



ABSTRACT

Svitlana Herasymenko

*Department of Obstetrics, Gynecology,
and Family Planning, Sumy State
University, Sumy, Ukraine*

Iryna Nikitina

<https://orcid.org/0000-0001-6595-2502>
*Department of Obstetrics, Gynecology,
and Family Planning, Sumy State
University, Sumy, Ukraine*

Svetlana Smiian

<https://orcid.org/0000-0002-7679-2302>
*Department of Obstetrics, Gynecology,
and Family Planning, Sumy State
University, Sumy, Ukraine*

CLINICAL PATHOGENETIC SUBSTANTIATION OF THE REGENERATIVE TREATMENT OF PARTURIENTS WHO SUFFERED FROM OBSTETRICAL HAEMORRHAGES

The publication is devoted to an urgent problem of modern obstetrics – the study of pathophysiological changes in the organism of parturients after obstetrical haemorrhages, improvement of restorative treatment, as well as reduction of complications in the puerperium and prevention of their occurrence.

The aim of the study: to increase the effectiveness of restorative treatment of women in labor who suffered obstetric bleeding by studying the features of the clinical course, mechanisms of pathogenetic disorders, and their correction using ozone therapy.

Materials and methods. A comprehensive clinical and laboratory examination of 150 women in labor was carried out, including 120 women (the main group) who suffered bleeding during childbirth and the early postpartum period. The control group consisted of 30 women with the physiological course of labor, childbirth and the early postpartum period. The state of lipid peroxidation (LPO) in parturient women was evaluated by the content of primary lipid products in the blood plasma – diene conjugates (DK) according to the method of B.V. Gavrilov (1983) and secondary molecular products – malondialdehyde (MDA) using the reaction with 2-thiobarbituric acid. The activity of the enzymatic link of the antioxidant system (AOS) was determined by the content of catalase in peripheral blood erythrocytes using the substrate hydrogen peroxide and glutathione peroxidase (GPO) using the P-phenylenediamine substrate. The Spielberg–Hanin scale of state and trait anxiety was used to study the state of the psycho-emotional sphere in parturient women. Morphological examination of preparations of placentas and surgically removed uteri was carried out with staining of sections with hematoxylin and eosin, picrofuchsin according to Van Gieson.

Results. Basic etiopathogenetic factors of the development of obstetric haemorrhages were examined, changes in the psychoemotional status of the patients were detected, haematological and metabolic indices, parameters of oxidation-antioxidation homeostasis and endogenic intoxication were studied, as well as

morphofunctional disorders in placentas and uteruses. The efficacy of the restorative treatment of the parturients, who had moderate and massive haemorrhages during delivery, with the use of medical ozone in combined treatment versus traditional methods of treatment was studied.

Conclusion. From the first day of the puerperium, free-radical lipid peroxidation increases, the activity of the enzymatic and non-enzymatic links of the antioxidant system increases, endogenous intoxication increases, and lactate and pyruvate levels increase. In the placentas of women in labor who suffered bleeding during labor, there is a violation of the synthesis of type IV collagen in the basal membranes of vessels and the phenomenon of endothelial dysfunction in the form of increased expression of endothelin by the endotheliocytes of the vessels of the decidual membrane ($53.8 \pm 2.9 \mu\text{a}$) and the villous chorion ($46.0 \pm 2.6 \mu\text{a}$). In the uterus, an increase in the expression of endothelin by endotheliocytes of the spiral arteries of the uterus ($57.8 \pm 8.56 \mu\text{a}$) was detected, in combination with a violation of the synthesis of stromal collagen of type I and III and type IV in the basal membranes of vessels.

Keywords: obstetrical haemorrhages, puerperium, restorative treatment, ozone therapy.

Corresponding author: Iryna Nikitina, Department of Obstetrics, Gynecology, and Family Planning, Sumy State University, Sumy, Ukraine
e-mail: nikitina1med@gmail.com

РЕЗЮМЕ

Світлана Герасименко

Кафедра акушерства, гінекології та планування сім'ї, Сумський державний університет, м. Суми, Україна

Ірина Нікітіна

<https://orcid.org/0000-0001-6595-2502>

Кафедра акушерства, гінекології та планування сім'ї, Сумський державний університет, м. Суми, Україна

Світлана Сміян

<https://orcid.org/0000-0002-7679-2302>

Кафедра акушерства, гінекології та планування сім'ї, Сумський державний університет, м. Суми, Україна

КЛІНІКО-ПАТОГЕНЕТИЧНЕ ОБГРУНТУВАННЯ ВІДНОВЛЮВАЛЬНОГО ЛІКУВАННЯ ПОРОДІЛЬ, ЩО ПЕРЕНЕСЛИ АКУШЕРСЬКІ КРОВОТЕЧІ

Публікація присвячена актуальній проблемі сучасного акушерства – вивченню патофізіологічних змін в організмі породіль після акушерських кровотеч, удосконаленню відновного лікування, а також зменшенню ускладнень у післяпологовому періоді та попередженню їх виникнення.

