Journal of Pharmaceutical Research International

32(29): 60-66, 2020; Article no.JPRI.62740
ISSN: 2456-9119
(Past name: British Journal of Pharmaceutical Research, Past ISSN: 2231-2919, NLM ID: 101631759)

Menstrual Irregularities Frequency in Reproductive Age Women with Chronic Parenteral Viral Hepatitis and Insufficiency of Antioxidant Factors

M. A. Rashidova[1*], L. F. Sholokhov[1], M. A. Darenskaya[1], S. I. Kolesnikov[1] and L. I. Kolesnikova[1]

[1]Federal State Public Scientific Institution «Scientific Centre for Family Health and Human Reproduction Problems», 664003 Irkutsk, Str. Timiryazeva 16, Russian Federation.

Authors' contributions

This work was carried out in collaboration among all authors. All authors read and approved the final manuscript.

Article Information

DOI: 10.9734/JPRI/2020/v32i2930884
Editor(s):
(1) Dr. Mohamed Fathy, Assiut University, Egypt.
Reviewers:
(1) Tatielly Kruk, Federal University of Parana, UFPR Hospital Complex of Clinics of Paraná, Brazil.
(2) Aline Henz, Universidade Federal do Rio Grande do Sul, Brazil.
Complete Peer review History: http://www.sdiarticle4.com/review-history/62740

Original Research Article

Received 06 September 2020
Accepted 10 November 2020
Published 19 November 2020

ABSTRACT

Background: Our previous study of the lipid peroxidation and antioxidant defense system (LPO-AOS) state in women with chronic viral hepatitis (CVH) showed the content of fat-soluble vitamin alpha tocopherol significant reduction. Reproductive health of women with CVH needs special attention. The objectives of this study was to determine the frequency of menstrual disorders in the group of women with CVH with marked alpha tocopherol insufficiency.
Study Design: A case-control study.
Place and Duration of Study: A study was conducted at Scientific Centre for Family Health and Human Reproduction Problems and in the hepatological department of the Irkutsk clinical hospital of infectious diseases from 2010 to 2014. This work was performed with the use of equipment of Collective research centre "Center for the development of progressive personalized technologies for health" SC FHHRP, Irkutsk.
Methods and Results: Our study included 44 reproductive age women with CVH and comparable age 28 healthy women. All women underwent clinical examination and questionary survey. We found alpha tocopherol insufficiency in 95.5% cases of patients with CVH and menstrual disorders.

**Corresponding author: E-mail: rashidovama@mail.ru;*

Conclusion: Our results suggest that menstrual disorders in patients with CVH may be associated with alpha tocopherol insufficiency.

Keywords: Antioxidant protection; chronic viral hepatitis; women; reproductive age; menstrual cycle disturbances.

ABBREVIATIONS

LPO-AOS: The lipid peroxidation and antioxidant defense system
CVH : Chronic Viral Hepatitis
ATP : Adenosine-Triphosphoric Acid
HBV : Hepatitis B virus
HCV : Hepatitis C virus

1. INTRODUCTION

Viral hepatitis infection with the parenteral transmission is one of the most common infection diseases, and it puts at risk people's health [1]. B, C and B+C mixed hepatitis are the most frequent to be found. One of the essential characteristics of hepatitis C is that patients develop a chronic form in 60-70% of cases [2]. Even though a chronic form of hepatitis persists only in 5-10% of patients with acute hepatitis B, the number of cases of chronic hepatitis are continually increasing. In Irkutsk region (Russian Federation) among chronic viral hepatitis infections, the chronic viral hepatitis C (HCV) takes the leading position – 86.1%, and chronic viral hepatitis B (HBV) ranks the second – 13.9% [3]. Chronic HCV and HBV have an overall pathologic effect on all body systems [4,5]. Reproductive health of women with these infections is of concern. We believe that determination of the major criteria to assess menstrual disorder risks in reproductive women with chronic viral hepatitis is a crucial task.

Deficit of such fat-soluble vitamins as alpha-tocopherol and retinol, which are antioxidants, are known to affect the reproductive system functioning. In our previous studies of lipid peroxidation and antioxidant defense system (LPO-AOS) processes we found that women with chronic viral hepatitis had marked decrease in fat-soluble vitamin – alpha-tocopherol [6,7]. Alpha-tocopherol is the main antioxidant stabilizing membrane lipid bilayer at the molecular level and provides optimal functioning of membrane receptors, systems of membrane transport, and membrane enzymes. This also includes electron transport chains determining energy storage in the cell and ATP production, and enzymes of the monooxygenase system providing biosynthesis of essential endogenous compounds such as corticoids and sex hormones [8]. Considering the significant influence of alpha-tocopherol on different parts of the reproductive system [9,10], we assessed the frequency of menstrual disorders in the group of patients with chronic viral hepatitis with marked alpha tocopherol insufficiency.

