THROMBOTIC MICROANGIOPATHIES IN PREGNANCY AND THE POSTPARTUM PERIOD

GEBEİLİK VE LOHUSALIKTAKİ TROMBOTİK MİKROANJİYOPATİLER

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SUMMARY

Detection of trombocytopenia and hemolytic anemia during pregnancy and the postpartum period alarms the physician because these are recognized as the signs of severe potentially life-threatening syndromes such as pregnancy-associated thrombotic thrombocytopenic purpura (TTP), hemolysis-elevated liver enzymes-low platelet count (HELLP) syndrome, and postpartum hemolytic uremic syndrome (PHUS). Subsequent to different initial insults the final pathologic processes produce similar clinical pictures, and although their treatments differ considerably many times differential diagnosis of these three clinical syndromes is impossible before starting empiric treatment. Plasmapheresis with plasma exchange is the treatment of choice for TTP and PHUS whereas delivery is indicated for HELLP syndrome. Once recognized patients with thrombotic microangiopathies should be transferred to tertiary care hospitals where the mother and infant can get adequate treatment.

(Key words: HELLP Syndrome, Hemolytic Uremic Syndrome, Thrombocytopenic Purpura)

ÖZET

Gebelik ve lohusalık döneminde trombositopeni ve hemolitik aneminin saptanması hekimleri tedirgin eder, çünkü bu bulgular trombotik trombositopenik purpura (TTP), hemoliz, yüksek hepatik enzimler, düşük trombosit sayısı (HELLP) sendromu ve postpartum-lohusalık hemolitik üremik sendromu (PHUS) gibi hayatı tehdit edici birkaç sendromun belirtileridirler. Patogenezde değişik olaylar yer alsa da sonuçta bu sendromlarda birbirine benzer klinik tablolar ortaya çıkar ve çoğu kez ampirik tedavi başlamadan ayını tanı yapmak imkansız gibidir. Plasma değişimi plasmaferez TTP ve PHUS tedavisinde gereklı iken HELLP sendromunda gebelliğin sonlandırılması gereklidir. Farkındıklarını takdirde trombotik miroanjipatili gebeler ve lohusalar tam teşekküllü hastanelere sevk edilmelidirler.

(Anahtar Sözcükler: HELLP Sendromu, Hemolitik Üremik Sendrom, Trombositopenik Purpura)

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Thorombotic microangiopathies of pregnancy and postpartum period include thrombotic thrombocytopenic purpura (TTP), hemolysis-elevated liver enzymes-low platelet count (HELLP) syndrome and postpartum hemolytic uremic syndrome (PHUS). Annual incidence of TTP is approximately 0.1 case per 100,000 in general population, and TTP cases are most prevalent in the third and fourth decades of life. The reported incidence of HELLP syndrome varies between 4% and 14% among patients with preeclampsia(1). The incidence of preeclampsia is usually about 5% of all pregnancies(2). The obstetrician is much more likely to confront HELLP syndrome than TIP in a pregnant patient. In one study the frequency of HELLP syndrome compared to frequency of TTP was 70 to 1 (3). Majority of PHUS cases are recorded in children; annual incidence is around 1 and 3 cases per 100,000 children at ages <15 and <3 years respectively (4). PHUS rarely occurs in adults and if seen after pregnancy is often called postpartum hemolytic uremic syndrome (PHUS) or postpartum acute renal failure (PARF).

Whether TTP and PHUS be considered two distinct diseases or different expressions of the same disease has not been established (5). It is very difficult to separate the two syndrome especially among adults at least clinically. However there is a general agreement that the diagnosis of HUS is made for infants and children, and TTP for adults for the similar set of clinical and laboratory findings. Both HUS and TTP can be seen in association with pregnancy, cancer, infections, and the use of chemotherapeutic agents (4). If thrombotic microangiopathy appears during pregnancy, the clinical picture may resemble both TTP and HUS. In this setting TTP is the most commonly used term, but TTP/HUS should imply the same disease.

