Chapter 5

Reproductive Aging: Perimenopause and Psychopathological Symptoms

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Additional information is available at the end of the chapter

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Abstract

The female reproductive axis essentially comprises of the hypothalamic-pituitary-ovarian axis and the mullerian-derived structures. The reproductive axis ages to a non-functional state (menopause) much earlier than the other organ systems do, at a time when a woman is otherwise healthy. The basis of reproductive senescence in women is oocyte depletion in the ovary. Perimenopause is defined by menstrual cycle and endocrine changes, such as disturbed ovarian-pituitary-hypothalamic feedback relationships, inaccurate estrogen levels, and decreased progesterone levels. Many psychopathological changes can take place, but most commonly women experience mild cognitive impairment, anxiety, irritability, mood swings, and depression. Estrogens influence depression and depressive-like behavior through interactions with neurotropic factors and through an influence on the serotonergic system.

Keywords: reproductive aging, menopausal transition, perimenopause, estrogen, progesterone, neurotransmitters, mental disorders

1. Introduction

The belief that behavioral disturbances are related to manifestations of the female reproductive system is an ancient one that has persisted to contemporary times [1].

This belief regarding the middle-aged years and the negative outlook of the perimenopause is not completely irrational. There are some events that support impressions such as the completion of the reproductive period, separation from children, care for very old parents and relatives, onset of illness, retirement, or financial insecurity. Perimenopausal changes are not

symbols of some "ominous changes" but are instead a part of reproductive aging, which appear much earlier in life than do the various other physiological organ system changes due to somatic aging.

Reproductive aging is a natural process that begins at birth and proceeds as a continuum. The basis of reproductive senescence is oocyte depletion, a steady-state loss through atresia and ovulations. The decline in reproductive capacity is accompanied by increased risk of psychogenic disturbances, osteoporosis, and cardiovascular and cerebrovascular diseases.

There is a lot of evidence from basic science, epidemiological data, and interventional studies to indicate that estrogens are positively influencing mental well-being. Depressive symptoms and even an upsurge in the incidence of some mental disorders have been observed around the menopause, suggesting the direct involvement of instant loss of estrogen activity in mental health.

2. Stages of reproductive aging

Menstruation is the regular discharge of blood and mucosal tissue from the inner lining of the uterus through the vagina as a result of periodic hormonal changes.

Menarche is the first menstruation, and **menopause** is the point in time when permanent cessation of menstruation occurs following the loss of ovarian activity [1]. The term is derived from the Greek words "men" (month) and "pausis" (cessation). Menopause is confirmed 12 months after the onset of amenorrhea.

The years prior to menopause are known as the perimenopausal transitional years. An older, more popular, and less precise term is **climacteric**, the expression derived from the Greek word for "ladder" and should be used only when talking to patients and in the lay press, not in scientific papers [2].

The 2001 Stages of Reproductive Aging Workshop (STRAW) proposed a new nomenclature and staging system for objectifying ovarian aging, including menstrual and quantitative hormonal criteria to define each stage, and has been reviewed and updated in 2011 [3]. The "**STRAW+10**" staging system is widely considered as the gold standard for characterizing reproductive aging through menopause.

It divides the adult female life into three main phases:

- Reproductive
- The menopausal transition
- Postmenopause.

The phases include a total of seven stages centered around the final menstrual period (Stage 0). The reproductive phase is divided into stages −5, −4, and −3 (early, peak, and late reproductive phase, respectively). The menopausal transition phase consists of stages −2 (early) and −1 (late), whereas the postmenopausal phase contains stages +1 (early) and +2 (late) (**Table 1**).

Stage	−5	−4	−3b	−3a	−2	−1	+1a	+1b	+1c	+2
Terminology	Reproductive phase				Menopausal transition		Postmenopause			
	Early	Peak	Late		Early	Late	Early			Late
					Perimenopause					
Duration	Variable				variable	1–3 years	1 year	1 year	3–6 years	Remaining lifespan
Principal criteria										
Menstrual cycle	Variable to regular	Regular	Regular	Subtle changes in flow length	Variable length (≥ 7 days difference)	Interval of amenorrhea of ≥60 days				
Supportive criteria										
Endocrine			Low	Variable	↑ Variable	↑ >25 IU/L	↑ Variable		Stabilizes	
FSH			Low	Low	Low	Low	Low		Very low	
AMH				Low	Low	Low	Low		Very low	
Inhibin B										
Antral follicle count			Low	Low	Low	Low	Very low		Very low	

Adapted from Harlow et al. [3].

Table 1. The 2011 STRAW+10 staging system for reproductive aging in women.

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The system does not use age as the criterion for determining reproductive staging. The **principal criteria** are the menstrual cycle patterns [1], which can be described with regularity of menstrual bleeding, frequency of onset, duration of menstrual flow, and heaviness (or volume) of menstrual flow. Regular menstrual cycles are usually the outward manifestation of cyclical ovarian activity and ovulation.

The **supportive criteria** include endocrine parameters such as serum concentrations of follicle stimulating hormone (FSH), anti-müllerian hormone (AMH), and inhibin-B. **Subjective data**, such as menstrual flow changes, are considered too subjective and variable, particularly between ethnic groups, to be included in the criteria. Vasomotor symptoms are the only exception, and have been included in the system only as **"descriptive" criteria**.

The main vasomotor symptoms are hot flashes and cold or night sweats. Hot flash is a sensation of heat, usually involving the face and neck and upper part of the chest. It is caused by a transient dilation of the blood vessels of the skin.

Women who have undergone hysterectomy or endometrial ablation cannot be staged by menstrual bleeding criteria. Reproductive stages in these women can only be assessed using the supportive endocrine criteria.

STRAW+10 stages are outlined in the following paragraphs.

2.1. Late reproductive stage

As defined by STRAW+10, in the late reproductive phase (Stage −3a), there are subtle changes in menstrual cycle characteristics. The cycles get shorter, early follicular phase FSH levels increase and become more variable, and the AMH and antral follicle counts get low (**Table 1**).

2.2. Early menopausal transition

Stage −2 is marked by increased variability in menstrual cycle length with consecutive cycle-to-cycle variation of 7 days or more. Early follicular phase FSH levels are elevated and variable, and AMH and antral follicle counts are low (**Table 1**).

2.3. Late menopausal transition

In Stage −1, menstrual cycles are characterized by increased variability in cycle length and the occurrence of amenorrhea lasting 60 days or longer. There are extreme fluctuations in hormonal levels, an increased prevalence of anovulation, and FSH levels are greater than 25 IU/L in a random blood draw. Vasomotor symptoms are likely to occur. This stage is estimated to last, on average, 1–3 years and ends with the last menstrual period (**Table 1**).

