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Thrombophilic Complications in the Development of Gestional Hypertension (Review)

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Abstract

The literature review provides data on the role of thrombophilic conditions in obstetrics and gynecology: infertility, pre-embryonic loss, early miscarriages, intrauterine growth retardation syndrome, preeclampsia, thrombosis, antenatal fetal death, miscarriage and fetal loss syndrome. The issues of not only thrombotic, but also non-thrombotic mechanisms of the influence of thrombophilia on reproductive losses, the use oflow-molecular-weight heparins in combination with Diosmin (Phlebodia-600) to improve the outcome of labor in women with a history of fetal death and hereditary thrombophilia

Keywords: thromboembolic complications, thrombophilia, antiphospholipid syndrome, fetal loss syndrome

Thromboembolic complications (TEC) continue to be one of the leading causes of maternal morbidity and mortality worldwide. In 1884, Rudolf Virchow was the first to describe the three main factors in the development of thrombosis, which include a slowdown in blood flow, damage to the vascular wall and changes in blood properties. After that, a number of mechanisms predisposing to thrombosis were identified and studied, however, even with a thorough analysis of all risk factors, the cause of thrombus formation in 50% of cases remains unknown (the so-called "idiopathic" thrombosis) [3,5]. In fact, physiological pregnancy is characterized by all the signs of Virchow's triad, i.e. itself, the development of pregnancy andlabor process associated with the formation of an increased ability to thrombus formation [2, 3, 13]. This is due, firstly, to the physiological increase in the production of a number of factors of the coagulation cascade (VII, VIII, X, von Willebrand, fibrinogen, protein S), which is considered as a compensatory mechanism that reduces the risk of bleeding during labor; and, secondly, with venous stasis inherent in late gestation. In combination, this leads to a significant increase in the likelihood of developing such thromboembolic complications (TEO) as deep vein thrombosis (DVT) of the lower extremities, pulmonary embolism (PE), thrombosis of valve prostheses, thrombotic complications in thrombophilia and antiphospholipid syndrome 1 (APS) [1, 3, 6–9]. An increased tendency to thrombosis is also one of the important factors,

Venous thromboembolism (VTE), manifested as TEC or DVT, occur in 0.5–2.2 cases per 1000 population, depending on the population studied [1]. Among the female population, the risks of VTE are higher than among men, which is associated with contraception, pregnancy, the course of the postpartum period and hormone therapy, incl. local. During pregnancy, the risk of VTE increases 5-10 times compared to non-pregnant women of comparable age [6, 7].

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During pregnancy, hereditary and acquired coagulation disorders (infections, inflammation, obesity, dehydration, etc.) are also risk factors. The postpartum period poses an even higher risk [18], and during this period it increases 15–35 times compared to age-matched non-pregnant women [6, 9, 10]. The daily risk of pregnancy-related VTE is most pronounced during the first 3–6 weeks. after childbirth [17–19]. Thereafter, it declines rapidly, although a small residual risk may persist for 12 weeks. after childbirth [7, 10, 21]. In the structure of the causes of maternal mortality, although not the primary place, is obstetric embolism [1]. Maternal mortality is 0.1 per 100,000 births during vaginal delivery and 10 times higher (1–1.6 per 100,000) after caesarean section [19].mother, but also the fetus.

Preeclampsia is the most serious complication of pregnancy and remains one of the main causes of maternal and perinatal morbidity and mortality [1, 2, 3, 15, 16]. Researchers of the problem of genetic and acquired thrombophilia in different countries of the world, independently of each other, have established the dominant role of antiphospholipid antibodies, mutations and polymorphisms of genes predisposing to thrombophilia in the pathogenesis of preeclampsia and other complications of pregnancy [6, 8, 18]. In addition, the study of the problem of thrombophilia allowed a deeper understanding of the pathology of the mechanisms of implantation, trophoblast invasion, placentation and the formation of complications in the "mother - placenta - fetus" system.

