EFFE C T o F s o M e  B i o C h e M i C a l  F a C T o R S  o N  F E M A L E  R E P R O D U C T I V E  F U N C T I O N

Natalia Gudinskaya1, Oksana Boiko2, Rushaniya Mukhamedzyanova2, Yuriy Dotsenko2, Shakhrydin Tokhtarov2, Anzhela Ramaeva3, Galiya Khairulaeva4, Polina Gudinskaya1

1 Astrakhan State Medical University, Astrakhan; 2 Grozny Republican Clinical Hospital named after Sh.Sh. Ependiev, Grozny; 3 Alexandro-Marinsky Regional Clinical Hospital, Astrakhan Region; 4 Tinaki Rehabilitation Center, Astrakhan Region, Russia

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ABSTRACT — The study aimed to determine the effect of certain biochemical factors on the female reproductive function. Analysis showed that two biochemical factors classified as inflammatory markers have a significant difference in their concentrations in women with impaired fertility and those without fertility disorders. These are C-reactive protein (CRP) and lactoferrin (LF). It is reasonable to assume that these inflammatory markers are associated to some extent with the development of reproductive disorders due to possible formation of inhibin A/LF complexes, which may reduce the biological activity of inhibin A, in patients’ serum. The effect of CRP on inhibin A activity is most likely to be systemic and associated with the effect of CRP high concentrations on inhibin A function on the body level. In particular, it is possible that CRP has an effect on IL-1β synthesis in ovarian follicles.

KEYWORDS — C-reactive protein, lactoferrin, interleukins, fibrinogen, α2 macroglobulin reproduction.

INTRODUCTION

According to a number of researchers, an inflammatory process in patients, accompanied by a number of biochemical factors in the serum, may reduce the relevance of sufficient levels of inhibin A, belonging to the group of Smads [2]. Inhibin A is a protein secreted by ovarian granular cells, among others, and it has an effect on the secretion of follicle-stimulating hormone (FSH). Inhibin A is present in blood plasma and in follicular fluid in large quantities. Its main function is to inhibit folliculotropin secretion by the pituitary gland by affecting the hypothalamus [7, 11].

Factors that cause a decrease in the biological activity of inhibin A primarily include cytokines and acute-phase proteins. Finding out the causes of a decrease in the level and activity of inhibin A in women with inflammatory diseases of the reproductive system, including infectious diseases, will both improve the quality of diagnosis and provide new opportunities for the development of fertility treatment methods [1, 3, 8, 10].

The study aimed to determine the effect of certain biochemical factors on the female reproductive function.

MATERIALS AND METHODS

The study is focused on the blood serum of women with chronic inflammatory processes, in particular chronic trichomoniasis. Blood serum of almost healthy fertile women having no trichomoniasis, including in past medical history, was used as a control.

160 women with chronic trichomoniasis were examined. They were from 22 to 29 years old, with the average age of 24.1±3.45.

The level of inhibin A in the blood serum of all the examined women was determined with the method of enzyme immunoassay on days 3–5 of the menstrual cycle, as recommended by WHO. 35 healthy fertile donor women without trichomoniasis and with no history of STDs (the average age of 24.3±1.41), were examined as a control.

The phenotype of lymphocytes was determined using a fluorescent microscope with monoclonal antibody straining (produced by State Research Center Institute of Immunology, Moscow, Russia). Immunoglobulin levels in the serum were measured with the standard method of radial immunodiffusion (Mancini method), for which monospecific antisera were used (National Research Center for Epidemiology and Microbiology named after Academician N.F. Gamaleya, Moscow, Russia). The content of immunoglobulins was expressed in mg/%.

Cytokines were produced through spontaneous synthesis of IL-1β, IL-8, IL-10 and IFNγ. Lymphoid cells were preincubated for 24 hours. The concentration of the above cytokines was determined with immunoenzyme method. Concentrations of IL-1β, IL-8 were determined using test kits produced by Protein Contour (St. Petersburg), the ones of IL10 and IFNγ – with Immunotech test kits (France).

Lactoferrin was determined with immunoenzyme method using test kits produced by Cytokine company (St. Petersburg).

