The aim of the study – to evaluate changes in cellular immunity in rhesus-sensitized women in response to IVIG administration and the prognostic effectiveness of a method for the prevention of isoimmunization in the next pregnancy.

Materials and Methods. The study was performed on the basis of City Maternity Hospital No. 7 (Odessa) in 2014–2019. 37 rhesus-sensitized women were randomly split in two clinical groups: main clinical group (n=19) where patients received human immunoglobulin for intravenous administration, and control group (n=18) where patients did not receive IVIG.

Results and Discussion. The state of cellular immunity in rhesus-sensitized women is characterized by a moderate decrease in the absolute and relative indices of T-lymphocytes while increasing the number of B-lymphocytes. The NK cell population did not differ from the control group. When analyzing subpopulations of T-lymphocytes, it can be concluded that the number of T-helper cells is increased and the number of T-suppressors is proportionally reduced. These changes explain the increase in the number of B-lymphocytes as a result of increasing antigenic load on cell receptors. In the group of women who received IVIG therapy, the ratio of chances of normalization of cellular immunity was 18.41 (95 % CI 2.62–166.74), T-helper – 14.93 (95 % CI 2.45–107.8), T-suppressors – 14.57 (95 % CI 2.13–127.57) and B-lymphocytes – 31.87 (95 % CI 4.1–333.41). According to the ROC analysis, the quality of the statistical model of IVIG application corresponds to AUC = 0.843 (95 % CI 0.689–0.941).

Key words: pregnancy; rhesus sensitization; human immunoglobulin for intravenous administration.

CLINICAL EFFECTS OF HUMAN IMMUNOGLOBULIN ADMINISTRATION IN WOMEN WITH RHEUS SENSITIZATION AT THE PRE-GRAVID STAGE

The state of cellular immunity in rhesus-sensitized women is characterized by a moderate decrease in the absolute and relative indices of T-lymphocytes while increasing the number of B-lymphocytes. The NK cell population did not differ from the control group. When analyzing subpopulations of T-lymphocytes, it can be concluded that the number of T-helper cells is increased and the number of T-suppressors is proportionally reduced. These changes explain the increase in the number of B-lymphocytes as a result of increasing antigenic load on cell receptors. In the group of women who received IVIG therapy, the ratio of chances of normalization of cellular immunity was 18.41 (95 % CI 2.62–166.74), T-helper – 14.93 (95 % CI 2.45–107.8), T-suppressors – 14.57 (95 % CI 2.13–127.57) and B-lymphocytes – 31.87 (95 % CI 4.1–333.41). According to the ROC analysis, the quality of the statistical model of IVIG application corresponds to AUC = 0.843 (95 % CI 0.689–0.941).

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One of the most effective and widely tested methods of immunotherapy of autoantibody hyperproduction diseases is the treatment with high doses of intravenous immunoglobulin (IVIG) [1, 4]. IVIG is a medicine of normal polyclonal immunoglobulin derived from the pool of several thousand donors, which determines the content of all IgG, including antibodies to exogenous antigens, natural antibodies and anti-idiotypic antibodies [1, 6]. It is known that anti-idiotypic antibodies bind and neutralize pathogenic antibodies and interfere with their interaction with the autoantigen. Fragments (F)ab(2) contained in IVIG reduce functional activity or block the binding of autoantibodies to the corresponding autoantigens, such as antibodies to D-antigen [6, 7]. The suppressive effects of IVIG may also be due to its effect on B-lymphocyte receptors, which leads to a decrease in immunoglobulin production [1, 4, 6].

However, the mechanisms underlying the inhibition of B-lymphocyte proliferation during IVIG administration have not yet been studied. It is known that the binding of anti-idiotypic antibodies to antigenic determinants and surface IgM or IgG on B lymphocytes causes a decrease in antibody production. In addition, IVIG can reduce the level of antibodies, because the medicines contain antibodies to CD5 receptors of B lymphocytes [4]. Moreover, a number of studies have shown that IVIG induces apoptosis of B- and some T-cell lines [1].

The changes in cellular immunity in rhesus-sensitized women, the use of IVIG is a pathogenetic treatment.

**THE AIM OF THE STUDY** – to evaluate changes in cellular immunity in rhesus-sensitized women in response to IVIG administration and the prognostic efficacy of the method for the prevention of isoimmunization in subsequent pregnancy.

