EFFICIENCY EVALUATION OF THE IMPROVED TREATMENT AND PREVENTION COMPLEX IN PREGNANT WOMEN AFTER ASSISTED REPRODUCTIVE TECHNOLOGIES

INTRODUCTION

Endocrine disorders preceding pregnancy can cause gestational complications in women whose pregnancy occurred after assisted reproductive technologies (ART) [1, 12, 21]. Development of hormonal disorders, especially in the early stages of gestation, can be the result of hyperandrogenism, luteal phase insufficiency, ovarian hyperstimulation, and further affect the course of pregnancy and fetoplacental complex [3, 8, 13, 20, 23, 24]. Changes in the progesterone, estrogen, androgens, human chorionic gonadotropin β (β-hCG), and placental hormones value are most common [6, 10, 15]. The main role in regulating of normal physiological belongs to the chorion and trophoblast, which produce β-hCG, that is determines the level of steroid synthesis by the corpus luteum and contributes to the mother’s adaptive responses to the gestational process [11, 12, 15, 22].

Study objective: to determine the role and effectiveness of the proposed therapeutic and preventive complex and psychoemotional correction of hormonal disorders in the pregnancy dynamics in pregnant women after ART to improve the antenatal observation and prevention of obstetric and perinatal complications.

MATERIALS AND METHODS

A prospective clinical examination of 299 pregnant women was performed:

• the main group included 249 women with a pregnancy after ART;
• the control group included 50 pregnant women with spontaneous pregnancy and its physiological course, who were registered in antenatal clinic in 6–8 weeks of gestation.

Main group is divided into subgroups depending on therapy and cause of infertility:

• subgroup I – pregnant women with tubal- peritoneal type of infertility in anamnesis (subgroup IA – 49 women, subgroup IB – 45 women);
• subgroup II – pregnant women with endocrine type of infertility in anamnesis (subgroup IIA – 48 women, subgroup IIB – 39 women);
• subgroup III – pregnant women with a history of male infertility (subgroup IIIA – 36 women, subgroup IIIB – 32 women).

Letter A in a title of subgroup means that women received the proposed treatment, prevention and psychoemotional correction; letter B means that pregnant women were observed in accordance with generally standards of obstetric care regulated by orders of the Ministry of Health of Ukraine.

Pregnant women of the studied groups were representative by age, family and social status, and place of residence, which allowed us to further evaluation of the differences caused precisely by the etiological factors of infertility.

All women were examined in accordance with the orders of the Ministry of Health of Ukraine No. 417 “Methodological recommendations for outpatient obstetric and gynecological care” from 15.07.2011 [7], No. 787 “The procedure for using ART in Ukraine” from 09.09.2013 [6] and No. 579 “About approval of the procedure for sending women to infertility treatment using ART according to absolute indications for budget funds” from 29.11.04 [8].

The recommended complex of therapeutic and preventive measures for pregnant women after ART is:

1. Progesterone support (micronized progesterone orally and vaginally 200–400 mg twice a day) up to 12 weeks, followed by adjustment of the dosage of progesterone drugs depending on the clinical picture of pregnancy.

2. Magnesium saturation (magnesium oxide light 342 mg and magnesium carbonate light 670 mg, which corresponds to magnesium ions 365 mg, one effervescent tablet once a day during pregnancy).

3. Folic acid 200 μg of folic acid and metfolin 200 μg, 1 tablet 1 time a day orally with meals before pregnancy and during the first 16 weeks of pregnancy.

4. L-arginine aspartate in a solution for oral use 5 ml (1 ml of the solution contains L-arginine aspartate 200 mg) 3 times a day from the 8th week to the 16th week of pregnancy [5, 14].

5. ω-3 polyunsaturated fatty acids 1 capsule three times a day starting from the 12th week of pregnancy.


Psychocorrection classes were conducted in a closed homogeneous group (from 7 to 12 participants) with a frequency of 3 times a week for 1.5 hours for 2–3 weeks. Psychocorrection was based mainly on the method of catatime-imaginative ex-
experience of images, as well as elements of body-oriented methods and autogenic training. Negative triggers were identified and destroyed, which improves the psychological and somatic state. In addition, the work in the group was aimed at harmonizing the individual, merging it with people around them, getting out of the narrow egocentric world, and engaging in transpersonal experiences [4, 19].

Descriptive and variational statistics using the Student’s criterion and the Fischer angular transformation method were using. Obtained results were calculated with using Statistica for Windows and Microsoft Excel 2016 programs. Discrepancies were determined as possible at p <0.05.

