

Regulatory autoantibodies in women with risk factors for postpartum haemorrhage depending on childbirths parity

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Abstract: Background: Obstetric haemorrhage is one of the major causes of maternal mortality and morbidity in the world. This complication is not decreasing in Kazakhstan and this tendency is proved by the results of confidential audit. Multiparous women have one of the highest rates of obstetric haemorrhage. In recent time there are a lot of data regarding the role of regulatory autoantibodies system in pathogenesis of gestational complications which also include obstetric haemorrhage. The aim of this research is to evaluate the regulatory antibodies level in women with risk factors for postpartum haemorrhage depending on childbirths parity. **Materials and Methods:** 126 pregnant women have been examined, i.e. 96 pregnant women of haemorrhage risk group and 30 pregnant women with physiologic gestation and childbirth course. Pregnant women of risk group have been divided into 2 groups depending on outcome of childbirth: basic and comparative groups. Basic group included 65 women, who had postpartum haemorrhage, i.e. 37 multiparous (5 and more childbirth) women were in the 1st subgroup, and 28 primipara (1 childbirth) and bipara (2-4 childbirth) women were in the II subgroup. Comparative group included 31 women of risk group without postpartum haemorrhage. The level of regulatory autoantibodies in blood serum of all pregnant women was determined in 3rd trimester of pregnancy using the enzyme-linked immunosorbent assay technology. **Results:** We found that 75,4% of women from the basic group had pathologic characteristics of average individual immune reactivity, which had predominantly decreasing tendency. At the same time, 39,2% of women in comparative group had domination of relative autoantibodies hyperproduction. Imbalance of immune system became worth with increasing of childbirths parity, and that was correlated by volume of haemorrhage after childbirth. **Conclusion:** Obtained data show that obstetric haemorrhages were progressed against the background of the most expressed changes in regulatory autoantibodies content, which had interrelation with the parameters of haemostasis. Moreover, it was defined that this imbalance was more often widespread among multiparous women than among primipara and bipara women.

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1. Introduction

Obstetric haemorrhage is one of the main reasons of maternal mortality and morbidity in the world [1]. According to official statistics of Republic of Kazakhstan, relative share of obstetric haemorrhages among the causes of maternal mortality was 20,3% in 2009, 11,9% in 2010, 15,2% in 2011 and 23,1% in 2012, but confidential audit data considering this issue had the other figures, i.e. 30,7% in 2009 and 29,0% in 2010 [2]. Postpartum haemorrhage has considerable relative share among obstetric haemorrhages and their frequency has no tendency to decrease. Therefore, according to W. Callaghan et al [3], the frequency of postpartum haemorrhages in USA had grown by 26% from 1994 till 2006, and the frequency hypotonic haemorrhage has been considerably increased (by 50%). Almost the same growth rates of postpartum

haemorrhages from 1994 till 2002 (by 28,9%) have been registered by C.A. Cameron et al in their research [4]. More than 2/3 of blood loss, which also threatened the women's life, is connected with abnormalities in haemostasis [5, 6, 7, 8].

It is generally thought that maternal mortality connected with postpartum haemorrhage can be prevented in the majority of cases [9]. In this regard, much attention is paid to the forecasting issues, because they are considered to be ground of preventive measures of this pathology.

Last years there are a lot of publications, which are related to the marker changes in the immune system [10, 11, 12, 13, 14], including natural regulatory antibodies, which are responsible for the embryogenesis process in the phase of preclinical manifestations within different extragenital and

obstetric pathology. Thus, correlation between different content of embryotropic autoantibodies with the volume of blood loss in postpartum period has been defined [15]. The aim of this research is the studying of regulatory antibodies level of multiparous women in comparison with primipara and bipara women of obstetric haemorrhages risk group, considering the fact, that Kazakhstan is region with the high birth rate and multiparous women have contributed greatly to the frequency of obstetric haemorrhages.

