УДК: 618.39-021.3-092:616.45-001.1/.3:616-005:614.876
DOI: 10.24061/2413-4260.XVI.2.60.2026.17

THE ROLE OF STRESS IN THE PATHOGENESIS OF PREGNANCY LOSS: TWO DIMENSIONS OF A SINGLE PROBLEM

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Abstract.

The impact of stress factors on the course of pregnancy remains a relevant issue in modern perinatology. This article addresses the role of stress-related responses at the placental level in women exposed to ^{137}Cs, and the role of psychoemotional stressors in the pathogenesis of pregnancy loss – presented as two aspects of the same problem. The article draws on the results of prior studies examining morphological and immunohistochemical placental damage resulting from ^{137}Cs incorporation, and the psychological components of recurrent pregnancy loss.

Aim of the study. *To determine markers of miscarriage in the setting of chronic stress.*

Materials and methods. *The study enrolled pregnant women with a history of miscarriage and signs of threatened termination of the current pregnancy (Group 1), and pregnant women with uncomplicated pregnancies and an unremarkable obstetric history (Group 2, control). Gamma spectrometry of placentas from both groups demonstrated ^{137}Cs accumulation at varying activity levels. The consequent biological effect was oxidative stress. The magnitude of the stress response was assessed by serum levels of diene conjugates (DC) and malondialdehyde (MDA). Antioxidant capacity was evaluated by measuring the activity of catalase, glutathione S-transferase, and superoxide dismutase (SOD). Psychological screening comprised assessment of personal stress perception, psychoemotional tension, anxiety, and asthenia. The study was conducted in accordance with the principles of the World Medical Association Declaration of Helsinki on Ethical Principles for Medical Research Involving Human Subjects. Informed consent was obtained from all participants prior to enrolment. Ethical approval was granted by the Medical Ethics Committee of the State Institution «Institute of Pediatrics, Obstetrics, and Gynecology named after Academician O. M. Lukyanova of the National Academy of Medical Sciences of Ukraine» (Protocol No. 3, 07 June 2017; Protocol No. 3, 20 April 2023). Statistical analysis was performed in Microsoft Excel, with Fisher's angular transformation applied where appropriate. Differences between compared values were considered statistically significant at $p < 0.05$ (confidence level exceeding 95%). The study was carried out under two institutional research projects: «To develop novel and refine existing technologies for the diagnosis, prevention, and treatment of premature pregnancy termination in women with pregnancy loss, examining the role of contemporary environmental exposures» (2018-2020, state registration No. 0118U000039), and «To develop diagnostic and therapeutic measures for the prevention of pregnancy loss in women in Ukraine during martial law» (2024-2026, state registration No. 0123U103153).*

Results. *Psychosocial adaptation disorders – comprising elevated personal stress perception, anxiety, and asthenia – were identified in women with pregnancy loss. The destructive effect of ^{137}Cs is mediated by oxidative stress and results in placental dysfunction. The severity of these effects is determined by ^{137}Cs activity and the adequacy of antioxidant protection. A specific activity of ^{137}Cs exceeding 10.4 Bq/kg is critical for pregnancy outcome. A 2.25-fold elevation of DC in the first trimester relative to controls indicates activation of free radical reactions. Prognostically unfavourable findings include SOD deficiency and MDA excess exceeding 10% in the first trimester. Increased generation of lipid peroxidation (LPO) products with impaired neutralisation and utilisation at the onset of pregnancy constitutes the pathophysiological basis for placental dysfunctionA first-trimester MDA elevation of 17.4% relative to controls serves as a trigger for late preterm birth. The risk of early preterm birth and intrauterine fetal death is increased when first-trimester maternal blood MDA levels exceed those of controls by 23.4%, particularly when accompanied by an 18.2% reduction in SOD activity, indicating impaired antioxidant defence and early decompensation of adaptive mechanisms.*

Conclusions. *Oxidative and psychoemotional stress play a decisive role in the pathogenesis of pregnancy loss. Radionuclide decorporation and activation of placental adaptive processes represent promising strategies for mitigating the effects of internal radiation exposure. Enhancement of pregnant women's adaptive potential through strengthening psychoemotional resilience and fostering a positive orientation toward pregnancy and motherhood is of comparable importance for the prevention of pregnancy loss.*

Keywords: *Recurrent Pregnancy Loss; Placenta;^{137}Cs; Stress; Peroxide Hemostasis.*

Introduction

Sustaining population growth amid an unfavourable demographic situation represents a challenge of national importance for Ukraine, and within the system of state priorities, particular attention is directed toward the health of future generations. The health of the neonate is substantially determined by the intrauterine conditions of fetal development [1], and adverse environmental conditions predispose to obstetric and perinatal complications, impairing postnatal and social adaptation. The reduction of reproductive losses therefore remains the primary goal of obstetrics.

In the 1980s, World Health Organization (WHO) experts identified four major determinants of human health [2]. Genetic factors were estimated to account for 15-20%, environmental factors for 20-25%, quality of medical care for 10-15%, and lifestyle factors for 50-55%, rendering lifestyle and environmental conditions the most influential determinants. Lifestyle encompasses the standard of existence of an individual in society. A regular

ISSN 2226-1230 (PRINT) ISSN 2413-4260 (ONLINE)

daily routine, balanced nutrition, adequate physical activity, and psychoemotional stability constitute the foundations of a healthy lifestyle. Pregnant women represent one of the most vulnerable population groups, particularly during periods of social upheaval, as pregnancy and childbirth are themselves associated with profound changes in lifestyle, perception, and psychophysiological functioning. The war has fundamentally altered the lives of the Ukrainian population, functioning as a powerful psychological stressor capable of precipitating depressive disorders and heightening anxiety. Warfare also carries significant environmental consequences, including contamination of soil, water, and air [3, 4]. The combination of chronic psychosocial stress and deteriorating environmental conditions undermines the maintenance of a healthy lifestyle and, in pregnant women, may result in obstetric complications, including pregnancy loss [5, 6].

