ANTIOXIDANT COMPLEX SELMEVIT IN HEMOSTASIS CORRECTION AT SOME UTERINE SURGERIES (report III)

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Overseeing 486 productive age women subjected to uterine cavity abrasion for the diagnostic purpose or for the purpose of legal abortion, hysterectomy by laparoscopic or laparotomic methods, cesarean section it is proved that a surgical intervention intensifies the registered in them lipid peroxidation acceleration, general blood clotting and the acceleration of thrombin-fibrinogen interaction in blood flow. The inclusion of the complex antioxidant selmevit into a usual therapy course (in pre- and post-surgical periods) restricts these shifts and accelerates their disappearance, somehow restricts intraoperative blood losses, that mitigates the risk of thromboembolic episodes.

Thromboses and embolias – are very dangerous complications of operative interventions on the uterine, the tissues of which – are the sources of fibrillation factors (FF). The uterine surgeries result in the outlet of the tissue factor, the connections like plasmatic FF V, VII, X, XIII and proaggregants [1, 2] into the blood flow. The most serious and frequent intraoperative complications – floods, thromboembolias – are connected with hemocoagulation changes [3]. Like other operative interventions, the uterine surgeries are attended by the lipid peroxidation (LPO) acceleration. The use of antioxidants limits the hemocoagulation shifts [4] like in other surgical interferences [5, 6]. The information about positive effects of antioxidants in the thromboembolias prophylaxis, their relations at obstetric-gynecologic pathology with hemocoagulation shifts, the absence of contraindications to vitamins-antioxidants application, the possibility of outpatient use substantiate their corrective effect [7 – 10].

The **purpose** of the work is the estimation of hemocoagulation changes, morphofunctional properties of thrombocytes (TC), LPO and antioxidant potential (AOP) in women after uterine surgeries, the advisability of selmevit antioxidant complex use for the hemostatic shifts prophylaxis.

Objects and methods of research

The women were examined at gynecological and maternal obstetric services of the Tyumen Regional Center of Maternity and Child Welfare Service and maternity hospital N3. The clinical and laboratory examination was carried out the day before and in 1, 3-4, 5-7 days after the operation (complaints and anamnesis study, general visual inspection, special obstetric and gynecological examination, bacterioscopy of cervical channel fluid, sheath and urethra, USI of true pelvis organs). The surgery duration, arterial tension, pulse, breathing rate, somatic temperature, anaesthesia form, intraoperative blood loss were taken into account. In the postsurgical period the thrombo-hemorrhagic complications frequency, hospitalization time, bed days were estimated. The throbmocytic hemostasis was estimated defining the thrombocytes (TC) number [11], their morphologic forms, the number and size of aggregates per 100 free cells, the quantity of aggregate-forming TC per 500 free cells; small (2-3 TC) and big aggregates (4 and more TC) per 100 free cells [12]. The hemocoagulation was estimated defining the ATR, APTT [13], prothrombin ratio (PR) [14]; for the thromboplastin international sensitivity index (ISI) account the PR was raised to the ISI power pointed at the marking and the international normalized ratio (INR) was calculated; the fibrinogen (FG) concentration was defined gravimetrically; the solvable fibrin-monomeric complexes (SFMC) [14], fibrin split products (FSP), antithrombin III activity (AT-III) [15], plasminogen reserve index

(PRI) (the reagents of the "Technology-Standard" firm, Barnaul) and f P_3 [16]. The LPO was estimated on the level of diene conjugates (DC) and malondialdehyde (MDA) [17]. The AOP was judged on the level of vitamin E in erythrocytes [18]. The mathematical treatment was performed by the variance analysis method for small series of observations calculating the arithmetic mean (M), its mean error (m), the mean-square deviation (σ), confidence coefficient of Student (t) and the degree of possibility (p).

The most abundant uterine surgeries (Table 1) were subject to observation. For this purpose two uniform groups were formed: the *comparison group* (usual preoperative preparation and postoperative treatment) and the *main group* (women received selmevit in addition to the usual therapy). The age, social status, clinical-anamnestic characteristics, occurrence of somatic and gynecological diseases, surgical indications and their scope were the same in both groups.

