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The condition of hormonal homeostasis in the first trimester of pregnancy after the application of assisted reproductive technologies

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The article represents results of a prospective examination of pregnant women whose anamnesis was complicated by infertility and were treated by the means of assistant reproductive technologies application.
The objective: **to study features of hormonal homeostasis in pregnant women after ART application in the dynamics of I trimester of pregnancy in order to improve the tactics of antenatal surveillance and prevention of obstetric and perinatal complications.**
Materials and methods**. To achieve this aim in the dynamics of prospective study, 299 pregnant women were comprehensively examined, were divided into two groups. The main group included 249 women whose pregnancy occurred as a result of ART application. The control group consisted of 50 pregnant women with spontaneous onset of pregnancy and its physiological course, which became registered at the antenatal clinic in 6-8 weeks of pregnancy.**
Basic clinical and laboratory studies, which included a general analysis of blood and urine were conducted to all pregnant women of the examined groups. The concentration of β-HG, placental hormones (progesterone and estradiol), pituitary gland (prolactin) and adrenal glands (cortisol (K)), which more reflect the dynamic development of pregnancy and affect its course and intrauterine fetal condition were determined in blood plasma of women after treated infertility.
Results**. The determination of the main hormones that provide implantation and further progression of pregnancy in women of the main group after the use of therapeutic cycles of ART indicates the need for their dynamic monitoring during the first trimester of pregnancy. Detecting an insufficient levels of sex hormones during the initial examination, we considered it appropriate to refer the pregnant woman to the risk group for the development of pregnancy complications with hormonal parameters, and assessed their insufficiency as a risk factor for the threat of miscarriage, which from our point of view requires a complex correction to prevent clinical manifestations of the threatening abortion. One of the main factors of possible adverse course of pregnancy after art is insufficient level of β-HG at the stage of establishing the fact of pregnancy and during the first trimester. Our research found that in significant majority of cases, pregnancy after ART application over tubal-peritoneal, and endocrine types of infertility takes place in progesterone failure that causes the occurrence of violations of the processes of implantation and development of the ovum and clinically evident miscarriage since I trimeter pregnancy.**
Conclusions**. The revealed deviations in the concentration of stress-associated hormones cortisol and prolactin with a high probability may indicate an increased stress load, which in pregnant women after the application of ART therapeutic cycles manifests already from the beginning of pregnancy. We consider it appropriate to continue the dynamic examination of these indicators during pregnancy and to continue further in-depth examination of pregnant women after the ART application.**
Key words: *pregnancy, infertility, assisted reproductive technologies, cortisol, prolactin.*

Стан гормонального гомеостазу у I триместрі вагітності після застосування допоміжних репродуктивних технологій

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У статті наведені результати проспективного обстеження жінок з обтяженим безплідністю анамнезом, вагітність у яких настала у результаті застосування допоміжних репродуктивних технологій (ДРТ).
Мета дослідження: вивчення у динаміці I триместра гестації особливостей гормонального гомеостазу у вагітних після застосування ДРТ для вдосконалення тактики антенатального спостереження та профілактики акушерських і перинатальних ускладнень.
Матеріали та методи. Для досягнення поставленої мети у динаміці проспективного спостереження комплексно обстежено 299 вагітних, яких розподілено наступним чином: до основної першої групи увійшли 94 жінки з трубно-перитонеальним фактором безплідності; другу основну групу сформували з 87 жінок з ендокринним фактором безплідності; до третьої основної групи включено 68 жінок, безплідність яких зумовлена чоловічим фактором. До контрольної групи увійшли 50 жінок зі спонтанним настанням вагітності та її фізіологічним перебігом, що ставали на облік щодо вагітності у терміни 6–8 тиж.
В обстежених вагітних проводили загальноприйняті клініко-лабораторні дослідження, які включали загальний аналіз крові та сечі. У плазмі крові жінок досліджуваних груп визначали концентрацію β-ХГ, плацентарних гормонів (прогестерон і естрадіол), гіпофіза (пролактин) та надниркових залоз (кортизол), які найбільше відображають динамічний розвиток вагітності і впливають на її перебіг та внутрішньоутробний стан плода.
Результати. Визначення основних гормонів, які забезпечують імплантацію і подальше прогресування вагітності у жінок основних груп після використання лікувальних циклів ДРТ, свідчить про необхідність їхнього динамічного моніторингу протягом I триместра вагітності. У разі виявлення недостатніх рівнів статевих гормонів під час первинного обстеження вважали за доцільне віднести вагітну до групи ризику щодо розвитку ускладнень вагітності за гормональними параметрами і оцінювали їхню недостатність як фактор ризику загрози невиношування. Це потребувало комплексної корекції задля попередження клінічних проявів загрози переривання вагітності. Одним з основних чинників можливого несприятливого перебігу вагітності після застосування ДРТ є недостатній рівень β-ХГ на етапі встановлення факту наявності вагітності та протягом I триместра. Дослідження виявили, що у достовірній більшості випадків вагітність у жінок після використання ДРТ з приводу трубно-перитонеального та ендокринного типів безплідності перебігає в умовах прогестеронової недостатності. Це зумовлює порушення процесів імплантації та розвитку плідного яйця і клінічно проявляється невиношуванням вагітності, починаючи вже з I триместра.
Заключення. Виявлені відхилення у концентрації стрес-асоційованих гормонів кортизолу та пролактину з великою долею вірогідності може свідчити про підвищену стресову завантаженість, яка у вагітних після застосування лікувальних циклів ДРТ маніфестує вже від початку гестації. Саме тому є доцільним продовжити динамічне дослідження цих показників протягом вагітності та подальше поглиблене обстеження вагітних після застосування ДРТ за іншими параметрами.
Ключові слова: *вагітність, безплідність, допоміжні репродуктивні технології, кортизол, пролактин.*

