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Role of epilepsy in women's reproductive function

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ABSTRACT

According to the World Health Organization, epilepsy is one of the most common neurological diseases worldwide, affecting approximately 50 million people. In 2020, the overall prevalence of epilepsy in the Russian Federation was 2.49 patients per 1,000 population, and 366,134 patients with epilepsy were registered in Russia. Approximately 40% of patients with epilepsy are women of reproductive age. The course of epilepsy in women of reproductive age has its characteristics, which are associated with daily and monthly cyclic rhythms. Epilepsy has various physiological consequences owing to the use of antiepileptic pharmaceutical therapy. This review aimed to summarize up-to-date information on the effect of epilepsy on women's reproductive health. Electronic databases of PubMed, eLibrary, and Google Scholar were searched for relevant publications. The following keywords and their combinations were included in the search strategy: "epilepsy", "reproductive health", "sex hormones", "pregnancy", "menstrual cycle", "fetal", "neonatal", "epilepsy", "reproductive health", "sex hormones", "pregnancy", "menstrual cycle", "fetal", and "neonatal". The search was conducted among studies published before December 2023. Women are particularly concerned about epilepsy throughout their reproductive years. Infertility rates increased in people experiencing psychological stress and impaired physiological processes that support reproductive health. Thus, doctors must examine the physiological effects of antiepileptic and anticonvulsant drugs. The main goal of therapy is to provide women with epilepsy with a seizure-free life, excellent overall well-being, and improved health. The current plan is achievable if the practitioner is familiar with the sexual effects of epilepsy at the molecular level. However, modern treatment methods cannot be available to every woman because of limited resources.

Keywords: epilepsy; reproduction; woman; fertility; pregnancy; sexual dysfunction.

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Роль эпилепсии в репродуктивной функции женщин

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АННОТАЦИЯ

По данным Всемирной организации здравоохранения, эпилепсия — одно из самых распространённых неврологических заболеваний в мире, которым страдают около 50 млн человек. Общая заболеваемость эпилепсией в Российской Федерации в 2020 г. составляла 2,49 на 1000 человек, а общее число зарегистрированных больных эпилепсией в России — 366 134 человека. Среди больных эпилепсией около 40% составляют женщины репродуктивного возраста. Течение эпилепсии у женщин репродуктивного возраста имеет свои особенности, которые связаны с суточными и месячными циклическими ритмами. Эпилепсия имеет широкий спектр физиологических последствий, обусловленных противоэпилептической фармацевтической терапией**.**

Цель обзора — обобщение актуальной информации о влиянии эпилепсии на женское репродуктивное здоровье. Авторами проведён поиск публикаций в электронных базах данных PubMed, eLibrary и Google Scholar. Стратегия поиска включала следующие ключевые слова и их сочетания: «эпилепсия», «репродуктивное здоровье», «половые гормоны», «беременность», «менструальный цикл», «фетальный», «неонатальный», «epilepsy», «reproductive health», «sex hormones», «pregnancy», «menstrual cycle», «fetal», «neonatal». Поиск проводили среди исследований, опубликованных до декабря 2023 г. Женщины особенно обеспокоены эпилепсией в течение всего репродуктивного возраста. Показатели бесплодия повышаются в результате психологического стресса, с которым сталкиваются люди, страдающие эпилепсией, и нарушения физиологических процессов, поддерживающих репродуктивное здоровье. Кроме того, врач должен изучить физиологические последствия применения противоэпилептических и противосудорожных препаратов. Главная цель терапии состоит в том, чтобы обеспечить женщинам с эпилепсией жизнь без приступов, хорошее общее самочувствие и улучшение состояния здоровья. Текущий план достижим, если практикующий врач знаком с половыми различиями течения эпилепсии на молекулярном уровне. Ограничение заключается в том, что современные методы лечения не могут быть доступны каждой женщине в условиях ограниченных ресурсов.

Ключевые слова: эпилепсия; репродукция; женщина; фертильность; беременность; сексуальная дисфункция.

