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Depression in postmenopause: interdisciplinary approach in management and perspectives for rehabilitation

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Abstract

Surgical and natural menopause is often associated with depression symptoms. Along with the postpartum period, perimenopause is a “window of vulnerability” for depression development, because decline in estrogen level accounts for extinction of reproductive function, emotional disorders, genitourinary menopausal syndrome, which are combined with non-endocrine risk factors, such as decreasing income levels, low social support, and stress. Although a direct relationship between blood estrogens level and depression has not been demonstrated, the relation between menopause symptoms and depression has been proven, i.e., the symptoms of menopause can be considered as risk factors. Here, we summarize the current view on the correct counseling and routing of menopausal women with depression symptoms in primary health care facilities, the principles of managing patients with risk factors, including genitourinary menopausal syndrome, as well as methods of rehabilitation and informational support. This will aid to improve the quality of medical care for such patients.

Keywords: depression, anxiety, menopause, risk factors, psychosocial discomfort, genitourinary menopausal syndrome, GUMS, antidepressants, menopausal hormone therapy, MHT, stress, rehabilitation, digital health care, patient routing, interdisciplinary interaction

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Депрессия у женщин в менопаузе: организация междисциплинарного подхода в лечении и перспективы реабилитации

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Резюме

Хирургическая и естественная менопауза нередко сопровождается симптомами депрессии. Наряду с послеродовым периодом перименопауза представляет собой «окно уязвимости» для развития депрессии, поскольку снижение уровня эстрогенов обуславливает угасание репродуктивной функции, эмоциональные расстройства, генитоуринарный менопаузальный синдром, которые сочетаются с неэндокринными факторами риска, например, снижением уровня дохода, низким уровнем социальной поддержки, стрессом. Хотя прямая связь между уровнем эстрогенов в крови и депрессией не продемонстрирована, доказана связь между симптомами менопаузы и депрессией, т. е. симптомы менопаузы можно рассматривать в качестве факторов риска. В статье обобщен современный взгляд на правильное консультирование и маршрутизацию женщин с симптомами депрессии в менопаузе в условиях первичного звена здравоохранения, принципы ведения пациенток с факторами риска, включая генитоуринарный менопаузальный синдром, а также методы реабилитации и информационной поддержки. Это поможет повысить качество оказания медицинской помощи таким пациенткам.

Ключевые слова: депрессия, тревога, менопауза, факторы риска, психосоциальный дискомфорт, генитоуринарный менопаузальный синдром, ГУМС, антидепрессанты, менопаузальная гормональная терапия, МГТ, стресс, реабилитация, цифровое здравоохранение, маршрутизация пациентов, междисциплинарное взаимодействие

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Introduction / Введение

Depression is a pathological condition which affects more than 300 million patients worldwide and often leads to significant personal, social, and economic damage [1–3]. According to the World Health Organization, depression is one of the leading causes of morbidity, mortality, and suicide [4, 5].

The prevalence of depression among women of different age groups is about 2-fold higher than in men [6]. Compared to men, women more often suffer from anxiety and psychosomatic manifestations. In addition, women vs. men are 4 times more likely to develop a unipolar depression [7]. This phenomenon initiated many research studies assessing epidemiology, possible pathogenetic mechanisms, including the socioeconomic

Highlights**What is already known about this subject?**

- ▶ The prevalence of depression in women is 2 times higher than in men; upon that, unipolar depressions occur 4 times more often, which suggest about differences in pathogenetic mechanisms.
- ▶ Surgical and natural menopause presents a "window of vulnerability", because lower estrogen levels are combined with changes in the woman's lifestyle and overall health.
- ▶ Data on the prevalence of depression in postmenopausal women are limited; approaches to treatment and rehabilitation are not entirely perfect.

What are the new findings?

- ▶ Data from epidemiological studies on the prevalence of anxiety and depression in surgical and natural menopause women are summarized.
- ▶ A direct relationship between estrogen deficiency and symptoms of depression has not been shown in clinical studies. However, a relationship between the symptoms of menopause caused by decreased estrogen levels and developing depression has been demonstrated ("a domino theory").
- ▶ The properly organized consultation by an obstetrician-gynecologist and the routing algorithm from an obstetrician-gynecologist to a neurologist, psychologist, and/or psychiatrist based on the symptoms of depression, severity, and rehabilitation approaches of patients with depression in menopause is discussed.

How might it impact on clinical practice in the foreseeable future?

- ▶ Obstetricians and gynecologists play a pivotal role in identifying and treating symptoms of depression in women, because they are often those as healthcare professionals who might be first contacted by such women. Therefore, the awareness of obstetricians and gynecologists about the proper management of women with anxiety and depression will improve the quality of medical care.
- ▶ Comprehensive, personalized rehabilitation and elements of responsible self-treatment using digital health care solutions will markedly improve the psycho-emotional state and quality of life of postmenopausal women with depression.

component, genetic predisposition and a variability in hormone levels, as well as the strategy and tactics for controlling female level of anxiety and depression.

It was found that women are most vulnerable to developing depressive states at certain stages of life: the so-called "vulnerability window" opens during the luteal phase of the cycle, in the postpartum period, and during menopause [1]. However, it is often difficult to discern of whether such conditions are a natural consequence of endocrine status or induced by social and psychological factors, such as female stress due to childbirth in fertile age or separation from grown-up children, changing occupation to lower income job, or retirement during the period of peri- and postmenopause [7, 8].

Perimenopause is the most difficult "window of vulnerability" in the context of the developing depression,

Основные моменты**Что уже известно об этой теме?**

- ▶ Встречаемость депрессии у женщин в 2 раза выше, чем у мужчин; при этом в 4 раза чаще имеют место униполярные депрессии, что говорит об отличиях в патогенетических механизмах.
- ▶ Хирургическая и естественная менопауза представляет собой «окно уязвимости», поскольку снижение уровня эстрогенов сочетается с изменением образа жизни и общего состояния здоровья женщины.
- ▶ Данные о распространенности депрессии у женщин в менопаузе ограничены; подходы к лечению и реабилитации не вполне совершенны.

Что нового дает статья?

- ▶ Обобщены данные эпидемиологических исследований распространенности тревоги и депрессии у женщин в хирургической и естественной менопаузе.
- ▶ Прямой связи между дефицитом эстрогенов и симптомами депрессии в клинических исследованиях не показано, однако продемонстрирована связь вызываемых снижением уровня эстрогенов симптомов менопаузы с развитием депрессии («теория домино»).
- ▶ Рассмотрена организация правильного консультирования акушером-гинекологом и алгоритм маршрутизации от акушера-гинеколога к неврологу, психологу и/или психиатру на основе выявляемых в ходе осмотра симптомов депрессии и их степени выраженности, а также подходы к реабилитации пациенток с депрессией в менопаузе.