The problem of thrombophilia is of particular importance in preeclampsia.

According to the world's researchers, as well as according to our data, it was found that 80% of patients with preeclampsia had thrombophilia [1, 3, 15, 16]. And such a high incidence of thrombophilia allows us to consider it as the most important etiopathogenetic factor in the development of preeclampsia. Thrombophilia promotes the development of endotheliopathy when the vascular endothelium is damaged by complexes of anti-phospholipid antibodies (APA), homocysteine and products of its metabolism, reduces the production of natural anticoagulants with an increase in procoagulants, which leads to an increase in the level of von Willebrand factor and fibronectin, which, in turn, are simultaneously factors of pathogenesis and disseminated intravascular coagulation and preeclampsia. The risk of preeclampsia increases significantly when genetically determined thrombophilia is combined with antiphospholipid syndrome (APS) [13,15,20].

The term thrombophilia is used to describe a heterogeneous group of bleeding disorders (acquired or inherited) that are accompanied by a significant increase in the risk of arterial or venous thrombosis [16]. Antiphospholipid antibodies (APA), or antiphospholipid syndrome (APS), is the most common acquired thrombophilic disorder in pregnant women. It is diagnosed based on the presence of an increase in IgG and IgM levels (GpL or MpL> 20) or the presence of a lupus anticoagulant [15, 19]. The most common hereditary thrombophilic disorder in pregnant women is mutations in factor V Leiden, the prothrombin gene, and the tetrafolate reductase gene. Over the past two decades, numerous epidemiological and case-control studies have been conducted to investigate the relationship between thrombophilia and pregnancy complications.

The association between severe preeclampsia at less than 34 weeks of gestation and antiphospholipid syndrome was first described Murashko A.V.in 2011 [19, 23]. Based on this report, recommendations were made to screen for antiphospholipid syndrome in all women who

developed severe preeclampsia at less than 34 weeks of gestation and to treat them for antiphospholipid syndrome in subsequent pregnancies. Since the publication of this publication, the results of other studies have been published, some have confirmed the existence of a link between the presence of antiphospholipid antibodies and preeclampsia, and some have denied [6, 7]. Indeed, the authors of recent publications believe that there is no need for routine screening for antiphospholipid syndrome in women with early preeclampsia [6].

The link between preeclampsia and hereditary thrombophilia was first mentioned in the publication Zhou F. andet al. in 2020 [8]. Until this time, many retrospective and case-control studies have been conducted, investigating the relationship between the carriage of thrombophilic mutations and preeclampsia. These studies have served as the basis for several reviews [1,3,4]. It turned out that the results were very mixed. However, a meta-analysis of all case-control studies showed that only the Leiden mutation is accompanied by an increased risk of preeclampsia (risk 1.18, 95% CI, 1.14-2.87) [4, 7]. The reasons for these differences in results can partly be explained by the lack of well-organized large prospective studies that would assess the risk of preeclampsia in pregnant women without symptoms of preeclampsia, but with the carriage of thrombophilia genes, and partly due to the large heterogeneity of patients. included in case-control studies [1, 5]. Almost all studies assessed the prevalence of carriage of thrombophilia genes in women with complicated, severe preeclampsia who were admitted to specialized obstetric centers. In addition, most of the studies included healthy women with full-term pregnancies as controls. Therefore, the reliability of the results of such studies can be doubted, since they overestimate the prevalence of carriage of thrombophilia genes in the study group and underestimate in the control group. In addition, studies show significant differences in the severity of preeclampsia and the timing of pregnancy at delivery in the study group [4], as well as significant differences in race and ethnicity. For instance, All studies found an association between severe preeclampsia, especially with gestational age less than 34 weeks, but no such association with mild preeclampsia or full-term pregnancy. Also, a large multicenter prospective observational study of 5168 pregnant women showed that the Leiden mutation rate was 6% among white patients, 2.3% among Asian women, 1.6% among Hispanics, and 0.8% among blacks [1, 3]. Thus, if only white women were included in the study, then the association between hereditary thrombophilia and preeclampsia became obvious [8], and in studies that included Hispanics or black women, the carriage of Leiden mutation or prothrombin gene mutation was rare and was not associated with preeclampsia. especially when gestation is less than 34 weeks, but there is no such association in the presence of mild preeclampsia or full-term pregnancy. Also, a large multicenter, prospective observational study of 5168 pregnant women showed that the Leiden mutation rate was 6% among white patients, 2.3% among Asian women, 1.6% among Hispanics, and 0.8% among black women [9, 10]. So, if the study included only white women, then it became clear an association between hereditary thrombophilia and preeclampsia [8], and in studies that included Hispanics or black women, the carriage of the Leiden mutation or prothrombin gene mutation was rare and was not associated with preeclampsia. especially when gestation is less than 34 weeks, but there is no such association in the presence of mild preeclampsia or full-term pregnancy. Also, a large multicenter, prospective observational study of 5168 pregnant women showed that the Leiden mutation rate was 6% among white patients, 2.3% among Asian women, 1.6% among Hispanics, and 0.8% among

