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Stress hormone levels in women with infertility in the third year of the war in Ukraine

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This paper examines the impact of chronic stress caused by the war in Ukraine on the development of mental disorders and impaired reproductive health in women. The study is based on hormonal factors, particularly prolactin and cortisol, in the context of the general adaptation syndrome. War conditions create unique stress effects that disrupt the functioning of the nervous, endocrine, and immune systems. Analysis of changes in hormonal balance is essential to understanding nature's adaptation.

The study **aimed** to analyze the relationship between prolactin and cortisol levels in women with infertility who are under the psychological and emotional impact of war in Ukraine.

Materials and methods. The research was conducted using statistical data on air raid alarms and three separate measurements of prolactin and cortisol levels in 23 patients with infertility.

Results. Within 108 days of research, 268 airstrikes were announced, causing anxiety over a total duration of 45,873 minutes, with an average duration of 171.2 minutes and a median of 80.5 minutes. The mean prolactin levels were 10.41±0.87, 14.34±1.57, and 20.54±5.24, while cortisol levels were 9.36±1.15, 8.49±0.80, and 9.35±1.71. Baseline prolactin levels correlated with cortisol.

Conclusion. The data obtained indicate normalization or reduction of prolactin and cortisol levels, which may suggest the development of stress resistance in patients with infertility or their presence in the second stage of the general adaptation syndrome. The results emphasize the need to revise traditional paradigms of hormonal regulation, stress factors, and infertility.

The research was carried out in accordance with the principles of the Declaration of Helsinki. The study protocol was approved by the Local Ethics Committee of the institution mentioned in the paper. The informed consent of the patient was obtained for conducting the studies.

No conflict of interests was declared by the authors.

Keywords: stress, psycho-emotional stress, infertility, prolactin, cortisol, post-traumatic stress disorder, general adaptation syndrome.

Рівень гормону стресу в жінок із безпліддям на третьому році війни в Україні

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У цій статті проаналізовано вплив хронічного стресу, спричиненого війною в Україні, на розвиток психічних розладів та порушення репродуктивного здоров'я жінок. Дослідження базується на гормональних факторах, зокрема на пролактині та кортизолі, у контексті загального адаптаційного синдрому. Військові умови створюють унікальні стресові ефекти, які порушують роботу нервової, ендокринної та імунної систем. Аналіз змін гормонального балансу є важливим для розуміння адаптації природи.

Дослідження мало на **меті** проаналізувати взаємозв'язок між рівнями пролактину та кортизолу в жінок із безпліддям, які перебувають під психологічним та емоційним впливом війни в Україні.

Матеріали та методи. Дослідження проводилося з використанням статистичних даних про сигналізацію повітряного нальоту та трьох окремих вимірювань рівнів пролактину та кортизолу у 23 пацієнтів із безпліддям.

Результати. Протягом 108 днів дослідження було оголошено про 268 авіаударів, які викликали занепокоєння загальною тривалістю 45 873 хвилини, із середньою тривалістю 171,2 хвилини та середньою тривалістю 80,5 хвилин. Середні рівні пролактину становили 10,41±0,87, 14,34±1,57 і 20,54±5,24, а рівні кортизолу – 9,36±1,15, 8,49±0,80 і 9,35±1,71. Вихідні рівні пролактину корелювали з кортизолом.

Висновок. Отримані дані свідчать про нормалізацію або зниження рівня пролактину та кортизолу, що може свідчити про розвиток стресостійкості у хворих на безпліддя або про наявність у них II стадії загального адаптаційного синдрому. Результати підкреслюють необхідність перегляду традиційних парадигм гормональної регуляції, факторів стресу та безпліддя.

Дослідження виконано відповідно до принципів Гельсінської декларації. Протокол дослідження ухвалено Локальним етичним комітетом зазначеної в роботі установи. На проведення дослідження отримано інформовану згоду жінок.

Автор заявляє про відсутність конфлікту інтересів.

Ключові слова: стрес, психоемоційний стрес, безпліддя, пролактин, кортизол, посттравматичний стресовий розлад, загальний адаптаційний синдром.

Post-traumatic stress disorder (PTSD) is a serious mental condition that occurs after experiencing traumatic events, such as war, and is accompanied by severe emotional distress. The risk of developing PTSD increases in the presence of certain factors that are the subject of ongoing scientific debate [11].