**MATERIALS AND METHODS.** The study was performed on the basis of City Maternity Hospital No. 7 (Odessa) in 2014–2019. In accordance with the standards of medical care, 37 rhesus-sensitized women were conducted according to the orders of the Ministry of Health of Ukraine No. 676 issued on 31.12.2004 “About approval of clinical protocols on obstetric and gynecological care – pregnancy management in women with immune conflicts” and No. 417 issued on 15.07.2011 “On the organization of ambulatory obstetric and gynecological care in Ukraine” [2, 3].

To evaluate the effectiveness of the use of human immunoglobulin for intravenous administration in complex therapy of rhesus sensitization, all women observed by stratified randomization method were divided into two groups.

Group I – the main group, consisted of 19 women with rhesus-sensitization, who, with the aim of preventing the development of hemolytic disease of the fetus and newborn, was introduced IVIG. The selection of patients in the main group was performed according to the following criteria: medicine for the next pregnancy of women with rhesus antibodies and obstetric obstetric history (antenatal fetal death from hemolytic disease in history, etc.); initially high rhesus antibody titer level (1:32 and above), 6–12 months postpartum. Exclusion criteria were severe extragenital diseases in decompensation stage. Contraindications to this therapy were allergic reactions to the introduction of immunoglobulins.

Intravenous immunoglobulin was administered at a dose of 5.0 grams in the amount of 2 transfusions at intervals of 1–2 days. The initial rate of transfusion was 1.4 ml/kg body weight / hour, after 10 minutes with good tolerability of the drug speed gradually increased to a maximum of 1.9 ml/kg body weight /hour and kept it until the end of administration. Intravenous immunoglobulin was administered under the control of blood pressure and heart rate. There were no responses to immunoglobulin administration.

Group II – (comparison group) consisted of 18 rhesus-sensitized women who were under standard care at the same time interval after delivery.

The cellular level of immunity was determined by flow cytometry (BD FACS apparatus, BD Biosciences, USA) [5].

Statistical analysis of the obtained data was carried out using the packages STATISTICA 10.0, IBM SPSS Statistics 22.0, MedCalc 14.8.1 and Microsoft Excel 2010 with the application AtteStat 12.5, an online SISA calculator (Simple Interactive Statistical Analysis).

**RESULTS.** Absolute and relative indicators of cellular immunity in different groups of women with rhesus sensitization are presented in tables 1 and 2. All absolute and relative indicators of cellular immunity in the standard-management group of women did not statistically differ significantly during the observation period (Table 3, 4).

In the group of sensitized women who received IVIG, indicators of absolute and relative cellular immunity were statistically significantly different by most indicators (Tables 5 and 6).

| Indices | CD3+ | CD3+CD16/56+ | CD3+HLA-DR+ | CD3+CD4+ | CD3+CD4+HLA-DR+ | CD3+CD8+ |
|---------|------|-------------|-------------|----------|-----------------|----------|
| Before treatment | 56.81±1.69 | 4.08±0.41 | 2.83±0.32 | 59.59±1.39 | 4.59±0.46 | 16.48±1.34 |
| Control | 60.11±2.14 | 4.5±0.55 | 2.65±0.46 | 58.5±2.3 | 3.05±0.42 | 17.83±1.91 |
| Main | 72.68±1.98* | 5.36±0.46 | 4.05±0.42 | 52.47±1.94* | 3.75±0.54* | 24.47±1.7* |

* Statistical significance of differences with indicators before treatment р<0.05
### Table 2. Absolute indices of cellular immunity in different groups of women with rhesus sensitization

| Indices                  | CD3+   | CD3+CD4+ | CD3+CD8+ | CD19+   | CD3-CD16/56+ |
|--------------------------|--------|----------|----------|---------|--------------|
| Before treatment         | 1.12±0.07 | 1.55±0.08 | 0.38±0.04 | 0.68±0.05 | 0.27±0.06    |
| Control                  | 1.31±0.11 | 1.51±0.13 | 0.38±0.06 | 0.6±0.07  | 0.38±0.1     |
| Main                     | 1.5±0.09*  | 1.22±0.09*  | 0.49±0.06 | 0.36±0.05* | 0.29±0.09    |

* Statistical significance of differences with indicators before treatment р<0.05