The female reproductive system responds to prolonged exposure to adverse external and internal factors through adaptive reactions that may progressively acquire pathological characteristics [7, 8]. The psychoemotional state of a woman exerts a measurable influence on pregnancy outcomes, and an association between stress and pregnancy loss has been established [9, 10]. Recurrent pregnancy loss constitutes a profoundly distressing experience for affected couples. Bereavement is accompanied by disappointment, anxiety, hopelessness, and emotional dysregulation – psychological sequelae that represent key components of the recurrent pregnancy loss syndrome [11].

An understanding of the mechanisms underlying stress vulnerability enables the prediction, prevention, and treatment of post-stress pathological conditions. Despite its paramount clinical importance, stress as a physiological phenomenon remains incompletely characterized. Although stress is commonly associated with adverse health outcomes, it fundamentally represents the body's adaptive response to physical or psychoemotional stimuli (stressors). In response to a stressor, an individual either avoids its impact or adapts to new environmental demands. Long-term adaptation is acquired through moderate repeated exposure to stress, whereas excessive stressor exposure leads to failure of adaptation, development of pathology, or death. The constancy of the body's internal environment is an indispensable prerequisite for life, and disruption of homeostasis is inherently stressful. The stress response is directed at restoring homeostatic equilibrium. Accordingly, efforts to preserve pregnancy must encompass protection against both stressors and stress-mediated tissue damage. The study of individual stress resilience is clinically relevant for predicting pregnancy outcomes, as pregnant women differ substantially in their susceptibility or resistance to stress-related disorders.

The emotional sphere constitutes a primary component of adaptive responses, reacting immediately to changes in an individual's environment and determining subsequent humoral influences. The psychophysiological profile of an individual is governed by the activity of cortical and subcortical brain structures. The limbic system and autonomic nervous system mediate sympathoadrenal and vagotonic responses that regulate adaptive mechanisms. A woman's emotional state, mood, anxiety level, and perception of her impending motherhood exert a significant influence on the course of pregnancy and on the physical and mental health of the child [12]. The style of experiencing pregnancy is regarded as an important characteristic of the psychological component of the gestational dominant, which regulates neuroimmune-hormonal processes within the mother–placenta–fetus system [13].

Pregnancy is characterised by intensified emotional reactivity, with each woman's experience shaped by her individual psychophysiological profile and obstetric history; nevertheless, anxiety about the pregnancy outcome represents a universal concern among pregnant women. In the early stages of pregnancy, adaptation to the new physiological state is accompanied by symptomatic manifestations that give rise to cognitive interpretations and emotional responses – including anxiety, fear, or joy – which may either alleviate or intensify physical symptoms. A particular concern is recurrent pregnancy loss, in which pregnancy itself becomes a psychotraumatic factor, activating latent experiences associated with prior reproductive loss. Negative emotional states during gestation are associated with placental dysfunction, fetal growth restriction, and pregnancy loss [9-13]. Psychoanalytic approaches enable exploration of deeply rooted irrational emotions and resolution of internal conflicts. The elucidation of the psychological component of pregnancy loss remains an important objective of obstetric science.

Activation of stress-implementing systems and catecholamine release is regarded as a physiologically appropriate stress response; however, chronic stress precipitates sympathoadrenal and hypothalamic-pituitary-adrenal dysfunction, shifting stress reactions from adaptive to destructive [8, 14, 15]. The resultant hyperproduction of adrenaline and noradrenaline activates humoral immunity and cytokine expression while suppressing cellular immunity, and the ensuing immunological deviations serve as predictors of inflammation, uncontrolled apoptosis, and pregnancy loss [8, 11, 15].

Women are additionally exposed to various chemical stressors. Although four decades have elapsed since the Chornobyl Nuclear Power Plant accident, its consequences continue to affect the Ukrainian population. The principal radiological threat is posed by ^{137}Cs, and ecosystems contaminated with ^{137}Cs serve as a persistent source of human exposure. Prolonged low-intensity radiation exposure is more hazardous than a single high-intensity exposure. The biological effects of ^{137}Cs are attributable to its absorption into the bloodstream and accumulation in organs with heightened radiosensitivity, including the placenta. Oxidative stress induced by ^{137}Cs disrupts the histoarchitecture of the placenta, and the severity of these effects is governed by ^{137}Cs activity. Decompensation of placental reserve capacity represents the proximate cause of pregnancy loss [16, 17].

Oxidative stress represents an integral component of normal pregnancy, regulating the onset of parturition. At the cellular level, oxidative stress induces fetal cell senescence, which in late-stage normal pregnancy is physiologically justified, as fetal cell senescence exerts a uterotonic effect that triggers the onset of labour [18Preterm birth, by contrast, results from placental and fetal damage caused

by oxidative stress exceeding the capacity of antioxidant defence mechanisms. Assessment of the antioxidant system is therefore essential for preventing adverse extremes during pregnancy [16-21].

The biochemical response to stressors is complex, with peroxide homeostasis representing a critical determinant of successful pregnancy outcome [19]. The activation of pro-oxidant reactions constitutes the general pattern of response to any stressor, and psychoemotional stress and oxidative stress are interrelated components of the pathogenesis of recurrent pregnancy lossThe study of biochemical processes in pregnant women subjected to prolonged neuroemotional and radiation exposure is relevant to the prediction and prevention of pregnancy loss.

Objective

To determine markers of pregnancy loss in the setting of chronic stress.

Materials and methods

The present article draws on the results of studies examining morphological and immunohistochemical changes in the placenta resulting from ^{137}Cs incorporation, and identification of psychological factors associated with pregnancy loss [16, 17].

