*Università degli Studi di Padova*
*Dipartimento di Scienze Ginecologiche e della Riproduzione Umana*
*Scuola di Specializzazione in Ginecologia e Ostetricia*
*Direttore Prof. Giovanni Battista Nardelli*

# HELLP

**Dr.ssa Cristiana Nardi**

*R.M. 38 aa*
*26+2 s.g*
*PARA 0202*

# *CASO CLINICO*

*Anamnesi Familiare: ndp*
*Anamnesi Fisiologica: nega allergie, nega EP, nega fumo*

*Anamnesi Patologica Remota: Mutazione in Eterozigosi per fattore V Leiden, Omozigosi per mutazione MTHFR*

*Anamnesi Ostetrica:*

*2004 TC a 32 sg per IUGR con alterazioni flussimetriche e oligoidramnios (F 1295 gr). Puerperio complicato da Hellp Syndrome*

*2006 TC a 36 sg per IUGR e anidramnios (M 2600 gr) (EBPM). Puerperio complicato da iperpiressia di ndd*

*Terapia in atto: CardioASA*

*Eco del II trimestre: biometria e morfologia fetale regolare,LA regolare, doppler arteria uterina sx RI 0,78, dx RI 0,86 con incisura dicrota bilaterale*
*Eco a 24+2 s.g. : CA al 10° centile, emodinamica materna RI medio 0,73 con notch bilaterale*

# CASO CLINICO

*Ecografia ostetrica a 26+2 s.g.: biometria fetale al 5° centile, stima peso 665 gr, emodinamica fetale nella norma, LA regolare, emodinamica materna con PI > 95° centile, placenta posteriore, presentazione cefalica, buon tono fetale.*


*Monitoraggio PA0: buon controllo*
*Esami di Laboratorio nei limiti: si segnala ALT 44 U/L*

*Bentelan 12 mg i.m. 1° e 2° dose*
*Sospesa CardioASA*
*Inizia tp con Enoxaparina 4000 UI 1 fl s.c.*

# *Evoluzione Clinica*

*Monitoraggio ecografico quotidiano: invariato*
*PAO buon controllo*
*Esami di Laboratorio: ALT 47 U/L stabili, per il resto nella norma*

*In 6 giornata post ricovero (27 +1 s.g.):*
*Episodio di dolore epigastrico notturno*
*Esami di Laboratorio Urgenti:*
*AST 237 UI/L, ALT 159 UI/L, PTLS 101.000/uL, LAD 598 U/L, Hb 110 g/L,*
*PT 116, PTT 25 sec, AT III 82%*
*PAO 150/90: Inizia terapia antipertensiva con Nifedipina 20 mg x 2*
*Ecografia : BCF e MAF visualizzati, emodinamica fetale regolare, LA regolare*

*TAGLIO CESAREO*
*HELLP Syndrome*

***Neonato Femmina***
***645 gr***

# *Post-Operatorio*

*Monitoraggio PAO : buon controllo con la terapia, Proteinuria 24 h 0,25 gr*
*Esami di Laboratorio:*
*AST 94U/L, ALT 175 U/L, HB 108 g/L, PTLS 124.000/uL*

*Iperpiressia: GB negativi, PCR in calo, procalcitonina negativa, esami colturali neg*

***Terapia:***
*Enoxaparina 4000 fl s.c. x 6 settimane*
*Adalat 20 mg 1cp x 2*
*Tp Antibiotica*

***Controllo in post degenza:***
*Hb 111, PTLS 466.000/u/L,*
*AST 15 U/L, ALT 14 U/L,*
*proteinuria 24 0,11 gr*

***Esame Istologico Placentare:***
*Aree di necrosi ischemica,*
*dissociazione emorragica,*
*depositi subcoriali di fibrina*

***Outcome Materno***
*Stop Tp antipertensiva*
*Buone condizioni generali*

***Outcome Neonatale (39+5)***
*Sepsi da Klebsiella P.*
*Enterocolite necrotizzante*
*Retinopatia III stadio*
*Patologia neonatale*

# *HELLP Syndrome*

- *(H) Emolisi*
- *(EL) Incremento degli enzimi epatici*
- *(LP) Piastrinopenia*

- *Incidenza 0,2-0,8%*
- *10-20% associazione con preeclampsia-eclampsia*
- *28-36 s.g.*
- *< 28 s.g. severa*
- *70% pre-partum, 30% post-partum (48 h)*
- *Tasso di ricorrenza dal 2 al 27%*

