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Review article

Thrombotic microangiopathies of pregnancy: Differential diagnosis

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ABSTRACT

Thrombotic microangiopathy (TMA) disorders are characterized by microangiopathic hemolytic anemia, thrombocytopenia and end-organ injury. In pregnancy and postpartum, TMA is most commonly encountered with HELLP (hemolysis, elevated liver enzymes, low platelet count syndrome) or preeclampsia with severe features, but rarely TMA is due to thrombotic thrombocytopenic purpura (TTP) or atypical hemolytic uremic syndrome (aHUS). Due to overlapping clinical and laboratory features, TTP and aHUS are often mistaken for preeclampsia or HELLP. Unfortunately, delays in appropriate diagnosis and treatment may be life-threatening. Our objective is to alert obstetrician-gynecologists, certified nurse midwives, family medicine providers, and subspecialty consultants, to the range of TMA disorders that may occur in and around pregnancy. To do this, we have provided a review of individual disorders that comprise the differential diagnosis of pregnancy TMA, and we have proposed a systematic approach to make an accurate diagnosis with readily available clinical and laboratory data. In complex or critical cases, we recommend a multidisciplinary team approach (e.g., Critical Care, Hematology, Maternal Fetal Medicine, Nephrology) to expedite diagnosis and treatment, which may be life-saving.

1. Introduction

Thrombotic microangiopathy (TMA) disorders are characterized by microangiopathic hemolytic anemia, thrombocytopenia and end-organ injury [1–4]. In pregnancy, TMA is most commonly encountered with HELLP (hemolysis, elevated liver enzymes, low platelet count syndrome), a fulminant and life-threatening disorder that contributes disproportionately to maternal and neonatal morbidity [5–7]. In most cases, HELLP occurs together with preeclampsia, a hypertensive disorder characterized by systemic inflammation and endothelial injury [8–10]. The definitive treatment for preeclampsia and HELLP is delivery, after which maternal health usually improves steadily [8,11]. However, preeclampsia and HELLP must be distinguished from other TMA disorders that warrant non-delivery interventions, such as eculizumab for atypical hemolytic uremic syndrome (aHUS) [12,13] or plasma exchange for thrombotic thrombocytopenic purpura (TTP) [13–15].

TMA in pregnancy should be considered a medical emergency. Delays in diagnosis and treatment may be life-threatening [16–18]. Maternal complications include renal failure, seizure, stroke, pulmonary edema, disseminated intravascular coagulation (DIC), blood transfusion, admission to the intensive care unit (ICU), and death [16–19]. Timely decision making may be delayed because TMA disorders have overlapping clinical features [20–23] and diagnoses cross disciplines (e.g., Hematology, Nephrology, Maternal Fetal Medicine). In pregnancy or postpartum, aHUS and TTP are often misdiagnosed as HELLP or preeclampsia with severe features (PE-SF). Confusion arises because PE-SF and HELLP are common complications of pregnancy, while aHUS and TTP are rare disorders. However, obstetric care providers must be alert to laboratory or clinical features that differentiate individual TMA disorders.

Here, we review the differential diagnosis for TMA in pregnancy and postpartum. Our objective is to alert obstetrician-gynecologists, certified nurse midwives, family medicine providers, and subspecialty consultants, to the range of TMA disorders that may occur around pregnancy. We will present specific lab criteria and review pertinent signs and symptoms of each TMA, to help narrow the diagnosis and guide appropriate care. Timely and correct treatment of pregnancy associated TMA may be life-saving.

2. Preeclampsia with severe features (PE-SF)

Preeclampsia has been labeled the disease of theories, due to its heterogeneous and mercurial nature [24,25]. Descriptions of preeclampsia have existed since antiquity, but diagnostic criteria have continued to evolve. At the Boston Lying-in Hospital in the mid-1930's,

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Table 1
Diagnostic criteria for severe features of preeclampsia over time (American College of Obstetricians and Gynecologists).

Severe Feature	Before 2002	2002–2013	2013-Present
Blood pressure	≥160 mmHg systolic or ≥ 110 mmHg diastolic	≥160 mmHg systolic or ≥110 mmHg diastolic	≥160 mmHg systolic or ≥110 mmHg diastolic
Kidney	Proteinuria ≥5 g in 24hr	Proteinuria ≥ 5 g in 24hr	Not applicable
	Oliguria < 400 ml in 24hr	Oliguria < 500 ml in 24hr	Not applicable
	Not applicable	Not applicable	Creatinine > 1.1 mg/dl or 2× baseline
Brain/Eyes	Cerebral or visual disturbances	Cerebral or visual disturbances	Cerebral or visual disturbances
Lungs	Pulmonary edema or cyanosis	Pulmonary edema or cyanosis	Pulmonary edema
Liver	Not applicable	Impairment of liver function	Liver enzymes ≥ 2x normal
	Not applicable	Severe or persistent abdominal pain in epigastric area or right upper quadrant	Severe or persistent abdominal pain in epigastric area or right upper quadrant
Placenta/Fetus	Not applicable	Fetal growth restriction	Not applicable
Platelet count	Not applicable	< 100,000/μl	< 100,000/μl

mild preeclampsia was described in women with moderate hypertension and no more than a slight trace of albumin in the urine [26]. Severe preeclampsia was defined by marked hypertension and albuminuria. These descriptions have framed the diagnosis of mild and severe preeclampsia for more than half a century. Over time, it has become clear that additional signs and symptoms, aside from blood pressure and urine protein, define severe preeclampsia. The evolution of severe criteria for preeclampsia, as put forth by the American College of Obstetricians and Gynecologists (ACOG), is shown in Table 1 [8,27].

