The link between sex hormones and depression over a woman's lifespan (Review)

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Abstract. Major depressive disorder represents one of the most common psychiatric diagnosis, and was ranked by World Health Organization as the third cause of morbidity and mortality worldwide, expecting to become the first cause by 2030. The prevalence of depression is higher in women than in men, once the puberty sets. This may be explained by the hormonal fluctuations, estrogen and progesterone, over a woman's lifespan. Some of the women may experience severe mood symptoms during the luteal phase of the menstrual cycles, known as premenstrual dysphoric disorder. In addition, it has been shown that the use of hormonal contraceptives, especially oral contraceptives (OC), may determine an induced depressive disorder. The risk of induced depressive disorder is even higher in women who start an OC treatment during adolescence, mainly because this is the period when the hormonal milieu is developing. Another important period of hormonal fluctuations is after delivery. It is described such as a hormonal 'withdrawal state' because in a matter of days postpartum, the hormonal levels decrease down to the levels of a non-pregnant woman. It is worth to mention that this extreme decreasing of estrogen and progesterone is not enough in order to develop postpartum depression. It has been suggested that postpartum depression may be a consequence to differential activation of estrogen genes. Fortunately, since 2019, Food and Drug Administration approved the first specific hormonal treatment for postpartum depression, represented by brexanolone. The last period of hormonal changes is the transition to menopause, in which depressive symptoms may be determined by day-to-day hormonal fluctuations. There is a lot more to explore in this field for future research, regarding if there really is a direct link between the levels of estrogen and progesterone and depressive disorder, and also regarding different hormonal therapies.

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1. Introduction

Depression: prevalence and sex differences. Major depressive disorder represents one of the most common psychiatric illnesses, and it affects the psychosocial functioning and quality of life of those affected. In 2008, major depression was ranked by World Health Organization as the third cause of mortality and morbidity worldwide, and it may become the first cause by 2030 (1).

The prevalence of unipolar depression is higher in women than in men, with an average ratio of 2:1. Most of the studies found that this difference between men and women is influenced by age and hormone levels; therefore, before puberty, the average ratio between men and women is 1:1. The prevalence of depression in women, starts increasing with puberty, and the typical ratio of 2:1 is reached among adolescents within the age of 15 to 18 years (2-4).

A possible cause for the higher prevalence in women may be the periods of hormonal changes during the lifespan of women, including puberty, intake of hormonal contraceptive use, pregnancy, menopause, and even the monthly end of the luteal phase (5).

Sex hormone levels during the menstrual cycle

Hypothalamic-pituitary-gonadal (HPG) axis. It is well known that primary abnormalities in the hormonal axes, including gonadal axes, are associated with affective symptoms. The

secretion of gonadotropin-releasing hormone (GnRH) is pulsatile, and the hypothalamus makes it from neurons found in the medial preoptic area. GnRH stimulates the anterior pituitary, and in response, it releases luteinizing hormone (LH) and folic-stimulating hormone (FSH) into the bloodstream. These two hormones stimulate the ovaries in order to produce estradiol (E2) and progesterone, and the testicles in order to produce testosterone. E2, progesterone, and testosterone regulate their activity by inhibiting HPG axis activity in the hypothalamus and pituitary gland via feedback inhibition. This feedback inhibition is complex in women and regulates the 28-day menstrual cycle. These hormones also bind to albumin and other proteins to access the receptors and different tissues (6).

The phases of the menstrual cycle are represented by: i) A follicular phase that lasts for 14 days, in which the levels of FSH and LH are low, but the levels of E2 start to climb steadily; ii) an ovulation phase, when there is a burst of GnRH release and a rapid rise in the levels of LH, which are triggering the release of an ovarian follicle; and iii) the luteal phase, which lasts for 14 days when the levels of LH and FSH return to the normal levels, and within the ovary, the corpus luteum produces high levels of E2 and progesterone, in order to prepare the uterus for a possible pregnancy. If the pregnancy does not occur, the levels of E2 and progesterone fall, and the menstrual bleeding begins.

There are periods of significant changes in the levels of these hormones, such as puberty, intake of oral contraceptives (OC), pregnancy and menopause. All these changes may trigger a depressive episode (5).

Estrogen. There are two nuclear receptors (ERs) for E2, which bind to estrogen response elements on DNA in order to modulate gene transcription. These two receptors are ERa and ERb. It is also described as a fast-acting receptor for E2 in the membrane. ERs are found in both women's and men's brains, with similar distribution but with a higher number of receptors in the female brain. ERs are found in the cortex, which has a vast density in the temporal cortex, hypothalamus, amygdala and hippocampus (7). ERa are highly expressed in the hypothalamic nuclei, and because of that, they mediate reproductive functions. ERb are expressed in the paraventricular nucleus and limbic system, and they may have a role in regulating the E2 mediated effects on mood and HPA activity (5). Evidence shows that E2 protects the brain from affective disorders, cognitive decline and neurodegenerative disorders (8-10). E2 was demonstrated to activate brain regions that are implicated in emotional and cognitive functions, such as the dorsolateral prefrontal cortex and amygdala, via functional brain imaging (11).

Progesterone. Estradiol, the quintessential sex hormone in women, plays a pivotal role in mood and cognition modulation, and is intricately linked to all reproductive transitions. However, women also produce another vital sex hormone: Progesterone.

