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How the therapy for endometriosis affects the hormonal status in female infertility

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Abstract

Aim. To determine changes in the values of pituitary and ovarian hormones in women with endometriosis-associated infertility, as well as to evaluate the impact of endometriosis therapy on hormonal parameters

Materials and Methods. Sixty-nine women with small-sized endometriomas with adenomyosis (target group) and 50 women with tubal infertility (controls) were examined. The values of pituitary (luteinizing and follicle-stimulating hormones, prolactin) and ovarian (estradiol, tubular antimullerian hormone) hormones were studied. The comparison of

quantitative indicators between the studied groups of women was carried out using the Mann-Whitney U-test, the statistical significance of the results was assessed at a level of not less than 95% (risk of error not more than 5% - $p < 0.05$).

Results

Infertile women with endometrioma and adenomyosis have lower AMH levels than infertile women with tubal factor. Among patients with endometriosis, there is an increase in serum FSH, LH, prolactin and estradiol compared with women without endometriosis.

Dienogest moderately inhibits the secretion of FSH and LH; it has almost no effect on blood AMH and estradiol values. The use of dienogest can moderately increase the level of prolactin, It is noteworthy that these indicators are within the reference range. The use of diferelin for the treatment of endometriosis has a more active effect on the hormonal status of patients, given the decrease in such indicators as FSH and LH, AMH, estradiol and prolactin

Conclusions. Women with infertility against the background of endometriosis have minor changes in the hypothalamic-pituitary-ovarian system, which indicates the need to develop medical measures in order to correct them.

The use of dienogest compared to diferelin affects the hormonal status of patients with endometriosis to a lesser extent, given the pronounced anti-proliferative effect.

Key words: endometriosis; pituitary hormones; ovarian hormones; hypothalamic-pituitary-ovarian system; infertility; dienogest; a-GnRH; diferelin.

Introduction

Genital endometriosis is one of the most pressing problems of modern gynaecological practice. To date, for over than 150-years, this pathology has been debated among experts [1, 2]. As reported by epidemiological studies, 90-99% of patients are diagnosed with this disease at the age of 20 to 50 years, most often in the reproductive period, regardless of ethnic and socio-economic background [3, 4].

According to modern concepts, genital endometriosis is a dyshormonal, immune-dependent and genetically determined pathological process, the pathophysiology of which is based on the emergence and growth of endometrioid heterotopias outside the normal location of the uterine mucosa. By its morphofunctional characteristics, this newly formed tissue is identical to the endometrium, it does not show malignant properties, despite proliferative growth and the possibility of metastasis [5].

Endometriosis is characterized by increased local secretion and sensitivity to estrogen, as well as resistance to progesterone.

There are three main forms of endometriosis, which differ in clinical significance and therapeutic approaches: 1) superficial peritoneal endometriosis (SPE); 2) ovarian endometrioma; (OE) 3) deeply infiltrative endometriosis (DIE) (ESHRE).

The gold standard for assessing the disease severity is diagnostic laparoscopy with or without biopsy and histological confirmation. This procedure is employed not only for diagnostic but also for therapeutic purposes in mild and moderate grades.

Many scientific studies have found that endometriosis is associated with infertility. Various authors report that 25-50% of women with infertility are diagnosed with endometriosis and the peritoneal form of endometriosis is accompanied by infertility in 60-80% of cases [6-10]. The meta-analysis by Barnhart [11] revealed that pregnancy rates in women with endometriosis were one half as high as in those of women with tubal pregnancy. It is also noteworthy that such forms of deep endometriosis as endometriomas contribute to the development of infertility. There are studies on their effect on the ovarian reserve.

A two-year retrospective cohort study in the United States (2015) showed that in patients with infertility and endometriosis with or without ovarian surgery, ovarian reserve markers were worse (lower AMH and higher FSH) than in the group of male infertility factor [12].

In 2019, one of the studies revealed that women with endometrioma had a significantly lower serum AMH and a dynamically faster decrease in its blood level compared to its age-related decrease. It is indicative of the harmful effects of this growth on the ovarian reserve [13].

