

Application of Ozone in Prevention and Treatment of Intrauterine Fetus Infection

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Abstract

105 pregnant women of a risk group with intrauterine fetus infection and newborns were examined. According to laboratory findings (levels of lipid peroxidation (LP) and antioxidant defense system (AODS), immune status, infectious agents in amniotic liquids, phagocytosis activation) the patients were divided into 2 groups, the 1st group comprising 60 intrauterine infection carriers without inflammation signs and the 2^d group of 45 patients showing the signs of the inflammatory process. Each group was subdivided into the trial group treated with [ozone](#) and control one with conventional methods of treatment. The patients received ozonated saline infusions intravenously for 3-5 days, ozone concentration - 800mcg/l.

The study demonstrated maximal therapeutic effect in patients of the 1st group (the normalization of LP and AOS indices (72%), improvement of immune indices (42%).78% of women with disturbances of uteroplacental blood flow showed a tendency to correction in dopplemetric indices. No cases of infectious agent transiting into a fetus were registered in the 1st group. The described effects were not revealed in the 2^d group Ozone was found to have its maximal effect in cases of TORCH infection agents being present without the signs of inflammatory process activation, thus, lessening the percentage of intrauterine fetus infection.

Introduction

The latest decade showed an increasing interest to the role of infectious agents in the intrauterine fetus lesion. According to Russian authors the incidence of intrauterine infection (IUI) resulting in perinatal mortality ranges from 10% to 37.5%(1,2). The mechanism of IUI development is known to be a complicated one and to evoke multiple debates concerning the questions of infection transition into the infectious process. Subclinical or latent course makes this pathology difficult to diagnose and in cases of pregnancy limits the range of medications necessary for the treatment (3,4,5). It gives rise to a search for new methods to enhance the therapeutic efficacy for this pathological condition.

The aim of the study was to estimate medical [ozone](#) capacities in a complex treatment of pregnant women with a risk of intrauterine fetus infection and to develop differential schemes of treatment regarding risk factors.

Material and Methods

A complex examination and treatment of 105 women with IUI risk factor, pregnancy terms of 22-36 weeks, was done dynamically. Irrespective of the revealed associative microflora from the cervical canal, the patients were divided according IUI risk factors.

The 1st group was made up of patients with chronic foci of extragenital infection, the 2nd - with chronic foci of genital infection. According to the method of treatment each group was subdivided into trial (with medical ozone) and controls (conventional) ones. The 1st group consisted of 42 patients in the trial subgroup and 18 - in the control one, the second - 28 and 17, respectively.

Conventional therapy met the latest requirements of intrauterine infection treatment and consisted of macrolidic antibiotics, recombinant interferons and immunoglobulins for intravenous use (in cases of viral infections), antioxidants and remedies to improve uteroplacental fetal blood flow. The clinical trial included antibacterial treatment combined with ozonotherapy with minimal use of other medications.

The patients of the trial subgroups received 5 intravenous infusions of medical ozone, done every day. Medical ozone was produced by 15-minutes barbotage 200ml of sterile saline (9%NaCl) with ozone/oxygen mixture, ozone concentration being 800mcg/l. Medical oxygen, released from a gas-container, was delivered into the ozonator at a rate of 1l/min. The chosen single dose was substantiated by experiments *in vitro* on isolated blood of pregnant women with IUI risk factors. The choice was made due to the revealed effect on significant decrease of LP processes intensity and AODS activation in blood samples.

All patients had biochemical tests done before and after the treatment. The assessment was made of the levels of LP primary and final products alien conjugates (DC), according to V.Iank in method and Shilbases (SB), according to D.Fletcher. Chemoluminescent method was used to calculate total antioxidant activity (TAOA) in blood serum.

Hormone-producing function of feto-placental complex (FP(-)) was estimated during the 2nd trimester by estradiol and placental lactogen contents in peripheral blood. Hormones content was studied by radio-immune method with the use of standard sets. The assessment of FPC state in women with IUI was done by ultrasonic scanning with the use of »Aloka SSD-630i« (Japan), SIM-5000 Plus and SIM-7000 Plus (Italy-Russia).

Immunological tests included calculation of T and B-lymphocytes and their main subpopulations with the use of monoclonal antibodies; of CIC levels, of immunoglobulins- IgA, IgM, IgG (according to Mancini) and of spontaneous and luminol-dependent chemoluminescence of neutrophils.

Morphological examination of afterbirth was done with methods of light microscopy. Polymerase chain reaction was used to reveal causative agents of non-gonococcus urogenital infection in midstream cervical canal, amniotic liquids as well as from the samples taken from nose, throat and from urine of newborns on the first and fifth days of life. Immuno-fermental analysis was done in 92 cases to define the level of specific antibodies in blood.