The study enrolled pregnant women with a history of reproductive losses and signs of threatened termination of the current pregnancy (Group 1), and pregnant women with uncomplicated pregnancies and an unremarkable obstetric history (Group 2, control). ^{137}Cs accumulation at varying activity levels was detected in the placentas of both groups, accounting for observed differences in pregnancy outcomes. Volumetric activity of ^{137}Cs in placental tissue was measured by gamma spectrometry with the isotope sample analyser RC-101 (Japan). ^{137}Cs is a beta-gamma emitter with a half-life of 30.1 years, emitting gamma quanta at an energy of 662 keV, which are detected by the instrument; measured activity was divided by sample mass, with results expressed in Bq/kg. The nature of placental damage attributable to ^{137}Cs was assessed by morphological examination. Placental samples were analysed according to a standardised protocol comprising organometric measurements and examination of the umbilical cord, membranes, and both the fetal and maternal surfaces of the placenta (Form No. 013-1/0) [16]. Light microscopy was employed to identify involutional-dystrophic, dyscirculatory, and inflammatory changes.

Based on the outcome of the current pregnancy, women in Group 1 were stratified into subgroups. In subgroup 1a, pregnancy culminated in term delivery despite signs of threatened miscarriage throughout gestation; in subgroup 1b, late preterm birth occurred; and in subgroup 1c, early preterm birth was recorded.

In placentas from the control group, ^{137}Cs activity did not exceed 1.0 Bq/kg – a level insufficient to induce morphological changes or impair placental functional capacity.

In subgroup 1a, ^{137}Cs activity in placental tissue ranged from 1.1 to 4.4 Bq/kg. Morphological examination revealed circulatory disorders in 30% of placentas and dystrophic changes in 50% of samples; nonetheless, pregnancy was successfully prolonged to term, reflecting preserved compensatory capacity of the placenta.

In subgroup 1b, ^{137}Cs activity ranged from 4.5 to 10.4 Bq/kg and was accompanied by injury to the maternal stroma. The maternal surface of the placenta exhibited areas of ischaemia, haemorrhages, afunctional zones, and detachment of the decidual membrane, while signs of inflammation were detected in approximately 80% of fetal membranes.

In subgroup 1c, ^{137}Cs activity in placental tissue exceeded 10.4 Bq/kg. Damage to both maternal and fetal placental structures at this activity level constituted a probable cause of fetal death. Morphological examination revealed immaturity of intermediate and terminal villi, inflammation of the decidual membrane, and globally impaired vascular perfusion attributable to total detachment of the decidual membrane. A ^{137}Cs activity exceeding 10.4 Bq/kg is therefore considered lethal to the fetus.

Stress screening was performed in 84 women from Group 1 and 30 women from Group 2, comprising assessment of stress perception, psychoemotional tension, personal anxiety, and asthenia [22]. Laboratory investigations were carried out in 70 of the 84 women in Group 1; the remaining 14 women, as internally displaced persons during wartime, continued antenatal follow-up at healthcare facilities in other regions, primarily in western Ukraine.

Stress perception was assessed by the Perceived Stress Scale (PSS), with a score of 32 points corresponding to a high stress level.

Psychoemotional tension was measured by the PSM-25 scale, on which a score below 100 points indicates psychological adaptation to stress, a score of 100-154 points corresponds to moderate psychoemotional stress, and a score of 155 points or above indicates maladaptation and psychological discomfort.

Personal and situational anxiety were assessed by the Spielberger Anxiety Scale, with scores of 20-34 points indicating low anxiety, 35-45 points indicating moderate anxiety, and scores above 45 points indicating high anxiety.

The degree of asthenia was assessed by the Minnesota Multiphasic Personality Inventory (MMPI), with scores below 50 points indicating the absence of asthenia, 51-75 points indicating minor asthenic manifestations, 76-100 points indicating a moderate asthenic state, and 101-120 points indicating pronounced asthenic syndrome.

The autonomic nervous system response to stressors was evaluated by measuring pulse rate and blood pressure, with reference to the height, weight, and age of the participant. A functional change index below 2.6 points indicates satisfactory adaptation; 2.6-3.0 points indicates strained adaptation mechanisms; 3.1-3.5 points indicates unsatisfactory adaptive capacity; and a value exceeding 3.5 points indicates adaptive failure.

Activation of stress-implementing systems was quantified by cortisol levels in blood and 24-hour urine.

The intensity of oxidative stress was evaluated by serum levels of diene conjugates (DC) and malondialdehyde (MDA), and the status of the antioxidant defence system was assessed by measuring the activities of catalase, glutathione S-transferase (GST), and superoxide dismutase (SOD). Biochemical analyses were performed on a Specol-11

ISSN 2226-1230 (PRINT) ISSN 2413-4260 (ONLINE)
KEY TITLE: NEONATOLOGÌÂ, HÌRURGÌÂ TA PERINATAL'NA MEDICINA (ONLINE)
ABBREVIATED KEY TITLE: NEONATOL. HÌR. PERINAT. MED. (ONLINE)

spectrophotometer (Germany). DC concentrations were determined by spectrophotometric analysis of the lipid extract, exploiting the ultraviolet absorbance of diene conjugates at 233 nm. MDA levels were quantified by measuring the absorbance of the 3-methyl-2-thiobarbituric acid–MDA complex at 532 nm in 10 mm cuvettes under acidic conditions and elevated temperature. Catalase activity was determined by monitoring the decrease in hydrogen peroxide concentration at 240 nm. GST activity was measured based on the absorbance of the complex formed between reduced glutathione and chlorodinitrobenzene at 340 nm. SOD activity was assessed by the rate of formazan formation in reactions with nitroblue tetrazolium at 560 nm.

The study was conducted in accordance with the principles of the World Medical Association Declaration of Helsinki on Ethical Principles for Medical Research Involving Human Subjects. Informed consent was obtained from all participants prior to enrolment. Ethical approval was granted by the Medical Ethics Committee of the State Institution «Institute of Pediatrics, Obstetrics, and Gynecology named after Academician O. M. Lukyanova of the National Academy of Medical Sciences of Ukraine» (Protocol No. 3, 07 June 2017; Protocol No. 3, 20 April 2023).

Statistical analysis was performed in Microsoft Excel (2016), with Fisher's angular transformation applied where appropriate. Differences between compared values were considered statistically significant at $p < 0.05$ (confidence level exceeding 95%).

