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# ANALYSIS OF SERUM INTERFERONS AND IL-28B IN PREGNANT WOMEN WITH CHRONIC VIRAL HEPATITIS B

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✓ ***Resume***

***A two-fold suppression of serum IL-28 was revealed in women with hepatitis B compared with the data of practically healthy pregnant women. Thus, it was revealed that in the group of pregnant women with hepatitis B, the IL-28 value was 3.74±0.92 pg/ml, while the norm for practically healthy pregnant women was 12.8±0.75 pg/ml, which significantly differed. Thus, our studies have shown that the values of interferon gamma and IFN-lambda, which are pronounced antiviral proteins, are significantly suppressed against the background of chronic viral hepatitis B in pregnant women in the early stages of pregnancy, which can lead to pronounced suppression of cellular immunity and activation of viral replication. Research in this area will be continued in order to understand the etiopathogenesis, the features of the course of the infectious process and the prediction of the course of the disease. IFN-gamma is a powerful activator of innate immunity, therefore, the suppression of IFN-gamma and IFN-lambda in women with HCV indicates the suppression of not only antiviral immunity, but also the systemic immune response. Thus, our studies have shown that the values of interferon gamma and IFN-lambda, which are pronounced antiviral proteins, are significantly suppressed against the background of chronic viral hepatitis B in pregnant women in the early stages of pregnancy, which can lead to pronounced suppression of cellular immunity and activation of viral replication. Research in this area will be continued in order to understand the etiopathogenesis, the features of the course of the infectious process and the prediction of the course of the disease.***

***Keywords: interferons, immunity, antiviral effect, interferon system, antiviral immunity protection, viral hepatitis B.***

# АНАЛИЗ СЫВОРОТОЧНЫХ ИНТЕРФЕРОНОВ И ИЛ-28В У БЕРЕМЕННЫХ ЖЕНЩИН С ХРОНИЧЕСКИМ ВИРУСНЫМ ГЕПАТИТОМ В

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✓ ***Резюме***

***Выявлено двухкратное подавление сывороточного ИЛ-28 у женщин с гепатитом В по сравнению с данными практически здоровых беременных женщин. Так, выявлено, что в группе беременных с гепатитом В значение ИЛ-28 составил 3,74±0,92пг/мл, при норме для практически здоровых беременных - 12,8±0,75пг/мл, что достоверно различалось. Таким образом, проведенные нами исследования показали, что значения интерферона гамма и ИФН-лямбда, которые являются выраженными противовирусными белками значительно подавлены на фоне хронического вирусного гепатита В у беременных женщин в начальных сроках беременности, что может привести к выраженному подавлению клеточного иммунитета и активации репликации вируса. Исследования в данной области будут продолжены, с целью понимания этиопатогенеза, особенностей течения инфекционного процесса и прогнозирования течения заболевания. ИФН-гамма является мощным активатором врожденного иммунитет, поэтому и подавление ИФН-гамма и ИФН-лямбда у женщин с ХВГВ свидетельствует о подавлении не только противовирусного иммунитета, но и системного иммунного ответа. Таким образом, проведенные нами исследования показали, что значения интерферона гамма и ИФН-лямбда, которые являются выраженными противовирусными белками значительно подавлены на фоне хронического вирусного гепатита В у беременных женщин в начальных сроках беременности, что может привести к выраженному подавлению клеточного***

***иммунитета и активации репликации вируса. Исследования в данной области будут продолжены, с целью понимания этиопатогенеза, особенностей течения инфекционного процесса и прогнозирования течения заболевания.***

***Ключевые слова: интерфероны, иммунитет, противовирусное действие, система интерферонов, противовирусная защита иммунитета, вирусный гепатит В.***