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癫痫在女性生殖功能中的作用

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摘要

根据世界卫生组织的数据，癫痫是世界上最常见的神经系统疾病之一，大约有5000万人受到影响。2020年，俄罗斯联邦的癫痫总发病率为2.49‰，登记在册的癫痫患者总数为 366 134 人。约40%的癫痫患者是育龄妇女。育龄妇女的癫痫病程有其自身特点，与昼夜和月经周期节律有关。抗癫痫药物治疗会对癫痫患者的生理产生广泛的影响。

本综述旨在总结关于癫痫对女性生殖健康影响的最新信息。作者在电子数据库PubMed、eLibrary和Google Scholar中搜索了相关出版物。搜索策略包括以下关键词及其组合：эпилепсия（癫痫），репродуктивное здоровье（生殖健康），половые гормоны（性激素），беременность（怀孕），менструальный цикл（月经周期），фетальный（胎儿），неонатальный（新生儿）。搜索对象为截至 2023 年 12 月发表的研究。妇女在整个生育期对癫痫尤为关注。由于癫痫患者面临的心理压力以及维持生殖健康的生理过程受到干扰，不孕率会增加。此外，医生应检查抗癫痫和抗惊厥药物的生理影响。治疗的首要目标是让女性癫痫患者过上没有癫痫发作的生活，保持总体健康状况良好，并改善健康状况。如果医生熟悉癫痫在分子水平上的性别差异，目前的计划是可以实现的。其局限性在于，在资源有限的环境中，不可能让每个妇女都能获得现代治疗。

关键词：癫痫；生殖；妇女；生育能力；怀孕；性功能障碍。

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According to the World Health Organization, epilepsy is one of the most common neurological diseases worldwide, affecting approximately 50 million people, [1]. In 2020, the overall prevalence of epilepsy in the Russian Federation was 2.49 cases per 1,000 population, and 366 134 patients with epilepsy were registered in Russia [2]. Approximately 40% of patients with epilepsy are women of reproductive age [3]. The course of epilepsy in women of reproductive age has its characteristics, which are associated with daily and monthly cyclic rhythms [4]. Epilepsy has various physiological consequences owing to the use of antiepileptic pharmaceutical therapy [5]. Fluctuations in the levels of sex hormones (gonadal steroids and gonadocorticoids) during puberty, menarche and menstruation are associated with the development of seizure disorders in women [6]. Some antiepileptic drugs lower the levels of sex hormones and can affect the efficacy of combined oral contraceptive pills (COCPs), decrease birth rate and contribute to the development of infertility which may be due to the disruption of the hypothamamic-pituitary-adrenal axis [7]. Antiepileptic drugs lower the concentration of bioavailable sex steroids affecting the menstrual cycle control and the effectiveness of contraception. These drugs can suppress natural sex steriods leading to reproductive disorders [7–8]. Pregnancy in women with epilepsy is of special concern. The pharmacokinetics of antiepileptic drugs changes in pregnancy possibly leading to an increased seizure frequency [9]. Combination treatment of patients with epilepsy controls seizure activity and protects long-term health condition. Extension of knowledge about the influence of epilepsy on reproductive health of women might help healthcare professionals that treat this group of patients in their everyday practice.

This review aimed to summarize the up-to-date information on the effect of epilepsy on women's reproductive health.

Electronic databases of PubMed, eLibrary, and Google Scholar were searched for relevant publications. The following keywords and their combinations were included in the search strategy: "эпилепсия," "репродуктивное здоровье," "половые гормоны," "беременность," "менструальный цикл," "фетальный," "неонатальный," "epilepsy", "reproductive health", "sex hormones", "pregnancy", "menstrual cycle", "fetal", "neonatal." The search was conducted among studies published before December 2023. All authors independently screened the titles and abstracts of the studies and retrieved the full text of the relevant articles. Duplicates and non-full-text articles were excluded. Full-text articles were assessed according to the following inclusion criteria: the study was published in English or Russian, the study was conducted with human subjects and animals.