Как это может повлиять на клиническую практику в обозримом будущем?

- ▶ Акушеры-гинекологи играют определяющую роль в выявлении и лечении симптомов депрессии у женщин, поскольку именно они часто являются первыми специалистами здравоохранения, с которыми контактируют такие женщины. Поэтому осведомленность акушеров-гинекологов о должной организации ведения женщин с тревогой и депрессией позволит улучшить качество оказания медицинской помощи.
- ▶ Комплексная персонифицированная реабилитация, а также элементы ответственного самолечения с использованием решений цифрового здравоохранения позволяют значительно улучшить психоэмоциональное состояние и качество жизни женщин с депрессией в постменопаузе.

because it is characterized by multimodal changes: dynamically altered hormonal profile and the extinction of reproductive function are combined with aging of other organs and tissues, accompanied by changes in sexuality, lifestyle and general health. Therefore, the approach to controlling depressive disorders in peri- and postmenopausal women should be multifaceted and interdisciplinary [9].

Obstetricians and gynecologists play a decisive role in identifying and treating symptoms of depression in women because they attend antenatal clinics more often than other medical institutions. For many of them, the outpatient obstetricians and gynecologists are the first health professionals with whom women suffering with symptoms of depression come in contact. Therefore, it is essential that obstetricians and gynecologists would

be aware of the methods of detecting and treating depression. Meanwhile, the results from a recent survey by the American obstetricians and gynecologists showed that more than a third (34.1 %) of respondents do not conduct regular screening for depression in perimenopausal patients [1]. Although 85.7 % of obstetricians and gynecologists believed they could recognize depression in perimenopausal women, only about half (55.8 %) of them were confident in their ability to treat such patients. At the same time, higher awareness of depression, female gender, and personal experience of dealing with depression were associated with higher rates of depressive disorders detected by obstetricians and gynecologists [1]. Unfortunately, no such studies have been carried out in Russia. Therefore, the relevance of raising the level of knowledge about depression among obstetricians and gynecologists casts no doubt.

Definition and classification / Определение и классификация

Depression (from Latin *depressio* – to press down, oppress) is a mental disorder characterized by a pathologically low mood (hypothymia) with a negative, pessimistic of self, personal position in the surrounding reality, and future. Depressive mood changes with a distortion of cognitive processes are accompanied by motor inhibition, decreased motivation for activity, and somatic vegetative dysfunctions. Depressive symptoms negatively affect social adaptation and quality of life [10].

The causes of endogenous depression lie in the genetics and biochemistry of the central nervous system (CNS). Reactive depression, as its name implies, arises as a person's reaction to external conditions – stress induced by external factors, such as the loss of a loved one, etc. At present, it is no longer recommended to oppose endogenous and reactive depression because it turned out that the term "endogenous depression" is rather contradictory [10, 11].

According to the international classification of diseases of the 10th revision (ICD-10), a depressive episode holds a central place in the taxonomy, with the symptoms as follows: a decrease in mood compared to the norm for a given person for most of the day and lasting at least 2 weeks; decreased pleasure in activities usually associated with positive emotions; increased fatigue. There may be also decreased concentration, self-esteem, pessimism, insecurity, self-flagellation, suicidal tendencies, sleep and appetite disturbances.

There are distinguished a single depressive episode (ends with complete recovery and returns to previous level); recurrent (unipolar, repetitive) depression (repeated depressive episodes with no episodes of elevated mood and hyperactivity). Bipolar disorder (change from depressive to manic phases), including

bipolar disorder (BAD) types 1 and 2 (BAD-1 is characterized by the presence of at least one extensive manic or mixed as well as one depressive episode; BAD-2 – by the presence of at least one hypomanic and one depressive episode). Cyclothymia (non-prominent mood swings, "mild" bipolar depression) and dysthymia (gloomy mood, feeling of unmotivated dislike for loved ones, constant internal discontent, and irritation reflecting character traits; it is "milder" than recurrent depression) are also distinguished [7, 10–13].

Prevalence of depressive disorders / Распространенность депрессивных расстройств

Considering the growing life expectancy, the number of postmenopausal women worldwide comprises around 1 billion subjects. Although there is still a widespread stigmatization of menopausal symptoms and mental disorders, the world is changing, so that more women attempt to pay attention to such manifestations looking also for methods to control them. There is also a growing awareness of women about opportunities for drug and non-drug therapy of menopausal and depressive disorders. Therefore, the prevalence and incidence rate of depressive disorders in the peri- and postmenopausal female cohorts has been steadily increasing worldwide.

An increase in the level of depressive and anxiety symptoms was recorded in large-scale studies conducted in the UK, Italy, Australia, and the United States [14–17]. In a recently published Canadian study involving over 50 thousand women aged 45–64, 18.6 % of them had depression [17, 18]. In Russia, it is much higher: according to different researchers, the rate of anxiety-depressive disorders varies from 40.6 to 95.8 % [19, 20].

In a study by G. Perugi et al. with 538 patients of both sexes, it was confirmed that women vs. men had it at higher rate. In addition, differences in the type of depression were found as well: compared to men, women were 4 times more likely to have unipolar depression, anxiety, psychosomatic disorders and more often hospitalized in specialized hospitals [21]. Also, another study demonstrated that women over 40 vs. younger age are more likely to have unipolar depression [22]. Thus, endocrine factors can influence the prevalence as well as the nature and severity of depression symptoms suggesting about differences in the pathogenesis of depression in women and men [7].

Differences in the rate of depression, anxiety, and stress symptoms between women in peri- and postmenopause and age-matched men were found even in the presence of comorbidities accompanied by chronic pain syndrome [23].

Figure 1 compares gender differences in the risk of developing depression and a schematic representation

of serum estradiol level dynamics at different periods of a woman's life. From puberty onwards, depression is higher in women vs. men throughout lifespan. The most significant gender differences occur during perimenopause, after which the prevalence of depression in women decreases and approaches that one in men. Also, during menopause, the most pronounced fluctuations in the estradiol level are observed, which demonstrates the relation between changes in the concentration of female sex hormones and a risk of developing depression [24].