Состояние гормонального гомеостаза в I триместре беременности после применения вспомогательных репродуктивных технологий

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В статье приведены результаты проспективного обследования женщин с отягощенным бесплодием анамнезом, беременность у которых наступила в результате применения вспомогательных репродуктивных технологий (ВРТ).

Цель исследования: изучение в динамике I триместра гестации особенностей гормонального гомеостаза у беременных после применения ВРТ для совершенствования тактики антенатального наблюдения и профилактики акушерских и перинатальных осложнений.

Материалы и методы. Для достижения поставленной цели в динамике проспективного наблюдения комплексно обследовано 299 беременных, которых распределили следующим образом: в основную первую группу вошли 94 женщины с трубно-перитонеальным фактором бесплодия; вторую основную группу сформировали из 87 женщин с эндокринным фактором бесплодия; в третью основную группу включены 68 женщин, бесплодие которых обусловлено мужским фактором. В контрольную группу вошли 50 беременных со спонтанным наступлением беременности и ее физиологическим течением, что становились на учет по беременности в сроки 6–8 нед.

У обследованных беременных проводили общепринятые клинико-лабораторные исследования, которые включали общий анализ крови и мочи. В плазме крови женщин исследуемых групп определяли концентрацию β-ХГ, плацентарных гормонов (прогестерон и эстрадиол), гипофиза (пролактин) и надпочечников (кортизол), которые больше отражают динамичное развитие беременности и влияют на ее течение и внутриутробное состояние плода.

Результаты. Определение основных гормонов, которые обеспечивают имплантацию и дальнейшее прогрессирование беременности у женщин основных групп после использования лечебных циклов ВРТ, свидетельствует о необходимости их динамического мониторинга в течение I триместра беременности. При выявлении недостаточных уровней половых гормонов при первичном обследовании считали целесообразным относить беременную к группе риска по развитию осложнений беременности с гормональными параметрами и оценивали их недостаточность как фактор риска угрозы невынашивания. Это нуждалось в комплексной коррекции для предупреждения клинических проявлений угрозы прерывания беременности. Одним из основных факторов возможного неблагоприятного течения беременности после применения ВРТ является недостаточный уровень β-ХГ на этапе установления факта наличия беременности и в течение I триместра. Исследования обнаружили, что в достоверном большинстве случаев беременность у женщин после использования ВРТ по поводу трубно-перитонеального и эндокринного типов бесплодия протекает в условиях прогестероновой недостаточности. Это обусловливает нарушение процессов имплантации и развития плодного яйца и клинически проявляется невынашиванием беременности, начиная уже с I триместра.

