9. THE MODERN MATERNAL HEMODYNAMIC FEATURES FOR PREDICTION OF PREECLAMPSIA

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Despite a significant volume of literature regarding placental dysfunction in PE, data regarding the cardiac changes associated with PE are more scant, and also more controversial. The conventional belief was that early PE is associated with reduced cardiac output (CO) and increased total vascular resistance (VR), with maternal cardiac function succumbing early in the disease process. With regard to late PE, the original data implied that this was a condition of raised CO and reduced total VR, however this model has not been reported consistently. The majority of PE is late, and has classically been described as “maternal” PE. By and large, maternal PE remains unexplained. We were proposed that whilst intrinsic placental dysfunction and the mal-adaptation of the maternal cardiovascular system leads to early-onset PE, late PE is associated with an acquired placental dysfunction as a result of the maternal heart not being able to meet the demands of the placenta.
The fundamental difference between man, as an upright creature, in the postural form of adaptation to earthly gravity from animals with pronograde postural statics and quadrupedal locomotion, and hence in the exceptional relevance for his CVS of the gravitational (hydrostatic) factor of blood circulation. And not just in the dynamic organization of the circulatory state of the cardiovascular system, but in the hemodynamic support of pregnancy and human life activity as a whole in the characteristic specific conditions of upright.
Objective: To evaluate the predictive values of the circulatory syndromes in preclinical possibilities development of PE.
Investigations of the circulatory syndromes of CVS and hemodynamic supporting of pregnancy was carried out in the first trimester in 114 women with physiological pregnancy (PP) and in 132 pregnant women with GE who had preeclamplasia in the II and III trimesters. The control group consisted of 137 healthy non-pregnant women. The comprehensive registration of main parameters of the central and peripheral hemodynamics was conducted through the standard method of tetrapolar thoracic and regional rheography in the condition of active orthostatics (immediately in standing position) and clinical repose (15-20 min after translocation pregnant women in lying position) (Fig.1). We determined of circulatory syndromes by correlation of minute volume of blood (MVB) while standing/lying – I type (hypokinetic condition) and III type (hyperkinetic condition) of hemodynamics. The hemodynamic risk was determined in accordance with the index of hemodynamic nonoptimality (IHN).
Women who had GE, there was a significant ($p < 0.01$) decrease in the proportion of optimal states with type I and a significant ($p < 0.01$) increase in states with type III of the circulatory state of the CVS. This type was associated with a suboptimal and strained state of hemodynamics in the regime of antigravitational supply of blood circulation in the basic postural conditions of a person's life activity creature (standing, sitting, walking) and pregnant with minimizing restorative capacities in a lying position. In women with PP in the I trimester according to the integral criteria CAS-2,3 and IHN were a clear trend in optimization of circulatory support of pregnancy (CSP) which was expressed in a decrease in the manifestation of circulatory syndromes of hemodynamic risk.
In pregnant women with GE, there were an obvious prevalence of circulatory unbalanced states. In the first trimester in total for CAS-2,3 and IHN nevertheless, a significantly significant (specific) group among the circulatory units that did not differ from the state of PP and with negative dynamics was not determined, then already in II and especially III trimesters CSP significantly ($p < 0.01$), the conditions with a negative orientation were prevailed. In general, CSP with GE was characterized by a negative dynamics in comparison with physiological pregnancy. Not only negative dynamics was observed in the abdominal circulation, but in the I and II trimesters the proportion of pregnant women with IHN > 30% with GE were significantly more prevalent in our investigation ($p < 0.05$).
Comparison of the circulatory condition of the CVS by differences in the manifestation of the hyperreflectivity of arterial vessels between the PP and GE (Fig. 1) in the standing position were demonstrated the adaptive orientation, which is expressed in PP in a significantly lower manifestation of hyperresistive arterial blood vessel syndromes (green). Conversely, non-adaptive directionality in GE was reflected in the systemic enhancement of hyperresistance in comparison with PP (red color).

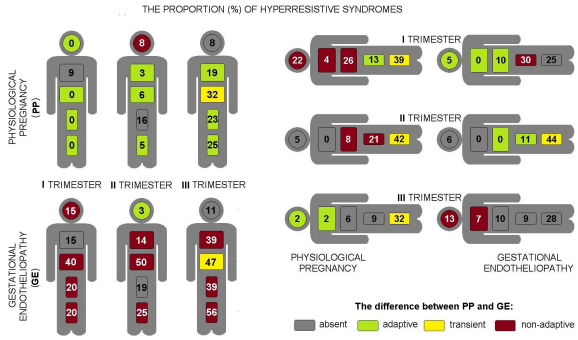

Figure 1. The comparative anthropophysiological characteristics of the hemodynamic model of the circulatory condition of the CVS

According to our investigations the optimization of hemodynamical supporting in PP was mechanism of vasodilator "slippage" of arterial vessels from the systemic vasoconstriction as the hemodynamic equivalent of endothelial activity. The predictors of PE in pregnant women were hyperkinetic type of circulation (by an anthropophysiological ratio of standing/lying), integral indicators of functional depreciation of the circulatory syndromes of CVS - hemodynamic risk (by IHN> 30%), circulatory syndromes of arterial or venous blood insufficiency in abdominal and pelvic regions.
Conclusions. Preeclampsia as a disease entity not solely due to the placenta, but as a cardiovascular-placental syndrome. Our results obtained that the predictors of PE were hemodynamic syndromes of insufficiency and circulatory limitation. During physiological pregnancy, there was a pronounced manifestation of the circulatory phenomenon of " slippage" of the abdominal vessels and an increase in the autoregulatory component of the hemodynamic support of the feto-placental complex, with gestational endotheliopathy - a significant limitation of CAS.

