



Reproductive Hormones and Female Mental Wellbeing

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Abstract: Fluctuating hormone levels during the menstrual cycle and major reproductive cycle stages have been linked to mood changes, mental health conditions, and an increased likelihood of psychotic episodes. This knowledge could potentially be used for the predictive modeling of exacerbations and mood deterioration through the collection and analysis of data from wearables and apps. A literature search for a narrative review has been conducted using selected keywords in Pubmed, Embase and Google Scholar. Based on published data, it can be seen that hormonal changes affect the severity of symptoms in several mental health conditions, including depression, PMDD, PTSD, bipolar disorder and schizophrenia. The influence of FSH, LH, testosterone, and other hormone precursors has also been investigated, but there is less information available regarding their impact. E2 levels have been measured as a treatment–response biomarker and have demonstrated significant predictive ability for treatment responder groups. On the other hand, FSH has been demonstrated to be helpful in predicting treatment non-responder groups in schizophrenia. Monitoring reproductive hormones in combination with wearables or digital solutions has the potential to predict mood changes more effectively. Precise and frequent hormone measurements might prove to be more effective than relying on absolute threshold levels. Further research is needed to validate the utility and precision of hormone use in the field of mental health.

Keywords: reproductive hormones; mental health; depression; estrogen; progesterone; mood; predicting; pms; pmdd; modeling



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1. Introduction

Women suffer from mood and anxiety disorders up to two times more than men, depending on the specific disorder in question [1,2]. Several factors have been identified in this discrepancy, such as men’s higher self-esteem compared with women’s, the influence of sex hormones, a higher tendency for rumination and body shaming in women, as well as societal factors such as discrimination, stress and gender inequality [3]. Fluctuating hormone levels are believed to contribute to the issue. In a typical menstrual cycle, the levels of follicle-stimulating hormone (FSH) and luteinizing hormone (LH) experience an initial rise, which prompts the maturation of the ovarian follicle. Additionally, there is a gradual increase in the production of estradiol (E2), reaching its highest point just prior to ovulation. This surge in estradiol triggers a notable peak in LH and FSH levels, subsequently leading to the synthesis of progesterone by the corpus luteum. The concentration of progesterone reaches its peak approximately 6–8 days after ovulation [4]. These natural changes in reproductive hormones in women have been associated with mood changes and mental health conditions. It is, therefore, important to examine whether this information could be used to improve the understanding, management and prediction of mental health conditions, as well as during treatment monitoring to improve patients’ outcomes. We seek to investigate whether hormone measurements are associated with mental health outcomes and if so, in what way. Additionally, to our knowledge, there is no research that focuses

on predictive modeling of exacerbations based on hormone monitoring. Using innovative technology and predictive modeling, including wearables and apps for data collection, it may now be possible to predict mood changes and mental health conditions through fluctuations in hormone levels [5].

2. Results and Discussion

This review includes $n = 76$ papers in total, of which $n = 5$ introduce the topic and $n = 13$ relate to the processes behind reproductive physiology and mood, including the physiological background of these changes. Then, $n = 58$ papers describe hormone levels and mental health conditions, including depression ($n = 14$), premenstrual syndrome and premenstrual dysphoric disorder ($n = 9$), anxiety disorders ($n = 8$), post-traumatic stress disorder ($n = 2$), bipolar disorder ($n = 4$), schizophrenia ($n = 8$), obsessive-compulsive disorder ($n = 3$), future directions (10).

2.1. Reproductive Physiology and Mood

During menstruation women often experience psychological distress, decreased self-esteem, reduced social engagement, substance use, and self-harm, which is related to the physical discomfort they may feel. In addition, reviews often find exacerbations of mental health conditions during the luteal phase and early follicular phase (menstruation) [6]. A positive impact of estrogens on mood is noticed around ovulation when levels are high. Women report feeling more attractive before ovulation based on a large diary study in 872 women (580 naturally cycling) across 70 consecutive days where ovulatory increases in self-perceived attractiveness and sexual desirability were recorded in naturally cycling women [7]. Sex hormones also influence facial emotional processing (FEP) in women in various reproductive stages of their lives [8]. For instance, one review reports five studies that found that FEP is enhanced during the follicular phase and the preovulatory phase when the concentration of estradiol is higher and progesterone is low, while two studies reported neutral findings [8]. This demonstrates a pattern of enhanced emotional perception in women depending on their stage of the menstrual cycle and shows that women's emotions are influenced by hormonal fluctuations.