PROBLEM OF EPILEPSY IN WOMEN

Epilepsy is a neurological disorder characterized by unprovoked seizure attacks, which can significantly lower the quality of life and contribute to the development of reproductive disorders, including fertility, pregnancy, childbirth and contraception. This is due to the fact that hormonal imbalances in the woman's body are directly bound to the seizure frequency and the efficacy of antiepileptic pharmaceutical therapy [3]. Since some antiepileptic drugs increase the risk of fetal congenital anomalies, achievement and maintenance of healthy pregnancy in women with epilepsy may be challenging [5, 9]. Moreover, emotional and physical stress during labor may contribute to the development of a seizure disorder [10]. To provide patients with epilepsy with appropriate healthcare and support, it is crucial to understand the complicated and multifaceted connection between epilepsy and reproductive health. Irregular menstrual cycle, hormonal imbalances and infertility are just some of the effects of epilepsy on reproductive health. It is important to reach appropriate seizure control before pregnancy, because seizures in pregnant women may be rather dangerous [10]. Further we will discuss the mechanisms of impact that epilepsy have on women's reproductive health, including hormonal imbalances, sexual dysfunction, pregnancy and specific contraception.

HORMONAL IMBALANCES

Epilepsy has a significant effect on hypothalamic and pituitary hormone levels [11]. Also, some of the antiepileptic drugs may significantly alter the levels of sex steroids synthesized by the adrenal glands and the ovaries [12]. Gonadotropin secretion from the anterior pituitary is controlled by gonadotropin releasing hormone (GnRH) [13]. GnRH is released by the hypothalamus in a pulsatile manner and stimulates the production of gonadotropins, such as follicle-stimulating hormone and luteinizing hormone (LH) by the pituitary. FSH and LH stimulate the synthesis and secretion of sex steroids from the gonads, providing negative feedback to the pituitary and the hypothalamus [14].

Seizures can interfere with cortical regulation of hypothalamic hormone secretion, leading to disruption of the hypothalamic-pituitary axis [14]. The primary examples of endocrine disorders in women with epilepsy are irregular pituitary response to GnRH, changes in the secretion of LH by the pituitary, increased LH and prolactin levels [15]. There are several mechanisms that initiate these endocrine disorders. Ictal discharges can cause direct and episodic changes in the hypothalamic-pituitary-adrenal system, while epileptogenic damage can lead to prolonged dysfunction of the hypothalamic-pituitary-adrenal axis [16]. Antiepileptic drugs can alter the activity of hypothalamic-pituitary-adrenal axis, disrupting the negative feedback loop and directly affecting the incoming signals. Endocrine disorders can occur due to the disruptions in the hypothalamic-pituitary-adrenal axis, which, in turn, can alter hormone levels.

It is important to mention, that women with epilepsy often develop hyperprolactinemia. Early studies showed that after tonic-clonic and focal (with or without a loss of

consciousness) seizures the pituitary prolactin level more than doubled, while in non-epileptic paroxysmal conditions it did not change [17]. However, in the prospective study in 2021, the authors did not report statistically significant differences in prolactin levels in patients with epileptic and non-epileptic conditions [18]. The level of prolactin starts to increase during the first 5 minutes of the seizure, peaks after 15 minutes and remains increased for an hour, before returning to the baseline. The increase in prolactin level is thought to be caused by stress and hormonal imbalance during the seizure. An increased prolactin level may have various effects, including ovarian suppression and sexual dysfunction. The understanding of alterations in the prolactin level during seizures can be helpful in the research of pathogenesis of epilepsy and the development of new treatment methods [18].