The study was carried out under two institutional research projects: «To develop novel and refine existing technologies for the diagnosis, prevention, and treatment of premature pregnancy termination in women with pregnancy loss, examining the role of contemporary environmental exposures» (2018-2020, state registration No. 0118U000039), and «To develop diagnostic and therapeutic measures for the prevention of pregnancy loss in women in Ukraine during martial law» (2024-2026, state registration No. 0123U103153).

Results and discussion

The magnitude of the stress effect is determined by the duration of stressor exposure, the state of the autonomic nervous system, the degree of psychoemotional tension, and the extent of activation of stress-implementing systems. Inadequate adaptation of maternal physiology predisposes to pregnancy complications. Women in Group 1 had a history of 2 to 9 prior pregnancies; habitual miscarriage was documented in 35.8% of cases, with pregnancy loss occurring in the first trimester in 76.3% and in the second trimester in 7.9% of affected women. Preterm birth had been recorded in 22.0% of women in this group. Early preterm births resulted in stillbirth, whereas late preterm births resulted in live-born premature neonates requiring prolonged rehabilitation; among the latter, 5.6% were subsequently assigned disability status.

Women in the control group were not exposed to comparable stressors, and their perceived stress levels remained within physiological ranges.

Stress perception in Group 1 was elevated, with a mean PSS score of 39.8 ± 0.4 points, compared with 26.2 ± 0.3 points in the control group ($p < 0.05$). Psychoanalytic assessment identified two dominant psychotypes in Group 1: psychotype A – highly anxious women with neuropsychic lability (n = 54; 64.3%); and psychotype B – emotionally stable women with preserved adaptive capacity (n = 30; 35.7%). Notably, 90% of women with psychotype B belonged to subgroup 1a, whereas the majority of women in subgroups 1b and 1c were classified as psychotype A. A. Psychotype classification was based on assessment of anxiety level, perceived stress, psychoemotional stability, asthenic manifestations, and adaptive mechanisms (Table 1).

Table 1

Criteria for psychotype formation in pregnant women with habitual miscarriage

Criterion	Psychotype A	Psychotype B
Anxiety level	High anxiety; pronounced tendency toward worry and fears	Moderate or low anxiety; emotional control and positive thinking
Psychological stability	Emotional lability; mood fluctuations	Emotional stability; appropriate stress responses
Perceived stress level	High perceived stress, emotional distress and rapid cognitive overload	Moderate or low perceived stress
Asthenic symptoms	Pronounced asthenic symptoms; emotional exhaustion	Moderate asthenic symptoms; preserved energy and work capacity
Adaptive coping mechanisms	Reduced adaptive responses, negative affect and impaired mobilisation of internal resources	Adequate adaptive mechanisms; effective coping with stressful situations

Assessment of experienced stress levels, together with somatic, behavioural, and emotional indicators, revealed a state of disadaptation and psychological discomfort in pregnant women of Group 1 (Table 2). Prior experiences of reproductive loss were associated with greater psychological discomfort in women with psychotype A than in those with psychotype B. The threat of pregnancy loss induced pronounced anxiety and fear. Psychoemotional tension in women with psychotype B decreased toward the end of the second trimester, when the critical periods of reproductive risk had elapsed; however, psychological discomfort recurred after 36 weeks of gestation, driven by anxiety about the outcome of impending delivery.

Personal anxiety levels in women with pregnancy loss, stratified by psychotype, are presented in Table 3. Women with psychotype A demonstrated high personal anxiety, whereas those with psychotype B exhibited moderate anxiety levels throughout gestation

Table 2

Stress experience index according to the PSM-25 scale in pregnant women of Group 1, stratified by psychotype across gestational trimesters (M ± m, points)

Psychotype variants	n	Value of the indicator by gestational age (weeks)			
		before 12 weeks	13-24	25-36	37-40
A	54	159.1 ± 2.4	159.6 ± 2.8	160.4 ± 3.4	149.2 ± 3.1
B	30	156.2 ± 3.3	153.7 ± 3.1	132.8 ± 3.1*	146.2 ± 3.3

*Note. * Statistically significant difference relative to psychotype A, p < 0.05*
Scale interpretation:
below 100 points – psychological adaptation;
100-154 points – moderate psychoemotional stress;
155 points and above – maladaptation and psychological discomfort

Table 3

Personal anxiety index according to the Spielberger Anxiety Scale in pregnant women of Group 1, stratified by psychotype across gestational trimesters (M ± m, points)

Psychotype variants	n	Value of the indicator by gestational age (weeks)			
		before 12 weeks	13-24	25-36	37-40
A	54	48.4 ± 2.2	48.0 ± 1.8	46.4 ± 1.8	45.2 ± 1.8
B	30	40.2 ± 1.8*	38.4 ± 1.9*	34.2 ± 1.6*	36.2 ± 1.6*

*Note. * Statistically significant difference relative to psychotype A, p < 0.05*
Scale interpretation:
20-34 points – low anxiety;
35-45 points – moderate anxiety;
above 45 points – high anxiety

Pronounced asthenic manifestations were characteristic of women with psychotype A, whereas moderate asthenia predominated in those with psychotype B (Table 4). Accordingly, stress-protective therapy was indicated to a greater extent in women with psychotype A than in those with psychotype B.

Table 4

Asthenia index in pregnant women of Group 1, stratified by psychotype across gestational trimesters (M ± m, points)

Psychotype variants	n	Value of the indicator by gestational age (weeks)			
		before 12 weeks	13-24	25-36	37-40
A	54	109,8 ± 2,4	106,2 ± 3,4	104,8 ± 2,4	90,8 ± 3,1
B	30	83,9 ± 1,3*	81,1 ± 2,4*	77,2 ± 1,3*	76,5 ± 1,3*

*Note. * Statistically significant difference relative to psychotype A, p < 0.05*
Scale interpretation:
51-75 points – mild asthenia;
76-100 points – moderate asthenia;
101-120 points – severe asthenia

The pathogenesis of obstetric complications resides in the desynchronisation of adaptive reactions within the functional mother–placenta–fetus system [6, 17, 18]. Based on the calculated functional change index, tension of adaptation mechanisms was observed in 55.3% of women in Group 1, whereas adaptive failure was recorded in 7.9%. In the control group, autonomic function was assessed as satisfactory in 76.5% of women, with the remainder exhibiting moderate tension of adaptive mechanisms.