The received digital data were calculated with variational statistics method, using MEDST software, developed at the Department of Informatics and Electronic Equipment of Novgorod Medical Academy.

Results and Discussion

Examination of pregnant women with IUI risk factors, treated with ozone, displayed its selective effect according to risk of fetal infectious lesion. Ozone was found to be of the most pronounced effect in the 1st group of patients with chronic foci of extragenital infection. The use of ozonotherapy in that group allowed to lessen the risk of anemia by 1.6 times and to achieve double decrease of late gestosis. The weakness of labor activity was observed 1.4 times less often compared with control group. Particular attention should be drawn to the fact, that patients with chronic foci of extragenital infection treated with medical ozone had fewer cases (by 55%) of preliminary amniotic outflow, that is regarded a clinical manifestation of initial stage of intrauterine infection. It should also be noted that among the newborns of that group perinatal encephalopathy of hypoxic genesis was found to have 2.3 times less occurrence, compared with the group where mothers were on conventional treatment.

Comparative analysis of clinical course of pregnancy, labor activity, postnatal period and the condition of newborns in the second group (with chronic foci of genital infection) provided profound advantages of medicinal immunocorrectors opposed to ozone. The use of immunoglobulins and of recombinated interferons resulted in 1.8 decrease in the incidence of EPH-gestosis in patients with chronic foci of genital infection. Episodes of acute viral infection of respiratory organs developed in 1.6 times fewer cases than in the 1st group. Preliminary deliveries were not common for this group of women that were on medicinal immunocorrectors compared to those treated with ozone. Undue amniotic outflow occurred in 60% of cases compared to 93% of the 1st group undergoing ozonotherapy.

Different clinical effect of medical ozone and of conventional treatment was found to have distinct pathogenic basis.

While studying the processes of free radicals oxidation in women of both groups, we established distinct differences at the initial stage of lipid peroxidation processes and the activity of antioxidant defense system. According to these parameters it became possible to predict the success of a certain kind of therapy. The DC level in women with chronic foci of extragenital infection was 20% higher and of SB -7% over the normal range. The highest level of TAOA was registered in this group, though there occurred some decrease in 32% of women.

The patients with chronic foci of genital infection had double increase in initial DC concentration, with SB - 2.77 times exceeding the normal level. Serum TAOA had 1.86 times decrease.

Medical ozone was found to produce its maximal effect in patients of the first group, where DC and SB had 40% and 10% decrease, respectively and TAOA level elevated by 44% ($p < 0.05$). The rate of TAOA growth was found to be delayed in control subgroup compared to that in the trial one.

In patients with chronic foci of genital infection medical ozone in chosen safe dosage appeared to be less effective compared with medicinal immunocorrectors. Due to medicinal immunocorrectors effect DC level diminished by 86% (24% in the 1st group), SB had double decrease (14% in the 1st). Serum TAOA had 45% elevation, thus, exceeding the parameters of the 1st group with medical ozone - by 54% on the average ($p < 0.05$). The development of changes in the levels of LP primary and final products is presented in Table I.

Table I. The Effect of Ozonotherapy and of Conventional Treatment on DC and SB Levels in Patients with IM Risk Factors.

Index	<u>Group I</u>		<u>Group II</u>	
	Trial	Control	Trial	Control
DC before <u>therapy</u>	0,27±0,012	0,25±0,011	0,55±0,02	0,52 ±0,026
DC after	0.193±0.009 :5 0,05	0212±0.01 p:5 0,05	0.42±0.02 p > 0,05	028±0.01 :5 0,05
Normal DC in health <u>pregnant</u> women	0.214±0.01			
SB before <u>therapy</u>	15.61±0.69	15.01±0,71	40.2±2.01	42.44±2.12
SB after	142±0.7 <0,05	1434±0.68 p <0,05	34.42±2.06 p <0,05	20.72±1.01 <0,05
SB in healthy <u>pregnant</u> women	14.49±0.71			

In the course of the study the correlation between different parameters has been calculated. Reverse correlation has been established between DC and SB contents with estriol level, estriol having antioxidant properties ($R = -0.6$).

The analysis of immune system in patients with chronic foci of extragenital infection revealed minimal changes on the cellular immunity level with IgM being increased by 31 % and IgG tending to decrease, phagocytic activity of neutrophils being within normal limits.

The patients of the second group displayed as much as 1.5 times decrease of T-lymphocytes due to T-helpers subpopulation (CD 4+), increase of B-cells (CD 19+). IgM concentration exceeded the normal range as much as 2.45 times and IgG concentration had a double decrease. We could not but note high level of circular immune complexes (CIC) and insufficient phagocytic activity of neutrophils.