Antiepileptic drugs act on the hypothalamic-pituitary-adrenal axis by directly binding to cortical centers and disrupting the negative feedback. Antiepileptic drugs affect neurochemicals which regulate hypothalamic-pituitary-adrenal axis, such as gamma-aminobutyric acid (GABA), endogenous opioids, serotonin and glutamate [19]. Antiepileptic drugs which induce cytochrome P450 enzymes increase steroid metabolism and binding [20]. Antiepileptics which decrease steroid hormone levels are oxcarbamazepine, carbamazepine, phenytoin, topiramate, and phenobarbital. Antiepileptic drugs, which inhibit this enzymatic pathway increase steroid hormone levels. Lamotrigine and gabapentin are thought not to alter steroid hormone levels [21]. Physicians should consider possible hormonal imbalances associated with antiepileptic drug use, which disrupts reproductive functions. Changes in duration and regularity of the menstrual cycle are an important indicator of an anovulatory cycle. Hirsutism, obesity and acne are the symptoms of increased androgen levels and androgen hypersensitivity [22]. Hyperandrogenemia may be accompanied by disorders of lipid metabolism and glucose intolerance, which have severe long-term consequences for women's health [22].

EPILEPSY AND WOMEN'S REPRODUCTIVE HEALTH

A decrease in reproductive function might be due to a variety of factors. According to the study by Parfenova et al., individuals with epilepsy get married and have children less frequently [23]. Although a lot of studies have been conducted, pregnancy-associated risks in this group of patients remain unclear. Many physicians do not recommend pregnancy for patients with epilepsy due to concerns about possible complications for the mother and the baby [24]. In women with epilepsy pregnancy is especially challenging. There is a lack of knowledge about pregnancy-related risks in patients with epilepsy and methods of their correction among healthcare providers. Thus, further investigations of the problem are needed. It is important to note, that the circumstances of every woman are different, and planning of the pregnancy should be personalized according to the woman's health and seizure control.

IRREGULAR MENSTRUAL CYCLE, POLYCYSTIC OVARY SYNDROME AND ANOVULATION

Women with epilepsy are more prone to the development of menstrual cycle disorders, including shortened (<23 days) and prolonged (>35 days) menstrual cycles. According to the study by Bosak et al., 28.8% of women with epilepsy reported irregular menstruations with about one-third of them being anovulatory, in contrast to 12% in women without the disease [25]. Anovulatory periods are more often seen in women with generalized epilepsy, compared to women with symptomatic focal epilepsy. Antiepileptic drugs, except for gabapentin, phenobarbital, carbamazepine, phenytoin, and lamotrigine, have been associated with anovulatory periods. Women with primary generalized epilepsy who took antiepileptic drugs were at the greatest risk [26]. Fifty-five percent of menstrual cycles in this group of patients were anovulatory. Ovulation deficiency, caused by epilepsy and antiepileptic drugs, might be due to hormonal imbalances and ovarian dysfunction [22]. Uncontrolled LH secretion by the pituitary regardless of the GnRH level indicates the disruption of the hypothalamic-pituitary axis. In women who took antiepileptics which stimulate cytochrome P450 system a significant decrease in testosterone and estradiol levels and an increase in steroid-binding globulin level was reported [27]. Also, in women who took antiepileptics inhibiting cytochrome P450 enzymes, adrenal and gonadal androgen levels were significantly increased [28]. Women who took lamotrigine and gabapentin, which do not affect the cytochrome P450 enzymes, did not have hormonal imbalances [29].

Obesity, polycystic ovaries, acne, hirsutism, increased FSH/LH ration, increased androgen levels, impaired insulin sensitivity and prolonged anovulation are the symptoms of polycystic ovary syndrome (PCOS). This syndrome is associated with infertility, increased cardiovascular risk, dyslipidemia, diabetes mellitus, impaired insulin sensitivity, endometrial carcinoma, and possibly, breast cancer [30]. Anovulation usually leads to irregular menstruations or their absence. Without regular ovulation the probability of pregnancy significantly decreases. This can cause amenorrhea or irregular menstruations. The most common cause of anovulation is PCOS. Characteristic signs of PCOS are multiple ovarian cysts, hormonal imbalances and impaired insulin sensitivity. Anovulation is also associated with some other unfavorable sequalae, including increased risk of endometrial hyperplasia and a risk of endometrial cancer over time. PCOS in women with epilepsy is usually triggered by antiepileptic therapy [29]. In most cases ovulation can be stimulated using fertility drugs, such as clomiphene citrate or letrozole.

