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Hemostatic Disorders in Pregnancy

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ABSTRACT

Pregnancy is characterized by several changes in the hormonal milieu, which though physiological, may aggravate problems in specially those with pre-existing risk factors and may be associated with serious morbidities detrimental to both maternal and fetal health and maybe mortality even. This article reviews cardinal knowledge regarding major hemostatic disorders during pregnancy with special reference to thrombo-embolic disorders. The description includes the basic etiopathogenesis, prominent symptoms/complications and the latest trends in treatment of the common hemostatic anomalies in reference to the pregnant state.

KEYWORDS : Pregnancy, Hemostatic disorders, Thrombotic

Article

Pregnancy is characterized by several changes in the hormonal milieu, which though physiological, may aggravate problems in specially those with pre-existing risk factors and may be associated with serious morbidities detrimental to both maternal and fetal health. Fate of major hemostatic disorders in pregnancy is discussed below.

Thromboembolic Disorders in Pregnancy

Traditionally, the risk of venous thrombosis and pulmonary embolism in otherwise healthy women is considered highest during pregnancy and the puerperium.[1]The reported incidence of venous thrombo-embolism ranges from 0.5 to 1.7 per 1000 deliveries, depending on the population studied. [2, 3]

Predisposition

During pregnancy there is an increased predisposition to stasis, local trauma to the vessel wall as well as hyper coagulability, all three being components of the classic Virchow's triad given by Rudolph Virchow in 1956., thus increasing predisposition to thrombosis. Other risk factors include maternal age of 35 years or more, prior history of thrombosis, history of prior oral contraceptive use, smoking, surgery, co-morbidities like hypertension, cancer, paraplegia or other states of prolonged immobilization and various complications of pregnancy and childbirth.[4]

Thrombophilias

Inherited or acquired deficiencies of the inhibitory proteins of the coagulation cascade are collectively referred to as thrombophilias, which can lead to hypercoagulability and an increased predisposition to thrombotic tendencies. Important naturally occuring anticoagulants and their relevance is being discussed below.

Although Antithrombin III deficiency is rare, it is the most thrombogenic kind of the heritable coagulopathies[1].There is a moderately high incidence of late pregnancy complications and poor pregnancy outcomes. Monitoring of antithrombin III levels in pregnancy induced hypertension may even help in assessing fetal jeopardy. [5]

Protein C is a natural anticoagulant, which in the presence of protein S, controls thrombin generation by inactivating factors Va and VIIIa. Protein C levels are unchanged during normal pregnancy, except for a small increase at 28-32 weeks [6]. Protein C deficiency increases the risk of thrombosis during pregnancy and in women on oral contraception[7]. Activated Protein C resistance is characterized by resistance of plasma to the anticoagulant effects of activated protein C. The most common cause for this is the factor V Leiden mutation.

Protein S is also a natural anticoagulant which decreases thrombin generation. A second trimester fall in protein S levels is physiologic pregnancy adaptation. Women with a thrombo-embolic event appearing for the first time during pregnancy should have investigations for protein S deficiency delayed until the postpartum period, to avoid misdiagnosis and treatment[8].

Neonatal homozygous protein C or S deficiency is usually associated with a severe clinical phenotype known as purpurafulminans, which is characterized by extensive thromboses in the microcirculation soon after birth[9]. Condition may even be life threatening if timely interventions are not done, which include infusions of fresh frozen plasma and heparinization during the acute episode and oral anti-coagulant therapy during the symptom-free period [10].

Prothrombin G20210A mutation is a missense mutation in the prothrombin gene leading to an excessive accumulation of prothrombin, which may then be converted to thrombin. Heterozygous mutations are uncommon and homozygous mutations are even more so[11].

Homocysteine is derived by demethylation of the essential amino acid methionine. Its metabolism depends primarily on three enzymes and several co-factors (vit B6, B9 and B12). Genetic abnormality in these vitamins leads to hyperhomocysteinemia which is a pro-thrombotic state[12]. The most common cause of elevated homocysteine is the C667T mutation of the enzyme 5, 10-methylene-tetrahydrofolate reductase, which impairs the generation of MTHF. Hyperhomocysteinemia is associated with the syndromes of repeated miscarriages, pre-eclampsia, abruptio placentae, thrombo-embolic events, neural tube defects and perhaps with fetal death in utero and intra-uterine growth retardation [13].

Antiphospholipid antibodies are distinctly associated with a syndrome characterized by reccurrentthromboses and adverse pregnancy outcomes, including, early abortion, intra-uterine fetal growth restriction and even fetal demise. They are commonly found in patients with systemic lupus erythematosus[14].