## СУРУНКАЛИ ВИРУСЛИ ГЕПАТИТ Б БИЛАН ОҒРИГАН ҲОМИЛАДОР АЁЛЛАРДА ЗАРДОБ ИНТЕРФЕРОНЛАРИ ВА ИЛ-28Б ТАҲЛИЛИ

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***Гепатит Б билан оғриган аёлларда ил-28 қон зардобининг икки баробар кўтарилиши деярли соғлом ҳомиладор аёллар маълумотларига нисбатан аниқланди. Шундай қилиб, гепатит В билан касалланган ҳомиладор аёллар гуруҳида ИЛ-28 қиймати 3.74 га тенг бўлган 0.92 пг/мл, амалда соғлом ҳомиладор аёллар учун қиймати 12.8 га тенг бўлган 0.75 пг/мл еди, бу сезиларли фарқ қилди. Шундай қилиб, бизнинг тадқиқотлар вирусга қарши оқсиллар interferon gamma ва ИФН-lambda қийматлари, сезиларли даражада у ҳужайра иммунитети ва вирус репликациясини активлаштиришга олиб келиши мумкин.Хомиладорлик ерта босқичларида, ҳомиладор аёлларда сурункали вирусли гепатит В фонида юқори еканлигини кўрсатди. Бу соҳадаги тадқиқотлар етиопатогенезни, инфекцион жараённинг кечиш хусусиятларини ва касалликнинг кечишини башорат қилишни тушуниш мақсадида давом еттирилади. ИФН-gamma тугма иммунитетнинг кучли фаоллаштирувчисидир, шунинг учун СВГВ ли аёлларда ИФН-gamma ва ИФН-lambda нинг antiviral иммунитетни емас, балки тизимли иммунитетни ҳам юқорилашинини кўрсатади. Шундай қилиб, бизнинг тадқиқотлар вирусга қарши оқсиллар interferon gamma ва ИФН-lambda қийматлари, сезиларли даражада иммунитет ва вирусли репликация активлаштиришга олиб келиши мумкин.Хомиладорлик ерта босқичларида, ҳомиладор аёлларда сурункали вирусли гепатит В фонида юқори еканлигини кўрсатди. Бу соҳадаги тадқиқотлар етиопатогенезни, инфекцион жараённинг кечиш хусусиятларини ва касалликнинг кечишини башорат қилишни тушуниш мақсадида давом еттирилади.***

***Калит сўзлар: интерферонлар, иммунитет, вирусга карши таъсир, интерферон тизими, вирусга карши иммунитетни ҳимоя қилиш, вирусли гепатит Б.***

### Relevance

Currently, about 240 million people are infected with the hepatitis B virus, and in the past two decades, the prevalence of infection has ceased to depend on the economic status of the country [2,4,5,9]. Globalization and associated migration processes have led to an increase in the incidence of HBV [5,9,11,14]. Uzbekistan also faced the same problems, where the prevalence of HBV, according to expert estimates, reaches up to 23% of the population.

It is known that HBV occurs as an acute and chronic infection, and in all cases is due to the parenteral mechanism of transmission of the pathogen. Acute infection occurs in the form of cyclic parenchymal hepatitis with or without jaundice, which in 95% of patients ends in recovery. The remaining 5% develop chronic HBV, and it is in this group of patients that there is a high risk of developing complications associated with HBV - liver cirrhosis and hepatocellular carcinoma, from which more than half a million people die annually in the world, and the costs of treatment, including liver transplantation, are estimated at billions of dollars [8,12,14,16].

Importantly, the prevalence of HBsAg among pregnant women has not been clearly established. For example, in the USA, the infection is detected in 0.7-0.9% [5,9], in European countries the prevalence ranges from 0.1 to 5.6% [6,8,9,12,15], in Russia it reaches 0.5% [5,8,11,13].

Viral hepatitis B is a ubiquitous infectious disease. It is believed that about 2 billion people are infected with the hepatitis virus, and about 2 million patients die annually from the pathology associated with HBV infection [1,3,6,10,11,14].

An increase in the incidence of viral hepatitis B inevitably leads to increasing involvement of women of reproductive age, including pregnant women, in the epidemic process [6,8,9,10,12]. Hepatitis B remains one of the most common infections in pregnant women, which is why scientific medicine and practical health care face the problem of the influence of the viral process on the course of pregnancy, childbirth, and the postpartum period, as well as the effect of pregnancy on the course and outcomes of viral hepatitis [11,13, 15,16]. Today, a unified tactic has not been developed in the clinical and laboratory diagnosis of viral hepatitis in pregnant women. The number of pregnancy complications in women with parenteral viral hepatitis is almost two times more likely than in non-ill women, and complications in childbirth are 1.5 times more common [5,8,10,11].

The effect of IFN-λ on the immune system since its discovery has been the object of close attention, and at present the existence of such an effect is undeniable, however, the mechanism by which IFN-λ regulates the adaptive immune response is still not fully understood [5,8, 12.14]. IFN-λ was found in a wide range of animals, and its antitumor, anti-inflammatory, and antiviral effects were registered [7,9,10,11]. It has been shown that IFN-λ plays a role in the pathogenesis of infectious diseases, in particular viral hepatitis [9,15].

As you know, different interferons differ in cellular origin. Thus, IFN-α is produced by monocytes, macrophages, neutrophils, and B-lymphocytes [16]. IFN-α formation inducers are mainly viruses (RNA- and DNA-containing) [12,13]. As is known, the antiviral effect of interferons is associated with their ability to suppress the processes of transcription and translation of the viral genome. The effect of IFN-α on the immune response is manifested in the induction of the production of certain cytokines (in particular, proinflammatory ones) [7,8]. Again, it is important to note that at sufficiently high doses, interferons suppress both humoral and cellular immune responses, but at more moderate concentrations they have an immunoregulatory effect [6,16].