**The HELLP syndrome: Clinical issues and management. A Review**
Kjell Haram[1], Einar Svendsen*[2] and Ulrich Abildgaard[3]
**BMC Pregnancy and Childbirth**

# Eziologia

European Journal of Obstetrics & Gynecology and Reproductive Biology 166 (2013) 117–123

## Pathogenesis of the syndrome of hemolysis, elevated liver enzymes, and low platelet count (HELLP): a review

Ulrich Abildgaard [a,*], Ketil Heimdal [b]

*Fattori Ereditari*
*Fattori di Rischio Genetici*

**Table 1**
Genetic variants associated with an increased risk of HELLP syndrome.

| Gene variant | HELLP compared to | HELLP (n) | OR (95% CI), p | Effect | Reference |
|---|---|---|---|---|---|
| Glucocorticoid receptor gene (GCCR), Bcll SNP polymorphisms | Healthy pregnant<br>Severe PE | 17 | 2.89 (1.45–5.74) p = 0.004<br>2.56 (1.26–5.23) p = 0.013 | Altered immune sensitivity and glucocorticoid sensitivity | [18] |
| Toll-like receptor 4 gene (TLR4), D299G T399I polymorphisms | Healthy pregnant<br>PE | 177 | 4.7 (2.0–1.9)<br>2.3 (1.3–4.3) | Uncontrolled or harmful inflammation, ineffective immunity | [19] |
| VEGF gene (VEGFA), C-460T<br>G+405C polymorphisms | Healthy pregnant<br>Healthy pregnant | 16 | 3.03 (1.51–6.08)<br>3.67 (1.05–6.08) | Angiogenesis and vasculogenesis, arterial muscular relaxation | [16] |
| FAS (TNFRSF6) gene, homozygous polymorphism in A-670G | Healthy pregnant | 81 | 2.7 (1.2–5.9) | Immune regulation, apoptosis. Liver disease | [15] |
| FV Leiden | Healthy pregnant | 71 | 4.5 (1.31–15.31) | Thrombophilia | [17] |

*Fattori di Rischio Materni*

High body mass index (BMI) and metabolic syndrome 6 months postpartum were associated with PE but hardly for HELLP [22]. The antiphospholipid-antibody syndrome (APLS) may be associated with early onset of HELLP [23]. A first pregnancy is probably not associated with a greater risk of HELLP [24] but is associated with a considerably higher risk of PE [11]. Infertility treatment increases the risk of PE whereas pre-conceptual exposure to seminal fluid reduces the risk, supporting a pathogenetic role of immune maladaptation [9]. It is probable, but unknown if these conditions influence the risk of HELLP.

## Biomarkers nel sangue materno predittivi di HELLP e PE

**Table 2**
Biomarkers in maternal blood predicting early onset HELLP or PE.

| Biomarker | Gestation weeks | HELLP | PE | Ref. no. | Function of marker |
|---|---|---|---|---|---|
| PP 13 | 8–14 | ↓ | ↓ | [29] | Development of fetal/maternal interface, immune regulation |
| | 24–37 | ↑ | ↑ | [28] | |
| PlGF | 8–14 | ↓ | ↓ | [29,32] | Angiogenic, prevents hypertension |
| | Term | ↓↓ | ↓ | [33] | |
| VEGF | 14–21 | n.e. | ↓ | [30] | Angiogenic, prevents hypertension |
| | 32 | ↑ | ↑↑ | [31] | |
| sFlt1 | 10–17 | n.e. | ↑ | [32] | Inhibits VEGF and PlGF. Anti-angiogenic |
| | 25–40 | ↑↑ | ↑ | [33,35] | |
| sEndoglin | 10–17 | n.e. | ↑ | [32] | Inhibits TNF-β, inhibits vasodilation. Anti-angiogenic |
| | Preterm | ↑↑ | ↑ | [34]ª, [35]ᵇ | |
| | Term | ↑ | ↑ | [36] | |

PP 13, placental protein 13; PlGF, placental growth factor; sFlt1, sVEGFR-1; n.e., not examined; ↑, higher than in pregnant controls ($p < 0.05$); ↑↑, higher than ↑ ($p < 0.05$); a, Levels in two women with HELLP higher than in 32 women with PE; b, Semiquantitative data.

