

The Efficacy of Treatment with Valtrex of Genital Herpes in Pregnant Women

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Abstract

Numerous publications are devoted to different aspects of genital herpes (GH) in pregnant women, to its negative influence over the development of gestation period and the high incidence of perinatal mortality and morbidity. At the same time, the opinions over the administration of antiviral treatment in pregnant women, is controversial. **The study purpose:** To evaluate the efficacy of treatment of GH infection with Valtrex in pregnant women. **Material and method:** A retrospective study done during the years 2008-2009. The entire group of 70 pregnant women, included in the research, suffered from GH during their pregnancy period. The group was divided into 2 groups, group I - which received antiviral treatment and group II - which did not receive any antiviral treatment. **Results and discussions:** The pregnant women who have not received antiviral treatment, compared to the group I, had a higher level of recurrent miscarriages, premature births, oligo- and polyhydramnios, fetal growth retardation and placental insufficiency. In group II, 11.2% of early neonatal newborns died, the rate of neonatal morbidity reached up to 54.6%, compared to group I, where there were no neonatal deaths and the perinatal morbidity rate is of 10.5%. The study, on children who were born by the mothers infected with genital herpes and who did not receive any treatment during pregnancy, has allowed us to determine 20.3% cases of neurological pathologies, compared with group I, where we had just 3.5% cases. **Conclusions:** The high incidence of the recurrent miscarriages, perinatal mortality and morbidity, the neurologic sequelae in children who were born by women who have had GH infection during their pregnancy and did not receive any etiological treatment, allow us to advise the administration of Valtrex in antiviral treatment during pregnancy.

Key words: genital herpes, pregnancy, Valtrex.

Эффективность Валтрекса у беременных с генитальным герпесом

Многочисленные публикации посвящены различным аспектам беременности у женщин с генитальным герпесом, который имеет негативное влияние на развитие беременности, с высоким уровнем перинатальной смертности и заболеваемости. Мнение о назначении противовирусного лечения у беременных не однозначно. **Цель:** Эффективность лечения Валтрексом генитального герпеса у беременных. **Материал и методы:** Ретроспективное исследование в течение 2008-2009 года. Исследуемая группа из 70 беременных делится на две группы: I – с использованием противовирусного препарата Валтрекс и II – без лечения генитального герпеса. **Результаты и обсуждение:** У беременных, которые не получали противовирусное лечение был высокий уровень репродуктивных потерь, преждевременных родов, мало- и многоводие, синдром задержки роста плода и плацентарной недостаточности, по сравнению с I группой. Во II группе 11,2% новорожденных родились мертвыми, неонатальная заболеваемость достигла 54,6%, по сравнению с I группой, где отсутствует гибель плода и перинатальная заболеваемость составляет 10,5%. Дистанционное исследование детей, рожденных у матерей с генитальным герпесом, которые не получали никакого лечения во время беременности, позволило определить неврологические заболевания в 20,3% случаев, по сравнению с I группой в 3,5% случаев. **Выводы:** Высокий уровень репродуктивных потерь, перинатальной смертности и заболеваемости, неврологические осложнения у детей, мамы которых не получали этиологического лечения, позволяют рекомендовать назначение противовирусной терапии Валтрексом во время беременности.

Ключевые слова: генитальный герпес, беременность, Валтрекс.

Introduction

The herpes virus infectious pathology is a stringent problem of contemporary obstetrics being first placed in the perinatal morbidity and mortality structure.

The rates of maternal-fetal transmission of herpes simplex virus (HSV) in pregnant women with primary and recurrent herpes infection, is of 1.4 to 32% cases [1, 2]. In most cases, the fetus is infected during maternal viremia, via the transplacental passage of the HSV or via continually increasing cervical secretions throughout the entire gestation period. The fetal viremia will appear within 2-3 weeks after the infection, and then it will be followed by viruri and viraemia. If the transplacental infection occurs within the first 20 weeks of gestation, then in 34% cases they end up in miscarriages. If it occurs within the first 20-34 weeks, then 30% of pregnancies

