DOI: 10.20514/2226-6704-2022-12-4-276-284
EDN: OJJERG
УДК 618.1/.2-06:616.89-008.1

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ДИАГНОСТИКА И ТЕРАПИЯ ПСИХОСОМАТИЧЕСКИХ РАССТРОЙСТВ ГЕНЕРАТИВНОГО ЦИКЛА ЖЕНЩИН В ОБЩЕЙ МЕДИЦИНСКОЙ ПРАКТИКЕ (ОБЗОР ЛИТЕРАТУРЫ)

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Diagnosis and Therapy of Psychosomatic Disorders in Reproductive Cycle of Women in General Medical Practice (Review)

Резюме

Своевременное выявление врачами общей медицинской практики психических и психосоматических расстройств у пациенток при планировании, а также во время ведения беременности и в послеродовый период, остается значимой медицинской задачей. Частота встречаемости гетерогенных психосоматических расстройств (аффективные, тревожные, дисморфические, соматовегетативные, психотические) на фоне менструаций, беременности и в послеродовом периоде достигает 80 %. В свою очередь, психосоматические расстройства являются факторами риска для отсроченного наступления и сокращения продолжительности менструаций, развития предменструального синдрома, неадекватных эмоциональных реакций при менструациях, перебоев в цикле, снижения регулярности и удовлетворенности половой жизнью, фертильности, невынашивания беременности, сокращения лактационного периода, раннего наступления менопаузы с большой длительностью и клинической тяжестью пременопаузы и др. При индивидуальном подходе к назначению схемы лечения требуется учитывать факторы риска (наследственность, коморбидные расстройства, пол, возраст и др.) развития нежелательных явлений (НЯ), баланс эффективности и безопасности лекарственных средств.

Ключевые слова: *психические расстройства, депрессия, тревога, дисморфическое расстройство, психозы, предменструальный синдром, беременность, лактация, послеродовый период*

Конфликт интересов

Авторы заявляют, что данная работа, её тема, предмет и содержание не затрагивают конкурирующих интересов

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Источники финансирования

Авторы заявляют об отсутствии финансирования при проведении исследования

Статья получена 25.11.2021 г.

Принята к публикации 09.03.2022 г.

Для цитирования: Медведев В.Э. ДИАГНОСТИКА И ТЕРАПИЯ ПСИХОСОМАТИЧЕСКИХ РАССТРОЙСТВ ГЕНЕРАТИВНОГО ЦИКЛА ЖЕНЩИН В ОБЩЕЙ МЕДИЦИНСКОЙ ПРАКТИКЕ (ОБЗОР ЛИТЕРАТУРЫ). Архивъ внутренней медицины. 2022; 12(4): 276-284. DOI: 10.20514/2226-6704-2022-12-4-276-284. EDN: OJJERG

Abstract

The incidence of different psychiatric disorders (affective, anxious, dysmorphic, psychotic) during menstruation, pregnancy and the postpartum period reaches 80 %. Mental disorders are risk factors for the delayed onset and shortening of menstruations, manifestation of the premenstrual syndrome (PMS), inadequate emotional reactions during menstruations, disruptions in the menstrual cycle, decreased regularity and satisfaction of sexual activity, fertility, pregnancy failure, reduction of the lactation period, early onset of menopause with long duration and clinical severity of premenopause, etc. An individual approach to treatment should take into account risk factors (heredity, comorbid disorders, sex, age, etc.) of adverse events (AD), the balance of efficacy and safety of drugs.