As well as within a single menstrual cycle, mood changes are expected during normal physiological milestones, such as menarche, pregnancy and perimenopause. Some studies on the role of hormones and emotional disposition and aggression in young adolescents report that hormones are only correlated with behavioral changes in boys, not in girls. Higher levels of androstenedione have been found to be associated with increased behavioral issues, such as acting out and aggressive episodes, in boys [9]. Post-pregnancy hormonal fluctuations are also known to cause transient mood changes in women, the so-called 'baby blues'. Sadness, anxiety and low mood typically peak a few days after birth and resolve spontaneously within 2 weeks [10]. For a similar reason, women, before menopause, have also been demonstrated to report mood changes related to the fluctuations in their reproductive cycle. Between 15% to 50% of women report experiencing depressive symptoms as part of this transition [11].

There are several hypotheses on how estrogens and progesterone contribute to brain anatomy and functioning. The main three suggest that estrogens have an impact on serotonin and dopamine neurotransmitters, as well as mitochondrial function:

The serotonin hypothesis was investigated in animal and human studies. Serotonin plays a key role in emotional responses [12]. It has been shown to impact empathic abilities and has been positively associated with recovery from depression. In a small study of eighteen postmenopausal women, it was found that estradiol increased serotonin receptor responsiveness to the agonist *m*-chlorophenylpiperazine through the prolactin and cortisol response [13]. This finding is important in demonstrating the role of serotonin in women. Decreased serotonergic activity is implicated in increasing vulnerability to affective disorders in postmenopausal women.

Dopaminergic signaling is another possible pathway for regulating mood through estrogen and progesterone. Dopamine is recognized for its role in regulating various functions, such as pleasure, addiction, decision-making, motivation, motor control, and learning, earning it the nickname of the ‘reward neurotransmitter’. Its effects are mediated by several dopaminergic areas in the brain. In 2018, Del Río et al. summarized the influence of estrogen and progesterone. Estrogens have been found to increase the levels of dopamine by reducing its breakdown and reuptake, as well as increasing the number of dopaminergic receptors. Allopregnanolone in the nucleus accumbens has been shown to enhance dopamine release, which could prevent behaviors such as drug abuse and reduce depression. Conversely, in the prefrontal cortex, allopregnanolone has been found to inhibit dopamine release, which could potentially affect emotional regulation in various situations. The impact of progesterone on dopaminergic systems is contingent upon the concurrent presence of estrogen and the specific site of activity [14].

Progesterone and estrogens modulate allopregnanolone. Progesterone is believed to have a calming effect on mood. In preclinical studies, it demonstrated positive modulation of GABA receptors by converting to allopregnanolone, leading to anxiolytic and antidepressant effects. Bernardi et al. in 2003 and Pluchino et al. in 2005 suggested that estradiol positively modulates allopregnanolone, thereby increasing its effect [15,16].

Mitochondrial function. Estrogen’s impact has been summarized by Klinge in an extensive review. It is believed to regulate the expression of genes that control mitochondrial functions, including metabolism, apoptosis, fission, and fusion. This impact is made possible through binding to estrogen receptors α and β , as well as G-protein coupled estrogen receptors, and controlling nuclear gene transcription and intracellular signaling events [17].

In 2019, Dubol et al. conducted a systematic review and suggested that cortico-limbic brain structures are receptive to the modulatory effects of reproductive hormones. They found that these structures show increased activity during ovarian hormone fluctuations and reduced gray matter volumes in the hippocampus, among other findings [18]. Therefore, studies demonstrate that natural changes in hormone levels can increase brain function and structure, thereby affecting mood and cognition.

Over the course of a menstrual cycle, the levels of female reproductive hormones fluctuate significantly, which in turn leads to fluctuations in the mechanisms described above. Overall, the evidence suggests that fluctuations in hormone levels, particularly the withdrawal of estrogen, pose a risk to women’s mental health.

2.2. Hormone Levels and Mental Health Conditions

Estrogens and progesterone have numerous effects, including promoting neuroplasticity, influencing both structural and functional changes, and being associated with emotional processing, mood and cognitive disorders. Mental health conditions, however, are complex and can be influenced by various factors, such as genetics, infections, and hormonal disorders.