2. MATERIALS AND METHODS

A case-control study was conducted at Scientific Centre for Family Health and Human Reproduction Problems in the laboratories of pathological physiology, physiology and pathology of the endocrine system and in the hepatological department of the Irkutsk clinical hospital of infectious diseases from 2010 to 2014. This work was performed with the use of equipment of Collective research centre "Center for the development of progressive personalized technologies for health" SC FHHRP, Irkutsk.

We recruited women of reproductive age who then were divided into two groups according to clinical and anamnestic and laboratory data. One group comprised 44 patients with confirmed chronic HBV and/or HCV (mean age 28.9 ± 7.5) with histology activity indices, fibrosis stages, replication and integration stages (no significant changes were revealed between them), and the control group included 28 healthy women (mean age 30.8 ± 2.9).

2.1 Inclusion and Exclusion Criteria

Inclusion criteria for the group with CVH:

- Reproductive age from 18 to 40 years;
- No confirmed endocrine pathology;
- Confirmed chronic HBV or HCV;
- Informed consent of the patient.

Exclusion criteria for the group with hepatitis:

- Failure to conform with the inclusion criteria;
- Alcohol or medication abuse;
- Drug addiction;
- Smoking;

- Confirmed mental disorders;
- Tuberculosis;
- Diabetes;
- Oncology;
- Pregnancy or lactation;
- Taking hormonal therapy;
- Severe somatic disorders.

Inclusion criteria in the control group:

- Reproductive age from 18 to 40 years;
- No acute forms of any disease or acute exacerbation of chronic disease at the moment of investigation;
- Informed consent.

Exclusion criteria for the control group:

- Alcohol or medication abuse;
- Drug addiction;
- Smoking;
- Confirmed mental disorders;
- Tuberculosis;
- Diabetes;
- Oncology;
- Pregnancy or lactation;
- Taking hormonal therapy;
- Chronic diseases in a patient's history.

We used blood serum, blood plasma, and hemolysate as the material for the study. Before any therapy prescribed, in the fasted state, from 8 to 9 a.m., after 15-minute rest, blood sampled from median cubital vein, using disposable vacuum blood collection tubes (on the 3-9th day of the menstrual cycle (if it is present) or in the presence of amenorrhea).

Blood was delivered to the laboratory in the periodnot exceed 60 minutes.

Chronic hepatitis was diagnosed using epidemic and clinical data. It was confirmed by specific antibodies detection by means of enzyme-linked immunosorbent assay. Intensity of inflammation was determined using histology activity index according to the classification of Knodell R.G. et al. (1981).

We conducted analysis of four menstrual cycle characteristics: regularity, cycle length, and duration and intensity of menses.

Participants of our study reported no menstrual disorders before hepatitis onset.

Intensity of lipid peroxidation processes was assessed by the blood plasmacontent of substrates with conjugated double bonds, concentration of diene conjugates, ketodienes and conjugated trieneswere measured the method based on intense absorption of conjugated dienehydroperoxide structures at 220, 232, and 278 nm. The content of TBA-reactive substances was determined fluorimetrically.

We estimated the state of the antioxidant defense system by the level of the total antioxidant status (TAS), concentration of retinol and alpha tocopherol. The reference values for α-tocopherol were 7–21 μmol/L and for retinol—0.70–1.71 μmol/L.We determined activity of superoxide dismutase (SOD), concentration of reduced (GSH) and oxidized (GSSG) glutathiones in the hemolysate [11]. Measurements were made using spectrofluorophotometer Shimadzu RF-1501 (Japan).

Blood serum was tested on concentration of hormones: prolactin, luteinizing hormone (LH), follicle-stimulating hormone (FSH), cortisol, testosterone, 17 OH progesterone (17 OHP) and estradiol by the immunoenzyme method in the analyzer COBOS (USA).

2.2 Statistical Data Analysis

Software package STATISTICA 6.1 Stat-Soft®Inc USA was used to conduct statistical analysis. Biometric analysis included analysis of contingency tables with assessment of statistical values of one-sided Fisher's exact test.

To classify obtained data, to assess the quality of classification and to choose the most informative features we used multifactorial discriminant analysis [12]. Assessment of the frequency of antioxidant insufficiency in patients with chronic hepatitis (limits of normal values of the antioxidant defense system for groups of virtually healthy individuals) were calculated with Yates' correction ($M \pm t*m$).