2.4. Early postmenopause

FSH levels continue to increase while estradiol levels continue to decrease until approximately 2 years after the final menstrual period (stage +1a and +1b) (**Table 1**). Stage +1c represents the period of stabilization of high FSH levels and low estradiol levels. The entire early postmenopause lasts approximately 5–8 years.

2.5. Late postmenopause

As defined by STRAW+10, further changes in reproductive endocrine function (Stage +2) are attributable predominantly to somatic aging. Symptoms such as urogenital atrophy progress during the remaining lifespan. Urogenital atrophy is a cluster of symptoms including vaginal dryness, painful intercourse (dyspareunia), vulvar pruritus, burning, discomfort, as well as recurrent urogenital infections.

3. Reproductive physiology of perimenopause

Perimenopause is a period of reproductive aging that includes the early and late menopausal transitions (Stages −2 and −1) and the first year of early postmenopause (Stage +1a). It usually occurs in the late fourth to fifth decade of a woman's life and lasts approximately 15 years.

It is characterized by three major hormonal changes [1, 4, 5]:

- Disturbed ovarian-pituitary-hypothalamic feedback relationships
- Inaccurate estrogen levels
- Decreased progesterone levels.

3.1. Changes in ovarian-pituitary-hypothalamic feedback controls

Ovarian control of gonadotropin secretion is normally achieved by feedback control mechanisms, including estradiol, progesterone, and ovarian regulatory proteins. FSH is secreted in pulses by the anterior pituitary under the influence of hypothalamic gonadotropin-releasing hormone, with a direct inhibitory feedback by estradiol and inhibin B, and stimulatory action of activin [1]. Recent research has clarified that a fall in inhibin B is the basis for FSH rise with ovarian aging [5, 6]. With a decreasing follicular pool, inhibin B levels, produced by small antral follicles, decline and thus allow FSH levels to rise in the early follicular phase.

Follicular growth in the early follicular phase is under control of FSH, which stimulates the granulosa cells of antral follicles to produce estradiol and inhibins.

Between days 5 and 7 of the menstrual cycle, selection of a follicle takes place whereby only one dominant follicle is destined to ovulate from the cohort of recruited follicles, and the remaining ones are to undergo atresia.

With dominant follicle selection and a subsequent rapid rise in estradiol, the pituitary responds by releasing a luteinizing hormone (LH) surge, which in turns triggers ovulation [1].

The LH surge occurs 34–36 hours prior to ovulation. In order for the positive feedback effect to trigger the LH release, estradiol levels must be greater than 200 pg/mL for at least 48 hours in a continuous duration [1]. Ovulation occurs approximately 10–12 hours after the LH peak, and the dominant follicle is almost always >15 mm in diameter on ultrasound [7].

During menopausal transition, the follicular phase is shortened and associated with accelerated ovulation, which in turn occurs at a smaller follicle size [8].

With time, the age-related hypothalamic modifications cause a decrease in estrogen sensitivity and the mid-cycle LH surge becomes more erratic. Furthermore, it is hypothesized that the higher FSH levels might interfere with oocyte release and with progesterone production [9].

Additional perimenopausal feedback imbalances that lead to anovulation involve changes in LH and estradiol secretion. Despite the occurrence of a normal estradiol peak, an LH surge does not follow.

Finally, despite high follicular phase estradiol levels, cycles may have no evidence of either an estradiol or an LH peak, and hence there is no ovulation [5]. The hypothalamus and/or the pituitary can become insensitive to estradiol feedback resulting in anovulation.

It is known that with higher baseline FSH levels, average LH levels may remain normal in the perimenopausal transition. Changes however appear in the dynamics of LH release. Although estradiol levels are not significantly different, cycling perimenopausal women appear to lack the slow-frequency, high-amplitude LH pulsatility characteristic of the luteal phase and resulting in decreased progesterone levels.

3.2. Inaccurate estrogen levels

Estradiol is the main ovarian estrogen produced by follicular granulosa cells. FSH activates the aromatase enzyme, which converts androgens to estrogen.

During the follicular phase, serum estradiol levels rise in parallel to follicle size growth as well as to the increasing number of granulosa cells [1, 10]. In the presence of estradiol, FSH stimulates the formation of luteinizing hormone (LH) receptors on granulosa cells allowing the secretion of small quantities of progesterone, which exerts a positive feedback on the estrogen-dependent pituitary LH release [1].

Recent scientific reviews have shown intermittently high levels of estrogen during the perimenopause. This evidence contradicts the assumption of dropping or overall lower estrogen levels during the perimenopause and invalidates the casual use of the term “estrogen deficiency” as a synonym for perimenopause [5].

Santoro and coauthors were the first to propose the then-radical concept about high estradiol levels [11]. The observation was confirmed by a meta-analysis comparing samples from women of reproductive age to those from perimenopausal women within the same research center. Mean estradiol levels were statistically higher in perimenopausal women [9] (29% in the follicular phase and 22% in the late luteal phase).

Higher estradiol levels are a common result of a higher number of recruited estradiol-producing follicles, while that in turn results from the net effect of rising FSH levels. As previously discussed, FSH increases early in the follicular phase due to changes in the feedback control mechanisms: impaired suppression of FSH by higher estradiol levels and lower intraovarian production of inhibins and, on the other hand, by the stimulatory input of both activin and gonadotropin-releasing hormone [4].

FSH changes are also related to the second estradiol peak during the luteal phase in the form of a “luteal out of phase” (LOOP) event. Hale and coauthors estimated that about a third of

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all menopausal transition cycles show evidence of these events, with a higher estradiol peak following the normal mid-cycle estradiol peak [4, 12].

3.3. Menstrual cycle during menopausal transition

After menarche, it usually takes several years for regular menstrual cycles to establish. Bleeding that can be defined as a "period" is described according to the following four parameters:

- Regularity of onset
- Frequency of onset
- Duration of menstrual flow
- Heaviness (or volume) of menstrual flow [13].

The normal frequency of menses is between 24 and 38 days [4]. During the **early menopausal transition**, menstrual cycles remain regular, with a cycle-to-cycle duration variation of 7 days or more; for example, a cycle length of 24 instead of the previously established years-long regularity of 31 days. **Late menopausal transition** is characterized by two or more skipped menstrual bleedings and at least one intermenstrual interval of 60 days or more.

