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Proteflazid® in the treatment and prevention of human herpesvirus infection in pregnant women: a meta-analysis of clinical trials results

Abstract: Conducted a meta-analysis of the results obtained in clinical trials to evaluate the clinical efficacy Proteflazid® in the treatment of pregnant with herpes viral infection. On 6 controlled trials involving 524 pregnant women from 2003 to 2012. The results show that the Proteflazid® in pregnant women with human herpesvirus infection pregravid during preparation and during pregnancy has a positive effect on pregnancy, helps prevent obstetric complications, improves cellular immunity.

Keywords: meta-analysis, herpes virus, human herpesvirus infection, pregnancy, Proteflazid®.

One of the urgent problems of modern obstetrics is the impact of viral infection on the gestation course, the childbirth, the postpartum period, the state of the fetus and the newborn. Human herpesvirus (HHV) infection is one of the most common diseases in the world [1]. In recent years there has been a tendency to increase the
frequency of HHV infection in pregnant women and its ability to the epidemic spread under certain conditions [2].

HHV infection during pregnancy is a significant risk factor for the development of obstetric and perinatal complications, and their frequency depends on the form of herpes infection with a clear predominance of various pathological conditions against the background of recurrent infections [3].

In recent years, chronic persistent viral and bacterial infections have played a leading role in the recurrent miscarriage etiology. The frequency of this pathology during pregnancy reaches 67.1-76.3% [2].

The development of infection is contributed by the inhibition of cellular and humoral immunity during pregnancy due to physiological immunosuppression by reducing the number and the activity of T and B lymphocytes, increased production of corticosteroids, estrogen and progesterone. The main feature of the immune status in herpes infection is the formation of secondary immunodeficiency. Therefore, combination of infection and pregnancy seems particularly unfavorable and is accompanied by various complications of pregnancy, perinatal morbidity and mortality [2].

Peculiarities of pregnancy combined with HHV infection:
- herpesvirus infection in pregnant women usually occurs in the form of genital localized forms; more common is a relapsing form of the infection;
- during pregnancy, primary infection is rather atypical, especially in the later stages;
- asymptomatic course of the disease is associated with the highest rate of infection in utero.

The outcome of pregnancy against the background of HHV infection at overall unfavorable solution is different and depends on the gestational age when the infection occurred: in the 1st trimester (12 weeks) the pregnancy is complicated by spontaneous abortions, anembryonic gestation; in the 2nd trimester (13-27 weeks) fetal abnormalities (3.6%), spontaneous abortions (20.1%) failed abortion (5.4%) are diagnosed; in the 3rd trimester (28-36 weeks) fetal death (10.9%), fetal abnormalities (7.6%), premature birth (7.3%) occur [10].

The issue of HHV infection efficient therapy is still a key focus of physicians of various specialties due to an annual increase in the number of patients with severe disease with often transition to a chronic process. Today, the search of efficient and
safe drugs of prolonged use is conducted [12]. HHV infection treatment in pregnant women is associated with difficulties, due to the fact that most of known antiviral drugs have adverse effects on the fetus.

A modern drug that worked well for many years and can be widely used in obstetric practice in the treatment of pregnant women with HHV infection is Proteflazid®. Proteflazid® has no toxic, mutagenic, teratogenic influence. It is a safe drug for the use in obstetric practice [1].

Proteflazid® is a drug with direct antiviral action against DNA viruses. Active ingredient of the drug Proteflazid® (flavonoids) inhibits the synthesis of viral DNA in the infected cells through inhibition of virus specific enzymes, such as DNA polymerase and thymidine kinase.

The drug Proteflazid® promotes the synthesis of endogenous α- and γ-interferons up to the physiologically active level (without the occurrence of the phenomenon of refractoriness), which increases the local nonspecific resistance to viral and bacterial infections, and normalizes the immune status. The drug also prevents the accumulation of lipid peroxidation products (inhibits free radical reactions) and is an apoptosis modulator, causing the death of infected cells.

It was shown in clinical trials that the drug Proteflazid® helps to restore the immune function of the body by arresting viral replication at local application (suppositories and vaginal swabs with a solution of the drug), thus ensuring a significant improvement in cellular immunity as well as quick and efficient elimination of the agent.

It should be noted that the drug Proteflazid® shows high bioavailability, it is not toxic, it can be actively used in pediatrics, for the pregravid preparation, and for the prevention and the treatment of herpesvirus infections in pregnant women [1]. The drug Proteflazid® prevents the disease relapse and prolongs the period of remission.