There have also been studies showing that when using assisted reproductive technologies, the rate of implantation in women with endometriosis-associated infertility is 1.5 times lower than that of those with tubal infertility, which necessitates a more thorough assessment of endometrial susceptibility. Patients with endometriomas larger than 3 cm in diameter are also found to have impaired oocyte quality. Similarly to the above studies, patients of the endometrioma group had a significantly lower AMH level compared to those of the tubal infertility group [14].

To summarise, the investigation of endometriosis effect on the reproductive hormones in female infertility is still relevant. At the same time, it is important to study how endometriosis therapy affects these indicators and the ability to conceive without assisted reproductive technologies.

Aim. To investigate changes in the level of pituitary and ovarian hormones in female endometriosis-associated infertility, as well as the impact of endometriosis therapy on the hormonal status of the women.

Materials and Methods

This prospective study was conducted in the State Institution "Ciscarpathian Centre for Human Reproduction" of the Ministry of Health of Ukraine (Ivano-Frankivsk) from 2019 to 2020. One hundred and nineteen women were selected and divided into two groups: the control group - 34 patients with tubal infertility and the target group of women having small-sized endometriomas of one of the ovaries, adenomyosis and infertility; male and other infertility factors were excluded in both groups. These patients were examined for pituitary (luteinizing and follicle-stimulating hormones, prolactin) and ovarian (estradiol, antimullerian hormone) hormonal parameters, all examined women were determined serum levels of the above hormones on day 1-3 of the menstrual cycle. The studies were performed by enzyme-linked immunosorbent assay on an Immulite 2000 analyzer (Siemens Healthcare Diagnostics Inc., USA).

During the study, when prescribing endometriosis therapy, the target group was divided into two subgroups, based on the drug used: subgroup II^a included 35 women having small-sized endometrioma with adenomyosis who took Dienogest 2 mg orally once a day for 3 months; The second subgroup (II^b) was made of 34 women diagnosed with small-sized endometrioma with adenomyosis who received intramuscular injections of 3.6 mg Diferelin 1 g / month (3 injections in 3 months).

The mean age of women in the two subgroups of TG_2 (with endometriosis) was 30.9 ± 2.6 and 29.9 ± 1.2 years, respectively, in the control group - 30.1 ± 1.4 ($p > 0.05$), respectively. This shows that no statistically significant differences in age between these subgroups were found, so this homogeneity made it possible to more accurately compare them by other criteria.

Comparison of quantitative indicators between the studied groups of women was carried out using the Mann-Whitney U-test, the statistical significance of the results was assessed at a level of not less than 95% (risk of error not more than 5% - $p < 0.05$).

Results and discussion

In order to assess the functional condition of the pituitary-ovarian system in all examined women, there were determined serum levels of the following hormones: FSH, LH, AMH, estradiol and prolactin on day 1-3 of the menstrual cycle (Table 1).

Table 1 - Serum reproductive hormones in target and control groups, M ± SD

Groups of women	n	FSH, IU/L	LH, IU/L	E_2, pg/ml	Prl, ng/ml	AMH, ng/ml
Target	69	8.04±2.32	7.01±2.49	75.79±13.97	14.97±5.2	2.17±0.74
Control	50	6.17±2.03	4.94±1.52	70.9±10.16	7.24±2.15	2.56±0.70
p	-	p<0.001*	p<0.001*	0.102	p<0.001*	p<0.05

Notes:
* - the difference between the two subgroups of TG is statistically significant for the respective indicators, p <0,001

When comparing the data shown in table 1, it was found that FSH levels in women of TG (8.04 ± 2.32 IU / l) vs CG (6.17 ± 2.03 IU / l) were statistically significantly different (p <0.001). There was also a statistically significant difference between LH levels in women of these two groups (7.01 ± 2.49 IU / l versus 4.94 ± 1.52 IU / l, respectively; p <0.001). The level of prolactin was also statistically significantly higher in women of TG than in controls (14.97 ± 5.2 ng / ml vs 7.24 ± 2.15 ng / ml, respectively; p <0.001). Blood AMH in patients with endometriosis was 2.17 ± 0.74 ng / ml, which was statistically different from that (p <0.05) of patients with tubal infertility without endometriosis (2.56 ± 0.70 ng / ml). There was no statistically significant difference in serum estradiol in women of both clinical groups (75.79 ± 13.97 pg / ml vs 70.9 ± 10.16 pg / ml, respectively; p> 0.05).