The war in Ukraine has the potential to exacerbate PTSD in women due to internal and external stressors, which can be characterized by the general adaptation syndrome (GAS) as a universal response of the body to harmful factors, first described by Hans Selye in 1936 [21].

Thus, PTSD can and should be analyzed through the theory of GAS, which consists of three stages: alarm reaction (non-specific mobilization), resistance, and exhaustion or decompensation [5,20]. In PTSD, the body remains in the resistance stage for an extended period, causing chronic stress in the nervous, endocrine, and immune systems, leading to psychophysiological exhaustion and dysfunction of other body systems [4,17]. In patients with PTSD, the regulation of prolactin and cortisol synthesis is disrupted due to the constant activation of stress response mechanisms [22,24].

Studies in animal models have shown that stress response involves an initial, short-term increase in prolactin synthesis followed by a prolonged decrease in secretion to medium and low hormone concentrations [8,19].

Prolactin production has been reported to be reduced in war veterans [14]. Some studies suggest that prolactin and cortisol levels in PTSD remain normal or may increase [8,19]. Chronic stress can lead to hyperprolactinemia and/or hypercortisolemia [1,15], which negatively impacts the menstrual cycle and fertility. Cortisol levels in PTSD may be either elevated or decreased [22].

On the other hand, among the many causes underlying fertility disorders, hyperprolactinemia is considered a significant factor associated with PTSD [15]. Functional hypothalamic disorders may also develop, causing a sharp decrease in stress hormone levels [12].

Stress hormone production is considered a multifactorial condition with natural and pathological origins. Among factors that can underline different concentrations of prolactin and cortisol in a woman's serum, there are significant differences depending on the stages of GAS [9]. The prolactin and cortisol levels differ between GAS's first and second stages and may naturally have a protective and positive role [7].

Considering the significant role of the endocrine system in the development of infertility, the **aim** of the study was to investigate the connection between psycho-emotional stress and infertility in women undergoing treatment programs using assisted reproductive technologies in Ukraine at the end of the third year of the war.

Materials and methods of the study

The study is designed as a cohort study and is based on two data arrays. The first array focuses on the stress induction model during a prolonged war, which we analyzed using data on air raid alerts in Kyiv and Kyiv region, Ukraine. The second array presents the results of a cohort hormonal examination of patients who underwent treatment using assisted reproductive technologies. Most folliculogenesis control cycles were carried out in natural or semi-natural cycles (gonadotropin-releasing hormone antagonists were prescribed at the final stages of folliculogenesis). Recombinant human chorionic gonadotropin was used as an ovulation trigger before oocyte retrieval.

The study was conducted simultaneously with the collection of the first dataset, spanning from November 1, 2024, to February 16, 2025. Data for the background analysis was obtained from open sources. Information on air raid alerts in Kyiv and Kyiv region was recorded in the primary data table. Additionally, data on falling debris, destruction, and hits from drones, missiles, or their fragments were collected from open sources (these data were not categorized separately). Patients underwent testing during the first visit, with follow-up testing conducted each month (second and third times). The analysis of air raid data was essential to assess the risks associated with psycho-emotional stress effects.

The primary criterion for including patients in the research group was that the women had remained in Ukraine continuously from the start of the war until the time they were referred to a specialized center for human reproduction. *The inclusion criteria* for the study required participants to be women of reproductive age who resided in central Ukraine, ensuring constitutional standardization and regional consistency within the study population.

The analytical sample included hormonal study results from 23 women with endocrine-related infertility. The average age of the women in the study group was 37.5 years (minimum 27; maximum 39), with a median age of 36.2 years. Blood samples were collected randomly once a month from November 1, 2024, to February 16, 2025. Prolactin and cortisol levels were measured in blood serum during the follicular phase of the menstrual cycle. The follicular phase was confirmed by determining FSH, LH, estradiol, and progesterone levels (though these specific values were not listed in the article). The results confirmed that the hormonal examinations were conducted during the follicular phase of the menstrual cycle. Peripheral blood samples were collected between 9:00 and 10:00 AM, and the analysis of the results was outsourced to the Synevo laboratories.

Statistical data processing was performed using licensed software. AnalystSoft Inc. – statistical analysis program for macOS®. Version v 8. Appendix: StatPlus Statistics+Analysis. Content provider: AnalystSoft Inc. Statistical significance of the results was assessed using p-values with a critical threshold of $p<0.05$, where values below this threshold indicated statistically significant differences or effects. The strength and direction of the linear relationship between variables were analyzed using Pearson's correlation coefficient (r), with $|r|\geq 0.7$ interpreted as a strong correlation, $0.3\leq|r|<0.7$ as moderate, and $|r|<0.3$ as weak.