**Purpose of the work.** Meta-analysis and evaluation of clinical efficacy of the drug Proteflazid® in pregnant women with HHV infection (HSV-1, HSV-2, CMV).

**Materials and Methods.** Information about clinical trials of the effectiveness of the drug Proteflazid® in the treatment and prevention of HHV infection in pregnant women was obtained with the help of information search engines on the Internet. The list of publications selected for the meta-analysis reflecting the effectiveness of the drug Proteflazid® in the treatment and prevention of HHV infection in pregnant women between 2003 and 2012 is presented in Table 1.
Table 1

The list of publications selected for the meta-analysis reflecting the effectiveness of the drug Proteflazid® in the treatment and prevention of HHV infection in pregnant women

<table>
<thead>
<tr>
<th>Author</th>
<th>Year</th>
<th>Country</th>
<th>General number of patients</th>
<th>Scope of application of the drug Proteflazid®</th>
<th>Clinical study results</th>
</tr>
</thead>
<tbody>
<tr>
<td>Symrok V.V. [9]</td>
<td>2003</td>
<td>Ukraine</td>
<td>34</td>
<td>Herpes virus manifestations and CMV in pregnant women</td>
<td>Reduction in complications of pregnancy, including the development of utero-placental insufficiency</td>
</tr>
<tr>
<td>Nikolaeva S.V. [8]</td>
<td>2007</td>
<td>Ukraine</td>
<td>140</td>
<td>Pregravid preparation and the course of pregnancy in women with miscarriage against the background of herpes virus infection</td>
<td>Improvement in the function of immune system, reduction in the intensity of viral replication, positive impact on the course of pregnancy</td>
</tr>
<tr>
<td>Nagornaya V.F. [2]</td>
<td>2007</td>
<td>Ukraine</td>
<td>80</td>
<td>Pregnant women with miscarriage against the background of herpes virus infection</td>
<td>Improvement in the function of immune system, reduction in the frequency of relapses of herpes virus infection</td>
</tr>
<tr>
<td>Azimova E.I. [7]</td>
<td>2011</td>
<td>Uzbekistan</td>
<td>60</td>
<td>Recurrent genital herpes in pregnant women with fetal death in history</td>
<td>Improvement in the function of immune system, Improvement in the function of placenta, reduction in obstetric and perinatal complications in women</td>
</tr>
<tr>
<td>Benyuk V.O. [1]</td>
<td>2012</td>
<td>Ukraine</td>
<td>90</td>
<td>Herpes virus infection in pregnant women with metabolic syndrome</td>
<td>Improvement in the function of immune system, significant reduction in obstetric and perinatal complications in women</td>
</tr>
</tbody>
</table>

**Software:** In order to ensure a higher degree of reliability of the results two specialized programs RevMan and SPSS were used at the same time.

**Inclusion and exclusion criteria**

The studies to be included in the meta-analysis shall meet the following criteria:

1. Controlled studies providing for control or a control group are focused on studying clinical efficacy of the drug Proteflazid® in the treatment and the prevention of HHV infection (HSV-1, HSV-2, CMV) in pregnant women.
2. It is necessary to confirm the clinical diagnosis of diseases identified in pregnant women.

3. Published data on the effectiveness of the drug Proteflazid® are complete.

In accordance with the inclusion and exclusion criteria, 6 controlled clinical trials of the drug Proteflazid® efficiency in the treatment of HHV infection in pregnant women were included in the meta-analysis, and 3 clinical trials were excluded.

The selected 6 trials included 359 pregnant women from experimental group and 185 pregnant women from the control group.

The patients underwent a thorough examination before and after the treatment, including the generally accepted clinical and laboratory tests, ultrasound study, study of cellular and humoral immunity. Polymerase chain reaction (PCR) was used as a general diagnostic method.

Meta-analysis of clinical trials reflecting the results of the drug Proteflazid® efficiency in the treatment of HHV infection in pregnant women was conducted in accordance with the following statistically significant indexes:

- Dynamics of cell-mediated immunity (CD3, CD4, CD19, CD8, immunoregulatory index) against the background of the treatment of HHV infection with the drug Proteflazid® in pregnant women:

  1. The relative T-lymphocytes (CD3) count in the blood of pregnant women with HHV infection, %.
  2. The relative T-helper-inducer lymphocytes (CD4) count in the blood of pregnant women with HHV infection, %.
  3. The relative T-suppressor lymphocytes (CD8) count in the blood of pregnant women with HHV infection, %.
  4. The relative B-lymphocytes (CD19) count in the blood of pregnant women with HHV infection, %.
  5. The value of the immunoregulatory index (CD4/CD8) in pregnant women with HHV infection.