Later, during the study, we decided to analyse the concentration of gonadotropins, prolactin and estradiol in women of two subgroups of TG (Table 2).

Table 2 - Serum reproductive hormones in women of two subgroups of TG and CG, M ± SD

Groups of women	N	FSH, IU/L	LH, IU/L	E_2, pg/ml	Prl, ng/ml	AMH, ng/ml
II^a	35	7.55±1.92	6.85±2.88	82.34±20.35	13.76±4.31	2.13±0.76
II^b	34	8.52±2.75	7.17±2.19	85.63±13.39	16.18±6.22	2.20±0.65
CG	50	6.17±2.03	4.94±1.52	70.9±10.16	7.24±2.15	2.56±0.70
p_{IIa-C}		0.005*	0.001*	0.005*	0.001*	0.030*
p_{IIb-C}		0.001*	0.001*	0.001*	0.001*	0.019*
$p_{IIa-IIb}$		0.094	0.606	0.432	0.074	0.682

Notes:
* - the difference is statistically significant versus the corresponding indicator of CG, p <0,001;
** - the difference is statistically significant between the two subgroups of TG for the respective indicators, p <0,05.

As can be seen from Table 2, FSH levels in women with endometriosis are statistically different in both subgroups from patients in the CG (patients of the first subgroup 7.55 ± 1.92 IU / l versus 6.17 ± 2 , 03 IU / l, respectively, p <0.001, patients of the second subgroup 8.52 ± 2.75 IU / l versus 6.17 ± 2.03 IU / l, respectively, p <0.001). There was no difference between the indicators in women of two subgroups (7.55 ± 1.92 IU / l vs 8.52 ± 2.75 IU / l, p = 0.094).

Serum LH in women with endometriosis exceeded that in controls (6.85 ± 2.88 IU / l in patients of the first subgroup vs 4.94 ± 1.52 IU / l in women of CG, respectively; p <0.001; 7.17 ± 2.19 IU / l in women of the second subgroup vs 4.94 ± 1.52 IU / l in the control group, respectively, p <0.001). LH values of both subgroups did not differ statistically (6.85 ± 2.88 IU / l vs 7.17 ± 2.19 IU / l, p = 0.606).

The level of prolactin in patients with endometriosis from the first subgroup is found to be statistically different from its level in controls (13.76 ± 4.31 ng / ml vs 7.24 ± 2.15 ng / ml, respectively; p <0.001). These indicators differ statistically if we compare the data of patients from the second subgroup with the control group (16.18 ± 6.22 ng / ml vs 7.24 ± 2.15 ng / ml, respectively; p <0.001). When comparing the values of the survey of women of both subgroups, no statistically significant difference is seen (13.76 ± 4.31 ng / ml vs 16.18 ± 6.22 ng / ml, p = 0.074.)

Estradiol levels in women of both subgroups II^a and II^b did not differ statistically significantly (82.34 ± 20.35 pg / ml vs 85.63 ± 13.39 pg / ml, respectively, p = 0.432). However, a comparison of the values of women of each subgroup with those of patients of CG revealed a statistically significant difference (82.34 ± 20.35 pg / ml in II^a vs 70.9 ± 10.16 pg / ml in CG, p = 0.005; 85.63 ± 13.39 pg / ml in II^b vs 70.9 ± 10.16 pg / ml in women of CG, p = 0.001),.

When comparing AMH values between the subgroups of TG, no statistically significant difference was found (2.13 ± 0.76 ng / ml in II^a vs 2.20 ± 0.65 ng / ml in II^b, p> 0.05). However, a statistically significant difference was found between the values of two subgroups of women with endometriosis and the control group (p = 0.030 between II^a and CG and p = 0.019 between II^b and CG).

It should be noted that the assessment of FSH levels in women with endometriosis of TG revealed the statistically significantly higher values in both subgroups than in women with tubal infertility factor of CG (7.55 ± 1.92, 8.52 ± 2 , 75 vs 6.17 ± 2.03, respectively; p <0.001). In endometriosis, LH levels are also statistically significantly higher in women of the two subgroups than in patients of CG without endometriosis (LH = 6.85 ± 2.88, 7.17 ± 2.19 vs 4.94 ± 1.52, respectively, p <0.001). Similarly, a comparison of serum prolactin values in

patients with endometriosis with those of the controls revealed a statistically significant difference ($p < 0.001$).

