Research article

Effectiveness of Mirena® LNG-IUS in treating women with endometrial hyperplasia and climacteric syndrome

Tanzilya Teppeeva[1], Kanysh Karymshakova[1], Meerim Makenzhanova[1], Altynai Zhumabekova[2]

[1]Department of Obstetrics and Gynaecology named after M.S. Musuraliev, I.K. Akhunbaev Kyrgyz State Medical Academy, Bishkek, Kyrgyzstan
[2]Obstetrician-Gynecologist, City Maternity Hospital No. 2, Bishkek, Kyrgyzstan

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Corresponding author: **Altynai Zhumabekova.** Email: altynai.zhm@gmail.com

ABSTRACT

Introduction and Aim: Endometrial hyperplasia (EH) is a common cause of malignant tumors and a major health risk for perimenopausal women. In this study, systemic immunological markers in women with climacteric syndrome (CS) and EH will be examined in relation to the EH treatment option Mirena® levonorgestrel-releasing intrauterine device (LNG-IUS).

Materials and Methods: Examining 350 premenopausal women, 84 (23.4%) were diagnosed with EH. The type of EH was identified in 84 patients using a histological study and a diagnostic curettage of the uterine cavity. In view of more severe and considerable systemic immunity abnormalities in women with CS and EH, the indirect effect of levonorgestrel's intrauterine microdose excretion on systemic immunity was examined.

Results: Mirena® LNG-IUS has an indirect immune-corrective effect on systemic and humoral immunity in women with EH who have a pathological climatic course. It does this by stabilizing the neutrophil pool, activating the receptor function, and stabilizing the absorption and metabolic activity of neutrophilic phagocytes in the humoral system.

Conclusion: Due to the pathological progression of menopause and the appearance of EH, alterations in women's reproductive system during this period led to a significant decrease in the signs of CS after the first month of using Mirena® LNG-IUS.

Keywords: Perimenopausal period; climacteric syndrome; menopause; endometrial hyperplasia; levonorgestrel-releasing intrauterine system.

INTRODUCTION

Endometrial hyperplasia (EH) is of considerable medical and social relevance due to not only its high incidence but also its severe impact on the overall health of women in the perimenopausal period and as a common source of malignant tumors (1). Uterine fibroids, endometrial hyperplasia, and mammary gland hyperplasia take the top three positions in the order of severity of hyperplastic processes in a woman's reproductive system, accounting for 25–30%, 10–18%, and 37–42% of all cases, respectively (2–6). Anovulation, progesterone insufficiency, and estrogens' combined actions on the endometrium lead to EH, a hormone-dependent disease (7–11).

Progesterone deficiency and hypoestrogenism both result in excessive (uncontrolled) cell proliferation and a reduction in apoptosis. The hypothalamic-pituitary-ovarian system's malfunction, which is frequently a result of psychosomatic issues brought on by aging-related changes (12, 13), is the main cause of this illness.

In 15–40% of gynecological patients of all ages, EH is a prevalent gynecological disease, and 60–70% of all EH cases take place during the perimenopausal stage (1–18). Atypical hyperplasia occurs in cancer in 10–30% of instances (19).

Concomitant extragenital diseases are an urgent issue for Kyrgyzstan given the tendency of an increase in the frequency of hyperplastic processes of the reproductive system, conflicting approaches to the diagnosis and treatment of these conditions, the development of the most ideal diagnostic criteria, and the introduction of a differentiated approach to the choice of a method for EH treatment, taking into account the woman's age.

This study's goal was to evaluate how the EH treatment option Mirena® levonorgestrel-releasing intrauterine system (LNG-IUS) affects systemic immune markers in women with climacteric syndrome (CS) and EH.

MATERIALS AND METHODS

A total of 350 premenopausal women were examined, and 84 (23.4%) had EH. A histological analysis and diagnostic curettage of the uterine cavity were both employed in 84 individuals to determine the type of EH. This stage was necessary in order to investigate the background immunity parameters in women with EH against the background of pathological menopause and the potential for treating CS against the

background of EH. Considering that this group of women had contraindications for hormone replacement therapy in the pathological course of menopause, according to the therapeutic criteria used, it is not a coincidence that women with EH made up a distinct stage of the study. In fact, since progestins are used to treat EH, which inhibits the production of estrogen, which is required to cure all the symptoms of CS, this group of women does not receive significant assistance in the treatment of the condition. Researchers examined the clinical impact of the Mirena® intrauterine hormonal system as well as its impact on systemic immunity using an alternate therapy (local application of progestogens by their intrauterine injection). While using the levonorgestrel uterine system for HE correction, every immunological parameter was examined.