RESULTS

We drew attention to a significant increase in β-hCG in women of the studied groups in the first trimester against the background of proposed treatment. Special attention was paid to the β-hCG level at 5–6 and 7–8 weeks of pregnancy (gestational age of the onset of placental formation).

The average values of β-HCG in the IA subgroup against the background of proposed treatment and psychoemotional correction were as close as possible to the indicators in the control group and the physiological norm. The average β-HCG value at 3–4 weeks of gestation in the IA subgroup (121.3 ± 5.8 mIU/mL) was 33% higher than in the IB subgroup (91.2 ± 6.4 mIU/mL) (p <0.05). A similar trend persisted at 5–6 weeks. The average β-HCG value in the IA subgroup was 31% higher than in the IB subgroup (194.8 ± 8.1 mIU/mL and 147.6 ± 9.2 mIU/mL, respectively) (p <0.05). At 7–8 weeks the average β-HCG value in subgroup IA was 37% higher than in the subgroup IB (222.5 ± 9.4 mIU/mL and 162.2 ± 8.7 mIU/mL, respectively) (p <0.05).

A significant β-hCG increase in the dynamics of treatment was also noted in women with a history of endocrine infertility. The average β-HCG value at 3–4 weeks of gestation in subgroup IIA (131.8 ± 6.3 mIU/mL) was 32% higher than in the IIB subgroup (99.4 ± 8.3 mIU/mL) (p <0.05). The average β-HCG value at 5–6 weeks of gestation in the subgroup IIA significantly increased by 31% (199.1 ± 8.7 mIU/mL) than in the IIB subgroup (151.4 ± 11.3 mIU/mL) (p <0.05).

The average β-HCG value at 7–8 weeks of gestation in the subgroup IIA was 33% higher than in the IIB subgroup (226.4 ± 8.2 mIU/mL and 169.3 ± 7.9 mIU/mL, respectively) (p <0.05).

The average β-hCG value in the subgroups IIA and IIB did not have a significant difference in the dynamics of the first trimester compared to the control group (p >0.05).

Thinking about persistent progesterone deficiency in women with pregnancy as a result of ART cycles, which was confirmed by our studies, all women received progesterone support in accordance with the recommendations for management after ART. At the same time, we drew attention to a significantly higher increase in progesterone levels in women of subgroup IA, IIA and IIIA against the background of the proposed treatment. The role of psychoemotional correction in the progesterone regulation in women after ART is due to the inverse correlation between the levels of stress-implementing, gonadotropic and sex steroids, in particular in the prolactin/progesterone ratio, because pregnancy, which occurs against the background of chronic stress, and increased prolactin levels as a result, is characterized by progressive yellow body insufficiency with low secretory activity, that is lead to a significant progesterone decrease and progesterone-associated pregnancy complications.

The average values of progesterone levels in the IA subgroup significantly exceeded similar indicators in the IB subgroup against the background of the proposed treatment and psychoemotional correction. Starting from 3–4 weeks of pregnancy the average progesterone level in the subgroup IA was 49% higher than in the IB subgroup (131.9 ± 4.1 nmol/L and 88.4 ± 6.5 nmol/L, respectively; p <0.05). Progesterone value in the period of placentation (critical pregnancy period) in pregnant women who received the proposed complex (subgroup IA) significantly increased by 47% compared to the IB subgroup (164.4 ± 5.4 nmol/L and 111.2 ± 8.4 nmol/L, respectively; p <0.05). The average progesterone value at 7–8 weeks of pregnancy in the subgroup IA increased by 38% compared to women who received a generally treatment (subgroup IA – 193.9 ± 8.6 nmol/L; subgroup IB – 139.8 ± 10.3 nmol/L; p <0.05). A significant progesterone increase in the subgroup IA led to a significant decrease in the frequency of threatened miscarriage by 41.6% (I group before treatment – 66 (70.2%), subgroup I – 14 (28.6%), p <0.05 and spontaneous miscarriages among in group I (subgroup IA – 14 (28.6%), and subgroup IB – 26 (57.7%), p<0.05).