Differences of the compared values were considered significant at $p \leq 0.05$.

3. RESULTS AND DISCUSSION

We assessed the frequency of menstrual disorders in the group of women with chronic hepatitis. We found there were 5 types of menstrual disorders: amenorrhea (9 women), oligomenorrhea (2 women), opsomenorrhea (5

women), polymenorrhea (5 women), menorrhalgia (1 woman).

Analysis of the group of patients with chronic hepatitis showed that 50% of patients had menstrual disorders (Table 1).

Search for the most significant criteria, that would help to determine the risk of menstrual disorders development in women with chronic hepatitis was our priority task. To achieve that goal and differentiated these groups maximally we applied discriminant analysis which helped us to calculate linear classification functions depending on several most informative parameters.

We chose most informative parameters of all LPO-AOS and the neuroendocrine system regulation investigated criteria not correlating between each other to differentiate the two groups. Assessment of the parameters for their informative value was done with F-test at significance level $p \leq 0.05$.

The following criteria were found for the reproductive age women group with chronic hepatitis – prolactin, luteinizing hormone, testosterone and alpha tocopherol. For these criteria we constructed equations of the discriminant function:

$$F1 = -10.29 + 0.01 \times x1 + 0.52 \times x2 + 0.03 \times x3 + 0.97 \times x4,$$
$$F2 = -6.03 + 0.01 \times x1 + 0.26 \times x2 + 0.38 \times x3 + 0.62 \times x4,$$

Where

F1 – Linear classification function for assigning women of reproductive age with chronic parenteral viral hepatitis to the group with normal menstrual cycle,
F2 – linear classification function for assigning women of reproductive age with chronic hepatitis to the group with menstrual disorders,
x1-prolactin,
x2- luteinizing hormone,
x3-testosterone,
x4-alpha tocopherol.

To work with the classification functions, the values were standardized according to the formula: $Z = (X - m) / S$, where Z is the standardized value of the variable X, m is the mean value of the variable, S is the standard deviation.

Standardization is needed to bring all parameters to consistency. Relative value of the difference between the standardized parameters exactly conforms to the relative value of the difference between the primary parameters.

To assign the tested patient to the corresponding group, the values of each parameter were entered into the equations of the classification function. The assignment of an object to a certain group is performed according to the maximum value of the classification function. If the value was positive (F1 <F2) and the woman confirmed the presence of menstrual irregularities, then the result was recognized as truly positive (a = 17 people), otherwise it was recognized as false negative (c = 3 women);

If the value during testing was negative (F1> F2), and the patient did not experience any menstrual disturbances against the background of CVH, the result was recognized as truly negative (b = 19 patients), otherwise it was recognized as false positive (d = 5 women).

To determine the diagnostic significance of the selected parameters and the constructed classification equations in assessing the risk of menstrual disorders in patients with chronic hepatitis, the following parameters were determined:

- Sensitivity - the proportion of patients with a positive test result among women with chronic hepatitis with confirmed menstrual disorders, - $a / (a + c) \times 100\% = 85\%$,
- Diagnostic efficiency of the constructed classification equations (test accuracy) - the proportion of correct test results in the total number of results obtained - $(a + b) / (a + b + c + d) \times 100\% = 81.8\%$.

Thus, the inclusion of these parameters into the equations of classification functions can be considered as additional diagnostic criteria that are highly sensitive and help to assign women of reproductive age with CVH in the risk group for menstrual irregularities with an accuracy of 81.8%.

Fat-soluble vitamin alpha tocopherol is one of most important components of biosynthesis and hormones functioning, regulating the reproductive system [13]. If there is alpha tocopherol insufficiency in the body the level of gonadotropic hormones significantly reduces [14]. In this connection we then conducted the

Table 1. Frequency of different types of menstrual disorders in women with chronic hepatitis (%)

Type of a menstrual disorder	Proportion of the patients with chronic hepatitis (n=44), %
Amenorrhea(absence of menses)	20.5
Oligomenorrhea(menses duration is less than 2 days)	4.5
Opsomenorrhea(menses come extremely rarely: in 6-8 weeks)	11.4
Polymenorrhea(menses' duration is 7-12 days)	11.4
Menorrhalgia(the cyclic uterine bleeding, associated with menstrual cycle, lasting more than 12 days)	2.3