- The course of pregnancy and the development of obstetric complications in pregnant women with HHV infection against the background of the treatment with the drug Proteflazid®:

  1. The incidence of threatened abortion in women with HHV infection.
  2. The incidence of spontaneous abortion in women with HHV infection.
  3. The incidence of term (in time) birth in women with HHV infection.
**Dynamics of cell-mediated immunity (CD3, CD4, CD19, CD8, immunoregulatory index) during the HHV infection therapy with the drug Proteflazid®**

In terms of "relative T-lymphocytes (CD3) count in the blood of pregnant women with HHV infection" against the background of the drug Proteflazid® 100 pregnant women with HHV infection were studied, 50 of them were in the experimental group and 50 – in the control group.

In terms of "relative T-helper/inducer lymphocytes (CD4) count in the blood of pregnant women with HHV infection" against the background of the drug Proteflazid® 100 pregnant women with HHV infection were studied, 50 of them were in the experimental group and 50 – in the control group.

290 pregnant women were studied in terms of "relative T-helper/inducer lymphocytes (CD4) count in the blood of pregnant women with HHV infection", 220 of them with HHV infection taking the drug Proteflazid® were in the experimental group, and 70 healthy pregnant women not taking the drug Proteflazid® - in the control group.

290 pregnant women were studied in terms of "relative T-suppressor lymphocytes (CD8) count in the blood of pregnant women with HHV infection", 220 of them with HHV infection taking the drug Proteflazid® were in the experimental group, and 70 healthy pregnant women not taking the drug Proteflazid® - in the control group.

160 pregnant women with HHV infection were studied by the parameter “relative B-lymphocytes (CD19) count in the blood of pregnant women with HHV infection” after the treatment with the drug Proteflazid®, 80 of them are in the experimental group, and 80 – in the control group. (table 2).

**Table 2**

<table>
<thead>
<tr>
<th>Author</th>
<th>Experimental group</th>
<th>Control group</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>The relative B-lymphocytes (CD19) count in the blood of pregnant women with HHV infection treated with Proteflazid®, %</td>
<td>The relative B-lymphocytes (CD19) count in the blood of pregnant women with HHV infection not treated with Proteflazid®, %</td>
</tr>
<tr>
<td>Nikolaeva S.V. 2007</td>
<td>13.49</td>
<td>11.47</td>
</tr>
<tr>
<td>Azimova E.I., 2011</td>
<td>13.48</td>
<td>11.98</td>
</tr>
<tr>
<td>Benyuk V.O., 2012</td>
<td>13.48</td>
<td>11.98</td>
</tr>
<tr>
<td><strong>Total</strong></td>
<td><strong>80</strong></td>
<td></td>
</tr>
</tbody>
</table>
290 pregnant women were studied in terms of "The value of the immunoregulatory index (CD4/CD8) in pregnant women with HHV infection", 220 of them with HHV infection taking the drug Proteflazid® were in the experimental group, and 70 healthy pregnant women not taking the drug Proteflazid® - in the control group.

Results and Discussion

Data integration for analysis. Table 3 shows the group statistics for independent samplings for the index "The relative T-lymphocytes (CD3) count in the blood of pregnant women with HHV infection" against the background of administration of the drug Proteflazid® in experimental and control groups.

Table 4 shows the values of the test for independent samplings for the index "The relative T-lymphocytes (CD3) count in the blood of pregnant women with HHV infection" against the background of administration of the drug Proteflazid®.

