

Endothelial Dysfunction in the Extragenital Pathology Clinic: a New Approach to Problem Solution

As it is known, cardiovascular system (CVS) disorders are the most significant problems encountered in the extragenital pathology clinic (EGP), and the incidence of such problems remains at high level. Significant increase in cardiovascular morbidity (coronary heart disease, arterial hypertension, chronic heart failure, pulmonary hypertension) has been observed in mature women who decided to realize their reproductive potential. At that, presence of such disorders not only impacts on quality of life of women but is associated with high risk of maternal and perinatal mortality in case of pregnancy. Choosing the optimal approach to management of pregnancy with EGP, in particular with CVS disorders, key mechanisms of development of such states must be taken into account. Realizing specifics of EGP pathogenesis that accompanies pregnancy makes it possible to impact on the main factors of its development and so allows to decrease significantly the likelihood of complications and save lives to a mother and a baby.

To get answers to the most frequent questions concerning mechanism of development, diagnostics, prophylaxis techniques and management of pregnant women with EGP we interviewed a corresponding member of National Academy of Medical Sciences (NAMS) of Ukraine, chief of internal pathologic pregnancy department in State Institution "Institute of Pediatrics, Obstetrics and Gynecology of NAMS of Ukraine", Grand PhD in Medicine, professor Vladimir Isaakovich Medved and an Honoured Doctor of Ukraine, professor of the obstetrics, gynecology and fetal medicine department in Shupyk National Medical Academy of Postgraduate Education, Grand PhD in Medicine, Svetlana Ivanovna Zhuk.

In the course of the interview, the most urgent problems concerning EGP in pregnant women were discussed, and special attention was given to the prophylaxis of the states which underlie such disorders. Our readers may find out more about the subject matter.

So, let's start with the beginning...

Grand PhD in Medicine, Professor Vladimir Isaakovich Medved, shares his clinical experience and peculiarities in respect of management of pregnancy accompanied by EGP.

? Vladimir Isaakovich, please, tell our readers what consequences are associated with EGP in pregnant women.

It is known that EGP is a numerous group of diseases, syndromes and pathological states occurred in pregnant women which are united only because they are not gynecological diseases or common obstetric complications of pregnancy.

It must be taken into account that EGP may lead to worsening of pregnancy outcome both for a mother and for a foetus, increase in the incidence of complications of pregnancy, delivery and postnatal period, and in such a state a special mode of delivery may be required. However, high risk of maternal mortality remains the major danger when EGP occurs. Thus, the most common causes of maternal mortality according to EGP nosological structure are as follows: CVS diseases – 40.3 %, infectious pathology – 24.7 %, tumors – 14.7 %, and other diseases – 20.3 % of cases.

? What places are given to heart failure and arterial hypertension (AH) in the Clinic of EGP pregnancy? What is the direct predictor of such states?

According to "Diseases of blood circulation system morbidity in pregnant women" (2015) reported by the State Statistics Service of Ukraine, CVS diseases were registered in 6.9 % of women, at that, many of them were diagnosed heart failure.

In the most of cases, preexisting heart failure may progress post conception thereby raising the functional class of this pathology and therefore requires enhanced medical control.

Equally with heart failure, different hypertensive disorders amounting to 12 - 15 % of the general morbidity are also considered to be the most common CVS disorders. At that, 5 % refer to preexisting arterial hypertension (registered in the anamnesis before pregnancy) and 6 - 7 % refer to hypertension de novo (pregnancy-associated). Endothelial dysfunction is one of the main factors of the development of such disorders; gestational hypertension and pre-eclampsia are its direct clinical manifestations. Taking into consideration high morbidity of hypertensive disorders associated with endothelial dysfunction in pregnant women, the need in development and extensive application of the most informative diagnostic techniques along with their timely usage heightens.

? In your opinion, what diagnostic techniques are the most informative today? What diagnostic value in this respect does a circulatory vascular endothelial growth factor have?

Detection of the circulatory vascular endothelial growth factor is of high significance in respect of diagnostics of CVS disorders, in particular, hypertensive disorders and heart failure. However, in Ukraine, this method has not yet entered the routine obstetrical practice. At present, such CVS disorders as arterial hypertension and heart failure are diagnosed, first of all, on the basis of clinical manifestations and blood nitric oxide (NO) level.