The average progesterone values in subgroup IIA significantly exceeded similar indicators in the subgroup IIB against the background of the proposed treatment and psychoemotional correction. The average progesterone level at 3–4 weeks of pregnancy in the subgroup IIA was 95% higher than in the subgroup IIB (148.4 ± 6.2 nmol/L and subgroup 76.1 ± 4.3 nmol/L, respectively; p <0.05). The average progesterone level at 5–6 weeks of pregnancy in the subgroup IIA was 80% higher than in the subgroup IIB (169.8 ± 7.6 nmol/L, 94.3 ± 5.9 nmol/L, respectively; p <0.05). The average progesterone level at 7–8 weeks of pregnancy in the subgroup IIA was 73% higher than in the subgroup IIB (204.2 ± 10.8 nmol/L, 117.6 ± 8.7 nmol/L, respectively, p <0.05). A significant progesterone increase in women with a history of endocrine infertility led to a significant decrease in the frequency of threatened miscarriage by 37.1% (group II before treatment – 54 (62.1%), subgroup IIA – 12 (25.0%), p <0.05, and by 20% of the hemorrhagic syndrome frequency in pregnant women in the first trimester (before treatment – 20 (37.1%), subgroup IIA – 4 (8.3%), p <0.05).

There was no significant difference in progesterone levels in women of subgroup IIIA and IIB in the dynamics of the first trimester.

Proposed treatment complex in combination with psychoemotional correction in the subgroup IA, IIA and IIIA led to the establishment of estradiol levels within the physiological norm in the dynamics of the first trimester of pregnancy, which synergistically affected the progesterone/estradiol ratio (Table 1).

Special attention was paid to the level of stress hormones (cortisol and prolactin) against the background of the proposed treatment and psychoemotional correction in the first trimester of pregnancy. Repeated determination of cortisol and prolactin levels was performed 2 weeks after the start of the proposed psychoemotional correction for pregnant women in the IA, IIA, and IIA subgroups (Table 2).
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The average cortisol value in women of subgroup IA and IIA against the background of the proposed therapy in the first trimester of pregnancy was significantly 50% lower compared to the subgroup IB and IIB. Also, it was possible to significantly reduce cortisol levels in pregnant women with a history of male infertility factor. In subgroup IA, IIA and IIIA it was possible to bring cortisol indicators as close as possible to the physiological norm and to the indicators in the control group.

The average prolactin value in the IA subgroup against the background of the proposed therapy in the first trimester of pregnancy was significantly lower compared to the IB subgroup (Table 2).

A significant decrease in average prolactin levels was also observed in women of subgroup IIA and IIIA compared to the subgroup IIB and IIIB, respectively.

Thus, the positive effect of the proposed treatment and psychoemotional correction in the first trimester of pregnancy in women of subgroup IA, IIA and IIIA is confirmed by a significant increase in the average β-hCG level, especially in term of gestation, which correspond to the placenta formation, a significant increase in the average progesterone level, a significant decrease in the average estradiol and estrogen/progesterone ratio. This is reflected in a significant decrease of the progesterone-associated complications in the first trimester of pregnancy.

Significant decrease in the average cortisol and prolactin levels against the background of psychoemotional correction led to a balance of the central nervous system processes, which is reflected in the normalization of personal anxiety, reactive anxiety and is confirmed by the “attitude to pregnancy” test.

Special attention in our study was paid to the concentration of placental hormones (estradiol and progesterone) and stress hormones – pituitary (prolactin) and adrenal glands (cortisol), which most affect the pregnancy in the second and third trimesters.

Average estradiol index (Table 3) in the study groups in the second trimester (subgroup IA – 32.4 ± 2.6 nmol/L, subgroup IIA – 31.6 ± 2.1 nmol/L; subgroup IB – 32.1 ± 2.2 nmol/L, subgroup IIB – 34.3 ± 1.8 nmol/L; subgroup IIIA – 33.8 ± 2.7 nmol/L, subgroup IIIB – 32.5 ± 2.8, control group – 28.1 ± 3.4 nmol/L; Table 1. Average estradiol level and progesterone/estradiol ratio in the blood of pregnant women after ART in the dynamics of treatment
A progesterone increase in the studied groups occurred within the gestational norm, but there was more significant progesterone increase in pregnant women who received the proposed treatment complex, reaching the upper limit of the physiological norm. The positive effect of the proposed therapy contributed to a significant reduction in the threatening late spontaneous miscarriages in the group I (subgroup IA – 8 (16.3%), subgroup IB – 13 (28.9%), p <0.05), a decrease in the number of threatening premature birth by 24.0% (before treatment – 34 (36.2%), subgroup IA – 6 (12.2%), p <0.05). There was also a significant decrease in the number of threatened preterm birth between subgroup IA and IB (subgroup IA – 6 (12.2%), subgroup IB – 15 (33.3%), p <0.05) and placenta-associated complications during pregnancy in the second and third trimesters.