Table 1. Distribution of examined women in groups

№ group	Characteristics	n
1	Control – childbearing age women (II phase of menstrual cycle)	20
2	Women subjected to uterine cavity abrasion: - for purpose of legal abortion carrying out - for diagnostic purpose	140 90 50
3	Women subjected to conservative myomectomy: - didn't receive selmevit - received selmevit	79 49 30
4	Women after major uterine surgeries: - hysterectomy by laparotomy method - didn't receive selmevit - received selmevit - hysterectomy by laparoscopy method - didn't receive selmevit - received selmevit	155 136 76 60 19 10 9
5	Women subjected to cesarean section: - didn't receive selmevit - received selmevit	92 47 45
	Total:	486

Research results

At hysterectomy the operation time in the main group reduced by 3,0% (p >0,05), the intraoperatinal blood loss reduced by 15,2% (p >0,05), there were no complications registered. In the comparison group women undergone the *laparotomic hysterectomy* the surgery duration was reduced by 8,9% (p >0,05), the blood loss – by 15,7% (p< 0,05). The interconnection of hypercoagulation shifts and thrombembolias [20] allows speaking on the positive role of selmevit. In the main group women subjected to the conservative myomectomy the tendency to the surgery duration decrease (by 9,2%), the intraoperational blood loss decrease by 7,9%, the absence of thrombohemorrhagic complications (in the comparison group – 4,1%). In the main group women delivered with the help of *caesarian section* the intraoperational blood losses were lower by 13,8%, the operation time – by 21,9%, there were no postoperational thrombohemorrhagic complica-

tions registered (in the comparison group – 2,1%, i.e. I case).

Because of the limited article volume we document only a small part of the examined states – the conservative myomectomy. From the data of the Table 2 one can see that before the operation the APTT and TT are prolonged, the PR and INR are increased, the AT-III and PRI are reduced in the *comparison group*. In the *main group* the ATR was prolonged, the PR and INR factors became lower than in the comparison group, the AT-III and activity and PRI increased. In the comparison group women subjected to the conservative myomectomy the ATR was prolonged, the FG, SFMS and FSP levels were increased, the AT-III and PRI were decreased in 24 hours after the operation. The FG level decrease remained for 3-4 days, the ATR, AT-III, SFMC, FSP, PRI – for 7 days, the APTT, TT, PR, INR didn't differ from the initial ones, but didn't reach the control values. In the main group the TT, SFMC and FSP level increased, the AT-III and PRI level fell on the first day after the operation. On the 3-4th day the PRI and AT-III differences retained (compared to the pre-surgical values).

In the pre-surgical period in the comparison group there were differences from the control: the TC, S, SE, SAN, BAN, AN and f P_3 were increased, the DE number was decreased. The differences from the control were also registered in the main group women: the S, SAN and AN quantity were increased. Together with that the number of thrombocytes, SE, BAN and AN were authentically less (relative to the comparison group).

In the comparison group women in 24 hours after the operation the number of DE, SE, AFN, SAN, AN, f P_3 was increased and the number of D was decreased. The D, SE, NAF, SAN, AN and P_3 factors' differences from the pre-surgical ones retained for 3-4 days. Up to 7 days after the operation the S, SE, NAF, SAN, BAN and AN factors were decreasing and the D number was increasing. However, on the 5-7th day after the operation the SE, SAN, BAN and AN factors remained higher than those of the control.

In the main group patients the thrombocytic hemostasis changes after the operation were less manifested: on the first day the number of D, BAN, f P_3 were decreased, beginning with the 3-4th day the factors didn't differ from the pre-surgical ones, on the 5-7th day only SAN and AN are higher than in the control.

Table 2. Hemocoagulation, thrombocytic hemostasis and LPO before and after the laparoscopic conservative myomectomy in the comparison (1 line) and main (2 line) groups.

Factors	Control group, n = 20	Before operation	1 day	3-4 day	5-7 day
		without selmevit, n = 20, with selmevit n = 15	without selmevit, n = 20 with selmevit, n = 12	without selmevit, n = 20, with selmevit n = 12	without selmevit, n = 20, with selmevit, n = 12
ATR, sec	59,0±2,6	60,4±2,5 66,5±2,3*	70,1±5,7' 69±1,6	75,4±4,6' 60,6±2,6	75±3,1' 62,4±3,6
APTT, sec	40,6±1,3	46,2±1,5* 45,1±4,1	46,6±1,3 40,3±3,1	45,8±1,5 39,9±1,2	44,7±1,5 41,5±1,3
TT, sec	18,5±0,6	24,3±1,6* 19,2±1,6	24,5±1,5 23,7±0,9'	24,0±1,5 22,4±1,2	22±1,3 19,2±0,4
PR	1,4±0,1	2,1±0,3* 1,6±0,2"	1,7±0,2 1,9±0,2	2,6±0,3 1,6±0,1	2,2±0,3 1,5±0,1
INR	1,6±0,2	2,4±0,4* 1,9±0,2"	1,9±0,2 2,3±0,3	3,0±0,5 1,9±0,2	2,5±0,4 1,6±0,1#
FG, g/l	2,5±0,2	2,8±0,2 3,0±0,2	3,6±0,3' 2,8±0,3	3,4±0,2' 3,3±0,4	3,1±0,2 3,1±0,2