Заключение. Выявленные отклонения в концентрации стресс-ассоциированных гормонов кортизола и пролактина с большой долей вероятности может свидетельствовать о повышенной стрессовой нагрузке, которая у беременных после применения лечебных циклов ВРТ манифестирует уже от начала гестации.

Именно поэтому целесообразно продолжить динамическое исследование этих показателей в течение беременности и продолжить дальнейшее углубленное обследование беременных после применения ВРТ по другим параметрам.

Ключевые слова: *беременность, бесплодие, вспомогательные репродуктивные технологии, кортизол, пролактин.*

Prior to pregnancy, endocrine disorders can cause gestational complications in women whose pregnancy occurred after the application of assisted reproductive technologies (ART). The development of hormonal disorders, especially in the early stages of gestation, can be the result of hyperandrogeny, luteal-phase defect, ovarian hyperstimulation and have a further affect on the course of pregnancy and fetoplacental complex condition [1, 2, 7].

The most common changes deal the concentration of progesterone, estrogen, androgen, β-HG and placental hormones. In physiological pregnancy, the main role in the regulation of its normal development belongs to the chorion and trophoblast, which produce β-HG, which, in turn, determines the level of steroid synthesis by the corpus luteum of pregnancy and contributes to the adaptation reactions of the mother's body to the gestational process. One of the leading points which characterize the effectiveness of therapeutic cycles of ART is the determination of the β-HG level in the blood serum of a woman on 14–16 days after fertilization. The quantitative value of β-HG is an important prognostic factor for the further course of pregnancy and the development of possible complications. The dynamics of the average β-HG level in pregnant women after the ART application differs from that in a case of physiological pregnancy and has individual fluctuations which are associated with previous ovarian stimulation in assisted reproductive technology programs. The level of β-HG, which characterizes the condition of trophoblast, can indicate its functional decrease. And at the same time β-HG can be the first prognostic factor for determining the possibility of biochemical, ectopic and normal uterine pregnancy as well as be a marker of increased risk of complications [3].

The objective: to study features of hormonal homeostasis in pregnant women after ART application in the dynamics of I trimester of pregnancy in order to improve the tactics of antenatal surveillance and prevention of obstetric and perinatal complications.

MATERIALS AND METHODS

To achieve this aim in the dynamics of prospective study, 299 pregnant women were comprehensively examined, were divided into two groups. The main group included 249 women whose pregnancy occurred as a result of ART application. The control group consisted of 50 pregnant women with spontaneous onset of pregnancy and its physiological course, which became registered at the antenatal clinic in 6–8 weeks of pregnancy.

The main group of women whose pregnancy occurred as a result of ART application was divided into three groups, depending on the factor that caused infertility. The I group included 94 women with tubal-peritoneal factor of infertility, the II group was formed by 87 women with endocrine factor of infertility, and the III group included 68 women whose infertility was caused by the male factor. According to age, marital and social status and place of residence pregnant women of the study groups were representative, which allowed us further to judge the differences which were caused by etiological factors of infertility.

Basic clinical and laboratory studies, which included a general analysis of blood and urine were conducted to all pregnant women of the examined groups. The concentration of β-HG, placental hormones (progesterone and estradiol), pituitary gland (prolactin) and adrenal glands (cortisol (K)), which more reflect the dynamic development of pregnancy and affect its course and intrauterine fetal condition were determined in blood plasma of women after treated infertility.

THE RESULTS OF THE RESEARCH AND THEIR DISCUSSION

Taking into account the fact that the women of the examined groups were under dynamic observation starting from the treatment cycles of ART, we analyzed the quantitative levels of β-CG in 21 days after fertilization and during the first 12 weeks of pregnancy (table 1).

Table 1

The average level of β-HG in blood serum of studied women, mMo/ml (M±m)

Term of gestation (weeks)	The value of the indicator in the surveyed groups, n			
	The main Group, n=249			The control group, n=50
	I group, n=94	II group, n=87	III group, n=68	
3–4	91,2±6,4	99,4±8,3	119,4±7,9	126,3±9,4
5–6	147,6±9,2 *	151,4±11,3 *	184,5±8,1	191,9±11,7
7–8	162,2±8,7 *	169,3±7,9 *	199,7±11,3	214,2±14,1
9–10	100,2±5,4	104,3±6,4	121,3±10,1	131,1±10,8
11–12	66,6±4,4	71,7±6,2	81,1±6,8	86,3±7,5

Note: * – statistically significant differences compared to the control group (p<0,05).