Progesterone is produced mainly by the corpus luteum. Corpus luteum is a vascularized organ found in ovaries and develops from the remains of the ovulating follicle, with the help of LH, and exists for ~14 days after ovulation if the woman does not get pregnant. Progesterone production is relatively simple compared with estradiol, produced with the help of two enzymes. First, cholesterol converts into pregnenolone in the mitochondria by cholesterol side-chain cleavage enzyme, then pregnenolone converts into progesterone by 3b-hydroxysteroid dehydrogenase. A smaller amount of progesterone can be synthesized in the placenta, adrenals and in the brain.

Progesterone undergoes its main metabolic process in the liver, where it is acted upon by the enzymes 5a-reductase and 3a-hydroxysteroid oxidoreductase. This process results in the formation of allopregnanolone and pregnanolone, among other metabolites.

Allopregnanolone is also produced in the brain, but when progesterone levels are high, for example, during pregnancy and the luteal phase of the menstrual cycle, most of it is produced in the periphery. Adrenal glands can also produce allopregnanolone, especially during acute stress (12).

Sex hormones and serotonin. Estrogen and progesterone act as modulators for other neurotransmitters. One of these is the serotonergic system. Estrogen, in particular, may have a key in modulating the serotonin system via tryptophan hydroxylase. Studies performed on non-human subjects who were administered estrogen showed a potential to increase serotonin synthesis and decrease degradation, and in the dorsal raphe nucleus, a possible decrease of the inhibitory feedback (13). Estrogen also modulates the degradation of serotonin. However, this modulation depends on the subtype of the receptor, such as the brain area, and in the case of estrogen treatment, it depends on the duration of the treatment. Through these functions, estrogen can increase serotonin levels and decrease the serotonin reuptake (14). Another role is to increase serotonin receptors and serotonin's secretion, transport and reuptake. As for the receptors, estrogen has the role of upregulating 5-HT1 receptors and downregulating 5-HT2 receptors. It can also decrease the activity of monoamine oxidase (15).

2. Mood changes in young women during the menstrual cycle

Premenstrual dysphoric disorder and sex hormones. Some women develop severe mood symptoms during the late luteal phase of their menstrual cycle, known as premenstrual dysphoric disorder (PMDD). This may occur because progesterone and allopregnanolone, their metabolite, rise progressively after ovulation and fall rapidly during the late luteal phase. It is estimated that women affected by PMDD are ~5-8% (16).

According to the 5th edition of Diagnostic and Statistical Manual of Mental Disorders (DSM 5), PMDD is characterized by a list of 5 symptoms during almost all menstrual cycles, severe enough to interfere with women's daily function. As mentioned, the symptoms appear during the late luteal phase and disappear after the bleeding begins. The women experience sadness, episodes of crying, irritability, symptoms of hopelessness, anxiety, lack of focus on tasks, low interest in usual activities, tiredness, modified appetite, sleep disturbances, along with somatic symptoms such as bloating, articular and muscular pain, and breast tenderness (17).

The pathophysiology of PMDD does not include deficiency or excess of estrogen and progesterone. The problem may be the sensitivity of these women towards physiological changes in hormonal status, or there may be a problem with converting the two hormones into their metabolites. As mentioned, the

neuroactive metabolite of progesterone, allopregnanolone, may play a key role in the apparition of PMDD. A preclinical study on rats reproduced progesterone's fall during the late luteal phase. Because of that, it induced depressive symptoms such as immobility in the forced swim test; in the saccharin preference test, it showed anhedonia. In the social preference test, the rat models had reduced sociability (18). One study indicated that, as a response to stress, women suffering from PMDD and those without a PMDD diagnosis, but in both cases having a history of depression, revealed blunted ALLO response (19).

As for the effects on PMDD, the progestin-only contraceptive, drospirenone, was studied, and it had a positive effect on mood, alleviating the symptoms, when administered over a more extended period of time (20). Another study reported favorable results by using nomegestrol acetate combined with estradiol on premenstrual symptoms, including dysmenorrhea, negative mood and impaired attention in healthy women. They also compared the effects of nomegestrol acetate combined with estradiol, and drospirenone combined with ethinylestradiol, with improved results when given the first combination (21).

Contraceptive treatment and depression induced by them. Since the invention of the OC pill, which took place >50 years ago, >100 million women worldwide use it not only for avoiding unwanted pregnancies but also for treatment of menstrual pain, acne, hirsutism and polycystic ovaries syndrome.

Long-acting reversible contraceptives (LARCs). There are two major types of LARCs, subdermal implants and intrauterine devices (IUDs). This type of contraception has few failure rates, side effects and contraindications, and it is also affordable. An important thing to mention is that once removed, fertility returns rapidly. LARCs are appropriate for almost every woman, even if they are nulliparas or if they are <19 years old (adolescents) (22). The subdermal implant contains only progestins; its effect lasts 3 years and has a failure rate of only 0,1% (23). Concerning the menstrual cycle, most women experience light menstrual bleeding, and some of them amenorrhea, but 20% of them experience irregular menstrual cycles (24). In the United States, there are 5 types of IUDs: 4 hormone-realizing IUDs and 1 non-hormonal copper IUD. Their contraceptive effect lasts for 3-10 years and has <1% failure rate (23). The hormone-realizing IUDs contain levonorgestrel, which is a progestin. Levonorgestrel acts locally in the uterus by offering endometrial protection for women who have anovulatory cycles and also reduces heavy menstrual bleeding (25). The rate of IUD use is meager. In the United States, only 12% of women choose this type of contraception. The reasons why this poor choice exists include fear of pelvic infections, which are no longer the case, fear of pain when placed, changes in the menstrual cycle, and the lack of personal control over removal (26).