Мета дослідження: полягала в підвищенні ефективності відновлювального лікування породіль, які перенесли акушерські кровотечі, шляхом вивчення особливостей клінічного перебігу, механізмів патогенетичних порушень та їх корекції за допомогою озонотерапії.

Матеріали і методи. Проведено комплексне клініко-лабораторне обстеження 150 породіль, включно 120 жінок (основна група), які мали кровотечі в пологах та ранньому післяпологовому періоді. Контрольну групу склали 30 породіль з фізіологічним перебігом вагітності, пологів та післяпологового періоду. Стан перекисного окислення ліпідів (ПОЛ) у породіль оцінювали за вмістом у плазмі крові первинних продуктів ПОЛ – дієнових кон'югат (ДК) за методикою Б. В. Гаврилова (1983) та вторинних молекулярних продуктів – малонового діальдегіду (МДА) за допомогою реакції з 2-тіобарбітуровою кислотою. Активність ферментативної ланки антиоксидантної системи (АОС) визначали за вмістом каталази в еритроцитах периферичної

крові з використанням субстрату перекису водню та глутатіонпероксидази (ГПО) з використанням субстрату Ф-фенілендіаміну. Для вивчення стану психоемоційної сфери у породіль була використана шкала особистісно-реактивної тривожності Спілберга-Ханіна. Проводили морфологічне дослідження препаратів плаценти та хірургічно видалених маток з фарбуванням зрізів гематоксиліном та еозином, пікрофуксином за Ван Гізоном.

Результати. Вивчено основні етіопатогенетичні фактори розвитку акушерських кровотеч, виявлено зміни психоемоційного статусу хворих, досліджено гематологічні та метаболічні показники, показники окислювально-антиоксидативного гомеостазу та ендогенної інтоксикації, а також морфофункціональні порушення в плацентах і матці. Вивчено ефективність відновного лікування породіль, які мали помірні та масивні кровотечі під час пологів, із застосуванням медичного озону в комбінованому лікуванні порівняно з традиційними методами лікування.

Висновки. З першої доби післяпологового періоду посилюється вільнорадикальне перекисне окислення ліпідів, підвищується активність ферментативної та неферментативної ланок антиоксидантної системи, посилюється ендогенна інтоксикація, підвищується рівень лактату та пірувату. У плацентах породіль, що перенесли кровотечі під час пологів, спостерігаються порушення синтезу колагену IV типу в базальних мембранах судин і явища ендотеліальної дисфункції у вигляді підвищеної експресії ендотеліну ендотеліоцитами судин децидуальної оболонки ($53,8 \pm 2,9$ мка) і ворсинчастого хоріона ($46,0 \pm 2,6$ мка). У матці виявляється посилення експресії ендотеліну ендотеліоцитами спіральних артерій матки ($57,8 \pm 8,56$ мка), у поєднанні з порушенням синтезу колагену строми I і III типу та IV типу в базальних мембранах судин.

Ключові слова: акушерські кровотечі, післяпологовий період, відновлювальне лікування, озонотерапія.

Автор, відповідальний за листування: Ірина Нікітіна, кафедра акушерства, гінекології та планування сім'ї, Сумський державний університет, м. Суми, Україна
e-mail: nikitina1med@gmail.com

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INTRODUCTION / ВСТУП

Obstetric hemorrhages, which constitute an important medical and social problem, for decades continue to be the main cause of maternal mortality, occupying 25–30% of its structure. Despite the improvement of medical and preventive measures, the frequency of childbirth complicated by bleeding in Ukraine ranges from 4.5% to 11%. Obstetric

bleeding causes maternal disability and disrupts the reproductive and somatic health of women. This problem becomes especially important in connection with the growth of abdominal childbirth, the increase in the number of operative interventions during childbirth, in parallel with the decrease in the population health index, the decrease in the total number of births, and the increase in the level of

obstetric and gynecological diseases, extragenital pathology against the background of imperfect material and technical provision of maternity facilities [1].

