FEATURES OF HORMONAL FUNCTION IN PREGNANT WOMEN - DISPLACED PERSONS

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Abstract. Features of hormonal function in pregnant women - displaced persons. Zhabchenko I.A., Korniets N.G., Tertychna-Telyuk S.V. Harmonious and stable psycho-emotional state of pregnant women is an important condition of successful pregnancy course, fetal development and physiological childbirth. People are facing various problems related to mental health that vary from psycho-emotional stress to the mental disorders. Important factors that determine the physiology of pregnancy are the psycho-emotional state of the pregnant and fetoplacental complex. Among the consequences of severe stress during pregnancy is dizziness, tachycardia, trembling of limbs, elevated arterial pressure, unmotivated increase in nervousness and anxiety, sleep disorder, depression that lead to worsening of general condition of a future mother. The purpose of the study was to determine changes in the production of placental hormones and stress-associated hormones in pregnant women - displaced persons. To carry out the study, a randomised dynamic prospective clinical-paraclinical examination of 96 pregnant women (the main group) - displaced persons and 39 pregnant women (control group), who lived permanently in the territory of Ukraine under control, with gestation period after 22 weeks was used. Concentration of stress-associated (cortisol and prolactin) and placental (estradiol, progesterone, placental lactogen) hormones in serum was determined by solid-phase immunoassay. Increased estradiol concentrations and relative reductions in progesterone and placental lactogen, displacement of estrogen-progesterone equilibrium toward relative hyperestrogeny, increase in the concentration of stress-associated hormones were observed. The revealed hormonal and metabolic disorders in pregnant women, internally displaced persons, are biochemical markers of placental dysfunction, which testifies to the expediency of a comprehensive preconceptional preparation with the involvement of a psychologist and inclusion of preventive measures in the form of long-term progesterone support during pregnancy in the program of antenatal observation of such women.
Maintaining the health and life of the mother and the newborn is a major task of public health. Modern socio-economic conditions, environmental problems, prolonged stay in conditions of stress as a result of the military conflict in the east of Ukraine cause a negative impact on the health indicators of pregnant women and their children forming an unfavorable medical and demographic situation in the country. That is why the current direction of modern obstetrics in Ukraine is the prevention of obstetric complications, which are the cause of maternal morbidity and high level of perinatal mortality, the birth of infants with extremely low weight and, consequently, the growth rates of morbidity and disability since childhood.

Placenta plays one of the leading roles in pregnancy, because it supports the physiological balance between the environment, mother and the uterus [13]. Thus, only the physiological level of the placental hormones provides the necessary conditions for implantation, normal fetal development and timely delivery. In recent years, the number of studies devoted to the study of the effects of long-term stress on the hormonal reproduction function of the placenta has increased significantly. Undeniable is the fact that there is an imbalance of placental hormones, circulatory disorders in the utero-placental and placental-fetal passages, pathological changes in the placenta [1, 4, 10, 11]. Negative emotions, prolonged stress, fear, depression of pregnancies – displaced persons (PDP) greatly increase the risk of obstetric complications [1, 6] such as placental dysfunction (56.65%), preeclampsia (46.3%), miscarriage (10.9%) and premature (16.6%) pregnancy. Consequently, the psycho-emotional load that causes depression, fatigue, sleep disturbance, and increases anxiety, stimulates an active negative response from the placenta. Newborns born to women who were in a state of chronic stress during pregnancy are more likely to suffer from cardiovascular disease, diabetes mellitus and mental illness more often in childhood and adolescence [11].

For this reason, the issues of studying the psycho-emotional state of pregnant women and its impact on the development of pregnancy in women living in the zone of military aggression has attracted our attention.

The purpose of the study was to determine the changes in the production of placental hormones and stress-associated hormones in pregnant women – displaced persons for further improvement of the antenatal observation program.

MATERIALS AND METHODS OF RESEARCH

In order to achieve this goal, a dynamic prospective clinical and paraclinical examination of 96 pregnant women (main group) – displaced persons in the gestation period after 22 weeks, which were on treatment and gave birth to child in the maternity department of CCH in Rubizhne city and perinatal center of the city of Severodonetsk, Luhansk region. The control group consisted of 39 pregnant women living in territories controlled by Ukraine, randomly selected for prospective study.

