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Proteflazid: a meta-analysis of clinical studies to assess the efficacy and safety of pregnant

V.A. Benyuk[1,2], Y.V. Kuvita[2], A.I. Grinevich[4], O.B. Tonkovid[3], I.A. Usevich[1,2], O.C. Neymark[1,2]
[1]A.A. Bogomolets National Medical University, Kyiv
[2]Kyiv municipal maternity hospital №3,
[3]P.L. Shupyk National Medical Academy of Postgraduate Education, Kyiv
[4]State agency on science, innovation and informatization of Ukraine, Kyiv

The article presents results of a meta-analysis of clinical observations and long-term results of the use of «Proteflazid» in obstetrician practice. A meta-analysis of 24 cohorts post-marketing clinical observations, which covered 1,028 pregnant women proved high efficiency and safety of the drug in the treatment and prevention of viral and viral-bacterial infections during pregnancy, as well as preventing the development of perinatal complications.
Key words: *Proteflazid, pregnant women, the meta-analysis, viral infections, clinical studies.*

Prevention and treatment of viral and viral-bacterial infections in obstetric-gynecologic practice occupy a special place due to its prevalence and the possible consequences for the mother and child.

Treatment during pregnancy has some difficulties because of the inability to use drugs of many classes that are forbidden or not recommended for use in pregnant women. At the same time the drugs that simultaneously possess antiviral, immunomodulatory activity and are approved for use during the period of gestation, can not only improve the efficiency of the treatment of various diseases caused by viruses and thus reduce the frequency of obstetrician and perinatal complications of pregnancy.

One of these drugs is Proteflazid - original domestic drug of plant origin, which contains flavonoid glycosides of tufted hair grass (*Deschampsia catspitosa L.*) and bush grass (*Calamagrostis epigeios L.*) in its composition that based on the flavonoid oxygen-containing heterocycle. Such medical agents as Immunoflazid, flavozid and Proteflazid (Ltd SMC Ecopharm, Ukraine) also have analogous composition of the active ingredients.

The publications cited in the bibliography (references) were used for the meta-analysis of the results of clinical studies to evaluate the efficacy and safety of the Proteflazid in pregnant.

MATERIALS AND METHODS

3 independent expert obstetrician-gynecologists were taking part in the selection of publications to ensure the quality of the analysis. Publications identifier was made on the basis of selected studies in scientific publications, which includes the main author and year of publication, the number of pregnant women receiving Proteflazid (table 1).

Cohort, comparative, post-marketing, clinical retrospective studies were selected to conduct a meta-analysis.

Based on assessments of the effectiveness and safety of Proteflazid administration in pregnant, obtained in individual studies, we carried out a generalization and quantitative estimation of clinical effects in the form of a meta-analysis to assess the statistical significance of the results.

Table 1

Pregnant women who have taken the Proteflazid (publications identifier)

Author, year of publication	Number of pregnant
Mitsoda R.M., 2013	42
Serhienko S.M., 2003	48
Reznichenko G.I., 2005	130
Reznichenko N.A., 2004	18
Bikyk N.M., 2005	20
Bikyk N.M., 2006	20
Mintser O.P., Mitsoda R.M., 2006	49
Mitsoda R.M., 2007	42
Tanko O.P., 2007	30
Azimova E.I., 2011	30
Glazkov I.S., 2003	100
Grishenko O.V., 2005	21
Nogornaya V.F., 2007	20
Voloshyna N.N., 2007	136
Ostrovskaya O.N., 2002	42
Mitsoda R.M., 2006	35
Beniuk V.O., 2012	30
Vdovichenko Y.P., 2011	30
Genyk N.I., 2002	30
Borisova E.A., 2006	30
Zaiats-Kakhnovets O.I., 2005	50
Mitsoda R.M., 2005	26
Tanko O.P., 2006	30
Symrok V.V., 2003	19
Total	1028

24 studies (1028 pregnant women of the index group) were included in meta-analysis. Considering the diversity of clinical efficiency criteria in the individual studies, we have analyzed each of the criterions. The analysis does not include features that are encountered in individual studies (1-2 times). These results are presented in the publications themselves, and are not subject of generalization at this stage (before the appearance of new study results).

Statistical analysis was performed using a licensed version of the Stata 12 statistical package.

Table 2

Meta-analysis of risk of premature labor in Proteflazid administration (estimation of odds ratio)

Study	Odds ratio	Confidence interval 95%		Weight (%)
Genyk N.I., 2002	0,683	0,162	2,868	5,29
Glazkov I.S., 2003	0,574	0,297	**1,112**	**26,31**
Symrok V.V., 2003	0,138	0,006	3,119	3,03
Zaiats-Kakhnovets O.I., 2005	0,275	0,082	0,924	12,36
Tanko O.P., 2006	0,115	0,006	2,173	4,95
Borisova E.A., 2006	0,318	0,096	1,049	10,75
Mitsoda R.M., 2007	0,744	0,175	3,151	4,94
Vdovichenko Y.P., 2011	0,286	0,091	0,899	12,54
Beniuk V.O., 2012	0,286	0,091	0,899	12,54
Mitsoda R.M., 2013	0,385	0,092	1,603	7,28
Overall (OR)	0,402	0,275	0,586	100,00

Note: assessment of heterogeneity model: I^2=0, 0%, p=0,860.

RESULTS AND DISCUSSIONS

Risk of premature labor. The results of 10 studies: the index group (Proteflazid) - 399 pregnant women, control group -44pregnants were included in the analysis of the risk of premature labor. The obtained results is demonstrated imperceptible heterogeneity (typically) of assessment of results of separate studies - heterogeneity coefficient I^2=0, 0%, p=0,860. The reducing of probability of premature labor against the background of Proteflazid administration is registered in all presented studies. Generalized estimation of all results leads to the conclusion that the probability (60%) of premature labor when introducing Proteflazid administration in the treatment regimens is decreased substantially; integral estimated odds ratio OR=0,402 (95% CI=0,17 – 0,34); z=4,74 p=0,0001 (table 2).

