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THE FEATURES OF HEMODYNAMIC PREGNANCY SUPPORT WITN GESTATIONAL ENDOTHELIOPATHY

Topic: Pre-eclampsia and intrauterine growth-restriction (IUGR)

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Introduction. The preeclampsia is a multisystemic pregnancy-specific disease. The incidences of preeclampsia (PE) are 5 to 14% of all pregnancies in the world, contributes to 18% of preterm birth, and 10%-27% of global maternal deaths worldwide, while severe PE can develop to about 25% of all cases of preeclampsia. The formally defined as new-onset hypertension with proteinuria or other organ damage occurring after 20 weeks of gestation, PE characterized by endothelial dysfunctioncan clinically manifest anytime thereafter, including into the post-partum period. Although the cause of this pregnancy-specific syndrome is unclear, accumulating evidence suggests that preeclampsia results from an imbalance between pro- and anti-angiogenic factors, which damage maternal vascular endothelium, leading to the clinical manifestations of this condition.

In early gestational age, the decidua has been extensively studied to define the spiral artery remodeling process that occurs during pregnancy. The remodeling results from a complex interaction between maternal decidual immune cells in the uterine wall and invasive trophoblasts. During remodeling the arterial muscular layer is replaced by fibrinoid material, and the arterial diameter increases 4–12-fold. The process of optimal trophoblast invasion is often defective in preeclampsia, particularly in early-onset preeclampsia, affecting the endothelium (gestational endotheliopathy) but not the interstitial invasion pathway; the remodeling of myometrial spiral artery segments is particularly affected. However, defective remodeling is also seen in other cases of

perinatal pathology and even rarely in normal pregnancy. The resulting abnormal uteroplacental flow is associated with placental oxidative stress, probably from ischemia reperfusion injury of the placenta. It is not known why some woman with gestational endotheliopathy develop preeclampsia, while others do not.

It is important to understand that all organism mechanisms providing pregnancy depend, foremost, on the hemodynamic system and the priority role of the perfusion complex (volume–tube–pump–pressure–blood flow) and pumping function of heart. More research assures that preeclampsia is examined not so much as the first event in subsequent development for women with cardiovascular diseases, but rather as a special circulatory state due to not insufficient, in our view, but tense adaptation of the cardio-vascular system (CVS) in women, as straight-walking creatures, in pregnancy. However, a faithful parcel in determination of relations reason-result determines the necessity of establishment of certain factor or terms, according to which such adaptations show up in the CVS in pregnancy, and also determination of hemodynamic structure of perfusion mechanisms lying in and defining the orientation of this adaptation at physiological and pathological pregnancy. Such synergy substantially impacts tension of adjusting of blood circulation on a gravitational factor, especially in the upright position. In turn, antigravity tension of the CVS affects the blood circulation of pregnant women, which is critical for maintenance and development of fetoplacental circulation of blood. The real influence of formed biophysical terms related to pregnancy shows up from the second half of pregnancy, on circulation of blood and in the lying position.

So far, no recommended test exists that can predict the future onset of PE early in pregnancy. The previous research suggest that antigravity tension of the CVS is a circulatory basis for both early and late preeclampsia. It is thus necessary to mean that blood pressure (BP) in pregnant, to that attention is brought over its determination of the state of PE, is the external display (a result, but not reason) of adaptation changes of all difficult complex of maternal circulation of blood, especially its basic mechanisms of perfusion, in the hemodynamic fetoplacental complex and, actually, maternal organism of. Orthostatic proteinuria, which in preeclampsia is associated with arterial high BP, reflects tension of kidney link in the adaptation of the CVS to the

gravitational factor of circulation of blood and out of pregnancy. The prediction of preeclampsia early in gestation, before symptoms present, could guide the prophylactic use of potential therapeutic agents.

The aim of the study was an *anthropophysiological analysis of the circulatory components of hemodynamic gestational support in physiological pregnancy (FP) and women with gestational endotheliopathy who had high risk of PE and their association with the state of the pumping function of the heart.*

Material and Methods. The study was performed at the National Pirogov Memorial Medical University, Vinnytsya, Ukraine, under budget grant No. 0121 U109141. Observational clinical studies were undertaken on 114 women with FP and 131 pregnant women with gestational endotheliopathy (GEP). The former group consisted of 23 women in their first trimester, 38 women in their second trimester, and 55 women in their third trimester, whereas the latter group consisted of 20 women in their first trimester, 36 women in their second trimester, and 75 women in their third trimester. A control group was formed by 115 healthy nonpregnant women. General age of pregnant women was 17–36 years (n = 245); only four pregnant women were older than 30 years.

