

# DISHARMONY AND ITS CORRECTION IN PREMATURE OVARIAN INSUFFICIENCY

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DOI: 10.47750/pnr.2022.13.S08.409

## Abstract

The hormonal status of women with a diagnosis of STUMP, with removal of one ovary and without surgery were prospectively studied. The study of the hormonal background revealed ovarian insufficiency syndrome in women after surgical treatment. Our studies were carried out in the period from 1 month to 3 months, from 4 to 6 months and 7 months to 12 months after the operation. We investigated changes in the level of the main informative hormones FSH, E2, LH, AMH, since the other hormones, such as cortisol, prolactin, progesterone and testosterone in both groups have changed little, with the ovary preserved, the hormone level is somewhat maintained, thanks to the follicular apparatus in it. And in patients of the second group, ovulatory cycles and normalization of the hormonal background gradually approached the previous state after 9-12 months.

**Keywords:** premature ovarian insufficiency, "early aging", "early menopause", amenorrhea, infertility, hypomenstrual syndrome.

## Introduction

In the clinical recommendations of 2016, the European Society for Human Reproduction and Embryology (ESHRE) defines premature ovarian insufficiency (DPOI) as a clinical syndrome, the main manifestation of which is the cessation of ovarian function at the age of 40, characterized by menstrual dysfunction, increased gonadotropin levels and a decrease in estradiol concentration [1, 2, 3].

Despite the large number of studies conducted in this direction, the etiology of primary DPOI in most cases (over 50%) remains unknown [1,2,4]. Given the devastating consequences for the body of estrogen deficiency, limited opportunities in solving reproductive problems in women with DPOI and in most cases the loss of the follicular apparatus occurs gradually, there is an active search for the possibility of early diagnosis and prediction of this syndrome. These are markers of ovarian reserve AMH and inhibin B, whose levels begin to decrease long before the increase in FSH and cycle disorders [3,5,6,7,8]. Currently, active work is underway to predict the DPOI and develop diagnostic criteria for its preclinical forms.

## The purpose of the study

To study the hormonal landscape of premature ovarian insufficiency and choose the optimal hormonal correction.

## Materials and methods of research

The hormonal status of women diagnosed with DPOI was prospectively studied and they were divided into 3 groups: 1-the main group consisted of 54 women with removal of one ovary after gynecological operations for ovarian cysts; 2- the comparative group consisted of 55 patients with both ovaries but signs of DPOI and the control group of 30 healthy patients.

Hormone levels were assessed by immunochemiluminescent analysis on an automatic analyzer Maglum 2000 plus from Shibe (China). Blood sampling to determine the content of FSH, LH, progesterone, estradiol and anti-muller hormone was carried out in the morning, on an empty stomach from the ulnar vein. The resulting blood was centrifuged, the serum was frozen and stored at a temperature of 22-24C in labeled Eppendorf-type test tubes prior to analysis. The study of the hormonal background revealed ovarian insufficiency syndrome in women after surgical treatment and in women without surgical interventions, the absence of a normal menstrual cycle.

## Results and their discussion

The study of the hormonal background revealed ovarian insufficiency syndrome in women after surgical treatment. Our studies were carried out in terms from 1 month to 3 months, from 4 to 6 months and 7 months to 12 months after the operation. The level of hormonal changes was carefully studied in women with preserved ovaries and with ovarian removal in the first group in order to determine methods of rehabilitation and selection of appropriate therapy for this subgroup. We investigated changes in the level of the main informative hormones FSH, E2, LH, AMH, since other hormones such as cortisol, prolactin, progesterone and testosterone in both groups changed little. Thus, the average level of FSH a month after surgery in the main group was  $13.3 \pm 0.96$  mME/ml, and in the comparison group –  $5.5 \pm 0.5$  mME/ml ( $p < 0.05$ ); the level of LH in the main group was  $12.4 \pm 1.1$  mME/ml, and in the comparison group was  $6.1 \pm 0.84$  mME/ml ( $p > 0.05$ ). Normally, the E2 content in the follicular phase is 30-120 pg/ml. In the postoperative period, we noted a decrease in their secretion in the main group almost three times, and in the comparison group by 1.2 times. So estradiol in the main group was found to be  $36 \pm 7.1$  pg/ml in the main group, and in the comparison group –  $82.4 \pm 17.2$  pg/ml ( $p < 0.01$ ). In the early postoperative period, the level of E2 in the main group with preserved ovaries was  $43.0 \pm 1.36$ , and in the group with the removal of one ovary was slightly reduced - it was  $36.7 \pm 0.60$ , but the indicators of women in the 2 groups significantly differ -  $82.0 \pm 1.36$ . This is due to the trauma of the surgery and removal of the uterus and one ovary.

