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PRACA POGLĄDOWA
REVIEW

Exploring the connection between several neurosteroid hormones and first-episode psychosis and schizophrenia: A literature review

Wybrane hormony neurosteroidowe a pierwszy epizod psychozy i schizofrenii – przegląd literatury

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ABSTRACT

First-episode psychosis (FEP) and first-episode schizophrenia (FES) are serious psychiatric conditions. Neurosteroids, known to modulate central nervous system function, may play a role in the pathophysiology of these disorders. This review aims to evaluate current evidence on the relationship between these disorders and levels of several neurosteroid hormones. A literature review was conducted using PubMed and Google Scholar, focusing on original articles, reviews, and meta-analyses published between 2016 and 2025. Keywords relevant to neurosteroids and FEP and FES were employed. Findings regarding neurosteroid levels in FEP and FES are inconsistent. Several studies indicate reduced testosterone levels in affected individuals compared to healthy controls. Similar reductions in estrogen and progesterone have been observed, often correlating with increased symptom severity. In contrast, dehydroepiandrosterone and its sulfate show an opposite pattern, though research remains limited. These discrepancies highlight the need for further investigation into the role of individual neurosteroids in early psychotic disorders. Current evidence does not allow for definitive conclusions; however, emerging findings suggest that neurosteroid levels may be significantly altered in FEP or FES patients compared to healthy controls. Moreover, they may contribute to the clinical presentation of these disorders. Neurosteroids have potential as biomarkers for early psychosis, and advancing knowledge in this domain may offer novel diagnostic or therapeutic insight.

KEYWORDS

first episode psychosis, testosterone, DHEA, progesterone, estrogen

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STRESZCZENIE

Pierwszy epizod psychozy (*first-episode psychosis* – FEP) oraz pierwszy epizod schizofrenii (*first-episode schizophrenia* – FES) to poważne zaburzenia psychiatryczne. Hormony neurosteroidowe, które modulują funkcjonowanie ośrodkowego układu nerwowego, mogą odgrywać rolę w ich patofizjologii. Celem przeglądu jest ocena aktualnych danych dotyczących zależności między poziomami wybranych neurosteroidów a wskazanymi zaburzeniami. Przeprowadzono przegląd literatury z wykorzystaniem baz danych PubMed i Google Scholar, uwzględniając artykuły oryginalne, przeglądowe oraz metaanalizy opublikowane w latach 2016–2025. Zastosowano słowa kluczowe związane z hormonami neurosteroidowymi oraz FEP i FES. Wyniki badań nad poziomami hormonów neurosteroidowych w FEP i FES są niejednoznaczne. W kilku badaniach odnotowano obniżony poziom testosteronu u pacjentów w porównaniu z osobami zdrowymi. Podobne tendencje dotyczyły estrogenu i progesteronu, przy czym niższe poziomy korelowały z większym nasileniem objawów. Odmienny wzorzec zaobserwowano w przypadku dehydroepiandrosteronu i jego siarczanu, choć dane są ograniczone. Konieczne są dalsze badania nad rolą poszczególnych hormonów. Dotychczasowe dowody nie pozwalają na jednoznaczne wnioski, jednak sugerują, że u pacjentów z FEP lub FES poziom hormonów neurosteroidowych może znacząco różnić się w porównaniu ze zdrowymi osobami. Co więcej, zmiany poziomów hormonów neurosteroidowych mogą wpływać na obraz kliniczny tych zaburzeń. Hormony neurosteroidowe mają potencjał jako biomarkery wczesnej psychozy, a pogłębienie wiedzy w tym zakresie może przynieść istotne korzyści diagnostyczne i terapeutyczne.

SŁOWA KLUCZOWE

pierwszy epizod psychozy, testosteron, DHEA, progesteron, estrogen

Introduction

The first time a person experiences psychotic symptoms is known as the first episode of psychosis (FEP). In some cases, FEP is a standalone episode in a patient's life, while in others it can be a sign of a developing illness. Diagnoses may include schizophrenia-spectrum disorders, mood disorders, and other psychotic disorders such as delusional disorder [1]. According to the Diagnostic and Statistical Manual of Mental Disorders (DSM-V), the key features that characterize psychotic disorders are abnormalities across one or more of the following five domains: delusions, hallucinations, disorganized thinking (speech), grossly disorganized or abnormal motor behavior (including catatonia), and negative symptoms [2]. Depressive symptoms are common in schizophrenia-spectrum and other psychotic disorders, often accompanied by suicidal ideation or attempts. Suicide is one of the leading causes of death in this population, with 40%–50% experiencing suicidal thoughts, 20%–50% attempting suicide, and 4%–13% dying by suicide. FEP represents a particularly high-risk period, with suicidal ideation reported in 26.2%–56.5% of cases. Additionally, the risk of suicide death is 60% higher than at later stages of the illness [3]. Broad cognitive deficits are observed during FEP, with the largest in immediate verbal memory, executive function, processing speed, and social cognition [4]. Typically, FEP occurs in the third decade of life [5]. It appears that 12%–35% of individuals later diagnosed with schizophrenia experienced their first symptoms before the age of 20 [6].