Prolonged activation of stress-implementing systems in Group 1 was evidenced by elevated blood cortisol concentrations of 345.8 ± 6.1 nmol/L and accelerated urinary cortisol excretion of 283.7 ± 2.7 nmol/day, compared with control values of 284.4 ± 4.3 nmol/L and 136.4 ± 9.04 nmol/day, respectively ($p < 0.05$). Cortisol is a principal mediator of the stress response: glucocorticoids redirect metabolism toward increased energy expenditure, alter the response properties of physiological systems, and facilitate cognitive restructuring associated with adaptation to significant events. Chronically elevated cortisol concentrations are associated with an increased risk of various pathological conditions [23].

Habitual miscarriage thus constitutes a powerful stressor. The inability to sustain a pregnancy generates fear of subsequent conception attempts, and the cumulative negative experience of reproductive loss gives rise to a pathological psychological profile. The psychological component of recurrent pregnancy loss comprises elevated personal stress perception, anxiety, and asthenia, the combined effect of which exhausts adaptive mechanisms and perpetuates a cycle of pregnancy loss. The statistically significant differences identified within Group 1 according to psychotype confirm the contribution of psychological factors to the development of pregnancy loss.

Placental dysfunction, arising from anatomical damage and aberrant angiogenesis, represents the most frequent cause of reproductive losses. In Group 1, placental dysfunction developed as a consequence of internal

radiocesium exposure, which induced oxidative stress, with ^{137}Cs activity in placental tissue being a critical determinant of outcome. Reactive oxygen species in the intervillous space mediate damage to the chorionic tree, haemorrhages, and infarctions. Peroxide homeostasis is therefore a critical determinant of successful pregnancy outcome. The balance between pro-oxidants and antioxidants governs the body's resistance and tolerance to external influences. Elevated malondialdehyde (MDA) and diene conjugate (DC) levels exceeding the physiological capacity of the antioxidant system (AOS) are indicative of oxidative stress. Both intermediate and end products of lipid peroxidation (LPO) exert cytotoxic and mutagenic effects [18, 24-28].

From the onset of pregnancy, elevated blood levels of DC, lipid hydroperoxides, MDA, and reactive oxygen species were detected in Group 1. Oxidation of arachidonic acid resulted in the formation of primary LPO products – diene conjugates – which are toxic to lipoproteins, proteins, nucleic acids, and enzymes. DC levels in the first trimester exceeded control values by 2.25-fold, and by 1.25-fold and 1.50-fold in the second and third trimesters, respectively ($p < 0.01$) (Table 5), indicating sustained activation of free radical reactions throughout gestation.

Table 5

LPO parameters in the blood of examined women across gestational trimesters (M ± m)

Groups	n	Trimester	Diene conjugates, U/mL	Lipid hydroperoxides, μmol / ml	Malonic dialdehyde, μmol / ml	O_2, OH, H_2O_2
Group 1	70	I	62.8 ± 4.1*	2.13 ± 0.06*	149.6 ± 3.8*	63.8 ± 3.6*
		II	36.8 ± 3.2*	2.12 ± 0.07*	144.4 ± 2.6*	54.3 ± 4.3*
		III	46.8 ± 2.1*	3.34 ± 1.1*	152.2 ± 3.1*	58.6 ± 2.5*
Group 2 (Control)	30	I	27.9 ± 1.2	1.67 ± 0.04	128.4 ± 3.7	35.3 ± 2.8
		II	29.5 ± 1.2	1.77 ± 0.06	136.4 ± 2.9	36.4 ± 1.7
		III	31.1 ± 2.9	1.99 ± 0.14	142.6 ± 3.6	38.7 ± 1.9

*Note. * Statistically significant difference relative to the control group, p < 0.01*

The end products of LPO influence the synthesis of prostaglandins, thromboxanes, leukotrienes, glucocorticoids, and progesterone [25, 28], with MDA representing the most clinically significant among them. First-trimester MDA concentrations are predictive of pregnancy outcome: elevated MDA in early gestation increases the likelihood of placental dysfunction, preterm birth, and antenatal fetal loss. In subgroup 1a, first-trimester blood MDA levels exceeded baseline by 8.7% – an increment regarded as physiologically acceptable, consistent with the natural metabolic adaptation to pregnancy and the attendant increase in oxidative compound production; all pregnancies in this subgroup culminated in term delivery. A first-trimester serum MDA elevation of 17.4% relative to baseline was associated with an increased risk of late preterm birth, whereas a 23.4% elevation served as a predictor of early preterm birth (Figure 1). These findings confirm the prognostic value of dynamic MDA monitoring from early gestation and substantiate its application to risk stratification and individualised pregnancy management aimed at reducing the incidence of preterm delivery.