### Table 3. Result of variance analysis (One-way ANOVA) of relative indicators of cellular immunity in the study groups of women who received standard treatment

| Indices                  | Square Sum | Degree of freedom | SD  | F   | P     |
|--------------------------|------------|------------------|-----|-----|-------|
| CD3+                     | 131.892    | 1                | 131.892 | 1.338 | 0.253 |
| CD3+CD16/56              | 5225.453   | 53               | 98.593  |       |       |
| CD3                      | 5357.345   | 53               | 53     | 0.341 | 0.562 |
| CD3+CD4+                 | 2.071      | 1                | 2.071   | 0.341 | 0.562 |
| CD3+CD4+CD8+ HLA-DR     | 322.243    | 53               | 6.080   |       |       |
| CD3+CD4+                 | 324.314    | 53               | 53     | 0.182 | 0.671 |
| CD3+CD4+CD8+ HLA-DR     | 14.508     | 1                | 14.508  | 0.182 | 0.671 |
| CD3+CD4+CD8+ HLA-DR     | 4215.419   | 53               | 79.536  |       |       |
| CD3+CD4+CD8+ HLA-DR     | 4229.927   | 53               | 53     |       |       |
| CD3+CD4+CD8+             | 14.508     | 1                | 14.508  | 0.182 | 0.671 |
| CD3+CD4+CD8+ HLA-DR     | 3531.743   | 53               | 66.637  |       |       |
| CD3+CD4+CD8+ HLA-DR     | 3553.709   | 53               | 53     |       |       |
| CD3+CD4+CD8+ HLA-DR     | 0.431      | 1                | 0.431   | 0.031 | 0.862 |
| CD3+CD4+CD8+ HLA-DR     | 743.767    | 53               | 14.033  |       |       |
| CD3+CD4+CD8+ HLA-DR     | 744.197    | 53               | 53     |       |       |
| CD3+CD4+CD8+ HLA-DR     | 0.005      | 1                | 0.005   | 0.009 | 0.924 |
| CD3+CD4+CD8+ HLA-DR     | 29.042     | 53               | 0.548   |       |       |
| CD3+CD4+CD8+ HLA-DR     | 29.047     | 53               | 53     |       |       |
| CD3+CD4+CD8+ HLA-DR     | 0.000      | 1                | 0.000   | 0.000 | 0.991 |
| CD3+CD4+CD8+ HLA-DR     | 146.785    | 53               | 2.770   |       |       |
| CD3+CD4+CD8+ HLA-DR     | 146.785    | 53               | 53     |       |       |
| CD19+                    | 52.141     | 1                | 52.141  | 1.929 | 0.171 |
| NK                       | 0.490      | 1                | 0.490   | 0.011 | 0.917 |
| NK                       | 2365.755   | 53               | 44.637  |       |       |
| NK                       | 2366.245   | 53               | 53     |       |       |
Table 4. Result of variance analysis (One-way ANOVA) of absolute indicators of cellular immunity in the studied groups of women, where standard treatment was conducted

| Indices | Square Sum | Degree of freedom | SD | F   | P   |
|---------|------------|------------------|----|-----|-----|
| CD3+    | 0.432      | 1                | 0.432 | 1.913 | 0.172 |
| Within  | 11.964     | 53               | 0.226 |      |     |
| Total   | 12.396     | 54               |      |      |     |
| CD3+ CD4+ | 0.015    | 1                | 0.015 | 0.494 | 0.825 |
| Within  | 16.445     | 53               | 0.310 |      |     |
| Total   | 16.461     | 54               |      |      |     |
| CD3+ CD8+ | 0.000    | 1                | 0.000 | 0.000 | 0.995 |
| Within  | 4.111      | 53               | 0.078 |      |     |
| Total   | 4.111      | 54               |      |      |     |
| CD19+   | 0.080      | 1                | 0.080 | 0.711 | 0.403 |
| Within  | 5.937      | 53               | 0.112 |      |     |
| Total   | 6.016      | 54               |      |      |     |
| NK      | 0.145      | 1                | 0.145 | 0.918 | 0.342 |
| Within  | 8.392      | 53               | 0.158 |      |     |
| Total   | 8.537      | 54               |      |      |     |

