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Review article

THERAPEUTIC OPTIONS IN PREVENTING UTEROPLACENTAL UNIT HYPOXEMIA CAUSED BY TROMBOPHILIAS

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Abstract: A miscarriage is primarily defined as an unintentional loss of pregnancy before the 20th week of gestation. Both the practice and theory show that pregnancy losses up to the 10th week of gestation may, besides many other gynecological and microbiological causes, also be brought down to the existence of some of the acquired thrombophilia such as antiphospholipid syndrome. Numerous studies have been conducted to examine the efficiency of therapy administration to prevent adverse outcomes of pregnancy. Hereditary thrombophilia are more connected with adverce pregnancy outcomes.

Key words: pregnancy; thrombophilias, LMWH, therapy, outcomes.

INTRODUCTION

A miscarriage is primarily defined as an unintentional loss of pregnancy before the 20th week of gestation, observed both from the aspect of pathophysiology and anatomy. The clinical practice standard, in most developed and medium developed countries, allows the interpretation of premature delivery from the 24th week of gestation, namely the moment when type 2 pneumocytes are embryologically and anatomically formed. Moreover, some of the exceptionally economically developed countries define premature deliveries starting from the 20th week of gestation. Both the practice and theory show that pregnancy losses up to the 10th week of gestation may, besides many other gynecological and microbiological causes, also be brought down to the existence of some of the acquired thrombophilia such as antiphospholipid syndrome. However, even in the cases which should be further investigated, there should be a more detailed examination of other causes including chromosome aberrations, microbiological causes (incidence of ureaplasma, mycoplasma, chlamydia, as well as vaginosis or severely manifested human papilloma virus infections). Moreover, the part of cause is lying in the anatomic variations of the uterus, more frequently called anomalies (anomalies of the uterine body, existence of septum and sub-septum, polyps, myoma located in the area of chorionnidation or pathological vascularizations). The part of cause of early pregnancy losses may also be of hormonal nature, either by hormones related to primarily gynecological aspect or more frequently by hormonalaxes of the whole body, starting from hypophysis activities, hyperprolactinemia incidence, as well as inadequate function of thyroid and adrenal glands. The loss of pregnancy is partly related to complete organism state, chemodynamically as well as metabolically, adequate glucoregulation, the existence of inherited or acquired problems at the level of functioning of other organs, such as late detection of nephrological or urological problems. It should not be forgotten that hypoproteinemia, or hypovitaminosis and avitaminosis are also stated as potential causes of early pregnancy (1-6).

Studies concluded - not enough effect of antiaggregative or anticoagulative therapy

Several studies have been conducted to examine the efficiency of therapy administration (1). In the study based on adequate methodology, approved by Ethic Committee for disease protection Brest University hospital, the patients were followed in the period from 4th April 2007 to 31st October 2012. Results from 13 hospital centers in France were summarized. Criteria for inclusion were: pregnant patients aged between 18 and 45 with unexplained causes of miscarriage. Re-