2. Material and Methods

According to the earlier defined risk factors of obstetric haemorrhage [16], 117 women of haemorrhage risk group were chosen, subsequently 21 women were excluded, i.e. 6 of them had terminated of pregnancy before 22 weeks of gestational age, and 15 were operated by implementation of caesarean section. The last ones were excluded due to the fact that caesarean section itself is the risk factor of obstetric haemorrhage. 96 pregnant women, who gave birth by natural delivery were analysed.

They have been divided in two groups depending on labour outcome: basic and comparative. Basic group have included 65 women, who had haemorrhage in postpartum period: where 37 multiparous women were in the 1st subgroup and 28 primipara and bipara women were in the 2nd subgroup. Comparative group included 31 women of risk group, who had physiologic blood loss during childbirth. 30 pregnant women with physiologic gestation and childbirth course were examined as the control group.

If blood loss during childbirth was than 500 ml, i.e. less than 0,5% of body mass or less than 10% of total blood volume, it was considered as physiological. Blood loss considered to be pathologic if it was 500 ml and more.

All patients were subjected to general and obstetrical anamnesis by generally accepted criteria, i.e. extension study of coagulation profile and thrombocytic hemostasis. Content of regulatory autoantibodies were defined in 3rd trimester of pregnancy among all women using the enzyme-linked immunosorbent assay technology in blood serum: antineutrophil cytoplasmic antibodies ANCA; antibodies, which link with the thrombocytes proteins TrM-03; double-helix DNA; β 2-glycoprotein (β 2-GP); Fc-fragments IgG (rheumatoid factor); Collagen; Interferon-gamma; Interferon-alpha; e-NOS (NO-synthetase) and Angiostatin. According to the literature data [17]:

ANCA is the marker of thrombocytopathies, which is produced in increased quantity by endothelium of damaged vessels.

TrM-03 is one of the main components of thrombocyte's membrane, which is the marker of thrombocytopathies.

Double-helix DNA - the increased produce of autoantibodies to this antigen is the marker attribute of apoptosis processes activation.

β 2-Glycoprotein I is the main phospholipid, which links the plasma protein. Excess of autoantibodies in relation to this antigen is the marker attribute of Anti-Phospholipid syndrome (APS).

Collagen II is the main protein of connective tissue. Excess of autoantibodies in relation to this antigen characterizes the cicatricial and adhesive process of tissue.

Fc-fragment of IgG – increased generation of autoantibodies in relation to this antigen (rheumatoid factor) is the attribute of chronic inflammatory processes of any localization.

Nitricoxidesynthase (e-NOS) participates in regulation of vascular tone; it exposes vasodilatative effect on to placental vessels and also prevents adhesion and aggregation of thrombocytes in intervillous lacuna.

Angiostatin participates in fibrinolysis, regulates the vessel growth. Increasing of autoantibodies in relation to angiostatin can lead to the violation of blood coagulability and formation of collateral circulation.

Interferon-gamma is proinflammatory cytokine, which is produced by activated T-lymphocytes and activated natural killers.

Interferon-alpha stimulates the activity of macrophages (phagocytic activity) and natural killer cells (NK-cells).

Research results are shown in standard units (s.u.) [18], therewith the values of immune reactivity in the range from -20 up to +10 s.u. were considered to be normal, values from -20 up to -40 s.u. and from +10 up to +40 s.u. were considered as insignificant deviations from the normal range and values less than -40 and more than +40 s.u. were considered as significant deviations from the normal range.

1260 autoantibodies were determined in total.

Data processing was carried out on the personal computer using the standard software. Wilcoxon-Mann-Whitney test was used for the determination of statistical significance between comparable groups. Correlation analysis with the application of parametric correlation coefficient within limits from -1 up to +1 [19] was used for determination of interrelation between attributes.

3. Results

The age of examined women varied from 20 up to 42 years, and it was $31,2 \pm 0,9$ years in average in basic group; $35,7 \pm 0,5$ years in 1st

subgroup; 27,2±1,5 years in 2nd subgroup; 30,3±1,2 years in comparative group; and 29,4±0,5 years in control group.

Obstetric history in 1st subgroup of basic group was complicated by 16,2% of justifiable abortions, in 40,5% of cases - miscarriages, in 2,7% of cases - fetal loss syndrome; and in the second group: in 10,7% of cases - justifiable abortions, in 21,4% of cases - miscarriages. There were 12,9% of justifiable abortions and 9,7% of miscarriages in comparative group and 9,6% of abortions in anamneses and 6,7% of miscarriages in control group.