Transitionally higher estradiol levels are associated with heavy monthly blood loss and increased endometrial thickness (hyperplasia). In the Seattle Woman's Midlife Health study, the most common subjective menstrual cycle changes were flow-related and included a heavier menstrual flow in 29% and a longer duration of the flow in 20% [14]. Menstrual blood loss was greater following ovulatory rather than anovulatory cycles [15], especially if the ovulatory cycle followed a prolonged interval of anovulation, during which unopposed high estradiol levels contributed to abnormal excessive proliferative changes in the endometrium [16].

A quantitative study by Hale and coauthors shows that blood loss increases in its absolute values and in its variability across the peak reproductive, late reproductive, and late menopausal transition phases [17].

3.4. Fertility and menopausal transition

Perimenopause is the time period bridging the mature fully reproductive and the non-reproductive states. The loss of fertility is the first sign of reproductive aging and precedes the monotropic increase in FSH levels as well as changes in menstrual regularity [2].

The number of non-growing follicles is determined before birth, when oocytes multiply to a maximum of 6–7 million at mid-gestation. Oocytes are then rapidly lost due to apoptosis, leading to a population of 700,000 at birth and 300,000 at puberty.

The Wallace-Kelsey model matches the logarithm-adjusted non-growing follicle population from conception to menopause to a five-parameter asymmetric double Gaussian cumulative curve [18]. It is based on the assumption that the peak number of non-growing follicles at 18–22 weeks of gestation defines the age at menopause for every individual woman, and it does not take into account the recent evidence of neo-oogenesis during normal human physiological aging.

Wallace and Kelsey estimated that for 95% of women, only 12% of their maximum pre-birth non-growing follicle population is present by the age of 30 years and by the age of 40 years, only 3% of it remains (**Figure 1**). When only about 1000 oocytes remain, menopause occurs [19].

Consistent with the continuing apoptosis, along with the loss of oocytes during the 400–500 cycles of follicular recruitment in a normal reproductive lifespan, the most replicable and linear endocrine change throughout the menopausal transition is the progressive decline of AMH. It marks the decline in follicular mass and explains why fertility is impaired in women well before any disruption of menstrual cycle can be noticed [20, 21].

In the late reproductive stage, AMH is reduced 2 to 10 times compared to the peak reproductive stage (**Table 1**). Because of its minimal intra-cycle variation, AMH can be useful in late reproductive stage fertility assessment and in predicting the amount of time to menopause occurrence. In the early menopause transition stage, when a variable length of the menstrual cycle occurs, AMH drops to an almost undetectable level, reflecting the diminishing pool of around 1000 non-growing follicles.

Besides apoptosis, qualitative oocyte changes also occur. The accelerated follicular phase and monotropic rise of FSH appear to have an adverse effect, leading to a disorganized meiotic spindle assembly in oocytes of reproductively aged women [22].

3.5. Decreased progesterone levels

The luteal phase is 14 days long in most women. After ovulation, the remaining granulosa cells continue to enlarge and become vacuolated in appearance. The luteinized granulosa

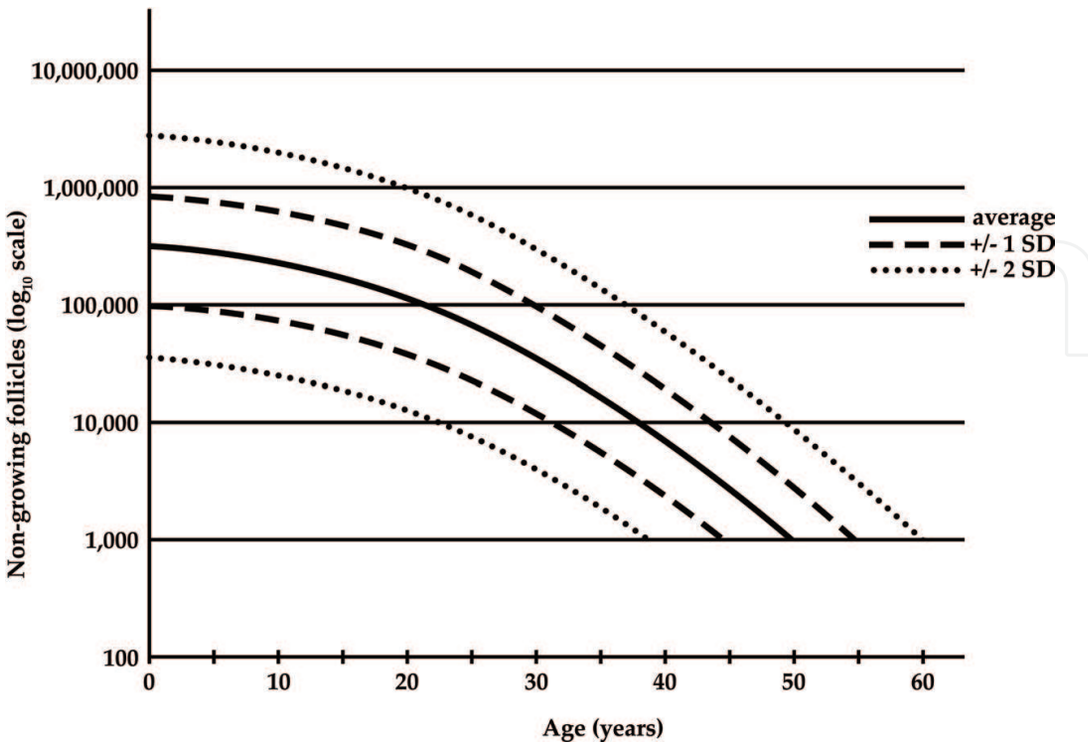

Figure 1. The hypothetical link between ovarian reserve and the age at menopause. This figure describes the hypothesis that an individual's age at menopause is determined by the peak non-growing follicle population count, established at around 20 weeks post-conception. Adapted from Wallace and Kelsey [18].

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cells, combined with the theca-lutein cells and the surrounding stroma, form the corpus luteum [1, 10]. The corpus luteum is a transient endocrine organ that predominantly secretes **progesterone**. Its primary function is to prepare the estrogen-primed endometrium for implantation.

Secretion of progesterone and estradiol correlates closely with LH level pulses. Eight to nine days after ovulation, peak production is achieved.