The statistical significance of the overall assessment of meta-analysis model (odds ratio): OR=0,402; z=4, 74 p=0, 0001. Results are presented graphically in Figure 1.

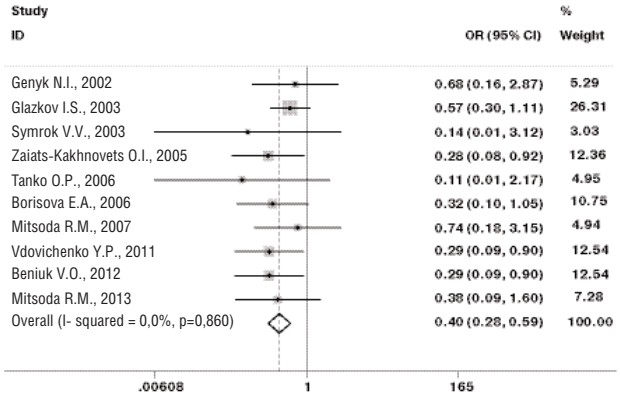

Fig.1 Meta-analysis of risk of premature labor in pregnant women (estimation of odds ratio) in Proteflazid administration

Table 3

Meta-analysis of threat and premature termination of pregnancy on the background of Proteflazid administration (estimation of odds ratio)

Study	Odds ratio	Confidence interval 95%		Weight (%)
Genyk N.I., 2002	0,117	0,025	0,546	10,33
Glazkov I.S., 2003	0,471	0,068	3,261	2,33
Symrok V.V., 2003	0,118	0,047	0,293	21,13
Zaiats-Kakhnovets O.I., 2005	0,053	0,006	0,472	7,38
Tanko O.P., 2006	0,274	0,072	1,037	6,61
Borisova E.A., 2006	0,557	0,218	1,424	9,47
Mitsoda R.M., 2007	0,609	0,195	1,897	5,96
Vdovichenko Y.P., 2011	0,237	0,081	0,693	10,65
Beniuk V.O., 2012	0,237	0,081	0,693	10,65
Mitsoda R.M., 2013	0,197	0,078	0,501	15,48
Integral estimation (OR)	0,240	0,168	0,343	100,0

Note: assessment of heterogeneity model: I^2=20, 8%, p=0,251.

Table 4

Meta-analysis of risk of discoordinated labor contractions on the background of Proteflazid administration (estimation of odds ratio - OR)

Study	Odds ratio	Confidence interval 95%		Weight (%)
Genyk N.I., 2002	0,438	0,128	1,495	12,36
Symrok V.V., 2003	0,471	0,068	3,261	4,39
Glazkov I.S., 2003	0,683	0,288	1,619	18,43
Mitsoda R.M., 2006	0,461	0,198	1,072	22,87
Tanko O.P., 2006	0,893	0,256	3,113	7,68
Vdovichenko Y.P., 2011	0,306	0,072	1,291	10,53
Beniuk V.O., 2012	0,306	0,072	1,291	10,53
Mitsoda R.M., 2013	0,337	0,096	1,177	13,23
Integral estimation (OR)	0,483	0,322	0,727	100,0

Note: assessment of heterogeneity model: I^2=0,0%, p=0,913.

There is a reduced risk of premature labor against the background of Proteflazid administration but statistically significant assessment (p<0, 05) is distinctive only in those studies where the confidence interval does not intersect 1 (reduction of risk from minimal to substantial) in all studies. Integral assessment of 10 studies confirms the hypothesis of Proteflazid effectiveness in reducing the chances of premature labor.

The risk of threat and premature termination of pregnancy. The analysis of the risk of threat and premature termination of pregnancy on the background of Proteflazid administration included 323 pregnant women of the index group Proteflazid) and 358 pregnant women of the control group (10 studies) (table 3).A significant reduction in the possibility of premature termination of pregnancy while taking Proteflazid is registered (76%) – odds ratio – OR=0,240 (95%CI=0, 17 – 0, 34). Presented studies have low assessment of heterogeneity I^2=20, 8%, p=0,251 (fig.2).

The statistical significance of the overall assessment of meta-analysis model (odds ratio): OR=0,483; z=3,5 p=0,0001.

The risk of discoordinated labor contractions. The analysis of the risk of discoordinated labor contractions on the background of Proteflazid administration included 312 pregnant women of the index group (Proteflazid) and 369 pregnant women of the control group (8 studies) (table 4).

The statistical significance of the overall assessment of meta-analysis model (odds ratio): OR=0,483; z=3,5 p=0,0001.

The results of individual studies do not allow suggesting a statistically significant reduction in risk of labor abnormalities, but the generalization of the results demonstrates a statistically significant (p=0,001) decrease in the probability of labor anomalies in Proteflazid administration (52%) – odds ratio – OR=0,483 (95%CI=0,32 – 0,73). It is also possible to note the high typicality of study results - the coefficient of heterogeneity model: I^2=0,0%, p=0,913. The results are presented graphically in Figure 3.

