GESTOSIS PREDICTION AMONG PATIENTS WITH HYPERANDROGENISM RECEIVING GLUCOCORTICOIDS

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ABSTRACT

The article examines the impact of glucocorticoids in patients with hyperandrogenism on Doppler indices of blood flow in the uterine and spiral arteries in term of 13-14 weeks of pregnancy and assessment of the importance of this method for gestosis predicting.

It has been found that in a group of pregnant women receiving glucocorticoids there is significant ($p < 0.05$) increase compared to the reference group and the control group of Doppler vascular resistance index in the uterine and spiral arteries. In our study, a serious complication as preeclampsia was met in 20 (51%) of the women in the group of patients with hyperandrogenism treated with glucocorticoids, which was significantly more often ($p < 0.05$), than 3 in the comparison group (18.75%) and control group - 3 (15%).

Keywords: hyperandrogenism, glucocorticoids, gestosis.

The main factor of the pathogenesis of gestosis and placental insufficiency is a lack or incomplete penetration of the trophoblast to the spiral arteries, which leads to a reduction of their lumen and subsequent placental ischemia. Modified placenta can provoke the formation of one or more factors that deplete the vascular cells, causing dysfunction of many organ systems [1]. The key point is forecasting in the diagnosis of pathological process. Over the past two decades, in literature you can find links to more than 100 different clinical, biochemical and biophysical research to predict the development of preeclampsia [2]. At the present stage, there is no ideal predictive test that meets all the necessary criteria. First, the lack of parity and family history are represented by two major predictive factors [3]. Ultrasound examination of the method of Doppler spiral arteries at 13-16 weeks of pregnancy may be helpful in the diagnosis of disruption of the normal process of trophoblast invasion, a prognostic test for determining the risk for complications such as preeclampsia [4]

The **aim** of our study was to evaluate the effect of steroid treatment among patients with hyperandrogenism on Doppler indices of blood flow in the uterine and spiral arteries in term of 13-14 weeks of pregnancy and to estimate the value of this method for the prediction of gestosis.

We conducted a prospective survey of the dynamics of 75 pregnant women from the first trimester of pregnancy with an analysis of the course and outcomes of pregnancy and childbirth. All patients were divided into 3 groups. The first group, the main group consisted of 39 women with various forms of hyperandrogenism which were receiving glucocorticoids (12 patients - metipred 1-4mg/a twenty-four hours' dose, 27 patients received dexamethasone 0, 5 ± 1mg/twenty-four hours) during pregnancy to prevent miscarriage. Among these, 19 patients had a mild form of adrenogenital syndrome, 2 with ovarian form, and 18 with mixed hyperandrogenism. The comparison group consisted of 16 patients with clinical and laboratory signs of hyperandrogenism (10 of them - with CAH , 6 - with mixed hyperandrogenism) who were not receiving glucocorticoids during pregnancy . The third group, the control group consisted of 20 healthy patients without somatic hyperandrogenism (dehydroepiandrosterone in the I trimester of 1,14-4,6 mg / ml , 17 oxyprogesteron 2-4,1 ng / ml, testoron 0,11-0,78 ng / ml) Diagnosis of hyperandrogenism in addition to the visible manifestations of masculinization installed in pregnancy, in the I trimester , based on the increased level of 17 oxyprogesterone , DHEA , free testosterone . Hormonal study was carried out using ELISA photometric analyzer («Multiscan", «Labisistems"). The diagnosis of adrenal (non-classical forms of congenital adrenal hyperplasia) was based on the definition of high basal level of 17 - oxyiprogesterone (17 SNPs) , dehydroepiandrosterone (DHEA -S) in the first trimester of pregnancy. In patients of the main group 5 and 7 patients group comparison reference values detected excess DHEA -S (4,78 ± 0,22 mg / ml) at 14 and 9 respectively increased 17 SNPs (7,07 ± 0,19 ng / ml). Molecular genetic testing is not performed. Clinical signs of androgenization