Despite erratically oscillating high estradiol levels, perimenopause is characterized by more steadily decreasing levels of progesterone. During menstrual transition ovulatory cycles, the decrease in progesterone levels results from diminished progesterone production, shortened luteal phase lengths, and a rising incidence of ovulation disturbance [5]—ovulation only occurs in 50% of cycles in women aged 46–50 years [5].

3.6. Physiological symptoms of perimenopause

In addition to menstrual cycle disturbances and reduced fertility, symptoms frequently seen and related to decreasing ovarian function are:

- vasomotor instability such as hot flushes and sweating,
- bone loss, and
- adverse changes in the lipid profile.

Not all women have them, and those who do, experience these symptoms in different combinations and at different intensities [2]. Quantification of these symptoms is difficult because they are subjective in nature. It has been observed that they vary markedly among ethnic groups, cultures, socioeconomic groups, and climates and that they do not correlate closely with menstrual cycle disturbances or endocrine changes.

Vasomotor symptoms are among the most frequently reported physiological symptoms and the most prominent ones during perimenopause. Their prevalence ranges from 30–75% [23].

A hot flush is a sudden episode of vasodilation in the face and neck, which lasts from a few seconds to several minutes and is accompanied by profuse sweating and an increase in heart rate [1, 23]. The frequency of hot flushes may range from a few per day to one every few minutes. Flushes are more frequent and severe at night or during periods of psychological stress and can affect a woman's quality of life, interfering with her work or other activities.

Hot flashes usually start occurring in the late menopausal transition (Stage −1), peaking in the first year after menopause (Stage +1a). Some women (10%) may continue to experience vasomotor symptoms for up to 15 years after menopause [1].

The physiology of the hot flush is still not understood. Studies suggest that these women have a narrower zone of temperature regulation, and therefore smaller changes in core body temperature produce compensatory responses such as vasodilation, sweating, and shivering [23]. The flush is not a release of accumulated body heat but a sudden inappropriate activation of the heat release mechanism.

The correlation between the onset of flushes and generally diminishing estrogen levels is confirmed by the effectiveness of estrogen therapy in the prevention of flushes, as well as by the absence of flushes in hypoestrogen states, such as gonadal dysgenesis [1].

A common belief still persists that **bone loss** begins and fractures occur in women with constantly low estrogen levels, during the late postmenopause. However, during perimenopause, an early and accelerated rate of bone loss has been observed, particularly in the lumbar spine [24]. In an Australian study, the estimated average annual rate of bone loss around the time of final menstrual period was 2.5% in the lumbar spine and 1.7% in the femoral neck [24].

These observations are in concordance with out current understanding of bone physiology: downward swinging estradiol levels release cytokines, especially "receptor activator of nuclear factor kappa-B ligand" (RANKL), that cause increased bone resorption [25, 26].

Also, there is additional compelling data, which suggest that perimenopausal bone loss is associated with high levels of FSH rather than falling levels of estradiol [27, 28]. Proving this is the fact that in perimenopausal women, FSH levels significantly correlate with bone resorption.

Still, the role of progesterone and inhibins in bone loss and its maintenance remain unclear. Inhibin B appears to inhibit osteoblastogenesis and osteoclastogenesis while also suppressing osteoblast and osteoclast development.

Several longitudinal studies have revealed that **adverse changes in the lipid profile** occur during the time between early menopausal transition and early postmenopause, such as increased LDL and triglycerides [23]. In spite of not directly influencing the development of insulin resistance or diabetes, data from the Study of Women's Health Across the Nation (SWAN) suggest that perimenopause is associated with the development of metabolic syndrome, including abdominal obesity, dyslipidemia, impaired glucose tolerance, and hypertension [29, 30]. As such, together with the decline in endothelial function that appears to occur around the last menstrual period, perimenopause represents the end of the life period in which estrogen effectively contributed to the prevention of cardiovascular diseases.

4. Perimenopause and future health risk

Postmenopause is not the main topic of this chapter. Still, we would like to summarize some key changes that occur during this time period [1, 23, 31]:

- Urogenital atrophy
- Osteoporosis
- Cardiovascular diseases.

The anatomy and function of the female lower genital tract are estrogen-dependent. With postmenopausal estrogen level decline, tissues lining the vagina, vulva, bladder, and urethra undergo **atrophy** leading to vaginal dryness, dyspareunia, vulvar pruritus, and other urinary difficulties such as recurrent urogenital infections. Unlike hot flushes and night sweating, which improve over time, symptoms of urogenital atrophy persist throughout the entire postmenopausal period [32, 33].

Postmenopausal low estrogen levels result in **bone resorption** due to excessive production of the cytokine RANKL and its natural inhibitor cytokine osteoprotegerin (OPG or TNFRS11A),

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by osteoblasts. Moreover, the age-associated vitamin D deficiency and impaired synthesis of active 1,25-dihydroxyvitamin-D_3 by the kidneys lead to secondary hyperparathyroidism, which further contributes to accelerated bone resorption [1, 23, 26].

It is well known that women have a lower incidence of cardiovascular risk factors and cardiovascular diseases than their male peers [34]. Estrogen modifies endothelial function by two primary mechanisms: modulation of NO activity and attenuation of vascular response to injury [35]. Estrogen promotes vasodilation through stimulation of eNOS and reduction of NO-synthase activity. At the level of the mitochondria in the vascular endothelium, estrogen stimulates oxidative phosphorylation and reduces mitochondrial production of ROS [36].

Following menopause, there is active progression of atherosclerotic lesions [37]; women also exhibit increases in blood pressure.

Subclinical development of vascular diseases manifests itself as increased carotid and femoral artery intima-media thickness and accelerated coronary artery calcium deposition, leading to arterial stiffness, which in turn causes impaired flow-mediated vasodilation [23]. The risk of stroke doubles during the first decade after menopause and ultimately exceeds that of men at older age.

4.1. Mood changes

Estrogens enter the brain through the blood-brain barrier and influence the neural activity by multiple pathways. In the central nervous system, they are involved in different processes including cellular protein production, neuronal growth and survival, neural transmission and function, and also synaptogenesis.

Estrogens act through both genomic and non-genomic mechanisms. Intracellular estrogen receptors (ER) are widely distributed, and ER subtypes are located in many of the areas that are associated with depression. During perimenopause, estradiol levels show an increase in oscillations, followed by a gradual decline in levels after early postmenopause. Changes in estradiol levels are correlated with region-specific changes in ER expression [38], and women with a greater amount of hormonal fluctuation during perimenopause are at greater risk for developing depression [39].

Estrogens can influence depression and depression-like behavior through an influence on the serotonergic system and through interactions with neurotrophic factors.

