INDICATORS OF DYNAMICAL PROINFLAMMATORY CYTOKINES IN WOMEN USING INTRAUTERINE CONTRACEPTIVES

Umida Yusupova, Farida Ayupova

Andizhan State Medical Institute, Uzbekistan

ABSTRACT

Birth rate regulation is a major problem of modern medicine. Unfortunately, frequency of artificial abortions is still high not only in developing, but also in developed countries. Abortion results in severe gynecologic and endocrine complications in the woman's body (Alieva, 2001).

Use of intrauterine devices (IUDs) is a most effective method of contraception. A great number of studies in the field of utilization and possible complications of IUDs revealed the occurrence of inflammatory diseases of small pelvis organs (IDSPo).

With this in mind, we studied the data obtained from 77 women using copper IUDs in maternity facility №2 of the city of Andizhan (Uzbekistan). Duration of patients' follow-up ranged 40 days to 6 months. Women did not have contraindications for IUDs according to WHO medical eligibility criteria. Blood was a material for study; it was taken in 40 days, 3 and 6 months following IUD insertion. After insertion of copper IUDs to women, a cytokine cascade was studied in dynamics. The serum content of IL-1, IL-6 and concentration of TNF α was measured in all patients according to the instruction attached to immunoenzymatic analyzer "AT-858" manufactured in China. The minimum concentration of TNF α reliably identified in this test system made 4 pg/ml.

During the study, the women of the test group showed increased proinflammatory cytokines. The further study of vaginal smears confirmed development of bacterial vaginosis in them that suggests a relation of complications due to IUDs with imbalance of the cytokine cascade.

Elevated serum concentration of cytokines was revealed in women with IUDs already on the first days of their application.

Sharp increase in IL-1 on days 40 and 90 after insertion of IUDs is associated with presence of complications in the form of expulsions and possible development of inflammatory diseases of small pelvis organs.

UDC CODE & KEYWORDS

■ UDC: 615 ■ Small pelvis organs ■ Intrauterine devices

INTRODUCTION

The problem of demand in those or other contraceptives and the frequency of utilization of various methods of contraception to obtain reliable internationally comparable epidemiological data on the use of methods of family planning has not been resolved definitively. According to researchers, an objective evaluation of a situation in regions on the use of contraception and a conscious influence on it, is possible only if a unified national reporting system is set up which would enable to receive accurate and continuous information on utilization, availability of various methods of contraception and their demand. At the current stage, data on the structure of some methods of contraception and their complications can be obtained only from women themselves by means of special studies carried out among them. Unfortunately, the existing reporting system on the use of contraception methods reliably reflects data on prescription and follow-up only for some of them. In model advisory facilities for women these indicators are traditionally developed on the basis of registration form No. 30 "Check up chart of dispensary patient," which is filled up by local doctors, and it is done almost always as a mere formality.

During the last years, an appreciable success has been achieved in the development of new, more perfect contraceptive agents, which are known as a basic method of prevention of abortions and their complications.

Wide introduction of modern methods of contraception into the practice of public healthcare of Uzbekistan is carried out rather for the creation of an optimal intergenetic interval needed for rehabilitation of women's health than for prevention of undesirable pregnancy. As ovulation and a risk of pregnancy associated with it are restored quickly after abortions, contraception in this situation should be used immediately. After the first trimester abortion, ovulation may occur already on day 11 and it takes place prior to the first menstrual bleeding. Hence, to avoid undesirable pregnancy and excessive growth of the family, it is necessary to use contraception.

Prevention of pregnancy in women of fertile age and observance of an intergenetic interval result in a 2-fold decrease in maternal and infant mortality (Bystrova, 2006; Backman, 2004). In this respect contraception is of great importance, especially in a postnatal period to maintain a reproductive health of women. In developing countries intrauterine contraception (IUC) is most popular. It is a method of choice for breastfeeding women who do not have contraindications to their utilization. IUC utilization, however, may cause development of adverse events and complications in terms of expulsions, disorders of a menstrual cycle and development of IDSPo (Ershov, 2006; Bahamondes et al., 2005). Still, observance of aseptic, well-timed control and estimation of the woman's state prevents occurrence of the said complications.