Taking into account the psychoemotional aspects of pregnancy complications, which are characterized by miscarriage, prematurity and chronic stress that accompanies pregnancy after ART, and causes of stress-associated hormones hypersecretion by the pituitary gland and adrenal glands, we believe that restoration of physiological gestational cortisol and prolactin levels can be considered as a marker of the therapy effectiveness and psychoemotional correction aimed at prolonging pregnancy.

We drew attention to a significant cortisol and prolactin decrease in the subgroup IA, IIA and IIIA at 23–24 and 33–34 weeks of pregnancy against the background of the proposed therapy and psychoemotional correction (Table 4).

Thus, the average cortisol value at 23–24 weeks of pregnancy in the subgroup IA decreased by 42% to 162.1 ± 8.9 ng/mL (subgroup IB – 231.7 ± 9.1 ng/mL, p <0.05). The average cortisol value in pregnant women with a history of endocrine infertility against the background of the proposed treatment was 154.4 ± 8.7 ng/mL, which is 62% less than in the IIIB subgroup – 251.6 ± 9.3 ng/mL (p <0.05). At the same time, the average cortisol value against the background of the proposed complex in women with a history of male infertility factor was 146.3 ± 10.2 ng/mL, which is 63% less compared to the IIIB subgroup – 238.5 ± 8.5 ng/mL (p <0.05). The average cortisol values in the subgroups IA, IIA, and IIIA approached the indicator in the control group and the physiological norm and had no significant differences (p >0.05).

| Table 3. Estradiol and progesterone levels in the blood of pregnant women after ART at 23–24 and 33–34 weeks of pregnancy, nmol/L |
|---|---|---|---|---|
| **Term of pregnancy (weeks)** | **Main group (n = 249)** | **Control group (n = 50)** |
| | I group (n = 94) | II group (n = 87) | III group (n = 68) | |
| | Subgroup IA (n = 49) | Subgroup IB (n = 45) | Subgroup IIA (n = 48) | Subgroup IIIB (n = 39) | Subgroup IIIA (n = 36) | Subgroup IIIIB (n = 32) |
| **23–24 weeks of pregnancy** | | | | |
| Estradiol | 32.4 ± 2.6 | 31.6 ± 2.1 | 32.1 ± 2.2 | 34.3 ± 1.8 | 33.8 ± 2.7 | 32.5 ± 2.8 | 28.1 ± 3.4 |
| Progesterone | 358.3 ± 10.9** | 245.8 ± 11.6* | 378.5 ± 11.2** | 286.1 ± 10.3* | 369.7 ± 10.1** | 289.3 ± 10.6* | 341.2 ± 6.9 |
| **33–34 weeks of pregnancy** | | | | |
| Estradiol | 50.4 ± 3.2** | 51.5 ± 2.6 | 52.7 ± 4.1** | 49.2 ± 2.3 | 51.8 ± 3.2** | 52.1 ± 3.1 | 44.3 ± 2.6 |
| Progesterone | 681.6 ± 11.4** | 501.7 ± 10.2* | 694.3 ± 12.5** | 478.6 ± 10.1* | 678.2 ± 12.3** | 538.7 ± 11.2* | 633.4 ± 5.8 |

* statistically significant differences compared to the control group (p <0.05); ** statistically significant differences between subgroups A and B.
Further cortisol study at 33–34 weeks of pregnancy in the main group noted significant differences in the indicators of women who received the proposed treatment and psychoemotional correction compared to pregnant women who were observed according to generally accepted norms.

The average cortisol value at 33–34 weeks of pregnancy in the IA subgroup increased in accordance with the physiological norm (209.6 ± 9.3 ng/mL), which is 47% less compared to the IB subgroup – 308.2 ± 9.7 ng/mL (p <0.05). The average cortisol value in the subgroup IIA was 213.5 ± 8.9 ng/mL, which is 48% less than in the subgroup IIB – 316.4 ± 9.1 ng/mL (p <0.05). At the same time, the average cortisol value in the subgroup IIIB was 201.3 ± 8.7 ng/mL, which is 39% less compared to the subgroup IIIB – 281.7 ± 11.4 ng/mL (p <0.05).

