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Experience of the Glycyrrhizin Acid Application for Treatment of Hepatitis B and C in Pregnant Women

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ABSTRACT

Viral hepatitis B and C in pregnant women is one of the most urgent problems in modern medicine. Since the conduction of basic antiviral therapy with α-Interferon and analogues of nucleosides is not recommended during pregnancy, it becomes urgent the search and introduction into viral hepatitis therapy of biologically active natural preparations that activate specific reactions of cellular immunity, possess antiviral activity and do not have significant side effects at long-term administration. One of such substances is glycyrrhizin acid (GA) extracted from roots of the Licorice. The purpose of present research is estimation of efficiency and safety of hepatitis B and C (HBC) treatment in pregnant women using the preparation Viusid for oral application (Catalysis, S.L., Spain) that contains GA, a complex of amino acids, vitamins and microelements. There were 75 women aged 19 to 32 at third trimester of pregnancy under our observation. Amongst them, 42 had verified hepatitis B, and 33 had hepatitis C. Following research methods were applied to diagnose the clinical course and to control the efficiency of treatment: serological hepatitis B markers HBSAg, HbeAg; anti-HBS, anti-HBE, and hepatitis C markers anti-HCV; molecular-biological (DNA HBV; RNA HCV); biochemical (AlAT, AsAT, bilirubin, alkaline phosphatase); ultrasonic investigations of the liver, fetus, and placenta. All the patients received basic therapy (disintoxication, metabolic, generally restorative, and dietary therapy). Besides basic therapy, 53 patients (30 hepatitis B patients and 23 hepatitis C patients) received, since 30-32nd week of pregnancy, Viusid preparation under scheme: 3.2 gm 3 times a day during 1 month. Before treatment, all the patients had increased blood level of AlAT, 2 or more times against the normal one; their virus load exceeded 1 million copies (5 + in 1 : 10000 solution) and, according to USI, diffusive alterations in the liver were detected. In the patients who received Viusid, viral hepatitis symptoms disappeared much faster as compared to control group, biochemical parameters of blood (levels of transaminases, bilirubin, and alkaline phosphatase) become normal, virus load in hepatitis B patients reduced, and the pregnancy complications rate in hepatitis B and C patients decreased. Therefore, the preparation Viusid, containing glycyrrhizin acid, possesses clinical efficiency at treatment of viral hepatitis B and C in pregnant women.

INTRODUCTION

Viral hepatites B and C are among the most widespread infections. The number of people in the world, who is infected by hepatitis B and C viruses, is estimated as hundreds of millions. In the recent years, the essential growth of hepatitis B and C morbidity is registered. Taking into account presence of a great number of patients with chronic forms of viral hepatitis, and easiness of transfer of hepatitis viruses by hemocontact way, these infections represent a threat not only for mother s organism, but also for the future child.

Recent studies reported that viral hepatites B and C cause extremely adverse effect on pregnancy course. Common complications in pregnant women suffering from viral hepatitis are gestosis, risk of abortion, oligohydramnios, fetus hypotrophy and hypoxia, premature birth, and bleedings in postnatal period [1, 2, 3]. The main problem is a real thread of child infection by the viruses during pregnancy and at delivery, followed by subsequent development of chronic viral hepatitis. Children born by mothers - carriers of hepatitis B virus, get infected in 10-30 % cases [2, 3, 4]. A number of studies has reported the transfer of the hepatitis C virus from mother to child, giving differing estimations of the transfer rate (from 0 up to 41 %) [5]. Generally, it is considered that 5 % of mothers, infected with hepatitis C virus, transfer the infection to their newborn children [2, 3, 4]. Virus load in a mother is an important risk factor of vertical transfer: it is known that such probability is higher if the concentration of hepatitis C RNA in mother s blood serum exceeds 106-107 copies per ml [1, 6]. The probability of fetus infection increases if mother get infected during pregnancy or if viral hepatitis turns to acute condition during pregnancy, because in these cases the aminotranferases level and quantity of viruses in the

blood increase. The risk of fetus infection also rises if pregnancy proceeds on the background of conditions or diseases which are followed by immunodeficiency (other attendant perinatal infections, AIDS-infection, autoimmune diseases, treatment by hormones etc.). It is necessary to note that activation of the virus infection during the 3rd trimester of pregnancy or, particularly, before delivery essentially worsens the prognosis of pregnancy and delivery outcome [1, 3, 4].

Taking into account peculiarities of chronic viral hepatitis course in pregnant women and antiproliferative and embryotoxic effects of basic antiviral preparations alpha-interferon, analogues of nucleosides and synthetic interferonogens therapy by specified preparations during pregnancy is not recommended [7, 8, 9]. Therefore, search of medical means for treatment of viral hepatitis in women during pregnancy is of a great priority. In this connection, the application of safe biologically active natural substances that activate specific reactions of cellular immunity, possess antiviral activity and do not cause significant side effects at long-term administration is appropriative. One of such substances is glycyrrhizin acid (GA) extracted from roots of the Licorice [10 - 16].