Analysis of the β-HG level demonstrates insufficient production of this hormone in pregnant women of group I and II group beginning from the 3–4 weeks of pregnancy. A similar trend continued throughout the whole I trimester. Significant differences in the level of β-HG were revealed in 5–6 and 7–8 weeks – gestational period of the placenta formation beginning: group I – 147,6±9,2, group II – 151,4±11,3, control group – 191,9±11,7 (p<0,05) and group I – 162,2±8,7, group II – 169,3±7,9, control group – 214,2±14,1 (p<0,05), respectively, which coincides with the occurrence of threatened abortion and the appearance of early gestosis signs in this pregnant women.

The most favorable and physiological was the dynamics of β-HG in pregnant women of the III and control groups. Having no significant differences, the dynamics of β-HG in III group pregnant women was maximally close to the dynamics of the control group women and, accordingly, the physiological norm (fig. 1).

It should be noted that with the further progression of pregnancy in pregnant women of II group, the content of this hormone grew more intensively in comparison with pregnant women and the I group being within the minimum permissible norm. The dynamics of the β-HG level in pregnant women of the III and control group did not differ much, which from our point of view may be due to a favorable extragenital and gynecological background.

One of the features of antenatal observation of pregnant women after ART application is the early progesterone support, which is aimed to neutralize the effects of estrogen-progesterone imbalance arising from the use of high doses of estrogens, gonadotropin-releasing hormone agonists and human menopausal gonadotropins in order to stimulate the superovulation. Hyperestrogenism in patients with endocrine infertility is one of the reasons of ovarian hyperstimulation syndrome (OHS), which is now considered as an ART program complication [4, 6]. Therefore, one of the most important aspects contributing to the reduction of reproductive losses after pregnancy which occurred as a result of ART application is the appointment of hormonal therapy support in the luteal phase of the induced cycle and in the early terms of pregnancy. In this regard, the literature widely discusses the issues which is related to the appropriateness and timing of hormonal therapy beginning [7, 8].

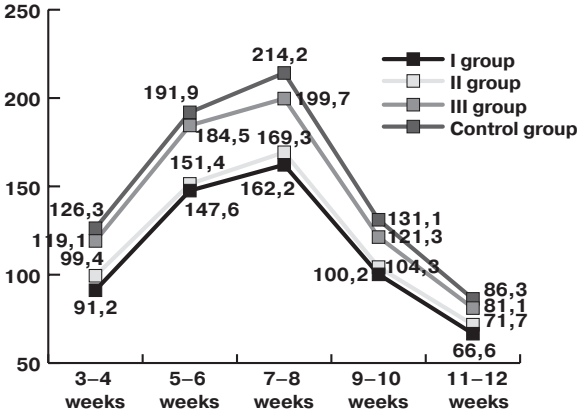

Fig. 1. Dynamics of the β-HG level in pregnant women after ART

Leading researchers note the expediency of large progesterone doses prescription due to insufficient corpus luteum functioning or in a case of multiple corpus luteum (as a result of puncture of a large number of follicles) and relative hyperestrogenemia in therapeutic cycles of ART. Others suggest limiting the appointment of drugs after the end of the luteal phase of the induced cycle, through the negative impact of high progesterone concentrations on the reproductive system of the fetus, in particular the occurrence of hypospadias. However, to date, there is no single point of view on the problem of diagnosis and correction of progesterone deficiency in pregnant women after the ART application [7, 8, 10].

In this regard, we analyzed the features of the hormonal parameters dynamics that ensure the course of the first trimester of induced pregnancies, and also tried to systematize these data to determine the risk group for pregnancy complications for changes in hormonal parameters that require appropriate and timely

Table 2

The average level of progesterone in I trimester in blood serum of studied women, nmol/l (M±m)

Term of gestation (weeks)	The value of the indicator in the surveyed groups, n			
	The main Group, n=249			The control group, n=50
	I group, n=94	II group, n=87	III group, n=68	
3–4	88,4±6,5 *	76,1±4,3 *	119,1±8,4 °	121,8±10,4
5–6	111,2±8,4 *	94,3±5,9 *	142,7±11,9 °	153,7±12,1
7–8	139,8±10,3 *	117,6±8,7 *	159,3±10,6 °	176,6±15,7
9–10	167,6±11,8 *	149,7±10,2 *	179,4±11,5 °	191,8±10,5
11–12	188,7±13,9 *	166,8±13,5 *	194,6±16,3 °	210,4±18,1

Note: * – statistically significant differences compared to the control group (p<0,05);
° – statistically significant differences between I, II and III group.