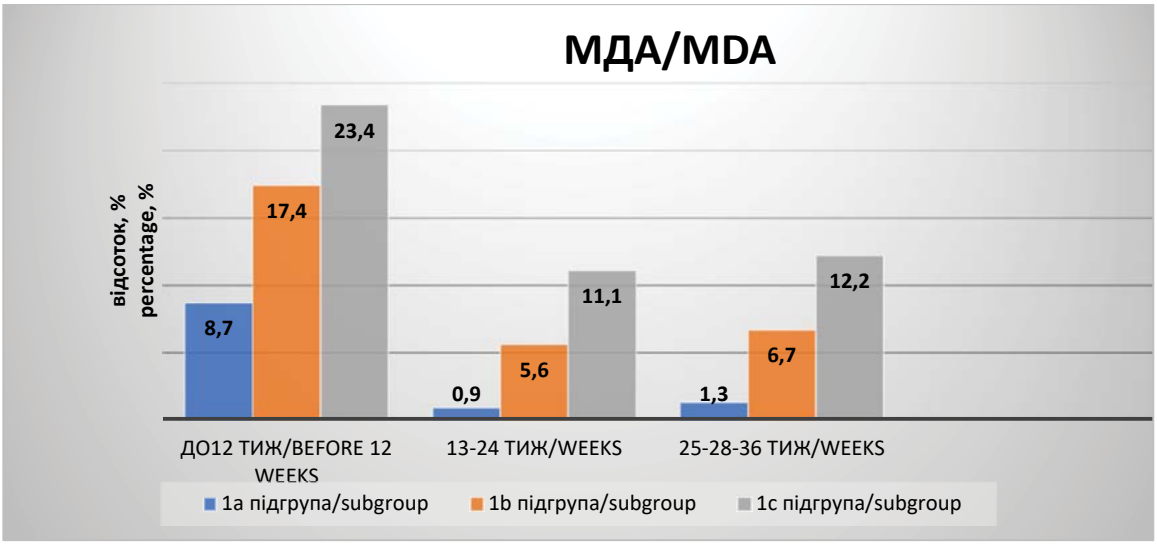

Figure 1. Percentage increase in blood MDA levels in pregnant women of Group 1 relative to the control group

Free radical neutralisation is effected by the antioxidant system (AOS) through four sequential stages of antioxidant protection. At the first stage of detoxification, toxic substances are partially neutralised by antioxidant enzymes: superoxide dismutase (SOD) converts superoxide radicals into hydrogen peroxide, catalase degrades hydrogen peroxide into water and oxygen, and ceruloplasmin attenuates free radical formation. The resulting hydrophilic metabolites subsequently undergo conjugation with glutathione, after which the conjugated derivatives are

excreted. The final stage comprises reparative regeneration of damaged molecules. Glutathione is regarded as a key antioxidant, supporting immune responses, metabolism, micronutrient homeostasis, proliferation, differentiation, and apoptosis [24, 27].

Women in Group 1 exhibited reduced levels of glutathione, SOD, and catalase (Table 6). Glutathione S-transferase activity was approximately half that recorded in the control group (Table 7), indicating suppression of detoxification mechanisms.

Table 6

AOS parameters in the blood of examined women across gestational trimesters (M ± m)

Groups	n	Trimester	Catalase, μmol H_2O_2 / ml	SOD, arb.u./mL/min	Reduced glutathione, μmol / ml
Group 1	70	I	25.7 ± 1.5*	47.8 ± 2.7	2.78 ± 0.02*
		II	38.6 ± 2.4	52.3 ± 2.8*	3.34 ± 0.06*
		III	32.5 ± 2.1*	49.8 ± 2.3*	3.02 ± 0.04*
Group 2 (Control)	30	I	38.5 ± 2.2	54.8 ± 3.6	3.58 ± 0.03
		II	40.6 ± 1.8	61.2 ± 1.4	3.62 ± 0.02
		III	44.8 ± 1.9	62.4 ± 2.6	3.74 ± 0.03

*Note. * Statistically significant difference relative to the control group, p < 0.01*

Increased generation of LPO products with impaired neutralisation and utilisation at the onset of pregnancy constitutes the pathophysiological basis for placental dysfunction. A first-trimester reduction in blood SOD activity of 13.0% served as a predictor of preterm birth in subgroup 1b. Decompensation of adaptive mechanisms, associated with early preterm birth and antenatal fetal death, was indicated by an 18.2% reduction in first-trimester blood SOD activity in subgroup 1c. SOD activity in subgroup 1a was maintained at levels sufficient to sustain adaptive and compensatory responses throughout gestation (Figure 2).

Table 7

Glutathione S-transferase activity in examined pregnant women (M ± m)

Groups and subgroups	n	GST activity, CDNB /mg protein/min
1a	30	1.99 ± 0.14*
1b	20	1.83 ± 0.18*
1c	20	1.82 ± 0.16*
Control	30	3.86 ± 0.23

*Note. * Statistically significant difference relative to the control group, p < 0.05*

The compensatory capacity of the mother–placenta–fetus system in these women was closely associated with blood SOD concentrations. Reduced SOD activity in the first trimester, accompanied by a 10% elevation in MDA relative to the control group, represented a prognostically unfavourable indicator for pregnancy outcome (Figures 1 and 2).