ETIOLOGY AND PATHOGENESIS

The causes precipitating thrombotic microangiopathies are not always clear. Classic HUS of childhood usually follows viral infections, gastroenteritis caused by verrotoxin-producing serotype of Escherichia coli (E. coli 0157:H7) or Shigella (10). Some patients receiving chemotherapy with certain agents, including mitomycin, cyclosporine, and cisplatin develop thrombotic microangiopathy resembling TTP/HUS (10). The etiologic factors involved in pregnancy associated TTP/HUS, HELLP syndrome and PHUS are unknown. Endothelial injury is thought to be the main determinant of the microangiopathic process (11). Agents found to be responsible for this endothelial injury in human studies include bacterial endotoxins, antiendothelial antibodies, anticardiolipin antibodies, immune complexes and drugs (11). Defective PGI2 bioavailability, defective nitric oxide (NO) production abnormal processing of FVII-vWF and endothelin release follows the endothelial damage (11). Platelet activation and adhesion occurs at the site of injury after the endothelial damage. This is consistent with the finding of "exhausted" circulating platelets and elevated levels of platelet released factors in the acute phase of HUS (11). The renal pathologic lesions of the thrombotic microangiopathies are characterized by edematous intimal expansion in arteries, fibrinoid necrosis of arterioles, and edematous subendothelial expansion in glomerular capillaries.

In TTP/HUS, the thrombotic microangiopathy is the result of platelet and vessel wall dysfunction as opposed to 'thrombin generated coagulation disruption' seen in disseminated intravascular coagulation (DIC) (12). The thrombi are essentially composed of degranulated morphologically altered plateles in contrast with the extensive fibrin in the microthrombi of DIC (4). The microangiopathic hemolytic anemia of TTP and HUS is distinguished from that of DIC by the lack of precisely abnormal prothrombin and partial thromboplastine times (4). In TTP and HUS the fibrinogen levels are characteristically normal and fibrin-fibrinogen degradation products are minimally elevated. Al-
though sensitive assays for fibrin degradation products may provide evidence of mild fibrinolysis, especially in HUS patients, nearly normal PT and PTT distinguishes the dominant fibrinolysis of DIC from the TTP/ HUS microangiopathies (4). Coombs negative hemolytic anemia with red cell fragmentation, thrombocytopenia and thrombotic microangiopathies.

In HELLP syndrome renal pathologic lesion is defined as capillary endotheliosis; and the hepatic lesion is described as periportal or focal parenchymal necrosis in which hyaline deposits of fibrin-like material can be seen in the sinusoids (13,14). Subcapsular hematoma of the liver is a serious but fortunately a rare complication of HELLP syndrome (15).

CLINICAL MANIFESTATIONS AND PROGNOSIS

In thrombotic microangiopathies what ever the initiating factors are, the final outcome is the development of hyalin thrombi in the microvasculature producing similar clinical pictures. The differential diagnosis of thrombocytopenia and hemolytic anemia during pregnancy and postpartum period includes pregnancy associated TTP (TTP/ HUS), PHUS- and HELLP syndrome. Precise diagnosis is important because the treatment of TTP is essentially different from that of HELLP syndrome. Some important features of these syndromes are summarized in Table 1. Pregnancy associated TTP can be encountered during any period of pregnancy. Generally TTP is characterized by pentad of hemolytic anemia, thorombocytopenia, neurologic symptoms, fever and renal dysfunction(6). In this syndrome neurologic symptoms like confusion, coma and seizures are more prominent as well as fever. HELLP is an acronym for hemolysis, elevated liver enzymes, and usually seen during the third trimester of pregnancy. Abdominal pain is seen usually in the epigastric or right upper quadrant area, due to the distension of hepatic capsule. Patients with HELLP syndrome have high rate of complications. In one study 84% DIC, 44% HELLP abruptio placentae, 13% cardiopulmonary arrest or cerebral injury and 6% ruptured liver hematomas were reported in patients with HELLP syndrome (2). Differential diagnosis of thrombotic microangiopathies during pregnancy is difficult because no single clinical feature or laboratory test is pathognomonic. Differentiation between the the pregnancy associated TTP and HELLP syndrome may not be possible even after the intensive evaluation of the clinical and laboratory findings. Early spontaneous resolution of the disease after delivery may be the strongest clue for the diagnoses of HELLP syndrome, but this does not help to determine the optimal therapy beforehand (7). Postpartum hemolytic uremic syndrome (PHUS) typically manifests after a normal delivery and has a symptom free interval between one day to 10 weeks (8). The incidence of PHUS is not more in patients who were preeclamptic (4). Hypertension is always found in PHUS (9). Lesions and symptoms tend to be more localized to the kidneys and renal dysfunction is the characteristic finding and neurologic symptoms are less frequent than in TTP (4). A bleeding tendency is seen in most of the patients. The gastrointestinal tract is the main site of bleeding(5). The prognosis of this form of adult hemolytic uremic syndrome (PHUS) is very poor in contrast to childhood hemolytic uremic syndrome.