Pronounced difference in the original immunity status in patients of both groups resulted in different effect of the compared methods of treatment. The use of medical ozone in the first group caused raise of T-lymphocytes in the peripheral blood by 8% on the average ($p < 0.05$), IgG concentration - by 37% and decrease of IgM by 30 % ($p < 0.05$).

Patients of the second group showed better response to medicinal immunocorrectors therapy. Recombinated interferons and immunoglobulins influenced on the elevation of T-lymphocytes level as much as 1.4 times, double increase of IgG concentration (50% of patients), IgM returning to normal range. Phagocytic potential of neutrophils raised as much as 1.5 times and

CIC having 2.3 decrease ($p < 0.05$). The changes in immunologic parameters in response to both kinds of treatment are presented in Table II.

Table II. Effect of Ozonotherapy and of Conventional Treatment on Cellular, Humoral Immunity and Ne Pha oc is activity in women with IUI Risk Factors

Index	Grou I		Grou II	
	Trial	Control	Trial	Control
CD + Before thera	42,2±0,07	45,0±0,068	29,1 ±0,064	34,3±0,41
CD + After therapy	45,0±0,2	49,2±1,2 <0,05	28,7±0,72 p >0,05	41,0±0,21 <0,05
CD + Before thera	18,4 ±1,0	21,1±0,9	32,4±0,9	29,2±1,0
CD + After therapy	19,7±0,4 < 0,05	17,2±2,7 p > 0,05	34,2± 1,7 p > 0,05	17,0±1,6 < 0,05
IgG Before therapy	10,0±0,46	9,22± 0,5 p <0,05	5,5 ± 0,4	6,1±0,6
IgG After therapy	13,7± 0,5	14,2±0,1 p <0,05	5,7±0,5 p >0,05	12,4±0,3 p <0,05
IgM <u>Before therapy</u>	2,2±0,05	2,8±0,04	3,5 ± 0,06	3,9 ± 0,05
IgM After therapy	1,5±0,06	1,45±0,05 p <0,05	3,2±0,04 >0,05	1,6±0,04 p <0,05
CIC <u>Before therapy</u>	0,110±0,04	0,09±0,1	0,384±0,05	0,287±0,03
CIC After therapy	0,112±0,07	0,082±0,02 p > 0,05	0,396±0,03 p > 0,05	0,124±0,06 p < 0,05
Ne functional potential <u>Before therapy</u>	7,5±0,02	7,9±0,04	5,4±0,02	4,8±0,01
Ne functional potential <u>After therapy</u>	8,0±0,02	8,2±0,02 p <0,05	5,8±0,06 p >0,05	7,2±0,02 p 0,05

In the course of the study there has been established reverse correlation of DC and SB levels with T-Lymphocytes contents ($R = -0.7$) in serum, exhibiting LP inhibiting effect on T-cells. There has also been noted reverse correlation between CIC contents and IgG.

With regard to the significance of FPC hormones there have been studied the levels of estriol and placental lactogen during the courses of ozonotherapy and conventional treatment. In the 1st group (women with extragenital infection) medical ozone induced the augmentation of estriol contents during the 2nd trimester by 20%, weekly growth exceeding the control one as much as 1.4 times ($p < 0.05$). Similar effect has been noted regarding placental lactogen, exceeding the control parameters as much as 1.6 times.

In the second group (women with genital infection) preferable treatment appeared to be that of medicinal immunocorrestors. It resulted in estriol concentration growth by 52%, placental

lactogen - by 20% ($p < 0.05$). The patients of the 2nd group did not have any definite changes in hormones levels after the course of ozonotherapy.

Taking into consideration important role of any changes in utero-placental bloodflow in the pathogenesis of intrauterine infection, all the patients of both groups had dopplerometric examination. In the 1st group with the course of ozonotherapy there has been noted the tendency to normalization of bloodflow changes in FPC vessels in 75% of patients. Besides, positive ozone effect could be revealed in more pronounced compensatory adaptive reactions on histological examination. In the second group (genital infection) disturbances in ureto-feto-placental blood flow were initially registered more often compared to those of the 1st group (as much as 4.4 times). Maximal effect in the 2nd group was achieved with immunocorrectors therapy. The resistance index returned to normal range in 37.5% of cases, exceeding that in the 1st group (as much as 1.4 times). Besides, immunocorrection done in due time resulted in better development of compensatory-adaptive capacities of afterborn.

Conclusion

Analysis of the received findings made it possible to work out well-grounded and differential recommendations in favor of a method of treatment for pregnant women with intrauterine infection according to risk factors.

The clinical trial demonstrated preferable ozone application in a complex prevention and treatment of women with chronic foci of extragenital infection, for it was in that group that valid positive ozone effect was marked concerning the most important homeostatic parameters.

For patients with chronic foci of genital infection the most preferable method of treatment was found to be the therapy with the use of immunocorrectors.

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