Le microangiopatie trombotiche in gravidanza

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Despite their extraordinary diversity, these collection of disorders are always defined by the presence of:

- Pregnancy
- Thrombocytopenia
- Microangiopathic haemolytic anaemia (MAHA)
- Small vessel thrombosis
- Organ injury
PREGNANCY

Despite TMA syndromes do not recognize a definite causative effect, pregnancy is a physiological event that MAY represents a favorable ground for the establishment of these syndromes.

Anticoagulant

Procoagulant
PREGNANCY IS A HYPERCOAGULABLE STATE

<table>
<thead>
<tr>
<th>Factor</th>
<th>Change</th>
</tr>
</thead>
<tbody>
<tr>
<td>Fibrinogen</td>
<td>Increased from 2.5 g/l to 5 g/l</td>
</tr>
<tr>
<td>Factor II</td>
<td>Slightly increased</td>
</tr>
<tr>
<td>Factor V</td>
<td>Slightly increased</td>
</tr>
<tr>
<td>Factor VII</td>
<td>Increased 10 folds</td>
</tr>
<tr>
<td>Factor VIII</td>
<td>Increased 2 folds</td>
</tr>
<tr>
<td>Factor XI - X</td>
<td>Increased</td>
</tr>
<tr>
<td>Factor XI</td>
<td>Decreased by 70%</td>
</tr>
<tr>
<td>Factor XII</td>
<td>Increased by 40%</td>
</tr>
<tr>
<td>Factor XIII</td>
<td>Decreased by 40%</td>
</tr>
</tbody>
</table>

and to make things worse...
Changes in ADAMTS13 during pregnancy

Perché un “equilibrio” pro-trombotico si trasforma in una situazione favorevole alla formazione di microtrombi con trombocitopenia secondaria da attivazione piastrinica?
TMA IN PREGNANCY

Pre-eclampsia/HELLP  p-TTP  p-aHUS
PE/HELLP syndrome

In 1982 Weistein described a unique group of obstetric patients with:

- Hemolysis (H)
- Elevated liver enzymes (EL)
- Low platelet count (LP)
PE/HELLP syndrome

epidemiology

- occurs in 0.2 - 0.8% of pregnancies
- in 70 - 80% of cases it coexists with preeclampsia...
- ... but it occurs in 15% in women with preeclampsia
- more frequent in older, multiparous, caucasian women
- risk of recurrence in a subsequent pregnancy is 19 - 27%

(55% of PE risk if HELLP < 28 sett)

Am College of Obstetricians and Gynecologists: Hypertension in Pregnancy. 1996
Sibai – Obstet and Gynecol 2004
Weinstein - Am J Obstet & Gynecol 1982
PE/HELLP syndrome

epidemiology

After delivery

> 37 weeks

27 - 37 weeks

< 27 weeks

Haram, : The HELLP syndrome clinical issues and management, BMC pregnancy childbirth, 2009
## PE/HELLP syndrome

### PATHOGENETIC MECHANISMS

<table>
<thead>
<tr>
<th>Gene variant</th>
<th>HELLP compared to</th>
<th>HELLP (n)</th>
<th>OR (95% CI), p</th>
<th>Effect</th>
</tr>
</thead>
<tbody>
<tr>
<td>Glucocorticoid receptor gene (GCCR), Bell SNP polymorphisms</td>
<td>Healthy pregnant</td>
<td>17</td>
<td>2.89 (1.45–5.74) <em>p = 0.004</em></td>
<td>Altered immune sensitivity and glucocorticoid sensitivity</td>
</tr>
<tr>
<td></td>
<td>Severe PE</td>
<td></td>
<td>2.56 (1.26–5.23) <em>p = 0.013</em></td>
<td>Uncontrolled or harmful inflammation, ineffective immunity</td>
</tr>
<tr>
<td>Toll-like receptor 4 gene (TLR4), D299G, T3991</td>
<td>Healthy pregnant</td>
<td>177</td>
<td>4.7 (2.0–1.9)</td>
<td></td>
</tr>
<tr>
<td></td>
<td>PE</td>
<td></td>
<td>2.3 (1.3–4.3)</td>
<td></td>
</tr>
<tr>
<td>VEGF gene (VEGFA), C-460T, C-405C</td>
<td>Healthy pregnant</td>
<td>16</td>
<td>3.03 (1.51–6.08)</td>
<td>Angiogenesis and vasculogenesis, arterial muscular relaxation</td>
</tr>
<tr>
<td>polymorphisms</td>
<td>Healthy pregnant</td>
<td></td>
<td>3.67 (1.05–6.08)</td>
<td></td>
</tr>
<tr>
<td>FAS (TNFRSF6) gene, homozygous polymorphism in A-670G</td>
<td>Healthy pregnant</td>
<td>81</td>
<td>2.7 (1.2–5.9)</td>
<td>Immune regulation, apoptosis, liver disease</td>
</tr>
<tr>
<td>FV Leiden</td>
<td>Healthy pregnant</td>
<td>71</td>
<td>4.5 (1.31–15.31)</td>
<td>Thrombophilia</td>
</tr>
</tbody>
</table>