Analysis of somatic history of the basic group showed that multiparous women had anaemia (23-62,1%) in the majority of cases, delitescence course of pyelonephritis (3-8,1%), varicose disease (5-13,5%), obesity of the 2-3 degree (9-24,3%). Primipara and bipara women had the anaemia in 13 cases (46,4%), 1 woman (3,6%) had delitescence course of pyelonephritis, 3 women (10,7%) had varicose disease, obesity of the 2-3 degree was occurred in 4 cases (14,2%). The medical history of comparative group was complicated by anaemia in 12 cases (38,7%), delitescence course of pyelonephritis in 1 case (3,2%), 2 women (6,5%) had varicose disease, obesity of the 2-3 degree in 3 cases (9,7%). Such a pathology appeared in control group as follows: 11(36,6%), 2 (6,6%), 4 (13,3%), 1 (3,3%), 1 (3,3%) correspondingly.

Analysis of gestation period showed that such pregnancy complication as preeclampsia was occurred among 19 (51,3%) women of the 1st subgroup of basic group, among 11 (39,2%) women of the 2nd subgroup, and among 11 (35,5%) patients of comparative group. Gestational hypertension was occurred among 10 (27%), 8 (28,6%) and 2 (6,4%) patients correspondingly. Antenatal fetal death among multiparous women occurred in 1 case (2,1%) in 34 weeks of gestation period, whereas there is no such cases in other groups.

9 (13,8%) patients of basic group and 6 (9,7%) women of comparative group had premature birth. Women of control group had all their childbirths in time.

Blood loss volume during childbirth and postpartum period was 500-999 ml in basic group in 67,7% of cases, 1000-1499 ml in 27,7% cases and more than 1500 ml in 4,6% cases. Average blood loss was 894,86±58,60 ml.

Blood loss was ranged from 600 up to 2300 ml in the 1st subgroup and it was 947,86±65,71 ml in average. 42,8% of multiparous women had massive blood loss, i.e. more than 1000 ml.

Blood loss was ranged from 500 up to 1400 ml in the 2nd subgroup and it was 824,83±49,21 ml in average. 17,9% of primipara and bipara women had massive blood loss, which is 2,4 times more rarely than pluripara had ($p<0,05$).

Total blood loss in comparative group was ranged from 180 up to 450 ml; 292,9±14,07 ml in average.

Blood loss volume in control group was ranged from 100 up to 280 ml; 179,31 ±10,66 ml in average.

28 (93,3%) of 30 pregnant women from control group had the levels of all researched autoantibodies within normal values. 2 (6,7%) of patients had weak deviations in serum levels of several researched autoantibodies, which were within the limits from -25 up to +24 s.u. Average absolute values of all researched autoantibodies levels in control group were within normal limits, i.e. in the range from -20 up to +10 s.u.

Conspicuous is the fact that, pregnant women, who subsequently had blood loss in postpartum period, had pathologic levels of serum content in one or another marker-autoantibodies in 367 (56,5%) of 650 determinations, while in comparative group this figure was in 5,5 times less (32 of 310) ($p<0,001$).

More detailed analysis showed that the most obvious changes were in the content of autoantibodies in relation to DNA, TrM-03 and ANCA. Therefore, only 15,4% of pregnant women of the basic group had normal levels of antibodies in relation to DNA, while this figure was 51,6% in comparative group. Comparison of this characteristic depending on childbirths parity showed that there were no multiparous women with normal level of autoantibodies in relation to DNA in the first subgroup. 33 patients had weak deviations from the normal level: 26-70,3% with increase (from +15,1 up to +32,7 s.u.) and 7-18,9% with decrease (from -23,9 up to -33 s.u.). There was obvious increase of autoantibodies in relation to DNA (from +42,1 up to +48,9) in 4 cases (10,8%).