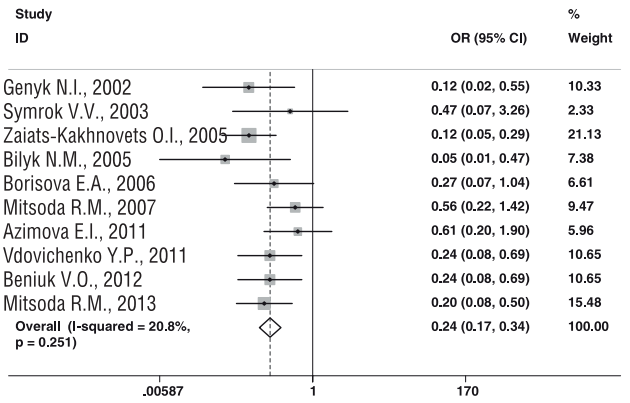

Fig.2. Meta-analysis of premature termination of pregnancy (estimation of odds ratio) on the background of Proteflazid administration

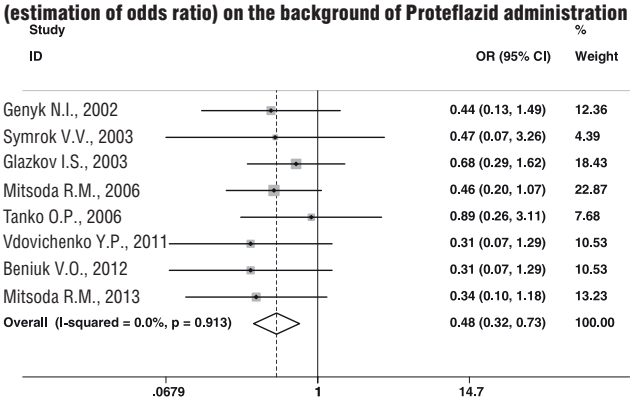

Fig.3. Meta-analysis of risk of labor abnormalities (estimation of odds ratio) in pregnant women on the background of Proteflazid administration

Table 5

Meta-analysis of risk of placental insufficiency on the background of Proteflazid administration (estimation of odds ratio - OR)

Study	Odds ratio	Confidence interval 95%		Weight (%)
Genyk N.I., 2002	0,438	0,128	1,495	18,80
Glazkov I.S., 2003	0,471	0,068	3,261	6,68
Vdovichenko Y.P., 2011	0,683	0,288	1,619	28,04
Beniuk V.O., 2012	0,461	0,198	1,072	34,80
Mitsoda R.M., 2013	0,893	0,256	3,113	11,68
Integral estimation (OR)	0,570	0,353	0,921	100,0

Note: assessment of heterogeneity model: I^2=0, 0%, p=0,891.

Table 6

Meta-analysis of risk of preeclampsia development on the background of Proteflazid administration (estimation of odds ratio - OR)

Study	Odds ratio	Confidence interval 95%		Weight (%)
Glazkov I.S., 2003	0,483	0,204	1,142	47,81
Tanko O.P., 2006	4,529	0,177	115,594	1,19
Azimova E.I., 2011	0,818	0,281	2,382	23,03
Mitsoda R.M., 2013	0,337	0,096	1,177	27,96
Integral estimation (OR)	0,568	0,322	1,001	100,0

Note: assessment of heterogeneity model: I^2=0, 0%, p=0,418.

The risk of placental insufficiency. The analysis of the risk of placental insufficiency includes 232 patients who have been taken Proteflazid and 252 patients of control group (5 studies) (table 5).

The statistical significance of the overall assessment of meta-analysis model (odds ratio): OR=0,570; z=2, 30; p=0, 0022.

A significant reduction in possibility of placental insufficiency in Proteflazid administration is registered (43%) – OR=0,570 (95%CI=0,353-0,921), p=0,022. In individual studies, the reduction of possibility of this disease has been also revealed, but a statistically significant assessment is formed only in the generalization of the results. The results are presented graphically in Figure 4.

The risk of preeclampsia development. The analysis of the risk of preeclampsia on the background of Proteflazid administration included 198 pregnant women of the index group (Proteflazid) and 212 pregnant women of the control group (5 studies) (table 6). The results of not all individual studies allow suggesting a statistically significant reduction in risk of preeclampsia development, but the generalization of the results demonstrates a statistically significant results (p=0,05) in the probability of preeclampsia in Proteflazid administration (43%) – odds ratio – OR=0,568 (95%CI=0,322 – 1,00). The high typicality of study results is also formed - the coefficient of heterogeneity model: I^2=0, 0%, p=0,418.

The statistical significance of the overall assessment of meta-analysis model (odds ratio): OR=0,568; z=1,96 p=0,050.

The results are presented graphically in Figure 5.

The risk of anemia in pregnancy. The analysis of the risk of anemia in pregnancy on the background of Proteflazid administration included 295 pregnant women with Proteflazid administration and 279 pregnant women of the control group (4 studies) (table 7). A significant reduction of the probability of anemia in pregnant women who have been received Proteflazid (47%) is confirmed – OR=0,526 (95%CI=0,365—0,781), p=0,001. In all of the studies the reduction of probability of this disease by the end of the studies revealed, but a statistically significant assessment is formed with a generalization of the results and a low level of heterogeneity of individual study assessments.

The statistical significance of the overall assessment of meta-analysis model (odds ratio): OR=0,526; z=3, 24; p=0,001.

The results are presented graphically in Figure 6.

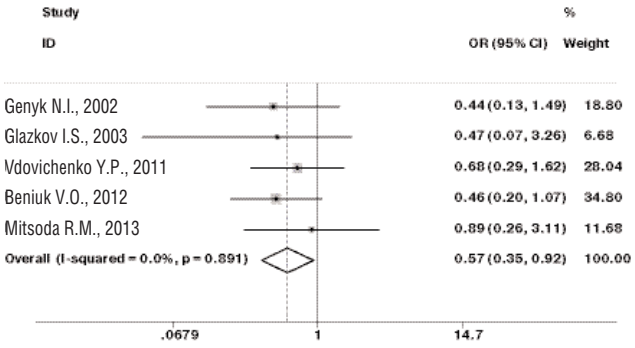

Fig. 4. Meta-analysis of risk of placental insufficiency on the background of Proteflazid administration (estimation of odds ratio - OR)