? What is the role of NO and what are the ways to maintain it at sufficient level?

In NO deficiency, there is a high risk of different CVS disorders in pregnant women including endothelial dysfunction that could lead to the intrauterine growth retardation, which is the most common complication. Under physiological conditions, NO is synthesized from the L-arginine, conditionally essential amino acid, with NO-synthase enzymes. That is why the most frequent causes of nitrogen deficiency are enzyme and amino acid deficiencies. At this, recovery of synthesis of sufficient quantity of NO-synthase is a complicated task while delivery of medication therapy with administration of NO donor substances is enough for replacement of L-arginine stocks.

? To your mind, what L-arginine products are preferable today and why?

One of the most qualitative representatives of this class drug products on the pharmaceutical market of Ukraine is a domestic product Tivortin. Its advantage is that it is available in two pharmaceutical forms: intravenous – when demanded quick onset of the therapeutic effect this form is the best one to start the treatment; and oral form – for further transfer of patients (on the principle of "switch" therapy). Appropriateness of prescribing oral form of Tivortin is conditioned by several factors: firstly, oral administration is less traumatic; secondly, such a method of administration does not demand presence of qualified personnel, obligatory visiting of a medical setting or hospitalization.

? Vladimir Isaakovich, taking into account your clinical experience, what is the most effective schedule of Tivortin administration?

In our clinical practice based on the State Institution "Institute of Pediatrics, Obstetrics and Gynecology of NAMS of Ukraine", we apply the administration schedule described in the major scientific studies devoted to Tivortin. According to this schedule, the treatment is started with the intravenous infusion of arginine hydrochloride in a 10 - 14-day regimen followed by oral arginine aspartate in a 30-day regimen. For such chronic diseases as arterial or pulmonary hypertension and heart failure, there is no fixed course of treatment. And if the therapeutic effect from arginine administration is observed in such patients the therapy is kept going on a continuous basis.



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? What place in your clinical practice is given to Tivortin and what are the prospects of its inclusion into up-to-date schemes of prophylaxis and treatment of cardiovascular diseases in pregnant women?

Tivortin must be a mandatory medication in hypertensive disorders or pulmonary hypertension. Relying on the positive experience of this product administration in cardiology for treatment of heart failure on the basis of the State Institution "Institute of Pediatrics, Obstetrics and Gynecology of NAMS of Ukraine", we are also planning to extend its therapeutic indications in the EGP Clinic.

Tivortin is appropriate to be administered as timely prophylaxis to women being at risk of development of foetal distress syndrome and intrauterine growth retardation syndrome.

Thus, there is an opportunity at least to gain time for later delivery if not to prevent the development of these pathological states, which is very important.

As to such issues as mechanisms of endothelial dysfunction development, diagnostic techniques, prophylaxis and treatment, we discussed in details with Grand PhD in Medicine, Professor Svetlana Ivanovna Zhuk.

? Svetlana Ivanovna, tell us, please, what place is given to pre-eclampsia in the statistics among all pregnancy complications and with what risks it is associated.

Pre-eclampsia is one of the most common and threatening complications of the pregnancy. Its occurrence significantly increases the risk of maternal and perinatal mortality and pre-eclampsia-associated placental insufficiency, in its turn, is fraught with such consequences as intrauterine growth retardation. In fact, pre-eclampsia as well as other pathological states in the obstetrics is bound up with microcirculatory bloodstream dysfunction accompanied by vascular endothelium damage and therefore by endothelial dysfunction.

? There is an opinion that over the last 20 years, the concept of endothelial dysfunction control as a factor of pre-eclampsia manifestations development – hypertension and proteinuria – has undergone no changes. At present, besides prescription of various methods of hypertension control, there is no definite approach to its management. Is it true?

Unfortunately, the reality is very much so. That is why the effective approach to pregnancy follow-up in patients at risk of endothelial dysfunction development is the timely and qualified diagnostics followed by the well-planned course of preventive treatment.