Table 3

<table>
<thead>
<tr>
<th></th>
<th>VAR2</th>
<th>N</th>
<th>Mean</th>
<th>STD</th>
<th>Standard error of the mean</th>
</tr>
</thead>
<tbody>
<tr>
<td>VAR1</td>
<td>1.00</td>
<td>2</td>
<td>64.7250</td>
<td>.0778</td>
<td>.05500</td>
</tr>
<tr>
<td></td>
<td>2.00</td>
<td>2</td>
<td>57.5150</td>
<td>.06364</td>
<td>.04500</td>
</tr>
</tbody>
</table>

Table 4

<table>
<thead>
<tr>
<th>Levene’s test</th>
<th>Student’s t-test</th>
<th>95% confidence interval of the difference of means</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td>F</td>
</tr>
<tr>
<td>VAR1</td>
<td>equality of dispersion is assumed</td>
<td>.</td>
</tr>
<tr>
<td></td>
<td>equality of dispersion is not assumed</td>
<td>101.459</td>
</tr>
</tbody>
</table>
The significance of the t-test for independent samplings (less than 0.05) indicates that the average value of the relative content of T-lymphocytes (CD3) in pregnant women with HHV infection taking the drug Proteflazid® differs significantly from the average value of the relative content of T-lymphocytes (CD3) in pregnant women with HHV infection not taking the drug Proteflazid®.

Table 5 shows the values of the test for the index "The relative T-helper/inducer lymphocytes (CD4) count in the blood of pregnant women with HHV infection" against the background of administration of the drug Proteflazid® for the experimental and control groups.

**Table 5**

**Group statistics for the index "The relative T-helper/inducer lymphocytes (CD4) count in the blood of pregnant women with HHV infection"**

<table>
<thead>
<tr>
<th>VAR</th>
<th>N</th>
<th>Mean</th>
<th>STD</th>
<th>Standard error of the mean</th>
</tr>
</thead>
<tbody>
<tr>
<td>1,00</td>
<td>2</td>
<td>39,8050</td>
<td>.14849</td>
<td>.10500</td>
</tr>
<tr>
<td>2,00</td>
<td>2</td>
<td>35,2100</td>
<td>.26870</td>
<td>.19000</td>
</tr>
</tbody>
</table>

Table 6 shows the values of the test for the index "The relative T-helper/inducer lymphocytes (CD4) count in the blood of pregnant women with HHV infection" against the background of administration of the drug Proteflazid®.

**Table 6**

**Values of the test for independent samplings for the index "The relative T-helper/inducer lymphocytes (CD4) count in the blood of pregnant women with HHV infection"**

<table>
<thead>
<tr>
<th>Levene’s test</th>
<th>Student’s t-test</th>
<th>95% confidence interval of the difference of means</th>
</tr>
</thead>
<tbody>
<tr>
<td>F</td>
<td>Val</td>
<td>t</td>
</tr>
<tr>
<td>VAR 1</td>
<td>equality of dispersion is assumed</td>
<td>21.167</td>
</tr>
<tr>
<td>equality of dispersion is not assumed</td>
<td>21.167</td>
<td>1.55</td>
</tr>
</tbody>
</table>
The significance of the t-test for independent samplings (less than 0.05) indicates that the average value of the relative content of T-helper/inducer lymphocytes (CD4) in pregnant women with HHV infection taking the drug Proteflazid® differs significantly from the average value of the relative content of T-helper/inducer lymphocytes (CD4) in pregnant women with HHV infection not taking the drug Proteflazid®.

Table 7 shows a group statistics for the index "The relative T-helper/inducer lymphocytes (CD4) count in the blood of pregnant women with HHV infection" against the background of administration of the drug Proteflazid® for the experimental and the healthy pregnant women.

<table>
<thead>
<tr>
<th>VAR7</th>
<th>N</th>
<th>Mean</th>
<th>STD</th>
<th>Standard error of the mean</th>
</tr>
</thead>
<tbody>
<tr>
<td>1.00</td>
<td>2</td>
<td>33.4550</td>
<td>9.12875</td>
<td>6.45500</td>
</tr>
<tr>
<td>2.00</td>
<td>2</td>
<td>37.3400</td>
<td>8.25901</td>
<td>5.84000</td>
</tr>
</tbody>
</table>

Table 8 shows the values of the test for the index "The relative T-helper/inducer lymphocytes (CD4) count in the blood of pregnant women with HHV infection" against the background of administration of the drug Proteflazid®.