Table 5. Result of variance analysis (One-way ANOVA) of relative indicators of cellular immunity in the study groups of women treated with IVIG

| Indices | Square Sum | Degree of freedom | SD | F     | P     |
|---------|------------|------------------|----|-------|-------|
| CD3+    | 3163.058   | 1                | 3163.058 | 33.001 | 0.000 |
| Within  | 5175.781   | 54               | 95.848   |       |       |
| Total   | 8338.839   | 55               |        |       |       |
| CD3+ CD16/56 | 20.630 | 1                | 20.630 | 3.663 | 0.061 |
| Within  | 304.164    | 54               | 5.633    |       |       |
| Total   | 324.794    | 55               |        |       |       |
| CD3+ HLA-DR | 18.608 | 1                | 18.608 | 4.883 | 0.031 |
| Within  | 205.792    | 54               | 3.811    |       |       |
| Total   | 224.400    | 55               |        |       |       |
| CD3+ CD4+ HLA-DR | 8.788 | 1                | 8.788 | 1.201 | 0.278 |
| Within  | 395.045    | 54               | 7.316    |       |       |
| Total   | 403.834    | 55               |        |       |       |
| CD3+ CD8+ | 800.859 | 1                | 800.859 | 12.705 | 0.001 |
| Within  | 3403.980   | 54               | 63.037   |       |       |
| Total   | 4204.839   | 55               |        |       |       |
| CD3+ CD8+ HLA-DR | 49.410 | 1                | 49.410 | 3.207 | 0.079 |
| Within  | 831.945    | 54               | 15.406   |       |       |
| Total   | 881.356    | 55               |        |       |       |
| CD3+ CD4+/ CD3+ CD8+ | 1.485 | 1                | 1.485 | 3.211 | 0.079 |
| Within  | 24.974     | 54               | 0.462    |       |       |
| Total   | 26.459     | 55               |        |       |       |
As a result of comprehensive treatment of rhesus-sensitized women using IVIG, a statistically significant decrease in the absolute (F = 12.054, p = 0.001) and relative (F = 24.583, p = 0.0001) numbers of B lymphocytes was observed. The indicators were consistent with those of the control group of women. In the group of women with standard observation, the level of B-lymphocytes did not change significantly (F = 0.711, p = 0.403 and F = 1.929, p = 0.171).

Discussion. Given the important role of immunoglobulins as regulators of the level of the immune response in the form of stimulating and suppressive effects on the B-cell system, there is a point of interest to evaluate the degree of change by subpopulations of T-lymphocytes. The state of cellular immunity in rhesus-sensitized women is characterized by a moderate decrease in the absolute and relative rates of T-lymphocytes while increasing the number of B-lymphocytes. The NK cell population did not differ from that of the control group. In the analysis of subpopulations of T-lymphocytes, we can conclude that the number of T-helpers is increased and the number of T-suppressors is proportionally reduced. These changes explain the increase in the number of B lymphocytes due to increasing antigenic load on cell receptors.

As a result of the therapy of rhesus-sensitized women, we can note a statistically significant normalization of the

| Table 6. Result of variance analysis (One-way ANOVA) of absolute indicators of cellular immunity in the studied groups of women receiving complex therapy |
|---|---|---|---|---|---|
| Indices         | Square Sum | Degree of freedom | SD  | F    | P    |
| CD3+            | 1.788      | 1                  | 1.788 | 8.662 | 0.005 |
| CD4+  CD8+      | 11.148     | 54                 | 0.206 |       |      |
| CD19+           | 12.937     | 55                 |       |       |      |
| NK              | 15.188     | 55                 |       |       |      |
| CD19+           | 0.149      | 1                  | 0.149 | 1.910 | 0.173 |
| CD8+            | 4.216      | 54                 | 0.078 |       |      |
| CD3+  CD8+      | 4.365      | 55                 |       |       |      |
| CD19+           | 12.272     | 55                 | 1.227 | 12.054 | 0.001 |
| NK              | 8.099      | 54                 | 0.004 | 0.028 | 0.867 |
| Total           | 2286.246   | 55                 | 42.307 |      |      |
In assessing the effectiveness of normalization of subpopulations of T lymphocytes, it is necessary to note the absence of statistically significant differences in the group of women with standard therapy: T-helpers – $\chi^2 = 2.37$, relative risk decreased by 71%, NNT = 4 at the significance level p = 0.12, T-suppressors – $\chi^2 = 0.71$, relative risk decreased by 60%, NNT = 4 at significance levels p = 0.40. In the group receiving IVIG therapy, T-helpers were $\chi^2 = 10.64$, the relative risk decreased by 78%, NNT = 2 at the significance level p = 0.001, T-suppressors – $\chi^2 = 9.16$, the relative risk decreased by 83%, NNT = 2, p = 0.02.