2.2.1. Depression

Depression is a serious medical condition that causes persistent feelings of sadness and loss of interest [19]. According to the Diagnostic and Statistical Manual of Mental Disorders, Fifth Edition (DSM-5), it is classified into five distinct disorders. In this review, we do not focus on the differences between the conditions, but rather on the studies that investigate the link between reproductive hormones and depression.

During childhood, there is no notable disparity in the prevalence of depression between boys and girls. However, around the age of 15, following the onset of menarche, there is a rapid increase in estrogen levels, which establishes the female predominance of depression incidence [20,21]. Furthermore, the disparity in depression rates between men and women is only evident during the reproductive period, and it returns to equal following menopause [22].

One of the factors contributing to the behavioral and emotional changes that occur during puberty are hormonal changes. Estradiol and testosterone levels have been established by Angold et al. as predictors of depression. Researchers have suggested that, during puberty, there is a point at which the increase in testosterone and estrogens reaches a threshold, making girls more susceptible to developing depression. However, they acknowledge that other factors, such as life events and cognitive style, play a crucial role in determining individual episodes of depression [23].

The impact of hormones during the reproductive period was examined in a Harvard study on moods and cycles. The study encompassed a sample of 976 women between the ages of 36 and 45. The findings reveal that the participating women who exhibited lower levels of estradiol and higher levels of FSH and LH had a documented history of episodes of depression [24].

Pregnancy is another time in women's lives with significant changes in hormone regulation. Rates of depression are higher among pregnant individuals compared with non-pregnant women. Gestational age correlates with the onset of depressive and anxiety symptoms, wherein the first trimester the prevalence is 7.5%, then increases to 12.8% in the second and 12.0% in the third trimester [25]. Following birth, women with a history of depressive symptoms during pregnancy are at higher risk of postpartum depression (PPD). The rapid changes in endogenous estrogen and progesterone levels at delivery are a contributing factor of PPD in susceptible women [26].

The literature also supports the existence of an association between reproductive hormones before and during the menopausal transition and depressive symptoms. In a systematic review with a meta-analysis, Georgakis et al. demonstrated that women who experience menopause at an older age and have a longer reproductive period have a reduced risk of developing depression in their later years [27]. In the Penn Ovarian Aging Study conducted by Freeman et al., women with a previous history of depression underwent six assessments of blood hormone levels over a four-year period. Samples were collected 12 times during a period of 2–6 days in the follicular phase. Depression scores correlated with the fluctuations (standard deviation) between results. This study demonstrated that years with greater variability in E2 levels were associated with an increased risk of developing depressive symptoms [28].

New studies, which measured hormones more frequently, confirmed that studying E2 variability using four blood samples over a span of 14 months showed positive associations between the frequency of fluctuations and depressive symptoms [29,30]. Similar results were found when measuring E2 in saliva and E3G in urine over a four-week period. These fluctuations were positively associated with depressive symptoms and predicted a higher level of weekly negative affect [29]. This suggests that fluctuations in E2 increase sensitivity to psychosocial stressors during the perimenopause transition and could potentially be utilized to predict periods of heightened sensitivity. In a separate study involving 436 women aged 35 to 47, which examined depression during the follicular phase, blood samples were collected and depression scale scores were evaluated. Individuals who experienced a rapid increase in FSH were less likely to exhibit depressive symptoms ($p \leq 0.001$). Symptoms also decreased with age following the menopausal transition ($p = 0.02$). In bivariate analysis, participant profiles with increasing E2 levels, which are associated with the early phase of transition to menopause, were found to be linked to depressive symptoms ($p = 0.053$), although the association was not statistically significant. These findings suggest that the hormonal changes that occur during the transition to menopause contribute to dysphoric mood. This is indicated by the increase in depressive symptoms during this period and the subsequent decrease in such symptoms in postmenopausal women [28].

In postmenopause, a study conducted on 265 older postmenopausal women examined the relationship between absolute physiological levels of estrogen and mood/cognitive functioning. The findings revealed that higher physiological serum concentrations of estradiol and estrone are linked to lower levels of depression and anxiety [31]. Conversely, another study involving 138 postmenopausal women examined the association between

endogenous hormones and depressive symptoms. The results indicate that there was no significant correlation between depressive symptoms and the absolute levels of sex-hormone binding globulin, testosterone, free androgen index, estradiol, free estradiol, or FSH. This suggests that monitoring fluctuations in hormone levels may be more effective than measuring absolute values [32].