**Table 8**

Values of the test for independent samplings for the index "The relative T-helper/inducer lymphocytes (CD4) count in the blood of pregnant women with HHV infection"

<table>
<thead>
<tr>
<th>VAR7</th>
<th>Levene's test</th>
<th>Student's t-test</th>
<th>95% confidence interval of the difference of means</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>F Val.</td>
<td>t Stat.sv.</td>
<td>Significance (2-sided)</td>
</tr>
<tr>
<td>equality of dispersion is assumed</td>
<td>1,213E14 .000 .446 2 .699 -3.88500 8.70475 -41.33850 33.56850</td>
<td></td>
<td></td>
</tr>
<tr>
<td>equality of dispersion is not assumed</td>
<td>-.446 1.980 .699 -3.88500 8.70475 -41.69820 33.92820</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>
The significance of the t-test for independent samplings (higher than 0.05) indicates that the average value of the relative content of T-helper/inducer lymphocytes (CD4) in pregnant women with HHV infection taking the drug Proteflazid® does not differ significantly from the average value of the relative content of T-helper/inducer lymphocytes (CD4) in healthy pregnant women not taking the drug Proteflazid®.

Table 9 shows a group statistics for the index "The relative T-suppressor lymphocytes (CD8) count in the blood of pregnant women with HHV infection" against the background of administration of the drug Proteflazid® for the experimental and the healthy pregnant women.

Table 10 shows the values of the test for the index "The relative T-suppressor lymphocytes (CD8) count in the blood of pregnant women with HHV infection" against the background of administration of the drug Proteflazid®.

**Table 9**

| Group statistics for the index "The relative T-suppressor lymphocytes (CD8) count in the blood of pregnant women with HHV infection" |
|-----------------|------------------|-----------------|-----------------|-----------------|
|                 | VAR12            | N               | Mean            | STD             |
| VAR11           | 1.00             | 2               | 21,2850         | 1.81726         |
|                 | 2.00             | 2               | 21,2650         | 1.78898         |

**Table 10**

| Values of the test for independent samplings for the index "The relative T-suppressor lymphocytes (CD8) count in the blood of pregnant women with HHV infection" |
|-----------------------------------------------|-----------------------------------------------|-----------------------------------------------|-----------------------------------------------|-----------------------------------------------|-----------------------------------------------|-----------------------------------------------|
| Levene’s test                               | Student’s t-test                              |                                               |                                               |                                               |                                               |                                               |
| F                                            | Val.                                          | t                                            | Stat. sv.                                      | Significance (2-sided)                         | Difference of means                          | STD error of difference                       | 95% confidence interval of the difference of means |
|                                             |                                               |                                               |                                               |                                               |                                               |                                               |                                               |
| VAR11 equality of dispersion is assumed      | 1.845E13                                      | .000                                         | .011                                          | 2                                             | .992                                          | .02000                                        | -7.73845                                      | 7.77845                                      |
|                                              | equality of dispersion is not assumed         |                                               |                                               |                                               |                                               |                                               |                                               |                                               |
|                                              | .011                                          | 2.000                                        | .992                                          | .02000                                        | 1.80318                                      | -7.74028                                      | 7.78028                                       |

The significance of the t-test for independent samplings (higher than 0.05) indicates that the average value of the relative T-suppressor lymphocytes (CD8) count in pregnant women with HHV infection taking the drug Proteflazid® does not
differ significantly from the average value of the relative content of T-suppressor lymphocytes (CD8) in healthy pregnant women not taking the drug Proteflazid®.

Table 11 shows a group statistics for the index "The relative B-lymphocytes (CD19) count in the blood of pregnant women with HHV infection" against the background of administration of the drug Proteflazid® for the experimental and control groups.

**Table 11**

**Group statistics for the index "The relative B-lymphocytes (CD19) count in the blood of pregnant women with HHV infection"**

<table>
<thead>
<tr>
<th></th>
<th>VAR12</th>
<th>N</th>
<th>Mean</th>
<th>STD</th>
<th>Standard error of the mean</th>
</tr>
</thead>
<tbody>
<tr>
<td>VAR13</td>
<td>1,00</td>
<td>3</td>
<td>13.4833</td>
<td>.00577</td>
<td>.00333</td>
</tr>
<tr>
<td></td>
<td>2,00</td>
<td>3</td>
<td>11.8100</td>
<td>.29445</td>
<td>.17000</td>
</tr>
</tbody>
</table>

Table 12 shows the values of the test for the index "The relative B-lymphocytes (CD19) count in the blood of pregnant women with HHV infection" against the background of administration of the drug Proteflazid®.

