is most probably multifactorial, involving physical and psychological factors, but among all biological factors, sex hormones are likely to be the major cause. Varying migraine prevalence rates among women with different hormonal statuses supports this notion.<sup>[59]</sup> While migraine prevalence of prepubertal children is %3-10 without any gender difference, after the onset of puberty migraine risk becomes 2-3 times more in females than in males like the other headache disorders.<sup>[60,61]</sup> Additionally the female to male ratio of migraine is 3.25 between the ages of 18-29 according to American Migraine Prevalence and Prevention study which has analyzed over 160,000 data. Further, this study showed women reported more migraine-related symptoms and disability.<sup>[62]</sup>

### *Ischemic stroke*

Stroke is the second leading cause of death and the third leading cause of disability in adults worldwide.<sup>[63]</sup> Hypertension, hypercholesterolemia, smoking, oral contraception, excessive alcohol

**Table 6. Features of stroke syndromes based on their anatomical location**

Middle cerebral artery stroke	Contralateral hemiparesis and hypesthesia Gaze towards to side of lesion Ipsilateral hemianopsia Receptive or expressive aphasia if the dominant hemisphere is affected Agnosia Inattention, neglect
Anterior cerebral artery stroke	Mental status is altered Judgment is impaired Contralateral cortical sensory deficits Contralateral weakness, greater in legs than arms Urinary incontinence Gait apraxia
Posterior cerebral artery stroke	Cortical blindness Contralateral homonymous hemianopia Altered mental status Visual agnosia Memory impairment
Vertebral/basilar artery stroke	Nystagmus Vertigo Diplopia and visual field deficits Dysarthria Dysphagia Syncope Facial hyperesthesia Ataxia

use, diabetes mellitus increase stroke risk.<sup>[64,65]</sup> Furthermore, migraine with aura patients has two times higher risk of stroke both between and during attacks<sup>[66-68]</sup> although migraine without aura does not increase the risk of stroke.<sup>[65,69]</sup> Studies show that migraine with aura is linked to increased E2 which leads to hypercoagulation and increased stroke risk.<sup>[70]</sup>

Strokes can be divided into ischaemic (85%) and hemorrhagic (15%) strokes, on a basic level.<sup>[71]</sup> Ischaemic strokes occur due to decrease in blood flow because of a thrombotic or an embolic condition in cerebral arteries. Hemorrhagic strokes are result of bleeding into the brain from ruptured vessels.<sup>[72]</sup>

Symptoms of ischemic stroke vary as to the part of the brain affected. Ischemic stroke syndromes and their symptoms are shown below in Table 6.<sup>[73]</sup>

COCs contain ethinyl estradiol, which causes substantial changes in both coagulation system and vascular wall.<sup>[74,75]</sup> Transformations such as increase in many coagulation factors increased fibrinolytic inhibitors Plasminogen Activator Inhibitor (PAI) activity and reduced natural coagulation factors may induce development of thromboembolic events as well as ischemic stroke.<sup>[76]</sup>

In order to lower hypercoagulopathy and related risk factors, lower dosages and progestin-only OCs were developed, despite contraceptive related stroke incidents still being reported.<sup>[77]</sup>

### *Bipolar disorder*

BD is a chronic mental disorder that reduces psychosocial functioning and is responsible for loss of nearly 10-20 years of life.<sup>[78-81]</sup> %30-50 of adults with BD have suicidal attempts in their lifetime. Additionally, deaths caused by suicide is 20-30 times more in individuals with BD than in the general population.<sup>[82]</sup>

BD is characterised by fluctuations in mood, between manic episodes and depressive lows. Manic episodes are an elevated mood that is often described as euphoric and extremely cheerful, activity and energy in most of the day that lasts at least one week. This episode includes exaggerated self-esteem or grandiosity, distractibility, increased goal directed activities, being more talkative than normal and decreased need for sleep. Hypomania is a mania-like mood which is less severe and lasts shorter.<sup>[41]</sup>

There are 2 diagnostic subtypes of BD. BD-I consists of one manic episode which is followed by hypomania or major depressive disorder, diagnostic criteria for BD-II is one hypomanic and major depressive episode without manic episode.<sup>[81]</sup>

The incidence of BD is nearly equal in men and women, but manic episodes occur more often in men. On the other hand there are many studies that prove the correlation between reproductive life cycle events and the course of BD.<sup>[50,52]</sup> The luteal phase of the menstrual cycle is related with more severe manic and depressive symptoms compared to other phases, because of the low hormone levels.<sup>[50,83,84]</sup> Also severity of psychosis symptoms increases in the postpartum period.<sup>[85,86]</sup> Studies show that psychosis symptoms may be improved with daily E2 treatment in women with postpartum psychosis and estrogen deficiency.<sup>[87]</sup>