The data obtained in women may indicate a gradual increase in the concentration of FSH, LH and PRL with the progression of endometriosis.

Summarizing the results of the examination of women with endometriosis, it should be noted that the levels of gonadotropic hormones and prolactin in them are within normal limits, as in women of CG [2] (FSH = 6.17 ± 2.03 IU / L, LH = 4.94 ± 1.52 IU / L, prolactin = 7.24 ± 2.15 ng / ml).

When comparing the above values of both subgroups of women with endometriosis included in the target group, no difference was found, which allowed us to start comparing the clinical effects of dienogest and dipherelin, taking into account the suppression of the progresion of endometriotic disease and preparation for the use of ART. The lack of statistically significant difference made it possible to perform an adequate comparison of the efficacy of the two well-known methods of treating endometriosis symptoms.

The next stage of the study was to analyse the functional condition of the pituitary-ovarian system in women during therapy for endometriosis. The evaluation of the results obtained was carried out based on a comparison of the hormonal indices of patients before the treatment with the data of the same patients three 3 months after receiving the treatment for endometriosis, namely dienogest in the subgroup one and Dipherelin in subgroup two.

Table 3 - Serum levels of reproductive hormones in women of two subgroups of TG and CG, M ± SD

Subgroups of women	II^a	$II^{a(dienogest)}$	$P(II^a)$	II^b	$II^{b\ (a\text{-}GnRH)}$	$P(II^b)$
n	35	35		34	34	
FSH, IU/L	7.55±1.92	6.5±1.61	0.017*	8.52±2.75	6.45±1.85	<0.001*
LH, IU/L	6.85±2.88	5.27±2,0	0.011*	7.17±2.19	4.49±1.88	<0.001*
E2, pg/ml	82.34±20.35	78.56±19.8	0.440	85.63±13.39	59.8±13.6	<0.001*
Prl, ng/ml	13.76±4.31	19.86±4.1	0.064	16.18±6.22	10.14±3.7	<0.001*
AMH, ng/ml	2.13±0.76	2.12±0.51	0.949	2.20±0.65	1.81+0.75	0.025*

Notes:

* - the difference between hormonal values after therapy and before treatment in women from one subgroups is statistically significant ($p < 0.05$, Wilcoxon rank sum test).

When comparing the data received against the background of treatment with dienogest, we obtained the following values among women of the first subgroup: after therapy

the level of FSH decreased (7.55 ± 1.92 IU / l, versus 6.5 ± 1.61 IU / l after dienogest) (Figure 1.), LH was also reduced 6.85 ± 2.88 IU / l versus 5.27 ± 2.0 IU / l after therapy (Figure 2.), in both cases the level of hormones after treatment decreased statistically significantly (p <0.05) (see Tab.3).