PE/HELLP syndrome
PATHOGENETIC MECHANISMS
The role of inflammatory response

✓ release into the maternal blood of syncytiotrophoblast particles (STBM)

✓ activation of complement (?)
  Fakhouri, Transfusion and Apheresis Science, 2016

✓ increase the blood levels of IL-6 and TNFα

✓ activation of vascular endothelial cells release of active multimeric vWF

✓ platelet aggregation and adherence of platelets to vessel intima
PE/HELLP syndrome

Pathogenetic mechanisms
PE/HELLP syndrome

PATHOGENETIC MECHANISMS

Liver and kidney dysfunction

- Placental-derived FasL (CD95L)
- Leukostasis
- Microangiopathy
- Glomerular endotheliosis
- Hypertension

- TNFα

- Hemolysis
PE/HELLP syndrome

CLINICAL SYMPTOMS

Epigastric or right upper abdominal quadrant pain in women with hypertension or PE could be indicative of the onset of HELLP syndrome. Up to 30–60% of women have headache; about 20% visual symptoms.

However, women with a HELLP syndrome might also have unspecific symptoms or subtle signs of preeclampsia or non-specific viral syndrome-like symptoms.
PE/HELLP syndrome

CLINICAL SYMPTOMS

So, if you are not sure...

...CHECK THE BLOOD!
PE/HELLP syndrome

LAB DIAGNOSIS

H (Hemolysis) – MAHA

- fragmented (schistocytes) or contracted red cells with spicula (Burr cells) in the peripheral blood

- increased serum LDH levels and decreased haemoglobin concentrations

- Low haptoglobin concentration (< 1 g/L – < 0.4 g/L) can be used to diagnose haemolysis and is the preferred marker of haemolysis

- Increased serum bilirubin (≥ 1.2 mg/100 mL)
## PE/HELLLP syndrome

<table>
<thead>
<tr>
<th>Class</th>
<th>Platelet</th>
<th>LDH</th>
<th>Enzymes</th>
<th>Maternal morbidity</th>
</tr>
</thead>
<tbody>
<tr>
<td>Class I</td>
<td>&lt; 50,000</td>
<td>&gt; 600 UI/L</td>
<td>AST or ALT &gt; 70 UI/L</td>
<td>40% - 60%</td>
</tr>
<tr>
<td>Class II</td>
<td>&gt; 50,000</td>
<td>&gt; 600 UI/L</td>
<td>AST or ALT &gt; 70 UI/L</td>
<td>20% - 40%</td>
</tr>
<tr>
<td>Class III</td>
<td>&gt; 100,000</td>
<td>&gt; 600 UI/L</td>
<td>AST &gt; 40 UI/L</td>
<td>20%</td>
</tr>
</tbody>
</table>
## PE/HELLP syndrome