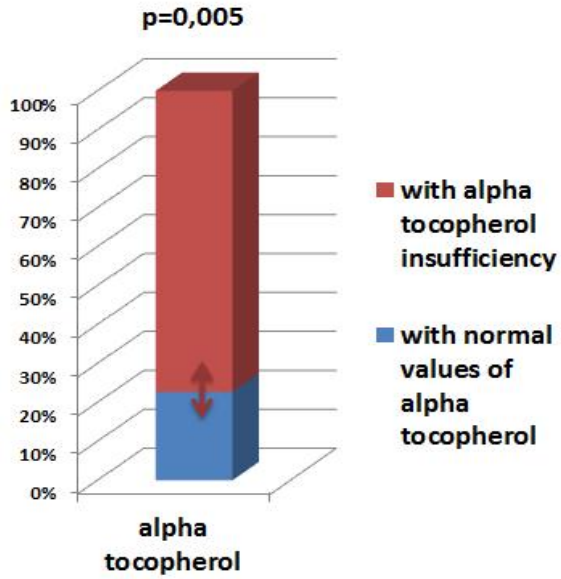

Fig. 1. Frequency insufficiency of antioxidant factors in reproductive age women with CVH

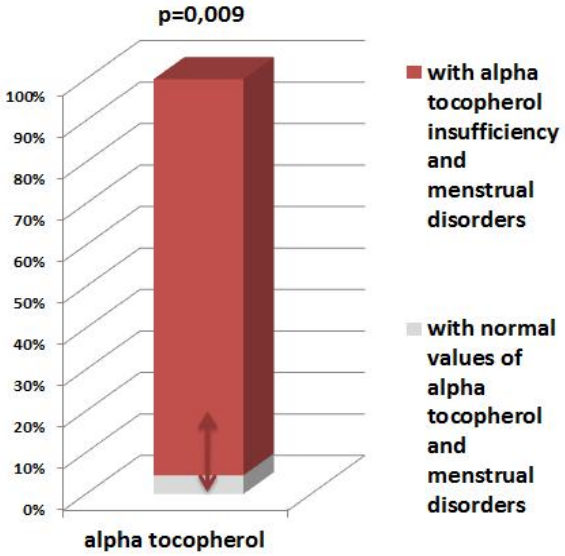

Fig. 2. Menstrual irregularities frequency in reproductive age women with CVH

frequency analysis of the prevalence of alpha tocopherol insufficiency in the studied group. Statistically significant alpha tocopherol insufficiency in 77.3% (p=0.005) of patients with chronic hepatitis (Fig. 1) was established. It may be a pathogenetic risk factor for developing disorders in a woman's reproductive system.

Analysis of the AOS state helped to determine the incidence of patients with menstrual disorders. Obtained results showed significant prevailing majority of patients with chronic parenteral viral hepatitis with marked alpha tocopherol insufficiency and presence of menstrual disorders (95.5% cases (p=0.009)) (Fig. 2). Tocopherol influences biosynthesis of gonadotropic and steroid sex hormones by regulation of cholesterol metabolism, and contributes to normal pregnancy and normal fetus development, prevents miscarriages and disorders of sex hormones. Insufficiency of this substance leads to the uterine malfunction in women [15].

4. CONCLUSION

Being a general inflammatory disease, chronic viral hepatitis lead to change in the state of all organs and systems of the body including main indicators of homeostasis. In addition to inadequate cell-mediated immune response to the viral infection there are disorders in the functioning of the system LPO-AOS. Analysis of the obtained results shows changes in the functioning of the system LPO-AOS in women of reproductive age with chronic parenteral viral hepatitis. These metabolic changes can intensify the pathologic process in the future and adversely affect the whole organism. Alpha tocopherol considerable insufficiency in women with chronic hepatitis greatly contributes to menstrual disorders development because of direct influence of this component of the AOS on the functioning of the reproductive system. We may suggest that menstrual disorders in women with chronic hepatitis can relate to alpha tocopherol insufficiency. Therefore, we can recommend prescription of antioxidants, amount of which should be chosen individually considering the patients disbalance. Timely correction of antioxidant insufficiency will help to prevent the development of menstrual disorders in patients with chronic hepatitis.

Further we plan to study not only the effect of CVH on reproductive health of women, but also its influence on the course and outcomes of the pregnancy. CVH may be of particular interest to obstetrician–gynecologists because of the risk of CVH transmission to the fetus.

CONSENTAND ETHICAL APPROVAL

We conducted our study in accordance with the ethical principles of World Medical Association Declaration of Helsinki (1964, 2013 edition). Our study was approved by the local Ethical Committee of Scientific Centre for Family Health and Human Reproduction Problems. All women signed informed consent to participate in the study.

