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Full Length Research Paper

Pathogenetic substantiation of the use of low molecular weight heparin in the prevention of recurrent pregnancy complications and reproductive losses in women with metabolic syndrome

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Metabolic syndrome is associated with at higher risk of developing various obstetric complications. The endotheliopathy, proinflammatory and prothrombotic status may play an important role in impaired invasion cytotrophoblast and impaired placental development that leads to fetal loss, pre-eclampsia and other obstetric complications in women with metabolic syndrome. It is necessary to conduct screening for latent thrombophilia (acquired and genetic forms), markers of thrombophilia, and perform mandatory antithrombotic therapy in patients with metabolic syndrome. This will optimize the principles of management of women with the metabolic syndrome in obstetric practice.

Keywords: Metabolic syndrome**,** obstetric complications, endotheliopathy, proinflammatory and prothrombotic status, antithrombotic therapy.

INTRODUCTION

One of the leading problems in obstetrics and gynecology at the moment can be considered the metabolic syndrome (MS). The relevance of the MS is considered primarily in terms of prognosis of pregnancy, childbirth and the postnatal period.

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It is recognized that metabolic syndrome is a pandemic of the XXI century. It is assumed that 25-35% of the population in Western countries suffers from metabolic syndrome.

In the medical literature there are various synonyms for MS, but the term “metabolic syndrome” and “insulin resistance syndrome” are used more frequently than others.

MS is a symptom of various metabolic disorders and/or diseases, which are the factors of early atherosclerosis and its cardiovascular complications.

The main symptoms and manifestations of MS are:

- Abdominal obesity;
- Insulin resistance (IR) and hyperinsulinemia (GI);
- Dyslipidemia;
- Arterial hypertension (AH);
- Impaired glucose tolerance (IGT);
- Early atherosclerosis;
- Disorders of hemostasis;
- Hyperuricemia and gout;
- Microalbuminuria;
- Hyperandrogenism.

In recent years, many researchers have proposed to extend the scope of the MS to include such components hepatic as steatosis and obstructive sleep apnea syndrome, as well as polycystic ovary syndrome (PCOS).

MS is characterized by oxidative stress, activation of lipid peroxidation, pro-inflammatory status. Changes in carbohydrate and lipid metabolism in MS are the main factors in enhancing the processes of free radical oxidation, which leads to a greater need of the organism in bio antioxidants, including antioxidant vitamins.

Earlier, the existing criteria for diagnosis of metabolic syndrome proposed by the WHO, the US Cholesterol Education Program experts, the American Association of Endocrinologists differed from each other in a complex list of symptoms of metabolic syndrome and indicators.

In April 2005, the International Diabetes Federation has defined uniform criteria for establishing the MS diagnosis.

Essential criteria MS is a central type of obesity (waist circumference>94 cm in men,>80 cm in women (Caucasian ethnicity)). Plus at least 2 out of 4 criteria:

1) Triglyceride ≥150 mg/dl (≥1.7 mmol/l) or specific treatment of dyslipidemia;
2) HDL cholesterol <40 mg/dl (<1.03 mmol/l) in men, <50 mg/dl (<1.29 mmol/l) in women or specific treatment;
3) Blood pressure>130/85 mm Hg or antihypertensive therapy;
4) Fasting glucose ≥100 mg/dl (≥5.6 mmol/l) or previously identified type 2 diabetes mellitus

Metabolic syndrome is characterized by central obesity type.

At present, special attention is paid to thrombophilic complications of MS.

J.D. Brunzell includes in the components of MS susceptibility to thrombosis and elevated plasminogen activator inhibitor 1 (PAI-1).

The pathophysiological bases of increased concentration and activity of PAI-1 in patients with MS are multi-faceted.

The obstetricians see the relevance of MS problems primarily in terms of prognosis of pregnancy, childbirth and the postnatal period.

One of the first in the world, in 1970 V.N. Serov conducted fundamental research on large clinical material and described a special form of menstrual disorder and reproductive function disorder with increased body weight after pregnancy or childbirth.

During obesity in women with MS there are often observed menstrual disorders, ovarian function disorders and infertility. In case of pregnancy the gestation process is complicated by the threat of termination of pregnancy, miscarriage, fetal death, fetal malnutrition often, the development of pre-eclampsia, until severe eclampsia and fetal death, high frequency of surgical interventions.

Such patients are at risk of the emergence of a wide variety of complications during childbirth and the postpartum period: violation of labor, fetal shoulder dystocia, bleeding during childbirth and the postpartum period, premature or delayed rupture of membranes, high incidence of surgical intervention, induction of labor.