In connection with the above, we studied the serum concentration of the main interferons and IL-28 in the group of pregnant women with chronic viral hepatitis B. For this purpose, 42 pregnant women with viral hepatitis B were examined, who were examined on an outpatient basis.

## Material and methods

42 pregnant women were examined at 4-2 weeks of gestation, with a history of chronic viral hepatitis B. The age of women was from 19 to 32 years.

Serum concentrations of IFN-alpha and IFN-gamma were also studied by the enzyme immunoassay using the Human test systems, Germany, 2020. Statistical processing of the results was carried out by calculating M ± m.

## Result and discussion

Analysis of IFN-gamma in the group of pregnant women with hepatitis B revealed that the level of serum IFN-gamma was suppressed with the value of the control group. Thus, it was found that in the group of pregnant women with hepatitis B, the value of IFN-gamma was 4.82±1.4 pg/ml, while the norm for practically healthy pregnant women was 14.2±0.9 pg/ml, which significantly differs. It has been established that the source of IFN-γ is activated T-lymphocytes and EKK (antigens and mitogens act primarily as activators). Among T-lymphocytes, IFN-γ producers are primarily cytotoxic CD8+ and helper CD4+ cells, however, when the latter differentiate into TX1 and TX2, only TX1 cells retain the ability to produce IFN-γ [4,7,12,15]. Consequently, IFN-gamma in the group of pregnant women with viral hepatitis B was significantly reduced, which indicates the formation of an immunodeficiency state. As is known, the activation of TH1-lymphocytes promotes the production of IFN-g, therefore, the suppression of IFN-gamma affects the suppression of cellular immunity against the background of a chronic viral process.

Interferons are a common name under which a number of proteins with similar structural and functional properties are currently combined, which in the vast majority of cases are actively produced by body cells when infected with a virus. These proteins are the most important components of the body's innate nonspecific defense against infections and tumor transformations. There are three main classes of interferons, where each class combines proteins of the same type (I, II, or III). The ratio of interferon to a particular type is determined by the type of receptor that binds them. Type I interferons have one common IFN-alpha receptor (IFNAR), consisting of an alpha subunit (IFNAR1) and a short or long beta subunit (IFNAR2). In mammals, this type includes the following main types of interferons: alpha, beta, omega, upsilon, kappa, and tau. Type II interferons bind to the IFNGR receptor and are represented by only one type, interferon-gamma. Type III interferons, lambda

interferons, bind to the IFNLR1 receptor .IFN has a pronounced antitumor, anti-inflammatory, and antiviral effect [6,7]. It has been shown that IFN plays a role in the pathogenesis of infectious diseases, in particular viral hepatitis [4,7,11,14]. In this regard, the serum concentration of the main IFN gamma and IL-28B was studied in the group of pregnant women with chronic viral hepatitis B, which is a type 3 interferon. For this purpose, pregnant women with viral hepatitis B, who were examined on an outpatient basis, were examined.

As shown above, the role of IL-28 is quite large, especially during the infectious process. Thus, the concentration of IL-28 in the blood serum of pregnant women was significantly suppressed compared with the value of pregnant women without viral damage. Thus, a significant decrease in IL-28 was found in the group of women with viral hepatitis B compared with the value of healthy women of reproductive age. It has been proven that normal values of IL-28 contribute to a pronounced antiviral attack, which is much reduced against the background of a chronic viral process. We found a two-fold suppression of serum IL-28 in women with hepatitis B compared with the data of practically healthy pregnant women. Thus, it was found that in the group of pregnant women with hepatitis B, the value of IL-28 was 3.74±0.92 pg/ml, while the norm for practically healthy pregnant women was 12.8±0.75 pg/ml, which significantly differed. According to the literature, the antiviral activity of IFN-λ in vitro was studied in various cell cultures against a variety of both RNA- and DNA-containing viruses [13,16]. It has been proven that the antiviral activity of IFN-λ in vivo studies is the ability to stimulate the immune system of the body as a whole in response to the invasion of a foreign agent. However, against the background of a chronic process, there is a depletion of the potential of IL-28, which will lead to suppression of production and the formation of an immunodeficiency state. There are indications in the literature that prophylactic administration of IFN-λ, like IFN-α, suppressed the initial replication of the virus, followed by suppression of IL-28. Consequently, IL-28 performs a decisive and non-redundant function in the body, which significantly limits the replication of the virus [2,3,5,9].