Schizophrenia is a chronic psychiatric disorder. The lifetime prevalence is estimated to be approximately 0.3%–0.7% [2]. Since the diagnosis of schizophrenia frequently follows an initial diagnosis of FEP, the five aforementioned symptoms constitute part of the diagnostic criteria. For a formal diagnosis of schizophrenia, there must be continuous signs of the disorder present for a minimum of six months. Schizophrenia is classified into several types based on the predominant symptoms. These are paranoid schizophrenia, hebephrenic schizophrenia, catatonic schizophrenia, simple schizophrenia, residual schizophrenia, and undifferentiated schizophrenia [5]. Additional symptoms may encompass mood disturbances, anxiety disorders, and self-related abnormalities. Affected individuals may exhibit phenomena such as derealization and depersonalization, as well as engage in behavior that is incongruent with contextual norms [2].

Schizophrenia is widely recognized as a multifactorial disorder, with a range of contributing factors influencing its onset. Genetic susceptibility, early-life brain injuries, and childhood infections play significant roles in the development of first-episode schizophrenia (FES). Additionally, psychosocial stressors are considered critical in the pathogenesis of the disorder. Longstanding evidence indicates that the onset of FES may be precipitated by the use of psychoactive substances [7]. Furthermore, it has been recognized over time that sex differences, gonadal steroid hormone fluctuations in particular, contribute to the emergence of FES and FEP. A hypothesis has been stated that sex hormones take part in the pathophysiology of schizophrenia [8]. Sex hormones – particularly estrogen, testosterone, progesterone, and dehydroepiandrosterone (DHEA), which will be discussed in this paper – interact with the central nervous system (CNS). Due to this function, they can be referred to as neuroactive steroids (NASs) [9].

NASs are synthesized both centrally (e.g., in the cortex, striatum, hippocampus, or hypothalamus) and peripherally (e.g., in the adrenal glands, gonads, or placenta). Their lipophilicity enables blood–brain barrier penetration, allowing modulation of neuronal activity via diverse cellular targets. They act through rapid and slow mechanisms involving ligand-gated ion channels, G protein-coupled receptors (GPCRs), and nuclear receptors. Key non-genomic targets include γ-aminobutyric acid (GABA) and N-methyl-D-aspartate (NMDA) receptors [10]. NASs modulate GABA receptors as either positive allosteric modulators (e.g., allopregnanolone) to enhance GABA activity or as negative modulators (e.g., DHEA-S) to inhibit receptor function. In the CNS, NASs are synthesized by neurons and glial cells, acting as local signaling molecules to modulate intercellular and synaptic communication. Neuronal NASs are produced at both presynaptic and postsynaptic sites; presynaptic synthesis contributes to activity-dependent release, influencing neurotransmission, while postsynaptic NASs modulate nearby receptors or presynaptic terminals. These actions position NASs as key modulators of neurotransmitter systems, including GABA, glutamate, and dopamine [10]. The detailed effects of individual NASs will be discussed in the following paragraphs. A summary of NASs' effects on the CNS is provided in Table I.

Table I. Impact of selected hormones on the central nervous system

Hormone	Influence on the CNS
Testosterone	Regulation of neuroplasticity in the hippocampus; promotion of neurogenesis and neuroregeneration; enhancement of neurotrophin expression; protection against apoptosis; mitigation of beta-amyloid toxicity
DHEA-S	Promotion of neurite growth, neurogenesis, and neuronal survival; modulation of the effects of cortisol on the brain against the potentially damaging effects of excessive cortisol activity; modulation of the action of the GABA-A, NMDA, and sigma-1 receptors
Estrogen	Modulation of the activity of important neurotransmitters: serotonin, dopamine, glutamate, and GABA; regulation of cognition, memory, neurodevelopment, and neuroplasticity; support in the growth of grey matter in the amygdala, the thalamus, and the hippocampal and parahippocampal areas
Progesterone	Influence on myelination; reduction of brain edema and inflammation; support in neuronal survival; modulation of the activity of astrocytes

CNS – central nervous system; DHEA-S – dehydroepiandrosterone sulfate; GABA-A – γ-aminobutyric acid type A receptor; GABA – γ-aminobutyric acid; NMDA – *N*-methyl-d-aspartate receptor.

Given this body of information, multiple questions arise. Are sex hormone levels in patients with FEP and FES different from those in the general population? How do hormonal changes affect the onset and development of schizophrenia? Are there any sex-specific differences in these fluctuations? This paper aims to address these questions and provide insight into the potential role of NASs in the onset of FEP and the manifestation of schizophrenia.

The relationship between steroid sex hormones and psychosis is extremely complex and is still being investigated [9]. Gaining a deeper understanding of it may be crucial to unraveling the pathophysiology of schizophrenia and paving the way for new therapeutic methods.