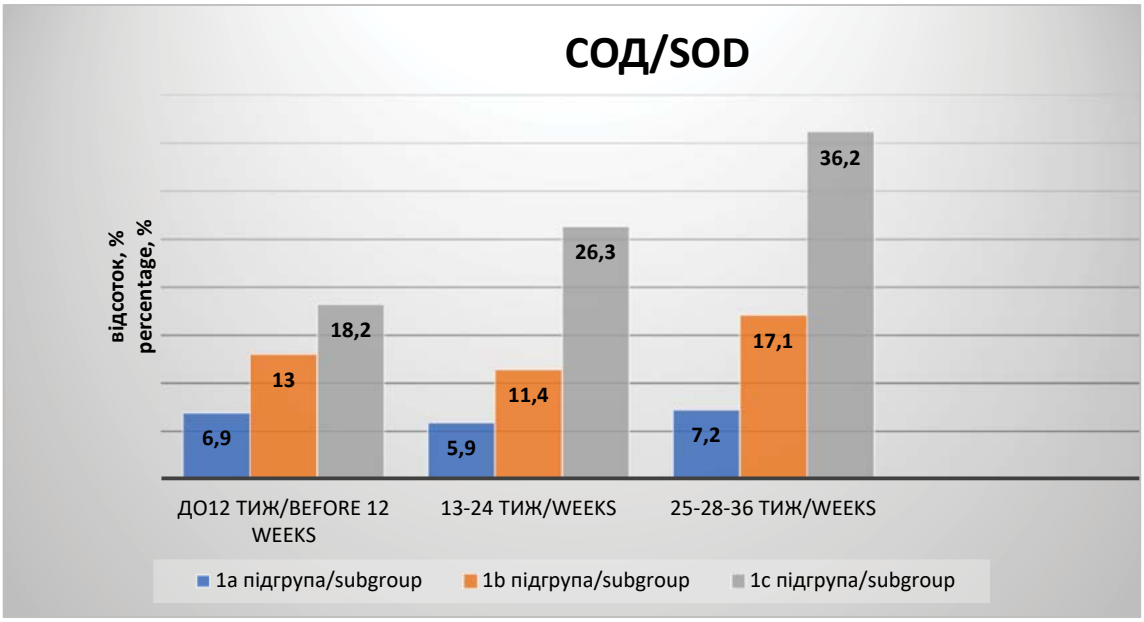

Figure 2. Percentage reduction in blood SOD activity in pregnant women of Group 1 relative to the control group

SOD and catalase activities are interrelated. Catalase protects cells from the damaging effects of hydrogen peroxide by degrading it into water and oxygen, and its activity reflects cellular oxygen demand [19, 24]. Catalase activity in subgroups 1b and 1c was reduced by 39.2% and 44.9%, respectively, in the first trimester (Figure 3). Second-trimester catalase activity dynamics indicated the development of adaptive reactions during this period; however, after 25 weeks of gestation, catalase and SOD activity declined in subgroups 1b and 1c, reflecting depletion of antioxidant defence mechanisms (Table 5, Figure 3).

Impairment of LPO regulation and antioxidant defence inevitably predisposes to hypoxia in organs and tissues. Oxidative stress activates the transcription of factors regulating inflammatory and immune responses, and insufficient homeostatic support by regulatory systems contributes to endothelial dysfunction, systemic inflammation, and mono- or multi-organ failure [8, 11, 15, 28]. Prolonged ^{137}Cs exposure depletes antioxidant defences, and placental ^{137}Cs activity exceeding 10.4 Bq/kg is considered critical for pregnancy outcome.

Serial determination of DC, MDA, SOD, and catalase concentrations in maternal blood represents a predictive approach to assessing oxidative stress intensity and stratifying pregnancy risk. Expansion of women's adaptive potential through strengthening psychoemotional resilience and fostering a positive orientation toward pregnancy and motherhood constitutes a promising strategy for the prevention of reproductive losses.

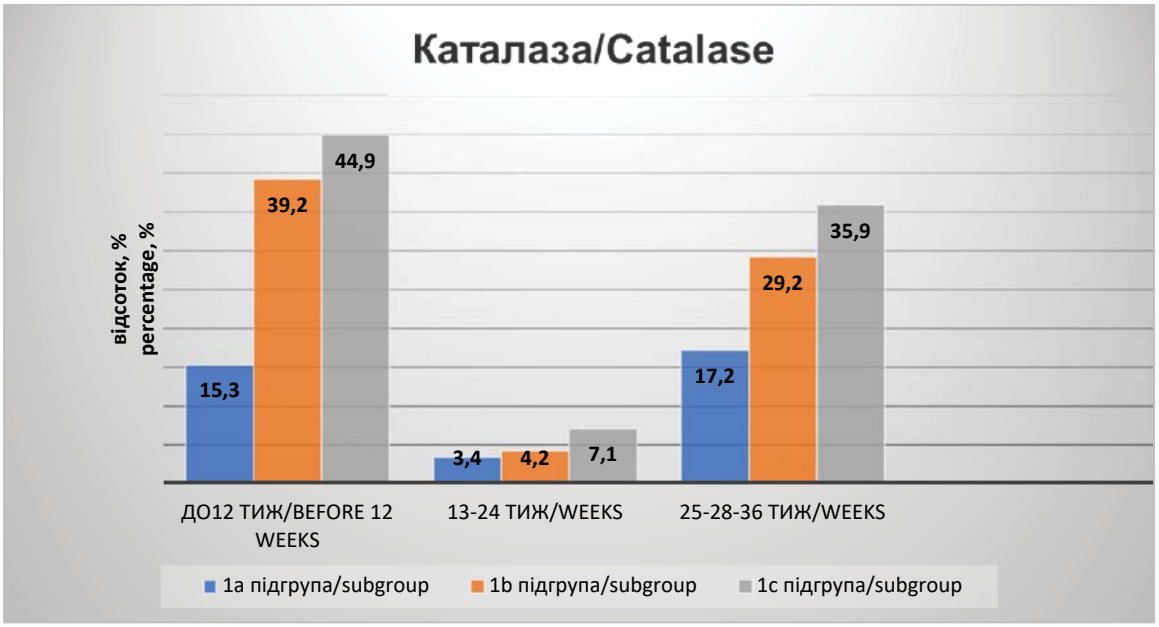

Figure 3. Percentage reduction in blood catalase activity in pregnant women of Group 1 relative to the control group

Conclusions

1. The psychological component of pregnancy loss comprises elevated personal stress perception, anxiety, and asthenia.

2. Two dominant psychotypes of psychosocial adaptation disorder have been identified in women with pregnancy loss: psychotype A – high anxiety with low neuropsychic resistance (64.3%); psychotype B – emotional stability with preserved adaptive capacity (35.7%). Premature termination of the current pregnancy occurred predominantly in women with psychotype A.

3. ^{137}Cs at varying activity levels is detectable in the placentas of Ukrainian women 39 years after the Chornobyl accident. Prolonged low-intensity radiation exposure disrupts the histoarchitecture and functional capacity of the placenta, with the severity of consequences determined by ^{137}Cs activity and the adequacy of antioxidant protection. A ^{137}Cs activity exceeding 10.4 Bq/kg is critical for pregnancy outcome.