2.2.2. PMS and PMDD

Premenstrual syndrome (PMS) is a disorder characterized by affective symptoms and clinically significant psychological and somatic manifestations during the luteal phase of the menstrual cycle [33]. A small study of 41 women aged 18–45 years, using blood samples, examined the associations between levels of progesterone and estradiol during menstruation and PMS symptoms [34]. Lower levels of progesterone and, to a lesser extent, estrogen during the luteal phase are predictive of the severity of peri-menstrual symptoms, as measured by the Daily Record of Severity of Problems (DRSP) scale. Though hormone levels in large studies fail to demonstrate clinical usefulness in diagnosis or treatment, they could potentially be used for predicting symptoms [35]. A similar study has demonstrated that the daily concentration of saliva progesterone decreased sharply 3 days before menstruation only in women with PMS symptoms, whereas in healthy women, a very gradual decrease was observed over 8 days [36].

Premenstrual dysphoric disorder (PMDD) is a psychiatric disorder characterized by the onset of negative mood and physical symptoms during the week before menstruation. It is a more severe presentation than PMS. In the luteal phases of their menstrual cycle, women with PMDD experience a combination of symptoms, such as irritability, in comparison with healthy women. This has been demonstrated by higher startle responses to noxious acoustic stimuli in the luteal phase, indicating that women with PMDD are more sensitive to negative stimuli during specific phases of the menstrual cycle [37]. Similarly to PMS, models have indicated that rapid progesterone withdrawal contributes to the symptoms associated with PMDD. This includes the significant role of one of the main metabolites, allopregnanolone [38]. Studies have also shown that the premenstrual change in progesterone is negatively correlated with fun-seeking behavior among women with PMDD. This means that women are less likely to engage in outgoing activities before menstruation [39]. Furthermore, the role of estrogen has been investigated in relation to the severity of PMDD symptoms. It has been revealed that low levels of estrogen during the early luteal phase are associated with worse psychological outcomes [40]. In general, individuals with PMDD are more sensitive to hormonal changes due to a decrease in the expression of serotonin transporters before the menstrual cycle, as observed in positron emission tomography imaging [41].

2.2.3. Anxiety Disorders

DSM-5 identifies several anxiety disorders, including panic disorder (PD) and generalized anxiety disorder (GAD). In women with PD, there are reports of an increase in the incidence and severity of panic episodes during the luteal phase, which occurs 5–8 days before menstruation [42]. Women with GAD also report experiencing more anxiety symptoms during the premenstrual phase compared with the follicular phase [43].

There is a well-established link in the literature that shows women with anxiety disorders are more vulnerable to the influence of gonadal hormones [44]. In a recent review by Kundakovic et al., it is suggested that the withdrawal of estrogen increases the likelihood of developing anxiety-related disorders [45]. This phenomenon is often known as premenstrual exacerbation (PME) and can be observed in both depression and anxiety. During this time, women may experience a worsening of mental health symptoms [46].

The vulnerability of women to reproductive hormones has been proposed through two mechanisms: one that facilitates the maintenance of anxiety symptoms after they appear, and another that alters certain vulnerability factors related to the development of anxiety. Low levels of estradiol and progesterone during menstruation lead to a decrease in

serotonin and allopregnanolone. This reduces GABAergic inhibition and causes problems with the regulation of the HPA axis, which increases vulnerability to anxiety disorders [47].

Furthermore, in a study on the formation of non-associative emotional memory, women were exposed to aversive film clips or images, and their responses were recorded. It was found that during the luteal phase, women reported significantly more spontaneous intrusive recollections (SIRs) compared with the follicular phase. Salivary levels of progesterone were positively correlated with SIR frequency ($r_2 = 0.23$, $r = 0.48$, $p = 0.001$). However, no such association was found for estrogen ($p > 0.7$). This suggests a possible role of progesterone in mediating anxiety symptoms [48].