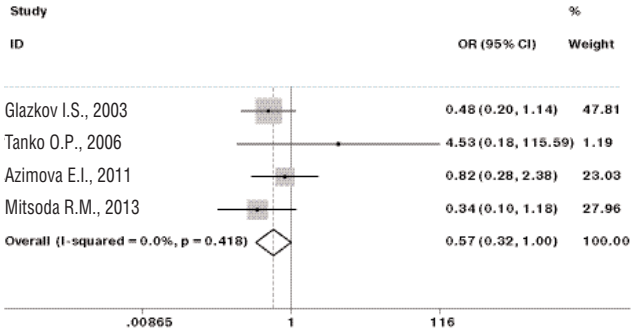

Fig. 5. Meta-analysis of risk of preeclampsia development on the background of Proteflazid administration (estimation of odds ratio - OR)

The risk of generalization of infection in pregnant women. In this meta-analysis the results of two studies were included based on the 3 options: 2 on the basis of generalization of infection, and 1 on the frequency of positive reactions to TORCH-infection. 279 patients with Proteflazid administration and 187 pregnant women of control group were included (table 8).

The statistical significance of the overall assessment of meta-analysis model (odds ratio): OR=0,658; z=1, 59; p=0,111.

There is a tendency to more favorable results of a statistically significant reduction in the risk of generalization of infection in pregnant women on the background of Proteflazid administration in index group – oR=0,658 (p=0,111) (Fig.7).

Table 7

Meta-analysis of risk of anemia in pregnancy on the background of Proteflazid administration (estimation of odds ratio - OR)

Study	Odds ratio	Confidence interval 95%		Weight (%)
Glazkov I.S., 2003	0,483	0,275	0,848	47,65
Tanko O.P., 2006	0,522	0,245	1,111	24,90
Azimova E.I., 2011	0,713	0,292	1,743	15,90
Mitsoda R.M., 2013	0,526	0,171	1,620	11,55
Integral estimation (OR)	0,526	0,365	0,781	100,0

Note: assessment of heterogeneity of the model: I^2=0,0%, p=0,912.

Table 8

Meta-analysis of risk of generalization of infection in pregnant women on the background of Proteflazid administration (estimation of odds ratio - OR)

Study	Odds ratio	Confidence interval 95%		Weight (%)
Symrok V.V., 2003	0,483	0,275	9,848	47,65
Reznichenko G.I., 2005(1)	0,522	0,245	1,111	24,90
Reznichenko G.I., 2005(2)	0,713	0,292	1,743	15,90
Integral estimation (OR)	0,658	0,393	1,102	100.00

Note: assessment of heterogeneity of the meta-analysis model: I^2=0, 0%, p=0, 6532.

The risk of vulvovaginitis in pregnant women. The analysis of the risk of vulvovaginitis in pregnant women on the background of Proteflazid administration includes 130 pregnant women of index group (Proteflazid) and 130 pregnant women of control group (2 studies) (table 9). The results of presented studies allow suggesting a statistically significant reduction in risk of vulvovaginitis, that it is also confirmed by the generalization of the results and demonstrates a statistically significant assessments (p=0, 0001) in the reduction of probability of vulvovaginitis in Proteflazid administration (65%) – odds ratio – OR=0,351 (95%CI=0, 21 – 0, 59). The in homogeneity of studies results on this criterion is formed - the coefficient of heterogeneity model: I^2=82, 9%, p=0,016 (fig.8).

The statistical significance of the overall assessment of meta-analysis model (odds ratio): OR=0,351; z=3, 97; p=0, 0001.

The risk of asphyxia in newborns. The analysis of the risk of asphyxia in newborns on the background of Proteflazid administration during pregnancy includes 8 studies: 454 pregnant women of index group (Proteflazid) and 426 pregnant women of control group (table 10).

The results of each presented study allow concluding that there is a tendency to reduce the risk of asphyxia in newborns on the background of Proteflazid administration. The generalization of results forms a statistically significant assessments (p=0, 0001) of the reducing of probability of asphyxia in newborns in Proteflazid administration (57%) – odds ratio – OR=0,534 (95%CI=0,385—0,741), p=0, 0001.

The statistical significance of the overall assessment of meta-analysis model (odds ratio): OR=0,534; z=3, 76; p=0,0001.The results are presented graphically in Figure 9.

The risk of encephalopathy in newborns. The meta-analysis of the risk of encephalopathy in newborns includes 222 patients of index group (Proteflazid) and 239 pregnant women of control group (table 11).

Against the background of low heterogeneity of the results (I^2=7, 5%), the generalization of data of 4 studies allow suggesting a statistically significant reduction in the risk of encephalopathy in newborns (48, 7%) on the background of Proteflazid administration during pregnancy – odds ratio – OR=0,513 (95%CI=0,393—0,806), p=0,004.

The statistical significance of the overall assessment of meta-analysis model (odds ratio): OR=0,513; z=2, 9; p=0,004.The results are presented graphically in Figure 10.

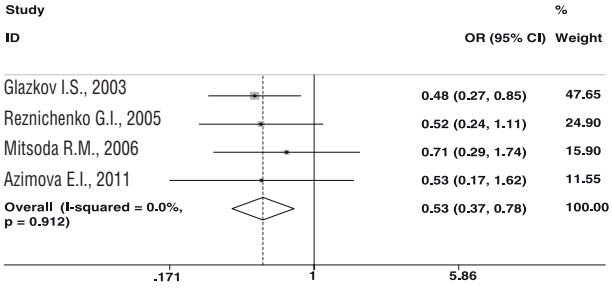

Fig. 6. Meta-analysis of risk of anemia in pregnancy on the background of Proteflazid administration (estimation of odds ratio - OR)