4. Serial determination of DC, MDA, SOD, and catalase concentrations in maternal blood enables assessment of oxidative stress intensity and stratification of pregnancy risk. Increased generation of LPO products at the onset of pregnancy, combined with impaired neutralisation and utilisation, constitutes the pathophysiological basis for placental dysfunction, the proximate cause of reproductive losses being placental insufficiency.

Contribution of authors. A. Zhyvetska-Denysova – study concept and design, data collection, data analysis and interpretation, manuscript writing; I. Vorobiova – study concept and design, editing, and final approval of the manuscript; L. Lozova – data collection; O. Shamaieva – data collection; N. Rudakova – data collection.

Conflicts of interest: the authors declare no conflicts of interest.

Financing. The study was funded by state resources under two institutional research projects: «To develop novel and refine existing technologies for the diagnosis, prevention, and treatment of premature pregnancy termination in women with pregnancy loss, examining the role of contemporary environmental exposures» (state

registration No. 0118U000039, 2018-2020) and «To develop diagnostic and therapeutic measures for the prevention of pregnancy loss in women in Ukraine during martial law» (state registration No. 0123U103153, 2024-2026).

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РОЛЬ СТРЕСУ В ПАТОГЕНЕЗІ НЕВИНОШУВАННЯ ВАГІТНОСТІ: ДВІ СТОРОНИ ОДНІЄЇ ПРОБЛЕМИ

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Резюме.

Вивчення впливу стресових факторів на перебіг вагітності є актуальним питанням у сучасній перинатології. У статті висвітлено роль стресових реакцій у жінок, які зазнали впливу ^{137}Cs на рівні плаценти, та психоемоційних стресорів у патогенезі невиношування вагітності, як двох аспектів однієї й тієї ж проблеми. Стаття базується на результатах власних минулих досліджень особливостей морфологічного та імуногістохімічного пошкодження плаценти внаслідок інкорпорації ^{137}Cs, а також психологічних компонентів невиношування вагітності.

Мета дослідження. Визначити маркери невиношування вагітності в умовах хронічного стресу.

Матеріали та методи. У дослідженні взяли участь жінки з невиношуванням в анамнезі та ознаками переривання поточної вагітності (перша група), а також вагітні з неускладненою вагітністю та анамнезом (друга група, контрольна). За допомогою γ-спектрометрії в плацентах обох груп спостерігалося накопичення ^{137}Cs з різною активністю. Результатом його впливу є оксидативний стрес. Силу стресової реакції оцінювали за рівнем дієнових кон'югатів (ДК) і малонового діальдегіду (МДА) у крові. Антиоксидантну активність визначали за допомогою показників каталази, глутатіон-S-трансфераза та супероксиддисмутази (СОД). Скринінгова діагностика стресу включала визначення особистісного рівня сприйняття стресу, психоемоційної напруги, тривожності та астенії. Дослідження проводилося відповідно до принципів Гельсінської декларації Всесвітньої медичної асоціації «Етичні принципи медичних досліджень за участю людей». Від вагітних жінок отримана інформована згода на участь у дослідженні. Дозвіл на проведення дослідження було отримано від Комітету з медичної етики ДУ «Інститут педіатрії, акушерства та гінекології імені академіка О. М. Лук'янової Національної академії медичних наук України» (Протокол № 3 від 07.06.2017 р; Протокол № 3 від 20.04.2023 р.). Статистичний аналіз проводили за допомогою програми Microsoft Excel з використанням кутового перетворення Фішера. Різницю між порівняльними значеннями вважали вірогідною при $p < 0,05$ (індекс вірогідності більше 95%). Дослідження проводилося в рамках дослідницьких проектів: «Розробити новітні та вдосконалити існуючи технології діагностики, профілактики та лікування передчасного переривання вагітності у жінок з невиношуванням з урахуванням впливу екологічних факторів в умовах сьогодення» (номер державної реєстрації 0118U000039, термін виконання 2018-2020 рр.), а також НДР «Розробити діагностичні та лікувальні заходи щодо попередження розвитку невиношування вагітності у жінок України в умовах воєнного стану» (номер державної реєстрації 0123U103153, термін виконання 2024-2026 рр.).

Результати. У жінок із невиношуванням вагітності виявлені розлади психосоціальної адаптації: високий рівень особистісного сприйняття стресу, тривоги і астенії. Руйнівний вплив ^{137}Cs пов'язаний з оксидативним стресом та розвитком плацентарної дисфункції. Екстремальні наслідки залежать від активності ^{137}Cs та адекватності антиоксидантного захисту. Питома маса ^{137}Cs вище 10,4 Бк/кг є критичною для вагітності. Збільшення ДК у I триместрі в 2,25 рази порівняно з контролем свідчить про активацію вільнорадикальних реакцій. Прогностично несприятливим є дефіцит СОД та надлишок МДА в I триместрі на 10%. Підвищена генерація продуктів перекисного окиснення ліпідів з порушенням нейтралізації та утилізації на початку вагітності закладає основу плацентарної дисфункції. Збільшення МДА у I триместрі на 17,4% відносно контролю є тригером пізніх передчасних пологів. Ризик передчасних пологів та внутрішньоутробної загибелі плода зростає, коли рівень МДА в крові вагітних жінок протягом I триместру на 23,4% вищий, ніж у контрольній групі. Одночасне зниження активності СОД на 18,2% проти контролю свідчить про порушення антиоксидантного захисту та ранню декомпенсацію адаптивних механізмів.

Висновки. Оксидативний і емоційний стрес відіграють вирішальну роль у патогенезі невиношування вагітності. Декорпорація радіонуклідів і активація адаптаційних процесів у плаценті є перспективним щодо зменшення впливу внутрішнього опромінення. Не менш важливим для запобігання втратам вагітності є підвищення адаптивного потенціалу вагітних жінок шляхом покращення психоемоційної стабільності й формування позитивної орієнтації на вагітність та материнство.

Ключові слова: звичне невиношування вагітності; плацента; ^{137}Cs; стрес; перекисний гемостаз.

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Received: September 21, 2026
Accepted: May 28, 2026
Published: June 29, 2026