Obstetric bleeding is an intense stress factor that leads to disturbances in macro- and microcirculation, acid-base status, water-electrolyte balance, hemostatic potential, redox, and enzymatic processes; they are accompanied by a decrease in the oxygen supply of organs and tissues, the development of multiple organ failure, metabolic disorders (the appearance of endotoxins in the bloodstream, the development of lactic acidosis, activation of lipid peroxidation, suppression of the activity of the antioxidant system) and homeostasis disorders in women in the postpartum period [2, 3].

Massive and moderate blood loss during childbirth causes a violation of adaptation processes in the body of the woman in labor, is accompanied by a decrease in protective capabilities and leads to the occurrence of complications, and in the future, to the progression of early and long-term consequences [4, 5].

There is no doubt about the connection between homeostasis disturbances during pathological blood loss and, as a result, the occurrence of postpartum purulent-inflammatory diseases, asthenovegetative and neuroendocrine syndromes, thrombotic complications, hormonal imbalance, hypogalactia, posthemorrhagic anemia [6, 7].

Taking into account the above, there is a need to implement modern, effective economic methods of restorative treatment aimed at various links of pathogenetic disorders due to blood loss. In this regard, ozone therapy is particularly promising, which provides a multi-component targeted effect, helps correct homeostasis disturbances, has pronounced antihypoxic, anti-inflammatory, immunomodulatory, detoxification, and antimicrobial effects, and regulates the body's pro- and antioxidant systems [8].

The aim of the study: to increase the effectiveness of restorative treatment of women in labor who suffered obstetric bleeding by studying the features of the clinical course, mechanisms of pathogenetic disorders and their correction using ozone therapy.

MATERIALS AND METHODS

A comprehensive clinical and laboratory examination of 150 women in labor was conducted, including 120 women (the main group) who suffered bleeding during childbirth and the early postpartum period. The control group consisted of 30 women in

labor with the physiological course of pregnancy, childbirth, and the postpartum period.

All 120 parturients of the main group were divided into two groups depending on the method of restorative treatment used. The first group consisted of 40 women in labor who experienced obstetric bleeding, in whom the tactics of managing the postpartum period were traditional. The second group consisted of 80 women in labor who suffered obstetric bleeding and received medical ozone as part of complex restorative treatment in the postpartum period.

Examination of women and treatment of obstetric bleeding were carried out in accordance with the normative documents regulated by the order of the Ministry of Health of Ukraine No. 205 of 24.03.2014.

Restorative treatment of women who suffered obstetric hemorrhages using ozone therapy was carried out according to the methodological recommendations "Application of ozone therapy in obstetrics and gynecology", approved by the Ministry of Health of Ukraine, the Ukrainian Center for Scientific and Medical Information and Patent and Licensing Work (Kyiv, 2005).

After 1–2 days of the postpartum period, after stopping the bleeding, adequate compensation of the lost blood volume and stabilization of hemodynamics, parturient women received medical ozone as part of complex treatment. To obtain an ozonated physiological solution, the ozone-oxygen gas mixture produced with the help of the Ozone UM-80 medical ozonator (certificate of state registration No. 2578 dated 03.26.2004) was passed through a 200 ml bottle with a sterile 0.9% sodium chloride solution for 10–15 minutes until full saturation within the set concentration, registered by the ozone concentration meter automatically. The supply rate of the ozone-oxygen mixture in the device was fixed at 0.5 l/min, with an ozone concentration in the gas phase of 0.4 mg/l. Considering the comparative instability of ozone in an aqueous medium, infusions of ozonized sodium chloride solution were performed immediately after the end of bubbling. The ozonated physiological solution was injected intravenously into the elbow vein at a rate of 10 ml/min, one time a day for 5 days.

The state of lipid peroxidation (LPO) in the family was assessed by the content of primary LPO products – active conjugates (DC) in the blood plasma according to the method of B.V. Gavrilov (1983) and secondary molecular products –

malondialdehyde (MDA) using the reaction with 2-thiobarbituric acid.

The activity of the enzymatic link of the antioxidant system (AOS) was determined by the content of catalase in peripheral blood erythrocytes using the substrate hydrogen peroxide and glutathione peroxidase (GPO) using the substrate P-phenylenediamine. The non-enzymatic link of AOS, represented by SH groups of thiol compounds, was calculated in the blood plasma of parturient women using Ellman's reagent.