There are multiple pathways through which estrogens impact serotonergic activity. Activation of ERs results in increased serotonin release by decreasing the number of presynaptic 5-HT_{1A} autoreceptors and 5-HT_{1A} postsynaptic heteroreceptors. ER activation also increases both pre- and post-synaptic expression of the serotonin transporter (SERT) and release of brain-derived neurotrophic factor (BDNF) [40]. Furthermore, plasma BDNF levels vary across the menstrual cycle [41], and women who have suffered from postpartum depression and/or premenstrual dysphoric disorders are at a greater risk of major depressive disorders during the transition to menopause, referred to as perimenopausal depression [40].

All of the above may also contribute to the pathology of the brain tissue and subsequently produce psychopathological symptoms.

5. Perimenopause and psychopathological symptoms

Perimenopause is primarily viewed as a reproductive transition; however, the symptoms of perimenopause are not just largely neurological in nature, but are also indicative of disruption in multiple estrogen-regulated systems (including thermoregulation, sleep, circadian rhythms, sensory processing, and several domains of cognitive function) [1, 42].

In the perimenopausal brain, there is an increased risk for some women of developing neurodegenerative diseases later in life [42, 43]. Neurodegeneration is the progressive loss of functional activity and trophic degeneration of nerve axons and their terminal arborizations following the destruction of their cells of origin or interruption of their continuity with these cells, and it occurs in Alzheimer's disease, Parkinson's disease, progressive supranuclear paralysis, frontotemporal dementia, corticobasal degeneration, Huntington's disease, prion diseases, amyotrophical lateral sclerosis, spinocerebellar ataxia, and multiple sclerosis [44–47].

Aging women face many challenges in the middle and older adult phases of life, becoming more vulnerable to distress [44, 48]. A gradual decline in functioning on multiple levels takes place, and women must adapt to most of them simultaneously. It is quite challenging to cope with physiological changes that not only involve strict perimenopausal symptoms but also include the occurrence of an array of possible diseases (cardiovascular, pulmonary, endocrine, oncological, etc.) and at the same time have to face many psychosocial changes, such as marital problems, grown-up children leaving home, occupational distress, or possible financial ordeals, to name a few. Therefore, in most cases, before neurodegenerative processes cause clinically relevant symptoms, many psychopathological changes can occur and women in perimenopause most commonly experience anxiety, mood swings, depression, insomnia, and mild cognitive impairment [49]. It is important to understand that perimenopausal estrogen level fluctuations may either alter already diagnosed mental disorders (for the better or for worse) or evoke psychopathological symptoms in otherwise mentally healthy women.

Psychiatric diagnosis has a long history of scientific investigation and application, with periods of rapid change, instability, and heated controversy associated with it, and despite efforts of scientists to advance a diagnostic classification system that incorporates neuroscience and genetics, psychiatric disorders cannot yet be fully distinguished by any specific biological markers. Hence, the symptom-based criteria are still used to classify mental illnesses such as psychotic disorders, mood disorders, anxiety and stress-related disorders, behavioral syndromes, personality disorders, mental disorders due to psychoactive substance abuse or due to known physiological conditions, intellectual disabilities, pervasive developmental disorders, and mental disorders with onset in childhood or adolescence [50–52].

The top five symptoms (between 84 and 88%) experienced by middle-aged women with serious mental illness were all problems related to psychological issues:

- Feeling depressed
- Feeling anxious
- Feeling tired or worn out

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- Feeling a lack of energy
- Experiencing poor memory [53].

Epidemiological studies on women in perimenopause show that the relationships between perimenopausal syndrome and mental disorders are strong and positive, with 1 in 4 women suffering from anxiety and approximately 1 in 7 women suffering from depression [54–56]. Usually, women with a history of poor adaptation to stress or specific personality traits, particularly neuroticism, are predisposed to menopausal syndrome, with more than half of women feeling more stressed due to menopause or approaching menopause, and describing menopause as an unpleasant experience that has had a negative effect on their emotional state [43, 53, 56, 57]. Research also showed that a later age of menarche carries more risk for psychiatric morbidity in perimenopause, because the exposure of women to neuroprotective and serotonin regulatory effects of estrogen is shorter [58].

5.1. Anxiety, anxiety-related substance abuse or dependence, and insomnia

Anxiety is a subjectively unpleasant feeling of dread over anticipated events, uneasiness, and worry, accompanied by muscular tension, restlessness, fatigue, or diminished concentration, and is not synonymous with fear, which is a response to a real or perceived immediate threat [59]. If anxiety lasts too long or is too intense in regard to the input stimuli, then anxiety disorders may develop.

Women are more prone to anxiety than men. On average, the proportion of total anxiety-related visits to the emergency department is higher among women than men [60]. In perimenopause, every fourth woman experiences higher levels of anxiety, with their anxiety state and trait scores higher in perimenopause than in postmenopause [61]. Furthermore, different personality trait predictors are important in different age subgroups; more specifically, anxious response predisposition might contribute to distress in the early stages of perimenopause, whereas anxiety sensitivity might add to distress closer to menopause [62].

Affected patients are usually very impatient to alleviate the symptoms. Despite a high addiction potential, benzodiazepines are among the most prescribed drugs for anxiety and one of the most used drug classes in the world [63, 64]. A quick solution of one mental disorder may produce another mental disorder—dependence. Benzodiazepine dependence develops in 35% of persons who take benzodiazepines regularly for 4 weeks or longer, and the majority of users will develop dependence after 4–6 months of daily use [65]. Women use psychotropic medication consistently more often compared to men and these differences also appear to be contingent on the specific mental disorder [66]. Benzodiazepine use was shown to be higher among women, in older age groups, when burdened with a severe degree of anxiety, and with decreasing income level [63–67].

Upon the abrupt discontinuation of the benzodiazepines, withdrawal symptoms may occur, e.g. sweating, tremor, dizziness, headache, insomnia, rebound anxiety, tachycardia, and elevated blood pressure, all of which can closely resemble perimenopausal symptoms, sometimes making it difficult to diagnose properly. This dependence may be controlled and ended through dose tapering and/or medication switching [68].

Due to the chronic nature of anxiety, long-term low-dose benzodiazepine treatment may be necessary for some patients, despite that, for example SSRI-antidepressants or second-generation antipsychotics administered in low doses are more suitable as they are not addictive [68]. A phenomenological study explored whether older women who are chronic benzodiazepine users identified themselves as dependent. Canham et al. report that the perceptions of dependence and addiction/abuse influenced benzodiazepine use, as the informants stated to avoid consumption of higher doses of benzodiazepines because of concerns of developing addiction [69].