Table 3

The average level of estradiol in I trimester in blood serum of studied women, nmol/l (M±m)

Term of gestation (weeks)	The value of the indicator in the surveyed groups, n			
	The main Group, n=249			The control group, n=50
	I group, n=94	II group, n=87	III group, n=68	
3–4	9,3±0,47 *	10,8±0,55 *	9,7±0,61 *	5,4±0,33
5–6	9,0±0,31 *	10,1±0,34 *	9,4±0,58 *	6,5±0,41
7–8	8,4±0,61	9,1±0,27 *	8,6±0,34	7,3±0,56
9–10	8,1±0,23	8,4±0,43	8,0±0,42	8,8±0,61
11–12	8,4±0,33	8,9±0,61	8,8±0,51	9,6±0,43

Note: * – statistically significant differences compared to the control group (p<0,05).

Table 4

Progesterone/estradiol ration in I trimester in blood serum of studied women, M±m

Term of gestation (weeks)	The value of the indicator in the surveyed groups, n			
	The main Group, n=249			The control group, n=50
	I group, n=94	II group, n=87	III group, n=68	
3–4	10,9±2,1 *	9,5±1,8 *	17,4±3,2	20,4±2,3
5–6	13,6±1,3 *	12,1±2,3 *	19,1±2,5	22,1±2,4
7–8	14,4±2,6 *	13,9±2,2 *	18,6±2,3	21,6±2,7
9–10	16,5±2,2	16,9±3,1	18,7±2,4	21,1±1,9
11–12	18,3±2,3	17,8±1,6	19,8±2,3	22,9±2,7

Note: * – statistically significant differences compared to the control group (p<0,05);
° – statistically significant differences between I, II and III group.

correction. To exclude or establish the fact of the progesterone deficiency presence, we examined the level of progesterone concentration in blood plasma in women of the study groups. The concentration of progesterone (P) during the first trimester of pregnancy is represented on the table 2.

Determination of the average level of progesterone in the blood serum of pregnant women of the main and control groups shows significant differences. Starting from 3–4 weeks of pregnancy, despite the basic progesterone support due to the ART program, the average level of progesterone in the blood serum of I and II groups of pregnant women significantly differed from the control group one (I group – 88,4±6,5; II group – 76,1±4,3; control group – 121,8±10,4; p<0,05) and III group of pregnant women (I group – 88,4±6,5; II group – 76,1±4,3; III group -119,1±8,4; p<0,05).

Analysis of progesterone growth dynamics (Fig. 2) during the first trimester in pregnant women of the main and control groups shows a slow increase in this indicator within the minimum physiological norm in pregnant women of I and II group.

Since the beginning of pregnancy, insufficient progesterone levels have been observed in pregnant women of II group – with endocrine type of infertility. The revealed regularities are confirmed by the data obtained from the analysis of gynecological anamnesis of examined pregnant women. Thus, menstrual irregularities were observed in 21 cases (38,9%), and polycystic ovaries – in 26 cases (48,1%) with pregnant women of the second group, who noted the presence of gynecological diseases in the history – 54 cases.

According to the literature, ULF is registered in every second woman with infertility and habitual miscarriage in the history [1, 9]. Insufficient synthesis of progesterone, as a result of insufficiency of the luteal phase of the menstrual cycle, leads to defective secretory transformation of the endometrium, changes in the function of the fallopian tubes, violation of implantation of a fertilized egg, which is clinically manifested by spontaneous termination of pregnancy in the first trimester. This fact can cause