Methodology

A review of the available literature was performed by searching PubMed and Google Scholar. The search string that was used to search the database was ("first episode psychosis" OR "first episode schizophrenia") AND ("testosterone" OR "testosterone level" OR "DHEA" OR "DHEA level" OR "DHEA-S" OR "DHEA-S level" OR "estrogen" OR "estrogen level" OR "progesterone" OR "progesterone level"). All relevant articles published between 2016 and 2025 were considered. In addition, the references cited within the identified studies were manually examined, leading to the inclusion of 3 additional articles published prior to the defined timeframe. Only articles written in English were considered. Duplicate records were removed. An initial screening was performed based on titles and abstracts and the studies that did not meet the inclusion criteria were excluded. The remaining articles were subjected to a comprehensive analysis of the study characteristics, sample sizes, methodologies, and key findings.

The database search, conducted using predefined search terms alongside the established inclusion and exclusion criteria, yielded 418 articles after duplicates were removed. Based on a review of titles and abstracts, 98 articles were shortlisted for further evaluation. A comprehensive full-text analysis of these articles was then carried out. Following the application of the selection criteria, 22 studies were ultimately included in the review. The necessary data was then extracted from the texts and compiled into a narrative synthesis.

Inclusion and exclusion criteria

This literature review concentrated on observational studies and randomized controlled trials that investigated the relationship between levels of various NASs and FEP or FES. A total of 16 clinical studies that met these specific criteria were identified and included. Additionally, 3 clinical studies that did not focus solely on first-episode cases but provided particularly relevant data were also incorporated. To enhance the contextual understanding and to support the interpretation of findings, 2 review articles and 1 meta-analysis were included. These sources offered comprehensive syntheses of existing evidence and helped to frame the individual studies within the broader scientific landscape. Case reports, animal studies, technical notes, dissertations, textbooks, studies involving children and studies that did not address the relationship between NASs levels and mental health disorders were excluded from the review. The quality of the selected studies was evaluated based on the appropriateness of the study design in relation to the research objectives, the risk of bias, the robustness of the findings, the rigor of statistical analysis, and the overall quality of reporting.

Testosterone

Role of testosterone in males and females

Testosterone, a key androgen, regulates male development, maturation, and aging [11]. In healthy adult males, Leydig cells synthesize 5–10 mg of testosterone per day, with minor contributions from the adrenal cortex and peripheral metabolism [12]. Testosterone drives secondary sexual characteristics, spermatogenesis, libido, and anabolic effects during puberty and adulthood [11]. Circulating testosterone is mostly protein-bound: ~66% to sex hormone-binding globulin (SHBG), ~30% to albumin, and only 2%–4% remains free, constituting the biologically active form.

In females, testosterone serves distinct physiological roles, acting as both an androgen and a precursor for estradiol synthesis [13]. During reproductive years, it is primarily produced by the ovaries and via peripheral conversion of adrenal and ovarian androgens: androstenedione and DHEA. Aromatization to estradiol occurs in ovarian and extragonadal tissues, the latter becoming predominant post-menopause. Testosterone influences both reproductive and non-reproductive functions and is positively associated with female sexual function. Therapeutically, testosterone has shown efficacy in treating female sexual dysfunction [13].

Testosterone in the CNS

In the CNS, testosterone acts mainly via androgen receptors (ARs), which are widely expressed, particularly in the cerebral cortex. Their distribution suggests broad neural functions mediated through intracellular ARs [14]. Beyond nuclear sites, ARs are also found in axons and dendrites, where they engage kinase signaling pathways. Classic AR signaling involves cytoplasmic AR dissociation from heat shock proteins, nuclear translocation with chaperones, and binding to androgen response elements in order to regulate gene transcription. In contrast, non-genomic actions are mediated by membrane-associated ARs, activating rapid pathways such as Akt and ERK/MAPK [15]. Testosterone promotes remyelination via neural ARs. In mouse models of demyelination (cuprizone and LPC), myelin repair was absent in Tfm mice lacking functional ARs and impaired in ARNesCre mice with neural-specific AR deletion, confirming the essential role of neural ARs [16]. Testosterone confers neuroprotection by upregulating neuroglobin in astrocytes and microglia under stress (e.g., injury, glucose deprivation, or kainic acid). It promotes neuronal differentiation, plasticity, synaptic density, hypothalamic connectivity, and neurite outgrowth. Testosterone also reduces astrocyte reactivity post-injury and protects against age-related neurodegeneration, partly by stabilizing mitochondrial membranes and reducing reactive oxygen species [17].

Correlations between testosterone and several neurotransmitters

Beyond its interaction with ARs, testosterone also modulates neurotransmitter and hormone levels. Notably, it has been shown to enhance serotonergic activity by upregulating the mRNA expression of the serotonin (5-HT) transporter [18]. This effect supports the therapeutic potential of testosterone in depressive disorders, although additional mechanisms, such as the promotion of neurogenesis, may also contribute [19].