get complicated and end up in antenatal fetal death, premature birth, and neurological diseases. More severe consequences occur when the infection happens within the first half of pregnancy, involving the central nervous system of the fetus, manifested by mental retardation, spastic quadriplegia and eye disorders [3, 4]. The ascending infection of the cervix is associated with the reproduction and accumulation of the virus in amniotic fluid and is manifested by polyhydramnios, intrauterine growth retardation, edema syndrome, prematurity, however the fetus is less affected than the transplacental infection. When the herpes outbreaks are present at per the via naturalis birth, the infection occurs through the superficial bruising, fetal conjunctivitis, absorption of amniotic fluids, and the penetration at the lung level causes atypical pneumonia. Due to HSV tropism of the nervous tissue, the infection

of the fetus can result in the occurrence of the hydrocephalus, microcephaly, ventricular expansion and gray matter atrophy [5, 6]. The innate herpes infection in the fetus has an incidence of one case in 5-10000 births, but the mortality in this group reaches 70%. At the same time, the surviving children suffer from severe neurological consequences. In the U.S. around 400 to 1000 children are born annually with inborn herpes infection, out of which just 15% remain healthy [7, 8, 9]. Currently, the target in the herpes infection treatment, in pregnant women, is reducing the disease's severity; to decrease the infectivity and the complications risk by inhibiting of viral replication, to stop the infection spreading, to prevent the intrauterine, intranatal and postnatal infection of the fetus. The majority of the antiviral products used in the therapy of the infections caused by herpesviruses act by inhibiting the synthesis of the viral DNA which are, from the chemical point of view, the nucleoside analogues of the purines and pyrimidines bases.

The most-used compounds in the treatment of infections caused by herpes viruses are acyclovir and its analogues - valacyclovir and gancyclovir. The recommended antiviral medications, in herpes infection, are the Valtrex pills, which is an L-valine ester of Acyclovir. In order for the acyclovir to become active it should be phosphorylated with the help of the thymidine kinase. The monophosphate is further converted into guanylate diphosphate kinase, and afterwards, by a number of cellular enzymes, is converted into triphosphate. The Aciclovir triphosphate interferes with the viral polymerase DNA and inhibits the DNA's replication. The Aciclovir is not toxic because the healthy cells cannot use it and the human DNA polymerase is not sensitive to acyclovir.

The aim of this study was to evaluate the efficacy of treatment with Valtrex of GH infection in pregnant women.

Material and methods

The study was conducted within the period 2008 -2009, in the Municipal Clinical Hospital No. 1 from Chisinau, being one of a clinical controlled kind, in a group of 70 pregnant women diagnosed with recurrent genital herpes in the period of their pregnancy. The herpes infection was diagnosed by the presence of the characteristic outbreaks on the vulva, vagina and cervix, positive serological reactions in HSV, assessed by PCR and IgM. The patients included in the study were divided into two groups: I - 35 pregnant women who received antiviral treatment with 500 mg Valtrex, twice a day for 5 days, initiated from the 16th week of gestation at each spurt of herpes reactivation, and group II - 35 pregnant women who received no treatment for various reasons. It also was studied and the psychomotor development in children < 1 year of age, whose mothers suffered of herpes infection during pregnancy.

All the data were entered into an electronic database using Epi Info software, version 3.3.2 (2005). In order to estimate the significance threshold, it was calculated the T-Student test, the confidence interval and the significance threshold.

Results

The average age of pregnant women included in the study ranged between 18 and 41 years of age, the average being 29.6 ± 1.9 years of age. Among the pregnant women, included in the study, we recorded: primiparous - $61.9 \pm 5.81\%$ cases, and multiparous - $38.1 \pm 5.42\%$ cases. The complicated obstetric anamnesis was found in $45.6 \pm 5.95\%$ of cases, including: $34.2 \pm 5.67\%$ had a history of medical abortions anemnesis, $62.1 \pm 5.79\%$ - spontaneous abortions, $12.7 \pm 3.98\%$ - stagnated pregnancies and $14.8 \pm 4.24\%$ - premature births.

Analyzing the obtained data, based on the herpes reactivation form, we found that in each second pregnant woman ($54.5 \pm 5.95\%$ of cases) we had, a mild form of 1-2 reactivations per year, $23.1 \pm 5.04\%$ cases of an average form of 3-4 reactivations per year, and a serious form in $4.6 \pm 2.50\%$ (5 and more reactivations per year) of cases.