*Placentazione Alterata*

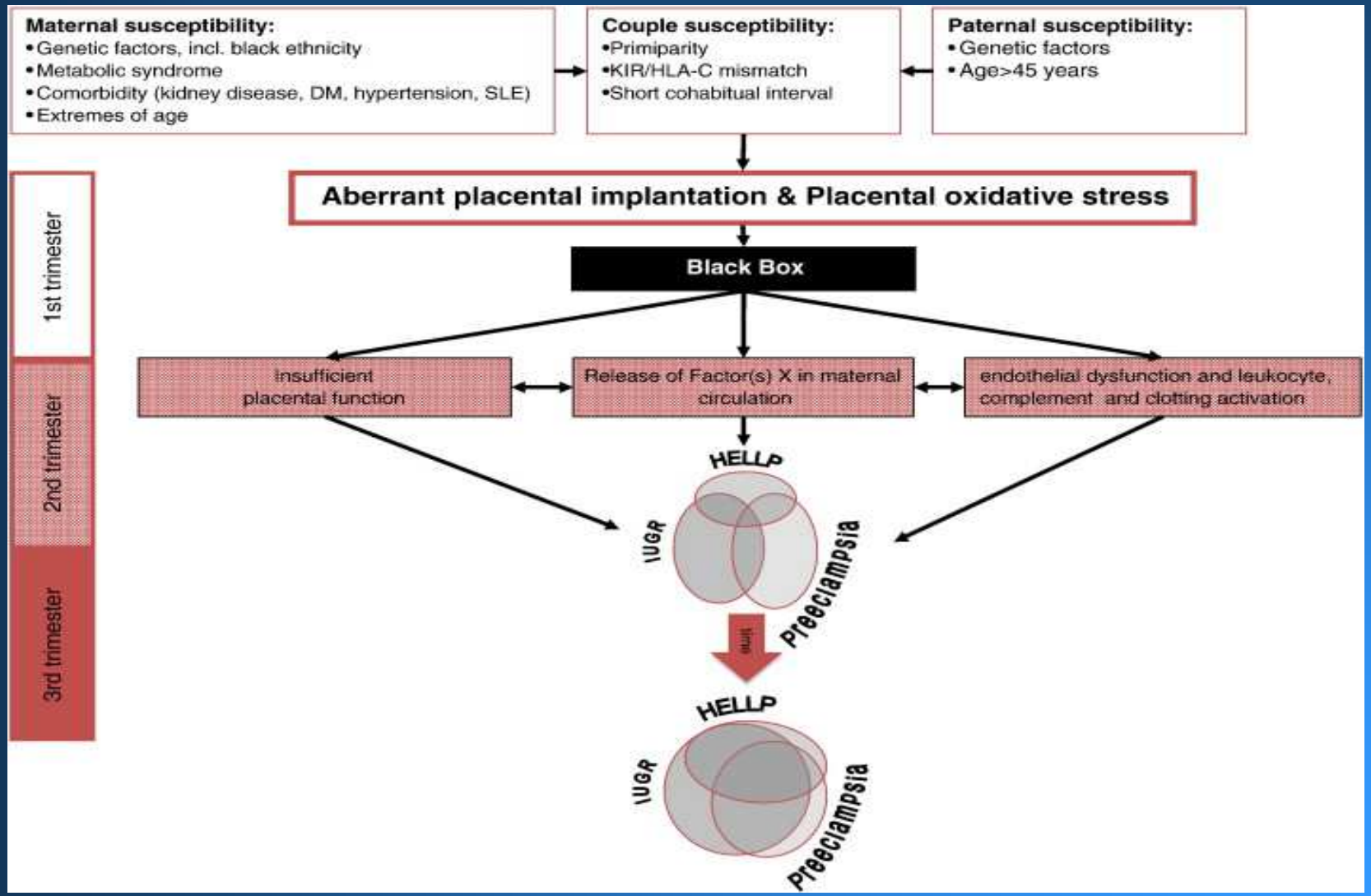
*Stress ossidativo Necrosi apoptosi*

*Insufficienza Placentare*

*Disfunzione endoteliale Ipertensione Endoteliosi glomerulare*

*↑risposta infiammatoria materna*

*Molecular Genetics of preeclampsia and HELLP syndrome*
*J.Jebbink, A.Wolters et al.*
*Biochimica et Biophysica Acta 1822 (2012) 1960-1969*