SFMC, mg/100 ml	3,5±0,1	3,8±0,4 3,6±0,2	6,7±0,6' 4,7±0,4'	5,2±0,5' 4,1±0,4	4,9±0,3' 3,8±0,3
FSP, mg %	0,547±0,02	0,562±0,03 0,554±0,02	0,640±0,02' 0,622±0,02'	0,632±0,02' 0,568±0,02	0,624±0,02' 0,562±0,02
AT III, %	95,1±2,7	80,4±3,2* 95,5±3,7"	66,8±4,6' 80,6±1,9'	70,6±3,8' 83,3±3,8'	71,2±3,1' 88,0±3,7
PRI, %	109,4±3,7	86,2±3,0* 99,1±2,1*"	68,6±3,0' 67,4±3,5'	73,1±2,8' 77,8±2,6'	77±3,2' 93,7±4,1
TC ($x10^9$)	248,5±5,4	376,4±22,6* 317,6±16,0 '	392,8±23,3 290,7±11,3	368,5±24,1 288,5±15,1	325,8±17,1 301,4±16,2
D, %	46,5±0,9	43,5±1,4 45,1±0,8	36,9±1,0" 48±0,8"	35,7±1,3" 47,2±0,7	43,1±1,7# 40,7±0,9#
DE,%	24,9±0,6	22,6±0,9* 23,7±0,6	28,7±1,2" 23,3±0,5	26,5±0,9" 24,5±0,5	26,9±1,4" 25,3±0,7#
S, %	18,0±0,5	23,4±0,9* 22,1±0,8*	21,3±0,8 21,7±0,5	24,3±1,3 20,4±0,6	17,9±0,9" # 18,5±0,6 #
SE, %	9,4±0,3	10,9±0,4* 9,0±0,3 '	13,6±0,6" 9,2±0,5	13,4±0,5" 9,4±0,4	11,5±0,4# 9,3±0,2
NAF (per 500 cells)	53,5±0,9	56,5±1,1 56,4±1,8	63,8±1,3" 53,3±1,6	63,1±1,1" 52,3±1,9	56,9±1,7# 53,3±1,7
SAN (per 100 cells)	7,7±0,7	12,3±1,9* 10,8±0,7*	22±2,0" 11,3±0,9	20,9±1,8" 11,6±1,1	14,8±1,8# 10,4±0,7
BAN (per 100 cells)	1,0±0,1	4,3±0,4* 1,1±0,3 '	4,7±0,6 2,0±0,3"	4,4±0,6 1,8±0,4	2,5±0,3# 1,4±0,3
AN (per 100 cells)	8,7±0,8	16,6±1,3* 11,9±1,0* '	26,7±2,6" 13,3±1,3	25,3±2,5" 13,4±1,5	17,3±2,1# 11,8±1,1
P_3, %	31,5±2,8	41,2±3,5* 36,6±3,7	60,3±4,1" 51,8±3,6"	53,4±3,9" 41,8±3,3	48,3±3,4# 39,7±4,2#
DC, nmol/ml	110,3±3,4	122,7±3,6* 121,2±3,5*	132,9±3,1" 132,6±3,4"	131,7±3,8" 126,5±3,6	129,8±4,1" 118,4±3,8
MDA, mol/ml	10,4±0,5	11,7±0,3* 10,9±0,4	14,1±0,4" 12,3±0,5"	13,6±0,5" 11,7±0,3	12,8±0,4" 11,2±0,4
Vitamin E, mol/ml	4,6±0,3	3,8±0,2* 4,1±0,2	3,2±0,2" 3,4±0,2"	3,3±0,1" 3,8±0,3	3,5±0,2 4,2±0,4

Designations here and in the text: ATR – activated time of recalcification, APTT – activated partial thromboplastin time, TT – thrombin time, PR – prothrombin ratio, INR – international normalized ratio, FG – fibrinogen, SFMC – soluble fibrin-monomeric complexes, FSP – Fibrin split products, AT III – antithrombin III, PRI – plasminogen reserve index; TC – thrombocytes, D – discocytes, DE – discoechinocytes, S – spherocytes, SE – spheroechinocytes, NAF – the number of aggregate-forming TC, SAN – small aggregates number with 2-3 TC per 100 free cells, BAN - big aggregates number with 4 and more TC per 100 free cells, AN – aggregates number – the total number of SAN and BAN per 100 free cells, DC – diene conjugates, MDA – malondialdehyde; * - authentically significant differences ($p \leq 0,05$) in healthy women, # - with values before the operation.