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Foreign authors reported the results of a large multicenter case-control study, which compared the incidence of thrombophilia in women with preeclampsia and in women with normal full-term pregnancies [2, 6, 7, 22]. The study included 808 Italian women who had thrombophilia, and the corresponding control group (808 people) - healthy women with uncomplicated full-term pregnancy. None of the patients had a history of thromboembolism and all underwent standardized thrombophilia screening within 4-12 months after the completion of the present pregnancy. The authors also divided their patients into groups according to the severity of preeclampsia (moderate or severe). In addition, maternal and fetal complications were compared in a group of patients with severe preeclampsia with or without thrombophilia.

An Italian study revealed that the incidence of hereditary or acquired thrombophilia is significantly higher in women with severe preeclampsia (50.7%) compared with the control group (17.2%), the risk of developing severe preeclampsia with carriage of thrombophilia is 4.9 times higher (95% confidence interval, from 3.5 to 6.9). In contrast, the authors found that there was no association between thrombophilia and mild preeclampsia (16.7% versus 14.9%, not statistically significant). Also, according to the results of this study, a very important conclusion was made - the combination of severe preeclampsia and thrombophilia is a risk factor for serious complications of pregnancy in the mother - for example, the development of severe preeclampsia before 28 weeks of pregnancy, placental abruption, disseminated intravascular coagulation, and acute renal failure. In addition,

However, it should be noted that in addition to strengths, this study also has weaknesses. This is the largest case-control study conducted in a relatively homogeneous population of white women. In addition, this is the first study to compare groups by severity of preeclampsia. Moreover, both the main and control groups were homogeneous in terms of age, number of births, body mass index, smoking, since all these factors affect the likelihood and severity of preeclampsia. Also, women with a history of vascular pathology were excluded from the study. In contrast to previous studies, a prerequisite for the diagnosis of thrombophilia was double-positive thrombophilic panel tests, and moderate to high levels of anticardiolipin antibodies were