Also, the majority of studies show that the severity of depressive disorders is higher in women with premature surgical menopause [25], although few studies suggested opposite conclusions [26]. Indicative data were obtained in the domestic study that assessed the level of anxiety and depression according to the HADS (Hospital Anxiety and Depression Scale) scale in women after surgery on borderline ovarian tumors [27, 28]. Group IA consisted of women of reproductive age after radical surgery (removal of both ovaries), group IB – women after organ preservation surgery (removal out of two ovaries), group II – women in perimenopause after radical surgery. On average, 36 days after surgery, group IA revealed a “subclinical” level of anxiety-

depressive disorders (9.7 ± 1.0 and 9.0 ± 0.8 points, respectively). In group IB, the level of anxiety and depression was found to be within normal range (5.2 ± 2.4 and 5.2 ± 2.0 points, respectively); in group IB, the level of anxiety required no therapy (7.1 ± 0.7 points), but depression was also assessed as “subclinical” (7.9 ± 1.5 points). At the same time, the indicators of anxiety and depression by the HADS scale were significantly higher than in groups IB and II.

It is typical that the higher the severity of the climacteric syndrome, the more likely depression and anxiety would develop that was convincingly shown in the recent domestic study conducted at the Almazov National Medical Research Centre [29] by using the Zung Self-Rating Depression Scale (SDS). In women with mild climacteric syndrome, mean anxiety score was 37.0 ± 2.3 , which corresponds to a low level of anxiety, and depression – 32.0 ± 6.4 points, i.e., they were not characterized by manifested depression. Women with an average severity of climacteric syndrome are characterized by a high level of anxiety (71.0 ± 4.2 points) and mild depression (57.0 ± 1.2 points), whereas those with severe climacteric syndrome had a high level of anxiety (76.0 ± 0.6 points) and a moderate degree of depression (68.0 ± 1.4 points).

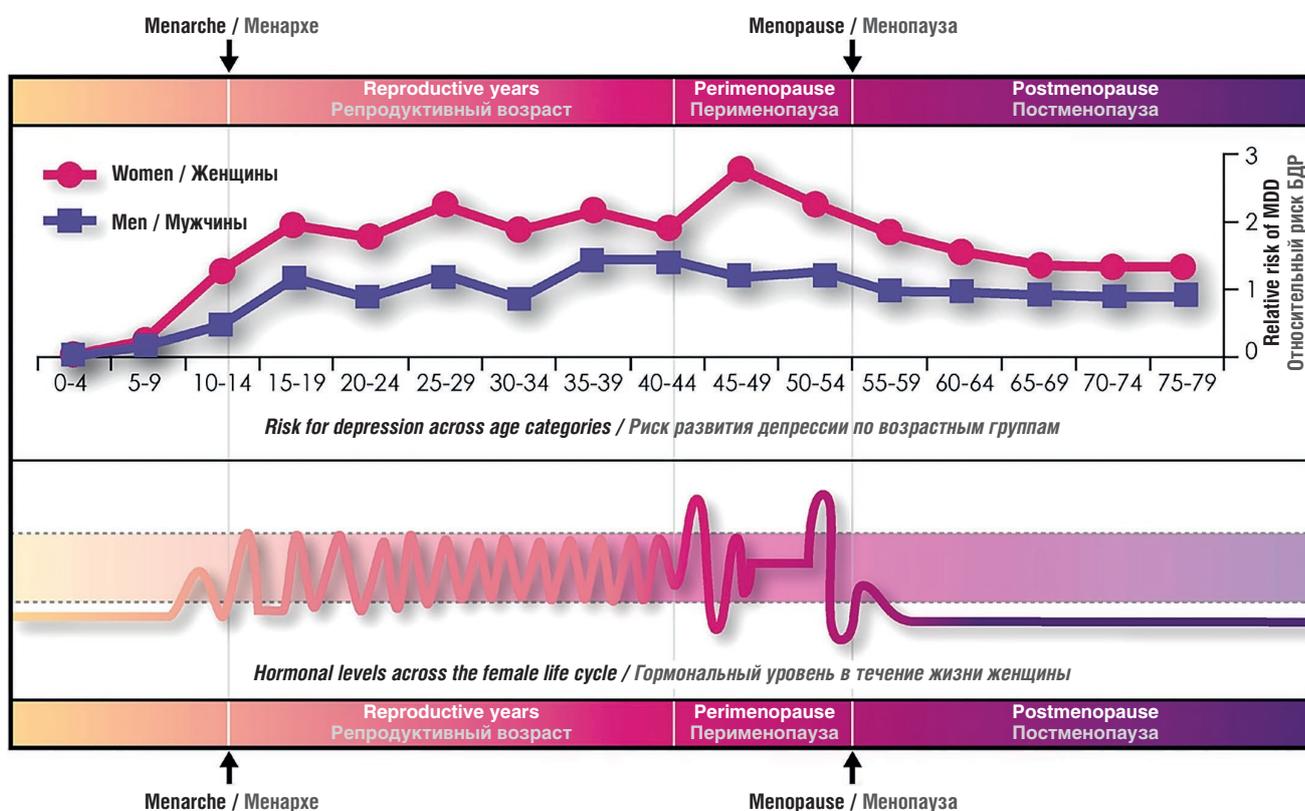


Figure 1. Gender-related differences in the risk of developing major depressive disorders (MDD) and serum estradiol levels at various periods of woman's life [24].

Рисунок 1. Гендерные различия в риске развития больших депрессивных расстройств (БДР) и уровень эстрадиола в сыворотке крови в различные периоды жизни женщины [24].

Pathogenesis / Патогенез

The relationship between the function of the reproductive system and the depression development was noticed long ago: as early as in 1890, J. Warnock discussed the relationship between the reproductive system and the CNS. At the beginning of the last century, M. Bleuler postulated a causal relationship between the endocrine system and mental illness, introducing the term "endocrine depression" [cit. by 7]. After estrone, estriol and estradiol were discovered in 1929, 1930 and 1933, respectively, by A.F.J. Butenandt and E.A. Doisy, researchers began to study a link between female sex hormones and mental disorders. In 1953, emergence of emotional disorders due to estrogen deficiency was demonstrated [30, 31].

Estrogen was mainly shown experimentally to be involved in neuromodulation, particularly in regulating serotonergic and noradrenergic systems, which play a pivotal role in the pathogenesis of depressive disorders. In particular, estrogens modulate elevated neuronal release of serotonin; contribute to augmented serotonin production and its reduced decay, specifically affect various subtypes of serotonin receptors (decreased production of monoamine oxidase via 5-HT1A receptors and increased binding to 5-HT2A receptors). Estrogens also influence increased norepinephrine synthesis and availability, expression of adrenergic receptor genes, and contribute to decreased rate of norepinephrine turnover (**Table 1**) [24].