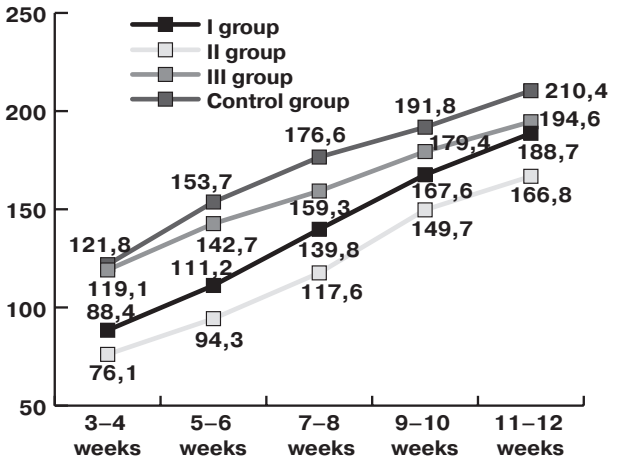

Fig. 2. Progesterone level dynamic in pregnant women after ART

the highest percentage of threatened abortions with bleeding in the first trimester of pregnancy among pregnant women of II group (II group – 62,9%, I group – 43,9%, III group – 28,6%, control group – 12,5%; p<0,05).

There is no doubt the importance, especially in the luteal phase of the ovarian-menstrual cycle and in the early stages of gestational period, of the concentration of estradiol in blood plasma. Insufficient estrogen production leads to impaired chorion development and decreased chorionic gonadotropin, which in turn contributes to the progression of chorionic tissue defect. Data on the dynamics of changes in estradiol (E) during the first trimester in women of the examined groups is represented in table. 3.

The level of estradiol in the early stages of gestation in I, II and III groups of pregnant women after ART application was increased almost in 1,5–2 times compared with the control group.

Table 5

The average level of cortosol in I trimester in blood serum of studied women, ng/ml (M±m)

Term of gestation (weeks)	The value of the indicator in the surveyed groups, n			
	The main Group, n=249			The control group, n=50
	I group, n=94	II group, n=87	III group, n=68	
3–4	184,3±12,1 *	190,2±12,7 *	177,4±10,7 *	122,4±12,3
5–6	203,5±13,7 *	200,4±13,6 *	193,7±12,1 *	143,1±11,7
7–8	219,4±12,9 *	223,0±14,7 *	208,2±13,1 *	161,2±12,1
9–10	231,4±11,2 *	246,8±13,4 *	228,3±11,4 *	185,7±11,9
11–12	251,1±13,4 *	261,7±12,6 *	246,4±12,3 *	192,9±14,7

Note: * – statistically significant differences compared to the control group (p<0,05).

Table 6

The average level of prolactin in I trimester in blood serum of studied women, ng/ml (M±m)

Term of gestation (weeks)	The value of the indicator in the surveyed groups (n)			
	The main Group (n = 249)			The control group, n=50
	I group, n=94	II group, n=87	III group, n=68	
3–4	101,6±7,2 *	121,2±5,7 *	111,4±6,4 *	64,4±6,1
5–6	147,2±8,4 *	143,4±6,2 *	138,2±5,3 *	71,8±5,2
7–8	166,3±6,9 *	169,5±6,7 *	161,7±8,7 *	84,3±6,9
9–10	181,1±7,9 *	189,1±7,2 *	184,7±9,1 *	93,5±7,1
11–12	197,4±8,1 *	194,3±7,6 *	200,4±7,3 *	99,7±6,4

Note: * – statistically significant differences compared to the control group (p<0,05).

There was a significant difference in the average value of this hormone in 3–4 weeks (I group – 9,3±0,47; II group – 10,8±0,55; III group – 9,7±0,61; control group – 5,4±0,33; p<0,05) and 5-6 weeks of pregnancy (I group – 9,0±0,31; II group – 10,1±0,34; III group – 9,4±0,58; control group – 6,5±0,41; p<0,05).

Starting from 7-8 weeks of gestation, the average value of estradiol in the main group was close to the average value of the control group, and from 9–10 weeks – the concentration of estradiol corresponded to the control group indicators (I group – 8,1±0,23; II group – 8,4±0,43; III group – 8,0±0,42; control group – 8,8±0,61; p>0,05). In the control group, the concentration of estradiol corresponded to the physiological value, respectively, up to a week of the gestational period.

Analyzing the progesterone/estradiol ratio (table 4) it was revealed that at the initial stages of gestation, the average coefficient of pregnant women of group I and II group significantly differed from the indicators of III and control group.

However, starting from 9–10 weeks of gestation, the progesterone/estrogen ratio of I and II group of pregnant women approached the value of III and control pregnant women.