Progestin-only contraceptives include the LARCs, levonorgestrel IUDs, a progestin-only OC, and depot medroxyprogesterone acetate (DMPA). The progestin-only OC or 'mini-pill', which contains norethindrone represents the traditional progestin-only pill. In order to reach its optimal effect, it must be received every day at the same time. Another form of progestin-only OC was developed for antiandrogenic effects and contains drospirenone. In order to be used as a treatment for premenstrual dysphoric disorder, acne and hirsutism and as a contraceptive, drospirenone was combined with ethinyl estradiol. The progestin-only OC have a failure rate of 7%. Also, they can be used during breastfeeding and for those women at risk for thromboembolism or stroke, which represent contraindications to medication that contains estrogen (23).

DMPA is represented by an intramuscular injection, administered every 12 to 14 weeks, and has a failure rate of 4%, which is caused by missing the injection appointment (27). Besides contraception, DMPA is used for heavy menstrual bleeding, dysmenorrhea and to prevent ovarian cysts. The side effects of DMPA include a significant increase in body weight, irregular menstrual cycles, and a decrease in bone mineral density, which fortunately is reversible (26).

Combined hormonal contraceptives include transdermal patches, vaginal rings and combined OCs (COCs) and contain progestin and estrogen. They are not only used for contraception but also for irregular menstrual cycles, dysmenorrhea, endometriosis, acne and hirsutism, reduced bone density, and for reducing the risk of endometrial and breast cancer (28). COCs contain 21 days of active pills, 7 days of inactive pills, or 7 days of not taking any pill. The menstrual cycle will appear in those 7 days of break or inactive pill. The side effects of COCs include vaginal bleeding, weight change, cramping and mood changes. The last one is the most frequent reason for discontinuation or change in contraceptive methods (29).

Synthetic versions of estrogen and progesterone form the COC, and when used, it suppresses natural hormonal production. It is known that natural fluctuation of sexual hormones, such as the late luteal phase, the postpartum period, or the premenopausal period, has been associated with the development of mood disorders. Therefore, the use of COC may also determine the apparition of mood symptoms (30). During COC use, estrogen synthesis is suppressed, and the low levels of E2 may contribute to the onset of affective symptoms.

It is important to mention that according to DSM 5 diagnostic criteria for major depressive disorder, symptoms should not be attributable to substances or medical conditions. Depressive symptoms caused by hormonal contraceptives might not qualify as major depressive disorder but rather as other conditions. In DSM-5, these specific disorders can be found as substance- or medication-induced depression, characterized by the clinical picture of depression, with symptoms such as depressed mood, anhedonia, and from the patient's medical history, there is evidence that the symptoms are due to a substance or medication (17). Furthermore, when talking about hormonal contraception and depression, it will be as 'induced depression' or 'induced depressive symptoms'.

There is also marked controversy about whether COC use can determine induced depression or not. It appears that adolescent girls are more prone to develop mood disorders due to COC use. Adolescence is the period in which the development of the sexual hormone milieu takes place, which are hormones that have a significant influence on brain development. One study conducted in the Netherlands examined whether COC use was associated with mood symptoms trajectory from adolescence into adulthood. They examined data from 178 girls, of which 33 began using COC in adolescence.

Their results suggested that those women who used COC early showed a stable trajectory of induced depressive symptoms determined by COC, and the non-users showed an increase in internalizing symptoms. It was questioned if this meant that COC had a protective effect (31). The vulnerability to induced depression as adult women, if COC use begins in adolescence, was reported by a study conducted in Canada. They found out that adolescent women who use OC have a higher 1-year prevalence of induced depressive disorder compared with females who start using OC after the adolescent period (32). Moreover, Skovlund *et al* (33) conducted a study that was a nationwide cohort-prospective study in Denmark. They analyzed a total of 1,061,997 women, 55,5% of them being on contraceptive treatment during the follow-up. They analyzed the effects of different types of contraceptives, including hormone-realizing IUDs, vaginal rings, transdermal patches and OC. The aforementioned study demonstrated a positive link between contraceptive use, especially those containing progestines, and induced depression and antidepressant use, especially in adolescent women (33). As for the long-term risk of developing depression after the use of COC early in life, a previous study found that women who began using COC during their adolescence had an increased risk of developing an induced depressive episode up to 6 years after the first use of COC. Their finding was most pronounced in women who had no history of any mood disorder in their adolescence (34).

One double-blinded randomized Swedish clinical trial, conducted on 202 women, 102 of them allocated to COC and 100 to placebo, suggested that women who had previous mood disorders were at great risk of developing induced mood symptoms during COC treatment. However, these findings only applied to the intermenstrual phase of the treatment cycle (35). Johansson *et al* (36) analyzed 264,557 women and concluded that after initiation of COC use, there was an increased risk of developing induced depression. Even though the risk decreased after prolonged use of COC, those who used it remained with a lifetime risk of developing even a major depression. The same study reported that in the first year after cessation, the depression risk was high, and they explained this risk to be the consequence of developing induced mood symptoms during the COC use; this is the reason why these women stopped taking COC, but the diagnosis of depression comes after the discontinuation. They also reported a high risk in women aged ≥20 years, but the risk was definitely higher among adolescents (36).