**Table 12**

**Values of the test for independent samplings for the index "The relative B-lymphocytes (CD19) count in the blood of pregnant women with HHV infection"**

<table>
<thead>
<tr>
<th></th>
<th>Levene's test</th>
<th>Student's t-test</th>
<th>95% confidence interval of the difference of means</th>
<th>Lower confidence contour</th>
<th>Lower confidence contour</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>F</td>
<td>Val.</td>
<td>t</td>
<td>Stat.sv.</td>
<td>Significance (2-sided)</td>
</tr>
<tr>
<td>VAR15</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>15,373</td>
<td>.017</td>
<td>9.841</td>
<td>4</td>
<td>.001</td>
</tr>
<tr>
<td></td>
<td>equality of dispersion is assumed</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>9.841</td>
<td>2.002</td>
<td>1.67333</td>
<td>.17003</td>
<td>.94228</td>
</tr>
<tr>
<td></td>
<td>equality of dispersion is not assumed</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

The significance of the t-test for independent samplings (less than 0.05) indicates that the average value of the relative B-lymphocytes (CD19) count in pregnant women with HHV infection taking the drug Proteflazid® differs significantly from the average value of the relative content of B-lymphocytes (CD19) in pregnant women with HHV infection not taking the drug Proteflazid®.
Table 13 shows the group statistics for the index "The value of the immunoregulatory index (CD4/CD8) in pregnant women with HHV infection" against the background of administration of the drug Proteflazid® in the experimental group and in healthy pregnant women.

### Table 13

**Group statistics for the index "The value of the immunoregulatory index (CD4/CD8) in pregnant women with HHV infection"**

<table>
<thead>
<tr>
<th></th>
<th>VAR16</th>
<th>N</th>
<th>Mean</th>
<th>STD</th>
<th>Standard error of the mean</th>
</tr>
</thead>
<tbody>
<tr>
<td>VAR15</td>
<td>1.00</td>
<td>2</td>
<td>1.5625</td>
<td>.30052</td>
<td>.21250</td>
</tr>
<tr>
<td></td>
<td>2.00</td>
<td>2</td>
<td>1.7635</td>
<td>.21708</td>
<td>.15350</td>
</tr>
</tbody>
</table>

Table 14 shows the values of the test for independent samplings of the index "The value of the immunoregulatory index (CD4/CD8) in pregnant women with HHV infection" against the background of administration of the drug Proteflazid®.

### Table 14

**Values of the test for independent samplings for the index "The value of the immunoregulatory index (CD4/CD8) in pregnant women with HHV infection"**

<table>
<thead>
<tr>
<th></th>
<th>Levene’s test</th>
<th>Student’s t-test</th>
<th>95% confidence interval of the difference of means</th>
<th>Lower confidence contour</th>
<th>Lower confidence contour</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>F</td>
<td>Val.</td>
<td>Stat. sv.</td>
<td>Significance (2-sided)</td>
<td>Difference of means</td>
</tr>
<tr>
<td>VAR15</td>
<td>equality of dispersion is assumed</td>
<td>.</td>
<td>.</td>
<td>-.767</td>
<td>2</td>
</tr>
<tr>
<td></td>
<td>equality of dispersion is not assumed</td>
<td>-.767</td>
<td>1.820</td>
<td>.530</td>
<td>-.20100</td>
</tr>
</tbody>
</table>

The significance of the t-test for independent samplings (higher than 0.05) indicates that the average value of the immunoregulatory index (CD4/CD8) in pregnant women with HHV infection taking the drug Proteflazid® does not differ significantly from the average value of the relative content of immunoregulatory index (CD4/CD8) in healthy pregnant women not taking the drug Proteflazid®.

The course of pregnancy and the development of obstetric complications during treatment with the drug Proteflazid®
94 pregnant women with HHV infection were studied by the parameter “The incidence of threatened abortion in women with HHV infection” after the treatment with the drug Proteflazid®, 59 of them are from the experimental group, and 35 – from the control group (table 15).

Table 15

The incidence of spontaneous abortion in women with HHV infection

<table>
<thead>
<tr>
<th>Author</th>
<th>Experimental group</th>
<th>Control group</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>The number of patients treated with the drug Proteflazid® who has spontaneous abortion</td>
<td>General number of patients</td>
</tr>
<tr>
<td>Symrok V.V., 2003</td>
<td>2</td>
<td>19</td>
</tr>
<tr>
<td>Nikolaeva S.V., 2007</td>
<td>13</td>
<td>40</td>
</tr>
<tr>
<td>Ecero</td>
<td>15</td>
<td>59</td>
</tr>
</tbody>
</table>

100 pregnant women with HHV infection were studied by the parameter “The incidence of threatened abortion in women with HHV infection” after the treatment with the drug Proteflazid®, 60 of them are from the experimental group, and 40 – from the control group.