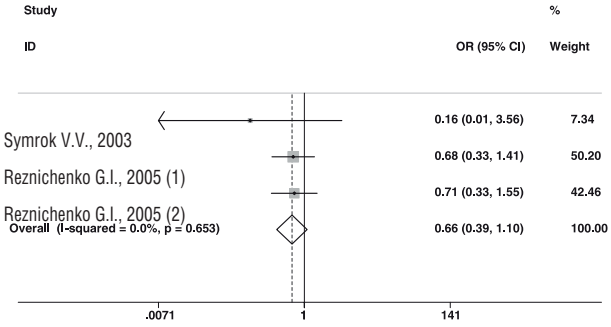

Fig. 7. Meta-analysis of risk of generalization of infection in pregnant women on the background of Proteflazid administration (estimation of odds ratio - OR)

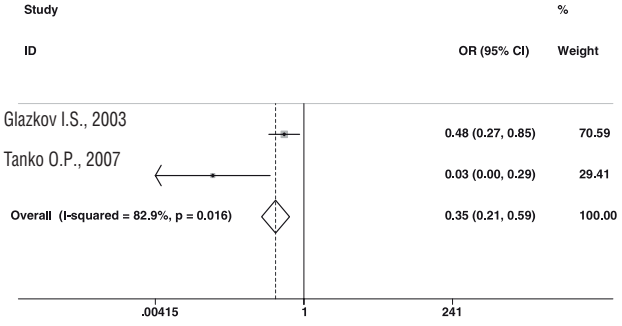

Fig. 8. Meta-analysis of risk of vulvovaginitis in pregnant women on the background of Proteflazid administration (estimation of odds ratio - OR)

Table 9

Meta-analysis of risk of vulvovaginitis in pregnant women on the background of Proteflazid administration (estimation of odds ratio - OR)

Study	Odds ratio	Confidence interval 95%		Weight (%)
Glazkov I.S., 2003	0,483	0,275	0,848	70,59
Tanko O.P., 2007	0,034	0,004	0,287	29,41
Integral estimation (OR)	0,351	0,209	0,589	100,0

Note: assessment of heterogeneity of the meta-analysis model: I^2=82,9%, p=0,016.

Table 10

Meta-analysis of risk of asphyxia in newborns on the background of Proteflazid administration (estimation of odds ratio - OR)

Study	Odds ratio	Confidence interval 95%		Weight (%)
Glazkov I.S., 2003	0,527	0,267	1,040	23,50
Zaiats-Kakhnovets O.I., 2005	0,444	0,140	1,411	9,10
Reznichenko G.I., 2005	0,616	0,317	1,194	22,14
Borisova E.A., 2006	0,154	0,007	3,365	2,71
Mitsoda R.M., 2007	1,354	0,525	3,494	7,33
Vdovichenko Y.P., 2011	0,398	0,131	1,210	10,08
Beniuk V.O., 2012	0,327	0,104	1,032	10,52
Mitsoda R.M., 2013	0,378	0,149	0,963	14,64
Integral estimation (OR)	0,534	0,385	0,741	100,0

Note: assessment of heterogeneity of the meta-analysis model: I^2=0, 0%, p=0,529.

We used the "effect size" indicator (also it is found under the name of "standardized mean difference" (SMD) to analyze the changes in quantitative and comparative assessment.

The standardized mean difference is used as the summary statistics in the meta-analysis, when all the studies are evaluated the same result, but the measurements are presented in different units, or have different absolute dynamics and variability of indicators. In this case it is necessary to standardize the study results in a single scale, before they can be combined.

The standardized mean difference expresses the effect size that was resulted in interference (the drug administration) in each study with respect to the variability of the results in each of groups. The assessment is given in the following way: how many times standardized effect size (change in indicator) in index group exceeds those in the comparison group.

In all studies, presented below, the "normalization of indicator» principle of assessment was used. The initial pathologic levels of indicators are restored to "normal levels" (reference value).Minor changes of indicator don't lead to its normalization. Conversely, significant changes in the direction of restoring of normal values of the test indicator are a confirmation of the effectiveness of interventions (drug administration).

Effect size in index group (Proteflazid) as related to the control group by CD3 indicator. The presented results in terms of CD3 indicator testify that according to four studies (120 patients of index group (Proteflazid) and 140 pregnant women of the control group), statistically significant prevalence in 3.33 times of effect size is registered in the group of pregnant women on the background of Proteflazid administration in comparison with control group – SMD=3, 33; (95%CI=2,94-3,73); p=0,0001 (table 12). This confirms the more intensive restoration of immunological characteristics in terms of CD3 indicator.

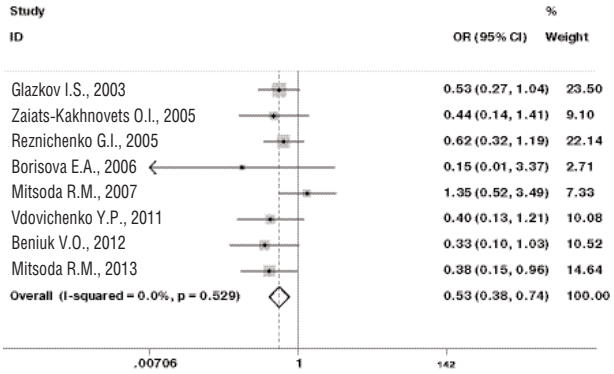

Fig. 9. Meta-analysis of risk of asphyxia in newborns on the background of Proteflazid administration (estimation of odds ratio - OR)

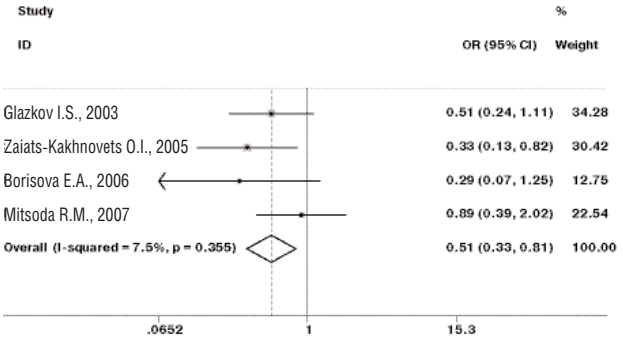

Fig. 10. Meta-analysis of risk of encephalopathy in newborns on the background of Proteflazid administration (estimation of odds ratio - OR)

Table 11

Meta-analysis of risk of encephalopathy in newborns on the background of Proteflazid administration (estimation of odds ratio - OR)

Study	Odds ratio	Confidence interval 95%		Weight (%)
Glazkov I.S., 2003	0,513	0,237	1,110	34,28
Zaiats-Kakhnovets O.I., 2005	0,329	0,132	0,824	30,42
Borisova E.A., 2006	0,286	0,065	1,253	12,75
Mitsoda R.M., 2007	0,891	0,393	2,024	22,54
Integral estimation (OR)	0,513	0,393	0,806	100,0

Note: assessment of heterogeneity of the meta-analysis model: I^2=7,5%, p=0,355.