The Spielberg–Hanin scale of personal and reactive anxiety was used to study the state of the psycho-emotional sphere in parturient women.

Morphological examination of preparations of placentas and surgically removed uteri was performed with staining of sections with hematoxylin and eosin, picrofuchsin according to Van Gieson, according to Malory, mucopolysaccharides were identified by the PAS reaction with amylase control, RNA was determined by the Brachet reaction with crystal ribonuclease control, DNA was determined by the Felgen–Rossenbeck reaction with amylase control. Immunohistochemical study of placentas and uteri was performed on paraffin sections by the indirect Kuhns method according to the method of M. Brosman (1979).

Collagen types I, III, and IV and endothelin were determined using the appropriate monoclonal antibodies (“Novocastra Laboratories Ltd”, “IMTEK Ltd”, Russia). The preparations were studied using a luminescent microscope ML-2, the intensity of the glow of endothelin was determined on a microfluorimeter with FEU-35. Morphological examination of uterine and placenta preparations was carried out using an Olympus BX-41 microscope with Olympus DP-Soft software.

The results of all conducted studies were subjected to statistical processing using the standard Microsoft Excel 2000 statistical analysis package using parametric analysis methods. The probability of differences in the compared groups was determined by Student's tables. In the work, the results were considered reliable at $p < 0.05$, and $p < 0.001$.

RESULTS

In terms of age, anthropometric indicators, place of residence, pregnancy, and childbirth parity, the compared groups of women were homogeneous. When analyzing the age structure of women who experienced obstetric bleeding, the high specific weight of young first-time mothers (13.75% in the

group with moderate blood loss) and old (50% in the group with massive blood loss) women drew attention. When examining the gynecological history and reproductive function, it was established that patients with bleeding during childbirth had significant gynecological morbidity: menstrual dysfunction (in 27.5% of women) caused by a failure in the mechanisms of neuroendocrine regulation; inflammatory diseases (in 16.67%), causing dystrophic, scarring and inflammatory changes in the myometrium. Also, in this group, a large number of surgical interventions causing disruption of the endometrial structure and damage to the neuromuscular apparatus of the uterus (involuntary and artificial abortions (in 10.83% and 27.5% of patients)), scraping of the uterine cavity (in 10%), diathermocoagulation of the cervix (in 10%).

Women who experienced obstetric bleeding more often had a complicated course of pregnancy, represented by anemia (in 69.17% of patients), preeclampsia (26.67%), fetoplacental insufficiency (23.33%), immunologic havoc (23.33%), threat abortion (19.17%), gestosis of the first half of pregnancy (15.83%), edema of pregnant women (15%) and pathological weight gain (13.33%).

The average volume of blood loss in the group of women with massive blood loss was 1835 ± 253 ml, and in the group of women with moderate blood loss, the average volume of blood loss was 880 ± 258 ml, respectively. In women of the control group, blood loss during childbirth was physiological; the average blood loss was 192 ± 14 ml.

When analyzing the hemogram of women in the studied groups who suffered bleeding from the first day after childbirth, a significant decrease in hemoglobin, hematocrit, the number of erythrocytes and platelets, a significant increase in the number of leukocytes and ESR, changes in the composition of the leukocyte formula of the blood: an increase in the number of rods and segmentonuclear leukocytes and a decrease in the number of lymphocytes and monocytes. The use of ozone therapy in women who suffered obstetric bleeding contributed to a more adequate correction of hemogram indicators, in contrast to women in labor who received only conventional treatment.

Analyzing the changes in LPO, it was established from the first day of the puerperium that there was a significant increase in the level of DC and MDA, both in parturients of groups 1 and 2 in relation to the control group. Under the influence of ozone therapy, the primary products of LPO (DC) on the 7th day after childbirth decreased slightly, while in the group

with generally accepted treatment, they continued to increase. The activation of LPO in women who suffered bleeding during childbirth was compensated by adequate strengthening of AOS protection after childbirth, which allowed to inhibit LPO in biomembranes and reduce peroxidation processes in tissues.

Therefore, ozone therapy had a positive effect on oxidant-antioxidant homeostasis as a result of an increase from the 1st to the 4th day after childbirth and a further decrease from the 4th to the 7th day of the puerperium of LPO products against the background of adequate stimulation of the AOS from the 1st to the 7th day after labor.