All pregnant women underwent a comprehensive clinical-laboratory and special obstetrical examination in full compliance with quality standards of the Order of the Ministry of Health of Ukraine dated July 15, 2011 N 417 [7]. The concentrations of stress-associated (cortisol, progesterone, placental lactogen) of serum hormones were determined by solid-phase enzyme-immunosay using Cortisol-IFA, Prolactin-IFA, Estradiol-IFA test systems.
(production of XEMA LLC, Russia), SteroidIFA-progesterone (LLC Alkor Bio Corporation, Russia),
DRG hPL (DRG, USA) on the Lazurite machine,
software DS Matrix 1.23 (Dynex technologies,
USA) at the Clinical-Diagnostic Center
Pharmbiotest (Rubizhne). The statistical processing
of the obtained results was carried out using
descriptive and variational statistics using Student's
criterion and Fisher's angular transformation method
[8]. The calculation of the results was carried out on
a personal computer using the licensed programs of
Statistica for Windows and Microsoft Excel 7.0.
Differences were determined as significant at
p<0.05.

RESULTS AND DISCUSSION

By age, family and social status preganants of
study groups were homogeneous, in further, this
allowed to judge about differences associated with
the state of the internally displaced person.

According to the results of the conducted studies,
in the second trimester of pregnancy there is no
significant difference in the concentration of estra-
diol (E2) in pregnants of both groups under study.
Thus, the average content of estradiol in pregnant
women in the main group was 15.02±1.2 nmol/l,
control – 14.43±0.88 nmol/l. However, in the dyna-
mics of observation there was a progressive increase
in the concentration of estradiol in the third trimester
and pregnants of both groups had concentration of
E2 which corresponded to the limits of gestational
norm. At the same time in pregnant – displaced
persons the average concentration of E 2 was by
12.28% higher than the similar indicator in the
control group and reached 17.65±0.46 nmol/l
(15.72±0.85 nmol/l – control group, p<0.05). These
changes testified to the tension of the hormone-
producing placental function and were considered by
us as one of the signs of the initial stage of placental
dysfunction (Table 1).

Table 1

| Estradiol, nmol/l | 22 – 23 weeks of gestation | 32 – 33 weeks of gestation |
|------------------|---------------------------|---------------------------|
| Main group, (n=96) | 15.02±1.2                 | 17.65±0.46*               |
| Control group, (n = 39) | 14.43±0.88            | 15.72±0.85                |

Note: * – difference is statistically significant as compared to control group, p<0.05

From the point of view of modern research [5, 9,
14], hyperestrogeny, which leads to the activation of
the hypothalamus-pituitary-adrenal system against
the persistent stress and causes stimulation of
neurons secreting corticotropin-releasing hormone
or norepinephrine has a negative effect on the degree
of anxiety, increases excitement and insomnia,
depens changes in the psycho-emotional state and
its consequences [5, 9, 11, 14].

Progesterone plays one of the main roles in the
physiological course and pregnancy maintenance, as
a protector of pregnancy. It blocks the α-adrenergic
stimulation, reduces the number of receptors to
oxytocin, directly affects the intracellular calcium
concentration, synthesis of prostaglandin F 2α and
receptors to it, enhances b-adrenergic tocolytic effect
in pregnancy. By regulating the activity of the
enzymes D-3b-hydroxysteroid-dehydrogenase and
3b-steroidsulfatase involved in the metabolism of
steroids, progesterone controls the level of estrogen
in myometrium; PG metabolite (5α-pregnenolone),
binding to the GABA receptors affects GABA-ergic
structures of the brain, providing neuroprotective
and anxiolytic effects and determining psycho-
emotional status of the pregnant woman [5, 11]. The
physiological level of PG has a positive effect on the
ultrastructural organization of myometrium, since it
inhibits the development of a coordinated
contraction of the smooth muscle fibrils of the
uterus.

Under the influence of long-term stress in the
body of a pregnant woman, there is a shift in the
losses of steroid hormones precursors towards
biosynthesis of glucocorticoids, which leads to the
development and manifestation of clinical effects of
progesterone deficiency [5, 11].