Some researchers do not correlate the use of COC with depression. A recent study conducted in the United States analyzed a total of 6,239 women aged 18-55 years, of which 1,742 never used OC, 3,823 used in the past, and 674 were using OC at the time of the study. It was reported that women using OC pills had a lower risk of developing an induced depression compared with those who used them in the past, and no difference between the current users and those who have never used OCs. Moreover, they strongly recommended observing other risk factors that contribute to the apparition of a depressive episode, such as ethnicity, marital status, personal income, history of debilitating diseases (for example, cancer), current use of antidepressants and personal history of major depressive disorder (37). Another research conducted in Sweden on 69 women aged 18-35 years, of which 37 were randomized to take COC and 32 to take a placebo, found strong evidence that COC use did not determine cognitive and emotional impairment. It showed that the strongest predictors were trait anxiety levels and reported history of hormonal contraceptive-induced mood symptoms for depressed symptoms (38).

In one study, healthy women who used COC, which included levonorgestrel and ethinyl-estradiol, reported a decrease in allopregnanolone and other progestin metabolites and a decrease in progesterone and pregnanolone. Even though the levels of these neuroactive steroids were low, they did not report adverse mood changes. To assess the adverse mood changes, they used Beck Depression Inventory, Premenstrual Syndrome Daily Ratings Form, Profile Mood States and Spielberg State-Trait Anxiety Inventory. Despite the low levels of neuroactive steroids, this meant that if healthy women use low doses of COC, and if those women have no history of mood and anxiety disorders, they will not experience mood or anxiety symptoms induced by COC use. This means that those women who experience mood and anxiety symptoms may have a vulnerability to neuro-steroid changes in the brain (39).

Morssinkhof *et al* (40) reported that OC use was not correlated with a higher risk of depression or with more severe depressive symptoms in women diagnosed with major depression. However, they had a positive correlation between OC use and insomnia. Women taking OC experienced severe insomnia symptoms, and it did not depend on whether they had the diagnosis of major depressive disorder, or not (40).

As for the suicidal risk in OC users, one study conducted on Swedish women aged 15-22 reported that this risk was increased after COC use. But it was also found out that the risk declines if the use of OC is prolonged. Between the progestines only OC and COC, a greater risk was reported in the first category (41). In another similar research from Denmark, women, this time aged up to 33 years old, also reported a high suicidal risk after the initiation of OC and also reported that this risk declined after 1 year of use. The highest risk was observed in adolescent women. They also reported that progestin-only contraceptives had a higher risk than COC (42).

The relative risk of suicide attempts was two-fold higher in women who used COC, after 1 month of using them, compared with non-users. The risk persisted 1 year, and started decreasing afterwards. The completion of the suicide attempts was 5-fold higher in COC users than in non-users. The high risk of suicide completion in former users remained also higher compared with non-users (42).

Conclusions. It appears that it is not possible to establish if there is a certain link between the use of COC and the development of induced depression. It is well known that OC are synthetic hormones, which when used, suppress the physiological hormone production. What is clear, is that if used during adolescence, because the brain and the endocrine system is still developing, there may be a risk for depression. Furthermore, it appears that women who had a previous depressive episode, or who experienced mood side effects from a previous use of COC, were more prone to develop once again mood symptoms. It is important to mention that the type of OC is relevant in the apparition of depressive symptoms. It appears that progestines-only OC are more prone to induce affective symptoms, compared with the new COC.

3. Depression and pregnancy

In the DSM 5, the diagnosis of post-partum depression is no longer available. If the onset is postpartum, then the specifier is added to the diagnosis of the current depressive episode: With postpartum onset, when the depressive episode occurs during pregnancy or within 4 weeks after delivery (17).

The peripartum period is one of the most susceptible periods, in which women may develop a depressive episode due to changes in the sexual hormone levels. A previous study suggests that 2/3 of pregnant women had symptoms that met the criteria for a depressive episode and that those women were not aware of having depression and did not receive psychiatric treatment (43). It appears that only 20% of those pregnant women who were diagnosed with a major depressive episode received proper psychiatric treatment (44). In addition, the occurrence rate of depression in the first 12 months postpartum is ~9-22% (45). One systematic review pointed out differences in prevalence and incidence between the different periods of time. It was found that the best estimates suggest that 18,4% of pregnant women meet the criteria for a depressive episode, and 12,7% of these women meet the criteria for a major depressive episode. The studies included in the systematic review suggest that 14,5% of pregnant women meet the criteria of a depressive episode, and 14,5% have a new depressive episode during the first three months after delivery, incidencewise (46).

Regarding personal history, women who were diagnosed with depression in the past had a 20-fold increased risk of developing postpartum depression. Furthermore, the age of the mother is a risk factor for postpartum depression: Adolescents and women aged ≥35 years having a history of depression showed the greatest risk (47).