current, habitual miscarriage was defined as more than two pregnancy losses before the 15th week of gestation in the patient with same paternal genomes and without offspring. Both partners' karyograms were done for all the included cases. There was no anatomic anomaly of the uterine body found. The absence of antiphospholipid syndrome, factor V Leiden disturbance and prothrombin G20210A mutation was established in all of the cases, as well as disturbances related to absence of protein S or C or antithrombin 3 deficiency. Cases with established indication for aspirin or anticoagulation therapy administration were excluded, namely all the conditions with high risk for deep venous thromboembolism or conditions of cardiovascular nature where the named therapy is necessary. Moreover, all standard contraindications for administration of 40 mg enoxaparin injections, such as anemia with less than 10g/dL or thrombocytes level below 150 x 10.3, or creatinine clearance level below 30 ml/h. After well-established terms for study following, all the women with confirmed pregnancies were randomized and, at the same time educated for therapy self-administration. All the patients were advised to take folic acid. The administration of therapy or placebo was blinded for researchers during the course of study. Enoxaparin Sanofi Aventis (branch ROVI for placebo enoxaparin syringes, Madrid, Spain) was used. All the participants were regularly followed by their clinicians, during the course of pregnancy and two months after delivery. Besides ultrasonography aspects, complete clinical state of the patient was analyzed, as well as laboratory tests, while all side-effects were noted in the treatment adherence notebook. Two subgroups were formed in the group of possible complications. Primary outcomes, obtaining healthy live offspring, as well as premature deliveries and low birth weight children. As secondary outcomes, the incidence of miscarriages, intrauterine fetal loss up to the 20th week of gestation, as well as the incidence of preeclampsia, low birth weight babies delivery, placental abruption and premature deliveries were analyzed. The laboratory evidence of maternal thrombocytopenia (defined as a number of thrombocytes under 0.6 in relation to basal level of thrombocytes which was under 100,000/mm^3) was followed, together with all skin reactions or bleeding episodes. During the analysis of 314 women results, 258 cases were followed, with 138 cases in the enoxaparin group and 120 cases in the placebo group. None of the 258 examined patients was lost during the study; however, one patient refused the treatment while in 5 cases the treatment had to be discontinued due to danger of bleeding and the fact that those patients did not want to further participate in the study. In 3 cases the therapy was stopped because of changes in the throat, skin reaction and the incidence of thrombocytopenia which was later confirmed to be heparin induced thrombocytopenia. The percentage of delivered babies was 66.6% in the enoxaparin group comparing to 72.9% in placebo group. Thrombocytopenia was found in 7 patients, out of which number 4 patients were in the therapy group while 3 patients were in placebo group.

Since the beginning of this study in 2006, only one placebo controlled study was performed, called ALIFE study, which did not prove efficiency of antiaggregation aspirin therapy administration (2).

The randomized SPIN STUDY showed no thrombophilia in over 85% of the cases. Moreover, the effect of improvement by administration of both aspirin and LMWH was not found (1, 2, 3).

In the HABENOX study, the efficiency of enoxaparin administration in relation to aspirin administration was not proven (4). This study concluded that the administration of enoxaparin in the dose of 40 mg per day did not increase the number of live birth in conditions when patients did not have thrombophilia or when reasons for pregnancy losses were undetermined. It is concluded that the administration of LMWH did not increase the chance for live birth in the conditions without thrombophilia and is considered that routine administration of this type of therapy may not be useful in patients without established thrombophilia. The authors state the limitation of their study to be the fact that pathohistological and physiological changes in angiogenesis of patients with congenital and acquired thrombophilia are expected, however caused by different mechanisms and expressed in different ways. Moreover, this study provides the information that even authors themselves find insufficiently well stated in relation to the existence or nonexistence of congenital or acquired hematologic or immune disturbance (5).

Studies concluded – moreeffect of antiaggregative or anticoagulative therapy

Within TREATS study, the incidence of complications in the first and second trimester was followed (6). From sudden miscarriages, over incidence of preeclampsia, the pregnant patients with established disturbances in factor V Leiden as well as prothrombin G20210A defect were followed (6).

The results of Nimes Obstetricians and hematologists Antiphospholipid Syndrome study (NOH-APS) were also analyzed, where a group of pregnant patients without diagnosed thrombophilia was primarily observed but where the incidence of antiphospholipid syndrome was also found. Study methodology included 6.318 patients with spontaneous abortion before the