Table 12

Meta-analysis of effect size comparison (standardized mean difference) in index group (Proteflazid)as related to control group in terms of CD3 indicator

Study	Odds ratio	Confidence interval 95%		Weight (%)
Azimova E.I., 2011	1,855	1,247	2,464	41,28
Nogornaya V.F., 2007	8,273	6,312	10,233	3,98
Nogornaya V.F., 2007	10,182	8,262	12,103	4,14
Genyk N.I., 2002	3,160	2,489	3,832	33,89
Tanko O.P., 2006	4,459	3,503	5,415	16,71
Integral estimation (SMD)	3,333	2,942	3,723	100,0

Note: assessment of heterogeneity of the meta-analysis model: I^2=96, 1%, p=0,0001.

The overall assessment of the excess of effect size in meta-analysis model:

SMD=3,333; z=16,7; p=0,0001. The results are presented graphically in Figure 11.

Effect size in index group (Proteflazid) as related to the control group by CD4 indicator. The presented results in terms of CD4 indicator testify that according to 6 studies (160 pregnant women of index group (Proteflazid) and 170 pregnant women of the control group), statistically significant prevalence in 2.88 times of effect size is registered in the group of pregnant women on the background of Proteflazid administration in comparison with control group – SMD=2, 88; (95%CI=2,55-3,20); p=0,0001 (table 13). This confirms the efficiency of Proteflazid in restoration of immunological characteristics in terms of CD4 indicator.

The overall assessment of the excess of effect size in meta-analysis model:

SMD=2,878; z=17,4; p=0,0001. The results are presented graphically in Figure 12.

Effect size in index group (Proteflazid) as related to the control group by CD8 indicator. The reduction and normalization of CD4 indicator were studied in 4 studies in pregnant women with viral infection. Heterogeneous effect sizes were registered on the dynamics of CD8, but in all publications of results the predominance of the index group against control group is presented (table 14).Only in one of four studies the standardized effect size reveals statistically significant difference in comparison with control group (Tanko O.P., 2007); SMD=0.32 (-0,19—0,83) (p>0,05).The other 3 studies demonstrated a significant predominance of CD8 dynamics in group with Proteflazid against control group: SMD is from 0,62 to 1,97.

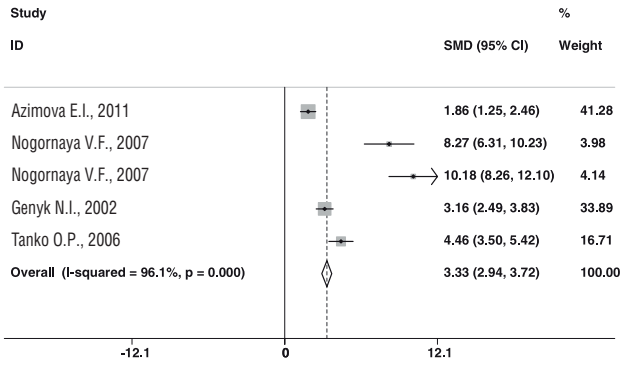

Fig. 11. Meta-analysis of prevalence of effect size of restoration on the background of Proteflazid administration in comparison with control group in terms of CD3 indicator

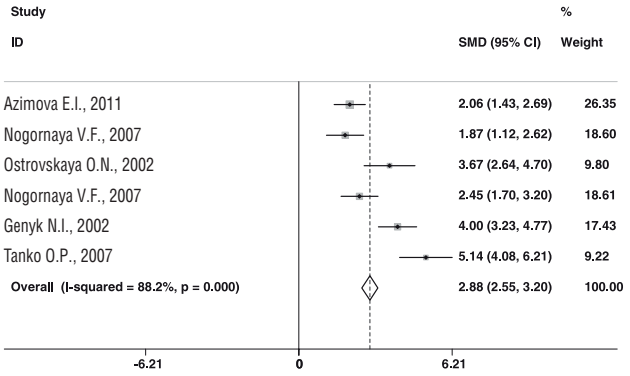

Fig. 12. Meta-analysis of prevalence of effect size of restoration on the background of Proteflazid administration in comparison with control group in terms of CD4 indicator

Table 13

Meta-analysis of effect size comparison (standardized mean difference) in index group (Proteflazid)as related to control group in terms of CD4 indicator

Study	Odds ratio	Confidence interval 95%		Weight (%)
Azimova E.I., 2011	2,057	1,428	2,687	26,35
Nogornaya V.F., 2007	1,872	1,123	2,621	18,60
Ostrovskaya O.N., 2002	3,671	2,639	4,703	9,80
Nogornaya V.F., 2007	2,454	1,705	3,203	18,61
Genyk N.I., 2002	4,000	3,226	4,774	17,43
Tanko O.P., 2007	5,145	4,081	6,209	9,22
Integral estimation (SMD)	2,878	2,555	3,201	100,0

Note: assessment of heterogeneity of the meta-analysis model: I^2=88, 2%, p=0,0001.