Repeated measurement several months after the operation revealed a sharp change in the hormonal background of  $37.7 \pm 1.36$  in women with removal of one ovary, and in the comparison group these indicators were  $77.8 \pm 1.36$ . This is explained by the fact that with the ovary preserved, the hormone level is somewhat maintained, thanks to the follicular apparatus in it. And in patients of the second group, ovulatory cycles and normalization of the hormonal background gradually approached the previous state after 9-12 months.

The levels of pituitary hormones (FSH and LH) increased in the early postoperative period, so FSH was  $13.3 \pm 0.96$  mME/ml in the main group, in the comparison group –  $5.5 \pm 0.5$  mME/ml, and the concentration of LH was  $12.4 \pm 1.1$  mME/ml and  $6.1 \pm 0.84$  mME/ml, respectively, in the groups. During the follow-up, the level of FSH in women of group 1 with one ovary preserved was  $9.3 \pm 0.10$ , and in women of group 2 this indicator is  $9.6 \pm 0.10$ , which means that this hormone is approaching normal. After 12 months, the level above this hormone differs sharply depending on the presence of the ovary. Since in women with one ovary preserved, this level of FSH is -  $15.5 \pm 0.10$ , and in the second group, FSH indicators approach the norm -  $11.3 \pm 0.10$ , but lag behind the indicators of the control group -  $14.1 \pm 0.34$ . Estradiol in women after removal of one ovary decreased 2.9 times, and in women of the second group only 1.2 times –  $36 \pm 7.1$  pg/ml and  $82.4 \pm 17.2$  pg/ml, respectively. The average level of FSH a month after surgery in the main group was  $13.3 \pm 0.96$  mME/ml, and in the comparison group –  $5.5 \pm 0.5$  mME/ml ( $p < 0.05$ ); the level of LH in the main group was  $12.4 \pm 1.1$  mME/ml, and in the comparison group was  $6.1 \pm 0.84$  mME/ml ( $p > 0.05$ ). Normally, the E2 content in the follicular phase is 30-120 pg/ml. In the postoperative period, we noted a decrease in their secretion in the main group almost three times, and in the comparison group by 1.2 times. Estradiol in the main group was found to be  $36 \pm 7.1$  pg/ml in the main group, and in the comparison

group –  $82.4 \pm 17.2$  pg/ml ( $p < 0.01$ ). In the early postoperative period, the level of E2 in the main group with preserved ovaries was  $43.0 \pm 1.36$ , and in the group with ovarian removal it was slightly reduced -  $36.7 \pm 0.60$ , but the indicators of women in the 2 groups significantly differ -  $82.0 \pm 1.36$ . This is due to the trauma of the operation and the removal of one ovary.

Repeated measurement a few months after the operation revealed a sharp change in the hormonal background of  $37.7 \pm 1.36$  in women with ovarian removal, and with a preserved ovary of  $77.8 \pm 1.36$  approaches the indicators of patients of the second group -  $92.0 \pm 1.36$ . This is due to the fact that with the ovary preserved, the hormone level is somewhat maintained, thanks to the follicular apparatus in it. And in patients of the second group, ovulatory cycles and normalization of the hormonal background gradually approached the previous state after 9-12 months. The levels of pituitary hormones (FSH and LH) increased in the early postoperative period, so FSH was  $13.3 \pm 0.96$  mME/ml in the main group, in the comparison group –  $5.5 \pm 0.5$  mME/ml, and the concentration of LH was  $12.4 \pm 1.1$  mME/ml and  $6.1 \pm 0.84$  mME/ml, respectively, in the groups. During the follow-up, the level of FSH in women of group 1 with one ovary preserved was  $9.3 \pm 0.10$ , and in women of group 2 this indicator is  $9.6 \pm 0.10$ , which means that this hormone is approaching normal. After 12 months, the level above this hormone differs sharply depending on the presence of the uterus and ovary. Since in women with one ovary preserved, this level of FSH is -  $15.5 \pm 0.10$ , and in the second group, FSH indicators approach the norm -  $11.3 \pm 0.10$ , but lag behind the indicators of the control group -  $14.1 \pm 0.34$ . A decrease in the level of AMH corresponds to a decrease in the number of follicles in the ovary. Upon further examination of the state of the ovaries, we found that the restoration of their structure and activity occurs gradually over the course of a year.