According to the results of the conducted study,
in pregnant women of both groups the average
progesterone content corresponds to the gestational
norm. At the same time in pregnant of the main
group already in the second trimester of pregnancy there is a significant decrease in the concentration of this hormone to 165.24±14.71 nmol/l (control group – 219.96±16.63 nmol/l; p<0.05), which is by 24.9% lower than in the control group. In the dynamics of pregnancy in women of the main group, the intensity of biosynthesis of progesterone was reduced. This is evidenced by an average index of its concentration, which in the third trimester of pregnancy was 200.91±5.22 nmol/l (control group – 250.55±17.93 nmol/l; p<0.05), corresponding to the lower limit of the average gestation norm, but being lower by 19.81% than in the control group (Table 2).

Table 2

| Progesterone nmol/l |
|---------------------|
| 22-23 weeks of gestation | 32-33 weeks of gestation |
| Main group, (n=96) | 165.24±14.71 * | 200.91±5.22* |
| Control group, (n = 39) | 219.96±16.63 | 250.55±17.93 |

Note. * – difference is statistically significant as compared to control group, p<0.05

Our results may testify to a persistent relative deficiency of this hormone, which plays one of the leading roles in the process of prolongation of pregnancy and birth of a mature newborn. That is why the relative lack of progesterone is one of the diagnostic criteria for the initial stages of placental dysfunction.

A specific marker of placental dysfunction is placental lactogen (PL) which has a purely placental origin [12], therefore, special attention was paid to the study of the dynamics of concentration of this particular hormone. As is known, a developed placenta synthesizes about 1 gram of PL per day, a small part of which enters the system of blood circulation of the fetus. This hormone is essential for the regulation of metabolic processes that occur between the body of the mother and the fetus, which grows intrauterinely. Together with prolactin, PL activates the processes of preparing the mammary glands of the pregnant woman for lactation and also supports the function of the yellow body, providing a progressive synthesis of PG. Thus, insufficient level of PL is considered to be a pathological state in which the supply of important nutrients and oxygen to the fetus is interrupted [12, 13].

In the course of our researches, it was found that the average concentration of PL during pregnancy in the main group corresponds to the limits of gestational norm (4.92±0.56 mg/l – in the second and 5.05±0.33 mg/l – in the third trimester), however, these indicators are by 27.9% and 28.0% lower than in the control group (in the second trimester – 6.82±1.67 mg/l, p<0.05, in the third – 7.01±0.57 mg/l, p<0.05). It is precisely in the pregnants of the main group that there is a significant exhaustion of the compensatory and adaptive possibilities of the placenta with the development of such disorders as intrauterine growth retardation syndrome, extreme early and early preterm labor (Table 3).

Table 3

| Lactogen, mg/l |
|----------------|
| 22 – 23 weeks of gestation | 32 – 33 weeks of gestation |
| Main group, (n=96) | 4.92±0.72 * | 6.82±0.65 |
| Control group, (n = 39) | 5.05±0.33* | 7.01±0.57 |

Note. * – difference is statistically significant as compared to control group, p<0.05
Thus, the obtained data on PL in the examined groups of pregnant women are consistent with the general trend, which also reflects the state of tension of the hormone-producing placenta function, which is attributable to the initial stages of placental dysfunction.

The concentration of cortisol (C) in the blood serum of pregnant women in the main group according to the results of the conducted studies in the dynamics of pregnancy at 22-23 weeks was 229.46±15.93 ng/ml, which is by 5.5% higher than the upper limit of the physiological norm and almost by 3.4% exceeds the similar finding in the control group (160.0±14.99 ng/ml; p<0.05). According to I.A. Zhabchenko and co-authors (2016) [2], with the increase in the concentration of cortisol in the blood plasma by three times, its concentration in myometrium increases by nine times, therefore most of the complications during pregnancy against chronic stress should be associated with disorder in production of this hormone. Concentration of C in the blood serum of women in the main group during pregnancy progressively increased and at 32-33 weeks it was 233.19±7.26 ng/ml, which exceeds the upper limit of the physiological norm by 7.3% and by 17.9% – average gestation finding in the control group (197.86±612.14 ng/ml; p<0.05) (Table 4).