### *Schizophrenia*

Schizophrenia is characterised by 3 symptom categories, including positive, negative and cognitive symptoms.<sup>[88,89]</sup> Positive symptoms include; delusions, hallucinations, disorganized speech, or grossly abnormal psychomotor behavior.<sup>[41]</sup>

Delusions are subjective and false beliefs based on inaccurate interpretation of an external reality that are fixed despite the light of evidence.<sup>[41,90]</sup> Persecutory delusions are the idea that the one is going to be harmed, harassed, and so on by others.<sup>[41]</sup> This delusion is the severest form of paranoia and generally seen in patients with a primary diagnosis of depression.<sup>[91,92]</sup> Referential delusions are misunderstood beliefs that environmental signs as certain gestures, comments, events and so forth are directed at oneself. Grandiose delusions are false beliefs about having exceptional abilities, power, knowledge, or fame.<sup>[41,93]</sup> These delusions are seen in two-thirds of bipolar disorder and half of schizophrenia patients.<sup>[94]</sup> Somatic delusions, in which an individual believes something wrong with their body or bodily functions as displacement, absence, or malfunction of a body part.<sup>[95]</sup> Erotomanic delusions are delusions of another person, generally someone with higher status, is in love with him/her.

Hallucinations are defined as perception-like experiences that occur in the absence of external stimulus. They are vivid, clear, located in external objective space and not under voluntary control. They may involve five senses and are named

according to these senses (Visual, auditory, olfactory, tactile and gustatory).<sup>[96]</sup>

Negative symptoms constitute the major part of schizophrenia related morbidity. There are five recognised negative symptoms. Diminished emotional expression, avolition, alogia, anhedonia, and asociality.

Diminished emotional expression, includes alogia which is an important restriction of speech output, and affective flattening that is characterised by reduction of facial expressions and body gestures.<sup>[97]</sup> Avolition represents a decrease in motivated self-initiated purposeful activities, the individual may sit long durations without participating in work or social activities.

Schizophrenia tends to affect both genders equally, but prognosis and response to treatment shows differences.<sup>[52]</sup> Males experience a start of peak between ages 18-25 which is 4 years earlier than women.<sup>[98,99]</sup> Also women experience a second peak around ages 45-49, suggested to be associated with decrease of ovarian hormones because of menopause.<sup>[99,100]</sup> Additionally during pregnancy schizophrenia symptoms improve, and postpartum symptoms get worse related to gonadal hormone levels.<sup>[101]</sup>

Male patients with schizophrenia tend to have more severe symptoms, and show less responses to medication, on the contrary female patients have higher remission and recovery.<sup>[102]</sup> In addition male patients experience more morphological brain abnormalities than women. For instance greater ventricular enlargement,<sup>[103]</sup> more severe frontal and temporal lobe atrophy<sup>[103,104]</sup> and greater abnormalities in white matter microstructure.<sup>[105,106]</sup>

At present, research into the use of hormonal therapies in schizophrenia is providing promising results.<sup>[107,108]</sup>

#### *Mood changes*

Between 32-60% of women stop using oral contraceptive pills (OCPs) in the first 6 months for varying reasons, including mood changes.<sup>[109-112]</sup> Understanding the way OCs affect mood is crucial, considering women have twofold risk of developing depression than men and hormonal fluctuations are linked to depression prevalence in women.<sup>[113-115]</sup>

In a double-blind randomized controlled study, women with mood disorders due to the use of COCs were examined, and some of these women were given placebo, while the remaining COCs

were given.<sup>[116]</sup> When the patients were examined at the end of the study, which lasted a few weeks, the women in the group using COCs had more mood swings, fatigue, and tendency to depression.<sup>[1]</sup> In addition, in a small, cross-sectional study conducted with a group of women in Norway, it was observed that an existing mood disorder decreased in women using COCs, while it was observed that this risk was increased in women using only progestin-containing OCs.<sup>[3,117]</sup> Additionally, several important and well-conducted studies have shown that HCs improves depressive symptoms. For instance, a large cohort study conducted in Denmark reported that the use of OCs increases the diagnosis of depression and the use of antidepressants in the later period.<sup>[3,118]</sup>

#### **Conclusion**

Current literature show that mental disorders such as migraine, BD, schizophrenia, and depression are more common in women compared to men, also prevalence changes between reproductive years and menopause. Sex hormones may affect mental disorders and mood changes by hypercoagulation and GABA pathway, but mostly their role remains unfold. In the light of the fact that sex hormone receptors are widespread, and these hormones have varying effects on brain, it is easy to understand that fluctuations, low or high levels of these hormones play a role in mental diseases and mood changes.

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