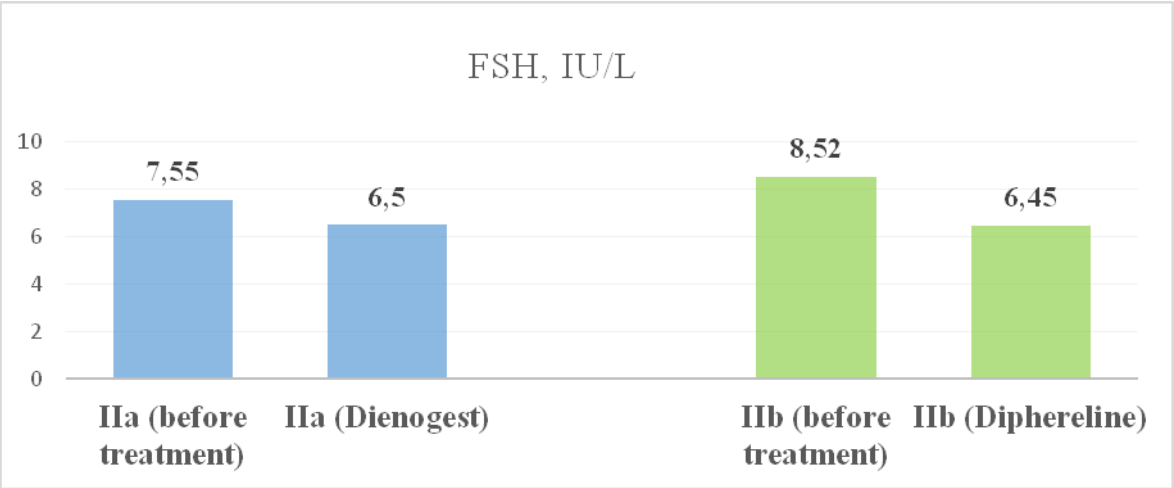

Figure 1.

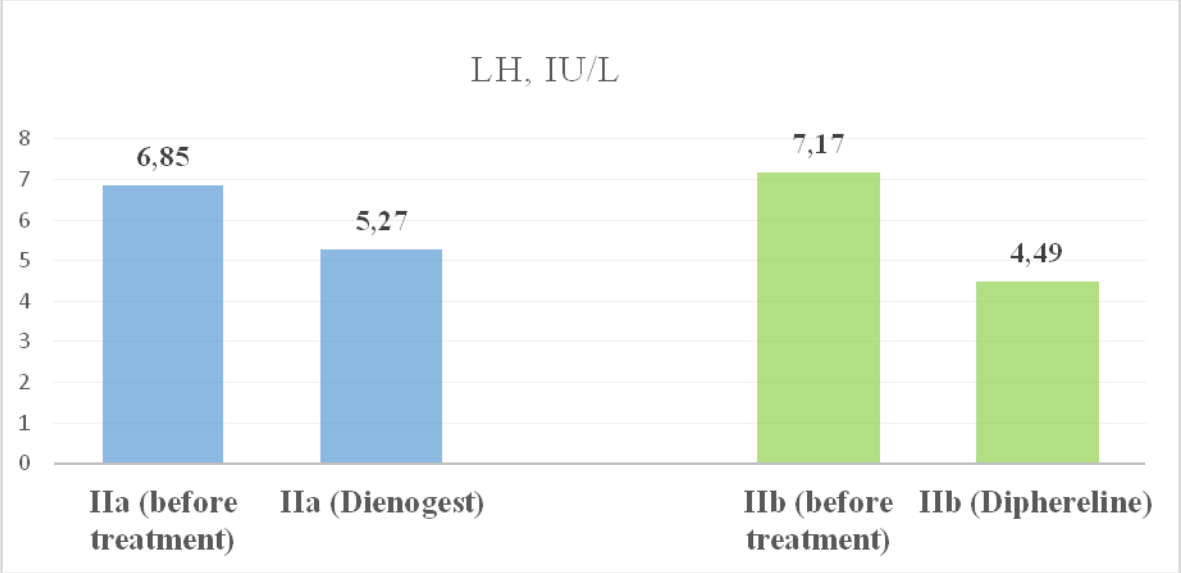

Figure 2.

Estradiol levels before and after treatment were 82.34 ± 20.35 pg / ml and 78.56 ± 19.8 (Figure 3.), respectively. The difference was not statistically significant. There was a slight increase in prolactin levels in women with endometriosis from 13.76 ± 4.31 ng / ml before treatment to 19.86 ± 4.1 ng / ml after it (p> 0.05) (Figure 4.). AMH values remained almost the same (2.13 ± 0.76 ng / ml versus 2.12 ± 0.51 ng / ml, p> 0.05) (Figure 5.).