The two representative hormones for pregnancy are estrogen and progesterone. There are different hypotheses regarding the two how they may contribute to the onset of postpartum depression.

Estrogen hypothesis. It is well known that during pregnancy, the levels of estrogen fluctuate significantly, and these fluctuations may contribute to the onset of a depressive episode. The estrogen levels rise during pregnancy, especially in the third trimester, because this hormone is synthesized primarily from the placenta. Estrogen levels rise to 100-1,000-fold during the third trimester, and they drop abruptly to pre-follicular levels by the fifth day after delivery (48). Mood symptoms such as depression, anxiety and irritability appear also in menstruation and menopause due to the low levels of hormones. Because of these fluctuations, numerous studies have shown that after delivery, there is an 'estrogen withdrawal state', and this may lead to postpartum depression. This is the most tested model of postpartum depression. Although some studies succeeded in confirming this hypothesis, there are several human and rodent studies that failed to support it. Some experimental studies managed to demonstrate that, after delivery, respectively, after the estradiol withdrawal, the subjects were showing signs of increased behavioral despair and depressive symptoms (49-51). Galea *et al* (49) conducted an experimental study on female rats, who, after being ovariectomized, were administered hormone replacement therapy in order to mimic pregnancy. The study analyzed three groups: the 'pregnant' group, another 'pregnant' group to which they administered estradiol benzoate during the postpartum phase, and a control group. It was found that estradiol administration during the postpartum period reduced depressogenic behavior, such as decreased immobility when exposed to a forced swim test. The group who continued to receive estradiol benzoate, also defecated less. Increased defecation in rats shows behavioral or emotional despair (49).

The effects of estrogen on mood symptoms are well known because of estrogen administration in women during menopause. The exact mechanism is not well known yet. However, estradiol stimulates the release of numerous neurotransmitters and hormones, such as serotonin, dopamine, gamma-aminobutyric acid, norepinephrine and corticosterone, which are essential in regulating mood. After delivery, when estrogen levels are decreasing abruptly, there may be a decrease in the availability of the neurotransmitters, or in the affinity or number of mono-amine receptors (52).

In rodents, estrogen levels remain low in the first and second trimester of pregnancy, and the levels rise during the final period of the third trimester. In humans, estrogen levels increase during all three trimesters of pregnancy. This may be the reason why the hormonal profile of human pregnancy is more vulnerable to estrogen withdrawal. One study tested estradiol withdrawal on both non-human and human species. In rat experiment 1, they administered high doses of estradiol over 5 days, followed by 5 days of withdrawal in which rats developed anhedonia. In the second rat experiment, during the withdrawal phase, rats showed decreased swimming and increased immobility during the forced swim test. The human results were similar to other studies, meaning that those women who had a history of postpartum depression were at high risk of developing another one (53).

Progesterone hypothesis. Progesterone has the role of preparing the uterus for pregnancy and maintaining the pregnancy. The metabolite allopregnanolone has neuroprotective functions in developing the fetus's central nervous system. At the beginning of the pregnancy, progesterone is produced by the corpus luteum, and beginning with 7-9th weeks of pregnancy, the placenta takes this role gradually. Before delivery, progesterone levels reach 200-2,000 nmol/l, and allopregnanolone rises ~10-fold the average value. The levels of these hormones drop significantly after delivery; half of progesterone is eliminated from the bloodstream in the first 30 min, and its levels reach the luteal phase levels in the first 2-3 h after delivery. Therefore, it is described as a 'withdrawal state' similar to the one caused by estradiol drop. Symptoms of depression and anxiety characterize postpartum blues and are a transitory state, which appears in the first week after delivery, and it affects 40-50% of women. Postpartum blues appears due to the abrupt drop in progesterone and allopregnanolone levels. Women with a history of postpartum depression are more prone to develop another depressive episode after delivery than women without a history of postpartum depression. It is well known that allopregnanolone binds to GABA receptors. Because of the significant drop in its levels after delivery, symptoms of anxiety and depression are precipitated by the withdrawal state (12).

A previous study tried to replicate the hormonal profile found during pregnancy by injecting the subjects with a gonadotropin-realizing hormone analog, leuprolide acetate 3.75 mg every month during the baseline phase, in order to produce hypogonadism, and afterward, in the addback phase, they used estradiol and progesterone in order to obtain high plasma levels of these hormones. In the withdrawal phase and follow-up, they changed the medication with a placebo, inducing an abrupt drop of plasma estradiol and progesterone levels, and the women were followed for another 8 weeks. They reported an increase in depressive symptoms in the withdrawal phase in those women who had a history of postpartum depression, but the comparison group had no symptoms of depression; for this group, symptoms started to show in the attack phase. This finding might have suggested that the women who had a history of postpartum depression responded differently when the levels of sex hormones dropped abruptly (54).

Another study tried to link anhedonia and other depressive symptoms to hormonal changes in euthymic women with a history of postpartum depression by using GnRH agonist to induce hypogonadism, then starting to increase the hormone levels by giving estradiol and progesterone medication, and finally, changing the medication after 8 weeks to induce the hormonal withdrawal. They also used functional magnetic resonance imaging to identify if the underlying mechanism could identify the women with a history of postpartum depression who were hormone sensitive in the pre-treatment phase and to observe those changes in striatal activation compared with those women who were not hormone sensitive. They reported that women with a history of postpartum depression developed anhedonia and other depressive symptoms in the addback and withdrawal phase, compared with women without a history of postpartum depression. Even though it was hypothesized that there would be a decreased activation during reward feedback in the putamen, caudate and nucleus accumbens in women who were hormone-sensitive and not in those who were not hormone-sensitive, they reported a decreased activation in both groups during hormonal withdrawal. Therefore, this method could not predict a woman's susceptibility to postpartum depression (55).