Taking into account the fact that patients with MS have a predisposition to thrombosis, as well as considering the role of thrombophilia in the pathogenesis of complications of gestational process and thrombosis, it should be noted that women with the metabolic syndrome are at high risk of developing complications of gestation process, thrombotic and thromboembolic complications.

Based on the above, for the systemic judgment of the pathogenesis of the main forms of obstetric complications in women with metabolic syndrome we undertook our study, the purpose of which was: to investigate the relationship between metabolic syndrome, thrombophilia and complicated pregnancy, as well as to optimize the tactics of pregnancy, childbirth and the postpartum period in females with the metabolic syndrome.

MATERIALSANDMETHODS

77 women with MS were examined to achieve the objectives of our study. 2 groups were identified among them:

Group I - 32 patients, whom we have been preparing for pregnancy and followedupduringtheentire gestational process, taking into account the disorders detected starting from fertile cycle and early pregnancy.

II group - 45 pregnant women who were examined and received treatment since the II or III trimester of

pregnancy.

The control group consisted of 150 pregnant women with physiological course of gestation.

Age of subjects ranged from 22 to 43 years old.

To diagnose MS, we used the recommendations of the US National Institutes of Health (Adult Treatment Pannel (ATP III), 2001) and the American Association of Clinical Endocrinologists (AACE, 2003).

The average weight of the women surveyed before pregnancy was 98.2 ± 4.02 kg. The average value of the body mass index (BMI) of the women surveyed was 35.3 ± 1.38 kg/m^2.

11 (14.3%) women had the history of primary infertility, 7 (9.1%) had the history of secondary infertility.

Analysis of obstetric history in groups I and II revealed a relatively high frequency of obstetric complications such as early and late miscarriage, preeclampsia, antenatal fetal death (AFD), and so forth.

Among extragenital pathology in the first place there were obesity and diseases of cardiovascular system: hypertension, neuro-circulatory dystonia of hypertensive type. In 2 (2.6%) women had a history of stroke.

The largest number of women had a family history of hypertension, of obesity, 34 (44.2%) were burdened with a family history of thrombotic complications (early myocardial infarction, stroke, thrombosis, pulmonary embolism).

Clinical and laboratory examination included instrumental methods - ultrasound, Doppler study of blood flow in the umbilical artery, uterine arteries and the arteries of the fetus, cardiotocography in dynamics, ECG, echocardiography; we used laboratory methods such as a clinicalblood tests, biochemical blood tests, urinalysis, infectious profile and study of the hemostatic system.

After asking a family history of thrombotic and surveyed the hemostatic system to detect thrombophilia (assay of molecular markers of thrombophilia - D-dimer,assay of antiphospholipid antibodies, assay of genetic thrombophilia).

The obtained data were processed and analyzed using parametric (normal distribution characteristic of the samples, as well as in cases where the sample size was >100) and non-parametric (in cases of free distribution of characteristic in the samples) methods for assessing the reliability of differences compared samples. Differences between compared samples were considered significant at a significance level (p) of less than 0.05. The calculation was performed using MS Excel 2002 software.

RESULTS AND DISCUSSION

Our study in 77 women with MS showed the presence of the genetic forms of thrombophilia in 100% of cases (with 26.0% in the control group). One of the most important results of the research seems to us the detection of 100% of the multigenic thrombophilia (two or more defects) in the examined patients. This characteristic feature of multigenic thrombophilia was the prevalence in the general structure of the genetic forms of thrombophilia polymorphisms “675 4G/5G”of PAI-1 gene (94.8%) - 73 women. In most cases, women with MS had homozygous form of the PAI-I gene polymorphism - 51 (66.2%) patients.

In a large percentage of cases polymorphism occurred in the gene tPA - 68.8%, then– polymorphism of “I/D” ACE gene - 53.2%, polymorphism “455 G/A” in the fibrinogen gene - 52.3% that indicates the presence of endogenous hypofibtinolysis in this category of women.

Also, the high frequency was detected formutationsin methylenetetrahydrofolate reductase gene MTHFR C677T (heterozygous form) and for polymorphisms of platelet receptors GpI.

PAI-1 plays an important role during implantation. In conditions of enhancing the level of PAI-1, fibrinolysis is dramatically suppressed, there is insufficient destruction of the extracellular matrix and the implantation of the blastocyst in the endometrium, thereby disrupted the formation of the system mother-placenta-fetus. On the one hand is the cause of infertility and early preembryonic andembryonic losses, and on the other hand leads to placental abnormalities and forms the pathogenetic mechanism of obstetric complications.