However, a direct relation between estrogen deficiency and depression has not been confirmed. In 1973, G. Winokur examined 71 women with diagnosed affective disorders before or after menopause, and showed that the risk for such conditions did not differ significantly comprising 6.0 % and 7.1 % before and after menopause, respectively [32].

The majority of subsequent cross-sectional and long-term clinical studies found no evidence for direct relation between menopause and depression, but they demonstrated a link between symptoms of menopause and depression. Thus, the domino theory has become confirmed so that decreased estrogen level causes

symptoms inherent in menopause: vegetative-vascular (hyperhidrosis, headaches, hot flashes, chills, dizziness, tachycardia, sympathoadrenal and vagoinular crises), psycho-emotional (irritability, sleep disturbances, decreased mood, attention, memory impairment), urogenital (dryness, itching, burning sensation in the vagina, recurrent urinary tract infections, dyspareunia, dysuria, urinary incontinence), musculoskeletal (accelerated bone loss – osteopenia, osteoporosis; increased risk of fractures, sarcopenia), whereas menopausal symptoms, in turn, along with external causes of stress (health problems, decreased income, separation from loved ones, etc.) result in developing depressive-anxiety disorders and lowered quality of life (**Fig. 2**). At the same time, the rate of decreased female sex hormone level plays a more critical role than the absolute parameters of their content in the blood serum. It accounts for the greater severity of menopausal symptoms and the higher risk of depression in women with surgical vs. natural menopause [31].

Risk factors / Факторы риска

An interesting approach was offered by C.N. Soares, highlighting the risk factors in menopausal women for

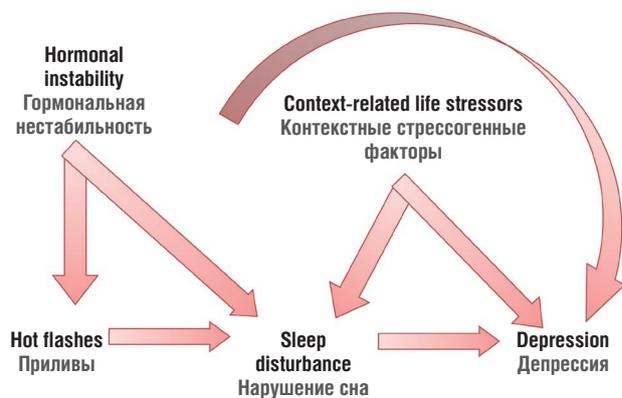


Figure 2. Pathways of depression associated with menopause [9].

Рисунок 2. Пути развития депрессии, связанной с менопаузой [9].

Table 1. Estrogen-related effect on the serotonergic and noradrenergic systems [24].

Таблица 1. Влияние эстрогенов на серотонинергическую и норадренергическую системы [24].

Effect on the serotonergic system Влияние на серотонинергическую систему	Effect on the noradrenergic system Влияние на норадренергическую систему
Modulation of neuronal serotonin release Модулирование высвобождения серотонина нейронами	Increased norepinephrine availability Повышение доступности норадреналина
Increased serotonin production Повышение синтеза серотонина	Increased norepinephrine production Повышение синтеза норадреналина
Decreased level of serotonin degradation Снижение уровня распада серотонина	Altered expression of adrenergic receptor genes Изменение экспрессии генов адренергических рецепторов
Effect on serotonin receptor subtypes Влияние на подтипы серотониновых рецепторов	Decreased rate of norepinephrine turnover Снижение скорости оборота норадреналина

the development of depression associated with the continuum (continuum-related) and factors associated with the "window of vulnerability" [2].

The risk factors associated with the continuum are present throughout a woman's life: these are demographic or socio-economic factors (lack of job, low educational level, etc.); health factors (higher body mass index, smoking, chronic diseases, etc.); psychosocial factors (low social level support, stressful life events). Predictors for major depressive disorder consist of prior depressive episode and a history of hormone-dependent affective symptoms such as premenstrual dysphoric disorder or postpartum depression. In other studies, postpartum depression is recognized as a predisposing factor for the development of subsequent depression associated with menopause [5].

Risk factors associated with the "window of vulnerability" are transient: fluctuations in estradiol and follicle-stimulating hormone levels during the menopausal transition; symptoms of menopause (vasomotor symptoms – hot flashes, sleep disorders, urogenital disorders, etc.); deterioration in general health and decreased performance due to chronic diseases; psychosocial stressors (stressful life events occurring during menopause).

Non-endocrine risk factors / Неэндокринные факторы риска

In the study enrolling 477 women, the main non-endocrine risk factors for developing depression were identified such as changes in relationship with loved ones due to abandonment by grown-up children ("empty nest syndrome"); chronic stress; health problems; death of a close friend or family member. Less prominent non-endocrine factors were worsened socioeconomic status, age, childhood sexual abuse, and recent acute stress, as well as divorce and childlessness [7, 33].

In a recent cross-sectional study with 485 postmenopausal women aged 35–78, death of a partner or divorce were recognized as risk factors for depression in postmenopausal women; alcohol consumption; any disease requiring constant medication; the presence of any physical disabilities; a history of mental disorders, as well as, interestingly, cohabitation with 4 or more children [34].

Such striking differences in the set of important risk factors recognized for development of depression in postmenopausal women can be explained by differences in methodology and different age of patients – the second study included women with surgical menopause. In any case, these risk factors are quite common in women aged 45–50 years (the age of menopausal transition) [7, 33].

Regarding the development of alcohol dependence, it may imply a vicious circle: alcohol consumption is a risk factor for depression, but psycho-emotional disorders, in

turn, are a risk factor for emerging alcohol dependence. The risk of developing alcohol dependence in women increases sharply during menopause, for which the most dangerous female age is of 50–59 years [35].

Endocrine risk factors / Эндокринные факторы риска

Although depression is not directly related to the level of female sex hormones in the blood, a relationship has been confirmed between estrogen concentration and psychological well-being. Thus, dysphoria and anxiety are associated with the concomitant decrease in estrogen levels in perimenopause. In case of former dysphoria or affective disorder, menopause can trigger depression. Low estradiol content at the neurophysiological level contribute to decreased concentration, which correlates with more pronounced manifestations of depression and symptoms of menopause at the behavioral level [7, 36].

Of note, there were obtained prominent data in meta-analysis analyzing 14 clinical trials with total of 67,714 women, where the following pattern was revealed: the production of estrogens lasting longer period throughout lifespan upon more extended period of fertility in women with later age of menopause correlated with lower risk of depression in postmenopausal period [37]. Thus, the risk of developing depression in women aged ≥ 40 years is 50 % lower than in younger women with premature menopause, and the risk of developing severe depression is reduced by 5 % every 2 years if menopause has not occurred.