The indirect impact of levonorgestrel's intrauterine microdose excretion on systemic immunity was investigated considering more severe and substantial abnormalities of systemic immunity in women with CS and EH. Prior to the development of the intrauterine system, baseline investigations of the aspects of systemic immunity in women with EH were conducted. In one month, the LNG impact of the intrauterine system Mirena® on the systemic immune markers was assessed.

The collected data is shown as mean ± standard deviation. Statistical analysis was performed using Excel.XLSTAT v2020.1 (Microsoft, Addinsoft, France). To ascertain the significance of group differences, the Mann-Whitney test was used. Two probability levels (0.05, 0.001, and 0.01 correspondingly) were present. The data obtained was kept confidential, and the study was authorized by the I.K. Akhunbaev Kyrgyz State Medical Academy Bioethics Committee (Protocol No. 1 dated January 20, 2014).

RESULTS

Leukocyte and neutrophil counts significantly increased in patients with EH when the phagocytic link of immunity was examined against the backdrop of the LNG coil (Table 1). The increase was from 3.44±0.23 to 3.98±0.19, $p<0.01$ for leukocytes and from 38.1±1.07 to 41.1±0.54, $p<0.01$ for neutrophils.

An improvement in the depressed effect on the neutrophil pool was seen when micro-dose levonorgestrel was introduced. The stabilization of the absorption function through the activation of phagocytosis, 58.3±2.9 ($p<0.05$), and an improvement in the metabolic function of neutrophilic phagocytes through a decrease in the number of neutrophils containing reactive oxygen species in granules from 67.9±1.99 to 59.2±1.97 during treatment were all noticed by an increase in T lymphocytes up to 43.7±1.94 ($p<0.05$).

Humoral immunity

In patients with EH on the background of levonorgestrel micro-dose local effect, a statistically significant increase in B lymphocytes was recorded, both in absolute terms, from 169.3±15.1 to 182.3±16.1x10^9 g/l, and in percent, from 7.04±0.31 to 7.27±0.31, ($p<0.05$) (Table 2).

In patients receiving dosed levonorgestrel therapy, the level of immunoglobulin M significantly dropped, close to levels seen in women without EH from 136.2±4.20 to 125.3±4.22%, $p<0.05$. Immunoglobulin G and A did not significantly alter. Through a stabilizing impact on the quantity of B lymphocytes and the level of immunoglobulin M, which promotes the reduction of chronic and infectious processes and the start of autoimmune disorders, it should be considered that Mirena® LNG-IUS also indirectly regulates the humoral chain immunity.

Table 1: Women with CS and a history of EH are affected by the Mirena® LNG-IUS phagocytic chain of immunity

Phagocytic chain immunity markers	**Clinical groups**		
	CS+EH on the background of LNG system, n=43	**CS+HE, N=79, before treatment**	**CS without HE, n=54**
Leukocytes, 1x10^9/L	3.98±0.19**	3.44±0.23	6.18±1.93*
Neutrophils, %	41.1±0.54**	38.1±1.07	44.0±1.18*
Neutrophils, abs. number in 1 mcl	2801±194	2972±244	2867±202
T lymphocytes, %	43.7±1.94	44.0±2.3	42.4±1.97*
Phagocytosis activity, %	58.3±2.9**	49.4±3.4	63,7±3.2*
Active neutrophils in nitro blue tetrazolium test, %	59.2±1.97**	67.9±1.99	57.1±2.13

Note: EH - endometrial hyperplasia; CS - climacteric syndrome. ** - $p<0.05$-0.01 - reliability of differences between groups before and after treatment; * - $p<0.05$-0.01 - reliability of differences between indices after treatment with indices of women without EH.

Table 2: Influence of the Mirena® LNG-IUS on the state of humoral immunity in women with CS and EH history

Humoral chain immunity markers	Women with CS+ EH on the background of LNG-IUD, N=43	Women with CS without EH, N=54	Women with CS+EH, N=79
B-lymphocytes, %	7.27±0.31**	7.6±0.40	7.04±0.31
B-lymphocytes abs. number in 1 mcl	182.3±16.1*	191.7 ±13.9	169.3±15.1
Immunoglobulins M, mcg %	125.3±4.22*	124.±4.19	136.2±4.20
Immunoglobulin G, mcg %	979.2±19.4**	990.4±17.2	977.3±20.9
Immunoglobulins A, mcg %	120.1±12.3**	136.4±18.2	118.7±14.1

Note: ** - p<0.05 - reliability of differences between groups before and after treatment; * - p<0.05 - reliability of differences between indices after treatment with indices of women without EH.