Apparently, the high incidence of miscarriage (early and late), antenatal fetal death, history of infertility in patients with MS confirms the above statement.

Besides polymorphism PAI-1 gene during pregnancy there may also be present other additional factors contributing to the level of PAI-1, such as hypoxia, cytokines, activation of the renin-angiotensin-aldosterone system and so forth.

It is necessary to emphasize the role of angiotensin-converting enzyme in the pathogenesis of obstetric complications in pregnant women with MS and genetic thrombophilia, since it is well known that this enzyme is a key in the remodeling of the spiral arteries during pregnancy. It is noteworthy that in high level of ACE there are also observed additional hypofibrinolytic and vasoconstrictor effects.

Angiotensin-converting enzyme converts angiotensin I to angiotensin II, which increases the production of PAI-1 by endothelial and smooth muscle cells, while the effect of ACE is carried out not only through ACE receptors type 1: Angiotensin II is converted to angiotensin IV, which acts on specific receptors (AT-IV-receptors), with a resulting increase in PAI-1 level and a decrease in nitric oxide (NO).

ACE reduces production of t-PA and NO by inactivating bradykinin which is a source of t-PA and NO.

We believe that the genetic polymorphism of the ACE gene is an independent risk factor for complications of gestation in pregnant women with MS.

Elevated levels of homocysteine cause damage to the

vessel wall, thereby violating the normal procoagulant-anticoagulant balance. Hyperhomocysteinemais viewed nowadays as a factor of the risk of a number of obstetric complications - habitual miscarriage, preeclampsia, premature placenta detachment, thrombosis and thromboembolism.

Combined forms of thrombophilia (genetic and acquired (APA) form) - were found in 14 (18.2%).

The high incidence of thrombophilia in women surveyed has allowed us to treat it as an essential etiopathogenetic factor in the development of obstetric complications in women with MS. It should also be noted that women with the metabolic syndrome are at risk for the development of thrombotic and thromboembolic events.

As already noted, the prospective group consisted of 77 women with MS, including 32 patients who were counseled and tested by us before pregnancy or early in pregnancy, and then conducted throughout pregnancy until delivery and the postpartum period (I group). The rest of the 45 pregnant women were screened, counseled and received therapy within II or III trimester of pregnancy (II group).

When diagnosing hereditary or combined multigenic thrombophilia we prescribed antithrombotic prophylaxis differentiated depending on the cause and degree of its severity, the presence of homo- or heterozygous form of mutations, leading to a state of thrombophilia, and depending on the detection of circulating levels and markers of thrombophilia (D-dimer) and platelet aggregation activity.

In preparation for pregnancy patients in group I were prescribed vitamin therapy (and in the presence of APS or platelet receptor polymorphism -mini-dose of aspirin - 75 mg per day). The support vitamin therapy included folic acid (at least 1 mg per day), polyunsaturated fatty acids (omega-3), vitamin and mineral supplements for pregnant women. Patients with mutant C677T MTHFR and hyperhomocysteinemia receiving higher doses of folic acid (4 mg daily) and also received the B group vitamins in tablet form. In the fertile cycle and the onset of pregnancy patients the treatment carried out previously was supplemented with low molecular weight heparin (LMWH) Enoxaparinumnatrium in the prophylactic dose. Also, after the therapist consultation antihypertensive therapy was prescribed. In I trimester, we also administered preparations containing magnesium to women with MS, since we found that MS patients have a pronounced deficiency of magnesium.

Pregnant patients in Group II examined in the II or III trimester (n-45), taking into account the detected violations began receiving LMWH, aspirin, anti-oxidants and vitamin therapy.

All patients before prescribing LMWH, then 10 days later, and monthly thereafter underwent control of the level of thrombophilia markers - we measured D-dimer, homocysteine levels in plasma, platelet aggregation. This was necessary in order to determine baseline thrombophilia, select the appropriate baseline dose of anticoagulants and antiplatelet agents, and monitor the effectiveness and safety of drugs.

The best pregnancy outcomes we observed in patients of I group.

After analyzing the incidence of pre-eclampsia in present pregnancy among pregnant patients of I and II groups, we found that the incidence of pre-eclampsia in women in group II was significantly higher than that of group I pregnant patients.