Because the estrogen levels during pregnancy and postpartum are the same in both euthymic and depressed women, a previous study tried to identify early biomarkers to predict the risk of developing postpartum depression. They draw blood for mRNA measures in the first and third trimesters. It was found that between euthymic women and postpartum depressed, 786 transcripts in the first trimester and 116 transcripts in the third one were different. Of the 116 transcripts from the third trimester, 39 were involved in estrogen metabolism, estrogen-responsive, or estrogen signaling. Therefore, it was concluded that postpartum depression is a consequence of differential activation of estrogen genes. If the expression levels of those 116 transcripts are measured during the third trimester when the women are still euthymic, it can predict the onset of postpartum depression (56).

Hormonal treatment. Even though the first line of treatment for depression is represented by antidepressant, studies have tried to do a research on hormonal treatment as an adjuvant, for women diagnosed with depression, due to the major hormonal changes during pregnancy.

Two phase 3 trials, double-blind, randomized and placebo-controlled studies, conducted in the United States, randomly assigned women to receive either brexanolone 90 mg/kg/h (BRX90) intravenously, brexanolone 60 mg/kg/h (BRX60) or placebo, for a total time of 60 h in the first study, and in the second study BRX90 or placebo, for the same amount of time. Brexanolone is a form of injectable allopregnanolone with the propriety to modulate synaptic and extra-synaptic GABA-A receptors. The first study reported that brexanolone was far superior in its effect to the placebo. Moreover, there was also a difference between BRX90 and BRX60 in terms of effectiveness. The effect had its onset action after 60 h, and the positive response was sustained for up to 30 days. In total, 94% of the women who responded to brexanolone had no relapse after 30 days (57). Brexanolone intravenous infusion therapy is the first treatment specific for postpartum depression approved by the Food and Drug Administration in March 2019 (58).

Another study tried to identify if the treatment with transdermal estradiol is comparable with the brexanolone infusion. They conducted a double-blind, placebo-controlled trial on women diagnosed with postpartum depression who received either 100 mg/day of 17b-estradiol or a placebo patch. The results were not those expected. In the primary outcome, there were no significant differences between transdermal estradiol and placebo regarding treatment response or symptom remission. In the secondary outcome, a significant reduction in mood symptoms was reported after 3 weeks, compared with the placebo. However, after multiple comparisons and corrections, these differences between the estradiol patch and placebo were no longer significant (59).

Conclusions. There is a clear link between the 'hormonal withdrawal' after delivery, and the onset of postpartum depression, especially in those women who already had postpartum depression, and also there may be a genetic vulnerability to the abrupt drops of the serum hormone levels. It is important to mention that even though there is a history of postpartum depression, the same woman can respond different to the 'hormonal withdrawal' in a different pregnancy. At present, the only specific treatment for postpartum depression approved by FDA is the intravenous infusion with brexanolone. This opens a window to lower the burden and to actually have a sustained response for women with this diagnosis.

4. Depression and menopause

Hormonal changes during menopause. Menopause is defined by the absence of menstrual cycles for at least 12 months. The menopause transition lasts ~4 years, but this period can range from 0-11 years. In pre-menopause, women have regular menstrual cycles ranging from 22 to 35 days. In the early transition period, the women experience 7 days or longer in any direction, in cycle length, from their baseline, for at least 2 cycles. In late transition, the women have amenorrhea for 3-11 months. High levels of FSH and menstrual irregularities also characterize it. Moreover, the last period is represented by post-menopause, when women have amenorrhea for at least 12 months without having a hysterectomy. It is characterized

by high levels of FSH and LH and low levels of estradiol and progesterone (60).

In perimenopause, there are a lot of hormonal changes that may affect the mood. First, a high level of serum FSH can be detected, possibly due to the decline of ovarian follicles before menopause is set. The ovarian follicles develop in an erratic mode, resulting in anovulatory cycles and fluctuations in estrogen levels. Because of that, the pituitary gland is stimulated, via negative feedback, by the low levels of estrogen to produce high levels of FSH to stimulate the follicles to produce estrogen. Besides the low levels of estrogen during the menopause transition, there are also low levels of inhibin. Inhibin B regulates the secretion of FSH via negative feedback. LH production may be expected, but the low estrogen and inhibin B levels disrupt the normal secretion of FSH.

The production of different types of estrogen is also disrupted during the perimenopause period. 17-b-estradiol represents the most active form of estrogen and is produced in the ovaries and granulosa cells. Moreover, it can be produced from testosterone and androstenedione by converting them with the help of the enzyme named aromatase, along with estuarine, with estrone, a less active form of estrogen. Estrone can also be produced in the periphery, especially in postmenopausal women, by converting the adrenal androstenedione to aromatase. When menopause occurs, estradiol levels drop, and estrone becomes the main form of estrogen, derived mainly from the periphery. Because perimenopause can last several years, women experience intense fluctuation in the levels of sexual hormones. These changes can be experienced up to 2 years after menopause is set, when the hormone levels become more stable, and the main form of circulating estrogen becomes estrone (61,62).