10th week of gestation. The study exclusion criteria included thrombotic events (existence of at least one element of thrombosis of venous, arterial or small blood vessels type), except in conditions where the placenta was analyzed. All the patients who used antithrombotic, immunosuppressive or immuno modulating therapy were excluded. The study did not include patients whose determined cause of pregnancy loss was infection, metabolic, anatomic or hormonal pathology. Also, the women with HIV infection as well as hepatitis type B or C infection were excluded. Out of stated 6.318 patients, the study included 4.801 patients. All the patients had to fulfill two inclusion criteria. Their anamnesis data had to include 3 pregnancy losses before the 10th week of gestation, without any of the stated other possible causes of miscarriage, as well as both partners' karyotype. The other inclusion criterion was one pregnancy loss after the 10th week of gestation, confirmed by ultrasound, where the pathology analysis found no fetal developmental anomaly. All the patients included in the study were examined for: complete hemogram, fibrinogen, antithrombin 3, protein C, protein S, factor V Leiden (polymorphism F5 rs 6025) as well as disturbance in prothrombin gene G20210A (F2 rs 1799963). Besides, JAK 2 V 617 F mutation was followed as well as the analysis for the existence of antiphospholipid antibodies (aPLAbs). Further investigation did not include 152 patients with established incomplete form of thrombophilia and those with antithrombin 3, protein C and protein S deficiency, and patients with abnormal fibrinogen finding (JAK 2 V617F mutation). In the control group, which was formed, included persons completely free of thrombophilia. The group included 152 persons. Out of total number of negative thrombophilia persons, 3.604 agreed to participate in the study. The persons included in the study as a positive group had isolated Leiden disturbance as well as isolated prothrombin G20210A disturbance. There were totally 301 persons in the Leiden positive group and 279 persons in the G20210A positive group. The other positive group included 517 persons with existing elements for the diagnosis of antiphospholipid syndrome. At the end of summary, 796 persons with thrombophilia and 279 persons without thrombophilia were analyzed. Women with determined antiphospholipid syndrome were not followed in the course of this study. The obtained results show different effects in patients with positive Leiden or positive prothrombin G20210A disturbance. Patients with thrombophilia and previous habitual miscarriages, who did not use antithrombotic therapy in the new pregnancy, had an increased risk of sudden fetal death incidence in relation to the group of women who had negative finding to thrombophilia. There were less pregnancy losses and sudden fetal deaths in patients with established thrombophilia and administered prophylactic doses of LMWH. Moreover, they also had less hypertensive complications, such as preeclampsia, and less sudden preeclampsia developments. They had better results in delivering live newborns, capable for extrauterine life, comparing to the group of patients with thrombophilia and poor outcomes in patient history data. However, it is necessary to emphasize that patients with established thrombophilia and new pregnancy but without therapy were not examined. The study took this position due to the fact that in vitro data in experimental conditions show that LMWH may be considered a promoter of extravilloustrophoblast development and thus may stimulate their invasive processes (7, 8). In the analyses of late spontaneous miscarriages, by serial placental biopsies, in embryos with normal karyotype, the existence of decreased, completely reduced, trophoblast invasion was proven (9). This led to early embryo damage as a secondary complication of pathological trophoblast invasion (10). One of the studies proved the existence of heparin administration positive effects comparing to heparin binding epidermal growth factor on endometrial stromal cells (11).

The results obtained by examining therapy in the conditions of Leiden and G20210A mutations in the Italian study (5) confirm the benefits of therapy administration. These results are in favor of better pregnancy outcomes if LMWH is administered. Also, the obtained values of statistical data are consistent with the multicentric study conducted in Italy where it is confirmed that LMWH prophylaxis may decrease the risk of miscarriage in women with established Leiden mutation or prothrombin G20210A pathology (12). In relation to the incidence of preeclampsia, the clinical trials confirmed less frequent incidence of preeclampsia with Leiden and G20210A disturbances of the patients were administered LMWH. The same results on the frequency of preeclampsia are obtained in the similar study done in 2012 (13). The American College for Chest Physicians still holds the position that women with inherited thrombophilia and history of pregnancy complications should not use antithrombotic therapy (14, 15).

There are data on the usefulness of LMWH administration during pregnancy in women with standard type of thrombophilia (factor V Leiden and G20210A) as well as in newly established thrombophilia (MTHFR, PAI-1 and ACE) (15). In this study, "conventional" thrombophilia such as disturbance in factor V Leiden, prothrombin G20210A mutation, antithrombin 3, protein S and protein C deficiency were analyzed. Also, a "novel" group was analyzed which included disturbances in methylene tetrahydrofolate reductase (MTHFR), plasminogen activator inhibitor

(PAI-1) as well as angiotensin converting enzyme polymorphism (ACE). First trimester disturbances were followed, such as early abortion, then second trimester disturbances such as premature delivery, as well as late pregnancy disturbances such as premature delivery, intrauterine fetal growth restriction, intrauterine fetal death, preeclampsia, placental abruption and deep venous thrombosis. The study concluded that the administration of LMWH had no influence on decrease of earlyspontaneous abortions in conditions of thrombophilia. However, it is also stated that the frequency of intrauterine fetal death in treated patients in "conventional" group was decreased ($p = 0.011$). Comparing to the "novel" group, the incidence of fetal growth restriction, intrauterine fetal demise as well as premature deliveries was decreased. The study concluded that in conditions of "novel" thrombophilia, namely MTHFR, PAI and ACE polymorphism, the administration of LMWH was largely justified and needed further investigation.