It should be noted that endocrine risk factors can induce some of the above non-endocrine factors. For instance, if urinary incontinence due to thinning of the mucous membrane and decreased smooth muscle tone of the bladder develops in women with genitourinary syndrome upon decreased estrogen level, they may reduce the number of social contacts due to "fear of publicity". Therefore, endocrine and non-endocrine risk factors are distinguished rather arbitrarily.

Psychosocial discomfort / Психосоциальный дискомфорт

During menopause, many women experience vasomotor manifestations (hot flashes), reproductive system disorders negatively affecting sexual function (dryness, itching, burning sensation in the vagina, dyspareunia), as well as disorders of the urinary tract (recurrent cystitis, the need for more frequent toilet visits, urinary incontinence and associated discomfort). Urogenital disorders resulting from decreased female sex hormones are recognized as one of the leading causes for so-called psychosocial discomfort and the development of depression in peri- and postmenopausal women. On the one hand, inflammation, pain, and discomfort in the pelvic organs contribute to the development of psychosocial discomfort (a close relationship between

chronic pain and depression has been proven); on the other hand, lifestyle changes caused by urogenital disorders (dependence on the toilet, interpersonal problems, the need to change jobs, narrowing the circle of friends, fear of publicity, etc.) [8, 38].

These disorders negatively affect relationships in the family, at work and limit opportunities for recreation and entertainment. For instance, a woman begins to shy away from intimacy with her husband on far-fetched pretexts instead of openly discussing the problem. Psychopathological manifestations are often associated with dissatisfaction with sexual relations and their frequency [39]. In a study involving 300 menopausal women, impaired sexual function was found in 65.0 %, depression – in 29.3 %, and the correlation of these indicators was demonstrated [40]. The woman begins to avoid the usual entertainments because, e.g., she needs to disturb the audience in neighboring chairs several times during a theater performance to go to the toilet. A woman may decide to quit her job because, e.g., her subordinates and colleagues may notice the odor associated with urinary incontinence.

It should be noted that the number of working women over the age of 50 is increasing worldwide. Thus, in Great Britain, the proportion of women among the working population over 50 years old comprises 45 %, or 3.5 million in absolute terms [41]. Russia is no exception: since 2019, the retirement age has been increased. Whereas earlier, women retired at the age of 55, it has been elevated up to 60 years for women and 65 years for men [42]. Therefore, the relevance of controlling depression and psychosocial discomfort in older working women has been steadily increasing.

Psychosocial discomfort includes a loss of self-confidence, personal external attractiveness, problems with self-identification, which, together with age-related cognitive changes, such as inattention and memory loss, in the final period leads to lowered female quality of life and loved ones, a negative impact on the ability to work and social behavior, decreased well-being with loss of income, increased stress levels and increased risk of developing anxiety and depression [8, 38, 41].

Despite this, many women do not look for assistance due to awkwardness, potential adverse reactions from the surrounding people, or cultural taboos associated with this condition. A significant problem is the stigmatization of such disorders in society.

Clinical picture and diagnostics / Клиническая картина и диагностика

Primary care physicians meet almost 2 times more patients with mental disorders than psychiatrists on outpatient visits due to the presence of obstacles to accessing psychiatric services such as stigmatization

and low accessibility [43]. In many countries, including Russia, a criticized strategy of transferring the supervision on neurological and psychiatric patients from specialized centers to the public health care network is being carried out [44–46]. Therefore, the outpatient doctor needs to have information about the clinical picture, based on which it will be possible to recognize or suspect anxiety-depressive disorders.

The clinical picture is characterized by a combination of affective (anxious, melancholy, apathetic, dysphoric) and somatic vegetative disorders.

The most significant psychological signs of depression are melancholy, sleep disturbances, guilt, low self-esteem, and suicidal/death thoughts. With the predominance of the depressive component, a woman may hesitate to enter the office, have a stooped posture, an "absent" look, a mask-like facial expression with a lack of facial expressions. Answers to the doctor's questions are usually expressed in a low voice, monosyllabic, and after a pause. Disturbance in concentration is also characteristic [43]. Diagnostic questions may be as follows: "What brings you joy, makes you happy lately?"; "Do you often "fly away" in your thoughts to the past, and do you think that everything was bad, not as it should be?" A positive answer indicates the unequivocal presence of symptoms of anhedonia (joylessness), which is the "core" symptom of depressive disorders. With the predominance of the anxious component, a woman, on the contrary, can walk in with a brisk step, make impulsive, nervous movements, often change posture, have tense facial expressions, and shallow breathing. Despite the confusing speech with a tendency to monologue, unstable attention to the doctor's questions, the "absent" look is characteristic. Symptoms of autonomic disorders are often present: white or red dermographism, hyperhidrosis, tachypnea and tachycardia, arrhythmia, discomfort in the left side of the chest, fluctuations in blood pressure, feeling short of breath, dyspeptic disorders, chills, tremors. In this case, diagnostic questions may be: "Do you often feel inner tension, trembling with the inability to relax?"; "Do you often expect trouble, bad, indefinitely painful, which is about to come?" A positive answer indicates the presence of an alarming motor-vegetative symptom complex [43].

In clinical practice, subjective and objective scales named after Beck, Tsung, Hamilton, etc. are also widely used.

In elderly patients, electroencephalography (EEG) may be of diagnostic value [47]. There are indications that the imbalance of regulatory systems in the central nervous system during menopause and probable depression in women can manifest in two specific EEG patterns, which can be conditionally designated as moderately acute and desynchronized patterns [48].

Consulting and interdisciplinary interaction / Консультирование и междисциплинарное взаимодействие

Often, elderly patients, while communicating with a healthcare professional (either a neurologist, neuropsychiatrist, psychiatrist, or an obstetrician-gynecologist), avoid raising the issue of mood disorders, symptoms of depression, and urogenital disorders. Therefore, while communicating with a patient, doctor should proactively clarify whether this kind of disorder occurs [8].

Mild to severe depression should be managed by psychiatrists. However, many primary care physicians avoid explicitly specifying the need for a psychiatrist consultation in their medical records, because patients seeing such a recommendation, often begin to doubt about professional competence not believing that they might have been correctly “registered as mentally ill”.

Therefore, a compromise approach is to appoint a consultation with a neuropsychiatrist, psychologist, or psychotherapist and treat exogenous depression of mild degree with phytoestrogens, anti-anxiety, and mood-modulating drugs, as well as remove causes resulting in stress, anxiety, and depression.