10 (35,7%) of patients in the 2nd subgroup had normal values of antibodies level in relation to DNA. Other pregnant women had weak deviations of antibodies level, where 6-21,4% women had increase (from +14,8 up to +29 s.u.) of them, and 12-42,8% had decrease (from -23,9 up to -30,2 s.u.).

Analysis of antibodies level in relation to TrM-03 showed that there were 2,3 times less women with normal level of antibodies in comparison with women of the risk group, who had no subsequent haemorrhage ($p<0,001$). About

3/5 of pregnant women from the basic group had deviations of decreased antibodies production in relation to TrM-03, while only each tenth patient of comparative group had weak deviations. Analysis of this characteristic in dependence of childbirths parity also revealed significant differences. Thus, normal characteristics of antibodies level in relation to TrM-03 were registered in 13,5% of cases in the first subgroup and in 71,4% of cases in the second subgroup. At the same time, pathologic levels of autoantibodies in relation to TrM-03 with weak deviation (from -21,8 up to -34,3 s.u.) were decreased among 19 (51,4%) women related to the first subgroup and among 8 (28,6%) of women of the second subgroup (from -21,8 up to -32,3 s.u.). It ought to be remarked that significant production of autoantibodies in relation to this marker were registered in 35,1% of cases among multiparous women who had subsequent haemorrhage.

Our researches showed that 4/5 of women from comparative group had normal characteristics of autoantibodies level in relation to ANCA, while 1/3 of women from the basic group had the same result. 53,9% women of the basic group had decrease of autoantibodies level in relation to this marker, where 4,6% of them had obvious deviations. Whilst analysing this characteristic in dependence of childbirths parity it was defined that 8,2% of multiparous women of the basic group had obvious decrease of autoantibodies level (less than -40 s.u.), while there were no such cases in the second subgroup. At the same time, primipara and bipara women had insignificant decrease of antibodies production (from -20 s.u. up to -40 s.u.) in 50,0% of cases.

Characteristic of antibodies level in relation to β 2-Glycoprotein (β 2-GP) didn't differ significantly by groups. Thus, insignificant increase of antibodies production was registered in the basic group (from +10,2 up to +26,8 s.u.) in 60,0% of cases and 6,5% in the comparative group (from +10,2 up to +21,1 s.u.).

Pathologic levels of antibodies in relation to Fc-IgG (Fc-fragments) of immunoglobulins (rheumatoid factor) were revealed in each third woman, who had haemorrhage in postpartum period, while the same situation appeared only in each sixteenth woman in the comparative group. It was expressed in non-significant increase of this marker production (from +10 up to +40 s.u.). It was defined that there are no significant difference among them ($p > 0,05$) while comparing subgroups of the basic group.

Our researches showed that practically each second woman (49,2% of women), who subsequently had postpartum haemorrhage, had insignificant increase of autoantibodies in relation to Nitric oxide synthase, while patients of the comparative group had normal results. The same trend towards increasing of autoantibodies production was registered 1,3 times more often among multiparous women in comparison with primipara and bipara women ($p > 0,05$).

The similar trend is registered also in analyses of autoantibodies level in relation to Angiostatin. Pathologic level of autoantibodies in relation to Angiostatin with the weak deviation towards increasing were registered in 5,0 times more often in the basic group than in comparative ($p < 0,001$) and in 2,1 times more often in first subgroup in comparison with the second subgroup ($p < 0,001$).

The opposite pattern is noticed in analysis of autoantibodies content in relation to collagen, which is produced in decreased quantity in 60,0% of pregnant women of the basic group, while large majority of pregnant women (89,3%) of the comparative group had normal figures. 26 (70,3%) patients of the first subgroup had the results in the range from -20,4 up to -28,3 s.u. and 13 (46,4%) patients of the second subgroup had the results from -22,6 up to -27,8 s.u.

There were no significant differences ($p > 0,05$) in the comparative groups while analysis of antibodies characteristics in relation to interferon α and γ .

There is an opinion [18], that multivariable determination of serum content of autoantibodies of one specificity and comparison of obtained data with average population-based level (without regard to individual immune reactivity) very often misrepresent the real picture and lead to false diagnostic decision. Due to this fact, in order to avoid possible false interpretation of obtained data, we carried out analysis of average individual immune reactivity, which reflects general level of immune system activity.