Deep Venous Thrombosis

Both acquired and heritable thrombophilia show strong association with deep vein thrombosis associated with pregnancy[15].

Most cases of venous thrombosis during pregnancy are confined to the deep veins of the lower extremity. Usually, the left leg has been found to be particularly involved. This may result from compression of the left iliac vein by the right iliac and ovarian arteries, both of which cross the vein only on the left side[16] or due to the gravid uterus. Shian Chan W et al[17](2009) have suggested three objective variables ("LEFt"; left leg[L], calf circumference difference >2cm [E], and first trimester presentation[Ft]), which may improve the diagnostic accuracy of the diagnosis of deep vein thrombosis in pregnancy. Proximal deep vein thrombosis restricted to the femoral or iliac veins is seen in more than 60% cases[18].

Although venography remains the standard technique of confirming the clinical diagnosis, noninvasive methods have largely replaced it. Impedance plethysmography is also associated with increased false positive results during pregnancy. Compression ultrasonography is a noninvasive technique which is often combined with color doppler-sonography. Besides, real time ultrasonography may also as well be used. However, normal venous ultrasonography results do not necessarily rule out pulmonary embolism[19], because the thrombosis may have already embolized or because it arose from deep pelvic veins inaccessible to ultrasound evaluation. Torkzad et al[20]concluded that in pregnant females, there is only fair agreement between ultrasound and MRI for determination of extent of deep vein thrombosis into pelvic veins, with MRI showing consistently more detailed depiction of extension. Hence, MRI is preferred over ultrasonography for detection of deep vein thrombosis.

Anticoagulation is always initiated with either unfractionated or low-molecular-weight heparin for deep vein thrombosis. For women who are still pregnant, heparin therapy is continued, and for those developing thrombosis in the postpartum period, anticoagulation is begun simultaneously with warfarin. Most often, pain is soon relieved by these measures. After symptoms have completely abated, graded ambulation should be started. Elastic stockings are fitted and anticoagulation continued. Recovery to this stage usually takes about 7 to 10 days. Pulmonary embolism is a leading cause of maternal mortality specially in the western world[21].

Treatment of the thromboembolism during pregnancy begins with an intravenous heparin bolus followed by continuous infusion titrated to achieve full anticoagulation. Intravenous anticoagulation should be maintained for at least 5 to 7 days, after which treatment is converted to subcutaneous heparin. Injections are given every 8 hours to prolong the activated partial thromboplastin time (aPTT) to least 1.5 times control throughout the dosing interval. Treatment is continued for at least 3 months after the acute event. For women with antiphospholipid syndrome, aPTT cannot assess adequacy of anticoagulation with heparin, and anti-factor Xa levels since it may be falsely elevated, owing to the antibodies against phospholipids used in coagulation testing.

Anticoagulation with warfarin derivatives is generally contraindicated during pregnancy. These drugs readily cross the placenta and cause fetal warfarin syndrome (including craniofacial and retinal abnormalities) and even death, sometimes. They are safe, however, when ingested while breast feeding[22].

Clotting disturbances

Hemophilias

Hemophilia A and B are X-linked recessively transmitted. They are characterized by a marked deficiency of factors VIII an IX respectively. Hence, they are rare among women compared with men, except for when there is an inactivation of one X chromosome.

The degree of risk for each of these hemophilias is influenced markedly by the level of circulating factor VIII or factor IX. If the level is at less than or equal to 1%, the risk is major. In female carriers, activity is expected to average 50 percent. If levels fall below 10 to 20 percent, hemorrhage may occur even in them. These clotting factors increase appreciably during normal pregnancy and in carriers of hemophilia A and B, the risk of hemorrhage is reduced by avoiding lacerations, minimizing episiotomy, and maximizing postpartum myometrial contractions and retraction. Vaginal delivery is not contra-indicated and has been proved to be as safe as caesarean section[23]. After delivery, the risk of hemorrhage in the neonate increases, especially if circumcision is attempted[1].

vonWillebrand disease

It is the most commonly inherited bleeding disorder, and its prevalence is as high as 1 to 2 percent[24]. Most of the von Willebrand variants are inherited as autosomal dominant traits. Types I and II are the most common variants. Type III, which is the most severe of all variants, is phenotypically recessive. Pregnancy outcomes in women with von Willebrand disease are generally good but postpartum hemorrhage is encountered in up to 50 percent of cases[1].

Women with vWD still require close monitoring during pregnancy and thereafter. Although rare, antepartum hemorrhage may complicate spontaneous miscarriage or elective medical termination. There is currently no consensus on the optimal management of women with vWD during pregnancy. The limited evidence suggests that the use DDAVP is relatively safe during pregnancy[25].

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