DISCLAIMER

The products used for this research are commonly and predominantly use products in our area of research and country. There is absolutely no conflict of interest between the authors and producers of the products because we do not intend to use these products as an avenue for any litigation but for the advancement of knowledge. Also, the research was not funded by the producing company rather it was funded by personal efforts of the authors.

COMPETING INTERESTS

Authors have declared that no competing interests exist.

REFERENCES

1. Sattar SA, Tetro J, Springthorpe VS, Giulivi A. Preventing the spread of hepatitis B and C viruses: Where are germicides relevant? Am J Infect Control. 2001;29:187-97.
DOI: 10.1067/mic.2001.114233.
2. Gilson R, Brook MG. Hepatitis A, B, and C. Sex Transm Infect. 2006;82(Suppl IV):35–39.
DOI: 10.1136/sti.2006.023218.
3. Savilov ED, Chemezova NN, Astafev VA, Malov IV, Malov SI, Gavrilova TA, Burdanova TM, Vladykina AV, Chubukin EA. [Parenteral viral hepatitises in the Irkutsk region]. Acta biomedical scientifica. 2018;3(4):148-153.
DOI: 10.29413/ABS.2018-3.5.22
[Article in Russian].
4. Aman W, Mousa S, Shiha G, Mousa SA. Current status and future directions in the management of chronic hepatitis C. Virology Journal. 2012;9(1):57.
DOI: 10.1186/1743-422x-9-57.

5. Pirayvatlou PS, Alavian SM, Pirayvatlou SS, Pouyan SP, Mina M, Madjad E. Efficacy of DAA-based Antiviral Therapies for HCV Patients with Chronic Kidney Disease: A Meta-analysis. Journal of pharmaceutical research international. 2019;31(6):1-10.
DOI: 10.9734/JPRI/2019/v31i630328
6. Darenskaya MA, Grebenkina LA, Sholokhov LF, Rashidova MA, Semenova NV, Kolesnikov SI, Kolesnikova LI. Lipid Peroxidation Activity in Women with Chronic Viral Hepatitis. FRBM. 2016;100:S192.
DOI:
10.1016/j.freeradbiomed.2016.10.525.
7. Rashidova MA, Sholokhov LF, Darenskaya MA, Kolesnikova LI. Functional state of the thyroid gland and lipid peroxidation and antioxidant protection system in women of reproductive age with chronic form of parenteral viral hepatitis. Acta biomedical scientifica. 2019;4(1):31-35.
DOI: 10.29413/ABS.2019-4.1.5
[Article in Russian]
8. Atalyan AV, Shelokhov LF, Kolesnikova LI. Endocrine Markers of Fertility Potential in Reproductive Age Women with Idiopathic Hyperprolactinemia. Journal of pharmaceutical research international. 2020;32(23):71-77.
DOI: 10.9734/JPRI/2020/v32i2330790.
9. Jilani T, Iqbal MP. Vitamin E deficiency in South Asian population and the therapeutic use of alpha-tocopherol (Vitamin E) for correction of anemia. Pak J Med Sci. 2018;34(6):1571-1575.
DOI: doi.org/10.12669/pjms.346.15880.
10. Kolesnikova LI, Semyonova NV, Grebenkina LA, Darenskaya MA, Suturina LV, Gnusina SV. Integral indicator of oxidative stress in human blood. Bull Exp Biol Med. 2014;157(6):715-7.
DOI: 10.1007/s10517-014-2649-z.
11. Kamyshnikov VS. Handbook of clinical and biochemical studies and laboratory diagnostics, 3rd edition. Moscow. MEDpress-Inform. 2009;896
[Article in Russian].
12. Dokin VN, Mikhalvich IM. Fundamentals of probability theory and mathematical statistics in biomedical research. Manual.- Irkutsk. 2013;79. [ArticleinRussian].
13. Kolesnikova L, Semenova N, Madaeva I, Suturina L, Solodova E, Grebenkina L, Darenskaya M. Antioxidant status in peri- and postmenopausal women. Maturitas. 2015;81(1):83-87.
DOI: 10.1016/j.maturitas.2015.02.264
14. Kozak MV, Teplyĭ DL. Morphofunctional status of gonadotropic cells of the adenohypophysis at early stages of age involution. AdvGerontol. 2007;20(4):25-30.
[Article in Russian].
15. Wang S, He G, Chen M, Zuo T, Xu W, Liu X. The Role of Antioxidant Enzymes in the Ovaries.Oxidative Medicine and Cellular Longevity. 2017;2017:1–14.
DOI: 10.1155/2017/4371714

Peer-review history:
The peer review history for this paper can be accessed here:
http://www.sdiarticle4.com/review-history/62740