Addiction to other substances may also be present in middle-aged women. As the difference between women's and men's drinking rates decrease, the number and impact of older female drinkers is expected to increase, and due to differences in metabolism of alcohol, women are at higher risk for negative physical, medical, social, and psychological consequences associated with higher levels of alcohol consumption [70, 71]. Cannabis users described by Guillem et al. were in a greater percentage female, older, more dependent on marijuana, and with a high prevalence of affective and anxiety disorders [72]. Also, women are at higher risk of abusing opioids through a pathway of initial prescription painkiller use [73].

In clinical practice, sometimes it is challenging to distinguish between anxiety, psychoactive substance withdrawal, and sleep disorders. Insomnia is one of the hallmarks of perimenopause and occurs in approximately 40% of perimenopausal women [57, 58]. Hot flashes, night sweats, and other neurovegetative symptoms disrupt sleep, and insomnia may lead to depression [58]. Personality traits also predispose women to insomnia, and it can be most strongly related to neuroticism and DSM-IV personality disorder diagnoses, especially those of Cluster B (emotional, dramatic, and erratic/inconsistent styles) and Cluster C (anxious, fearful, and obsessive-compulsive styles) [56, 57]. Women with perimenopausal insomnia also have a history of greater sensitivity to severe premenstrual symptoms [57].

5.2. Depression

Depression is an affective disorder that causes a persistent feeling of sadness, dysphoria and loss of interest, or anhedonia. It is also called major depressive disorder or clinical depression. It affects feelings, thinking, and behavior and can lead to a variety of emotional and physical problems. Normal day-to-day activities become very troublesome, and sometimes life even seems not worth living. Depression is not a weakness, the patient cannot simply "snap out" of it, and it may require long-term treatment [74, 75].

The majority of findings indicate an increased susceptibility to depression during the perimenopausal transition [76, 77]. Perimenopausal depression is significantly associated with lower education, a rural background, a history of psychiatric illness in the family, a later age of menarche, and the late stage of perimenopause [56, 58]. Marital status, type of family, religion, and occupation seem not to be associated with depression in perimenopause [58]. Also, the timing and number of adverse experiences in the childhood and adolescence differentially impact risk and resilience for major depressive disorder across the female life span and during the menopause transition [78]. Repeated epidemiological studies throughout the world show that depression and anxiety prevalence rates are approximately 2:1 for women to men. As prevalence rates of depression and anxiety are approximately equal in boys and girls

until puberty, it has been hypothesized that the onset of menstruation in girls, triggered by increases in estrogen and other female gonadal hormones, may be responsible for increased depression and anxiety rates [79]. Paradoxically, sudden decreases in estrogen levels at other times of life, such as postpartum and perimenopause, are also accompanied by increased rates of depression and anxiety, thereby suggesting that it may be hormone ratios or changes, rather than absolute levels, which trigger depression and anxiety in vulnerable women [79].

Depressed mood was found to be associated with the severity of menopausal symptoms (somatic and psychological) [80]. Vasomotor symptoms were reported to be harbingers of oncoming depression and also may signal the presence of dysregulated hormones and neurotransmitters [77]. Psychological aspects of perimenopause, such as loneliness and life satisfaction, were reported to be influenced by personal and partner issues, which seem to play a much more relevant role than biological aspects [81]. Menopausal and affective symptoms, but also partner factors, were related to lower sexual function in middle-aged women [82]. Interestingly, the symptom triad of sleep disturbance, depressed mood, and sexual problems was shown to occur simultaneously in only 5% of perimenopausal women, particularly if they were surgically menopausal or in the late perimenopause [55]. Furthermore, this symptom triad was detected most often among women with fair or poor general health, less education, a lower socioeconomic status, and a greater psychosocial distress [54–56]. Women with perimenopausal depression also report significantly decreased quality of life, lack of social support, poor adjustment, and increased disability compared to non-depressed perimenopausal women [83].

In treating depression in perimenopause, relieving vasomotor symptoms may be a necessary dimension [77]. In milder forms of menopausal mood distress, hormone replacement therapy may be sufficient. However, if depression is severe, antidepressants should be prescribed [84–86]. The selective serotonin reuptake inhibitors (SSRIs) are the most frequently prescribed antidepressant drugs, because they are well tolerated and have no severe side effects. They rapidly block serotonin reuptake, yet the onset of their therapeutic action requires weeks of treatment [87]. Regular exercise is important and helps to strengthen the resilience of women [80]. Also, psychosocial interventions are often necessary to alleviate the symptoms of perimenopausal depression.

5.3. Bipolar disorder

Perimenopausal women may not suffer only from depression, but may also have had already diagnosed other affective disorders. Bipolar disorder is a common, recurrent, and severe psychiatric disorder that is characterized by extreme mood swings that include emotional highs (mania or hypomania) and lows (depression), or mixed states (simultaneously occurring manic and depressive symptoms) [88, 89].

Studies suggest that women with bipolar disorder are at a higher risk for mood episodes during periods of intense hormonal fluctuation (e.g. premenstrual, postpartum, perimenopause) [90–94]. Estrogen and progesterone were shown to modulate neurotransmitter systems and intracellular signaling pathways that are affected by mood stabilizing agents, and these findings may be relevant to the psychopathological aspects of bipolar disorder in women [90]. A progression in female reproductive stages is associated with bipolar illness exacerbation, partic-

ularly with lower mood and depression [91]. Interestingly, the exacerbation of perimenopausal symptoms can be predicted in major depressive disorder, but not in bipolar disorder [93].

Estrogen seems to be neuroprotective also in affective disorders. Bipolar disorder patients who were using hormone replacement therapy during perimenopause reported significantly less worsening of mood symptoms than the patients without hormone replacement therapy [95]. This should be considered while adjusting the medication for bipolar disorder in perimenopause.

5.4. Cognitive impairment

Perimenopausal women can also experience different degrees of cognitive impairment. It is characterized with diminished or impaired mental and/or intellectual function and includes deficits in overall intelligence (e.g. with intellectual disabilities) and specific and restricted deficits in cognitive abilities (e.g. attention, working memory, learning, executive function, etc.), or it may describe drug-induced cognitive malfunction (e.g. benzodiazepines, alcohol, illegal drugs, etc.).