The average cortisol values in the subgroups IA, IIA, and IIIB approached the indicator in the control group and the physiological norm and had no significant differences (p >0.05).

Similar trends continued with prolactin level. In pregnant women who received conventional treatment we noted a rather slow decrease of this hormone.

Rapid normalization of prolactin indicators in pregnant women who received the proposed treatment and psychoemotional correction is inherent. Already at 23–24 weeks of pregnancy at the first control examination we noted a prolactin decrease in the IA subgroup by an average 111% (124.3 ± 7.1 ng/mL) compared to the IB subgroup – 271.6 ± 7.6 ng/mL (p <0.05). At the same time the average cortisol value in the subgroup IIIB was 159.5 ± 10.1 ng/mL, which is 73% less compared to the subgroup IIIB – 277.3 ± 9.1 ng/mL (p <0.05).

The cortisol average values in subgroups IA, IIA, and IIIB approached the indicator in the control group and the physiological norm and had no significant differences (p >0.05).

**CONCLUSION**

Advanced therapy with micronized progesterone in combination with magnesium saturation, L-arginine aspartate, folic acid, ω-3 polyunsaturated fatty acids, as well as long-term psychoemotional correction is appropriate and effective compared to conventional therapy for pregnant women. This is confirmed by a progressive β-hCG biosynthesis increase by an average of 32%, progesterone by of 71%, restoration of estrogen-progesterone one ratio against the background of stress-associated hormones normalization (decrease of average cortisol by 47% depending on the pregnancy duration).

REFERENCES/ПІТЕРАТУРА


ОЦІНКА ЕФЕКТИВНОСТІ ВДОСКОНАЛЕНОГО ЛІКУВАЛЬНО-ПРОФІЛАКТИЧНОГО КОМПЛЕКСУ У ВАГІТНИХ ПІСЛЯ ЗАСТОСУВАННЯ ДОПОМІЖНИХ РЕПРОДУКТИВНИХ ТЕХНОЛОГІЙ

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STUDY BACKGROUND. The study included 299 pregnant women: the main group included 249 women whose pregnancy occurred as an ART result; the control group included 50 pregnant women with spontaneous pregnancy. Therapeutic and prophylactic complex for pregnant women after ART included: micronized progestogen, magnesium oxide, folic acid, L-arginine, aspartic acid, β-estradiol, furosemide, enalapril, atorvastatin calcium, glimepiride, cerivastatin, fentanyl transdermal system and physiotherapy. The study was conducted at the Obstetrics and Gynecology Department No. 3, Bogomolets National Medical University, Kyiv, Ukraine.

STUDY OBJECTIVE. To determine the role and effectiveness of the proposed therapeutic and preventive complex and psychosomatic correction of hormonal disorders in the pregnancy dynamics after assisted reproductive technologies (ART) to improve the antenatal and perinatal outcomes.

STUDY DESIGN. The study was a prospective, randomized, placebo-controlled, parallel clinical trial. The study included pregnant women who had received ART from January 1, 2010 to December 31, 2010. The study was conducted at the Obstetrics and Gynecology Department No. 3, Bogomolets National Medical University, Kyiv, Ukraine.

STUDY RESULTS. On the 7–8th week of gestation, the mean β-estradiol level in subgroup IA increased by 38% in comparison with subgroup IB. The mean β-estradiol level in subgroup IA was 73% higher than in subgroup IB (p <0.05). There was no significant difference in the progesterone level in subgroups IIIA and IIIB in the dynamics of the first trimester.

Conclusion. The average cortisol level in pregnant women during ART was significantly higher than in the control group (p <0.05). The average cortisol level in subgroup IA was 73% higher than in subgroup IB (p <0.05). There was no significant difference in the level of β-estradiol in subgroups IIIA and IIIB in the first trimester.

Conclusion. The study was conducted at the Obstetrics and Gynecology Department No. 3, Bogomolets National Medical University, Kyiv, Ukraine. The study included 299 pregnant women: the main group included 249 women whose pregnancy occurred as an ART result; the control group included 50 pregnant women with spontaneous pregnancy. Therapeutic and prophylactic complex for pregnant women after ART included: micronized progestogen, magnesium oxide, folic acid, L-arginine, aspartic acid, β-estradiol, furosemide, enalapril, atorvastatin calcium, glimepiride, cerivastatin, fentanyl transdermal system and physiotherapy. The study was conducted at the Obstetrics and Gynecology Department No. 3, Bogomolets National Medical University, Kyiv, Ukraine.

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