<table>
<thead>
<tr>
<th>Maternal complication</th>
<th>OCCURRENCE (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Eclampsia</td>
<td>4-9</td>
</tr>
<tr>
<td>Abruptio placentae</td>
<td>9-20</td>
</tr>
<tr>
<td>DIC</td>
<td>4-56</td>
</tr>
<tr>
<td>Acute renal failure</td>
<td>7-36</td>
</tr>
<tr>
<td>Severe ascites</td>
<td>4-11</td>
</tr>
<tr>
<td>Cerebral oedema</td>
<td>1-8</td>
</tr>
<tr>
<td>Pulmonary oedema</td>
<td>3-10</td>
</tr>
<tr>
<td>Subcapsular liver hematoma</td>
<td>1-2</td>
</tr>
<tr>
<td>Liver rupture</td>
<td>&lt;2%</td>
</tr>
<tr>
<td>Retina detachment</td>
<td>1</td>
</tr>
<tr>
<td>Cerebral infarction</td>
<td>Few case report</td>
</tr>
<tr>
<td>Cerebral haemorrhage</td>
<td>1.5-40</td>
</tr>
<tr>
<td>Maternal death</td>
<td>1-25</td>
</tr>
</tbody>
</table>
PE/HELLP syndrome

TREATMENT AND MANAGEMENT

Hypertension control

- α-methyldopa and nifedipine can be used as initial treatment in Class III o Class II patients with acceptable blood pressure level

- Labetalol is commonly recommended if immediate reduction is required

- Magnesium sulfate as convulsions prophylaxis
  (4 g over 15-30 min, followed by a maintenance dose of 0.5-1 g/hour)
PE/HELLP syndrome

TREATMENT AND MANAGEMENT

High-dose dexamethasone treatment

Dexamethasone treatment did not reduce maternal complications (such as acute renal failure, pulmonary edema and oliguria)

COHELLLP: collaborative randomized controlled trial on corticosteroids in HELLP syndrome

Leila Katz\textsuperscript{1*}, Melania Amorim\textsuperscript{2}, João P Souza\textsuperscript{3,4,5}, Samira M Haddad\textsuperscript{6}, José G Cecatti\textsuperscript{6} and COHELLLP Study Group
6 Using corticosteroids

For fetal lung maturation

If birth is likely within 7 days in a woman with pre-eclampsia:

- give 2 doses of betamethasone $^{2}$ 12 mg intramuscularly 24 hours apart between 24 and 34 weeks
- consider giving 2 doses of betamethasone 12 mg intramuscularly 24 hours apart at 35–36 weeks.

For HELLP syndrome

Do not use dexamethasone or betamethasone to treat HELLP syndrome.

NICE, Hypertension in pregnancy: diagnosis and management, 2010
PE/HELLP syndrome

PRACTICAL APPROACH

Standard corticosteroid treatment to promote fetal lung maturity (and to eventually increase the recovery of platelet count)

<table>
<thead>
<tr>
<th>Class</th>
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<td>&lt; 50.000</td>
<td>&gt; 600 UI/L</td>
<td>AST or ALT &gt; 70 UI/L</td>
<td>40% - 60%</td>
</tr>
<tr>
<td>II</td>
<td>&gt; 50.000 &lt;100.000</td>
<td>&gt; 600 UI/L</td>
<td>AST or ALT &gt; 70 UI/L</td>
<td>20% - 40%</td>
</tr>
<tr>
<td>III</td>
<td>&gt; 100.000</td>
<td>&gt; 600 UI/L</td>
<td>AST &gt; 40 UI/L</td>
<td>20%</td>
</tr>
</tbody>
</table>
Complemento TMA e gravidanza

**HELLP**

  - 2/33 pz presentavano mutazione di geni del complemento
  - 10 pz con HELLP avevano C3a, C5a e C5b9 elevati in fase acuta
- Fakhouri F, et al. 2008
  - 4/11 pz con HELLP + IR avevano mutazioni di geni del complemento
  - 21 pz con pre-eclampsia, 22 con HELLP, 24 controlli: no differenze in C3 e FH

**Pre-eclampsia**

- Haeger et al. 1991
  - 7/7, 4/7 e 0/7 pz con pre-eclampsia avevano rispettivamente C5a, C3a o C5b9 elevati al momento del parto rispetto ai controlli
- Burwick RM et al. 2009
  - 25 pz con pre-eclampsia avevano livelli urinari di C3a, C5a e c5b9 più elevati rispetto a controlli sani e ipertesi
Case report