Testosterone levels appear to be particularly significant in relation to dopaminergic function. Preclinical and clinical studies have linked NASs metabolized via 5α-reductase (5αR) – including testosterone – to dopaminergic dysfunction in neurological disorders [10]. 5αR inhibitors such as finasteride suppress dopaminergic activity by negatively modulating dopamine D1 and D3 receptors, without affecting D2 receptors, and have been proposed as potential therapies for neuropsychiatric disorders with dopaminergic hyperactivity [20]. As 5αR inhibitors do not directly bind to dopamine receptors, their effects likely stem from NAS-induced alterations in downstream D1 and D3 signaling [10].

An additional important consideration is the relationship between testosterone and estradiol levels. Both hormones can cross the blood–brain barrier, and neural estradiol is locally synthesized from testosterone [21], making this interaction complex and challenging to fully delineate. Further discussion on this topic is presented in the section addressing estrogen.

A key consideration is the reciprocal interaction between testosterone and the hypothalamic–pituitary–adrenal (HPA) axis, which regulates peptide and steroid hormones from the hypothalamus, pituitary, and adrenal glands [22]. Testosterone suppresses corticotropin-releasing hormone (CRH)-induced HPA activation, while HPA activation inhibits testosterone secretion. Although testosterone generally appears to reduce cortisol levels [22], findings are inconsistent, with some studies linking it to elevated cortisol and enhanced stress responses. Individuals with high trait dominance and elevated testosterone may be more susceptible to stress-related conditions such as mood disorders and substance abuse [23].

As demonstrated, the effects of testosterone on the CNS are multifaceted and remain incompletely understood.

Are testosterone levels different in FEP/FES patients?

Research investigating testosterone levels in individuals with FEP and FES remains limited. Among the available studies, findings have been inconsistent. Knytl et al. [9] examined testosterone levels in 16 FEP patients, 22 biological siblings of these patients, and 29 healthy controls. The siblings showed significantly higher testosterone levels than the controls, correlating with increased psychosis risk. No significant difference was found between the FEP patients and the controls, possibly due to early antipsychotic treatment, though conclusions cannot be drawn about the effects of medication because of its short duration. A study conducted in 2020 yielded similar findings, enrolling 51 drug-naive individuals with FEP who met the diagnostic criteria for schizophrenia [24]. Despite the absence of prior antipsychotic treatment, no significant difference in testosterone levels was observed between the patients and the healthy controls. Two additional studies reported findings consistent with those described above. The first study, conducted as an extension of one by the European Network of National Schizophrenia Networks Studying Gene-Environment Interactions (EU-GEI) at its facility in Bologna, Italy, examined a sample of 32 individuals with FEP who had already undergone antipsychotic treatment [25]. The second study included the same number of drug-naive FEP patients, comparing them to individuals experiencing an acute exacerbation of schizophrenia due to treatment nonadherence (DFP group), as well as to healthy controls [26]. Both studies found no significant differences in testosterone levels between the patients and the controls. Furthermore, the second study did not identify any significant differences in testosterone levels between FEP patients and those with previously diagnosed schizophrenia.

In contrast to the aforementioned findings, several studies have reported significant differences in testosterone levels. A 2016 study conducted at the First Affiliated Hospital of Zhengzhou University examined testosterone levels in 39 male and 42 female drug-naive individuals with FES [27]. Testosterone levels were lower in the male FES patients and "dramatically" higher in the female patients compared to the controls. In males, testosterone negatively correlated with negative symptoms; in females, it positively correlated with positive symptoms. It has been proposed that endogenous testosterone may protect cognitive function, with reduced levels being linked to cognitive impairment in drug-naive male FES patients. Thus, testosterone may serve as a biomarker for symptom severity. The neuroprotective role of testosterone was also highlighted and partially supported in a 2019 study by Petrikis et al. [28]. In that study, testosterone levels were compared between 87 drug-naive individuals of both sexes with FEP and healthy controls. The male patients showed significantly lower testosterone and SHBG levels than the controls, with no difference observed among the females. Additionally, a multivariate logistic regression indicated that each unit increase in total testosterone reduced psychosis risk by ~34%, and each unit of free testosterone by ~14%. These findings are particularly significant, as they suggest that testosterone may play a role in the pathophysiology and potential etiology of psychosis in men, rather than being solely a consequence of the disorder. One potential explanation for this phenomenon lies in the neuroprotective role of testosterone. It binds to ARs primarily in the hypothalamus and amygdala, with less binding in the hippocampus and frontal cortex. Its neuroprotective effects include regulating neuroplasticity in the hippocampus, promoting neurogenesis and neuroregeneration, enhancing neurotrophin expression, protecting against apoptosis, and mitigating beta-amyloid toxicity [28]. Two studies published in 2024, one by Hu et al. [29] and another by Hill et al. [30], confirmed a significant correlation between testosterone levels and FEP or FES in patients. The first study also revealed an intriguing finding: the female patients exhibited a higher rate of abnormal testosterone levels than the male patients. This result contrasts with the findings of the 2019 study discussed above. The authors concluded that abnormal testosterone levels have a more substantial impact on the course of FEP in females than in males.