We enrolled pregnant women with GEP, who were diagnosed when microalbuminuria was more than 5.0 mg/mmol (screening test) and endothelium-dependent vasodilation was less than 10% (approving test).

Multicentral description of “hemodynamic model” of the examined conditions was made basis on anthropophysiological research of the circulatory state of the CVS, using the diagnostic system ANTROPOS-CAVASCREEN, which is an innovative diagnostic complex for analyzing the performance of various blood circulation sections using noninvasive methods (thoracic and regional tetrapolar rheography, electrocardiography, BP measurement).

With the examined modes for BP was analyzed expression of circulatory syndromes of transitory heart failure (HF) at them hemodynamically identified by diagnostic algorithm worked out by us, as a system estimation of pumping function of heart (PFH) in the circulatory state of the CVS. PFH additionally was estimated by trimester measuring of cardiac output (CO, ml) and cardiac index on body weight (CI, ml/kg)

separately in standing and lying positions. By antropophysiological ratio of CO upright/lying (APR, %) typological description of dynamic organization of the circulatory state of the CVS was made. The last was presented by three types of blood circulation: type I or hypokinetic state, with the decrease of BP in standing position (93% and less) comparing to its size in a prone position; type II or eukinetic state, with BP of 94-106% from standing to lying position; and type III or hyperkinetic state, with increase of BP up to 107% or more in the upright position.

For the integral estimation of the analyzed condition of the CVS we additionally used system characteristics, including syndrome of greater biological age (aging, age-related depreciation) and syndrome of hemodynamic risk on the index of hemodynamic non-optimality (IHU > 30%), as well as regional and system estimation of syndrome of resistance (vasoconstrictions) of the arterial vessels of the head, lungs, stomach, pelvis, femur, and calf, and increases of the systolic post-loading (post+) on the left (LV) and right (RV) ventricles of the heart.

The data that support the findings of this study are available from the author on reasonable request. Differences between categorical variables were determined by the $\chi 2$ test with Yates continuity correction or the Fisher exact test for small samples (or the Mantel-Haenszel $\chi 2$ test with linear tendency for variables with >2 categories). Differences among ≥3 continuous variables were determined by 1-way ANOVA followed by post hoc procedures (Scheffe test) or by the Kruskal-Wallis 1-way test followed by the Mann-Whitney U test for non-normally distributed variables of signs and rule of specificity of predominating of bigger part of a selection or compared sub-groups (part) in selections of “control-pregnant” and “physiological pregnancy vs gestational endotheliopathy” with the accepted level of probability no less than 95%.

Results. It is necessary to mean that in position upright taking into account expression of the hypertensive state totally with a normative increase of MAP the stake of the states of CVS of pressor orientation for women arrived at 90–92%, demonstrating actuality of the tense of pressure adjustment in adaptation of CVS to the gravitational factor of circulation of blood for a human as straight-walking creature. There was a background to examine it as physiological basis of forming of the hypertensive condition, including, for pregnant women.

Our research for FP showed clear reduction of the hypertensive states to their absence in the lying position, and it was especially shown in the upright position up to the third trimester. Such dynamics at FP demonstrated optimization of the circulatory state of the CVS, at least on the mode of BP especially it was important for maturing of pregnancy in terms of straight-walking (sitting, upright, at walking). Clear growth of expression of hypotonic states was thus marked in the lying position, with 10% for women from control group to the first (39%) and the second trimesters - 32% ($P < 0.01$). The results of investigations also showed less expressed marked orientation in distribution of the modes for BP in the upright position determined at GEP. The hypertensive state was absent only in the first trimester. It appears in the second and third trimesters, though at lower levels (3–5%; $P \leq 0.05$) compared to nonpregnant women (10%). For GEP, the hypertensive states were presented in the lying position during all three trimesters, increasing three times (from 5% for nonpregnant women to 15% in GEP; $P < 0.05$).

It should be noted, that according to optimization of the state of the CVS on the mode of BP for pregnant raising of systolic function of heart, especially clearly expressed at physiological pregnancy, was marked. MVB (minute volume of blood), APR, and CI are homogeneous hemodynamic indexes and therefore they were taken for systole descriptions (parameters) of the hemodynamic providing of pregnancy on the PFH.