In the structure of the extra genital pathologies, the predominant diseases are the ones of the urinary system, of $51.2 \pm 5.97\%$ cases, iron deficiency anemia - $35.9 \pm 5.73\%$ cases, pathology in the endocin system - $20,3 \pm 5,26\%$ cases, but, from the statistic point of view, we didn't find any significant differences. In the group I, during pregnancy, we found imminent abortion in $16.8 \pm 4.47\%$ of cases, compared to group II - $47.8 \pm 5.97\%$ cases ($p < 0.001$). In group I, the pregnancy-induced hypertension was recorded in $19.1 \pm 4.69\%$ cases, in group II - $23.1 \pm 5.04\%$ ($p > 0.05$) cases.

After the ultrasound examination (USG) of the pregnant women included in the study, the pathology of the fetoplacental system was diagnosed in $25.9 \pm 5.24\%$ cases, for group I - $8.3 \pm 3.29\%$ ($p < 0.05$), and group II - $17.4 \pm 4.53\%$ of cases, the majority rate is taken by the fetoplacental insufficiency, in the group I where we recorded $5 \pm 3.15\%$ cases, while in group II - $7.5 \pm 3.15\%$ cases, fetal hypotrophy- in group I we recorded $3.5 \pm 2.19\%$ cases and in group II - $11.2 \pm 3.37\%$ cases, the polyhydramnios was found in group I - $3.5 \pm 2.19\%$ cases and in group II - $9.2 \pm 3.31\%$ cases, oligoamniosis was diagnosed in 0.0% cases in group I, and in group II in $11.2 \pm 3.37\%$ cases.

If we look at the way the pregnancy resulted in pregnant women from group II, we can see that they ended with: 3 cases of early miscarriage ($7.5 \pm 3.15\%$), 1 case of a late miscarriage ($3.5 \pm 2.19\%$), 2 cases stopped during their development ($7.5 \pm 3.15\%$), 1 case of antenatal fetal death ($3.5 \pm 2.19\%$), 2 cases of premature birth ($7.5 \pm 3.15\%$), comparing to the group I there was only one case ($3.5 \pm 2.19\%$) of early miscarriage and one case ($3.5\% \pm 2.19\%$) of preterm.

Analyzing the way the pregnancies ended, we observed the following results: $81.4 \pm 1.6\%$ of pregnant women, infected with genital herpes, gave births per vias naturalis, for $18.6 \pm 3.2\%$ cases there was done caesarean section, because the presence of herpes outbreaks starting from the 36th week of gestation, or the onset of labor with the presence of outbreaks on the cervix, vagina and vulva in the intact fetal membrane.

According to the data obtained from the study, the prenatal rupture of the amniotic membrane occurred in $12.5 \pm 3.95\%$ cases in group I, and in $32.6 \pm 5.60\%$ cases in group II. An

alkydiene period which was longer than 18 hours was present in $8.7 \pm 3.37\%$ parturients in group I, and in $36.9 \pm 5.77\%$ in group II. The birth distocies in pregnant women infected with herpes were present for $4.2\% \pm 2.39\%$ cases in group I, and $12.3 \pm 3.93\%$ in group II. The acute hypoxia of the fetus was estimated in $9.2 \pm 3.45\%$ cases in group I, and in $35.6 \pm 5.72\%$ cases in group II ($p < 0.001$).

Compared to the group II, where from all the pregnant women infected with genital herpes, they gave birth to alive newborn babies in $66 (89.5 \pm 3.66\%)$ cases, and in $4 (10.5 \pm 3.77\%)$ cases the babies were born dead, in group I, all the newborn babies were born alive ($p < 0.05$).

Assessing the Apgar newborns score after 1 and 5 minutes: in group I, we found less than 6 points- 2 cases and in group II - 6 cases, PR = 0.88, 7 points in group I -7 cases and in group II -9 cases, PR = 0.59, 8 points in group I - 18 cases and in group II -25 cases, PR = 0.42, 9 points in group I-1 case in group II - 0 cases, PR = 0.0.

We measured the weight of the neonates, with the average of 2960.3 ± 124.1 gr. A first degree of intrauterine fetal growth retardation was found in: group I - $16.5 \pm 4.44\%$ cases, in group II - $43.5 \pm 5.43\%$ cases ($p < 0.05$), 2nd degree in: group I - $4.4 \pm 2.45\%$ cases, and in group II - $24.6 \pm 5.15\%$ cases ($p < 0.01$), and 3rd grade: in group II - $4.1 \pm 2.37\%$ cases ($p > 0.05$).