The relationship between testosterone levels and the onset of FEP or FES appears to be highly complex. As outlined above, findings have been inconsistent across studies. A critical factor contributing to these discrepancies may be the treatment status of the participants, as some studies included drug-naive patients, while others did not. This distinction could significantly influence the interpretation of results. Despite these variations, the existing evidence suggests that further investigation is warranted, as testosterone levels may represent a potential biomarker for the prediction and progression of FEP/FES.

DHEA/DHEA-S

DHEA and its sulfated metabolite, DHEA-S, are endogenous hormones produced by the adrenal glands [31]. Their biological roles are still not fully understood, but without a doubt DHEA is a pivotal precursor for several other steroids, including testosterone, dihydrotestosterone (DHT), and androstenedione in men and estradiol, estriol, and estrone in women [32]. DHEA, like other androgens, mineralocorticoids, and glucocorticoids, is derived from pregnenolone, which in turn is synthesized from cholesterol. DHEA-S is the most abundant circulating steroid hormone in humans [31]. It is formed from DHEA through the action of SULT2A1. Although a small portion of circulating DHEA originates from the gonads, skin, and brain, the majority of DHEA and virtually all DHEA-S is produced by the adrenal cortex [33].

DHEA and DHEA-S are classified as neurosteroids because they can be synthesized de novo in the CNS, meaning that the brain does not rely solely on serum levels of DHEA-S. These hormones serve as precursors to approximately 50% of androgens in adult men, 75% of active estrogens in premenopausal women, and nearly 100% of active estrogens in women after menopause [34]. In addition to their role as precursors, DHEA and DHEA-S also independently exhibit androgenic and estrogenic activity, with androgenic activity being more pronounced.

Both DHEA and DHEA-S are secreted synchronously with cortisol, following a similar diurnal and episodic rhythm. While both hormones are widely distributed throughout the body, their highest concentrations are found in the brain. Plasma levels of DHEA and DHEA-S vary depending on age and gender, with levels being higher in men than in women across all age groups. Peak concentrations of these hormones occur in the third decade of life, after which they decline to 10%–20% of their peak values. It is suggested that, due to its potential influence on cognition, some age-related neurological disorders might be associated with a decline in systemic DHEA-S concentrations, but this subject requires further research [31].

The major biological actions of DHEA-S, excluding their estrogenic and androgenic activity, are neuroprotection, promotion of neurite growth, neurogenesis, neuronal survival, apoptosis, and catecholamine synthesis and secretion; they also exhibit antioxidant, anti-inflammatory, and anti--glucocorticoid effects [34]. DHEA has been shown to exert both agonistic and antagonistic effects on the AR and acts as an agonist at both estrogen receptor-α and estrogen receptor-β. In the brain, DHEA-S modulates the actions of the GABA-A receptor, the NMDA receptor, and the sigma-1 receptor, among others [31]. DHEA-S has also been shown to respond to stress and modulate the effects of cortisol on the brain. The co-release of DHEA in the acute stress response is thought to protect against the potentially damaging effects of excessive cortisol activity [35]. Consequently, alterations in DHEA-S levels, such as the decrease associated with aging, can influence cognition and mood [31].

What are the levels of DHEA/DHEA-S in FEP/FES?

Clinical studies of blood DHEA-S levels in patients with FEP have produced mixed findings.

Beyazyüz et al. [26] compared neurosteroid levels in untreated FES patients, untreated chronic schizophrenia patients in acute exacerbation, and healthy controls. Due to the rapid metabolism of DHEA to DHEA-S, only DHEA-S levels were measured. FES patients showed significantly higher DHEA-S than both chronic patients and controls, indicating a strong neurosteroid response that declines with disease progression. An elevated DHEA-S level may be considered a biomarker for schizophrenia, reflecting neuroprotective and stress-response roles.

Belvederi Murri et al. [25] studied 32 FEP patients (17 men and 15 women), mostly on antipsychotic medication, and 153 controls from normative hormone studies. No significant differences in DHEA levels were found between groups, with levels unaffected by antipsychotic dose, treatment duration, or recent cannabis use. In the women, DHEA correlated positively with negative symptoms and disorganization.