(**Section HDP-Preeclampsia**)

10. THE NEW METHODOLOGY FOR APPRAISAL OF MATERNAL HEMODYNAMICS

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Hypertensive disorders of pregnancy (HDP) remain one of the leading causes of maternal and perinatal morbidity and mortality worldwide. Pregnant women with HDP, regardless of the presence of traditional cardiovascular risk factors, have an increased risk of cardiovascular disease in the future after pregnancy. Gestational endotheliopathy (GE) involves insufficient generation of molecules, such as nitric oxide (NO), which is one of the main vasoactive mediators of the endothelium. In recent years, various methods of preventing GE have been developed and continue to be improved, but the problem is far from being solved. Preventive diagnostic procedures of maternal hemodynamics, especially before the clinical manifestation of perinatal pathology, can significantly improve perinatal outcomes endotheliotropic genesis. Multicentral description of "hemodynamic model" of the examined conditions (not pregnant and pregnant women) was made basis on antropophysiological 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 (thoracal and regional tetrapolar rheography, electrocardiography, BP measurement, electrometrial features of skin).

According to basic criteria and syndromal analysis of multicentral complex of hemodynamic characteristics of the "hemodynamic model" of providing of pregnancy was held special antropophysiological analysis of showing up (part in % on a selection) of the different modes is conducted on middle blood pressure (BPm) — hypo-, normo- and hypertensive on positions of body upright and lying.

Our results clearly demonstrate the value of the state of heart in this system maternal hemodynamic adjusting to pressor orientation, especially in position upright. The pregnant women those who have hemodynamically identified as nonoptimal hemodynamic supply of pregnancy, as a rule, perfusion type, in position upright marked more expressed (red blocks), as compared to the states without vasoconstriction (green blocks). By grey color marked blocks of circulation of blood, on which distinctions are absent. Optimization of the circulatory state of CVS during pregnancy by the regime of blood pressure, especially with normal pregnancy, was accompanied by a clear overall increase in systolic characteristics of the maternal hemodynamics. This orientation in the cardiac minute volume (CMV, ml) unambiguously manifested itself during all three trimesters as with normal pregnancy—lying and standing in total according to 24 characteristics out of 24 ($P < 0.01$), while with gestational endotheliopathy—by 18 out of 24 ($P < 0.05$).

Conclusion: For estimating the circulatory state of maternal hemodynamic 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 in lying and upright positions.

(**Section Methodology**)

11. THE FEATURES OF THE PREVENTION OF PREECLAMPSIA IN PREGNANT WOMEN WITH GESTATIONAL ENDOTHELIOPATHY IN THE FIRST TRIMESTER

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Low-dose aspirin (ASA) has been used during pregnancy, most commonly to prevent or delay the onset of preeclampsia. The Ukrainian National clinical guideline (2022) recommending daily 100-150mg from 12 weeks of gestation and continued until 35-36 weeks for women with highest risk development of preeclampsia. Most of the entheliotropic drugs are either not recommended during pregnancy due to a lack of reliable data about the absence of teratogenic and embryotoxic effects (resveratrol, meldonium), or are only undergoing clinical trials (statins proton pump inhibitors, metformin), or raise concerns about a possible link between prenatal exposure and neonatal death from pulmonary hypertension (sildenafil). In addition, all of the above drugs have a stimulating effect on the endothelium, which leads to the production of NO, but also to endothelial depletion. Therefore, it is very important to use a NO precursor from which the endothelium can synthesize the necessary substances. Thus, there is a need for a class of endotheliotropic agents that not only stimulate the endothelium to produce NO but also supply the substrate. The only substance that is a substrate for NO synthesis is L-arginine.

The objective: to evaluate the clinical effectiveness of L-arginine in the prevention of preeclampsia and reduction of other perinatal risks in patients with preclinical gestational endotheliopathy (GE). Women with GE in subgroup A received ASA per os at a dose of 75 mg per day (n=31), in subgroup B they received L-arginine per os at a dose of 4-4.2 g per day (n=33), and women with GE who refused prophylactic treatment were included in subgroup C (n=52).. Prophylactic treatment with L-arginine was carried out in a course regimen. The first course was prescribed from 12 to 14 weeks, the second course - from 16 to 18 weeks, and the third course - from 28 to 30 weeks of pregnancy. The clinical effectiveness of the therapy was assessed by comparing the number of cases of perinatal pathology in the I, II and III trimesters (threatening miscarriage, preeclampsia, placental dysfunction, perinatal losses).

The early administration of ASA and L-arginine to pregnant women with a moderate degree of perinatal risk (preconceptional GE) allowed not only to prolong pregnancy but also to reliably prevent the development of preeclampsia (RR 0.39, 95% CI: 0.18–0.84; p=0.02).

The more pronounced clinical efficacy of a course of L-arginine drinking solution (daily dose of L-arginine - 4.0-4.2 g) in pregnant women with pre-eclampsia may be associated with the endotheliotropic protective effect of the drug - a decrease in the number of preeclampsia cases (RR 0.19, 95% CI: 0.05-0.77; p=0.02) and placental hyperplasia/hypoplasia (RR 0.17, 95% CI: 0.04-0.68; p=0.01) compared with pregnant women who were diagnosed with GE and did not receive prophylactic therapy.

The prophylactic use of L-arginine in clinical practice during pregnancy is still under discussion, and more researches are needed to determine the optimal dose, initiation and duration of use for the best preventive or therapeutic effect.

(**Section HDP-Preeclampsia**)