In the cohort study, 50 women were followed in the period from July 2008 to September 2012 at the Department of Obstetrics and Gynecology of the University Hospital in Split, a tertiary referral center with about 4,500 deliveries per year. The methodology was based on establishing criteria for adverse pregnancy outcomes: the loss of embryo up to the 12th week of gestation, as the first trimester loss, but with previously established viability of the same embryo by ultrasonography; second trimester pregnancy loss between 12th and 21st week of gestation (plus 6 days); fetal growth restriction but with body weight under 5th percentile for gestational age and adapted to the population not standards; severe forms of preeclampsia defined as an arterial blood pressure over 160 systole and over 110 mmHg diastole together with proteinuria above 5g/24h; the incidence of HELLP syndrome (erythrocyte hemolysis, elevated liver enzymes and low platelets, under 100,000/ml); intrauterine fetal demise as well as fetal demise and death above 22nd week of gestation; premature delivery defined as delivery before the 37th week of gestation; each and every thromboembolic event immediately before or during the pregnancy; second trimester spontaneous abortion; intrauterine fetal death. Exclusion criteria were: patients under 42 years of age; the presence of acquired thrombophilia; uterine body congenital anomaly; perinatal infections (TORCH – toxoplasmosis, rubella, cytomegalovirus, herpes simplex virus); diabetes mellitus, chronic hypertension, endocrine disturbances, kidney transplantation, use of medications; multiple pregnancies, twins, triplets; abnormal first trimester screening tests, such as double and triple tests; pathological karyotype; established fetal anomalies. After the established pregnancy and proven embryo viability, LMWH therapy was administered. Inclusion period was from the 5th to the 9th week of gestation. Out of 50 women, 47 received dalteparin while only 3 received enoxaparin. Dalteparin doses were 2,500 IU/day and enoxaparin doses were 40 mg/day. In the period between 25th and 28th week of gestation, the doses were doubled, being 5,000 IU/day for dalteparin and 80 mg/day for enoxaparin. Both type LMWH therapies were administered up to 6 weeks postpartum. In the analyzed sample of 50 women there were 13 cases (26%) of factor V Leiden mutations, 5 cases (10%) of PT G20210A mutations, 6 cases (12%) of protein C mutations and 6 cases (12%) of protein S deficiency mutations while 25 women had MTHFR mutations. It is interesting to mention that there were 23 conditions of heterozygous MTHFR and 2 cases of homozygous MTHFR (50% of analyzed cases); in 33 cases (66%) PAI-1 polymorphism was found while 25 women (50% of the cases) had ACE polymorphism. Out of this number, the mutations were followed in terms of incidence of one, two or all three mutated genes for ACE polymorphism. Monogenic mutation was found in 7 patients (14%), two gene mutations in 25 patients (50%), three gene mutations in 16 cases (32%) and mutation of all four genes in 2 cases (4%) (15). Within the discussion part of the study, authors state several important comparisons. They primarily emphasized that it was the first time they had made the difference between congenital thrombophilia and divided them into segments, which was not done before. A rather small number of studies had observed "novel" thrombophilia and with conflicting conclusions. Ten papers had been stated confirming the data, i.e. having contradictory conclusions on the significance of LMWH administration in relation to adverse perinatal outcomes (16-26). They also found that there was no difference between the "conventional" and "novel" group in relation to the number of live born children or number of spontaneous abortions; a significant conclusion was the fact that there was no difference between the groups in the number of first and second trimester miscarriages. This was explained at the level of basic medicine, embryology, histology, as well as immunology. It is well-known that placentation takes place in two phases. The first phase is between the 8th and 12th week of gestation, while the placentation second phase is between the 16th and 18th week of gestation. This leads to the conclusion that the loss of pregnancy, whether in the first or second trimester, basically occurs due to inadequate placentation and that the moment when a woman would lose pregnancy does not depend on individual or other pregnancy characteristics, as well as individual response and woman's organism and placentation disturbance. The authors have concluded that the administration of LMWH contributed to the success of