134 pregnant women with HHV infection were studied by the parameter “The incidence of term (in time) birth in women with HHV infection” after the treatment with the drug Proteflazid®, 79 of them are from the experimental group, and 55 – from the control group.

Results and Discussion

Combining data for analysis. Fig. 1 presents a Forest plot of the results of the meta-analysis by identifying the odds ratio (OR) of incidence of threatened abortion in women with HHV infection after the treatment with the drug Proteflazid® in experimental and control groups.

Fig. 1. The results of the meta-analysis by identifying the OR of incidence of threatened abortion in women with HHV infection
χ-square test (P = 0.36) and I²-test (I² = 0%) indicate the heterogeneity of these studies, so a model with fixed effect has been chosen. P-value of the Fisher test (P = 0.003) shows the importance of the selected effect.

Odds ratio (OR = 0.22) indicates that the probability of incidence of threatened abortion in women with HHV infection after the treatment with the drug Proteflazid® in the experimental group is 4.55 times lower than in the control group.

The study conducted by Nikolaeva S.V. (2007) has the greatest weight, it states that the inclusion of the drug Proteflazid® in the complex therapy for pregravid preparation and correction during the pregnancy ensures the improvement of the immune system: the increase in the total number of T and B lymphocytes, the increase of immunoregulatory index (CD4/CD8), the decrease of the CIC concentration, the decrease of IgG titers to HSV 1.2 types, the disappearance of IgM titers to HSV type 1.2, the decrease in the intensity of viral replication and the reduction of antigenic load [8].

Fig. 2 presents a Forest plot of the results of the meta-analysis by identifying the OR of incidence of term (in time) birth in women with HHV infection after the treatment with the drug Proteflazid® in experimental and control groups.

χ-square test (P = 0.48) and I²-test (I² = 0%) indicate the heterogeneity of these studies, so a model with fixed effect has been chosen. P-value of the Fisher test (P = 0.0001) shows the importance of the selected effect.

Odds ratio (OR = 6.59) indicates that the probability of incidence of term (in time) birth in women with HHV infection after the treatment with the drug Proteflazid® in the experimental group is 6.59 times higher than in the control group.

The study conducted by Nikolaeva S.V. (2007) has the greatest weight, it states that the use of the drug Proteflazid® during pregnancy in patients with...
miscarriage against the background of HHV infection helps to reduce HHV infection relapses by 70%, the incidence of the threat of miscarriage by 55%, placental dysfunction by 35%, premature birth by 29.5%, and total perinatal losses by 35% [8]. The study conducted by Symrok V.V. et al. (2003) states that the course of pregnancy when using the drug Proteflazid® includes significantly fewer complications, including the development of placental insufficiency, and ends usually by the term birth with the birth of embryos in satisfactory condition. [9].

Fig. 3 presents a Forest plot of the results of the meta-analysis by identifying the OR of incidence of spontaneous abortion in women with HHV infection after the treatment with the drug Proteflazid® in experimental and control groups.

\[ \chi^2\text{-square test (P = 0.69) and } I^2\text{-test (I}^2\text{ = 0%) indicate the heterogeneity of these studies, so a model with fixed effect has been chosen. P-value of the Fisher test (P = 0.02) shows the importance of the selected effect.} \]

Odds ratio (OR = 0.20) indicates that the probability of incidence of spontaneous abortion in women with HHV infection after the treatment with the drug Proteflazid® in the experimental group is 5 times lower than in the control group.

According to this index, the most significant is the study conducted by Nikolaeva S.V. (2007). In the study conducted by Bilyk N.M. (2005) it is stated that the number of fixed-term birth in pregnant women taking the combination therapy consisting of the drug Proteflazid® was twice as much as compared to the control group, and the number of missed abortions and miscarriages was half as much [5].

**Sensitivity Analysis**

The sensitivity analysis was carried out in such a way as to assess the influence of each individual study on combined data by omitting individual research.
The results of the sensitivity analysis showed that no individual study influenced significantly the combined data, which indicates statistically reliable results.

**Assessment of publication bias**

Funnel plot was used for assessing the bias of publications included into the study (Fig. 4-6). Almost all of the ES values in Fig. 4-6 are within the funnel, which indicates the absence of bias.