Before prescribing therapy, a woman should be consulted on the manifestations of psycho-emotional disorders in peri- and postmenopause: provide information in an accessible form about the causes and modern treatment methods, including the expected duration on onset of therapeutic effect, contraindications, possible adverse events, and necessary lifestyle restrictions, as well as about disease prognosis [49].

Therapy / Лечение

It is good practice to draw up an individual treatment plan, taking into account the continuity of various stages of therapy, the effectiveness and tolerability of previous interventions, the clinical characteristics of the condition (e.g., the presence of a psychoautonomic syndrome, anxiety, sleep disturbances or atypical symptoms, etc.) [49]. The drugs of choice for moderate and severe depression are antidepressants (prescribed by a neuropsychiatrist or psychiatrist. An essential part of the prevention and treatment of depression in postmenopausal women is a therapy aimed at eliminating the endocrine risk factors associated with the “vulnerability window,” which should be prescribed by the obstetrician-gynecologist.

Antidepressants / Антидепрессанты

In case of verified moderate to severe depression, especially endogenous depression, it is necessary to use antidepressants. The most common in clinical practice are selective serotonin reuptake inhibitors (SSRI) – fluoxetine, sertraline, paroxetine, fluvoxamine, citalopram,

and selective serotonin and norepinephrine reuptake inhibitors (SSNRI) – venlafaxine, milnacipran [50].

A typical property of antidepressants is a positive effect on mood and the emotional sphere, improving both general condition and mental status. A neuropsychiatrist or psychiatrist chooses antidepressants. The preferred strategy is to administer balanced antidepressants with anxiolytic (anti-anxiety) properties in most cases allowing to avoid additionally prescribed anti-anxiety drugs, which is essential for preventing polypharmacy in elderly patients constantly taking several drugs to control various diseases and conditions (arterial hypertension, diabetes mellitus, chemotherapy for cancer, etc.) [8, 38, 51].

However, the patient should remember and to be guided that the therapeutic effect of using antidepressants is fully manifested 2–4 weeks later after therapy onset.

Menopause and old age are predictors of poor response to antidepressant therapy. Some studies have demonstrated the potentiation of the antidepressant effect while using menopausal hormone therapy (MHT), estrogens as auxiliary therapy. In a comparative placebo-controlled study, patients received sertraline and used transdermal patches with estrogen (main group) or placebo (comparison group). After 10 weeks, an equally significant decrease in the Hamilton Depression Scale scores was observed in both groups, but in women from the main group, improvement was achieved earlier (at 2–4 weeks) [52, 53]. In addition, a comparative study with 3 groups of depressed postmenopausal women using fluoxetine, a estradiol transdermal patch, or both, showed that the most effective was a combination of fluoxetine and estradiol [54]. In another study of depressed perimenopausal women with incomplete response to antidepressant therapy, estrogen vs. placebo showed significantly more profound decline in Hamilton scores. At the same time, escalating the estrogens dose for a short time along with a stable intake of antidepressants led to a significantly improved mood [55]. Because none of the antidepressants in the SSRI and SSNRI groups revealed superior efficacy and safety over others [56], the choice of a drug in women with recurrent depression should be based on data about the response to using previous drug: a complete response without adverse events, it should be continued, with a partial or no response, or with developing adverse events, other options should be considered.

In parallel with antidepressants, it is justified to use small antipsychotics, antiepileptic drugs (AEDs). In presence of severe anxiety symptoms, the addition of anxiolytics (tofisopam) is recommended, in case of sleep disorders – sedative herbal preparations [49]. It should be kept in mind that valproic acid used in bipolar affective disorder has a teratogenic effect, and therefore

should not be used in women with reproductive potential [57, 58]. It is also advisable to use means to eliminate the factors causing depression.

Therapy for reversing depression-triggering factors / Терапия для устранения факторов, вызывающих депрессию

Menopausal hormone therapy / Менопаузальная гормональная терапия

Evidence from clinical trials on the efficacy of MHT as a first-line therapy for depression in postmenopausal women is controversial. In a cohort of postmenopausal women without diagnosed depression, some studies confirmed the positive MHT effect on the dynamics of indicators on the depressive symptoms scale, while others did not.

In double-blind, placebo-controlled studies, estradiol has been shown to be effective in controlling the symptoms of depression in perimenopausal but not postmenopausal women. MHT has also proven to be an ineffective strategy for mood control in women lacking diagnosed depression [56].

It should be noted that there is clear evidence about a positive effect on psychological symptoms and cognitive function (primarily due to a decrease in vasomotor symptoms – hot flashes) while using MHT in women in surgical, but not in natural menopause [7, 59, 60]. At the same time, some studies have confirmed the effect of estrogen therapy on the feeling of well-being, improved mood, and decreased anxiety during estrogen therapy in peri- and postmenopausal women [7, 61]. Moreover, several clinical studies have shown that the positive effect of estrogens is leveled by progestins [7]. Used in monotherapy and combination with estrogens, androgens, on the contrary, are more effective than estrogen monotherapy [7, 33, 60, 62].

Estrogens can increase serotonin activity. Because the mechanism of antidepressants widely used in depression (SSRI, SSNRI) is associated with an effect on the serotonergic system, estrogens can potentiate the effect of such antidepressants. For instance, L. Schneider et al. in a study with 358 perimenopausal women with depression and receiving fluoxetine (286 patients) and fluoxetine and conjugated equine-estrogens (72 patients), demonstrated that in the first group, the improved Hamilton depression scale was 17.0 %, and in the second group – 40.1 % of women, respectively. Researchers have postulated that estrogens may potentiate the effects of fluoxetine [63]. Thus, from the standpoint of evidence-based medicine, the effectiveness of estrogens for depression remains still unproven. MHT can be used in women with mild depression to treat hot flashes, sleep disturbances, and other symptoms that lead to psychosocial

discomfort, depression, and anxiety. No reliable data on how effective it is to use MHT in adjuvant therapy for severe depression in peri- and postmenopausal women are available. At the same time, it has been proven that estrogens can improve the effect of SSRI [7, 63]. Perimenopause can be considered as a "window of opportunities" for prescribing MHT as an adjunct therapy for depression control [56]. However, the data on the role of MHT in depressive's control disorders in peri- and postmenopausal women are limited by number of randomized trials and the size of the patient sample, which complicates data interpretation and generalization.