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considered positive. The main weakness of the study is the selection to the control group (healthy pregnant women who gave birth to full-term babies). This group was not uniform in terms of gestational age at the time of delivery. In addition, the group of patients with preeclampsia was made up of women referred to a large specialized obstetric center due to a complicated course of pregnancy, so this group may not reflect the situation with severe preeclampsia in the region. These patient selection considerations may have led to an overestimation of the relationship between thrombophilia and severe preeclampsia and complicated pregnancy. Moreover, it is unclear whether the results of this study can be applied to an ethnically diverse population such as US women. In addition, the group of patients with preeclampsia was made up of women referred to a large specialized obstetric center due to a complicated course of pregnancy, so this group may not reflect the situation with severe preeclampsia in the region. These patient selection considerations may have led to an overestimation of the relationship between thrombophilia and severe preeclampsia and complicated pregnancy. Moreover, it is unclear whether the results of this study can be applied to an ethnically diverse population such as US women. In addition, the group of patients with preeclampsia was made up of women referred to a large specialized obstetric center due to a complicated course of pregnancy, so this group may not reflect the situation with severe preeclampsia in the region. These patient selection considerations may have led to an overestimation of the relationship between thrombophilia and severe preeclampsia and complicated pregnancy. Moreover, it is unclear whether the results of this study can be applied to an ethnically diverse population such as US women. These patient selection considerations may have led to an overestimation of the relationship between thrombophilia and severe preeclampsia and complicated pregnancy. Moreover, it is unclear whether the results of this study can be applied to an ethnically diverse population such as US women. These patient selection considerations may have led to an overestimation of the relationship between thrombophilia and severe preeclampsia and complicated pregnancy. Moreover, it is unclear whether the results of this study can be applied to an ethnically diverse population such as US women.

Until now, many questions remain unclear. Should all women with severe preeclampsia be screened for thrombophilia? This screening is very expensive and most patients will have negative results. If the results are positive, what will the doctors do in these cases? Some retrospective studies suggest that with a combination of severe preeclampsia and thrombophilia in subsequent pregnancies, the risk of severe complications (preeclampsia, intrauterine growth retardation, fetal death) is higher [2, 7, 21]. In addition, some researchers believe that treatment with heparins and low-dose aspirin, Diosmin (Phlebodia-600) as a prophylaxis will improve the outcome in subsequent pregnancies [4, 5, 22]. It was recently shown that low-molecular-weight heparins in combination with Diosmin (Phlebodia-600) improve the outcome in women with a history of fetal death and hereditary thrombophilia [1, 2, 10]. Thus, we see that there is an urgent need for a double-blind controlled trial that would help evaluate the benefits of using heparins during pregnancy in women with severe preeclampsia and a history of thrombophilia. Until such a study is done, screening all patients with severe preeclampsia for thrombophilia appears to be experimental.

CONCLUSION

From modern positions, the diagnosis of "thrombosis", which may hide a number of anomalies of the hemostasis system, cannot completely satisfy the clinician. The diagnosis of thrombosis is similar to the diagnosis of anemia, when, in addition to the characteristic clinical symptoms, the results of laboratory and instrumental studies are important for the doctor to determine the cause of the anemia and prescribe pathogenetically justified treatment. All patients with thrombosis and obstetric complications during pregnancy or in history (both personal and family) should be screened for hereditary forms of thrombophilia. This allows you to determine the further tactics of the patient's treatment, its duration, the choice of the drug, it allows you to prevent both thromboembolic and obstetric complications when planning a subsequent pregnancy,to give the patient recommendations on anticoagulant therapy in combination with Diosmin (Phlebodia-600) for a long time in the event of external risk factors for thrombosis (trauma, surgery), if necessary, conduct a study for thrombophilia in the patient's relatives.

From our point of view, various forms of thrombophilia are an intermediate mechanism of the pathogenesis of intrauterine fetal suffering. On the other hand, the presence of thrombophilia in parents raises the question of the need to examine the newborn in order to predict and prevent diseases in adulthood. The discovery of the genetic forms of thrombophilia and APS, the study of their role in the pathogenesis of thrombosis, the development of effective therapy and prevention of VTE allows us to say that thromboembolic complications are preventable causes of maternal mortality.

Correction of disorders in the hemostasis system in pregnant women with thrombophilia and miscarriage during the formation of the placenta until the end of trophoblast invasion is necessary not only for prolonging pregnancy, but also for preventing long-term complications of pregnancy (severe forms of gestational hypertension, placental insufficiency, IUGR).

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CONFLICT OF INTEREST

The authors declare that they have no competing interests.

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