So, according to the results of studies conducted since the discovery of IFN-λ, no one doubts that IFN-λ is polyfunctional. The role of IFN-λ as interferon that suppresses viral infections on the surfaces of the anatomical barriers of the respiratory tract, gastrointestinal tract, blood-brain barrier and liver has been studied quite widely and in detail. Relatively recently, works have appeared on the immunomodulatory role of IFN-λ and its direct and indirect effects on the function of immune cells in various inflammatory conditions, thereby explaining the higher safety profile compared to the undesirable pro-inflammatory effects of IFN-α. Interesting data in the field of infectology, as well as the availability of ready-made pegylated forms of IFN-λ, which have already passed clinical studies and showed a higher safety profile in them than pegylated IFN-α, open up scientific and clinical horizons for the study and use of IFN-λ.

Table 1.

**State of the main interferons of the immune system in pregnant women with CHBV, pg/ml**

| Indicators | Control group | Values of the study group of women with CHBV |
|---|---|---|
| IFN-gamma, pg/ml | 14,22 ±0,54 | 4,82 ±1,4 * |
| IFN-lambda, ng/ml | 12,8±0,75 | 3,74±0,92 * |

*Note: * - significance of differences between the studied groups of women (p<0.05)*

It should be noted that the serum level of IFN-gamma was reduced by 3.4 times compared to control values, and the level of IFN-lambda was also suppressed by 4.2 times, which also indicates the suppression of the antiviral activity of the immune system.

It has been established that the source of IFN-γ is activated T-lymphocytes and EKK (antigens and mitogens act primarily as activators). Among T-lymphocytes, IFN-γ producers are primarily cytotoxic CD8+ and helper CD4+ cells, however, when the latter differentiate into TX1 and TX2, only TX1 cells retain the ability to produce IFN-γ [4,7]. It is also important to note that the duration of synthesis of IFN-γ is longer than that of IL-2. The formation of IFN-γ may be associated with induction by the viruses themselves, and the production of IFN-γ is enhanced by itself, as well as IL-2 [2,8,10,12]. Among cytokines, the production of IFN-γ is enhanced under the influence of IL-1, in turn, the synthesis of IFN-γ is enhanced, and the differentiation of T-helpers towards TX1 cells, as a result of

all these humoral interactions, IFN-γ enhances the development of cellular immunity and suppresses manifestations of the humoral immune response. Therefore, in the implementation of its effector properties, IFN-gamma, developing a cellular immune response, plays an important role, especially in the implementation of the cytotoxic effect [5,8], while being a humoral product of cytotoxic T-lymphocytes and NK cells.

As shown above, the role of IL-28 is quite large, especially during the infectious process. Thus, the concentration of IL-28 in the blood serum of pregnant women was significantly suppressed compared with the value of pregnant women without viral damage. Thus, a significant decrease in IL-28 was found in the group of women with viral hepatitis B compared with the value of healthy women of reproductive age. It has been proven that normal values of IL-28 contribute to a pronounced antiviral attack, which is much reduced against the background of a chronic viral process. We found a two-fold suppression of serum IL-28 in women with hepatitis B compared with the data of practically healthy pregnant women. Thus, it was found that in the group of pregnant women with hepatitis B, the value of IL-28 was 3.74±0.92 pg/ml, while the norm for practically healthy pregnant women was 12.8±0.75 pg/ml, which significantly differed. So, according to the results of studies conducted since the discovery of IFN-λ, no one doubts that IFN-λ is polyfunctional. The role of IFN-λ as an interferon that suppresses viral infections on the surfaces of the anatomical barriers of the respiratory tract, gastrointestinal tract, blood-brain barrier and liver has been studied quite widely and in detail. Relatively recently, works have appeared on the immunomodulatory role of IFN-λ and its direct and indirect effects on the function of immune cells in various inflammatory conditions, thereby explaining the higher safety profile compared to the undesirable pro-inflammatory effects of IFN-α. Interesting data in the field of infectology, as well as the availability of ready-made pegylated forms of IFN-λ, which have already passed clinical studies and showed a higher safety profile in them than pegylated IFN-α, open up scientific and clinical horizons for the study and use of IFN-λ. IFN-gamma is a powerful activator of innate immunity, therefore, suppression of IFN-gamma and IFN-lambda in women with CVHB indicates suppression of not only antiviral immunity, but also the systemic immune response.

## Conclusion

Thus, our studies have shown that the values of interferon gamma and IFN-lambda, which are expressed antiviral proteins, are significantly suppressed against the background of chronic viral hepatitis B in pregnant women in the early stages of pregnancy, which can lead to a pronounced suppression of cellular immunity and activation of virus replication. Research in this area will be continued in order to understand the etiopathogenesis, features of the course of the infectious process, and predict the course of the disease

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