In 2013, ACOG revised the diagnostic criteria for preeclampsia, implementing some of the most significant changes to-date [8]. Notably, preeclampsia with severe features (PE-SF) is now diagnosed when new-onset hypertension occurs ≥20 weeks of pregnancy, in conjunction with at least one severe feature (Table 1), regardless of urine protein assessment. Proteinuria is still necessary to diagnose preeclampsia without severe features, but it is not required for PE-SF. ACOG's diagnostic revision reflects our modern understanding of PE-SF, as a heterogeneous, systemic inflammatory disorder, which progresses to endothelial injury and end-organ damage. While the kidney is often impaired in preeclampsia, other end-organs may also be affected, including the brain, eyes, and liver. As endothelial injury progresses, there is risk for capillary leak (e.g., pulmonary edema), as well as microangiopathic hemolytic anemia and thrombocytopenia, characteristic features of TMA.

3. Hemolysis, elevated liver enzymes, and low platelet count (HELLP) syndrome

In 1982, Dr. Louis Weinstein coined the term HELLP, which was defined by the triad of hemolysis (microangiopathic hemolytic anemia), elevated liver enzymes and low platelet count (thrombocytopenia) [7]. HELLP occurs from mid-gestation (> 20 weeks) through the immediate postpartum period. Women with HELLP usually have additional signs and symptoms such as malaise, nausea/vomiting, or abdominal pain in the right upper quadrant or epigastric area [6,7,28]. Initially HELLP was defined in the presence of preeclampsia, but it is now estimated that 15–20% of HELLP cases occur without hypertension or proteinuria [29,30]. In the initial description of HELLP, > 50% of cases had kidney injury with elevated blood urea nitrogen and serum creatinine [7], while coagulopathy and low fibrinogen were not common. However, larger case series show that DIC is a common finding in HELLP, especially in the setting of postpartum hemorrhage, placental abruption, or fetal demise [18,29,31].

Specific diagnostic criteria for HELLP is variable [6,32] and there is no consensus ACOG definition. Hemolysis is most commonly defined as ≥1 of the following: 1. abnormal peripheral smear suggesting microangiopathic hemolytic anemia (e.g., schistocytes); 2. total bilirubin > 1.2 mg/dl; 3. lactate dehydrogenase (LDH) > 600 U/L; or 4. haptoglobin < lower limit of normal [6]. Elevated liver enzymes are defined as aspartate transaminase (AST) or alanine transaminase (ALT) > 2× upper limit of normal (ULN). Low platelet count is defined as a level < 100,000/μl. In combination, these criteria are specific for HELLP, and maternal complications increase markedly. Common adverse outcomes include pulmonary edema, kidney injury, DIC, blood transfusion and ICU admission [19,29]. Women with only partial features of HELLP (1–2 criteria met) have better outcomes than women with complete HELLP (all 3 criteria met) [19]. ACOG does not recommend routine surveillance for hemolysis in women with gestational hypertension or preeclampsia [8]. However, testing for hemolysis is necessary and critical to diagnose, or rule-out, HELLP. Women without hemolysis are less likely to have TMA, and may have an alternative diagnosis such as acute fatty liver of pregnancy (AFLP) [22,33]. Those with Coombs positive hemolysis may have an auto-immune hemolytic anemia (AIHA) [34,35]. The differential diagnosis for HELLP is summarized in Table 2.

4. Thrombotic thrombocytopenic purpura (TTP)

TTP is a rare TMA disorder that is most often due to acquired inhibitory auto-antibodies against ADAMTS13 (a disintegrin and metalloproteinase with a thrombospondin type 1 motif, member 13), an enzyme that normally cleaves Von Willebrand Factor (VWF) [36–38]. Rarely, congenital TTP (Upshaw-Schulman syndrome) arises from mutations in the ADAMTS13 gene [3,39]. ADAMTS13 deficiency leads to accumulation of large VWF multimers, resulting in platelet aggregation and microvascular thrombosis. Reduced ADAMTS13 activity (< 10%), in the setting of otherwise unexplained microangiopathic hemolytic anemia and thrombocytopenia, is considered diagnostic for TTP [3,40,41]. In pregnant women that present with marked thrombocytopenia in the first half of pregnancy, TTP should be ruled out, because preeclampsia and HELLP are unlikely. Suspicion for TTP should also be high in those with personal or family history of TTP [42,43]. For women presenting with hemolysis and profound thrombocytopenia in the second half of pregnancy or postpartum, ADAMTS13 activity level should be sent to rule out TTP. This is critical because platelet transfusion can exacerbate the underlying disease in TTP and increase risk for neurological or cardiovascular events or death [44]. Instead, the primary treatment is plasma exchange, which removes the ADAMTS13 inhibitor from circulation [13–15].

The historical association between TTP and HUS has led to confusion and delay in the diagnosis of TTP [3]. Women with TTP do not necessarily present with the historical pentad of thrombocytopenia, hemolytic anemia, acute kidney injury, fever, and altered mental status. Hemolysis and thrombocytopenia may be the only features present in TTP. Registry data from 78 consecutive patients with acquired TTP found that 20% had no neurologic abnormalities, while only 5% had fever and 10% had acute renal failure [45]. Acute kidney injury, especially with marked elevation of serum creatinine (> 2× ULN), is more suggestive of aHUS. For those with TMA but an equivocal clinical picture, assessment of ADAMTS13 activity level is critical to narrowing