| Average concentrations of cortisol in the serum of women of the main and control group in the 2nd and 3rd trimester (M±m) |
|---------------------------------------------------------------|
| **Cortisol, ng/ml**                                            |
| **22 – 23 weeks of gestation**                                |
| **Main group, (n=96)** 229.46±15.93 *                        |
| **Control group, (n = 39) 160.0±14.99**                      |
| **32 – 33 weeks of gestation**                                |
| **Main group, (n=96) 233.19±7.26 *                           |
| **Control group, (n = 39) 197.86±12.14**                     |

* – difference is statistically significant as compared to control group, p<0.05

Thus, in pregnant women of the main group gestation course occurs against significant increase in the concentration of C, which is the biochemical basis of persistent stress in women of this group. Increasing concentration of precisely C triggers the mechanism of functional changes in the system of the hippocampus-hypothalamus-pituitary-adrenal glands, which results in the increase in blood pressure, the risk of development of insulin resistance in the fetus. According to S.I. Zhuk and co-authors (2017) [3], there is a system of "fetal programming" – manifestation of disorders that occurred during intrauterine state of the fetus already in adult age, because high concentration of C contributes to the change in the number of steroid receptors in the neuroendocrine system of the unborn child, resulting in increased biosynthesis of the hormone to the action of any causative agent from the outside in the future. Thus, a "false circle" is formed, which is the cause of a sustained increase in basal and stress-induced glucocorticoid content in the future in th adult person. The effect of glucocorticoids on the fetus changes the expression of genes that are responsible for the metabolism of glucose and lipids in the liver, which in adult age increases the possibility of metabolic disorders in the form of hyperlipidemia, glucose tolerance and hyperglycemia [3, 11].

At the same time, prolactin (PRL) concentration increases in the majority of pregnant women.

| Average concentrations of prolactin in the serum of women of the main and control group in the 2nd and 3rd trimester (M±m) |
|---------------------------------------------------------------|
| **Prolactin ng/ml**                                            |
| **22 – 23 weeks of gestation**                                |
| **Main group, (n=96) 326.31±11.29 *                          |
| **Control group, (n = 39) 271.16±7.13**                      |
| **32 – 33 weeks of gestation**                                |
| **Main group, (n=96) 400.42±5.35*                            |
| **Control group, (n = 39) 362.28±6.28**                      |

* – difference is statistically significant as compared to control group, p<0.05
Already in the second trimester, the content of this hormone exceeded the upper limit of gestational norm by 13.3% (326.31±11.29 ng/ml), and compared with the index of this hormone in the pregnant of control group (271.16±7.13 ng/ml, p<0.05) – by 20.3%. In the third trimester, the concentration of PRL in both groups was within the normal range, but in the main group this figure was higher by 10.5% (400.42±5.35 ng/ml and 362.28±6.28 ng/ml; p<0.05 respectively (Table 5).

Thus, the presence of persistent long-term stress, increased concentrations of PRL and C in pregnant women – IDP is obvious. At the same time, the role of hyperprolactinemia in the pathogenesis of the deficiency of the yellow body in the early stages of gestation and threat of abortion associated with it is assured. Thus, hyperprolactinemia also contributes to the progression of placental dysfunction, which is accompanied by an imbalance of placental hormones, circulatory disorders in the utero-placental and placental-fetal cortex, pathological changes in the placenta [4, 10] with the development of placenta-associated gestational complications.

CONCLUSION

Thus, for pregnant women from a group of displaced persons the following is characteristic:

1. Placental dysfunction with the disturbance of balance of the main placental hormones: increased estradiol concentration and the relative reduction of progesterone and placental lactogen, shift of estrogen-progesterone equilibrium towards relative hyperestrogenemia.

2. Increased concentration of stress-associated hormones – cortisol and prolactin.

3. The revealed hormonal-metabolic disorders in pregnant women – internally displaced persons are biochemical markers of placental dysfunction, which testify to the expediency of a comprehensive preconceptional preparation with the involvement of a psychologist and the inclusion of preventive measures in the form of long-term progesterone support during pregnancy in the program of antenatal observation of such women.

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