It is more than 20 years as GA has successfully been applied in Japan and other countries for treatment of viral hepatitis as a component of the injection preparation Neominofagin C (CHMC) that also includes amino acids amplifying action of GA. There was revealed the hepatoprotective action of GA at viral hepatitis both in monotherapy [17, 18] and in a combination with ursodeoxicholic acid [19] and essential phospholipids [20]. At that, fast normalization of aminotrasnferases levels and improvement of histological hepatitis markers were recorded in patients. A special research showed that continuous administration of GA for 10 years reduced the hepatocellular carcinoma occurrence rate in chronic VHC patients more than 2 times [15]. It is shown that immunomodulatory and antiviral effect of GA is due to activation of €¿‹ lymphocytes, amplification of interleukin IL-2 production, expression of IL-2R specific receptors and mediated amplification of alpha-interferon production [13, 16].

The purpose of present research is estimation of the efficiency and safety of treatment of hepatitis B and C in pregnant women using the preparation Viusid for oral application (Catalysis, S.L., Spain), containing GA, a complex of amino acids, vitamins and microelements.

MATERIALS AND METHODS

There were 75 women at the 3rd trimester of pregnancy aged 19 to 32 under our observation on the basis of a maternity hospital and advisory-polyclinic department of Isolation clinical hospital N 1 in Moscow.

42 of them had verified hepatitis B and 33 had hepatitis C. The duration of disease was from 1 up to 5 years in 46 observed patients. For the rest of them, duration of disease was not determined for certain, since HBSAg or HCV antibodies were revealed in them during scheduled inspections when pregnancy had already begun.

To diagnose viral hepatitis and to control the efficiency of treatment, following research methods were applied:

- ***Serologic*** - markers of hepatitis B: HBSAg, HbeAg; anti-HBS, anti-HBE; markers of hepatitis C: anti-HCV;
- ***Molecular-biological*** - (DNA HBV; RNA HCV);
- ***Biochemical*** (AlAT, AsAT, bilirubin, alkaline phosphatase);
- ***Ultrasonic investigations of the liver, fetus and placenta;***
- ***Biopsy*** - was not conducted.

All 75 patients received basic therapy that, according to recommendations [Order and methodical manual. Moscow, 2000] included disintoxication, metabolic, restorative and dietary therapy. Besides basic therapy, 53 patients (30 with hepatitis B and 23 with hepatitis C) received the preparation Viusid since 30-32nd week of pregnancy. The reception scheme of the preparation was 3.2 gm 3 times a day during 1 month.

During the treatment course, the estimation of condition of the obstetric status and development of the fetus (fetus hypotrophy, hypoxia) and placenta (ultrasonic investigation, Doppler blood flowmetry, antenatal cardiotocography) were conducted especially thoroughly. In view of revealed alterations, the correction of treatment-and-prophylactic actions was made, that was directed on improvement of uterineplacentary and renal blood flow and reduction of gestosis effect.

Treatment efficiency was estimated on the basis of dynamic clinical observation, data of laboratory and clinical research, including subjective and objective data collected weekly.

One of the indices of efficiency of the medical measures conducted was the decrease of the characteristic pregnancy complications rate occurring in viral hepatitis patients during the 3rd trimester of pregnancy: gestosis, threat of abortion, hydramnios, early rupture of amniotic fluid sac, powerless labor, and fetal anoxia.

RESULTS AND DISCUSSION

Before the beginning of treatment, in most patients there were recorded weakness, malaise, loss of appetite, nausea, sometimes vomiting, feeling of heaviness, dull ache in the right hypochondrium, hepato- and splenomegaly, subicteritiousness of skin and sclera. The jaundice phenomenon was observed in 32 viral hepatitis B patients (76.2 %), and in 5 viral hepatitis C patients (15.2 %). According to ultrasonic investigations, diffusive alterations in the liver were observed in most patients.

The analysis of clinical efficiency of treatment has shown that intoxication symptoms disappeared significantly faster in hepatitis B and C patients who received basic therapy in a complex with Viusid as compared to those who received basic therapy only (**Tables 1 and 2**).

Table 1: Effect of treatment on duration of intoxication symptoms in hepatitis B patients at the 3rd trimester of pregnancy

Symtom	***Symptom duration (days)***	
	Basic therapy + Viusid	Basic therapy
	n = 30	n = 12
Nausea	5 ± 1*	10 ± 1
Anorexia	4 ± 0,5*	9 ± 1
Heaviness and ache in the right hypochondrium	6 ± 1*	12 ± 2
Weakness and malaise	3 ± 0,4*	10 ± 2

* Difference between the groups is significant at $p < 0.05$

Table 2: Effect of treatment on duration of intoxication symptoms in hepatitis C patients at the 3rd trimester of pregnancy

Symtom	***Symptom duration (days)***	
	Basic therapy + Viusid	Basic therapy
	n = 23	n = 10
Nausea	5 ± 0,5*	12 ± 2
Anorexia	3 ± 0,4*	9 ± 1
Weakness and malaise	3 ± 1*	10 ± 1

* Difference between the groups is significant at $p < 0.05$

Before treatment, all the hepatitis B patients had increased blood level of AlAT and AsAT, 2 or more times against the normal one. Levels of general bilirubin and alkaline phosphatase exceeded the normal one. In all patients, HBSAg were revealed, and in most of them — also HbeAg. No seroconversion was detected. Virus load, determined by PCR method, exceeded 1 million copies (5 + in 1 : 10000 solution).