In perimenopause, cognitive performance does not decline, but improvement is also absent [96]. In the SWAN study, researchers observed that increased anxiety and depressive symptoms had independent and unfavorable effects on cognitive functioning [96]. Women reported trouble with recall of words and numbers, losing or misplacing items, difficulty concentrating, needing to use memory aids, and forgetting appointments. However, the perceived memory difficulties were predominantly a function of stress and multiple burdens resulting in diminished attention and concentration [96].

Perimenopause may have either just contemporary or long-term effects on cognitive function with women being disproportionally more than men affected with Alzheimer's disease and dementia [96, 97]. Cognitive function does not change linearly across perimenopause, and the decreases in attention/working memory, verbal learning, verbal memory, and fine motor speed may be most evident in the first year after the final menstrual period [98].

A premature menopause, either because of a premature bilateral ovariectomy or a premature ovarian failure, was associated with worse verbal fluency and visual memory in later life and also with a 30% increased risk of decline in psychomotor speed and global cognitive function over 7 years [99]. Hormone replacement therapy at the time of premature menopause appeared only partly beneficial for later-life cognitive functioning, and Ryan et al. warn that this should be considered as a part of risk/benefit ratio when deciding on ovariectomy in younger women [99].

It is noteworthy that women do not arrive at the menopause with equal risk of cognitive impairment or equal susceptibility to the effects of hormone replacement therapy [64]. Hormone replacement therapy can have health risks, such as hormone-dependent cancer or cardiovascular pathology that can also cause cognitive deterioration [100–102]. Therefore, it is very important to take into account as many pro and contra arguments for prescribing hormone replacement therapy, as possible.

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5.5. Psychotic disorders

Cognitive impairment, anxiety, and mood swings may also occur or worsen in perimenopausal women with psychotic disorders (e.g. schizophrenia, delusional disorder, transient psychotic disorders, or schizoaffective disorder). Schizophrenia is a complex mental disorder that is characterized by positive symptoms (e.g. abnormal perceptions and beliefs), negative symptoms (e.g. anhedonia and social withdrawal), cognitive deficits, and a decline from a previous level of functioning [103]. Schizophrenia and other psychotic disorders are increasingly thought of as neurodevelopmental disorders, where multiple hits accumulate during critical periods of central nervous system (CNS) development to cause the disorders [104, 105].

The loss of estrogens may lead to increased vulnerability for psychotic relapse, poor clinical outcome, and a need for increased antipsychotic dose [106, 107]. Furthermore, time since menopause is significantly negatively associated with antipsychotic response in postmenopausal women with schizophrenia, suggesting a decline in antipsychotic response after menopause [107]. Hormone replacement therapy during the perimenopause in women with schizophrenia ameliorates psychotic and cognitive symptoms and may also help affective symptoms [108]. Both hormone replacement therapy and changes in antipsychotic management should be considered for women with schizophrenia at menopause [108].

5.6. Neurocircuitry and perimenopausal psychopathology

An array of neurotransmitters and neuromodulators is involved in the occurrence of psychopathological symptoms, and although neuroscience has elucidated many psychopathological processes, the complexity of the field makes it impossible to obtain definite explanations just yet. Connectomics has already begun to map out large-scale neural circuit diagrams, including ultrastructural analysis of the human brain [109, 110]. It is noteworthy that neural circuits do not have fixed connective properties and the relative concentrations and mixture of neuromodulators at any given moment can provide yet another layer of dynamic functional connections within a circuit [109].

Neurotransmitters and neuromodulators generally alter circuit function on the timescale of seconds-to-minutes, and thereby they help fill the 'signaling gap' to a substantially slower processes of gene transcription and protein translation (i.e. on the timescale of hours or days) [109]. The production of steroid hormones within brain circuits can rapidly modulate their functional connectivity, thereby affecting the behavior [109]. Effects of long-term 17-β estradiol (E2) replacement on gene expression in brain nuclei were selective and revealed the greatest number of gene changes in the supraoptic nucleus, with no genes affected in the prefrontal cortex [111].

Estrogen has proven neuroprotective effects and estrogen receptors are particularly plentiful in the brain, especially in the hypothalamus, medulla, and limbic system, and therefore, it is not surprising that sudden changes in estrogen levels may affect mood, anxiety, and cognition [58, 79]. Interventional research on early postmenopausal women suggests that estrogen effects on serotonergic function may actually be a key mechanism relating mood and cognitive

symptoms in the menopausal transition [112]. Many biogenic amines like serotonin, dopamine, and norepinephrine can directly shift sensory representations through modulatory actions in the frontal lobe, midbrain, and thalamus [109]. A substantial body of evidence has already linked estrogen and serotonin, as well as estrogen and dopamine in the central nervous system [113, 114]. Serotonergic and dopaminergic pathways in the brain play an important role in the pathogenesis of anxiety, affective, and psychotic disorders, and monoamine oxidase A (MAO-A) is an important brain enzyme that metabolizes these biogenic amines. After estrogen level declines, MAO-A density may be elevated for a month or longer, and its change during perimenopausal age is very similar to its change during major depressive episodes and high-risk states for major depressive episodes, thus, being an interesting target for relieving of perimenopausal symptoms [115].

Estradiol (E2) was shown to increase the production of tryptophan hydroxylase (TPH), which represents the rate-limiting step in the synthesis of serotonin from its precursor tryptophan, and furthermore, E2 also inhibits the expression of the gene for the SERT and acts as an antagonist at the SERT, thus, increasing the concentrations of serotonin that remains available in the synapses for a longer period of time [114, 116–118]. E2 also modulates the actions of serotonin because the activation of E2 receptors affects the distribution and state of serotonin receptors [114]. Higher levels of E2 in the presence of progesterone upregulate E2 β receptors (ERβ) and downregulate E2 α receptors (ERα). ERα downregulation directly inhibits function of serotonergic 5-HT_{1A} receptors [114, 119]. Additionally, ERβ upregulation in turn upregulates 5-HT_{2A} receptors [114, 120]. Following 5-HT_{2A} activation of protein kinase C, 5-HT_{1A} receptors become unable to reduce serotonin production through negative feedback and serotonin concentrations increase [114]. Alterations in 5-HT_{1A}, 5-HT_{1B} and 5-HT_{2A} mRNA levels and an increase in synaptic serotonin levels reduce symptoms of anxiety, depression, and possible psychosis [121].