pregnancy management. Out of 50 cases, there were 48 deliveries and 2 spontaneous abortions (30). An impressive conclusion is the fact that different clinical complications of thrombophilia may be observed through different categories of disease. A unique position, confirmed by basic medicine, is that in conditions of thrombophilia trophoblast invasion disturbances are created during angiogenesis at the level of placental blood vessels. In the process of embryology, independently of thrombophilia, an intensive change occurs at the level of trophoblast cells, new blood vessels, together with the incidence of trophoblastapoptosis and coagulation in the intervillous space. Each type of thrombophilia is characterized by these disturbances. However, even though each subtype of thrombophilia has identical system of origin, the degree of different level in the process may be explained by the fact that other form of thrombophilia is attached to the existing thrombophilia, thus influencing one target base, by vector system, they basically express a stronger effect.

Another conclusion is related to the incidence of intrauterine fetal death as well as fetal growth restriction. Thus, the administration of LMWH in conditions with conventional thrombophilia reduced only the incidence of intrauterine fetal death, while in the group with novel thrombophilia both the incidence of IUGR and intrauterine fetal death was reduced, but also the number of premature deliveries. Regarding the incidence of preeclampsia, the number of patients with incidence of preeclampsia was reduced by administration of LMWH with statistical significance, especially in the conventional group. This study has proven that the administration of LMWH in the group with novel thrombophilia has decreased the incidence of IUGR, intrauterine fetal death, as well as preeclampsia. Not one of the patients had sudden fetal death, out of 50 cases in both conventional and novel groups. In the group of patients who did not receive LMWH, there were 5 cases of sudden intrauterine fetal death in the group with conventional thrombophilia while there were 9 cases of intrauterine fetal death in the novel thrombophilia group without LMWH therapy. The lack of this study is the fact that there were no patients that were continuously followed and they were not given therapy, since it would be unethical. Also, the analysis was performed only on congenital, inherited thrombophilia and not the acquired thrombophilia. The significance of LMWH administration was emphasized in both groups.

Studies about separate and combined antiaggregative and anticoagulative therapy

The significance of LMWH administration, as well as unfractionated heparin, was mentioned for the first time in the Langer studies in 1980 (27). The studies were performed on different bases and methodologies. The incidence of early pregnancy loss and late pregnancy loss was analyzed. Also, maternal complications during pregnancy were observed.

The fact that trophoblast cell differentiation, analyzed in vitro, is obviously promoted by heparin administration, has been shown in 2004. The study also observed the difference in the effects of unfractionated heparin and LMWH. By administration of LMWH, the effect of antiphospholipid antibodies is decreased. During in vitro studies, it has been proven that the bonding of antiphospholipid antibodies on trophoblast cells (28).

Aspirin, as the thrombocytes aggregation inhibitor, may reduce the coagulation activity within placenta. Since coagulation is a part of immune set of phenomena and activation of complement system, it is considered that the effect of aspirin should be primarily interpreted through immune prism of complement activity. In relation to preventing thrombocytes aggregation, the aspirin has a role by acting on preventing the activity of complements leading to increased coagulation (29). Clinical studies on the effect of antithrombotic therapy to pregnancy losses have been analyzed in relation to antiphospholipid syndrome (by administration of aspirin or heparin), as well as conditions of thrombophilia by use of different therapy. Regarding the loss of one fetus and the analysis of antiphospholipid syndrome, there are no valid and available data. In relation to multiple fetal losses, namely the incidence of recurrent or habitual miscarriages, studies have been done and were summarized in Cochran review in 2005 (30). The efficiency of heparin administration together with aspirin for these conditions has been confirmed by Ziakas study (31).