Key words: *mental disorders, depression, anxiety, dysmorphic disorder, psychoses, premenstrual syndrome, pregnancy, lactation, postpartum period*

Conflict of interests

The authors declare no conflict of interests

Sources of funding

The authors declare no funding for this study

Article received on 25.11.2021

Accepted for publication on 09.03.2022

For citation: Medvedev V.E. Diagnosis and Therapy of Psychosomatic Disorders in Reproductive Cycle of Women in General Medical Practice (Review). The Russian Archives of Internal Medicine. 2022; 12(4): 276-284. DOI: 10.20514/2226-6704-2022-12-4-276-284. EDN: OJJERG

ACTH — adrenocorticotropic hormone, AE — adverse events, BDD — body dysmorphic disorder (dysmorphia, dysmorphophobia), BPAD — bipolar affective disorder, DACH-syndrome (D — depression; A — anxiety; C — craving; H — hyperhydration), DSM — Diagnostic and Statistical Manual of mental disorders, GABA — gamma-aminobutyric acid, ICD-11 — International Classification of Diseases, OCD — obsessive-compulsive disorder, PMDD — premenstrual dysphoric disorder, PMS — premenstrual syndrome, PTSD — post-traumatic stress disorder, RID — relative infant dose, SNRIs — selective serotonin and norepinephrine reuptake inhibitors, SSRIs — selective serotonin reuptake inhibitors, TCAs — tricyclic antidepressants, TSH — thyroid stimulating hormone

Timely detection by general practitioners of mental and psychosomatic disorders in female patients during pregnancy planning, as well as during pregnancy and postpartum period, remains a significant medical issue.

The objective of this review was to analyze the results of basic research studies on the pathogenetic and clinical and dynamic characteristics of the generative cycle of a woman (menstrual cycle and pregnancy). Search by keywords “mental disorders”, “depression”, “anxiety”, “dysmorphic disorder”, “psychosis”, “premenstrual syndrome”, “pregnancy”, “lactation”, “postpartum”, “treatment” was conducted in the databases of articles published by domestic and foreign authors over last 25 years (PubMed, eLibrary, Scopus, and ResearchGate).

According to the scientific ideas predominating at late 20th — early 21st century, psychosomatic disorders associated with menstruation, pregnancy and postpartum period are caused by sharp and cyclic fluctuations in the level of blood estrogen, changes in the prevalence of estrogen receptors in brain structures associated with affect regulation (including amygdala, hippocampus, and hypothalamus), as well as suppression of the activity of GABAergic neurons (GABA, gamma-aminobutyric acid) by progesterone [1–2]. The other possible causes include decreased secretion of gonadoliberin, melatonin, stimulating effect of thyreoliberin on the secretion of thyroid-stimulating hormone (TSH), of corticoliberin on adrenocorticotropic hormone (ACTH), and of vasopressin on cortisol [1-2].

On the other hand, the mental/psychosomatic disorders in female patients are a risk factor for delayed onset and shortening of menstruation period, development of premenstrual syndrome (PMS), inadequate emotional reactions (fear, exaltation) during menstruation, irregularities in the menstrual cycle, decreased regularity (50.4 %) and satisfaction (62.2 %) with sexual life, decreased fertility (decreased number of ovulations, pregnancies, deliveries), miscarriage, reduced lactation period, early onset of menopause with a long duration and clinical severity of premenopause, etc. [3].

The first classifications of psychiatric disorders associated with the reproductive cycle in women included pregnancy-related disorders; postpartum disorders (first 6 weeks (4 weeks — 12 months) after childbirth), and lactation disorders (starting from the week 7 after childbirth) [4]. DSM-II (Diagnostic and Statistical Manual of mental disorders) (1968) also included “postpartum psychosis” as a diagnosis of exclusion. ICD-11 (International Classification of Diseases) has a separate section “Mental or behavioral disorders associated with the reproductive cycle”, with codes 6E20-6E21.

Mental disorders that are most often associated with the reproductive cycle of women and detected during general examination, include depressive, anxiety, dysmorphic, and psychotic complexes of symptoms.

Depressive symptoms are observed in premenstrual syndrome in 27 % of women; premenstrual dysphoric disorder (PMDD) with clear clinical signs — in 7 %. Depression is diagnosed in 5–41 % of pregnant women and in 12–22 % of women in postpartum period [5–7].

Clinical presentation of depression associated with female generative cycle is characterized by a predominance of asthenic, or asthenic and apathetic symptoms in combination with anxiety, phobias, dysphoria, lethargy, tearfulness, ideas of guilt, sleep disorders (hypersomnia), hyperphagia, somatic symptom disorders (hysteralgia). Dissociated (mixed) disorders are rather common: euphoric mood with total inactivity and motor retardation, as well as mood lability with causeless changes from depression to mania with euphoria and anger [8–9].