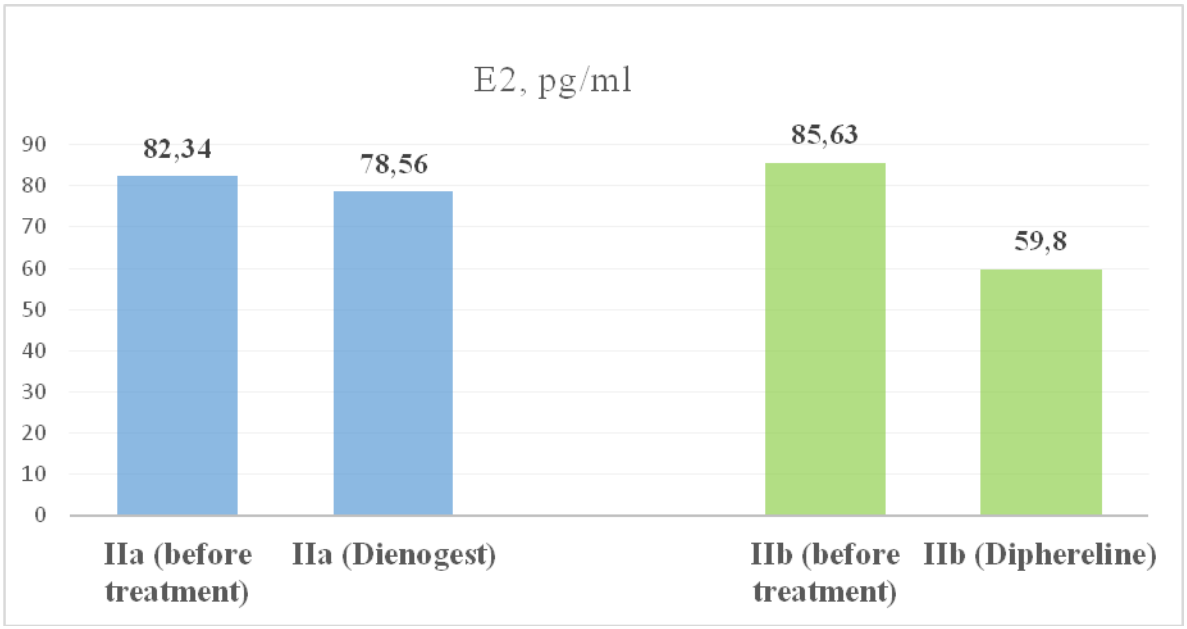

Figure 3.

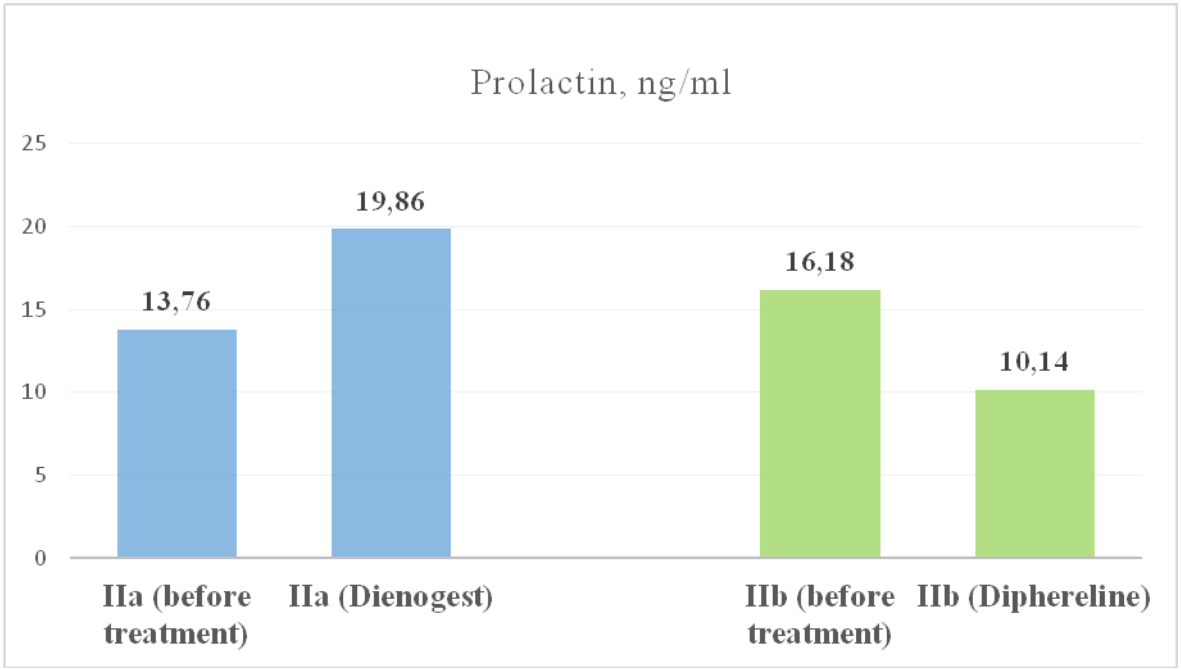

Figure 4.