Table 14

Meta-analysis of effect size comparison (standardized mean difference) in index group (Proteflazid) as related to control group in terms of CD8 indicator

Study	Odds ratio	Confidence interval 95%		Weight (%)
Ostrovskaya O.N., 2002	1,97	1,28	2,66	18,22
Nogornaya V.F., 2007	1,72	0,99	2,45	16,2
Azimova E.I., 2011	0,62	0,1	1,14	32,21
Tanko O.P., 2007	0,32	-0,19	0,83	33,37
Integral estimation (SMD)	0,94	0,65	1,24	100,0

Note: assessment of heterogeneity of the meta-analysis model: I^2=85, 1%, p=0,0001.

The overall assessment of the excess of effect size in meta-analysis model:

SMD=0, 94; z=6, 3; p=0, 0001. The results are presented graphically in Figure 13.

Effect size in index group (Proteflazid) as related to the control group by CD19 indicator. The presented results testify that according to 3 studies (80patients of index group (Proteflazid) and 80 pregnant women of the control group), the prevalence in 1,9 times of effect size is registered in the group of pregnant women on the background of Proteflazid administration in comparison with control group – SMD=1,905; (95%CI=1,497—2,313); p=0,0001 (table 15). This confirms the more intensive restoration of immunological characteristics. Significant heterogeneity of results (heterogeneity coefficient – I^2=95, 75%) can be caused by various conditions of studies (the severity of the pathological process, a different set of infections, the duration of examination, etc.)

The overall assessment of the excess of effect size in meta-analysis model:

SMD=1,905; z=9, 15; p=0,0001. The results are presented graphically in Figure 14.

Effect size in index group (Proteflazid) as related to the control group by IgG indicator. The presented results in terms of IgG indicator testify that according to 3 studies (79 pregnant women of index group (Proteflazid) and 95 pregnant women of the control group), the statistically significant prevalence in 1,29 times of effect size is registered in the group of pregnant women on the background of Proteflazid administration in comparison with control group – SMD=1, 29; (95%CI=0, 94—1, 63); p=0, 0001 (table 16). This confirms the efficiency of Proteflazid in restoration of immunological characteristics in terms of IgG indicator.

The overall assessment of the excess of effect size in meta-analysis model:

SMD=1,286; z=7, 26; p=0, 0001. The results are presented graphically in Figure 15.

Effect size in index group (Proteflazid) as related to the control group by CIC indicator. The presented results in terms of CIC indicator testify that according to 3 studies (90 pregnant women of index group (Proteflazid) and 112 pregnant women of the control group), the statistically significant prevalence in 1,55 times of effect size is registered in the group of pregnant women on the background of Proteflazid administration in comparison with control group – SMD=1,55; (95%CI=1,2—1,9); p=0,0001 (table 17). This confirms the efficiency of Proteflazid in restoration of immunological characteristics in terms of CIC indicator.

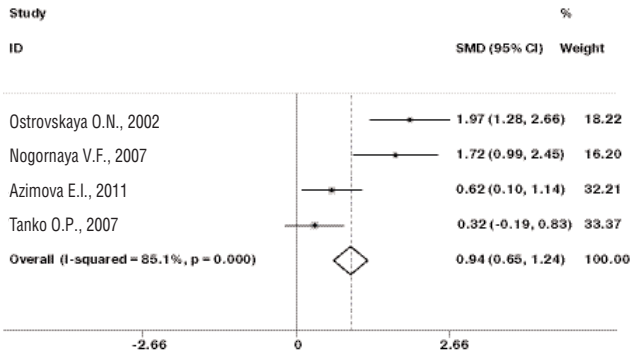

Fig. 13. Meta-analysis of prevalence of effect size of restoration on the background of Proteflazid administration in comparison with control group in terms of CD8 indicator

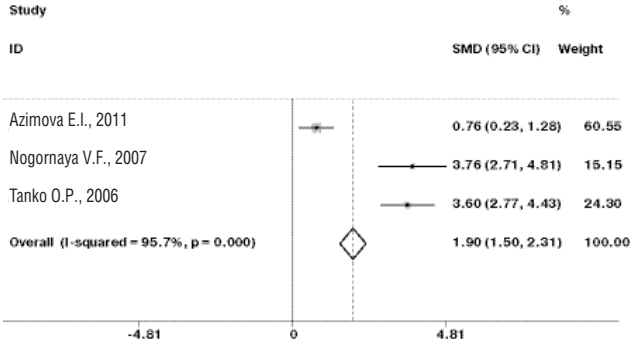

Fig. 14. Meta-analysis of prevalence of effect size of restoration on the background of Proteflazid administration in comparison with control group in terms of CD19 indicator

Table 15

Meta-analysis of effect size comparison (standardized mean difference) in index group(Proteflazid) as related to control group in terms of CD19 indicator

Study	Odds ratio	Confidence interval 95%		Weight (%)
Azimova E.I., 2011	0,759	0,234	1,284	60,55
Nogornaya V.F., 2007	3,762	2,713	4,810	15,15
Tanko O.P., 2006	3,602	2,774	4,430	24,30
Integral estimation (SMD)	1,905	1,497	2,313	100,0

Note: assessment of heterogeneity of the meta-analysis model: I^2=95, 75%, p=0, 0001.

Table 16

Meta-analysis of effect size comparison (standardized mean difference) in index group (Proteflazid) as related to control group in terms of IgG indicator

Study	Odds ratio	Confidence interval 95%		Weight (%)
Azimova E.I., 2011	0,091	-0,568	0,768	26,27
Nogornaya V.F., 2007	2,636	2,022	3,249	32,06
Ostrovskaya O.N., 2002	1,000	0,462	1,538	41,67
Integral estimation (SMD)	1,29	0,938	1,633	100,0

Note: assessment of heterogeneity of the meta-analysis model: I^2=93, 7%, p=0, 0001.