Fear extinction studies suggest that fluctuations in estrogen, specifically decreases in estrogen, can lead to an increased likelihood of developing anxiety disorders. This is because these fluctuations impair the natural processes involved in emotional responses to traumatic events, thereby increasing the propensity for anxiety disorders to develop. In a study on 37 healthy women, a significant linear relationship between estradiol levels and conditioned responses during extinction was demonstrated ($p = 0.026$) by Wegeer et al. This is particularly significant when considering potential treatment options, such as cognitive behavioral therapy (CBT) or exposure therapy, as reduced responses in certain phases of the cycle could result in ineffective treatment outcomes. Sex-specific differences in CBT interventions are currently rarely researched, with no investigations into the potential impact of hormones [49].

2.2.4. Post Traumatic Stress Disorder

Post-traumatic stress disorder (PTSD) is an example of an anxiety disorder that can develop after experiencing distressing or traumatic events. It is often characterized by intrusive thoughts, memories, nightmares, anxiety and negative mood patterns. It is yet another mental health condition that has a prevalence twice as high in women compared with men [50]. Studies also demonstrate that women with low estrogen levels and with fear-potentiated startle responses were higher for women with PTSD, when compared with normal and high estrogen groups. This suggests that estrogen levels might have the potential to be used to determine women's vulnerability to fear conditioning and possibly identify at-risk groups [50].

A notable limitation of these studies is the fact that women are often excluded from trials in order to reduce the source of variability. The body of evidence specific to women is more limited for this reason. Despite strong links in literature, one review identifies how the clinical translation of PTSD studies is inconsistent overall, something which may be attributed to the varying methods used in these studies [51].

2.2.5. Bipolar Disorder

This is a mental health condition that causes extreme shifts in mood, energy, activity and concentration [52]. Three types are identified: Type I, Type II and Cyclothymic disorder. The onset of the condition often coincides with puberty, which suggests a role of reproductive hormones. Similarly, some women also experience the onset of symptoms before menstruation, as is the case with certain other mental health conditions. Pregnancy seems to have a protective effect; however, the postpartum period is associated with a worsening of symptoms and the onset of postpartum psychosis [53].

A review by Meinhard et al. found two studies that explored the link between serum estrogen levels and bipolar disorder in women, as well as four studies that investigated the effectiveness of tamoxifen in producing antimanic effects. The results of the estrogen studies show that women with postpartum psychosis had low levels of estrogen and experienced significant symptom improvement after receiving estrogen treatment. The tamoxifen studies demonstrate that the drug was effective in producing antimanic effects [54].

Estradiol has also been demonstrated to play a role in the treatment of psychosis and manic episodes. In a study of 10 women with postpartum psychosis, their serum estradiol levels were measured at baseline and throughout a 6 week treatment period using only

sublingual estradiol. In all patients, the symptoms diminished significantly ($p < 0.001$) when the estrogen concentrations reached the normal range [55].

Currently, there is no research focusing on the predictive modeling of exacerbations based on hormone monitoring. Most studies focus on treatment modalities that aim to restore estrogen levels in order to enhance the effectiveness of antipsychotic medications.

2.2.6. Schizophrenia

Schizophrenia is a serious mental illness that is still poorly understood. Although individuals with schizophrenia exhibit a range of symptoms, treatment responses, and long-term outcomes, primary treatment involves antipsychotic drugs and psychosocial support. There is strong evidence of resistance to antipsychotic medications and new approaches have become more demanding. This indicates a potential in biological subtyping that affects the underlying neurobiology and may account for differences in treatment effectiveness [56].

There is a growing body of literature suggesting that estradiol and progesterone play a role in cellular processes and can influence both positive and negative psychological symptoms [57]. Deficiency in both males and females has been associated with the onset of psychotic symptoms. Because of their drug modulating abilities, premenopausal women require lower doses of antipsychotics [58]. Similarly to bipolar disorder, the worsening of symptoms is observed during estrogen withdrawal, such as during the postpartum period. Additionally, periods of high estrogen throughout a woman's life are associated with less frequent relapses [59]. The link with progesterone has been documented in the literature as being less clear. Some studies have suggested the neuroprotective roles of hormones, while others have shown a detrimental effect [60].