The state of cell-mediated immunity

The following modifications were seen in women with EH who received treatment with Mirena® LNG-IUS: Leukocyte counts increased from 5.12±0.21x109/l to 5.75±0.7x109/l, (P<0.05). Table 3 shows that throughout treatment, women's leuko-formula lymphocyte percentage increased from the baseline 37.9±0.4 to 28.4±1.9, (P<0.01). Comparing the results of mature T-lymphocytes in women with EH on the background of levonorgestrel micro-dose intrauterine excretion, it should be noted that their percentage and absolute content increased (from 46.2±2.03 to 50.7±0.86 (P<0.05), in absolute figures from 0.72±0.07 to 0.91±0.03, P<0.05; i.e., the potential for antigenic recognition and interaction of cells with different cells-effectors, including other lymphocytes and macrophages, has increased. Early T-lymphocyte functional activity was considerably increased by Mirena® LNG-IUS, leading to an increase in the quantity of active T-lymphocytes (from 22.9±2.34 to 30.7±2.4, P<0.001, in absolute values from 0.67±0.04 to 0.9±0.14, P<0.01). Early post-thymic T-lymphocyte precursors tended to decrease during treatment, both in absolute terms from 0.05±0.005 to 0.047±0.003 and in relative levels from 3.47±0.22 to 3.1±0.14. Levonorgestrel dosed administration had a stimulating impact on the level of total lymphocytes, as shown by their percentage and absolute increase (from 32.1±1.2 to 39.8±1.9, and in absolute values from 0.76±0.24 to 1.80±0.37, P<0.01).

Table 3: Influence of the Mirena® LNG-IUS on cellular immunity in women with CS and a history of EH

Cellular immunity markers	Units	CS+EH on the background of LNG-IUD n=43	CS+EH, n=79	CS without EH, n=54
Leucocytes, 10^9/l	%	M±m	M±m	M±m
	Abs	5.75±0.7	5.12±0.21*	6.05±0.9
Lymphocytes	%	37.9±0.4	28.4±1.9*	39.1±0.7
	Abs	2.77±0.3	2.11±0.11*	2.87±0.3
Mature T lymphocytes	%	50.7±0.86	46.2±2.03*	50.9±1.16
	Abs	0.91±0.03	0.72±0.07*	0.97±0.09
Active T lymphocytes	%	30.7±2.4**	22.9±2.34*	34.3±1.9
	Abs	0.9±0.14**	0.67±0.04*	1.22±0.4
Poorly differentiated T lymphocytes	%	21.3±0.8	18.1±1.7*	23.1±1.8
	Abs	0.67±0.002	0.29±0.12*	0.77±0.001
Postthymic T cells	%	3.1±0.14	3.47±0.22*	2.9±0.11
	Abs	0.047±0.003	0.05±0.005	0.043±0.003
Total T lymphocytes	%	39.8±1.9	32.1±1.2*	40.8±0.7
	Abs	1.80±0.37	0.76±0.24*	1.89±0.33
Complex T lymphocytes	%	51.9±0.3**	49.3±0.25*	54.1±0.6
	Abs	0.87±0.17	0.85±0.03*	0.89±0.11
Precursor T cells	%	2.4±0.06	2.09±0.04*	2.39±0.5
	Abs	0.05±0.008	0.041±0.003	0.053±0.004
Theophylline-resistant T cells	%	44.2±1.0	32.49±1.6*	42.1±0.9
	Abs	1.39±0.02	0.84±0.05*	1.31±0.12
Theophylline-sensitive T cells	%	24.2±0.7**	10.2±1.36*	21.2±1.7
	Abs	0.55±0.09	0.43±0.02*	0.58±0.03
TFR/TFS index	index	1.8±0.3	2.9±0.16	1.98±0.3
T cell precursors	%	35.09±0.9	36.23±0.93	32.01±1.13
	Abs	0.90±0.007	0.98±0.04	0.89±0.01

Note: * - p<0.05, <0.01, <0.001 - reliability of differences between groups before and after treatment; ** - p<0.05, <0.01, <0.001 - reliability of differences between indices in women without EH after treatment.

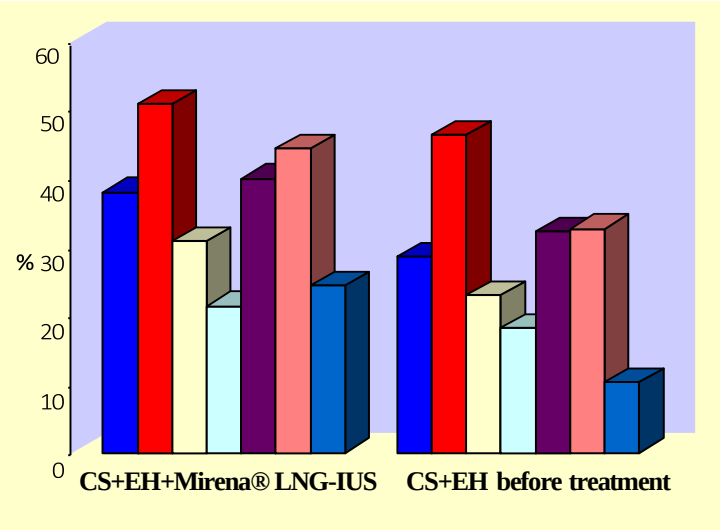

Fig. 2: Dynamics of the most notable cellular immunity alterations in women with EH and CS against the background of the Mirena® LNG-IUS.