We found (Fig.1) that only 24,6% of women from the basic group had normal characteristics of average individual immune reactivity, while this result was 60,8% in the comparative group. It ought to be remarked that only 16,2% of patients in the first subgroup had optimal values, while this figure was in 2,2 times less ($p > 0,05$) in the second subgroup.

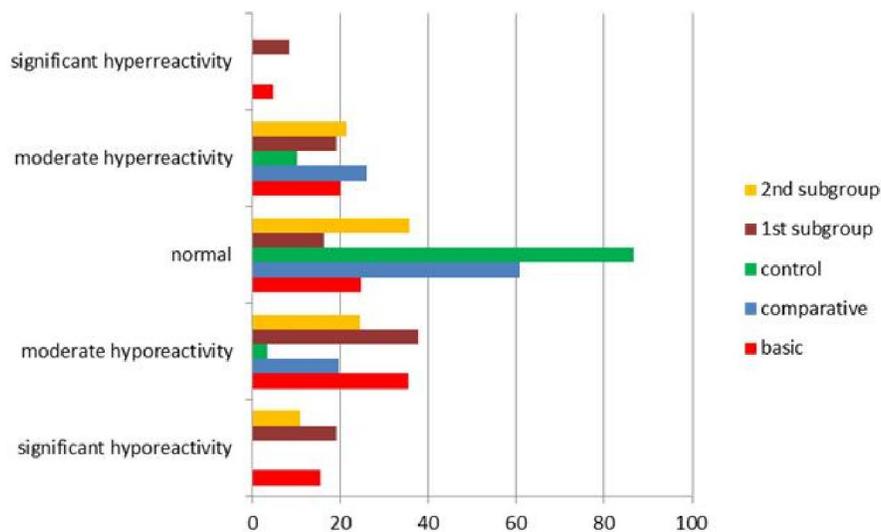


Fig. 1. The percentage of pregnant women in groups depending from the average individual immune reactivity

It is interesting that almost half of the patients (50,8%) from the basic group had decreased immune reactivity, that is in 2,6 times more than in the comparative group (19,4%) ($p < 0,01$). At the same time, the state of hyperreactivity was registered among 25,8% of patients in the comparative group and among 24,6% of women in the basic group. It was defined at more detailed analysis that slightly less than 2/3 of multiparous women and about 2/5 of primipara and bipara women, who had subsequent haemorrhage, had the hyporesponsiveness state.

The research of haemostasis showed that there was increase of prothrombin time - more than 14,7 sec and fibrinogen - more than 5,8 g/l (53,8%) in the most cases in the basic group (76,9%), while the result in comparative group was 19,4% and 3,2% correspondingly ($p < 0,001$). At the same time, reduction of thrombin time - less than 18 sec in 75,4% of cases, moderate reduction of thrombocytes ($165 \cdot 10^9 - 180 \cdot 10^9$) in 66,2% of cases, was typical for women, who had haemorrhage in postpartum period. These figures were 42,8% and 9,7% correspondingly in the comparative group. Only 1/3 of women from basic group and 3/4 of women from the comparative group had normal limits of APTT (activated partial thromboplastin time). This characteristic was increased among 33,% of women and decreased among 36,9% of them, who had subsequent haemorrhage. International normalized ratio was within normal limits in all groups. It was defined while comparing the first and the second

subgroups, that multiparous women had more obvious changes as in plasmic-coagulative so in thrombocytic elements of haemostasis in comparison with primipara and bipara women.

It is necessary to say that all haemostasis parameters of pregnant women from control group were within the normal limits.

Analysis of correlation dependence between the volume of blood loss and the level of regulatory autoantibodies showed the positive correlation dependence with e-NOS ($r = 0,4592$) and angiostatin ($r = 0,5836$), and negative correlation dependence with TrM-03 ($r = -0,5308$) and ANCA ($r = -0,4900$). Negative correlation dependence between blood loss volume and average immunologic activity ($r = -0,4498$) was quite interesting. Similar analysis between childbirths parity and level of regulatory autoantibodies showed that there is positive correlation dependence with autoantibodies level in relation to DNA ($r = 0,7168$) and negative correlation dependence with TrM-03 ($r = -0,3653$), angiostatin ($r = -0,3213$) and collagen ($r = -0,5243$). Characteristic of average immunologic responsiveness had the negative correlation dependence with childbirths parity ($r = -0,6034$).