It is also considerably worse than pregnancy associated TTP (4) (Table 1)

TREATMENT

Treatment strategies for pregnancy associated TTP and HELLP syndrome differ significantly because they have different pathogenic mechanisms. Treating HELLP syndrome mistakenly as TTP will unnecessarily delay delivery and may result in deterioration of the disease. In the reverse condition; mistakenly treating TTP as HELLP
<table>
<thead>
<tr>
<th>CLINICAL FINDINGS</th>
<th>TTP/HUS</th>
<th>HELP</th>
<th>PHUS(PARF)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Time of onset</td>
<td>anytime</td>
<td>3rd trimester</td>
<td>postpartum</td>
</tr>
<tr>
<td>Neurologic symptoms</td>
<td>often</td>
<td>rarely</td>
<td>maybe</td>
</tr>
<tr>
<td>Renal insufficiency</td>
<td>maybe</td>
<td>maybe</td>
<td>severe</td>
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<tr>
<td>Hypertension</td>
<td>maybe</td>
<td>often</td>
<td>often</td>
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<tr>
<td>Abdominal pain</td>
<td>rarely</td>
<td>often</td>
<td>rarely</td>
</tr>
<tr>
<td>Fever</td>
<td>usually</td>
<td>rarely</td>
<td>maybe</td>
</tr>
<tr>
<td><strong>LABORATORY DATA</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Thrombocytopenia</td>
<td>yes</td>
<td>yes</td>
<td>yes</td>
</tr>
<tr>
<td>Hemolitic anemia</td>
<td>+++</td>
<td>+ to +++</td>
<td>+++</td>
</tr>
<tr>
<td>PTT</td>
<td>normal</td>
<td>normal to ↑ ↑ ↑</td>
<td>normal</td>
</tr>
<tr>
<td>FDP</td>
<td>normal</td>
<td>normal to ↑ ↑ ↑</td>
<td>normal to ↑</td>
</tr>
<tr>
<td>vWF multimers</td>
<td>↑</td>
<td>normal</td>
<td>↑</td>
</tr>
<tr>
<td>Antithrombin-III</td>
<td>normal</td>
<td>depressed</td>
<td>normal</td>
</tr>
<tr>
<td>Serum aminotransferase</td>
<td>normal to ↑</td>
<td>normal to ↑ ↑</td>
<td>normal to ↑</td>
</tr>
<tr>
<td>Bilirubin</td>
<td>↑ ↑</td>
<td>normal to ↑ ↑</td>
<td>↑ ↑</td>
</tr>
<tr>
<td><strong>RENAL HISTOPATHOLOGY</strong></td>
<td>TMAP</td>
<td>GE</td>
<td>TMAP</td>
</tr>
<tr>
<td><strong>MATERNAL MORTALITY</strong></td>
<td>&lt;30%</td>
<td>2%</td>
<td>&gt;50%</td>
</tr>
<tr>
<td><strong>PERINATAL MORTALITY</strong></td>
<td>75-80%</td>
<td>10-60%</td>
<td>-</td>
</tr>
<tr>
<td><strong>TREATMENT</strong></td>
<td>PP+PE</td>
<td>delivery</td>
<td>PP+PE</td>
</tr>
</tbody>
</table>