Anxiety disorders, including panic, generalized, obsessive-compulsive disorder (OCD), post-traumatic stress disorder (PTSD), and tocophobia (pathological fear of childbirth), are most common in pregnant women (13 %) and in women in postpartum period (up to 43 %) [10–11].

Anxiety disorders with tropism to suspicious personalities, stress factors, interpersonal conflicts, complications of pregnancy (preeclampsia, etc.), are characterized by irritability, tension, moderate autonomic disorders (dizziness, drowsiness, lethargy) [12].

According to our observations, clinical presentation of a body dysmorphic disorder (dysmorphia, dysmorphophobia, BDD) associated with the generative cycle in 15–47 % of women is heterogeneous [13–15]. The most common symptoms include an unreasonable idea of a defect in appearance that is objectively minimal or even non-existent, excessive detailing of the nature of an imagined flaw or defect, detailed presentation or, at the contrary, inability to effectively describe a flaw in appearance. Sometimes female patients feel fear that other people will see an imagined deformation of their appearance; this can result in social isolation.

Along with general medical examinations, patients with BDD often visit aesthetic medicine specialists with bizarre requests (for example, to perform a facial tuck-up surgery at the age of 20–30, to achieve "perfect symmetry" (Goldilocks syndrome), etc.) [13–15].

Other signs of BDD are either excessive mirror gazing ("mirror symptom") in order to find the best view when the supposed "defect" is not visible, or to determine what kind of correction is required, or, on the contrary, "negative mirror symptom" when female patients remove all mirrors and other reflective objects from their place. Another particular sign of BDD is "negative photo symptom" (patients categorically refuse to get their picture taken) and "defect camouflage" with clothes, hair, make-up, and body position [15–17].

In 83 % of cases, aggression delegated to physicians (desire for surgeries and other medical procedures) in accompanied by a tendency to auto-aggressive behavior [18]. In addition to numerous and persistent visits to physicians and cosmetologists, patients constantly demand their family members to confirm (or refute) defects in their appearance, search for information (read special literature, popular publications) related to "defect" correction.

The incidence of psychotic states in the postpartum period is 1–2 per 1 thousand (3–5 % of women after childbirth) [11, 19]. Among the latter, about 43.5 % of cases are "isolated postpartum psychoses" [20]; 72–88 % belong to the structure of bipolar affective disorder (BPAD) type I or schizoaffective disorder [21, 22]; 12 % are within the dynamics of schizophrenia [22].

Prevalence of **premenstrual syndrome** (PMS/PMDD, N94.3 in ICD-10; "Pain and other conditions associated with female genital organs and menstrual cycle", N94.8; "Other specified mood [affective] disorder", F38.8; premenstrual tension syndrome, "cyclic disease", ovarian cyclic syndrome, premenstrual disease, premenstrual dysphoric disorder , DACH-syndrome (D — depression; A — anxiety; C — craving; H — hyperhydration [23]) is 25–95 % among all women [24]; 62.6–80 % in different regions of Russia; 70–100 % among women with mental disorders [23].

PMS is registered in 20 % of women under the age of 30; in 47 % of women at the age 30–39; in 55 % of women 40+ [26].

Upon that, PMS is clinically significant in 30–40 % of female patients of reproductive age, and in 4–5 % of them it leads to temporary disability [25].

The complex of symptoms in PMS includes more than 200 different psycho-emotional, somatic and autonomous, as well as metabolic and endocrine disorders with underlying hypothalamus dysfunction (Table 1) [1, 23].

Based on the most common symptoms, several types of PMS can be defined (Table 2), with only one of them (edematous) that does not include psychopathological signs [1, 25].