Garner et al. [35] examined cortisol, DHEA-S, and the ratio of the two in 39 FEP patients (14 neuroleptic--naïve and the remainder with ≤10 days of antipsychotic use) and 25 matched controls (ages 15–25) in Melbourne. Blood samples, clinical assessments, and stress ratings were collected at baseline and after 12 weeks to assess hormone differences, perceived stress, and clinical response during early treatment. In the healthy males, perceived stress correlated positively with DHEA-S and cortisol/DHEA-S ratio, whereas no such correlations were found in the male FEP patients. No significant differences in DHEA-S level or cortisol/DHEA-S ratio were observed between the FEP patients and the controls at baseline or 12-week follow-up, regardless of antipsychotic exposure. At baseline, DHEA-S was inversely correlated with negative and depressive symptoms, while the cortisol/DHEA-S ratio showed positive correlations with negative symptoms of depression, anxiety, and psychosis. A reduction in the ratio over time was linked to improved symptoms. The similar DHEA-S levels between FEP patients and controls may reflect adrenal exhaustion from pre-onset chronic stress, increasing vulnerability to depressive and negative symptoms. Findings suggest impaired stress hormone responses in FEP, with behavioral therapies such as cognitive-behavioral therapy potentially improving hormonal regulation and symptom outcomes [35].

As outlined above, the available data on the relationship between DHEA/DHEA-S and FEP or FES remains limited and yields inconsistent findings.

Estrogen

Role of estrogen in the human body

Estradiol, estriol, and estrone are estrogens, steroid hormones that influence reproductive, neuroendocrine, cardiovascular, skeletal, and immune systems [36]. Estrogen drives reproductive organ development and sexual characteristics [37], but is also implicated in pathologies such as osteoporosis, endometriosis, cancer, infertility, and obesity [36]. In the CNS, estrogen – particularly 17β-estradiol – modulates neurotransmitters linked to schizophrenia (serotonin, dopamine, glutamate, and GABA) [38] and regulates cognition, memory, neurodevelopment, and neuroplasticity [37] via genomic and non-genomic pathways [39]. These effects are mostly controlled by two nuclear estrogen receptors (ERs), alpha (Erα) and beta (Erβ), and G protein-coupled estrogen receptor (GPER-1) [38]. During adolescence, rising estrogen levels drive structural brain changes, including reduced grey matter in the prefrontal, parietal, and temporal regions [28]. Concurrently, regions rich in estrogen receptors – the amygdala, thalamus, hippocampus, and parahippocampus – show increased activity [28]. These same areas exhibit anatomical abnormalities, such as reduced grey matter, in schizophrenia [40].

Estrogen's further role in the CNS

As noted, estrogen is synthesized from testosterone in the CNS via the enzyme aromatase, which plays key roles in neural function [21]. Its presynaptic location and co-expression with ERs at synapses support the role of locally synthesized estradiol in modulating synaptic transmission. Aromatase is also found with ERs at the plasma membrane, indicating a mechanism for rapid, non-genomic estradiol function. Its activity is regulated by synaptic signals and neurotransmitters such as glutamate and dopamine [21]. During development, brain aromatase converts fetal testicular testosterone into estradiol, contributing to brain masculinization. It also influences sex-specific seasonal brain plasticity in males, which is linked to testosterone fluctuations [41]. Despite its importance, the estrogen-testosterone interaction via aromatase remains complex and not fully understood.

Importantly, estrogen levels influence both the dopaminergic and serotonergic systems. Estrogens modulate dopaminergic neurotransmission by enhancing dopamine synthesis in regions such as the nucleus accumbens and the striatum, while also reducing dopamine degradation in the nucleus accumbens. In addition, estrogens regulate the serotonergic system by increasing the activity of tryptophan hydroxylase, thus promoting the synthesis of serotonin (5-HT), and by modulating 5-HT receptor expression – both of which have substantial implications for mood regulation and the pathophysiology of depression. Estrogen exerts antidepressant-like effects by prolonging serotonergic signaling and decreasing 5-HT reuptake into presynaptic neurons. Once internalized, 5-HT reduces monoamine oxidase activity, thereby decreasing its own metabolic breakdown [42].

As demonstrated, estrogen exerts significant effects on the CNS beyond its well-established role in reproductive function.

The estrogen hypothesis

For the longest time, scientists have been pondering: "Why do women with schizophrenia often experience a later onset and milder symptoms than men?" Evidence shows that gonadal hormones influence the age of onset and symptom profile in FEP patients [8]. This has prompted research into hormone-related life events – menstruation, pregnancy, childbirth, and menopause – in psychiatric populations. As early as 1909, Kraepelin observed increased psychotic symptoms during periods of estrogen decline [43]. Subsequent studies have linked estrogen and disruptions in its signaling to schizophrenia pathophysiology [44]. In the 1990s, estrogen was termed "nature's natural psycho-protectant," leading to the "estrogen hypothesis" [45], which posits that low estrogen levels – e.g., during menstruation or menopause – worsen psychotic symptoms [46].

In a thorough systematic review and meta-analysis, Reilly et al. [47] analyzed 19 full-text studies involving 1,193 women diagnosed with a psychotic disorder with regard to demonstrating the menstrual exacerbation of psychotic symptoms. It outlined the significantly higher rates of psychiatric hospital admissions during the perimenstrual rather than the non-perimenstrual phase. Additionally, the authors highlighted a study conducted by Bergemann et al. [48], which identified a clear dependence between psychotic symptoms and low estrogen levels, and a concomitant worsening of well-being, as assessed by positive scores on the Positive and Negative Syndrome Scale (PANSS).