Eculizumab for the treatment of preeclampsia/HELLP syndrome

R.M. Burwick†, B.B. Feinberg∗

Department of Obstetrics and Gynecology, Division of Maternal Fetal Medicine, Brigham and Women’s Hospital, Harvard Medical School, 75 Francis St., Boston, MA 02115, USA

Classical pathway

IgM, IgG, immune complexes

C1q, C1r, C1s

→ C4, C2
→ C4b2a
→ C3 convertase
→ C3
→ C3a
→ C3b
→ C4bC2aC3b
→ C5 convertase
→ C5
→ C5a
→ C5b
→ C5b-9 (MAC)

Lectin pathway

Mannose residues

MBL, MASPss

→ C3
→ C3a
→ C3b
→ Factor H

Alternative pathway

Gram+, Gram-, bacteria, bacterial toxins (LPS)

C3 → C3a
→ C3b
→ Factor H
→ Factor H
→ C3bB
→ C3bBc3b

Eculizumab
PE/HELLP syndrome

TIMING OF DELIVERY

- > 34 weeks: immediate delivery after maternal stabilization
- 24-34 weeks: corticosteroids, after maternal stabilization, and delivery after 24 hours
Thrombotic Thrombocytopenic Purpura was originally characterized by the pentad:

- Thrombocytopenia
- MAHA
- Fluctuating neurological signs
- Renal impairment
- Fever

However, TTP can present without the full pentad.
TTP

CLASSIFICATION

- Upshaw-Schulman Syndrome
- Idiopathic TTP
- Secondary TTP
  - Pregnancy
  - Infection
  - Cancer
  - Bone marrow transplantation
  - Medication
TTP

EPIDEMIOLOGY

✓ incidence of 6 cases per million / year

✓ 10-25% of all TTP cases occur during pregnancy....

✓ peak between 30 and 40 years-old

✓ feminine predominance (2-3 F/1 M)

✓ ...TTP occurs in 1/100,000 pregnancies

✓ risk of recurrence in subsequent pregnancy in acquired TTP is about 20% and 100% in women with congenital TTP (Upshaw–Schulman-Syndrome - USS)
# Pregnancy-Associated TTP

## Epidemiology

<table>
<thead>
<tr>
<th></th>
<th>Antepartum</th>
<th>Postpartum</th>
</tr>
</thead>
<tbody>
<tr>
<td>&lt; 14 weeks</td>
<td>11.7%</td>
<td></td>
</tr>
<tr>
<td>14-28 weeks</td>
<td>55.5%</td>
<td></td>
</tr>
<tr>
<td>&gt; 28 weeks</td>
<td>32.8%</td>
<td></td>
</tr>
</tbody>
</table>

- 87.3% (n = 145)
- 12.7% (n = 21)
Pregnancy-Associated TTP

PATHOGENETIC MECHANISMS

Coagulation changes

Pregnancy is associated with physiological coagulation changes predisposing to hypercoagulability.

During the course of pregnancy vWF levels in plasma progressively increase to reach levels 2.5-3 fold higher at term while ADAMTS13 activity progressively decrease.

![Graph showing vWF levels and ADAMTS13 activity during pregnancy](image)
Pregnancy-Associated TTP

PATHOGENETIC MECHANISMS

Blood Flow

GPIb

VWF

Vessel Wall

ADAMTS13

Normal Hemostasis

No ADAMTS13

Microvascular Thrombosis

TTP
Pregnancy-Associated TTP

CLINICAL SYMPTOMS and LAB

- The most constant sign of TTP is **thrombocytopenia** and **neurological signs** (about 65%) associated with **fever**.

- During pregnancy, thrombocytopenia occurs commonly (6 to 10% of all pregnant woman).

Differential diagnosis:

- severity of thrombocytopenia
- presence of mechanical hemolytic anemia (schistocytes)
Pregnancy-Associated TTP

But, if you are not sure...