The use of a-GnRH resulted in the hormonal changes as follows: a decrease in FSH (8.52 ± 2.75 IU / l - before therapy versus 6.45 ± 1.85 IU / l – after therapy); similarly, LH value decreased from the average baseline value of 7.17 ± 2.19 IU / l to 4.49 ± 1.88 IU / l. The difference in values of both hormones was statistically significant ($p < 0.05$). As for the ovarian hormone estradiol, its values were the lowest against the background of diferelin therapy (59.8 ± 13.6 pg / ml versus 85.63 ± 13.39 pg / ml before treatment:), which was also

clinically manifested as periodic hot flashes and dryness of the mucous membranes. On average two months after the drug withdrawal, the manifestations disappeared without any other medication. AMH level also decreased from 2.58 ± 0.91 ng / ml to 1.81 ± 0.75 ng / ml after the above therapy (p <0.05).

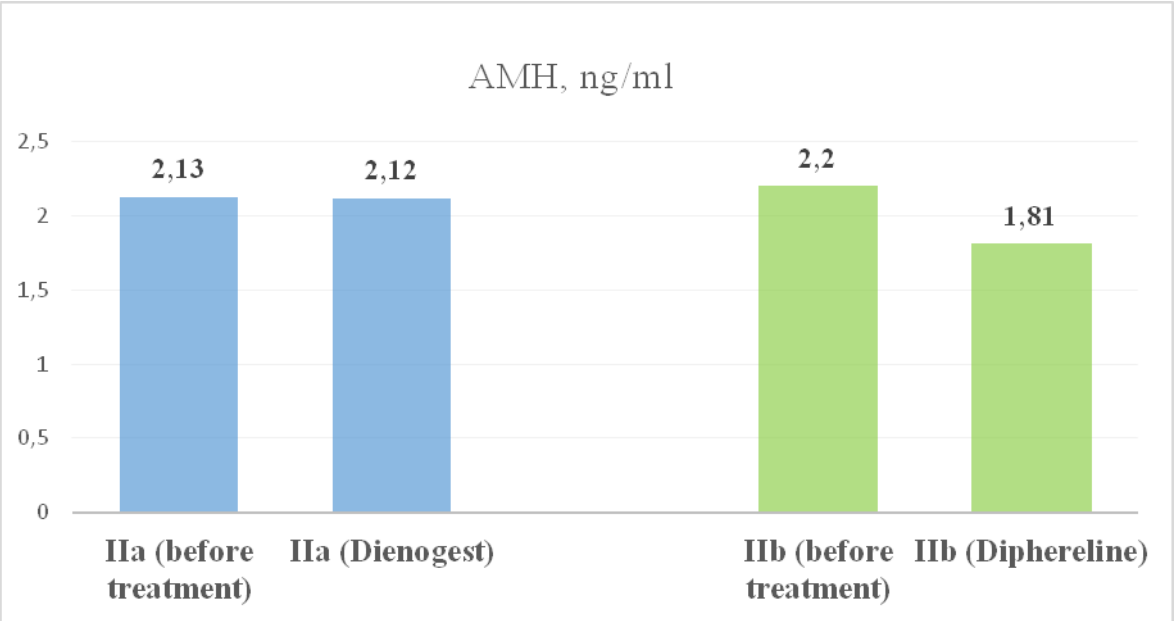

Figure 5.

If we evaluate the changes in serum prolactin, in contrast to the values in women of the first subgroup, who received dienogest, there is seen a tendency to an increase, in this case there was a reverse trend: to a decrease (10.14 ± 3.7 ng / ml versus 16,18 ± 6.22 ng / ml before therapy). The difference was statistically significant (p <0.05).