In the group of women with standard observation, the ratio of chances of normalization of cellular immunity was:

- T-lymphocyte level – 2.5 (95 % CI 0.41–16.32), T-helpers – 5.09 (95 % CI 0.73 – 44.16), T-suppressors – 3.07 (95 % CI 0.41 – 27.85) and B-lymphocytes – 2.5 (95 % CI 0.41 – 16.32).

In the group of women who received therapy with IVIG, the ratio of chances of normalization of indicators of cellular immunity was: by the level of T-lymphocytes – $18.41$ (95 % CI 2.62–166.74), T-helpers – $14.93$ (95 % CI 2.45–107.8), T-suppressors – $14.57$ (95 % CI 2.13–127.57) and B lymphocytes – $31.87$ (95 % CI 4.1–333.41).

The statistical model with standard observation of rhesus-sensitized women on the level of normalization of T-lymphocytes proved to be less effective in comparison with the model of “IVIG treatment”. The AUC in the standard observation group was $0.59$, the relative risk decreased by 50%, NNT = 6 at the significance level $p = 0.12$, T-suppressors – $\chi^2 = 0.62$, relative risk decreased by 60%, NNT = 4 at the significance level $p = 0.44$. In the group of women treated with IVIG, the AUC was $0.866$ (95 % CI 0.716–0.954), this indicator corresponds to the “very good” quality of the statistical treatment model.

In the group of women who received IVIG therapy, the odds ratio of normalization of cellular immunity indicators was: by the level of T-lymphocytes – $18.41$ (95 % CI 2.62–166.74), T-helpers – $14.93$ (95 % CI 2.45–107.8), T-suppressors – $14.57$ (95 % CI 2.13–127.57) and B lymphocytes – $31.87$ (95 % CI 4.1–333.41). According to the ROC analysis, the quality of the statistical model of the IVIG application corresponds to the “very good” level – 0.843 (95 % CI 0.689–0.941). According to the ROC analysis, the level of B lymphocytes in the compared AUC groups of women in with standard observation, the level of T-helper did not differ significantly from the indicators before treatment, AUC was 0.56 (95 % CI 0.385–0.725), indicating model quality as “unsatisfactory”. The AUC in the group of women treated with IVIG was 0.742 (95 % CI 0.575–0.870), it corresponds to a “good” quality of the statistical treatment model.

In the group with standard observation of the control panel of the level of T-suppressors recorded at the level of 0.566 (95 % CI 0.391–0.730) – “poor” quality of the model according to the Juden classification. In rhesus-sensitized women receiving complex therapy, the AUC for T-suppressors was 0.785 (95 % CI 0.622–0.902), which, in contrast to the previous group, corresponds to the “good” quality of the statistical model.

According to ROC analysis of the level of B lymphocytes in the compared groups, the AUC in women with rhesus sensitization and standard observation corresponded to the poor model quality – 0.58 (95 % CI 0.405–0.742). In the group of women receiving IVIG therapy, the quality of the statistical model corresponded to a “very good” level – 0.843 (95 % CI 0.689–0.941).

The ROS-analysis of the efficacy of therapy of rhesus-sensitized women IVIG on the normalization of cellular immunity showed (Fig. 1).
the comparison group corresponded to the poor quality of the model – 0.58 (95 % CI, 0.405–0.742).

The sensitivity of the use of IVIG was 0.82, specificity - 0.76, which corresponds to the high quality of the studied statistical model and allows to recommend for carrying out pre-gravidar preparation of women with Rh-isosensitization.

CONCLUSIONS. 1. The state of cellular immunity in rhesus-sensitized women, characterized by a moderate decrease in the absolute and relative indices of T-lymphocytes while increasing the number of B-lymphocytes.

2. The NK cell population does not differ from that of the control group.

3. In the analysis of subpopulations of T-lymphocytes, we can conclude that the number of T-helper is increased and the number of T-suppressors is proportionally reduced. These changes explain the increase in the number of B lymphocytes due to increasing antigenic load on cell receptors.

4. In the group of women who received therapy with IVIG, the ratio of the chances of normalization of indicators of cellular immunity was: by the level of T-lymphocytes – 18.41 (95 % CI 2.62–166.74), T-helpers – 14.93 (95 % CI 2.45–107.8), T-suppressors – 14.57 (95 % CI 2.13–127.57) and B lymphocytes – 31.87 (95 % CI 4.1–333.41).

5. According to ROC analysis, the quality of the statistical model for the use of IVG corresponds to a “very good” level – 0.843 (95 % CI 0.689–0.941) versus the control group corresponded to poor quality – 0.58 (95 % CI 0.405–0.742).

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