Specific dynamic characteristics of PMS allow identifying several types of alternating premenstrual disorders. Symptom(s) in *premenstrual tension* do not significantly affect the functioning of female patients; *PMS* during two menstrual cycles is characterized by at least 3 days of worsened state of health (mental and/or physical symptoms) that reduces functioning; *PMDD* is described by growing psychoemotional anxiety and depressive symptoms that affect functioning and have recurring course during several menstrual cycles; and *premenstrual enhancement* is an exacerbation of existing somatic diseases and mental disorders [2]. In the latter case, we are talking about a high comorbidity of PMS with unipolar depressive disorders and BPAD (60 %), dysthymia (53 %), anxiety disorders (80 %), and personality disorders [27–29].

Pregnancy is an important factor in the natural psychological development of a woman (status of maturity, establishing social identity, fulfilling the gender role, strengthening a marriage) [28].

General practitioners should keep in mind that some of the chronobiological characteristics of pregnancy are

Table 1. *Psychopathological symptoms of premenstrual disphoryc disorders*

«Negative»	«Positive»
Anxiety, fear or anxiety	Excess energy
Sadness	Widening of interests
Tearfulness	Increased capacity for work
Difficulty concentrating	Frequent changes in activities
Physical weakness	Increased social activity
Disorders of appetite and thirst	Self-confidence
Decreased libido	Increased libido
Headaches	Higher than in other days satisfaction with own appearance
Breast pain and tension	

Table 2. *Clinical variants of premenstrual disphoryc disorders*

Name	Leading symptoms
Emotional-affective	Subdepressive mood Dysphoria Tearfulness
Cephalgic	Migrainous or tension headaches
Crisis	Sympathoadrenal crises like panic attacks
Oedematous	Swelling and soreness of the mammary glands Facial swelling Bloating
Combined	

associated with a risk of not only somatic and/or intrapartum, but also mental complications. According to several studies, mother's age under 20 or 30–34+, three or more pregnancies, childbirth in winter or in demi-season (winter-spring) period in the northern hemisphere are comorbid with the "maternal prenatal stress", and with pathocharacterological or psychopathological (anxiety, panic, depressive, dysmorphic, psychotic) disorders in mothers [29–33]. At the same time, most female patients with severe prenatal stress (3.5–5 % of 6 %) have to take selective serotonin reuptake inhibitors (SSRIs) [34].

Development of prenatal stress during pregnancy is facilitated by hyperactivation of hypothalamic-pituitary-adrenal system [35], high levels of cortisol and penetration of 10–20 % of its amount through the placental barrier [35, 36], increased level of catecholamines (adrenaline, norepinephrine) in sympathoadrenal system [11], vasospasm of placenta, decreased uteroplacental blood flow and development of hypoxia in fetus [37], impaired neuronal proliferation and migration in fetus [34].

The prevalence of severe (high) prenatal stress reaches 6 % among all pregnant women [38]; 11.8 % in women at the 18th week of pregnancy, and 13.5 % in those at the 32nd week [39].

The established negative consequences of prenatal stress include increased risk of miscarriage, premature birth, obstetric problems, low birth weight of the child, impaired maternal interaction with child, development of somatic diseases (asthma, hyperlipidemia, diabetes mellitus, obesity, hypertension) in adolescence and adulthood [32, 40–43]. Several girls born in the setting of prenatal maternal stress have impaired ovulatory cycle, ability to conceive and carry a pregnancy, labor, lactation, development of postpartum depression; several boys have feminization and impaired spermatogenesis [43].

One of the complications of prenatal stress in 40 % of women is the persistent mental disorders after childbirth [10, 11], as well as the development of mental diseases in a child (delayed speech development, attention deficit hyperactivity disorder, behavioral, affective, cognitive disorders, autism, and schizophrenia) [42–43].

Psychosomatic disorders in postpartum period have been studies for quite along period[1]. Despite this, there is still no single idea about the duration of postpartum period: it is estimated as 3 weeks, or 4 weeks, or 12 months [20–22].