Correlation analysis showed (Fig.2) the positive dependence between content of fibrinogen and antibodies level in relation to TrM-03 ($r = 0,4485$), ANCA ($r = 0,3255$) and angiostatin ($r = 0,3886$), between the level of antibodies in relation to ANCA and prothrombin time ($r = 0,3963$), and also INR ($r = 0,3089$).

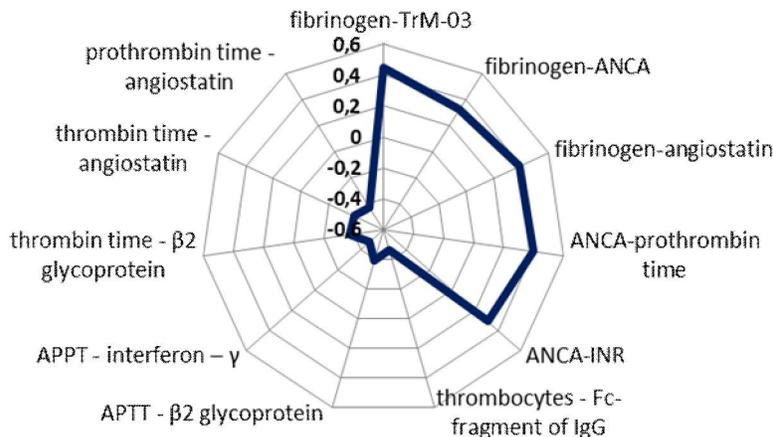


Fig. 2. Correlation between the level of regulatory autoantibodies and parameters of haemostasis

At the same time, negative correlation dependence between the content of thrombocytes and autoantibodies in relation to Fc-fragment of IgG ($r = -0,4576$) was revealed; between APTT characteristic and level of regulatory autoantibodies in relation to beta2 glycoprotein ($r = -0,3870$) and interferon - gamma ($r = -0,4776$); between thrombin time and autoantibodies in relation to beta2 glycoprotein ($r = -0,3716$) and angiostatin ($r = -0,3885$); between prothrombin time and antibodies in relation to angiostatin ($r = -0,4300$).

Therefore, the results of research show that imbalance of regulatory autoantibodies is accompanied by changing of homeostasis system parameters, that plays significant role in the subsequent obstetrical haemorrhage progression.

4. Discussions

Our study showed that obstetric haemorrhages progressed against the background of the most expressed changes in the autoantibodies content. Also, it was defined that this imbalance revealed more often among multiparous women, than among primipara and bipara that correlated with blood loss volume in postpartum period. It is well known fact that imbalances in serum content of different autoantibodies show the imbalanced pathologic activation of the one lymphocyte clones, which combines with pathologic suppression of the other clones activity [20]. High level of autoantibodies is more negative in prognostic view that can show excessive polyclonal activation of the immune system [21]. According to the literature data, natural antibodies, i.e. biological active molecules, are necessary for the body in strictly defined quantities, and due to this fact, not only increasing but also pathologic reduction of any autoantibodies content can lead to the pregnancy pathology [14, 22, 23, 24].

The most obvious changes of autoantibodies level are registered in double-helix DNA, TrM-03

and ANCA, provided that these changes were revealed both in hyperproduction and hypoproduction. In accordance with the literature data [18], increase of autoantibodies in relation to DNA indicates the activation of apoptosis, which was predominantly in infectious processes. According to the results of our study, the pregnant women of the basic group suffered from chronic infectious processes in 1,9 times more often in comparison with the pregnant women of the comparative group, and statistical frequency of this pathology was increasing with the increase of childbirth rate. At the same time [20], obvious hypoproduction of autoantibodies as the manifestation of long general immunological suppression of the body follows with the clearance violation, i.e. decrease of apoptosis products and other antigens removal, can lead to the chronic autointoxication by metabolic products. Revealed changes of antibodies production in relation to double-helix DNA can be also pathogenically connected with changes in haemostasis [25]. These changes often lead to vessel problems among pregnant women and influence on the progress of gestational process.