**Fig. 4. Funnel plot for the index “The incidence of threatened abortion in women with HHV infection”**

**Conclusions**

This meta-analysis allowed increasing the evidence base for the effectiveness and the safety of the drug Proteflazid® for treatment and prophylaxis of viral and concurrent infections in obstetrics.

The meta-analysis of clinical studies included 6 controlled trials covering 524 patients for assessing the clinical effectiveness of the drug Proteflazid® in the treatment of pregnant women with HHV infection:

The meta-analysis has been conducted according to 8 indexes:

1. The relative T-lymphocytes (CD3) count in the blood of pregnant women with HHV infection, %.
2. The relative T-helper-inducer lymphocytes (CD4) count in the blood of pregnant women with HHV infection, %.

Fig. 5. Funnel plot for the index “The incidence of term (in time) birth in women with HHV infection”

Fig. 6. Funnel plot for the index “The incidence of spontaneous abortion in women with HHV infection”
3. The relative T-suppressor lymphocytes (CD8) count in the blood of pregnant women with HHV infection, %.
4. The relative B-lymphocytes (CD19) count in the blood of pregnant women with HHV infection, %.
5. The value of the immunoregulatory index (CD4/CD8) in pregnant women with HHV infection.
6. The incidence of threatened abortion in women with HHV infection.
7. The incidence of spontaneous abortion in women with HHV infection.
8. The incidence of term (in time) birth in women with HHV infection.

This meta-analysis confirms the effectiveness and the safety of the drug Proteflazid®, based on the following obtained results following the dynamics of cellular immunity after HHV infection therapy with the drug Proteflazid®:

- The average value of the relative content of T-lymphocytes (CD3) in pregnant women with HHV infection taking the drug Proteflazid® differs significantly from the average value of the relative content of T-lymphocytes (CD3) in pregnant women with HHV infection not taking the drug Proteflazid®.

- The average value of the relative content of T-helper-inducer lymphocytes (CD4) in pregnant women with HHV infection taking the drug Proteflazid® differs significantly from the average value of the relative content of T-helper-inducer lymphocytes (CD4) in pregnant women with HHV infection not taking the drug Proteflazid®.

- The average value of the relative content of T-helper-inducer lymphocytes (CD4) in pregnant women with HHV infection taking the drug Proteflazid® does not differ significantly from the average value of the relative content of T-helper-inducer lymphocytes (CD4) in healthy pregnant women not taking the drug Proteflazid®.

- The average value of the relative T-suppressor lymphocytes (CD8) count in pregnant women with HHV infection taking the drug Proteflazid® does not differ significantly from the average value of the relative content of T-suppressor lymphocytes (CD8) in healthy pregnant women not taking the drug Proteflazid®.

- The average value of the relative B-lymphocytes (CD19) count in pregnant women with HHV infection taking the drug Proteflazid® differs significantly from the average value of the relative content of B-lymphocytes (CD19) in pregnant women with HHV infection not taking the drug Proteflazid®.
- The average value of the immunoregulatory index (CD4/CD8) in pregnant women with HHV infection taking the drug Proteflazid® does not differ significantly from the average value of the relative content of immunoregulatory index (CD4/CD8) in healthy pregnant women not taking the drug Proteflazid®.

The results of taking the drug Proteflazid® by pregnant women with HHV infection support the sustained effect of the drug on the course of pregnancy and the prevention of obstetric complications:

- the probability of incidence of threatened abortion in women with HHV infection after the treatment with the drug Proteflazid® in the experimental group is 4.55 times lower than in the control group;
- the probability of incidence of spontaneous abortion in women with HHV infection after the treatment with the drug Proteflazid® in the experimental group is 5 times lower than in the control group;
- the probability of incidence of term (in time) birth in women with HHV infection after the treatment with the drug Proteflazid® in the experimental group is 6.59 times higher than in the control group.

We can conclude that this meta-analysis of the results of clinical trials indicates a high efficacy and safety of the drug Proteflazid® used in obstetric practice for the treatment and prevention of HHV infection in pregnant women. Complex treatment with the inclusion of the drug Proteflazid® in the pregravid preparation and during pregnancy contributes to the positive effect on pregnancy and prevention of obstetric complications, improves cellular immunity, prevents the development of immunodeficiency, that in turn prevents obstetric and perinatal complications in women.

Given its high tolerability, high safety profile, combined effect on many elements of viral infections, the drug Proteflazid® can be recommended as an effective and safe antiviral agent for the treatment and prevention of diseases caused by HHV infection in pregnant women.

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