The most common mental disorders in postpartum period are anxiety (15–80 %) [11, 22], affective (10–33 %

[1] Hippocrates (400 BC) described a case of "puerperal delirium" with severe insomnia and restlessness that developed in a woman during a week after the delivery of twins. T. Ruggier (11th century) reported of "involuntary crying" in women after childbirth; he associated it with "the excessive moisture of the uterus". F. Plater (16th century) described delirium and anger in postpartum period. In the 18th century, F. Osiander, obstetrician, observed postpartum mania with rapid onset and increasing symptoms in the form of intense excitement, agitation, disorganized speech, as well as abnormal thoughts about motherhood ("the baby is still in the womb", "the baby is Jesus Christ", "the baby can fly"). L. Berger explained such symptoms as headache or stupor in postpartum period by "the irritating effect of breast milk on the brain." J. Esquirol, on the contrary, argued that the development of mental disorders is due to the suppression or impossibility of lactation [97–99].

of depressive, up to 20 % of hypomanic), and dysmorphic disorders [13–17, 44]. At the same time, symptoms of depression develop in 40 % of female patients during pregnancy [10, 11]. Postpartum depression increases the risk of depression in future, therefore, it is regarded as a marker of general susceptibility to affective disorders [18].

Management of psychosomatic disorders during menstrual cycle, pregnancy and lactation at general medical level

Analysis of literature sources revealed that the issue of pharmacological management of PMS and premenstrual enhancement remains debatable. To eliminate the physiological decrease in serotonin level in the luteal phase of cycle that is associated with decreased concentration of sex steroids, hormone replacement therapy (combined oral contraceptives, long-acting gonadotropin-releasing hormone agonists) are considered in combination with "general tonic" agents, vitamins, dietary supplements, physiotherapy [45, 46]. As an alternative option, decreased level of serotonin may be effectively compensated by short-term administration of its agonists, antidepressants of SSRI group [45].

Data on the psychopharmacotherapy of mental disorders in pregnant women are based not on the results of evidence-based clinical trials (that are difficult to conduct due to ethical issues and legal restrictions), but on the accumulated information on cases of self- or medical prescription of drugs due to the severe mental state of a woman.

The main principle for deciding whether to use drug treatment is the evaluation of benefit/risk ratio for mother and fetus in case of increased severity or recurrence of a mental disorder in the absence of proper pharmacotherapy. Psychotropic agents are used only in cases when the risk of persisting and developing mental disorder is clearly and significantly higher than the risk of adverse events (AEs). In particular, the choice of any medication should be based on the fact that all agents, in various amounts, penetrate the placental barrier. Effect of a drug product on fetus depends primarily on gestational age. In particular, in early pregnancy (up to 12 weeks), there is a possibility of developing severe structural anomalies, i.e. embryopathies [46].

We present data on the results of the administration of different groups of psychotropic agents by pregnant women.

8.7 % of women in the United States of America receive **antidepressants** during pregnancy [47]. In the world, the use of treatment with antidepressants during pregnancy increased 3-fold in the period from 1995 to 2005 [47]. At the same time, 57 % of women who stopped taking antidepressants due to pregnancy have to restart treatment for worsening mental state [47].

Pregnant women most often take thymoleptics of SSRI group. Experiments on mice/rats revealed that SSRIs reduce fetal body weight, slow down the development of motor reflexes, physical growth, impair learning ability, increase head circumference, cause anxiety, depression and mortality rate [10, 48].

Comparison of the range of neonatal AEs conducted by M.P. Marachev (2018) in children who were exposed to antidepressants during their mothers' pregnancy is presented in Table 3 [49].

Literature data demonstrated that the assertions about the teratogenic potential of **antipsychotic agents** have no evidence [49, 50]. However, the incidence of other neonatal AEs during administration of antipsychotics during pregnancy ranges from 15.6 to 34 % (Table 4).

It should be noted that in these studies, no evaluation of the presence of other potential factors for the development of these AEs was performed (hereditary background, ethnicity, smoking, substance abuse, obesity, diabetes mellitus, socioeconomic status, additional drug treatment) that were associated with them in the studies on other patient populations.

Normotimics have a negative impact on the development of fetus and children of mothers who used these agents in 2–8.6 % of cases (Table 5) [49].