Hormone levels have shown potential for predicting the outcomes of hormonal treatments in schizophrenia. Endogenous estradiol levels have been measured as a biomarker for treatment response. According to the findings of these studies, there appear to be two distinct subgroups within the 200 µg estradiol treated group being studied. One subgroup, identified as treatment responders, exhibited a decrease in Positive and Negative Syndrome Scale (PANSS) scores over time, while the other subgroup, identified as treatment non-responders, demonstrated stable PANSS scores over the same period. These measurements demonstrate that it is possible to accurately predict groups of treatment responders, indicating heterogeneity in treatment response and sensitivity to hormonal changes. Moreover, FSH blood serum levels were shown to be able to predict the non-responder group [56]. In the treatment arm around 80% of participants showed improvement, the baseline PANSS scores of the remaining treatment non-responders were significantly higher. Thus, increasing E2 levels are associated with a decrease in total PANSS symptom scores, providing support for the hypothesis that estrogen treatment directly improves the health of patients with schizophrenia [56].

Another study investigated FSH/LH ratios, as measured by chemiluminescent immunoassays, and demonstrated that they are not positively correlated with changes in mood scores and overall well-being in women with schizophrenia [61].

Recent literature has also pointed at the role of raloxifene, a class of selective estrogen receptor modulators, which has shown potential in reducing the incidence of manic episodes in patients with schizophrenia when added alongside normal doses of antipsychotic drugs [62]. In a clinical trial of 110 people, it was demonstrated that adding raloxifene reduces psychotic symptoms and improves cognition, social functioning and quality of life as compared with a placebo [63]. There is not currently any robust literature available on the use of this drug in other mental health conditions, but an investigation into bipolar disorder should be encouraged.

2.2.7. Obsessive–Compulsive Disorder

Obsessive–compulsive disorder (OCD) is a mental health condition characterized by unwanted thoughts and compulsive or repetitive behaviors. Karpinski et al. in their critical

review suggest that hormone levels in this condition are similarly associated with the negative onset of symptoms, as previously discussed. Women report symptom exacerbation before menstruation, as well as during the first and second trimesters of pregnancy when estrogen levels are relatively lower. Overall, both estrogen and progesterone have demonstrated regulatory effects on serotonin signaling, which is involved in the modulation of OCD symptoms [64]. Stein et al. further suggest that changes in the serotonergic system during pregnancy are implicated in the onset of OCD, with an increased incidence during pregnancy and increased depressive symptoms in the postpartum period [65]. In addition, Weiss et al. have concluded that there is a tentative association between gonadal hormones and the onset and exacerbations of OCD [66]. Women with elevated levels of estrogen and progesterone, such as those who utilize oral contraceptives, may encounter comparable symptoms to those observed during pregnancy. This similarity in symptomatology could potentially be attributed to a shared mechanism of action that precipitates the onset of these symptoms.

2.3. Future Directions

As described previously, hormone levels have been shown to be associated with changes in mood and symptoms of different mental health conditions. Estrogen and progesterone fluctuations appear to play a key role in the onset of PMS and PMDD symptoms. In other conditions, mental health status is also related to the changes around the cycle with a worsening of symptoms typically occurring before menstruation. This pattern is present in several mental health conditions, such as OCD, bipolar disorder and anxiety disorders. The influence of FSH, LH, testosterone, and other hormone precursors has also been investigated, but there is much less information available regarding their associations with mental health in women. Most notably, FSH has been demonstrated to be helpful in predicting treatment for non-responder groups with schizophrenia. However, there is currently a limited body of evidence documenting the clinical usefulness of utilizing hormones and monitoring changes in the menstrual cycle to aid in the management of mental health. The transient changes in hormone fluctuations have the potential to be utilized in symptom prediction and modeling.

Precise and frequent hormone measurements of women's hormone fluctuations might prove to be more effective than relying on absolute threshold levels. Understanding personal fluctuations in hormone levels has numerous benefits, not only from a reproductive standpoint but also in predicting exacerbations of certain mental health conditions during the menstrual cycle and other stages of the reproductive life cycle.

Based on evidence obtained from data collected by period tracking apps, recording symptoms throughout the menstrual cycle has been found to be helpful for women in managing symptoms and even increasing productivity at work, as indicated by their responses to in-app surveys [67]. Similarly, it has been shown that increased understanding of women's health improves health outcomes and enables the prediction of mental health and mood changes.