A disorder in regulation of an inflammatory process results in an essential change of its course. An important role is played by a shift of proinflammatory cytokines, in particular of IL-1, IL-6 and TNF α (Alieva, 2001).

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The WHO carried out a number of researches aimed at studying a relation between using IUDs and IDSPD occurrence. It was established that a risk of IDSPD occurrence was 6 times higher within the first 20 days following IUD insertion and it remained at the lowest level during the following 8 years of presence of a device in the uterine cavity. It is established that infections of the uterine cavity and the Fallopian tubes revealed within 3 weeks to 3 months following IUD insertion are associated with non-observance of aseptic during their insertion.

It may be assumed that till present Gynaecologists of the primary health care (rural medical points (RMP)) carry out insufficient regular examinations of women covered with contraception, and women themselves have no sufficient awareness of contraception issues.

Studies of an immune and cytokine status (proinflammatory and anti-inflammatory cytokines) as well as morphological studying of the state of the endometrium in women using IUDs are carried out inconsistently and, undoubtedly, that is of great importance in working out preventive measures targeted at decreasing IUD-related complication and promoting the efficacy of their utilization.

The points mentioned above stress a need in studying of the state of the immune system with the determination of proinflammatory and inflammatory cytokines in women using IUDs.

The aim of the research

The goal of this research was to study the dynamics of the cytokine cascade in the dynamics of IUC utilization.

Material and methods

Seventy-seven women with copper IUDs were monitored in maternity complex #2 of Andizhan. A follow-up period lasted 40 days to 6 months. The women did not have any contraindications for IUDs according to WHO medical eligibility criteria (Medical Eligibility Criteria for Contraceptive Use, 2000).

Blood was a material for the study, which was taken in 40 days, 3 and 6 months following insertion of IUDs. Studying of composition of a urogenital microflora is carried out. All the patients undertook a microscopic study of discharges from the cervical, urethral channels and vagina to detect the presence of urogenital infections.

After insertion of copper IUDs to women, a cytokine cascade was studied in dynamics. The serum content of IL-1, IL-6 and concentration of TNF α was studied in all patients according to the instruction attached to immunoenzymatic analyzer "AT-858" manufactured in China. The minimum concentration of TNF α reliably measured with this test system makes 4 pg/ml.

The data obtained were processed statistically using personal computer Pentium-IV with a software package Microsoft Excel 2003, including use of built-in functions of statistical management.

Results and discussion

The study showed that indicators of IL-1, IL-6 and TNF were high during the first 40 days.

On day 40 indicators of IL-1 were 1.16 times higher in comparison with month 3 after insertion of IUDs, and in comparison with month 6 the difference was 1.20 times higher. Such indicators suggest a possibility of development of IDSPD and other possible complications. IL-6 data on months 3 and 6 were already lower than on day 40 ($P < 0.001$). Although the TNF α indicators were not so high, they were reliably discernible at month 6 after insertion of IUC (Table 1).

Table 1: Levels of interleukins and TNF α in women with IUC

Indicator	Day 40	Month 3	Month 6
IL-1 pcg/ml	168.3 $\pm$ 2.29	144.4 $\pm$ 1.77	139.8 $\pm$ 1.26
IL-6 pcg /ml	30.06 $\pm$ 0.94	21.8 $\pm$ 0.53	20.7 $\pm$ 0.33
TNF α pcg/ml	66.3 $\pm$ 1.23	48.3 $\pm$ 3.13	44.17 $\pm$ 1.16

Source: Authors

It should be noted that a chronic inflammatory process in vascular walls induces a synthesis of proinflammatory cytokines besides the endothelium itself and immunocompetent cells which accumulate in the intima. This confirms a role of cytokines, rising of the serum content of IL-1, IL-6 and TNF α of the patients with IUC in diagnostics of IUD-related complications.