All the hepatitis C patients had increased blood level of AlAT and AsAT before treatment, 1.5 times against the normal one. Bilirubin level was increased in 4 patients (12.1 %), and alkaline phosphatase level — only in 1 patient (3 %). In all patients, anti-HCV were found. Virus load less than 1 million copies per 1 ml was recorded in 7 patients (21 %), virus load more than 1 million copies per 1 ml was recorded in 26 patients (79 %).

The analysis of dynamics of biochemical parameters of blood in pregnant women with hepatitis B and C has shown that in patients who received basic therapy in a complex with Viusid these parameters were restored much faster in comparison with patients, receiving basic therapy only (**Table 3 and 4**). At that, normalization of biochemical parameters during treatment was observed in all the hepatitis B and hepatitis C patients, receiving basic therapy in a complex with Viusid. At the same time, by the end of complete course of basic therapy (1 month), normalization of biochemical parameters was not observed in 3 hepatitis B patients (25 %) and in 3 hepatitis C patients (30 %).

Table 3: Effect of treatment on time of biochemical parameters normalization in hepatitis B patients at the 3rd trimester of pregnancy

Biochemical parameter	***Time of parameter normalization (days)***	
	Basic therapy + Viusid	Basic therapy
	n = 30	n = 9
AIAT	13 ± 1*	24 ± 2
AsAT	12 ± 2*	23 ± 2

* Difference between the groups is significant at $p < 0.05$

Table 4: Effect of treatment on time of biochemical parameters normalization in hepatitis c patients at the 3rd trimester of pregnancy

Biochemical parameter	***Time of parameter normalization (days)***	
	Terapia básica + Viusid	Terapia básica básica
	n = 23	n = 7
AIAT	15 ± 2*	26 ± 3
AsAT	13 ± 1*	24 ± 2

* Difference between the groups is significant at $p < 0.05$

Despite the short-term administration of combined therapy with Viusid application, by the end of treatment the decrease of virus load was observed in 21 hepatitis B patients (70 %) that is significantly more than value of the same parameter in patients receiving basic therapy only (25 %).

On the other hand, at treatment of pregnant hepatitis C patients, the decrease of virus load was not observed by the end of 1 month therapy neither at basic therapy, nor at combined therapy with Viusid. It is coordinated to the data of previous research which showed that decrease of virus load at a hepatitis C can be achieved only at long-term (not less than 3 months) administration of GA [13].

As it was already stated, the basic criterion of efficiency of treatment pregnant hepatitis patients is decrease of the pregnancy complications rate, that in many respects determines decrease of probability of antenatal or perinatal fetus infection by mother.

The application of Viusid in complex therapy of pregnant women with hepatitis B ensured lowering the rate of pregnancy complications that occur immediately before the delivery (see **Table 5**) thus providing its better safety. The application of Viusid in hepatitis C patients also resulted in a tendency of the pregnancy complications rate decrease (see **Table 6**).

Table 5: The treatment effect on the complications rate during the 3rd trimester of pregnancy in hepatitis B patients

Complications of pregnancy course	*Complication rate (%)*	
	Basic therapy + Viusid	Basic therapy
	n = 30	n = 12
Gestosis	23.3 %*	33.3 %
Threat of abortion	10 %*	16.7 %
Hydramnion	6.7 %*	8.3 %
Antenatal discharge of amniotic fluid	23.3 %*	25 %
Powerless labor	3.3 %.*	8.3 %
Fetal anoxia	16.7 %*	25 %

* Difference between the groups is significant at $p < 0.05$

Table 6: The treatment effect on the complications rate during the 3rd trimester of pregnancy in hepatitis C patients

Complications of pregnancy course	*Complication rate (%)*	
	Basic therapy + Viusid	Basic therapy
	n = 23	n = 10
Gestosis	8.6 %*	10 %
Threat of abortion	8.6 %*	20 %
Hydramnion	8.6 %*	10 %
Antenatal discharge of amniotic fluid	17,4 %*	20 %
Uterine inertia	8.6 %	10 %
Fetal hypoxia	13 %*	20 %

* Difference between the groups is significant at $p < 0.05$

CONCLUSION

1. The Viusid preparation containing glycyrrhizin acid, possesses clinical efficiency at treatment of viral hepatitis B and C in pregnant women.

2. Viusid possesses disintoxication action and it improves the condition of patients much faster than basic therapy.

3. Viusid normalizes metabolic processes and provides faster restoration of biochemical parameters in hepatitis B and C patients.

4. Viusid has antiviral effect that results in decrease of virus load in hepatitis B patients and stabilization of the infectious process in hepatitis C patients.

5. Application of glycyrrhizin acid as a component of the Viusid preparation ensures to decrease the pregnancy complications rate during the 3rd trimester and to increase probability of safe delivery in hepatitis B and C patients.

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