THROMBOTIC MICROANGIOPATHIES IN PREGNANCY AND THE POSTPARTUM PERIOD

GEBELİK VE LOHUSALIKTAKİ TROMBOTİK MİKROANJİYOPATİLER

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SUMMARY

Detecion of trombocytopenia and hemolytic anemia during pregnancy and the postpartum period alarms the physician becaus 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 platet count (HELLP) syndrome, and postpartum hemolytic uremic syndrome (PHUS). Subsequent to different initial insults the final pathologic processes produce similar clinacal 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 uremik 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 ayırıcı tanı yapmak imkansız gibidir. Plasma değişimli plasmaferez TTP ve PHUS tedavisinde gerekli iken HELLP sendromunda gebeliğin sonlandırılması gereklidir. Farkedildikleri takdirde thrombotik miroanjiopatili gebeler ve lohusalar tam teşekküllü hastanelere sevk edilmelidirler.

(Anahtar Sözcükler: HELLP Sendromu, Hemolitik Üremik Sendrom, Thrombotik 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 TTP in a pregnant patient. In one study the frequency of HELLP syndorme 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 disesase or different expressions of the same disease has not been established (5). It is very diffucult 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 associatioon 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 tought 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 thorombotic 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 microangiopath 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 microangiopaties 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, thorombotopenia, neurologic symptoms, fever and renal dysfunction(6). In this syndrome neurologic symtoms 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 complicatons. In one study 84% DIC, 44% HELLP abruptio placenta, 13% cardiopulmonary arrest or cerebral injury and 6% ruptured liver hematomas were reported in patients with HELLP syndrome (2). Diferential diagnosis of torombotic 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 o symtom 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 symtoms 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 from 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 1. Features of thrombotic microangiopathies in pregnancy and post partum period.

	TTP/HUS	HELP	PHUS(PARF)
CLINICAL FINDINGS			
Time of onset	anytime	3rd trimester	postpartum
Neurologic symptoms	often	rarely	maybe
Renal insufficiency	maybe	maybe	severe
Hypertension	maybe	often	often
Abdominal pain	rarely	often	rarely
Fever	usually	rarely	maybe
LABORATORY DATA			
Thrombocytopenia	yes	yes	yes
Hemolitic anemia	+++	+ to +++	+++
PTT	normal	normal to ⇧ ⇧ ⇧	normal
FDP	normal	normal to ⇧	normal to ⇧
vWFmultimers	⇧	normal	⇧
Antihrombin-III	normal	depressed	normal
Serum aminotransferase	normal to ⇧	normal to ⇧ ⇧	normal to ⇧
Bilirubin	⇧ ⇧	normal to ⇧	⇧ ⇧
RENAL HISTOPATHOLOGY	TMAP	GE	TMAP
MATERNAL MORTALITY	<30%	2%	>50%
PERİNATAL MORTALITY	75-80%	10-60%	-
TREATMENT	PP+PE	delivery	PP+PE

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,).

syndrome will result in unwarranted early delivery and the mother will be exposed to the risks of delivery before her disease is controlled and the fetus will face the problems of prematurity (7). Starting the exchange transfusion with normal plasma, plasmapheresis and better supportive management of anemia, hypertension, renal failure and fluid imbalance, have remakably improved the outcome during the last few decades (5,11). Plasmapheresis with plasma exchange is the procedure of choice to treat TTP or PHUS. This procedure either removes the offending agent(s) or adds the missing factor(s). With the thought that TTP /HUS patients might lack a plasma infusion was used in the treatment with good result (5). On the other hand plasma infusion without plasmapheresis has been shown to be less effective (7). The optimal duration and volume of plasma exchange is not clear. Prolonged daily plasma exchange (up to 12 days) may be required before clinical responses are evident (4). Monitoring serum

LDH concentrations and palatelet 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 microangiiopathies 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 dipridamole, do not appear to be benefical in classical HUS, but their use has been recommended for adult TTP/HUS and neurologic involment (11). For thrombotic microangiopathies antiplatelet theraphy 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 immuglobulin 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 inhibitig 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 propased in the treatment of thrombotic microangiopathies, bu controlled trials are needed (5,20).

Renal replacement theraphy 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). Aganist this approaches there is no satisfactory evidence that delaying delivery will improve mother and infant survial rates, so once the diagnosis of HELLP syndrome is made, delivery should not be delayed (8,14). If caesaren 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 gestional ages greater that 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

1. *Sibai BM, Ramadan MK. Acute renal failure in pregnancies complicated by hemolysis, elevated liver enzymes, low platelets.* ***Am J Obstet Gynecol.*** *1993 ; 168(6) : 1682-7*

2. *Sibai BM, Taslimi MM, El-Nazer A et al. Maternal-perinatal outcome associated with the syndrome of hemolysis, elevated liver enzymes, and low plateles in severe preelampsia-eclampsia.* ***Am J Obstet Gynecol.*** *1986 ; 155(5) 501-7.*

3. *Martin Jr JN, Steadman CM. Imitators of preeclampsia and HELLP syndrome . Critial care Jr JN, Steadman CM. Imitators of preeclampsia and HELLP syndrome. Critical care in obstetrics.* ***Obstet Gynecol Clin North Am.*** *1991 ; 18(2) : 181-196.*