Replacement of an antiepileptic drug to lamotrigine in women with PCOS corrects hyperandrogenemia, normalizes ovarian morphology and lipid spectrum, increasing high density lipoproteins level [31].

CONTRACEPTION IN PATIENTS WITH EPILEPSY

To avoid unintended pregnancy patients with epilepsy should use contraception. However, the choice of contraceptives might be difficult due to their interaction with antiepileptic drugs, which leads to decreased antiseizure effect. To find an appropriate contraception method which is both effective and does not affect antiepileptic therapy women with epilepsy should consult a specialist. For hormonal contraceptives, such as combined oral contraceptive pills (COCPs), contraceptive patches and intrauterine devices (IUDs), there might be dose adjustments or supportive measures required to provide maximal efficacy. Depending on the patient's wishes and history, non-hormonal methods of contraception, such as barrier contraception or copper IUD can also be an option.

COCP can interact with antiepileptics decreasing their efficacy and increasing the risk of seizures. In the study by Halane et al., antiepileptics which induce cytochrome P450 enzymes, such as carbamazepine and phenytoin, were reported to decrease the efficacy of hormonal contraceptives, leading to unintended pregnancy in patients with epilepsy [33]. Therefore, women using COCPs should use additional methods of contraception, such as condoms, or consider alternative methods of contraception, including copper IUD or progestin-only hormonal contraceptives, which are not affected by antiepileptics. In addition to hormonal contraception, barrier contraception (e.g., condoms, vaginal diaphragms and cervical caps) which is safe and effective might be used in patients with epilepsy, because it does not interact with antiepileptic drugs. However, in patients with epilepsy there is an increased seizure activity during sexual intercourse, which complicates the use of barrier contraception. Thus, physicians should discuss the risks and benefits of various contraception methods with patients and consider their seizure control while making recommendations on contraception. Women with epilepsy use various methods of contraception and their combinations, including hormonal contraception, such as progestin-only contraceptive pills, barrier contraception, subcutaneous implants, intramuscular injections, contraceptive patches, and vaginal rings. Most women with epilepsy also take antiepileptic drugs. A lot of drugs can interact with hormonal contraceptives, decreasing their efficacy or leading to poor seizure control [34].

EPILEPSY AND PREGNANCY

Pregnancy in patients with epilepsy is challenging due to altered seizure frequency, increased risk of complications, and the need to take antiepileptic drugs throughout the pregnancy. However, with proper healthcare and efforts most of the patients can conceive and give birth to a healthy child. Alterations in the frequency of seizures during pregnancy are unpredictable, since it might either increase or decrease. The frequency of seizures increased in 33% of pregnant women with epilepsy and decreased in 24%. Another 43% of women did not report changes in the frequency of seizures [35]. Therefore, it is necessary to control seizure activity throughout the pregnancy and adjust the dose of antiepileptic therapy to improve seizure control. The use of antiepileptics during pregnancy also affects fetal development and increases the risk of congenital fetal anomalies. The risk varies depending on the type and dose of antiepileptics being used. Some of the antiepileptics are associated with a higher risk compared to others. For example, valproic acid is associated with a higher risk of neural tube defects and other congenital anomalies [8]. Thus, clinical physicians should carefully evaluate the risks and benefits of antiepileptic drug use in pregnancy, consider alternative treatment methods or decrease the dose of antiepileptics to minimize the risk of congenital birth defects. To achieve appropriate seizure control, antiepileptic therapy should minimally affect the fetus. Most of the congenital anomalies, dysmorphic syndromes, neurocognitive development anomalies, and intrauterine growth restriction can be caused by prenatal antiepileptic drug exposure. Pharmacokinetics of antiepileptic drug changes in response to pregnancy-related physiological changes, which can lead to decreased concentration of the drug and worsening of the seizures. These effects may be prevented with drug level monitoring and dose adjustments throughout the pregnancy and during the postpartum period [36].