A leading place in development of an inflammatory process is manifested, as a rule, in a change of the cytokine cascade. A lot of research work is devoted to studying of systems of proinflammatory cytokine synthesis; however a majority of them has rather a pathophysiological than clinical orientation. At the same time, a possibility of use of an indicator of a level of proinflammatory cytokine production in clinical conditions is studied insufficiently.

In this connection, development of IDSPD was judged on a change in the content of cytokines in blood serum. The results of the study showed that from the very beginning of the study of IUD utilization, proinflammatory cytokines in blood serum were observed in women examined during all periods of the study.

An equal rise in serum cytokines was noted in utilization of IUDs on day 40. Between 3 and 6 months of IUD utilization, the results obtained showed that an action of contraceptives in all groups studied was identical.

Hence, copper IUD produces its effect on cytokine cascade rates. A rise in the dynamics of cytokines detected is an additional confirmation of the hypothesis on possible development of IDSPD on first 3 month utilization.

A disorder of regulation at any structural and functional level of organization causes an effect in which a measure of the bodily response to a pathogenic factor will not correspond to a degree of tissue damage. As a result, an inflammation will proceed inadequately to the damage, transform to a persistent form, involve in a pathological process, not only surrounding

tissues, but also the body in general, up to the development of a septic state. It should be stressed that in a persistent course of oxidative-destructive inflammation, peroxynitrite remains its main driving force.

It has been noted that a rise in cytokine concentration on month 3 following insertion of IUDs coincided in time with a polymenorrhea-like disorder of a menstrual cycle. It was found during further investigation that already during the study inflammatory diseases of genitals were developing in those women, which correlated with elevation of the content of proinflammatory cytokines. In 18% of women examined IUD expulsion was noted. Data on a bacteriological study of vaginal smears found the development of bacterial vaginoses in women with an increased level of cytokines.

During studying of indicators of the cytokine status on day 90 it was found that in a course of time a rise in cytokines studied was noted, which was not characteristic to a physiological state. In women with IUDs an increase in a number of apoptotic cells of a vascular endothelium occurred with rising in the level of TNF α that probably is associated with a rise in those cells, and it can be one of the factors promoting the development of complications in the form of expulsion of the device.

If it is borne in mind that a trigger of a menstrual cycle disorder is a dysfunction of the vascular endothelium in response to an inflammatory process, it becomes clear why a generalized dysfunction of hemostasis develops. The events mentioned are accompanied by a rise in the level of cytokines. Therefore, it can be assumed that a rise in the content of cytokines in women with IUDs is a pathogenic factor of complication development after their insertion. Determination of the cytokine content in women with IUDs can be important for predicting IUD- related complications.

Thus, the hyperactivity of the cytokine cascade noted in the beginning of an inflammatory process is an adverse sign and results in its hyperergic course in the first trimester following utilization of copper IUDs. Utilization of IUDs after 6 months and over showed that it is effective; patients have a normalization of activation markers that suggest on the restoration of a normal regulation of the body.

Until recent time it was considered that a cause of cell death is a direct toxic influence on cells, for example, of free radicals formed in disorder by metabolic processes associated with inflammatory processes.

Functioning of various components of the cytokine cascade requires a close interaction with other systems of a cellular metabolism.

Proinflammatory cytokines observed in blood serum in conditions of utilization of IUDs seem to be due to intensification of oxidative stress processes and intensive production of peroxide radicals breaking the balance between protective and damaging influences on vascular walls. In these conditions free radicals act as a type of a trap for nitrogen oxide molecules (NO), blocking its physiological action on vessels. This explains a rise in indicators of proinflammatory cytokines in dynamics in response to the development of inflammation and complications occurred in insertion of IUDs.

Conclusion

1. In women with IUDs concentration of cytokines in blood serum increases already from first days of their insertion.
2. A sharp rise of IL-1 on days 40 and 90 following insertion of IUDs is associated with the presence of complications in terms of expulsions and possible development of inflammatory diseases of small pelvis organs.

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