Impact on mental health. Because the activity of estradiol is mediated through its receptors, ERa and ERb, the polymorphisms in ER1 and ER2 genes could have a significant impact. It is considered that the antidepressant effects of estradiol are mediated through ERb. A previous study analyzed the polymorphism of ER1 and ER2 to explore if it is associated with the onset of depression later in life (63). The aforementioned study was conducted on 3,525 women who were in their post-menopause phase when their depressive symptoms developed. An association was found between the onset of depression later in life and the presence of an A allele for ER2 rs1256049 polymorphism in those women who were not using hormonal therapy, suggesting that even if there is a genetic risk factor, hormonal therapy can protect women for depression (63).

Certain studies indicate that women who are more sensitive to hormonal shifts during their lifetime have an increased risk of developing during the menopausal transition, a depressive episode, or experiencing a relapse of major depressive disorder (64). Longitudinal studies showed that the risk for depression during the menopause transition is 2-5-fold greater than in late menopause. Each used hormone levels and quantified the severity of depression in order to confirm the specific period in which the depressive episode occurred. If the women experienced a depressive episode only during the menopause transition, the risk appears to decline after the last menstrual cycle, up to 4 times. These findings indicate that the appearance of a depressive episode is not due to aging itself (65-68).

There is a lower risk of depression in women who have a faster rate of change in FSH. This can be explained by a stable hormonal profile with a more rapid rise in FSH levels and a faster menopausal transition (69).

The hormonal fluctuation, not the low levels of estradiol, determines the onset of depression during menopause transition (70). A previous longitudinal study reported significant hormonal fluctuation in women without a history of mood disorders who developed depressive symptoms, such as increased levels of FSH, low levels of LH and inhibin B, and also an increased variability of FSH, LH and estradiol (67).

Additionally, it appears that in order to develop depression during the menopause transition, it is not enough to have only the hormonal fluctuations. It appears that the personal history of depression represents a high risk, combined with the specific hormonal status. One longitudinal cohort study tried to determine the relationship between depression, menopausal transition, sex hormones and other predictors of depression. They reported increased depressive symptoms during the menopausal transition. After they managed to control other important factors such as history of depression, age, social and economic factors, hot flashes and ethnicity, the symptoms decreased after the menopause was installed. The depressive symptoms also decreased with age, with the oldest women being 66% less likely to develop depressive symptoms, which supported the fact that the symptoms decreased after menopause. For those women who had no history of depression, they were twice more likely to report depressive symptoms during the early transition phase (64). In another research, Freeman *et al* (69) performed follow-up in women in order to determine the ranges of depressive symptoms during 14 years. All women enrolled were in the premenopausal phase at the beginning of the study. They reported a high risk of depression before the final menstrual period and a low risk after the final menstrual period. However, again, the history of depression was a decisive factor for depressive symptoms. Women who already experienced a depressive episode had a 13-fold greater risk to develop another episode. For the women without a history of depression, the incidence of depression dropped after the final menstrual period, having a risk not markedly more significant than the risk for those women who never had a depressive episode (69). Also, regarding the personal history of depression, two Harvard studies reported a significant link between depression and ovarian failure. They conducted follow-up in ~1,000 women over 3 years, measured serum hormone levels, assessed the menstrual cycle characteristics, and performed psychiatric evaluations. It was found that women who had a history of depression were more prone to develop more significant fluctuations in serum hormonal levels. Furthermore, this group of women developed symptoms of depression earlier in perimenopause compared with those who had no history of mood disorders. A causal link could not be proved, but the development of depression and changes in ovarian function may be interrelated (71,72).

Treatment approaches. Regarding hormonal therapy during the menopause transition, there is also some controversy. Some studies reported that it is improved compared with a placebo,

and some concluded that hormonal therapy has equal effects. Morrison *et al* (73) showed in a randomized clinical trial that the treatment with estradiol has the same effects as a placebo, especially in older women who transitioned to menopause and had little or no response to estrogen therapy, suggesting that there is indeed a 'window' for hormonal therapy. However, estrogen is available in numerous forms, such as oral tablets, transdermal patches, subdermal implants, creams and intranasal or sublingual formulations. The efficacy of synthetic estrogen on mood depends on pharmacokinetics. Oral estrogen is metabolized through the liver. Therefore, it converts into a less active metabolite, estrone. On the other hand, transdermal patches avoid hepatic metabolization and provide a rapid rise in the levels of estrogen (62).

A previous study tried to examine for the first time the efficacy of transdermal estradiol combined with intermittent micronized progesterone to prevent the apparition of depressive symptoms during the menopausal transition (74). It was reported that during the 12-month intervention, 17% of women treated with the hormonal combination developed significant mood symptoms compared with 32% who received a placebo. They adjusted statistically for the vasomotor symptoms. Therefore, the results were statistically significant, and it could be said that the treatment with transdermal estradiol combined with intermittent micronized progesterone could prevent depressive symptoms. It should be mentioned that the hormonal treatment is safe in the pre-menopause phase, menopausal transition and early menopause, given at the lowest dose (74).