SEXUAL DYSFUNCTION

Another cause of the low birth rates in patients with epilepsy is epilepsy-associated sexual dysfunction. Men and women with epilepsy are reported to have a higher frequency of sexual disorders. In other chronic neurological diseases sexual dysfunction is usually represented by lack of sexual desire and potency. From 30% to 66% of men and 14% to 50% of women with epilepsy have sexual disorders [37]. In men with epilepsy sexual problems are characterized by lack of spontaneous nocturnal erections, erectile dysfunction and anorgasmia [31]. Studies have shown that more than one-third of women with epilepsy suffer from vaginismus, lack of vaginal lubrication, and dyspareunia while maintaining sexual desire [38]. Sexual dysfunction in patients with epilepsy is likely to have a complex mechanism [38]. The social development of some patients might be difficult. Seizures may reduce self-esteem, contributing to sexual dysfunction [38]. Epileptic activity in the areas of the brain responsible for sexual behavior may potentially play a role in the formation of sexual disorders. Changes in the pituitary gonadotropin levels may also influence the development of sexual disorders. Elevated prolactin, progesterone and testosterone levels and

low estrogen levels have been associated with sexual dysfunction in patients with epilepsy. In addition, some antiepileptics cause sexual dysfunction either directly or indirectly through hormonal changes [39].

TREATMENT OF SEXUAL DYSFUNCTION

Patients with epilepsy may experience sexual dysfunction, which is a complex problem caused by neurological abnormalities and antiepileptic drug use. Thus, sexual dysfunction can result from seizure activity or epilepsy-associated hormonal imbalances. Anxiety, depressed mood, and unsatisfaction with one's body appearance can exacerbate the problem. Open communication between spouses and a multidisciplinary approach including psychologists, gynecologists, and neurologists are crucial to address these issues [1]. Assessment of the patient's needs, epileptic status, comorbidities, and the available antiepileptic drugs are all necessary to determine the best treatment course for women with epilepsy-associated sexual dysfunction. Behavioral techniques that increase sexual activity, adjustment and dose reduction of the available antiepileptic drugs to each individual patient, monitoring of the development of tolerance, adjuvant treatment of sexual dysfunction, delayed drug intake (after the sexual intercourse), and targeted treatment of sexual dysfunction itself, may help control sexual disorders in women with epilepsy [38].

The treatment of sexual dysfunction caused by antiepileptic drugs is supportive therapy, including buspirone, cyproheptadine, yohimbine, neostigmine, amantadine, mianserin, and dexamphetamine. In patients with epilepsy, education and work with a psychologist, along with drug therapy, play a crucial role in the correction of sexual dysfunction. To date, there is no approved pharmaceutical therapy for orgasmic dysfunction and decreased sexual desire in women. Nonetheless, vaginal lubricants and hormone replacement therapy are effective in the correction of sexual arousal. Invasive treatment of reproductive disorders includes extracorporeal fertilization and intracytoplasmic injection of spermatozoids. To stimulate ovulation, human chorionic gonadotropin and follicle-stimulating hormone (FSH) are used, the eggs are then taken using transvaginal aspiration and fertilized *in vitro* [40].

CONCLUSION

Women are particularly concerned about epilepsy throughout their reproductive years. Infertility rates increased in people experiencing psychological stress and impaired physiologic processes that support reproductive health. Thus, doctors must examine the physiological effects of antiepileptic and anticonvulsant drugs. The main goal of therapy is to provide women with epilepsy with seizure-free life, excellent overall well-being and improved health. the current plan is achievable if the practitioner is familiar with the sexual effects of epilepsy at the molecular level. However, modern treatment methods cannot be available to every woman because of limited resources.

ADDITIONAL INFO

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