Today, there is a great number of scientific works both of domestic and foreign authors devoted to the detection of endothelial dysfunction by presence of a row of specific markers.

? What diagnostic criteria, in particular specific markers, are to be taken into consideration when defining the risk group?

At present, assessment of coagulogram is the most informative method of endothelial dysfunction diagnostics. On the results of coagulogram with due consideration of such specific markers as proinflammatory cytokines (interleukins γ -1 β , γ -8; tumor necrosis factor), thromboxane-prostacycline system, and NO level, it is possible to imply endothelium damage. Besides that, the state of microcirculatory bloodstream in early pregnancy can also be evaluated with use of instrumental techniques (invasive and noninvasive). It is extremely important for an obstetrician-gynecologist to assess the state of patient's bloodstream in as early pregnancy as possible. That is why, diagnostically, trophoblastic blood flow is of primary concern as it already develops at weeks 5-6 of gestation.

? To your mind, what of the primary preventive measures will be the most effective in this case? What accounts for appropriateness of the prophylaxis in the preconceptional period?

The earlier endothelial dysfunction is detected, the earlier it will be possible to consider preventive measures. Post conception correction of impairment of formed trophoblastic blood flow is a difficult task. That is why the concept of preconception preparation is of high importance. It is the very stage when preventive and therapeutic measures are characterized by the better efficiency; taking these measures allows to ensure better indices of microcirculation during pregnancy. Besides that, it cannot be forgotten about the necessity of detection and resolution of underlying causes of endothelial dysfunction development, namely: hormone disruptions, infectious diseases, any

EGP as well as habitual miscarriage of unknown etiology both in early pregnancy and in late pregnancy in the history. Anyway, all women having one of the above mentioned pathological states must take preventive treatment of endothelial dysfunction.

? What role is given to nitric oxide donator substances in the prophylaxis of the given pathology?

Maintenance of the normal endothelial function depends to a large extent on sufficient synthesis of NO that takes active part in vasodilatation and maintenance of basal vascular tone. That is why, as of today, prescription of NO donator substances – L-arginine products – is the only well-proven method of prophylaxis of pathological states associated with impairment of microcirculatory bloodstream. Tivortin is the very product developed specifically for administration in the obstetrics. It could be prescribed both for prophylaxis purposes in preconceptional period and for the treatment of endothelial dysfunction caused by low NO level in any pregnancy periods as need for the mentioned component in this period sufficiently increases.

? Svetlana Ivanovna, what place is given to Tivortin in your clinical practice?

According to the existing practice, there is no alternative to Tivortin in the obstetrics which is used as an agent for prophylaxis of pathological states associated with impairment of microcirculatory bloodstream. A large number of products improving hemorheology are not only not recommended for administration but, I would say, even prohibited in the obstetric practice and were withdrawn from the protocols and guidelines. So, in my clinical practice, I prescribe Tivortin almost to every third patient. Moreover, I would recommend using this product not only

in the obstetrics but also in the gynaecology. For example, routine treatment of such a common pathology as chronic pelvic pain syndrome, which is also accompanied by the endothelial dysfunction, as a rule gives no positive result, while inclusion of Tivortin into the standard treatment schemes allows to improve significantly therapeutic effect in such a syndrome.

? In your opinion, what are the prospects of inclusion of Tivortin into the up-to-date schemes of prophylaxis of pre-eclampsia and other possible complications associated with endothelial dysfunction?

Modern approaches to the development of protocols and guidelines have certain peculiarities. To start with, the mentioned normative documents are of advisory nature and, unlike those applied worldwide within the insurance medicine, do not take into account the recommendations for use of the certain medicinal products. In addition, any protocol or guideline on medical aid in Ukraine provides for off label prescription of the product that does not have indications in respect of certain pathology but at the same time is characterized by clinical effectiveness in respect to such pathology as evidenced by a row of studies. Even though, at present, there is no possibility to detail in the national recommendations use of Tivortin as a standard product for prophylaxis and treatment of endothelial impairments, it is also not graded as an off label product as it has pathogenetically grounded effect on bloodstream in such pathological states. So, it could be concluded that the prospects for this product inclusion into the normative documentation are very optimistic.

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