...CHECK THE BLOOD!
Pregnancy-Associated TTP

**DIAGNOSIS**

<table>
<thead>
<tr>
<th>DIFFERENTIAL DIAGNOSIS</th>
<th>Congenital TTP (n=10, 24%)</th>
<th>Acquired TTP (n=32, 76%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Nulliparity</td>
<td>100%</td>
<td>62.5%</td>
</tr>
<tr>
<td>ADAMTS13 &lt;10% at onset</td>
<td>100%*</td>
<td>100%**</td>
</tr>
<tr>
<td>Anti-ADAMTS13 at onset</td>
<td>0% (0/10)</td>
<td>72% (23/32)</td>
</tr>
<tr>
<td>*ADAMTS13 remained undetectable in remission</td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>9 patients recovered ADAMTS13 &gt;30% in remission and were diagnosed as aTTP</strong></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>


*Blood: 2012 vol 119 n 24*
Pregnancy-Associated TTP

TREATMENT AND MANAGEMENT: Before 24 weeks’

- Plasma exchange every 2 weeks
- If platelet count is < 150,000, increase weekly or Rituximab
Pregnancy-Associated TTP

TREATMENT AND MANAGEMENT: After 24 weeks’ laboratory studies

**LABORATORY STUDIES**

**CLINICAL PROFILE**

**FETAL MONITORING**

- Plasma exchange/Rituximab
- Bethametasone for fetal lungs maturity
- Magnesium Sulfate for fetal neuro-protection

**Immediately delivery** is recommended if not responding to plasma exchange or in severe IUGR
Atypical Haemolytic Uremic Syndrome is defined by the triad of

- Thrombocytopenia
- MAHA
- Severe renal impairment

In absence of Shiga-toxin (Stx) producing Escherichia coli (STEC)
The prevalence of aHUS is not precisely known (1-9/1,000,000).

Onset during childhood (≤ 18 years) appears slightly more frequent than during adulthood.

Feminine predominance in adults.

aHUS complicated about 1/25,000 pregnancies worldwide.
Pregnancy-Associated aHUS

EPIDEMIOLOGY

80% during the post-partum

**Pregnancy-Associated aHUS**

**PATHOGENETIC MECHANISMS**

- Alternative pathway

- Mutation in genes such as C3, CFB, CFH, CFI, MCP, e THBD
- Polymorphisms in genes such as CFH and CFHR1
- Autoantibodies to CFH

**C5a**
- Potent Anaphylatoxin
- Chemotaxis
- Proinflammatory
- Endothelial Activation
- Prothrombotic

**C5b-9**
- Cell Lysis
- Proinflammatory
- Platelet Activation
- Endothelial Activation
- Prothrombotic
Pregnancy-Associated aHUS

PATHOGENETIC MECHANISMS

- Mutation in genes such as C3, CFB, CFH, CFI, MCP e THBD
- Polymorphisms in genes such as CFH and CFHR1
- Autoantibodies to CFH

PREGNANCY → p - aHUS
Pregnancy-Associated aHUS

CLINICAL SYMPTOMS

- The most constant sign of p-aHUS is **severe renal impairment** and **hypertension** (80%)

- Most cases of p-aHUS occur during **postpartum** period with severe acute onset associated with **MAHA**

- In contrast, thrombocytopenia is moderate and neurological impairment is uncommon
Pregnancy-Associated aHUS

TREATMENT AND MANAGEMENT

- plasma infusions and plasma exchange (to start rapidly because of the high risk of ESRD)

- Complement activation modulators (eculizumab) represent promising therapeutic options for severe forms of aHUS
Pregnancy-Associated aHUS

eculizumab : mechanism of action
TMA IN PREGNANCY

**Pre-eclampsia/HELLP**
- Pregnancy exclusive
- Associated with hypertension
- Resolution with delivery (if antepartum)

**p-TTP**
- Usually associated with fever
- Neurological findings
- ADAMTS13 <10%

**p-aHUS**
- Renal involvement
- Postpartum period
- Complement gene mutation
TMA in Pregnancy

THANK YOU!