It was determined that haemorrhage among women of the risk group was developed against the background of reduced autoantibodies production in relation to TrM-03, provided that obvious hypoproduction of this marker were registered among pluripara women in the most of cases (89,2%), that can indirectly prove the chronicity and intensity of coagulation failure processes, which could prevent normal haemostasis during childbirth. Obtained data are consistent with the data of other authors [15], who also registered the reduction of antibodies in relation to the thrombocytes proteins of 94% of women in case of haemorrhage, provided that these changes were more obvious in case of massive haemorrhage. According to the scientists' opinion

[17], abnormal reduction of antibodies serum content in relation to TrM-03 is the marker attribute of pathologic haemorrhage (shows the expected pathologic haemorrhage during childbirth). Correlation analysis based on the results of our study, which revealed negative dependence between the volume of blood loss and antibodies in relation to the thrombocytes proteins, proves this point of view.

In accordance with the results of our study, most of pregnant women from the basic group had obvious hypoproduction of antibodies in relation to ANCA that correlates with the data of the other authors [26], which revealed the similar changes in case of massive blood losses in 53% of cases. Correlation analysis, which revealed the average negative dependence between the volume of blood loss and the level of antibodies in relation to this antigen, can prove the presence of immune processes in haemorrhages pathogenesis. At the same time, according to the data of the other scientists [15], weak deviation dominated among pregnant women, who had this complication. It is known that increase of autoantibodies produce to this antigen is the marker attribute of vascular intima (vasculitis) [24] that can be pathogenically connected with the abnormality of haemostasis system and subsequent progressing of haemorrhage among examined women. It is interesting that these changes were expressed more intensively together with the increase of childbirths parity.

The results of our research showed that pregnant women of the basic group had increased antibodies product in relation to e-NOS, angiotatin, fc igg, interferon α and γ and also to β 2-Glycoprotein, however these changes were not so obvious and expressed. At the same time, it should be noted that moderate hyperproduciton of antibodies in relation to e-NOS and angiotatin in the subgroup of multiparous women were in 1,9 and 2,5 times more in comparison with the subgroup of primipara and bipara women ($p > 0,05$ and $p < 0,001$ correspondingly). According to the literature data, increase of autoantibodies in relation to e-NOS can indicate the violation of vascular tone regulation [20], because endothelial nitrogen oxide has the vasodilatative effect onto the vessels, and also prevents adhesion and aggregation of thrombocytes in intervillous lacuna. Besides that, it was founded that the less the nitrogen oxide is formed, the stronger the contractile response for ATP of isolated uterus occurs [27]. At the same time, the increase of autoantibodies in relation to angiotatin follows with violation of blood coagulability and forming of collateral circulation. Correlation analysis showed that there is dependence between blood loss volume during childbirth and the level of regulatory

antibodies in relation to the factors, which influence on the angiogenesis processes. All these facts can confirm the fact that abovementioned factors play important role in the pathogenesis of obstetric haemorrhages.

Multiparametric determination of autoantibodies level confirmed primary obvious imbalance in immune system of patients, who had obstetric haemorrhage. It was defined that this complication was preceded by hyporeactivity condition of immune system, provided that this condition was met 3,3 times more often among multiparous women in comparison with primipara and bipara women ($p < 0,001$). Thus, negative correlation dependence was defined between parity in childbirths and average immunologic reactivity of the body ($r = -0,6034$). In addition, the presence of primary imbalance in autoantibodies production was followed by changes in haemostasis that in its own turn could influence on the complications during childbirth.

Therefore, carried out studies prove the role of the immune system in progressing of gestational complications, including obstetric haemorrhages. Risk of this pathology formation increases together with the increasing of childbirths parity, for which reason, this group of pregnant women need differentiated approach to the prenatal and childbirth care.

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