Genitourinary syndrome therapy / Терапия генитоуринарного синдрома

Urogenital symptoms of menopause, which may underlie psychosocial discomfort in peri- and postmenopausal women, are dryness, itching, burning sensation in the vagina, dyspareunia, decreased libido, and sexual activity, recurrent cystitis, urinary incontinence [8, 38, 51, 64]. If it is necessary to eliminate the causes of psychosocial discomfort, anxiety, and depression in the presence of urogenital disorders caused by estrogen deficiency, the obstetrician-gynecologist, as a rule, prescribes appropriate therapy.

In those patients who, in addition to disorders of the genitourinary tract, have systemic manifestations of the climacteric syndrome, systemic MHT, or woman refuses systemic MHT, e.g., because of fears of developing adverse events, then a drug of choice would be local form of estriol (cream, suppositories). It is necessary to explain to a patient with an anxious and suspicious emotional background that such forms have virtually no systemic effect.

Among all estrogens, estriol is solely exerts a selective effect on the urogenital tract, without affecting mammary gland proliferation and the uterine endometrium. While consulting a patient with urogenital disorders, it should be noted that after the completion of the treatment course, it is necessary to continue long-term maintenance therapy with estriol to prevent the recurrence of symptoms of urogenital disorders causing development of psychosocial discomfort [8, 38, 51]. This tactic often leads to an objective improvement in a woman's psychological state.

Magnesium supplements / Препараты магния

For peri- and postmenopausal women with symptoms of depression, anxiety, and stress, the use of organic magnesium salts is indicated. As known, glutamatergic system and N-methyl-D-aspartate (NMDA) CNS receptors acting in the pathogenesis of stress, cognitive and emotional disorders in stress-related disorders. Magnesium ions are universal natural stabilizers of all NMDA-receptor subtypes: at rest, the NMDA-receptor

channel is closed by a magnesium ion. Magnesium deficiency causes the activation of NMDA-receptors in combination with calcium channel opening, which leads to neuronal damage and dysfunction that might be clinically manifested as anxiety and depression [65].

In a large-scale Russia-wide study, a high prevalence of magnesium deficiency in postmenopausal women was demonstrated: in 72.3 % patients with climacteric syndrome who received no MHT, in 79.4 % patients with climacteric syndrome receiving MHT therapy, and in 82.1 % patients with osteoporosis [66].

Replenishment of magnesium deficiency in the general female population was accompanied by significant improved physical and psychological well-being, self-perception, micro-social support, and social well-being according to objective scales (Fig. 3).

The use of estrogen-containing drugs, such as MHT, may be associated with increased magnesium excretion, confirming the higher prevalence of magnesium deficiency in the group receiving MHT in this study. Preparations with organic magnesium salts potentiate the positive effects of MHT and aid to minimize the adverse effects of MHT on female body as well as control stress, anxiety, and depression [65, 66].

Vegetable proteins, phytoestrogens and polyunsaturated fatty acids / Растительный белок, фитоэстрогены и полиненасыщенные жирные кислоты

In addition to drug therapy, nutritional support can help controlling symptoms of depression and anxiety during menopause.

Not being steroid hormones, phytoestrogens (isoflavones of red clover and soy, lignans, coumestans, etc.) can act as weak estrogens [67, 68], in terms of effectiveness, they are noticeably inferior to endogenous

female sex hormones. However, at the same time, they have a balancing effect; i.e., they have a modulating effect and advantages in the safety profile. It should be noted that researchers cannot yet come to a consensus on how widely phytoestrogens can be used in menopausal disorders [67].

In 2021, a study was published wherein one group of menopausal women received 100 g/day of soy flour and flaxseed cookies daily for eight weeks, and another group – raw, unroasted peanuts and raw sesame seeds (90 g/day) mainly containing polyunsaturated fatty acids (PUFA). Women in both groups underwent an assessment of the Menopause Rating Scale (MRS), Beck Anxiety Inventory (BAI), Beck Depression Inventory-II (BDI-II), and a biochemical blood test. The women using the PUFA supplement showed significantly more marked decline in anxiety and depression on the BAI and BDI-II scales than the group who consumed soy biscuits. Interestingly, the PUFA supplementation also demonstrated antioxidant and anti-inflammatory effects, as evidenced by the dynamics in serum interleukin-6 and malondialdehyde levels (a marker of inflammation and an antioxidant marker, respectively). Similar results were shown in perimenopausal women as well [69].

A plausible mechanism of action is the ability of linoleic acid to cross the blood-brain barrier and interact with compounds that regulate mood, anxiety, and depression. According to another theory, the severity of depression may be indirectly influenced by the anti-inflammatory properties of linoleic acid [5, 69].

**Strategy for drug therapy /
Тактика медикаментозной терапии**

For perimenopausal women with severe menopausal symptoms and depression, MHT alone may be



Figure 3. Assessing dynamics in women's quality of life after 1 month taking a fixed-dose combination of 618.3 mg magnesium citrate and 10 mg pyridoxine [66].

Note: * $p < 0.001$ – significantly improved quality of life assessed by complex scales.

Рисунок 3. Оценка динамики качества жизни женщин после приема в течение 1 месяца фиксированной комбинации цитрата магния 618,3 мг и пиридоксина 10 мг [66].

Примечание: * $p < 0,001$ – статистически значимое повышение качества жизни по комплексным шкалам.

recommended to determine its tolerability and benefits for lowering mood and relieving symptoms of menopause. After that, it should be assessed as to whether is it possible to keep patient on MHT monotherapy or it might require to consult a specialized medical worker to prescribe antidepressants. Women with a history of depressive episodes and women with severe depression and/or severe suicidal tendencies should be referred to a neuropsychiatrist or psychiatrist for antidepressant therapy [56].

MHT should be individualized for the benefits of preventing osteoporosis, cardiovascular disease, and urogenital disorders as well as improving cognitive function and mood. The safety profile of the drugs must also be considered [56].

In addition to MHT, all women with depression in peri- and postmenopause, including those receiving antidepressants, should be prescribed magnesium preparations, B vitamins, vitamin D, phytoestrogens, and PUFA (linolenic acid) to control menopausal symptoms and symptoms of psychosocial discomfort, which are factors risk for developing depression.

Non-pharmacological methods / Немедикаментозные методы

Psychotherapy / Психотерапия

A. Beck formulated the cognitive triad of depression: a negative attitude to self (patient considers self to be deprived, chronically ill, and explains own failures by personal psychological, physical, or moral defects); to own experience (believes that the world around poses too high demands on subject or creates obstacles in the way of achieving goals); own future (believes in no success, awaits disappointment, a series of challenges and suffering) [cit. by 70].

One of the most effective psychotherapy methods is cognitive-behavioral therapy, which focuses on correcting such thinking characteristics of postmenopausal women with depression. It is most effective when the symptoms of the first component of the depression triad predominate [71, 72].