Inefficiency of aspirin alone administration has been favored in several studies. Some studies, done on limited number of patients, showed that aspirin had no effect in preventing spontaneous abortion. The analysis has been done in three separate studies and a total number of 71 patients were analyzed. The conclusion was that aspirin had no benefits, however comparing to the group without any treatment but had fetal loss. Pregnancy loss relative risk was 1.05 with 95% CI. The results of all three studies have been summarized (32).

Regarding the efficiency of administration of heparin alone, the studies - which were later accepted as quasi random because of the fact that most patients were subjected to heparin administration without the use of aspirin – conclude that the administration of heparin was much more efficient and contributed to better pregnancy outcomes. The examined cases were patients with antiphospholipid syndrome and history of at least two spontaneous abortions before the 20th week of

gestation. The patients were given LMWH (Bemiparin in the dose of 2,500 IU/day). 80 cases were analyzed. The study conducted in 2012 by Alalaf et al emphasizes higher effects of LMWH administration. Statistics given in the conclusion states RR for healthy live children in women who were given LMWH to be 1.20 (95% CI 1.00-1.43). It is interesting that the authors emphasize that all the patients were given the dose of 2,500 IU without mentioning BMI of the patients. Also the fact of inadequate randomization limits the contribution of these conclusions (33).

As for the combined administration of heparin and aspirin, the performed meta-analysis (34) concluded that in conditions of antiphospholipid syndrome there was higher impact on positive pregnancy outcomes if the administered therapy combined aspirin and LMWH. In 103 patients who received a combined therapy, with previous two or more miscarriages, there was a significant reduction in first trimester abortions, with high statistical significance, in relation to the results given by Ziakas in 2010 where only aspirin was administered. Ziakas study analyzed 109 patients (RR 0.26, 95% CI 0.14-0.48) (31).

In relation to the pregnancy loss analysis, there was no statistical significance in sample processing in combined LMWH and aspirin treatment comparing to the group with aspirin alone. Two groups and 96 women with combined therapy were observed, and compared with a group of 90 cases with aspirin alone therapy. Summarized pregnancy loss RR was 0.70 and without statistical significance (95% CI, 0.34-1.45) (31).

The same result is obtained in the analysis of any type of heparin (unfractionated or LMWH) comparing to the use of aspirin alone. In fact, the benefits of heparin administration in relation to first trimester fetal loss and aspirin alone therapy is undisputable, however without statistical significance (RR 0.39, 95% CI 0.24-0.65)(31).

The effects of aspirin alone administration as well as combination of aspirin and heparin were analyzed. However, if the cause of habitual miscarriage is unknown, none of the studies explicitly suggests the use of antithrombotic therapy. All the analyzed studies, even though they prove the positive effects of the therapy, conclude that it is necessary to continue further investigations.

CONCLUSION

We have a confirmation by basic medicine that in conditions of thrombophilia disturbances of trophoblast invasion is primarily created during angiogenesis.

That leads us to the conclusion that the loss of pregnancy, whether in the first or second trimester, basically occurs due to inadequate placentation, in cases when a woman would lose pregnancy does not depend on other more dominant individual or other reproductive characteristics.

Considering the fact that authors of all studies insiston further investigations, we have to agree that these findings make way for further, more detailed studies about this condition.

DECLARATION OF INTEREST

The autors declare that there are no conflicts of interests.

Sažetak

TERAPIJSKE MOGUĆNOSTI PREVENCIJE NASTANKA HIPOKSEMIJE UTEROPLACENTARNE JEDINICE IZAZVANE TROMBOFILIJOM

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Spontani pobačaj je primarno definisan kao nenamerni gubitak trudnoće pre 20. nedelje gestacije. I teorija i praksa pokazuju da gubitak trudnoće do 10. nedelje gestacije može, pored mnogih drugih ginekoloških i mikrobioloških faktora, da se svede na postojanje neke stečene trombofilije kao što je antifosfolipidni sindrom. Brojne studije su sprovedene da se ispita efikasnost primene terapije kako bi se sprečili negativnii ishodi trudnoće. Urođene trombofilije, više se povezuju sa kasnijim gubicima trudnoće.

Ključne reči: trudnoća; trombofilija; LMWH;terapija, ishodi.

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