Concentrations of α2-macroglobulin and C-reactive protein were determined with nephelometric method.
It is obvious that the lack of IFNγ production, on the one hand, reflects the impaired functional activity of CD4+ cells in the patients, and, on the other hand, may lead to infection tolerance.

The content of immunoglobulins IgA and IgM in the patients was within normal limits, though there were changes in their ratio (as a rule, an increase in the level of IgA and/or decrease in the level of IgM), which was identified in two thirds of the patients.

Therefore, examination of the cytokine profile in the women with chronic trichomoniasis clearly demonstrates prevailing development of the Th-2 type immune response.

It is known that cytokines initiate synthesis of secondary mediators of inflammation — acute-phase proteins — by hepatocytes. These include, among others, plasma glycoproteins produced by the liver in response to tissue damage. Plasma proteins are divided into several classes depending on the increase in their concentrations in case of acute-phase states. A decision was made to examine concentrations of lactoferrin (LF), C-reactive protein (CRP), α-2-macroglobulin and fibrinogen. According to the authors’ data, the level of CRP in the group of healthy women was 0.3±0.01 μg/ml. Its concentration in the patients showed more than 65-fold increase — up to 19.5±0.8 μg/ml (p < 0.001), but this is much lower than in most bacterial infections and more typical of chronic viral diseases.

The level of lactoferrin in the group of healthy women under examination was 445.0±104.0 ng/ml. Its concentration in the patient group was elevated almost 8-fold — up to 3,475.0±178.0 ng/ml (p < 0.001). Such values are more often seen in acute infections (including sexually transmitted diseases) and are not typical of most chronic bacterial infections at all, although bacteria are capable of synthesizing protein that is immunochemically similar to human lactoferrin [6, 10].

Then the authors performed a retrospective analysis of variation series, with the results obtained being grouped regardless of the concentration of inhibin A, and the inflammatory factors under study, in their relationship with the state of the reproductive function of the women having trichomoniasis. As mentioned above, infertility was observed in 30 women in the patient group with normal levels of inhibin A, while the rest kept fertile or had no reliable data on fertility disorders. The conducted analysis showed that only two inflammatory markers in the blood of the women having a chronic inflammatory process have a significant difference in their concentrations in the women with impaired fertility and those without fertility disorders. These are C-reactive protein and lactoferrin.

It is natural to assume that these inflammatory markers are associated to some extent with the devel-
opment of reproductive impairment in the women suffering from trichomoniasis. The authors admit possible formation of inhibin A/LF complexes in the patients’ serum which may reduce the biological activity of inhibin A. This is quite possible in at least two ways. Firstly, it is electrostatic interaction of several molecules of inhibin A, having a sufficiently high negative charge, with LF polycation. Secondly, there may be a mechanism of mostly hydrophobic interaction between LF molecules and inhibin A.

The CRP effect on inhibin A activity can hardly be explained with formation of complexes. They are most likely to be systemic and associated with the effect of CRP high concentrations on inhibin A function on the body level. In particular, it is possible that CRP has an effect on IL-1β synthesis in ovarian follicles. It is known from literature that this cytokine is synthesized by the granulosa cells and that high concentrations of IL-1β in the follicular fluid correlate with the degree of maturity and with the frequency of oocyte fertilization [1, 3, 11]. On the other hand, IL-1β is a pro-inflammatory cytokine that plays an essential role in inflammatory response unfolding. It can induce most of its local and general manifestations. It is also known that high concentrations of CRP (10 ng/mL and more) can inhibit IL-1β synthesis along with prostaglandin E2 and glucocorticoids.

**CONCLUSION**

Therefore, the study results can be summed up as follows. The group of patients with a chronic inflammatory process demonstrate significant variability in the concentration of inhibin A (4.3 — 29.4 ng/l). Secondary infertility was diagnosed in 63.2% of cases in the group of patients with reduced levels of inhibin A, while the group of patients with normal levels of inhibin A demonstrated only 12.9% of cases of secondary infertility development. It was found out that C-reactive protein and lactoferrin were the only acute-phase proteins that had a prognostic value and differed significantly in the groups of women with subsequent infertility and those with a chronic inflammatory process that was not complicated with infertility.

The authors declare no conflict of interest in the manuscript being submitted.

**REFERENCES**