People also find it helpful to monitor their mental health through digital apps, as it enhances their self-awareness. They can reflect on previous mood states to gain a better understanding of their own behavior and to plan their daily activities according to recent changes in mood [68]. In a study on predictive modeling of addiction relapses in a mobile health app, it was demonstrated that utilizing responses from weekly surveys exhibited high sensitivity and specificity, as well as clinical potential [69]. The combination of self-reported at-home testing, such as measuring urinary or salivary hormone levels, along with automated, remote, wearable sensor digital biomarker data collection can facilitate women's symptom prediction and understanding of their mental health conditions around hormonal changes throughout their lives [70].

Biomarkers can be identified to predict changes in mental health state, which women can use to better understand their well-being [71]. Most biomarkers currently used in psychiatry are biological in nature. These include gene markers that assess risk factors for

the development of conditions such as dementia, interleukin levels that identify the risk of schizophrenia, and enzyme levels that help determine appropriate therapies. Cortisol has been identified as a possible biomarker to predict individuals at high risk of depression, bipolar disorder and psychosis [72]. Moreover, testing urinary hormones has been shown to be a useful, safe and precise method for measuring 18 reproductive hormones. Home monitoring using urinary or saliva hormone levels could be a potential solution to increase adherence to testing [73].

There are certain limitations identified in the literature that are common in studies, such as low participation rates in regular sampling, especially for the collection of blood samples for lab-based investigations. Moreover, saliva hormones have been shown to be accurately measured for estrogen, but not for progesterone [74].

Certain limitations are also associated with self-monitoring and self-reporting symptoms, such as the lack of customization of these apps, the reluctance to report negative symptoms over positive ones, lack of adherence and irregular reporting [75]. Several apps are only available by prescription and, as a result, are not accessible to all users. Self-reporting in mental health apps is subject to reporting bias and is less objective compared with standardized lab measures.

Additionally, previous studies have found that monitoring hormones in menstrual cycles can be challenging due to the variability in levels both within and between cycles. This variability makes it difficult to establish clinically relevant thresholds that are not influenced by ovulatory activity [76]. Absolute hormone level monitoring has been undertaken in short-term studies, primarily due to the challenges associated with blood sample collection, and showed poor adherence to study protocols. For this reason, more large-scale, long-term data collection and further studies are necessary to establish improved databases.

3. Materials and Methods

A literature search was conducted using selected keywords in the following databases: Pubmed, Embase and Google Scholar. Literature was limited to the English language with no limit on publication dates. Animal studies, white papers, and qualitative studies were excluded. Relevant titles were extracted, and abstracts were screened for information. Keywords selected for the study were search strings including: 'hormone', 'FSH', 'LH', 'estrogen', 'progesterone', 'estradiol', 'sex hormones', 'menstrual cycle', 'menarche', 'menopause', 'mental health', 'depression', 'pmdd', 'pms', and 'pregnancy'. Search results were independently screened by two authors for eligible studies. The results were grouped into sections based on the discussed themes after an abstract screening. Full-text articles were obtained, and references were screened to identify any additional articles that were not included in the original searches.

4. Conclusions

The impact of hormones on women's emotional status and mood regulation has been extensively observed and described in literature for various stages of their lives, including menarche, the menstrual cycle, pregnancy and perimenopause. These hormonal changes can also impact and influence the severity of symptoms in several mental health conditions, such as depression, PMDD, PTSD, bipolar disorder and schizophrenia. Overall, monitoring reproductive hormones in combination with innovative technology, such as wearables or apps, holds the potential to predict mood changes more effectively. This can lead to the development of specific, personalized tools for patients to use at home and in clinical settings. Further research is needed to validate the utility and precision of hormone use in the field of mental health, specifically through large-scale trials that involve frequent hormone level sampling. This approach could effectively detect hormone variations in women.

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Abbreviations

DRSP	Daily Record of Severity of Problems
DSM-5	Diagnostic Statistical Manual of Mental Disorders, Fifth Edition
GABA	gamma-aminobutyric acid
GAD	generalized anxiety disorder
E2	estradiol
E3G	estrone-3-glucuronide
FEP	facial emotion processing
FSH	follicle stimulating hormone
LH	luteinizing hormone
OCD	obsessive-compulsive disorder
PANSS	the Positive and Negative Syndrome Scale
PD	panic disorder
PMDD	premenstrual dysphoric disorder
PMS	premenstrual syndrome
PPD	postpartum depression
PTSD	post traumatic stress disorder

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