All participants provided informed consent before their inclusion in the study, and the study protocol was reviewed and approved by the relevant Ethics Commission or institutional review board, ensuring compliance with ethical standards for research involving human subjects.

Results of the study

During the analyzed period (108 days), 268 air raid alerts were recorded in Kyiv and Kyiv region, amounting to 45,873 minutes. The average duration of an alert was 171.2 minutes, with a median duration of 80.5 minutes. The shortest alert lasted 4 minutes, while the longest extended to 947 minutes. The distribution of alert durations indicates that the midpoint is approximately one and a half hours, with the majority of alerts being declared for shorter periods, typically around half an hour. Regarding timing, 46.46% of the alerts occurred during the day, 38.28% at night, and 13.75% from night into the morning. Consequently, the combined proportion of nighttime alerts (including those extending into the morning) reached 52.03%. This suggests that residents of Kyiv and the Kyiv region were exposed to air raid alerts for more than half of the nighttime hours, likely contributing to psycho-emotional stress disorders and the potential accumulation of sleep disturbances.

Drone and missile debris were reported in 10.03% of incidents, while destruction was documented in 5.94% of cases, and direct hits by drones or missiles on specific objects occurred in 5.94% of instances. These events are associated with a higher likelihood that women in the affected areas heard or could have heard air defense operations and explosions. In 18 cases (6.69% of the total incidents), individuals sought medical assistance for various injuries (the exact number of people affected is not detailed in this study). Additionally, there were five reported fatalities, one of which resulted in the death of two individuals.

A strong and statistically significant correlation ($p<0.05$) of 0.74 was identified between the onset of air raid alerts in the evening transitioning into nighttime and the likelihood of prolonged alerts, indicating increased attacks during these periods. Additionally, a reliable moderate correlation was

Table 1

Summary of data on prolactin and cortisol levels

Variable	Descriptive statistics			
	Average value	Median	Standard deviation	Standard error average
Prolactin 1	10.40783	10.20000	4.16644	0.868762
Prolactin 2	14.33875	14.55000	4.46501	1.578619
Prolactin 3	20.54333	17.60000	12.83876	5.241400
Cortisol 1	9.35952	7.13000	5.28982	1.154334
Cortisol 2	8.48875	8.00000	2.27230	0.803380
Cortisol 3	9.35000	7.65000	4.20939	1.718478

Notes: cortisol levels were measured in micrograms per deciliter (mcg/dL), while prolactin levels were measured in nanograms per millilitre (ng/mL); 1 – testing during the first visit; 2 – testing during the second visit; 3 – testing during the third visit.

observed between evening or nighttime alerts and the probability of falling debris (0.64), destruction (0.40), and direct hits (0.30). A similar trend was noted during the nighttime, reinforcing the association between later hours and heightened risks of prolonged alerts and attack-related events.

The initial measurements of prolactin and cortisol levels during the study period (Table 1.) showed a correlation of 0.60. However, subsequent measurements of prolactin and cortisol levels demonstrated weaker correlations, with r≤0.3. A strong positive correlation (0.83) between prolactin and cortisol levels was observed at the final stages of IVF programs, specifically before the oocyte retrieval procedure.

Discussion

The main finding is that prolactin and cortisol levels play a significant role in the female reproductive system, and their elevation may be linked to infertility. Since prolactin is considered a stress hormone, it has been proposed that its increase during in vitro fertilization treatment could be a result of stress [6]. Studies have shown that infertile women exhibit a distinct personality profile compared to fertile women, characterized by higher levels of suspiciousness, guilt, and hostility, which are associated with elevated levels of stress hormones, particularly prolactin and cortisol [13]. Some researchers have observed that serum prolactin and cortisol levels rise during controlled ovarian stimulation for IVF, alongside increases in situational anxiety among infertile patients. However, other studies have not found a significant relationship between psychological indicators and levels of stress hormones, particularly prolactin, in patients undergoing IVF [10].