It should be noted that pre-eclampsia in women in group I developed in the later stages of pregnancy, compared with pregnant women of group II. 19 (59.4%) of pregnant women in group I developed preeclampsia, of whom in 15 (46.9%) women it was mild, and in 4 (12.5%) it was moderate. Late start pathogenetically substantiated therapy on the background of pre-eclampsia which began in 11 (24.4%) patients of group II led to the development of mild preeclampsia, in 24 (53.3%) to moderate, in 10 (22.2%) to the severe forms.

As a result, long-term treatment with antithrombotic and differentiated vitamin in continuous mode pregnancy in 32 patients in group I resulted in the birth of 33 living children (1 woman with twins). Fetal loss was not observed.

In group I, 20 patients (62.5%) gave birth by cesarean section, respectively, 12 (37.5%) - vaginally.

In group I indications for cesarean section were of combined nature. Indications for operative delivery were: burdened obstetric and gynecological history (antenatal fetal death, infertility I), age older than 30 years, nulliparous, pelvis injury in the anamnesis, congenital cataract, hypertension, resistant to therapy, progression of chronic fetal hypoxia.

In group I, the average weight of newborns was 3,319±260 g, height 50±1.5cm, the average Apgar score for group was 7.3 ± 0.3 – 8.1 ± 0.2 points.

In group II, 28 patients (62.2%) gave birth by cesarean section, respectively, 17 (37.8%) - vaginally. In most cases, the indication for surgical delivery was worsening the severity of pre-eclampsia, increase in severity of fetoplacental insufficiency (FPI), not amenable to medical correction.

In group II, the average weight of newborns was 3,117±256 g, height48.5±2.4cm, the average Apgar score for group was 6.8±0.6 – 7.4±0.6 points.

In 5group II patients, in cases where the therapy started too late it was not possible to avoid the loss of the fetus.