It is significant to note that the levels of both T-helpers and T-suppressors increased under the local effects of the introduction of hormone micro-doses (from 32.49±1.6 to 44.2±1.0 and 10.2±1.36 to 24.2±0.7, respectively). The TFR/TFS index increased significantly (from 2.9±0.16 to 1.8±0.3), reflecting the ratio of regulatory subpopulations and approaching the indices of women with CS without EH, suggesting a strong immune-stimulating effect.

Peripheral T cells and thymocytes, which contain poorly differentiated T cells, showed an upward trend in these cells' percentages following therapy, rising from 18.1±1.7 to 21.3±0.8 and absolute values from 0.29±0.12 to 0.67±0.002. During therapy, the proportion of zero lymphocytes on the immunogram did not substantially alter in women.

DISCUSSION

The typical course of therapy for EH is hysteroscopy, followed by the prescription of hormone medications, whose dosages depend on the woman's age, the presence of gynecological and somatic problems, and other factors (14-17).

However, the average EH recurrence rate is 50%, with a range of 26% to 70%. Because conservative methods of treating EH recurrent variations are inadequate, the need for hysterectomy has recently begun to rise in frequency (20). Post-hysterectomy complications happen 9% of the time, 1% of which are severe, and mortality occurs 0.008% of the time (21-23).

Mirena® LNG-IUS has no adverse effects on the blood coagulation system's parameters, nor does it cause hyper- or dyslipidemia or have a negative impact on blood pressure or body weight. The most commonly used approach is LNG-IUS. Clinical studies, however, revealed that this also possesses a variety of therapeutic qualities, many of which are specifically related to the impact of LNG on the endometrium.

The possibility of avoiding surgery is given a lot of thought when utilizing the Mirena® LNG-IUS; over 60% of women with bleeding linked to EH undergo this operation. Despite the success of surgical therapy, postoperative and anesthetic issues are a possibility. After three months, 85.2% of women with EH had a good response to Mirena® LNG-IUS, and several studies consider LNG-IUD to be the most effective form of therapy for EH in women of reproductive age. Longer, more in-depth investigations are necessary to support the findings of this study (22, 23).

As a result, more severe immune system disorders are seen in women with CS who also have EH (depression of T-lymphocytes with a disorder in their regulatory capacity ($P<0.01$), as well as depression of the T-helper and T-suppressor lymphocyte pools, which can lead to the development of insufficient production of regulatory cytokines and damage to target organs). In turn, immunoglobulin A, a component of humoral immunity, is also lacking. Levonorgestrel micro-dosing caused the depressive effect on the neutrophil pool to be reversed and the receptor function to be activated, which increased T lymphocytes to 43.7±1.94 ($P<0.05$), stabilized the absorption function of phagocytosis activation to 58.3±2.9 ($P<0.05$), and improved the metabolic function of neutrophil phagocytes.

Thus, the signs of CS were significantly decreased after the first month of using Mirena® LNG-IUS due to changes occurring in women's reproductive system during menopause, its pathological course, and the occurrence of EH. Mirena® LNG-IUS has an indirect immune-corrective effect on systemic and humoral immunity in women with EH who have a pathological climatic course. It does this by stabilizing the neutrophil pool, activating the receptor function, and stabilizing the absorption and metabolic activity of neutrophilic phagocytes in the humoral system.

The study done is essential and required in order to deal with the problems associated with providing

medical treatment for perimenopausal women and enhance the quality of life for this group of patients.

In Kyrgyzstan, a similar study has not yet been done. The development of intervention programs for both the general public and healthcare professionals is crucial to enhancing care for women going through menopause. Since many diseases frequently develop and manifest themselves during this period of the body's adaptation to new conditions of existence, which results from age-related evolutionary restructuring of the hypothalamic centers and secondary changes in the peripheral endocrine glands and target organs, therapeutic and diagnostic interventions are frequently necessary.

CONCLUSION

To investigate the therapeutic impact of using Mirena® LNG-IUS, the background immunological status indices of patients with EH on the background of CS were examined in this group of women. Women with EH received an additional evaluation for a reason—these patients frequently have contraindications to hormone replacement therapy in the pathological course of menopause because of the treatment standards that are being used. The clinical impact of the Mirena intrauterine hormonal system as well as its impact on the immunological state of women with EH on the background of CS was evaluated using an alternative treatment (local application of progestogens by their intrauterine administration through the Mirena intrauterine hormonal system).

CONFLICT OF INTEREST

Authors declare no conflict of interest.

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