The focus of reproductive medicine often centers on hyperprolactinemia, a common endocrine disorder of the hypothalamic-pituitary axis, with an incidence ranging from 0.4% in the general population to 17% in women with reproductive disorders [3]. Elevated serum prolactin levels in pathological hyperprolactinemia led to impaired release of follicle-stimulating hormone and luteinizing hormone (LH), resulting in anovulation and infertility in women [2].

In our study group, a prolactin-dependent endocrine mechanism of infertility was not established, as prolactin levels remained within normal limits. These findings contrast with existing literature that highlights prolactin's role in stress-related disorders, particularly its impact on neuropsychiatric conditions and reproductive health. Such studies emphasize that hyperprolactinemia contributes to infertility by suppressing gonadotropin secretion and ovulation [15].

The interaction between prolactin and cortisol in stress adaptation processes appears more logical, as suggested by our results. An imbalance in the synthesis of prolactin and cortisol may lead to functional hypothalamic disorders, which negatively impact both fertility and stress resilience [8]. Excessive or insufficient cortisol production under various stressors has been linked to infertility due to impaired reproductive function, often associated with conditions such as functional hypothalamic disorders. These conditions are further compounded by altered stress tolerance and impaired adaptation to stress [16]. Our findings on cortisol levels may indicate the depletion of stress-adaptive mechanisms, where the endocrine system, mainly its reproductive functions, becomes dysregulated or resistant and no longer responds effectively to prolonged stressors, such as those associated with ongoing war (e.g., frequent air raids).

Furthermore, impaired dopaminergic regulation of prolactin can lead to hyper- or hyperprolactinemia, disrupt cortisol homeostasis, and contribute to stress-induced infertility and functional hypothalamic disorders [25]. In this context, the observed normal levels of the studied hormones in women during the third year of the war in Ukraine may instead suggest a potential depletion of the hypothalamic-pituitary-adrenal-gonadal axis, reflecting a diminished capacity to respond to chronic stress.

Thus, it can be hypothesized that elevated prolactin and cortisol levels are more typical under acute stress conditions. In contrast, their reduction to "normal" levels may indicate the development of resistance to acute stressors, such as air raids, in the context of chronic stressors like the nearly three years of war in Ukraine. Other researchers have reported similar findings, suggesting the development of functional hypothalamic disorders under such conditions [12].

Studies indicate that prolactin and cortisol levels tend to rise in acute and subacute stress states [15] but may increase, remain normal, or decrease in chronic stress conditions [2,9]. This variability underscores the need for further research to reach consensus conclusions. Beyond the primary scope of this analysis, a point of scientific and practical interest is the observation of normal and low levels of prolactin and cortisol in infertile women who remained in central Ukraine since the start of the war, as well as in those who achieved pregnancy through assisted reproductive technologies. A statistically significant reduction in the incidence of preeclampsia was recorded in the first year of the war, and potential explanations for such effects have been discussed in the literature [18].

Comparison with other studies. Normal prolactin levels for women of reproductive age without fertility problems and any specific signs of stress in the central geographic zone of Ukraine are 20.8±1.29 ng/ml [1] and/or 13.5±5.6 ng /ml [15]. The results obtained in our study suggest a reduced secretion of stress hormones, such as prolactin and cortisol, among our sample of patients who have remained in Ukraine since the beginning of the war. However, we cannot directly compare our findings with pre-war data due to the unavailability of primary documentation from other studies.

Research limitations. Our findings have limited generalizability, as the unique conditions of prolonged stress associated with the nearly three years of war in Ukraine.

Practical significance. We hypothesize that the observed normal or low levels of prolactin and cortisol in our study population may reflect an adaptive resistance to intense and chronic stressors linked to the war in Ukraine.

Conclusions

The concentrations of prolactin and cortisol observed in the study group suggest a need to reconsider the generally accepted paradigms regarding the role and interplay of these hormones in women who remained in Ukraine during the war and were exposed to chronic psycho-emotional stress caused by the war and its components (e.g., air raid alerts, as examined in this study). This points to a model of stress-resistant women in the second phase, the resistance phase, of the GAS, as described by Hans Selye.

From our perspective, the study's results indicate that the examined group of women, and likely similar patient groups across Ukraine, are in the second stage of GAS – the resistance phase.

Further research is essential, as the unique stress-induced conditions in Ukraine provide a rare opportunity to study the long-term effects of chronic stress. Such investigations could shed light on many aspects of the general adaptation syndrome and its implications for stress resilience and reproductive health.

The authors declare no conflict of interest.

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