Along with transient changes in the hormone-producing function of the ovaries, we have identified stable changes in the level of AMH in the direction of its significant decrease. The level of AMH does not depend much on hormonal fluctuations caused by certain changes in a woman's body, and is considered the most accurate marker of ovarian function (ovarian reserve). A decrease in the level of AMH corresponds to a decrease in the number of follicles in the ovary. Upon further examination of the state of the ovaries, we found that the restoration of their structure and activity occurs gradually over the course of a year.

Table 1. Indicators of the hormonal status of the examined women

Indicator	FSH mME/ml	LH mME/ml	E pg/ml	AMG pg/ml
1 gr. removal of one ovary 1-3 months, n=54	$6,50 \pm 0,09$	$7,30 \pm 0,11$	$43,0 \pm 1,26$	$1,50 \pm 0,05$
2 gr. without surgery -1-3 months, n=55	$13,27 \pm 0,32$	$12,43 \pm 0,28^{***}$	$36,73 \pm 0,80^{***}$	$1,37 \pm 0,05^{***}$
1 gr. 4-6 months	$9,29 \pm 0,12$	$8,40 \pm 0,08$	$77,80 \pm 1,36$	$1,50 \pm 0,04$
2 gr. 4-6 months	$9,59 \pm 0,11^{***}$	$8,30 \pm 0,13^{***}$	$92,0 \pm 1,73^{***}$	$1,60 \pm 0,04^{***}$
2 gr. 7-12 months	$15,50 \pm 0,09$	$7,30 \pm 0,11$	$42,99 \pm 1,15$	$1,80 \pm 0,04$
1 gr. 7-12 months	$17,31 \pm 0,22$	$12,40 \pm 0,19^{***}$	$36,70 \pm 0,58^{***}$	$1,40 \pm 0,04^{***}$
Control group	$14,11 \pm 0,34$	$11,21 \pm 0,28$	$69,96 \pm 1,71$	$2,12 \pm 0,05$

**Note:** \* - differences relative to the control group data are significant (\*\*\*) -  $P < 0.001$ )

Based on the above-mentioned examinations of hormonal changes in women with preserved ovaries and with their removal, the following conclusions can be drawn:

In the postoperative period, women with the removal of one ovary had a persistent increase in the level of the hormone FSH, this was pronounced in women of group 1, these indicators are similar to those of the menopausal period. In the early postoperative period, it did not change dramatically from the indicators of the comparison group, but in further analyses, an increase in the level of this hormone was observed. This is due to the fact that the preserved ovary covers hormonal insufficiency for several months, but in the future the process of exhaustion also increases and approaches menopause. The preserved ovary cannot completely cover the function of the other ovary and hormonal fluctuations occur in the body. As can be seen from Table 4.2, the function of the preserved ovary will last to maintain hormonal homeostasis only for the early postoperative period, and in the future HRT is required. Considering the sharp decrease in the level of estrogens and an increase in FSH in women with the removal of one ovary and preservation in the active reproductive period, which coincides with the indicators of the menopausal period, requires non-consecutive timely administration of HRT, in order to prevent "early aging" of the body.

It can be assumed that a decrease in the level of estrogens contributes to a further increase in the tone of small vessels and the progression of deterioration of blood supply and, thus, a vicious circle arises. Surgical trauma, tissue edema cause deterioration of ovarian blood supply and a decrease in steroidogenesis, while a low level of estradiol, in turn, contributes to an increase in tone in the microvascular bed. This fact requires non-urgent rehabilitation measures.

## Conclusion

Based on the above-mentioned examinations of hormonal changes in women with preserved ovaries and with their removal, the following conclusions can be drawn:

In the postoperative period, women had a persistent increase in the level of the hormone FSH, this was pronounced in women of group 1 with the removal of one ovary, these indicators are similar to those of the menopausal period. However, in women of the second group, the presence of two ovaries also showed an increase in FSH. In the early postoperative period, it did not change dramatically from the indicators of the comparison group, but in further analyses, an increase in the level of this hormone was observed. This is due to the fact that the preserved ovary covers hormonal insufficiency for several months, but in the future the process of exhaustion increases and approaches menopause. The preserved ovary cannot completely cover the function of the other ovary and hormonal fluctuations occur in the body. The function of the preserved ovary will last to maintain hormonal homeostasis only for the early postoperative period, and in the future HRT is required. Considering the sharp decrease in the level of estrogens and an increase in FSH in women with one ovary and preservation in the active reproductive period, which coincides with the indicators of the menopausal period, requires urgent timely administration of HRT, in order to prevent "early aging" of the body.

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