The optimization of the circulatory state of the CVS during pregnancy accompanied by the clear increase of systolic descriptions on the PFH and shows up on all three trimesters, especially at FP. On MVB such orientation simply shows up during all three trimesters as at FP—lying and upright totally for 24 descriptions from 24 ($P < 0.01$) and at GEP—also for 18 from 24 ($P < 0.05$).

The orientation in the MVB unambiguously manifested itself during all three trimesters as with FP—lying and standing in total according to 24 characteristics out of 24 ($P < 0.01$), while with GEP —by 18 out of 24 ($P < 0.05$). If the manifestation of type III under hypotonic, normotonic, and hypertonic regimes in blood pressure was 8, 12, and 6%, respectively, then in case of FP it was 21, 36, and 50%, respectively (for all P positions <0.01) and for GEP, 48, 66, and 76% (for all positions $P < 0.01$). For gestational endotheliopathy in all modes of blood pressure, the representativeness of

the hyperkinetic state in the PFH standing (type III) was significantly higher compared to FP ($P < 0.01$). According to it, the marker of tension of hemodynamic alteration was a transition on the MVB to the hyperkinetic state in position from standing to lying—to type III of dynamic organization of the circulator state of CVS and system hyperresistance of arterial vessels, and by the predictor of insufficiency of adaptation of CVS was displayed mostly in the position upright by perfusion type, combining with circulatory syndromes limiting adaptive possibilities of arterial circulation.

Unlike position of body lying—upright CI increases for 10 from 12 characteristics (totally for three trimesters) at FP ($P < 0.05$), while at GEP—only for 7 from 12 (P>). At this CI at GEP in position upright was for less comparing to FP—for 9 descriptions from 12 ($P < 0.05$). Should be noted clear change during pregnancy of correlation MVB upright/lying (in %) on the index of APF, which is the typological reflection of dynamic organization of the circulator state of CVS and demonstrated at pregnancy in position upright hyperkinetic alteration of PFH and circulatory state of the CVS. It should be noted that all trimesters did not have any fundamental distinctions of expression of HF. An exception was made only by the hypertensive mode, which made expression of HF (50%) in II trimester, comparing to III trimester (44%).

Another feature in position upright and lying of the circulatory state of CVS on the analyzable “general” modes of BP was differentiation of display of tHF in a right and left heart, and also on basic circulatory syndromes—on the syndrome of decline of arterial perfusion and syndrome of venous stagnation and insufficiency.

Conclusions.

1. For hemodynamic providing of pregnancy such system of vasoconstriction has a critical value, especially for circulatory blocks, directly responsible for hemodynamic providing of fetoplacental link—abdominal and pelvic circulation of blood. Placenta, volume of amniotic fluid, and self-weight of fetus in max decrease influence of gravitational (hydrostatical) pressure at straight-walking (sitting, upright, walking). However direct dependence of the hemodynamic providing of fetoplacental complex from maternal circulation of blood is saved, both from regional, especially abdominal and pelvic and the circulatory state of CVS in general and its central link—pumping function of heart.

2. Expression of autonomic “slipping out” of arterial vessels of abdominal and pelvic circulation from under system vasoconstriction, probably because of endothelium-depending humoral mechanism, determine phenomenon of optimization of the circulatory state of CVS at the beginning of pregnancy, especially expressed at FP, and inhibition of pathological changes.

3. Estimating the circulatory state of CVS for pregnant, and nonpregnant, necessary to be oriented not on the mode of BP, but on condition of basic perfusion mechanisms a “volume of blood—pumping function of heart—vascular capacity—blood stream” and regulators of autonomic regional blood flow—endothelial function providing distribution of peripheral circulation of blood, and it explained that gestational endotheliopathy is the prominent predictor component of disorder hemodynamics supply pregnancy and development of preeclampsia.

4. In fact, the state of perfusion mechanisms that form the basis of hemodynamic support of any somatic condition and especially pregnancy, taking into account the formation of a feto-placental complex «above organism» and necessity of hemodynamic adaptation of CVS of pregnant as straight-walking creature, to formed exceptional organism situation not only in gestational feature, but also in aspect of adaptation.

5. The marker of tension of hemodynamic alteration was a transition to the hyperkinetic state in position from standing to lying - to III type of dynamic organization of the circulator state of CVS and system hyperresistance of arterial vessels, and by the predictor of insufficiency of adaptation of CVS was displayed mostly in the position upright by perfusion type, combining with circulatory syndromes limiting adaptive possibilities of arterial circulation.