Other methods of psychotherapy can also be applied – interpersonal, psychodynamic, etc. It should be noted that psychotherapy is not an alternative to drug therapy but should be applied within general therapeutic interventions.

Stress prophylaxis / Профилактика стресса

Stress is one of the risk factors for depression in peri- and postmenopausal women. Moreover, at the age of menopausal transition, the number of situations and prerequisites for emerging distress (excessive stress) becomes higher. During the consultation, the patient's attention should be paid to the recommended

age-related duration of sleep (7–8 hours), compliance with sleep hygiene rules. A balanced diet is important because healthy eating habits reduce exposure to stress. Regular physical activity relieves stress as well as enhances adaptation and stress resistance. For women in menopause, at least 30 minutes of moderate-intensity physical activity 5 times a week is applicable, especially aerobic exercise, jogging, Nordic walking, cycling. Recommendations should be adjusted individually, taking into account the current state of health [65].

During the period of self-isolation due to COVID-19 pandemic, the recommendations on basic anti-stress skills, which might be apply independently, look especially relevant. These include diaphragmatic breathing, which should be used in moments of solid emotional arousal or regularly two times a day for 5 minutes; techniques for the adequate release of emotions (personal diaries, conversation with a partner or girlfriend); change of activity for convenient switching of attention, relaxation training, time management, etc. [65].

Rehabilitation / Реабилитация

Rehabilitation is essential primarily for patients with surgical menopause. This was shown in a comparative study, where the indicators of anxiety and depression were monitored for 12 months in patients after radical surgery for ovarian tumors. Two groups were formed: group I – 29 women who decided to follow "active (complex) rehabilitation", group II – 33 patients who preferred "passive rehabilitation". "Active rehabilitation" included a set of measures designed for 10–12 month-period, individually developed considering the primary diagnosis, concomitant diseases, complications of anticancer therapy, and general condition. It included diet therapy, adequate fluid intake, body weight control, individual and group psychotherapy, health path, remedial gymnastics, herbal medicine, immune disorders, physiotherapy procedures. Most rehabilitation measures were carried out at rehabilitation centers and sanatorium-resort treatment institutions. The dynamics were assessed using the HADS scale. After 12 months of rehabilitation, the level of anxiety in group I decreased from 10.97 to 5.72 points, almost by 2-fold lower that of depression – from 9.79 to 5.34 points. In group II, the dynamics of decreased anxiety and depression were markedly worse: from 11.00 to 8.55 points and from 9.45 to 9.33 points, respectively. There was also a positive trend in restoring sexual function [28].

Similar results were demonstrated in an earlier clinical study of medical rehabilitation for women with induced menopause after radical surgical treatment due to cervical cancer. After 6 months, the level of anxiety was reduced by 23.2 %, and depression by 13.6 % [73].

Thus, complex personalized rehabilitation can significantly improve women's psycho-emotional state

and quality of life with depressive manifestations during surgical menopause. Unfortunately, in Russia, patients currently have no opportunity to receive comprehensive rehabilitation on a complimentary basis, so access to rehabilitation procedures remains limited, despite the proven effectiveness.

Digital healthcare / Цифровое здравоохранение

The Internet has been increasingly playing a pivotal role in providing patient information and a range of primary health care interventions.

In addition to telemedicine advice, which was implemented even before the SARS-CoV-2 virus spread, the importance of digital health and related Internet-based services were actualized during the COVID-19 pandemic, when the need for social distancing arose. The approaches to medical care organization and control over the population have changed [41]. Many examples can be referred to: this is an appointment with a doctor through the portal of public services, electronic passes during 2020 lockdown, and the QR code system to distinguish between those lacking vaccination with domestic vaccines against SARS-CoV-2 in 2021 as it was introduced in China, USA, and EU countries.

Digital health can be an effective way for women to find advice, exchange information about the disease, and access interventions related to their concerns in confidence, without restrictions on time, place, or social circle. An example of such an initiative is the Consultation project for women planning pregnancy, implemented in a hybrid format of face-to-face events as well as online broadcasts and pages in social networks Facebook and Instagram [74]. Such safe, efficient, and high-quality digital health resources can be successfully developed to meet the needs of other patient cohorts, e.g., women in menopause [41]. Also, critical is the knowledge and awareness of women about menopause and the related disorders, particularly depression. In Russia, a social project, "School of Women's Health", is already starting under the auspices of the Institute of Preventive and Social Medicine, aimed just to increase women's awareness of own health, diverse periods of life, including menopause and its features, which should be paid attention to and consult a doctor promptly.

These approaches help accessing up-to-date health information for women from remote areas and following busy, high-employment life, providing new, accessible, and inclusive opportunities to empower women and improve their quality of life. However, this can only work if the medical information is presented in a form understandable to a non-health professional. It should

be emphasized that despite the limited research on the efficacy and safety of digital health strategies for the vast majority of therapeutic options, such evidence has been accumulated for mental health: for middle-aged, high-income, and employed women, these approaches demonstrate clinically effective results in mild to moderate depression and anxiety [41, 75].

Another issue is the quality of information exchanged by influencers in Instagram and inpatient forums: it varies most often being based on opinions, personal experiences, or myths rather than scientific evidence. In addition, because the digital health market is largely unregulated, there is a risk that several players will put commercial benefits at the expense of ethics [41]. This situation increases the vulnerability of post-menopausal women while choosing safe and evidence-based digital therapeutic interventions and self-help resources.

Conclusion / Заключение

Depression in women with surgical and natural menopause seriously complicates both female life and her family members, perpetuating the vicious circle of problems associated with changes in lifestyle and health status during the menopausal transition. Given the frequent presence of suicidal thoughts, depression should be treated as a life-threatening condition. Therefore, depression in women with menopause is recognized as a condition that needs timely correction.

The management of such patients should include interdisciplinary interaction involving a neurologist, psychologist, and psychiatrist, if necessary.

Because in the conditions of modern healthcare, women with depression in menopause more often refer to the primary visit to an obstetrician-gynecologist than to specialized medical doctors, it is essential to recognize its symptoms promptly and establish interaction between primary care doctors and specialized medical professionals.

In addition to antidepressants, a therapy should be prescribed to prevent menopausal symptoms that induce anxiety-depressive disorders.

The management of women with symptoms of anxiety and depression in menopause, in addition to drug therapy, should include comprehensive, personalized rehabilitation. Also, in conditions of limited access to professional medical care (which is especially important in the era of the COVID-19 pandemic), it is justified to use digital health solutions. This set of measures will improve the quality of medical care for women with depression in menopause.

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