Discussion

This study revealed that FSH and LH levels in women with endometriosis-associated infertility were significantly higher than those in female infertility caused by tubal factor (p> 0.05). Patients with endometriosis had a lower blood level of AMH than in the group with tubal infertility without endometriosis, which may be indicative of a negative impact of endometriosis on the ovarian reserve. Serum estradiol values did not differ significant between both clinical groups (75.79 ± 13.97 pg / ml (TG) versus 70.9 ± 10.16 pg / ml (CG), respectively; p> 0, 05). Significantly higher prolactin values were found in the group of women with endometriosis (14.97 ± 5.2 ng / ml), compared with controls (7.24 ± 2.15 ng / ml). Estradiol is known to stimulate prolactin receptors in the uterus, i.e. in endometrioid heterotopias, there is a hyperstimulation of these receptors. H9owever, high levels of prolactin

inhibit estrogen activity [8]. Therefore, it is still unknown what is primary - the growth of prolactin due to the progression of endometriosis, or vice versa.

When assessing the functional state of the pituitary-ovarian system in women against the background of endometriosis therapy, it was found that dienogest therapy results in decreases tin FSH and LH levels. The data obtained indicate that there is inhibition of cyclic secretion of FSH and LH, accompanied by anovulation, decidualization of the stroma, as well as atrophy of endometriosis foci.

The evaluation of estradiol values before and after dienogest therapy (82.34 ± 20.35 pg / ml versus 78.56 ± 19.8, respectively) revealed the minor differences, which can have a positive effect, because such therapy allows avoiding the development of symptoms of estrogen deficiency while maintaining a pronounced anti-proliferative effect.

The study found a slight increase in prolactin levels in women with endometriosis after treatment (13.76 ± 4.31 ng / ml versus 19.86 ± 4.1 ng / ml, $p > 0.05$), almost no changes of AMH (2.13 ± 0.76 ng / ml versus 2.12 ± 0.51 ng / ml, $p > 0.05$). It is noteworthy that these data are within the reference values.

When using diferelin, a decrease in FSH was detected (8.52 ± 2.75 IU / l before therapy versus 6.45 ± 1.85 IU / l after therapy); a similar trend to the decrease of LH from the baseline values of 7.17 ± 2 , 19 IU / l to 4.49 ± 1.88 IU / l, there was a statistically significant difference between the values of both studied indicators ($p < 0,05$). Given that hormonal studies were performed after three injections of diferelin, these changes can be explained by the fact that the introduction of a-GnRH transiently increases the secretion of LH and FSH, but then it causes desensitization and decreased receptors, resulting in decreased synthesis and secretion of gonadotropins.

Examining changes in estradiol concentrations, the largest difference in these parameters was found under the influence of diferelin therapy, namely, a decrease to 59.8 ± 13.6 pg / ml versus 85.63 ± 13.39 pg / ml before treatment, which clinically manifested as periodic hot flashes and dryness of the mucous membranes, These manifestations of estrogen deficiencydisappeared without any other medication on average two months after drug withdrawal. It should be noted that the level of AMH also decreased to 1.81 ± 0.75 ng / ml after receiving the above drug ($p < 0.05$). Before treatment, it was 2.58 ± 0.91 ng / ml, which may be indicative of reduction in the ovarian reserve at the time of taking a-GnRH.

The assessment of the effect of diferelin on prolactin showed a decrease to 10.14 ± 3.7 ng / ml versus 16.18 ± 6.22 ng / ml before therapy, which is significantly different, $p < 0.05$).

Conclusion

Infertile women with endometrioma and adenomyosis have lower AMH levels compared to women with tubal factor infertility, which may indicate a decrease in ovarian reserve in these patients due to the negative impact of endometrioid heterotopias on the ovarian tissue.

Among patients with endometriosis, there is an increase in serum FSH, LH, prolactin and estradiol compared with women without endometriosis.

Dienogest moderately inhibits the secretion of FSH and LH; it has almost no effect on blood AMH and estradiol values, given the latter indicator, estrogen deficiency symptoms are not seen in a pronounced antiproliferative effect on the endometriosis foci

The use of dienogest can moderately increase prolactin levels, there is a need for further research with the appropriate design.

Diferelin for the treatment of endometriosis has a more active effect on the hormonal status of patients, given the decrease in FSH and LH, AMH, prolactin, and especially estradiol, which causes discomfort to patients in the form of hot flashes, dryness of mucous membranes two months after the end of gonadotropin-releasing hormone agonist therapy.

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