During the morphological and immunohistochemical examination, pronounced dyscirculatory, dystrophic, involutive, and sclerotic processes against the background of moderately expressed compensatory and adaptive changes were revealed in the placentas of mothers who had undergone bleeding. Sclerotic processes in the villi were caused by increased synthesis of interstitial collagen types I and III in the stroma and collagen type IV, both in the syncytial basement membranes and in the walls of the vessels of the villi.

It was determined that the placentas of women in labor with clinical manifestations of bleeding had

signs of delayed maturation of the villous chorion, as well as the phenomenon of endothelial dysfunction in the form of increased expression of endothelin by the endotheliocytes of the vessels of the decidual membrane and villous chorion. The average indicator of the intensity of the glow of endothelin in the vessels of the decidual membrane ($53.8 \pm 2.9 \mu\text{a}$) was higher ($p < 0.001$) than that of the control group ($39.1 \pm 2.32 \mu\text{a}$). The degree of expression of endothelin in the vessels of the villous chorion ($46.0 \pm 2.6 \mu\text{a}$) was also higher ($p < 0.05$) than that of the control group ($36.2 \pm 4.0 \mu\text{a}$), but lower ($p < 0.05$) corresponding parameter of the decidual membrane.

DISCUSSION

Thus, our research proved that the use of ozone therapy can increase the effectiveness of restorative treatment for women who suffered bleeding during childbirth. On the basis of the conducted research, a number of the main etiopathogenetic factors of the development of obstetric bleeding were revealed, the features of the functional state of the brain were established, changes in the psycho-emotional status of the patients were detected, hematological and metabolic indicators, parameters of oxidative-antioxidant homeostasis were studied, and morphofunctional disorders in the placenta and uterus due to bleeding were studied.

dysfunction in the form of increased expression of endothelin by the endotheliocytes of the vessels of the decidual membrane ($53.8 \pm 2.9 \mu\text{a}$) and the villous chorion ($46.0 \pm 2.6 \mu\text{a}$).

3. In the uterus, an increase in the expression of endothelin by endotheliocytes of the spiral arteries of the uterus ($57.8 \pm 8.56 \mu\text{a}$) was detected, in combination with a violation of the synthesis of stromal collagen of type I and III and type IV in the basal membranes of vessels.

CONCLUSIONS / ВИСНОВКИ

1. From the first day of the puerperium, free-radical lipid peroxidation increases, the activity of the enzymatic and non-enzymatic links of the antioxidant system increases, endogenous intoxication increases, and lactate and pyruvate levels increase.

2. In the placentas of women in labor who suffered bleeding during labor, there is a violation of the synthesis of type IV collagen in the basal membranes of vessels and the phenomenon of endothelial

PROSPECTS FOR FUTURE RESEARCH / ПЕРСПЕКТИВИ ПОДАЛЬШИХ ДОСЛІДЖЕНЬ

The proven effectiveness of the proposed method of treatment, which is simple, cost-effective, and safe, allows to reduce the medication load on the body, reduce the time of childbirth in the hospital, prevent the occurrence of complications in the

postpartum period, reduce the likelihood of early and long-term consequences after pathological bleeding, contributes to the prevention of disorders somatic and reproductive health in women.

CONFLICT OF INTEREST / КОНФЛІКТ ІНТЕРЕСІВ

The authors declare no conflict of interest.

CONNECTION WITH RESEARCH WORK / ЗВ'ЯЗОК З НАУКОВИМИ ПРАЦЯМИ

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AUTHOR CONTRIBUTIONS / ВКЛАД АВТОРІВ^{A B C} Svitlana F. Herasyenko^{E F} Iryna M. Nikitina^{B E} Svetlana A. Smiian**A** – Work concept and design**B** – Data collection and analysis**C** – Responsibility for statistical analysis**D** – Writing the article**E** – Critical review**F** – Final approval of the article.**REFERENCES/СПИСОК ЛІТЕРАТУРИ**

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INFORMATION ABOUT THE AUTHORS / ВІДОМОСТІ ПРО АВТОРІВ

Svitlana F. Herasyenko – Cand. Med. Sciences, Associate Professor of the Department of Obstetrics, Gynecology and Family Planning, Sumy State University, Sumy, Ukraine

Iryna M. Nikitina – Dr. Med. Sciences, Professor of the Department of Obstetrics, Gynecology and Family Planning, Sumy State University, Sumy, Ukraine

Svetlana A. Smiian – Cand. Med. Sciences, Associate Professor of the Department of Obstetrics, Gynecology and Family Planning, Sumy State University, Sumy, Ukraine