4. *Ives HI,Daniel TO. Thrombotic microangiopfhies (Hemolytic-uremic syndrome and thrombotic thrombocytopenic purpura).In: Brenner BM, Rector FC, eds.* ***The Kidney.*** *4th ed. Philadelphia: W.B. Baunders Company; 1991 : 1519-27.*

5. *Remuzzi G, Schieppati A, Ruggenenti P, Bertani T. Thrombotic thrombocytopenic purpura, hemolytic-uremic syndrome, and acute cortical necrosis. In: Schrier RW, Gottschalk CW eds.* ***Diseases of Kidney.*** *5th ed. Boston: Little, Brown and Company; 1993 : 2063-80.*

6. *Bithell TC. Thrombotic thrombocytopenic purpura and other forms of nonimmunologic platelet destruction, In: Lee GR, Bitchell TC, Foerster J, Athens JW, Lukens JN, eds.* ***Wintrobe's Clinical Hematology.*** *9th ed. Philadelphia: Lea Febiger; 1993 : 1356-62.*

7. *Permezel M, Lee N Corry J. Thrombotic thrombocytopenic purpura in pregnancy.* ***Aus NZ J Obstet Gynaecol,*** *1992 ; 32 : 278-80.*

8. *Maikranz P, Katz Al. Acute renal failure in pregnancy.* ***Obset Gynecol Clin North Am.*** *1991 ; 18 : 333-43.*

9. *Foerster J. Red cell fragmentation syndromes. In: Lee GR,Bitchell TC, Foerster J, Athens JW, Lukens JN, eds.* ***Wintrobe's Clinical Hematology.*** *9th ed. Philadelphia: Lea Febiger; 1993 : 1211-24.*

10. *Shafer Al. Thrombotic thrombocytopenic purpura in pregnancy. In Stein JH, ed.* ***Internal Medicine.*** *4th ed. St. Lois: Mosby-Year Book, Inc. ; 1994 : 801-2.*

11. *Ruggenenti P, Remuzzi G. Thrombotic miroangiopathies.* ***Criti Revi in Oncol Hematol.*** *1991 ; 11 : 243-65.*

12. *Martin JN, Files JC, Blake PG et al. Plasma exchange for preeclampsia.* ***Am J Obstet Gynecol.*** *1990 ; 162 : 26-37.*

13. *Saltiel C, Legendre C, Grunfeld JP. Hemlolitic uremic syndrome in association with pregnancy. In: Kaplan BS, Trompeter RS, Moake JL, eds.* ***Hemolitic Uremic Syndrome and Thrombotic Thrombocytopenic Purpura*** *New York: Marcel Dekker, Inc .; 1992 : 241-54.*

14. *Barton JR, Riely CA, Adamec TA, Shanklin DR, Khoudry AD, Sibai BM. Hepatic histopathologic condition does not correlate with laboratory abnormalities in HELLP syndrome (hemolysis, elevated liver enzymes, low platelet count).* ***Am J Obstet Gynecol.*** *1992 ; 167(6) : 1538-43.*

15.*Barton JR, Sibai BM. Care of pregnancy complicated by HELLP syndrome.* ***Gastroenterol Clin North Am.*** *1992 ; 21 (4)927-50.*

16. *Venkat KK,Tkach D,Kupin W, Mozes M, Oh HK,Raman BKS, Visscher D, Lee MW. Reversal of cyclosporine-associated hemolytic-uremic syndrome by plasma exchange with fresh-frozen plasma replacement in renal tr ansplant recipients.* ***Transplant Proc.*** *1991 ; 13 : 1256-7.*

17. *Bolin P, Jennette JC, Mandel SR. Cyclosporin-associated thrombotic microangiopathy:succesful retreatment with cyclosporine.* ***Renal Failure.*** *1991 ; 13:275-8.*

18. *Zachariae H,Hansen HE, Olsen TS. Hemolytic uremic syndrome in a patient with systemic sclerosis treated with cyclosporine A.* ***Acta Derm Venerol (Stockh).*** *1992 ; 72 : 307-9.*

19. *Kierdorf H, Maurin N, Heintz B. Cyclosporinefor thrombotic thrombocytopenic purpura.* ***Ann Int Med.*** *1993 ; 118 : 987.*

20. *Wang Ym Walsh SW, Guo J, Zhang J. The imbalance between thromboxane end prostacyclin in preeclampsia is associated with an imbalance between lipid peroxides and vitamen E in maternal blood.* ***Am J Obstet Gynecol.*** *1991 ; 165 : 1695-700.*

21. *Goodlin RC, Cotton DB, Haesslein HC. Severe edema-proteinuria-hypertension gestosis.* ***Am J Obstet Gynecol.*** *1978 ; 132 : 595.*

22. *Thiagarajah S, Bourgeous FJ, Harbert GM, Claudle MR. Thrombocytopenia in preeclampsia: associated abnormalities and management principles.* ***Am J Obstet Gynecol.*** *1984 ; 150 : 1-7.*