PTT, partial thromboplastin time; FDP, fibrin degradation products; vWF, von Willebrand Factor; TMAP, thrombotic microangiopathy; GE glomerular endotheliosis; PP, plasmapheresis; PE, plasma exchange PHUS, postpartum hemolytic uremic syndrome PARF, postpartum acute renal failure. (5,7,11,13,15,22).
LDH concentrations and platelet count is valuable to evaluate the intensity of the therapy (5,12). Successful treatment with plasma exchange has allowed prolongation of the pregnancy for more than a month eliminating the problems of immaturity (4). Steroids have been widely used in thrombotic microangiopathies with the rationale that they improve platelet survival time and response to steroids alone has been reported in occasional patients (11). Steroids have always been employed as a part of treatment in thrombotic microangiopathies but their solitary effect is not very clear (11). Antiplatelet agents, such as aspirin and dipyridamole, do not appear to be beneficial in classical HUS, but their use has been recommended for adult TTP/HUS and neurologic involvement (11). For thrombotic microangiopathies antiplatelet therapy does not look appropriate while thrombocyte count is diminished but may have a role in preventing thrombotic complications when thrombocyte counts rebound during the resolution of the disease.

Intravenous immunglobulin infusions (0.5 mg/kg/day for consecutive days) was recommended as a means of neutralizing platelet-agglutinating activity present in TTP plasma; however, this treatment have been associated with anaphylaxis and infections secondary to inhibition of Fc receptor mediated immune clearance (11). Splenectomy is also tried in TTP as in other forms of thrombocytopenia but it is speculated that the results obtained from splenectomy could be due to the intraoperative administration of blood or concomitant steroid and antiplatelet treatments (5,11). Immunosuppressive therapy is indicated if above mentioned measures fail, There are several case reports which documented usefulness of cyclosporine in the management of TTP and HUS (7,16,17). Cyclosporine is reported one of the drugs that causes HUS and hence its usage in treatment of TTP and HUS seems controversial (18) Cyclosporine precipitates HUS probably by inhibiting prostacyclin production by endothelium (18). Cyclosporine if used appropriately may arrest disease activity and may prove to be a useful alternative therapy for patients with thrombotic microangiopathies by unknown mechanisms (19). Vincristine and other immunosuppressive agents may be particulary useful in preventing relapses in chronic forms of TTP (67). Recently vitamin E treatment has been proposed in the treatment of thrombotic microangiopathies, but controlled trials are needed (5,20).

Renal replacement therapy is required more often for patients with PHUS than the patients with TTP (9). If needed dialysis therapy should be started early and performed on a daily bases; and sudden shifts in extracellular volume and hypotension or bleeding complications should be avoided (8).

Definitive treatment for HELLP syndrome is the delivery of the infant and placenta. Elimination of placenta and supporting decidual tissue is the mainstay of the treatment. Goodlin considered hypovolemia as the cause of this syndrome and hence recommended plasma volume expansion with 5% albumin, he reported a 10% success rate in prolonging pregnancies in such patients (21). Tiagaryan et al reported an increase in platelet count and improvement in liver enzyme levels in 5 patients treated with prednisone and betamethasone (22). Against this approaches there is no satisfactory evidence that delaying delivery will improve mother and infant survival rates, so once the diagnosis of HELLP syndrome is made, delivery should not be delayed (8,14). If caesarean section is indicated, general anesthesia should be preferred because epidural anesthesia may cause significant bleeding in epidural space (2). Infrequently parturient women fail to show improvement within 72 hours of delivery, in these rare patients with unremitting disease alternative therapy such as plasmapheresis with plasma exchange is recommended (1,12).

When the diagnosis not clear whether the
patient has TTP or HELLP syndrome, it is recommended that, at gestational ages greater than 34 weeks, antithrombin-III (AT-III) levels should be drawn and the patient should be delivered (4). AT-III levels are usually depressed in HELLP syndrome. If the AT-III levels are not depressed and the patient fails to recover quickly after delivery then plasma exchange therapy should be started for presumptive TTP (4). If the gestational age is less than 28 weeks, plasma therapy should be delivered (4), but in no time fetal status should be taken prior to maternal well-being (8).

In conclusion, thrombotic microangiopathies of pregnancy and postpartum period should be treated in tertiary care units promptly and correct steps should be followed to diagnose and treat these patients.

REFERENCES