In the III group of pregnant women after therapeutic cycles of ART due to male factor of infertility, the content of progesterone and estradiol during the entire follow-up period approached the indicators of women with spontaneous pregnancy.

In some women of I and II group, we observed a reduced content of estradiol and progesterone alone or in combination. In 18 (19,1%) women of I group and in 22 (25,3%) women of II group, reduced levels of E and P in the blood serum were revealed during the primary hormonal examination at 3–4 weeks, which characterized the insufficiency of the yellow bodies and the placenta, which is formed as a result of the previous hyperestrogen stimulation in the treatment cycle of ART.

In women with hormonal abnormalities, significantly low (against the appropriate period, respectively) levels of E and P were observed in 12 (12,8%) women of I group and 16 (18,4%) women of II group. Low levels of only P were observed in 6 (6,4%) women of I group and in 9 (10,3%) women of II group, low levels of E – in 4 (4,3%) women of I group and in 6 (6,9%) women of II group. The percentage of women with deviations in the level of E and P at the initial examination (3–4 weeks) in pregnant women of both groups after ART was almost the same, which indicated the similarity of the initial conditions of entry into pregnancy of these women.

Considering pregnancy after therapeutic cycles of ART from the stress load point of view on the body of the future mother, we determined the level of stress hormones – cortisol (C) and prolactin (Pl) in the dynamics of I trimester of pregnancy [5, 9].

The results of cortisol determination in the examined groups showed an increase in its concentration from the beginning of gestation in pregnant women of I, II and III group, while in the control group women this indicator was significantly lower and was at the level of physiological norm (table 5).

The physiological course of pregnancy is characterized by a balance of C positive and negative effects. In the first trimester of pregnancy, cortisol activates the production of HCG, shows a suppressive effect on cellular and humoral immunity, stimulates the growth and invasion of trophoblast. From another side it limits the functioning of the cytokine-prostaglandin system, inhibits the growth of the placenta and embryo due to the activation of the inhibitor-1, as well as the induction of apoptosis [10]. Therefore, to maintain homeostasis during pregnancy, it is necessary to have an adequate production and concentration of C. Given the fact that the concentration of C in the myometrium increases by nine times with an increase in its concentration in blood plasma by three times [9], most complications during pregnancy are associated with a violation of this glucocorticoid biosynthesis.

Indicators of Pl in the serum of pregnant women of the main group in the first trimester were significantly increased compared with the physiological norm and indicators of pregnant women of the control group (table 6).

These patterns are consistent with the research of T.F. Tatarchuk et al. (2016) [8] who revealed an inverse correlation between the levels of stress-implementing,

gonadotropic and sex steroids, in particular in the prolactin/progesterone ratio, was revealed. Therefore, it becomes obvious the role in the pathogenesis of early termination of pregnancy, develops against the background of increased biosynthesis of Pl, progressive insufficiency of the corpus luteum with low secretory activity. In this case, the content of progesterone in the blood serum is reduced almost threefold and remains at a low level throughout the luteal phase.

CONCLUSIONS

Thus, the determination of the main hormones that provide implantation and further progression of pregnancy in women of the main group after the use of ART therapeutic cycles indicates the need of dynamic monitoring during the first trimester of pregnancy. When detecting insufficient levels of sex hormones during the initial examination, we considered it appropriate to refer the pregnant woman to the risk group for the development of pregnancy complications with hormonal parameters, and assessed their insufficiency as a risk factor for the threat of miscarriage, which from our point of view needs a complex of correction to prevent clinical manifestations of the threat of abortion.

One of the main factors of possible adverse course of pregnancy after ART application is insufficient level of β-HG at the stage of establishing the fact of pregnancy and during the first trimester. Our research found that in significant majority of cases, pregnancy after ART application due to tubal-peritoneal, and endocrine types of infertility takes place in progesterone failure that causes the occurrence of violations of the processes of implantation and development of the ovum and clinically evident miscarriage since I trimester of pregnancy.

The revealed deviations in the concentration of stress-associated hormones such as cortisol and prolactin with a high probability may indicate an increased of stress load, which in pregnant women after the use of ART therapeutic cycles manifests from the beginning of pregnancy.

Due to this we consider it appropriate to continue the dynamic examination of these indicators during pregnancy and to continue further in-depth examination of pregnant women after the application of ART on other parameters.

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