The overall assessment of the excess of effect size in meta-analysis model:

SMD=1,55; z=8,7; p=0,0001. The results are presented graphically in Figure 16.

Many other immunologic markers that in some studies have also shown a tendency or statistically significant predominance of restoration dynamics on the background of Proteflazid administration against the control group were not included in the analysis, due to methodological limitations of meta-analysis techniques. Mostly due to the limited number of such results or complexity of the data comparison.

CONCLUSIONS

Presented meta-analysis of cohort, comparative, randomized, post-marketing, retrospective, clinical studies involving pregnant patients, was conducted to evaluate the efficacy and safety of Proteflazid administration in treatment of viral and viral-bacterial infections. The group of patients who have been administrated Proteflazid, included 1028 women.

Comparative analysis confirmed the prevailing efficiency of Proteflazid administration according to the following clinical criteria: the risk of premature labor, the risk of threats and premature interruption of pregnancy, the risk of labor abnormalities, the risk of placental insufficiency, the risk of preeclampsia development, the risk of anemia in pregnant women, the risk of generalization of infection, the risk of vulvovaginitis, the risk of asphyxia and encephalopathy in newborns.

In the analysis of quantitative indicators, the prevalence of effect size is registered in terms of CD3, CD4, CD 8, CD19, IgG, CIC indicators is registered in a group of pregnant women who have been administrated Proteflazid, compared with the control group, that indicates the efficiency of Proteflazid in restoration of immune system indicators in viral and viral-bacterial infections.

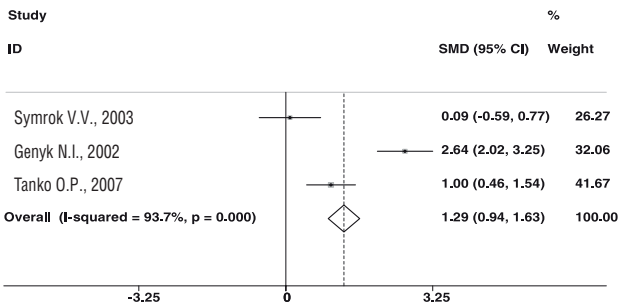

Fig. 15. Meta-analysis of prevalence of effect size of restoration on the background of Proteflazid administration in comparison with control group in terms of IgG indicator

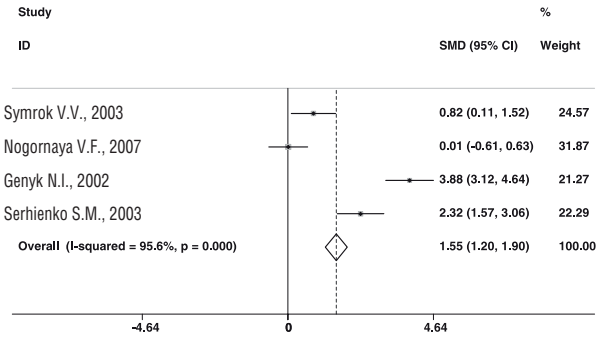

Fig. 16. Meta-analysis of prevalence of effect size of restoration on the background of Proteflazid administration in comparison with control group in terms of CIC indicator

Side effects are not revealed. Clinically significant pathological abnormalities of lab values are not registered on the background of Proteflazid administration that testifies its efficacy and safety in treatment and prevention of viral and viral-bacterial infections in pregnant women.

Table 17

Meta-analysis of effect size comparison (standardized mean difference) in index group(Proteflazid)as related to control group in terms of CIC indicator

Study	Odds ratio	Confidence interval 95%		Weight (%)
Symrok V.V., 2003	0,816	0,111	1,522	24,57
Nogornaya V.F., 2007	0,012	-0,607	0,632	31,87
Genyk N.I., 2002	3,880	3,121	4,638	21,27
Serhienko S.M., 2003	2,316	1,575	3.057	22.29
Integral estimation (SMD)	1,55	1,196	1,896	100,0

Note: assessment of heterogeneity of the meta-analysis model: I^2=68, 1%, p=0, 0001.

Proteflazid: a meta-analysis of clinical studies to assess the efficacy and safety of pregnant

V.A. Benyuk, Y.V. Kuvita, A.I. Grinevich, O.B. Tonkovid, I.A. Usevich, O.C. Neymark

The article presents results of a meta-analysis of clinical observations and long-term results of the use of «Proteflazid» in obstetrician practice. A meta-analysis of 24 cohorts post-marketing clinical observations, which covered 1,028 pregnant women proved high efficiency and safety of the drug in the treatment and prevention of viral and viral-bacterial infections during pregnancy, as well as preventing the development of perinatal complications.

Key words: Proteflazid, pregnant women, the meta-analysis, viral infections, clinical studies.

Author credentials

Benyuk Vasiliy Alekseevich - A.A. Bogomolets National Medical University, 7, Vasilyi Kuchera Str., Kyiv, 03148; tel.: (044) 405-02-51

Kuvita Yuriy Vasilevich - Kyiv municipal maternity hospital №1,7, Vasilyi Kuchera Str., Kyiv, 03148; tel.: (044) 405-34-86

Grinevich Aleksandr Iosifovich - State agency on science, innovation and informatization of Ukraine, 13, Shevchenko boulevard, Kyiv, 01601; tel. (067) 321-31-91

Tonkovid Oleg Borisovich - P.L. Shupyk National Medical Academy of Postgraduate Education, 7/9, Stretenskaya Str., Kyiv, 01025; tel.: (044) 405-02-51

Usevich Igor Anatolevich - *A.A. Bogomolets National Medical University, 7, Vasilyi Kuchera Str., Kyiv, 03148; tel.: (044) 405-02-51*

Neymark Oleg Svyatoslavovich - A.A. Bogomolets National Medical University, 7, Vasilyi Kuchera Str., Kyiv, 03148; tel.: (044) 405-02-51

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The article was received on 08.09.2014