Hormonal treatment also improves self-reported sleep, both the latency (women needed fewer minutes to fall asleep) and the number of awakenings. Sleep disturbances in women who find themselves in the menopausal transition are due to both depression and vasomotor symptoms (hot flushes) (75).

However, there can also exist a risk in hormonal therapy, depending on the type of administration. A large Danish cohort study conducted on 825,238 women reported an increased risk of developing depression in those women who used systemically administered hormonal therapy (oral and transdermal), with a higher risk between ages 45 and 50 during the first year of hormonal therapy. Women <54 years had no risk of depression in locally administered hormonal therapy (intravaginal and intrauterine), and for those who were ≥54 years, the risk was low (76).

Conclusions. The menopausal transition is the last period in a woman's life, when she can experience depressive symptoms due to hormonal fluctuations. It is important to mention that the depressive symptoms are not determined by the low levels of estradiol, but by the day-to-day fluctuations, especially the increased levels of FSH. If the menopause transition occurs rapidly, and the high levels of FSH become stable in a short period of time, the depressive symptoms may not appear. But it appears that the unstable hormone levels are not enough in order to develop depression; the personal history of depression is also important. Anyway, even though a depressive episode may be developed due to hormonal fluctuations, the risk of another one decreases over time, because in late menopause there are no more of these fluctuations. But the symptoms of depression can be managed with the help of hormonal therapy, if it is administered during an opportune 'window', which is in the beginning of the menopause, premenopausal phase, menopausal transition and early menopause. In late menopause, this type of therapy is no longer helpful, and can do more harm due to the adverse effects of the hormonal therapy, such as thromboembolism.

5. Conclusions

It appears that after puberty, the risk of depression for women is higher than for men. This can be explained by the hormonal fluctuations during important periods in a woman's life, such as the postpartum period and menopause transition. These hormones are represented by estrogen and progesterone. Besides these fluctuations in the levels of sexual hormones, it is important to observe if there is a personal history of depression or a personal susceptibility. It is not well established if contraceptive treatment alone can induce a depressive episode. Regarding contraceptive use, it can be stated that the risk is greater for those women who start early in life using them, in adolescence, to develop a depressive episode induced by contraceptives. Also, the risk of OC to induce depression is grater when there is a personal history of depression or a personal history during a previous contraceptive use.

Another important period of hormonal fluctuation is the postpartum period, when a personal history of postpartum depression may predict another one. There is a clear link between the 'hormonal withdrawal' after delivery, and the apparition of postpartum depression, due to the abrupt fall of hormonal levels. Fortunately, there is a specific hormonal treatment for this condition, approved by Food and Drug Administration in 2019, which is the brexanolone intravenous infusion.

The last period of hormonal fluctuations in a woman's life, represented by the menopause, can also trigger a depressive episode, but all the risk factors have to be considered, and to establish if the depressive episode is indeed determined by those fluctuations. In this case, the depressive symptoms are not determined by the low levels of sex hormones; they are determined by those unstable levels of hormones, which occur in the pre-menopause phase, menopause transition and early menopause. After the menopause is set, and there are no more hormonal fluctuations, the risk lowers.

Also, hormonal therapy, even regarding contraception, or estrogen therapy for the menopausal transition, must be indicated carefully and it must be investigated if there is any risk in recommending it, psychiatric or somatic.

6. Further research

Future research is required in this field, regarding if a direct link between the levels of estrogen and progesterone and depressive disorders really exists, and also regarding different hormonal therapies.

Further research is needed in this direction to clarify if the use of OC and depression are indeed connected. These types of studies are difficult to conduct and their duration is markedly long. In order to get close to determine the link between OC and depression, it would be important to determine the family history of affective disorders, the personal history of

depression, to know exactly if any of a woman's day to day treatment, if there is one, can induce a depressive episode. Furthermore, a personal alcohol or drug abuse, which are other possible risk factors for depression, must be taken into consideration; only afterwards the effects of OC on mood can be studies. As aforementioned, this type of study is difficult to conduct, as it depends on the compliance of the subjects, and it requires a lot of time in order to establish if OC can induce a depressive episode during the use of OC, or after a number of years from cessation.

As further investigations for postpartum depression, it would be an option to conduct more epigenetic studies, in order to find out if there really is a way to prevent the on-set of postpartum depression. But these types of studies can be expensive to conduct, and even if there would be a way to prevent it, probably not every woman at risk could afford the prevention. Another idea of a further research could be the finding of a hormonal treatment for postpartum depression, such as brexanolone.

Additionally, further research in the area of perimenopausal depression is needed. It would be important to include in further studies all the risk factors for depression, in order to identify if a depressive episode during this period of time is related to hormonal fluctuations or not. It would also be interesting to investigate through epigenetic studies, similar to those conducted for postpartum depression, if a depressive episode due to hormonal fluctuations could be prevented.

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Availability of data and materials

The data generated in the present study may be requested from the corresponding author.

Authors' contributions

IPH and IVM conceived and designed the study, and collected data. IPH, BDCS and RP analyzed and interpreted the results, and prepared the draft of the manuscript. All authors read and approved the final version of the manuscript. Data authentication is not applicable.

Ethics approval and consent to participate

Not applicable.

Patient consent for publication

Not applicable.

Competing interests

The authors declare that they have no competing interests.

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