The LPO speed in the pre-surgical period in the comparison group was higher than in the control one: the DC and MDA level was increased; the vitamin E level was decreased. In the main group women the DC increase was less high; the rest LPO factors didn't differ from the control ones.

On the first day after the operation the DC and MDA level increased and vitamin E level – decreased in the comparison group; that retained up to 3-4, and DC and MDA – up to 5-7 days.

In the main group on the first day of the operation the content of DC and MDA increased, vitamin E – decreased. On the 3-4th day and on the 5-7 day there were no authentic differences compared to the pre-surgical ones found.

So, the prescription of selmevit to the women subjected to conservative myomectomy by laparoscopic method restricts the LPO shifts, coagulative and thrombocytic hemistasis mitigating the risk of thrombo-hemorrhagic complications.

After other operations (uterine cavity abrasion for diagnostic purpose, for legal abortion performance, hysterectomy by laparoscopic or laparotomic method, cesarean section) the changes of coagulative and thrombocytic components of hemostasis, the LPO speed changes were the same in directivity differing in intensity. As a whole, the intensity of shifts is consistent with the latitude of the operative intervention: the more significant the tissue traumatism is – the more evidently the LPO is promoted, the AOP is decreased and the TC coagulative activity is increased. At all kinds of the studied surgical aggressions the shifts degree and their duration were lower in the patients of main groups, i.e. the groups having received selmevit. In all the observations the signs of hypofibrinogenemia of consumption expressed in various measures to the power proportional to the LPO shifts intensity and the degree of TC activation became apparent.

Thus, various traumatism degree uterine interventions promote the activation of coagulative hemostasis to the power depending on the extent of the operation. The hemostasis activation reaches the degree resulting in the development of secondary hypocoagulemia – the hypocoagulemia of consumption. The TFI products level reflecting the acceleration of continuous intravascular clotting (CIC) in the blood flow testifies to the FG consumption. Considering the fact that the CIC acceleration attends obstetric-gynecologic operative interventions, one can assume that in these situations the disseminated intravascular clotting is initiated [15].

At the same time, after surgical interventions, thrombocytes activate – their ability to aggregate formation and release reaction increases. On the basis of hemocoagulation and TC changes time sequence data at extreme conditions or factors [5] the TC activation has been reputed to be the initiator of hemocoagulative shifts in our observations.

The fact that together with the activation of hemostasis the LPO accelerates and the AOP dies out [4] testifies that the activation of the hemostasis coagulative component after the operative intervention into the uterine cavity is conditioned by the LPO acceleration, as it is shown in other pathological states determined by various extreme conditions or factors [8, 10]. The abovementioned has been acknowledged by the fact that the introduction of selmevit increasing the AOP and inhibiting LPO diminishes the hemostatic shifts caused by the operation upon the uterine and the hemostatic profiles are normalized quicker (it is common knowledge that vitamins composing selmevit do not influence hemostasis essentially in conditions of health [8], but normalize hemostasis if its disorders are connected with the LPO activation [8, 10]. It testifies that the LPO shifts initiate hemostatic shifts as it was shown in the experiment [5, 6]. The abovementioned is also confirmed by the fact that the antioxidant effect is manifested, although to a not large extent, by an intraoperative blood loss decrease – the factor depending on the hemostasis state.

So, our findings confirm the idea about the connection between hemostasis and free-radical oxidation at the LPO level, and it proves the applicability of selmevit in pre-surgical preparation and post-surgical treatment as means of non-specific correction of hemostatic shifts appearing at the states attended with an oxidative stress, at gynecological diseases requiring surgical aggression, in particular.

Conclusions

1. In women with uterine surgical indications the LPO speed, the TC aggregate-forming ability, general blood coagulability and TFI markers content are increased. In 24 hours after uterus lining biopsy or abortion by conservative myomectomy the shifts are redoubled without reaching the critical extent.

2. In women subjected to laparotomic or laparoscopic hysterectomy, cesarean section the hemostatic shifts reach the degree of the blood DIC initial stage (the shifts do not disappear by the 5-7th day after the operation).

3. The supplement of usual therapy with selmevit (before and after the uterine surgeries) reduces the hemocoagulation shifts degree in the pre-surgical period, and especially the shifts caused by an operative intervention.

4. At all the examined states the blood clotting activation is connected with the LPO acceleration and AOP decrease. The prescription of selmevit restricts both of them that allows associating the selmevit effect with its antioxidant properties.

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