Assessing the newborns from both groups we determined, that 4 early neonatal ($11.2 \pm 3.37\%$) newborns from the group which did not receive any treatment, died. At the morphopathological examination were diagnosed such pathologies as meningoencephalitis, neonatal sepsis, generalized peritonitis.

We had $3.5 \pm 2.19\%$ cases of conjunctivitis, $9.2 \pm 3.31\%$ cases of spasms, and $20.0 \pm 4.81\%$ cases of viral pneumonia. At the USG in the 3rd day after the postpartum, we had 7 cases ($20.0 \pm 4.81\%$) of newborns with ventriculomegaly. We did not have any baby death in group I, 2 ($5.7 \pm 2.77\%$) newborn babies suffered from viral pneumonia, and we had 1 ($3.5 \pm 2.19\%$) case of ventriculomegaly.

The result obtained for children born by mothers with genital herpes who received no treatment during pregnancy has allowed us to determine: 2 ($5.7 \pm 2.77\%$) cases of hydrocephalalgia, 4 ($11.2 \pm 3.77\%$) cases of epilepsy, and 2 ($5.7 \pm 2.77\%$) cases of retarded psychomotor development, comparing with those from group I, where there were no neurological pathologies ($p < 0.05$).

Conclusions and discussions

The study results show that the pregnancy in women with untreated herpes infection ended up with 6 times more

frequently reproductive miscarriages than for the ones from the group who received treatment. In the group II, we had 3 times the frequency of fetoplacental pathology and of amniotic fluid were found in the and 3 times more frequently than in group I.

The analysis of the obtained results allowed us to emphasize that the births where the parturients were infected with herpes and did not receive antiviral treatment were complicated by the prenatal rupture of the amniotic membrane four times more frequently than for the ones who received antiviral treatment.

The children from mothers with untreated GH suffer from various pathologies, especially neurological ones both in the neonatal period and during the first year of life.

In the case of herpetic infection, the optimal way of birth, must be determined by the clinical form of the genital herpes, confirmed by the presence of rash on the labia, vagina and cervix and positive serological reactions to HSV- 1 and 2 (PCR or IgM).

The high levels of perinatal mortality and morbidity in group II, delayed neurological sequelae in children whose mothers suffered genital herpes in pregnancy and received no etiologic treatment, allow us to recommend the administration of antiviral treatment, with Valtrex, in pregnancy, which has to be initiated as early as possible, for every spurt of the herpetic reactivation, after 16 weeks of gestation.

References

1. Burlacu A. The algorithm of diagnosis and behavioral tactics of pregnant women with chlamydia and genital herpes. *Buletin de Perinatologie*. 2003;2:42-47.
2. Burlacu A. Valtrex in the preconceptional preparation of patients with habitual interruption of pregnancy. *Buletin de Perinatologie*. 2006;3:117-119.
3. Cernescu C. Antiviral drugs. Bucuresti: „Carol Davila” University. 2003;220.
4. Fife KH, Corey L. Herpes simplex virus. In: Holmes KK, ed. Sexually Transmitted Diseases, 2nd ed, Chap 77. New York: McGraw-Hill, 1990;941-52.
5. Neamtu SD, Badea M. Torch Complex, Implications in the neo - natal morbidity and mortality. *Craiova Medicală*. 2006;8(Supliment 1):87-90.
6. Spănu C, Bârca L, Rusu G. Diagnostic and treatment options in herpes infection. *Buletinul Academiei de Ştiinţe din Moldova. Ştiinţe Medicale*. 2005;4:58-61.
7. Spănu C. Herpes simplex infection - clinical features - epidemiology, evolution, diagnosis, treatment, prevention. Practical guide, 2006.
8. Gavriluc M, Casian M, Spănu C, et al. The infection of the central nervous system by the herpes simplex virus: diagnostic and therapeutic considerations. *Anale Ştiinţifice ale USMF „Nicolae Testemitanu”*. Vol. 5: Probleme ale sănătăţii mamei şi copilului. – Ed. I. – Ch.: Medicina, 2000;305-310.
9. Overall IC. Herpes simplex virus infection of the fetus and newborn. *Pediatr. Ann*. 1994;73;2:194-198.