Table 3. *Neonatal Adverse Events of Antidepressants*

Drugs	Adverse Event
TCA: Clomipramine	Increased risk of cardiovascular defects
SSRI: Paroxetine	Cardiovascular malformations Persistent pulmonary hypertension, respiratory distress Tremor Hypoglycemia (19 %)
SNRI: Venlafaxine	Relatively safe
Duloxtine	Insufficient data
OTHER: Mirtazapine Trazodone	Insufficient data

Note: TCA — tricyclic antidepressants, SSRIs — selective serotonin and noradrenaline reuptake inhibitors, SSRIs — selective serotonin and noradrenaline reuptake inhibitors

To assess the effect of medications on a child in postpartum period (period of breastfeeding), the parameter of "relative infant dose" (RDI) is used, i.e. dose received by the child with breast milk in relation to the maternal dose and expressed as a percentage. For example, SSRI antidepressants (citalopram, escitalopram, fluoxetine) pass well through the placental barrier and into breast milk [49–51].

The dose is considered "relatively safe" for the child with RDI <10 % (Table 6) [49–51].

Psychotherapy of psychosomatic disorders of the reproductive cycle in female patients is aimed at building constructive psychological defense (in particular, self-control and responsibility) and adaptive coping strategies (reattribution with a decrease in the threatening meaning of somatized symptoms, development of conviction in the absence of a life-threatening physical disease, adequate assessment of a real-life situation, and refusal to manipulate) [51].

Table 4. *Neonatal Adverse Events of Antipsychotics*

Adverse Events (frequency)	Group /Drugs	
	Traditional	**Atypical**
	Haloperidol Flufenazine	Aripiprazole Quetiapine Clozapine Olanzapine Risperidone
Obstetrical (34 %)	Preterm birth	
Neonatal (15,6-21,6 %)	Prematurity Neurodevelopmental delay Central neurology system abnormalities Respiratory Cardiology (heart defects) Gastrointestinal pathology Low body weight Diabetes mellitus	

Table 5. *Neonatal Adverse Events of Mood Stabilizers*

Drugs	Neonatal Adverse Events, frequency (%)
Lithium	4,1-8 % Cardiovascular abnormalities, Epstein's abnormality, arrhythmia, hypoglycemia, non-sugar diabetes, thyroid dysfunction, goiter, dullness, lethargy, liver abnormalities, and respiratory disorders
Valproates	4,5-8,6 % Congenital defects (interventricular septal defect, roto-facial defects, hypospodias, abnormal upper limb bone structure, hypoplasia of finger phalanges, neural tube defects) The neuro-psychic development disorders Behavioral
Carbamazepine	4-5 % Congenital malformations (spina bifida, single ventricle and atrioventricular septal defect, atrial septal defect, cleft palate, hypospadias, poplidactyly, craniosynostosis)
Lamotrigine	2-5,6 % Isolated cleft palate or cheiloschisis

Table 6. *Relative Infant Dose (RID) of Psychotropic Drugs*

Drugs	RID <10 % «relatively safe», %	RID>10 %
Antidepressants SSRI	Sertraline Paroxetine Fluvoxamine	Citalopram Excitalopram Fluoxetine
Antidepressants TCA	Amitriptyline (1,5 %) Clomipramine (2,8 %) Imipramine (0,15 %)	
Mood Stabilizer	Valproates Carbamazepine	Lamotrigine (9,2–18,3 %) Lithium (12–30,1 %)

Note: RID — relative infant dose, TCA — tricyclic antidepressants, SSRIs — selective serotonin and noradrenaline reuptake inhibitors, SSRIs — selective serotonin and noradrenaline reuptake inhibitors

Conclusion

Thus, psychosomatic disorders associated with abnormal menstrual cycle, pregnancy and lactation period, have a significant negative impact on the social functioning of a woman and the mental and somatic health of a fetus and child. Diagnosis, management and prevention of these disorders is a complex multidisciplinary challenge that requires the involvement of both general practitioners and specialists (i.e., gynecologist, psychiatrist, neurologist).

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