The 5-HT_{1A} and 5-HT_{1B} receptors are both inhibitory transmembrane receptors that are located throughout the brain [82]. 5-HT_{1A} receptor is the most studied for its role in depression, but it also modulates anxiety behavior, bipolar disorder, and post-traumatic stress disorder [122]. Also, several lines of evidence support a stimulatory influence of serotonin on the hypothalamo-pituitary-adrenal axis (HPA) in humans and rodents, mediated, in part, by the 5-HT_{1A} receptor. Evidence suggests that the brain serotonergic system has a higher potential for stimulating the HPA axis in females, and under basal conditions, females express higher levels of serotonin than males in brainstem, limbic forebrain, and cortex [123]. The 5-HT_{1A} receptor not only drives the stimulatory effect of serotonin on the HPA axis but is also a critical determinant of the antidepressant response [123]. 5-HT_{1B} receptor is best known for its role in regulating aggressive and impulsive behavior, but it also modulates depression and it has been implicated in the neural basis of dysregulation of reward processing, thus being associated with drug and alcohol abuse [122].

5-HT_{2A} antagonists have antidepressant-like, anxiolytic, and antipsychotic effects [122, 124]. There is extensive evidence, from both animal and human studies, that the characteristic effects of hallucinogens are mediated by their agonistic interactions with the 5-HT_{2A} receptor [125]. The loss of estrogen in perimenopause leads to a decreased density of 5-HT_{2A} receptors and a lower activity of serotonin, which could explain aberrant temperature regulation,

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including hot flashes and night sweats [114, 126]. The nighttime prevalence of hot flashes and night sweats could be a result of the conversion of serotonin to melatonin at night, resulting in lower circulating serotonin levels [127].

Female steroid hormones also promote dopaminergic neuron survival and protect them from degeneration, as shown in the E2 modulation of striatal neural pathways [128]. Dopamine receptors (D_1, D_2, D_3, D_4, and D_5) are G-protein coupled and mediate all of the physiological functions of dopamine, ranging from voluntary movement and reward to hormonal regulation and hypertension [129]. In the brain, dopamine receptors mediate affect, attention, impulse control, decision-making, motor learning, sleep, reproductive behaviors, and the regulation of food intake [129]. On the basis of their structural, pharmacological, and biochemical properties, these receptors are classified as either D_1-class dopamine receptors (D_1 and D_5) or D_2-class dopamine receptors (D_2, D_3, and D_4). All clinically effective antipsychotics possess the ability to block D_2 dopamine receptors. Dopamine D_2 receptors play a critical role in the development of psychotic symptoms [129–131]. In the brain of ovariectomized rats, estrogen treatment increased levels of dopamine transporters and lowered dopamine D_2 receptor density in the nucleus accumbens and in the caudate nucleus, but also normalized norepinephrine pathway [132, 133].

Current scientific evidence suggests that the path to psychopathology is laid by the adverse interaction of multiple risk genes and environmental factors, a constellation that predisposes individuals to the subtle disturbances in brain neurotransmission that ultimately lead to overt emotional and behavioral symptoms [134].

Antidepressants and antipsychotics control psychopathological symptoms due to their predominant antagonistic effect on various combinations of serotonin and dopamine receptors subtypes, and research supports an important role of add-on estrogen in alleviating mood, anxiety, and psychotic symptoms in perimenopause.

5.7. Psychosocial context in perimenopause

Adaptation to biological changes of perimenopause is largely affected with the psychosocial context of middle-aged women's lives, and studies show that these circumstances may have a greater effect on symptomatology than any biological changes. Hence, we must be careful about an overly reductionist receptor-based and hormonal approach to mood or cognitive symptoms and have to take into account the evidence that psychosocial factors act via epigenetic mechanisms in the pathogenesis of mental disorders [75, 131]. Epigenetic remodeling takes place throughout adult life, under the influence of environmental factors such as nutrition, drugs, and chemical, physical, and psychosocial factors, and psychotherapies were suggested to be conceptualized as epigenetic "drugs," or at least as therapeutic agents that act epigenetically very similarly or complementary to drugs [131–133].

Middle adulthood is the period in life characterized by gradually decreased biological and physiological functioning [134]. As previously described, a subgroup of vulnerable women may suffer from the hormonal changes naturally occurring during the perimenopause and coinciding with the manifold psychosocial changes coming together during this phase of

life [106]. In this midlife transition, an intense reappraisal of all aspects of life takes place, and it may result either in decisions to keep most life structures that were built through decades, such as marriages and careers, or major shifts may be made, such as divorce or a job change, and the latter may represent a true midlife crisis, accompanied by significant emotional turmoil for the individual and others [134]. Another phenomenon described in middle adulthood is an empty nest syndrome, the time when the youngest child is about to leave home. Parents may become depressed, and this is especially true of women whose predominant role in life has been mothering [135].

Psychopathological symptoms in perimenopause occur as a result of complex changes on several levels of female functioning, may it be biological or psychosocial. Middle-aged women must adapt to loss of sex hormones, and this transition is sometimes extremely troublesome. If they already suffered from any mental illness while being younger, the perimenopausal transition is even harder. If they also live in unfavorable circumstances, lack the support from significant others, are physically ill and poor, it is reflected in the severity of perimenopausal syndrome and a higher incidence of mental disease during perimenopause. These patients need a special attention from different medical practitioners. It is vitally important to tailor the therapy individually while carefully listening to the minute details of what burdens each woman the most. Psychotherapy, regular exercise, social interventions, and partner counseling are just a few of possible actions that may alleviate the severity of perimenopausal and psychopathological symptoms, while the combination of the prescribed medications must be fine-tuned and supported with the estimation of expected true benefits.

Last but not least, women with serious mental disorder have deficits in knowledge regarding menopause [53]. Therefore, educational programmes are necessary and should offer valuable information on natural course of perimenopause and strategies to alleviate perimenopausal symptoms, i.e. teaching the women how to reduce stress, eat healthy, engage in different activities, regularly take the prescribed medication if needed, and also recognize the perimenopausal symptoms and learn how to differentiate them from possible serious diseases that need professional help. Perimenopause cannot be prevented, but many of the perimenopausal symptoms can and should be reduced, and that holds true also for perimenopausal psychopathological symptoms.

6. Conclusion

Menopause is an event in a woman's life that marks the end of reproductive function. The process of reproductive aging is gradual and begins in the early menopausal transition. The decline in ovarian estrogen production causes physical symptoms, metabolic changes, and influences the mood and cognition. The relationships between perimenopausal syndrome and mental disorders are strong and confirmed with many different studies. Given these findings, in the future, strategies to locally regulate hormone bioavailability may offer greater therapeutic potential in the fight against age-related disease.

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