Expanding on this, a Spanish study conducted by Barrau-Sastre et al. [49] on 42 women with FEP between the ages of 18 and 45 analyzed the estrogen levels based on their cycle length, age at menarche, and years of difference between the onset of FEP and menarche. The research did not find a relationship between age at menarche and onset of illness, yet it documented that women with shorter menstrual cycles demonstrated enhanced cognitive flexibility and inhibition capacity. This study did not rely on laboratory data, such as blood samples, but rather on questionnaires and clinical interviews, which are often prone to biases and personalized responses, thereby limiting its overall reliability and the generalizability of its findings.

A retrospective case-control study by Pons-Cabrera et al. [43] compared sex hormone levels in drug-naive women of reproductive age with FEP and healthy controls, with samples collected during the luteal phase. FEP patients showed elevated follicle-stimulating hormone – FSH (7 U/L) and luteinizing hormone – LH (8.4 U/L) compared to controls (3.5 U/L and 5.7 U/L, respectively). Despite the higher FSH, 17β-estradiol levels were lower in the FEP patients (75.3 pg/mL) than in the controls (151 pg/mL), supporting the estrogen hypothesis that reduced estrogen may contribute to psychotic symptoms.

Supporting the estrogen protection hypothesis, a narrative review by Culbert et al. [46] examined whether menopause and hormonal fluctuations increase the risk of psychosis. Schizophrenia is more common in men (1.4:1) [8], with male incidence peaking at 20–29 years; there are two peaks in women: at ages 20–39 and around menopause [8]. While psychosocial factors may contribute, the menopausal peak is largely attributed to declining estrogen. The review highlights studies linking low estrogen to increased psychotic symptoms and calls for further research into hormonal and psychosocial factors in midlife psychosis to inform treatment [46].

Sezer et al. [50] studied FSH, LH, prolactin, estradiol, and progesterone in 32 female schizophrenia patients, taking samples during follicular and periovulatory phases and assessing symptoms via PANSS. Mean estradiol levels were 25.16 pg/mL (follicular) and 59.83 pg/mL (periovulatory), below normal ranges (25–100 and 150–450 pg/mL, respectively). Although estrogen is typically lower in schizophrenia, these abnormal levels may also result from antipsychotic treatment. Contrary to the earlier research by Barrau-Sastre et al. [49], this study found a positive correlation between late age of menarche and severe schizophrenic symptoms.

Another study, conducted by Hursitoglu et al. [38], consisted of 36 schizophrenia patients and 30 controls aged 18–65, excluding those with menstrual irregularities, hormone therapy, pregnancy, or menopause. GPER-1 levels were measured and symptoms were assessed via PANSS. The men showed elevated GPER-1 compared to the controls, while there was no difference among the women. Nevertheless, this study highlights ERs' role in schizophrenia and suggests that elevated GPER-1 in male patients warrants exploring GPER-1 agonists for potential treatments to reduce symptom severity.

As shown, the role of estrogen in the pathophysiology of FEP and FES could be significant. There are numerous studies and clinical observations in the literature related to abnormal levels of estrogen in schizophrenic patients. Notwithstanding these reports, the precise mechanism of how the sex hormones influence the onset, progression, and course of schizophrenia remains unknown. Therefore, further studies with larger sample sizes and laboratory methodologies are needed to confirm these results.

Progesterone

Progesterone is a steroid hormone. It is produced by gonadal tissue, the adrenal cortex, and the placenta during pregnancy [51]. It is a precursor for glucocorticoids and other sex steroids, such as testosterone and estradiol. Beyond its primary role, progesterone also attaches to intracellular progesterone receptors in the cytoplasm of cells across the body. Once bound to these receptors, progesterone is transported into the nucleus, where it interacts with genetic material to control the activity of specific genes [51]. Progesterone also exerts an influence on the brain, impacting myelination and reducing brain edema, inflammation, and the activity of various substances, such as hemostatic proteins [52].

Progesterone, as well as other NASs like cortisol, is a key factor in the development and functioning of the CNS throughout life. In adulthood, these steroids have a considerable impact on the activity of various neurotransmitter systems involved in the pathophysiology of psychosis, including the dopaminergic, glutamatergic, and GABAergic systems [25]. Within the CNS, progesterone is synthesized from cholesterol. The initial step involves the enzymatic conversion of cholesterol to pregnenolone via the action of cytochrome P450 side-chain cleavage enzyme. Pregnenolone is then further metabolized into progesterone by 3β-hydroxysteroid dehydrogenase [53]. Like other NASs, progesterone exerts its effects in the CNS through two distinct mechanisms. The first involves the classic pathway via nuclear progesterone receptors (PRs), while the second operates through non-classic, membrane-associated receptors that mediate rapid, non-genomic actions. The enzymes involved in these pathways are expressed in both neuronal and glial cell populations [16]. Evidence suggests that membrane-bound PRs play a role in promoting neuroregeneration and may underlie progesterone's neuroprotective effects by supporting neuronal survival [54].