and hormonal survey data (basal level) were the basis for the appointment of glucocorticoids. It was found that 18 patients of the main group had the increased 17 SNPs with simultaneously increasing testosterone (1, 46 ± 0, 19 ng / ml), while 7 of these patients had elevated cortisol (689 ± 0, 12 ng / l). This status is assessed by doctors as prenatal hyperandrogenism of mixed origin (recommended steroid treatment under the control of hormones up to 32-34 weeks), including patients with hypercortisolemia. In the analysis of somatic history of women surveyed revealed that in the first, the study group was found 18 (46.1 %) of nosology. In the comparison group extragenital pathology was observed in 8 (50 %) cases (the 11 women in the first group and 3 in the second there was a combination of nosologies (obesity and hypertension). Moreover, all patients, both in the core and in the comparison group had ovarian and mixed form of hyperandrogenism. The greatest significance of this aspect is to identify the connection of hyperandrogenism (as a symptom of metabolic syndrome and PCOS.) In the main group with a large base in retrospect (since before or during pregnancy, the syndrome was not identified), we can refer 11 (28.2%) patients (all 11 patients increased 17ONP and testosterone) among which the combination of the following symptoms was observed:

- abdominally - visceral type of obesity (BMI >27 kg / m)
- hypertension (hypertension , 2 cases of hypertensive type NCD 9 cases
- hyperandrogenism.

In the comparison group metabolic syndrome occurred in 3 (10%) women. In the control group there were no such patients.

Aggravated obstetric anamnesis among patients of the main group was observed among 8 women (20.5%), including fetal loss syndrome among 6, one or more spontaneous abortions - 4 cases, non-developing pregnancy, late miscarriage (fetal death), ectopic pregnancy had 1 woman; severe preeclampsia in the first birth had 1 woman. The frequency of aggravated anamnesis among patients of the second group was 25%, 4 cases, including the case of developing pregnancy -2, 1 case of late miscarriage (fetal death), 1 case of premature birth at 32 weeks, so the two groups are comparable on this indicator. In the control group, the frequency of aggravated anamnesis among patients were significantly lower ($p < 0.05$) was 2 (10%) cases.

In our study, the main method of Doppler prediction of preeclampsia was carried out using the machine of the expert class «Medison-Acuvix XQ», equipped with a block of color Doppler, power Doppler and pulsed. Doppler sonography study of blood flow velocity curves in both uterine arteries in the umbilical artery, as well as in the spiral arteries by the developed technique in term of 13-14 weeks was performed (A.N. Strizhakov et al. , 1998).

The study was performed in obstetric program of devices, a frequency filter was set at 50 Hz, the Doppler angle of no more than 60, volume control completely blocked vessels' gap. To assess the CSC following indicators of vascular resistance were calculated: resistance index (MI), systolic and diastolic ratio (S / D). The study was combined with ultrasound in screening time (13-14 weeks).

The obtained data were processed by the method of variation statistics using Microsoft Excel, with the calculation of the arithmetic mean deviation, standard deviation, with the following definition is similar to the characteristics of different groups with the calculation of Student's t test. Statistical significance was considered proven if possible errors less than 5% or P <0, 05.

The received data is represented in the table.

Table 1.

Indicators of uterus-placental blood flow in the period of 13-14 weeks pregnancy

	Uterine arteries		Spiral arteries	
Group	IR	SDR	IR	SDR

Main n=39	0,73±0,04	3,08±0,14	0,63±0,03	2,22±0.23
comparison group n=16	0,58±0,08	2,32±0,32	0,50±0,01	1,77±0,17
Control n=20	0,55±0,04	2,14±0,11	0,48±0,05	1,69±0,21

Thus, we see in the group of pregnant women treated with glucocorticoids significant ($p< 0.05$) increase of vascular resistance in the uterine and spiral arteries compared to the comparison group and the control group of Doppler indices. We can assume that receiving glucocorticoids , contributing to endothelial dysfunction, leading to disturbances in the hemostatic system , suppression of fibrinolysis [5 , 8] , leads to disruption of trophoblast invasion and placentation , which is reflected in the indices that we have found in increasing vascular resistance. According to data of Musaeva Z.M., Pitskhelauri E.G. (2000) diagnostic criteria for pre-clinical stage of preeclampsia LMS in the uterine arteries of more than 2.4, more than 1.85 in the spiral may be considered. Patients who are at risk, prevention of preeclampsia was conducted, beginning with the period of 16 weeks (dipyridamole 25 mg 3 times a day) due to the continuing glucocorticoid therapy.