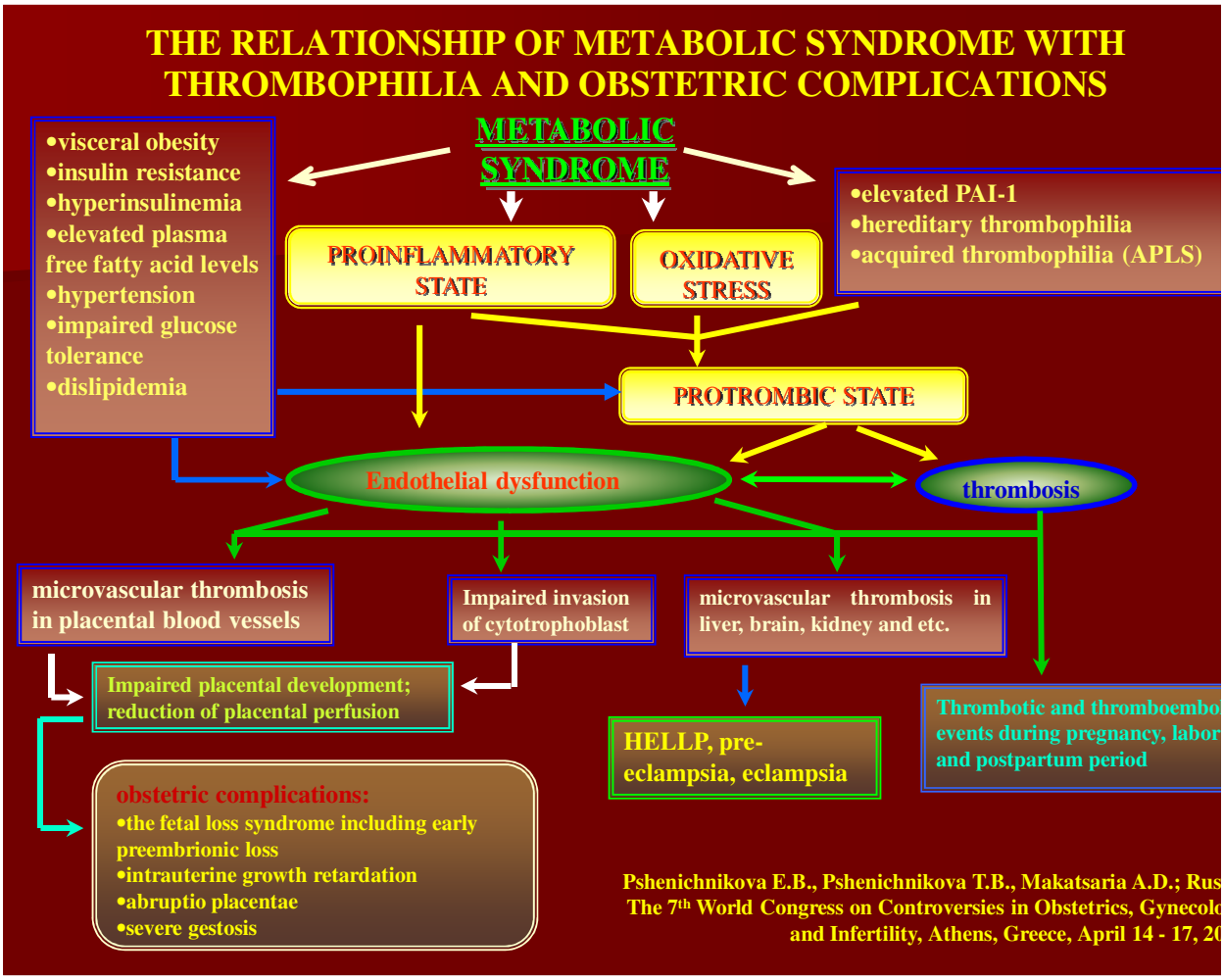

Figure 1. Relation between metabolic syndrome, thrombophilia and obstetric complications.

Thus, the sooner antithrombotic therapy is started, the better are the pregnancy outcomes.

The main principles of prevention of obstetric complications in women with metabolic syndrome and combined thrombophilia:

1. Decreaseofbodyweight
2. Start of therapy in fertile cycle

Fertile cycle

- Vitamin E orotherantioxidants
- Polyunsaturated fatty acids (“Omega-3”)
- Folic acid not less than 1 mg (at MTHFR mutation C677T not less than 4 mg)
- In case of MTHFR mutation C677T and hyperhomocysteimemia - vitamins B6, B12 are necessary
- Aspirin 50-75 mgperday
- LMWH (Enoxaparinumnatrium) in the prophylactic doses QD s/c (on condition of high level of D- dimer)
- Multivitamins.
- Preparations of natural progesterone if indicated.

Continued therapy throughout pregnancy and the postpartum period.

I trimester

- Same + LMWH, cancellation of hirudotherapy with the onset of pregnancy at case her application.

II, III trimester of pregnancy

- Same + iron supplements, calcium (if necessary), dosage adjustment LMWH taking into account the results of hemostasiogram, ultrasound, doplerometry.

Postpartum period

- LMWH for at least 10 days in prophylactic doses, multivitamins.

CONCLUSION

Summing up the work, we found it necessary to present our views on the pathogenesis of the main forms of obstetric pathology in women with MS.

The presence of the main manifestations of the metabolic syndrome (insulin resistance, hyperinsulinemia, hypertension, dyslipidemia, obesity) and the presence of oxidative stress and pro-inflammatory status leads to the development endotheliopathy in individuals with metabolic syndrome. Endotheliopathyis aggravated by prothrombotic status (elevated PAI-1, the presence of a genetic and/or acquired (APS) forms of thrombophilia). In addition, the prothrombotic status is an independent factor for thrombosis in these patients. Endotheliopathy, microthrombosis and state of hypofibrinolysis lead to disruption of the implantation process, the invasion of the trophoblast and placentation, in the future this may lead to the development of preeclampsia, FPI, fetal growth retardation, fetal loss syndrome (WBS), premature detachment of normally situated placenta (PDNSP) for pregnancy. In addition, microthrombosis of vessels of liver, brain, kidneys can lead to the development of severe preeclampsia (HELLP- syndrome, preeclampsia, eclampsia). Also, these patients are at high risk for the development of thrombosis and thromboembolism during pregnancy, childbirth and the postpartum period (Figure 1).

Summarizing the analysis of our own data, as well as world literature data, we concluded that in patients with MS there is a genetic thrombophilia. In some people with MS we also found circulation of APA (APS - in the presence of laboratory evidence and clinical manifestations). Of particular note is that genetic research shows the majority of women with MS have genetic form ofhypofibrinolysis, which, in our view, can play an important role in the violation of the implantation process, trophoblast invasion and placentation. Taking into account the dependence of successful pregnancy on implantation processes, invasion of trophoblast and placentation, as well as connecting the effect of antithrombotic drugs in the full development of these processes, we can conclude that the early (with childbearing cycle and early pregnancy) therapy with the use of antithrombotic drugs, vitamins and antioxidants in patients with MS and genetic thrombophilia, as well as the circulation of APA, can prevent the development not only of thromboembolic complications, but also to avoid a violation of the trophoblast invasion,implantation process, placentation, reduced placental perfusion and preeclampsia development, FPi, syndrome, intrauterine fetal growth retardation, CSE, premature detachment of normally situated placenta. The earlier antithrombotic therapy is started, the more favorable is the course gestational process and the outcome of pregnancy in women with MS who have a history of infertility, CPR, pre-eclampsia, FPI, AFD in previous pregnancy. At the same time late initiation of therapy with the use of anticoagulants in the conditions of preeclampsia and FPI was ineffective.