Are progesterone levels different in FEP/FES patients?

The role of progesterone in schizophrenia has been less studied than estrogen's role. There are studies on progesterone in the context of schizophrenia, but the results are not conclusive. Some studies propose that the hormone may have a neuroprotective effect, as seen in animal models of cognitive dysfunction and positive symptoms, while others indicate a negative correlation between the hormone and symptom modulation in patients [55]. Based on the available clinical studies, it has been suggested that there is a link between lower symptom scores and high progesterone levels (which occur during the luteal phase of the menstrual cycle in women). As Belvederi Murri et al. [25] proved, male patients experiencing FEP had lower progesterone levels than healthy controls. In addition, lower progesterone levels were associated with more severe positive symptoms, implying a possible involvement of this hormone in the pathophysiology of psychotic disorders. Animal studies also demonstrate an inhibitory effect of progesterone on hyperactive behavior. Recent reports indicated that baseline progesterone levels were significantly elevated in FES patients who had not yet received antipsychotic treatment, in comparison to healthy controls [39]. This has led to the hypothesis that lower progesterone levels in the early phase of the illness may be linked to more effective response to antipsychotic treatment. Other studies reported that males receiving long-term treatment had notably higher progesterone levels than the healthy male subjects, but subsequent research showed that the increase occurred only in men [56].

Endogenous progesterone levels fluctuate throughout a woman's life, influenced by factors such as contraceptive use and the premenopausal period. During perimenopause, progesterone declines, potentially increasing the risk of initial psychiatric disorders. However, no specific association with schizophrenia-spectrum disorders has been identified [57]. Hormonal fluctuations also occur with contraceptive use. Oral contraceptives vary in composition, dosage, and administration. Studies indicate that progestogen-only pills (POPs) are more frequently associated with psychiatric symptoms than combined oral contraceptives (COCs) [58]. It has also been found that different types of progestogens can affect mood in different ways, with newer formulations being linked to fewer adverse effects. Hormonal contraception suppresses endogenous hormone production, replacing it with synthetic analogs; COCs additionally reduce testosterone and increase SHBG. While scant research has been published on the mental health effects of these changes in women using oral contraceptives, we already know that hormonal fluctuations can cause mood swings in women who are not using contraception. It is also worth noting that fluctuations in estrogen and progesterone, particularly premenstrually, can exacerbate psychiatric symptoms in sensitive individuals. Puberty and menopause further elevate mental health risk [49,58].

In summary, after analyzing the available studies and publications, no definitive relationship between progesterone levels and the occurrence of FEP and FES can yet be established. More research on larger patient groups is needed to draw concrete conclusions. Such studies may potentially lead to disease prevention.

Conclusions

As discussed above, the data regarding the potential role of NASs in FEP and FES is relatively recent and presents compelling avenues for investigation. Findings appear to vary based on the specific type of hormone being examined. In the case of testosterone, multiple studies have reported reduced hormone levels in FEP/FES patients. Notably, an especially important logistic regression analysis conducted by Petrikis et al. [28] highlighted the potential involvement of testosterone levels in the onset of FEP, possibly attributable to its neuroprotective properties. Moreover, certain studies emphasize the significance of testosterone in female patients with respect to FEP/FES, thereby extending the focus beyond male populations, where this hormone is traditionally considered to play a central role. With regard to DHEA/DHEA-S, the available studies are limited and have yielded inconsistent results. Nonetheless, elevated DHEA-S levels have been proposed as a potential biomarker for schizophrenia.

In the context of estrogen, several studies examining FEP/FES in female patients lend support to the estrogen hypothesis, highlighting the hormone's neuroprotective properties. Reduced estrogen levels – such as those observed during menstruation or menopause – have been positively correlated with increased severity of FEP symptoms, with positive symptoms notably intensifying during the perimenstrual phase. Although the findings remain somewhat inconclusive, the evidence suggests that, akin to testosterone, estrogen plays a significant neuroprotective role in the pathophysiology of FEP and FES. Our review identified the least amount of available data concerning progesterone. In comparison to estrogen, the effects of progesterone in the context of FEP have been substantially less explored. While some evidence suggests reduced progesterone levels in FEP patients and indicates that progesterone, similar to estrogen, may exert neuroprotective effects on the CNS, the current body of literature does not allow for definitive conclusions.

In conclusion, additional research is necessary to clarify the potential involvement of NASs in the pathophysiology of FEP and FES. Although the current findings are preliminary, they underscore the promise of this area of study. Advancing knowledge in this domain may contribute substantially to improving clinical insight and optimizing therapeutic approaches for affected individuals.

Authors' contribution

Study design – A. Gładysz
Data collection – A. Gładysz, A. Dydyna, M. Mościcka, M. Gierlik
Manuscript preparation – A. Gładysz, A. Dydyna, M. Mościcka, M. Gierlik
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