In our study, a serious complication as preeclampsia was found among 20 (51%) of the women in the group of patients with hyperandrogenism treated with glucocorticoids , and only 3 patients (18.75 %) of pregnancies complicated by mild preeclampsia in the comparison group ($p < 0.005$). The Indicators of the second group were compared with a control group (healthy pregnant women); there were 3 (15 %) cases of mild gestosis.

The mean dose of glucocorticoid medication among patients of the main group with preeclampsia counting on dexamethasone was 0,89 ± 0,12 mg / day, which was significantly higher ($p < 0.005$) than among patients without clinical preeclampsia - 0,41 ± 0,24 mg / day. The duration of receiving this medication during pregnancy among women with preeclampsia was on average 30, 4 ± 1, 24 a week, which was significantly longer than among patients of the main group without preeclampsia (mean 24, 4 ± 1, 6 weeks).

Thus, we see that with the increase in the number of glucocorticoid medication taken during pregnancy the frequency of pregnancy complications such as preeclampsia increases.

The increase in the severity of preeclampsia on the background of the therapy was noted in 9 cases among patients of the main group. The severity of preeclampsia was assessed by a scale recommended by the Health Ministry. Preeclampsia moderate severity at the time of delivery (9-11 on a scale of Gojko - Savelevoj) had 5 (12%) of women, severe preeclampsia, eclampsia - 4 (10 %) patients of the main group. Clinical diagnosis of pre-eclampsia were: increase in diastolic blood pressure of more than -110 mm. Hg (all 4-100 %), edema (from 2-50 %), proteinuria in a daily sample of more than 3 g / l (average 3, 11 ± 0, 6), all pregnant women complained of a headache and the presence of " grid before eyes ", nasal congestion, in one case fibrillary twitching of the facial muscles was occurred. We see that 8 of 9 patients with medium and severe preeclampsia are patients with mixed hyperandrogenism, who had an increase of 17ONP and testosterone, all 8 women had hypercortisolemia (average 711 ± 15, 2 ng / L), which can be considered as an analogue of insulin resistance and hyperinsulinemia . All 8 patients had visceral - type abdominally obese (BMI> 27 kg / m), hypertension (1 case of hypertension, hypertensive type NDCs on 7 cases). These were patients with the metabolic syndrome.

This fact is not surprising because endotheliopathy plays a major role in the pathogenesis of the metabolic syndrome and preeclampsia [7]. Then what is the role of glucocorticoids which they receive?

The discovery of elevated levels of androgens among our patients in the 1st trimester (17ONP and testesterona) was the reason for the appointment of such medication as dexamethasone

or metipred to correct hyperandrogenism (the data of 8 patients who received them until 34-35 weeks). Among these patients there was a hyper-reactivity of the hypothalamic- pituitary - adrenal system. Small already existing excess of cortisol in combination with exogenously administered medication of long action glucocorticoid (dexamethasone), which is not amenable to inactivate the enzyme systems of placenta, reduces insulin sensitivity, contributes to the development of insulin resistance with compensatory hyperinsulinaemia, and of progression of endothelial dysfunction and as a consequence of this is the development of preeclampsia, with its rapid progression, despite treatment.

From our research, we conclude:

1. Glucocorticoid treatment, which increases endothelial dysfunction in the first trimester, when there are processes of implantation, trophoblast invasion, causes changes in placentation which we have discovered during Doppler.
2. Pathogenetically unreasonable, is the prescription of this medication to patients with ovarian and mixed form of hyperandrogenism, patients with metabolic syndrome and existing dysfunction of gipatolamo-pituitary-adrenal system. A prescription of glucocorticoid medication promotes the progression of existing endothelial dysfunction, contributes to the development of moderate and severe forms of preeclampsia.
3. From the study we can see that with the increase in the number of glucocorticoid medication received during pregnancy increases the frequency of pregnancy complications such as preeclampsia.

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