Since the MS includes pro-inflammatory status, oxidative stress, vitamin and mineral imbalances, endothelial dysfunction, this, in turn, is an additional factor for activation of the hemostatic system withalready existing thrombophilia.

Thus, we believe that thrombophilia and endogenous hypofibrinolysis can be attributed to the MS criteria.

Due to the key role of thrombophilia in the pathogenesis of the main forms of gestation complications of in women with MS prevention of these complications involves the use of drugs normalizing the function of the coagulation system. Drugs of choice currently worldwide are drugs from the group of low molecular weight heparins (LMWH). One of the determining factors of the use of heparins in obstetrics is the lack of teratogenic and embryotoxic effects because they do not cross the placenta.

The mechanism of the effect of LMWH on the hemostatic system is similar to that of unfractionated heparin. Heparin causes 1,000 fold increase of antithrombin III activity, resulting in effective inhibition of thrombin, Factor X and IX. At sufficiently high concentrations of heparin it is able to provide an additional inhibitory effect on thrombin through heparin cofactor II. Efficacy of heparin in patients with APS is due not only to its effect on the hemostatic system, but also due to the ability to adsorb antiphospholipid antibodies, prevent their binding to target cells and inhibit complement.

LMWH is capable of inhibiting leukocyte-endothelial interaction which is a key element in the inflammation process. LMWH has also anticytokine property as a result of the suppression of the production of the most important proinflammatory cytokine TNF-α.

Since, apart from this, there is no need for constant monitoring of the laboratory, outpatient NMG may be used, most often the patients themselves are trained to performinjections when chronic treatment is required. Thus, due to ease of use of LMWH preparations (firstly, the subcutaneous injection is made, and secondly - 1 times a day, in the third - the drug is readilypackaged in syringes) pregnant women with thrombophilia perform LMWH injections bythemselves throughout pregnancy.

Our studies show that today LMWHs are the drugs of choice in pregnant women with thrombophilia and MS, and can prevent the development not only of thromboembolic complications but also of major obstetric, which include miscarriage, gestation toxicosis, premature detachment of placenta, intrauterine growth retardation, antenatal deaths fetus, feto-placental insufficiency.

Regarding the dose of LMWH, depending on the severity of thrombophilia it is not always the same depending on the level of markers of thrombophilia (D-

dimer).

When evaluating the effectiveness of long-term use of LMWH one shall take into account both clinical and laboratory criteria. The effective prevention was shown by continuation of pregnancy to full-term gestation periods and the absence of intrauterine growth retardation, according to the US, the lack of intrauterine fetal suffering, according to Doppler and cardiotocography. In the process of pregnancy, we consider it necessary to study the molecular thrombophilia markers such as D-dimer, as they allow to:

- Establish the presence of thrombophilia;
- Justify antithrombotic prophylaxis;
- Monitor the effectiveness of antithrombotic prophylaxis;
- Carry out correction of the dose.

The most important laboratory criteria for the effectiveness of prevention include the reduction up to a full normalization of molecular markers of thrombophilia (D-dimer) and normalization of platelet aggregation activity.

Antithrombotic therapy is also indicated in preparation for any kind of surgery and in the postoperative period for prevention of thrombotic and thromboembolic complications in women with MS.

The management of pregnancy in women with MS should be done in conjunction with endocrinologist, general practitioner, cardiologist.

We believe it necessary to conduct screening for latent thrombophilia (acquired and genetic forms), markers of thrombophilia, andperform mandatory antithrombotic therapy in patients with metabolic syndrome. This will optimize the principles of management of women with the metabolic syndrome in obstetric practice.

In conclusion, it should be noted that the metabolic syndrome is a prime example of simultaneous combination of the so-called “big” syndrome: metabolic syndrome, disseminated intravascular coagulation syndrome, systemic inflammatory response syndrome, APS/APA, genetic forms of thrombophilia.

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