Pathogenesis of the syndrome of hemolysis, elevated liver enzymes, and low platelet count (HELLP): a review

Ulrich Abildgaard [a,*], Ketil Heimdal [b]

# *Alterazioni Placentari*

*5.4. Gene expression and histopathology in placenta*

A microarray profiling study on placenta samples at delivery revealed 54 genes differentially expressed in early onset HELLP and 350 genes in early onset PE [44]. The transcriptomes in the two syndromes largely overlapped. The inflammatory response was more pronounced in HELLP. Down-regulation was more frequent in HELLP (239 genes) than in PE (67 genes) [44].

Histopathological comparisons of term placentas have shown a lower frequency of intravillous thrombosis and villous infarcts in HELLP than in PE [45] or no difference [25]. Apoptotic and proliferation marker levels were higher in placenta from HELLP than in PE [46]. Decidual dendritic cells stained differently and reacted differently with decidual natural killer (dNK) cells in HELLP compared to PE [47]. The placental expression of Fas Ligand (FasL) was higher [48], and the expression in villous trophoblast increased in HELLP compared to healthy pregnancy and PE [49].

***HELLP rispetto a PE:***
***↓ trombosi e infarti***
***↑ apoptosi e proliferazione***
***↑ espressione di FasL placentare***

**Severe Preeclampsia With and Without HELLP Differ With Regard to Placental Pathology**

Marie-Therese Vinnars, Liliane C.D. Wijnaendts, Magnus Westgren, Annemieke C. Bolte, Nikos Papadogiannakis and Josefine Nasiell

*Hypertension.* 2008;51:1295-1299; originally published online March 24, 2008;



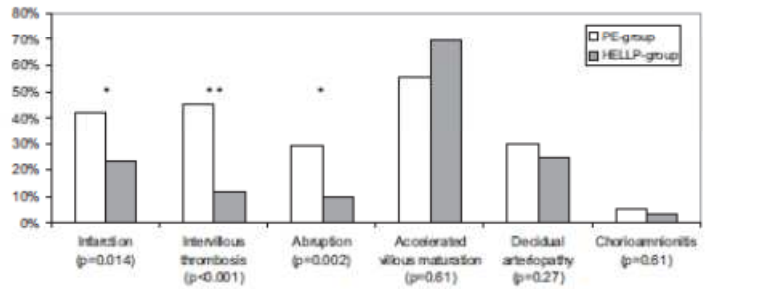
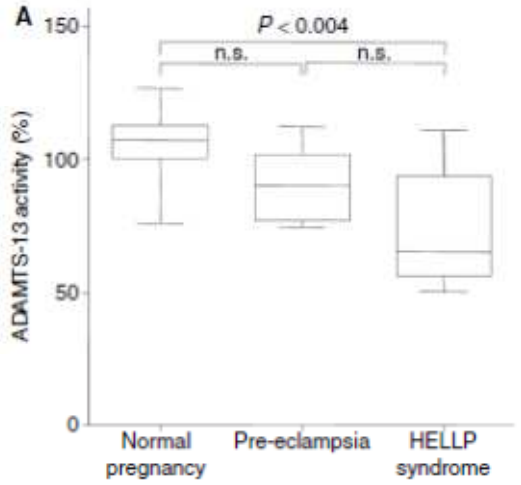



**Figure 1.** Histopathologic findings in placentas from PE (n=96) and HELLP (n=82) patients. *$P<0.05$; **$P<0.001$.

# Acute activation of the endothelium results in increased levels of active von Willebrand factor in hemolysis, elevated liver enzymes and low platelets (HELLP) syndrome

J. J. J. HULSTEIN,[1]* P. J. VAN RUNNARD HEIMEL,[1]† A. FRANX,‡ P. J. LENTING,* H. W. BRUINSE,† K. SILENCE,§ PH. G. DE GROOT* and R. FIJNHEER*¶

*J Thromb Haemost* 2006; 4: 2569–75.



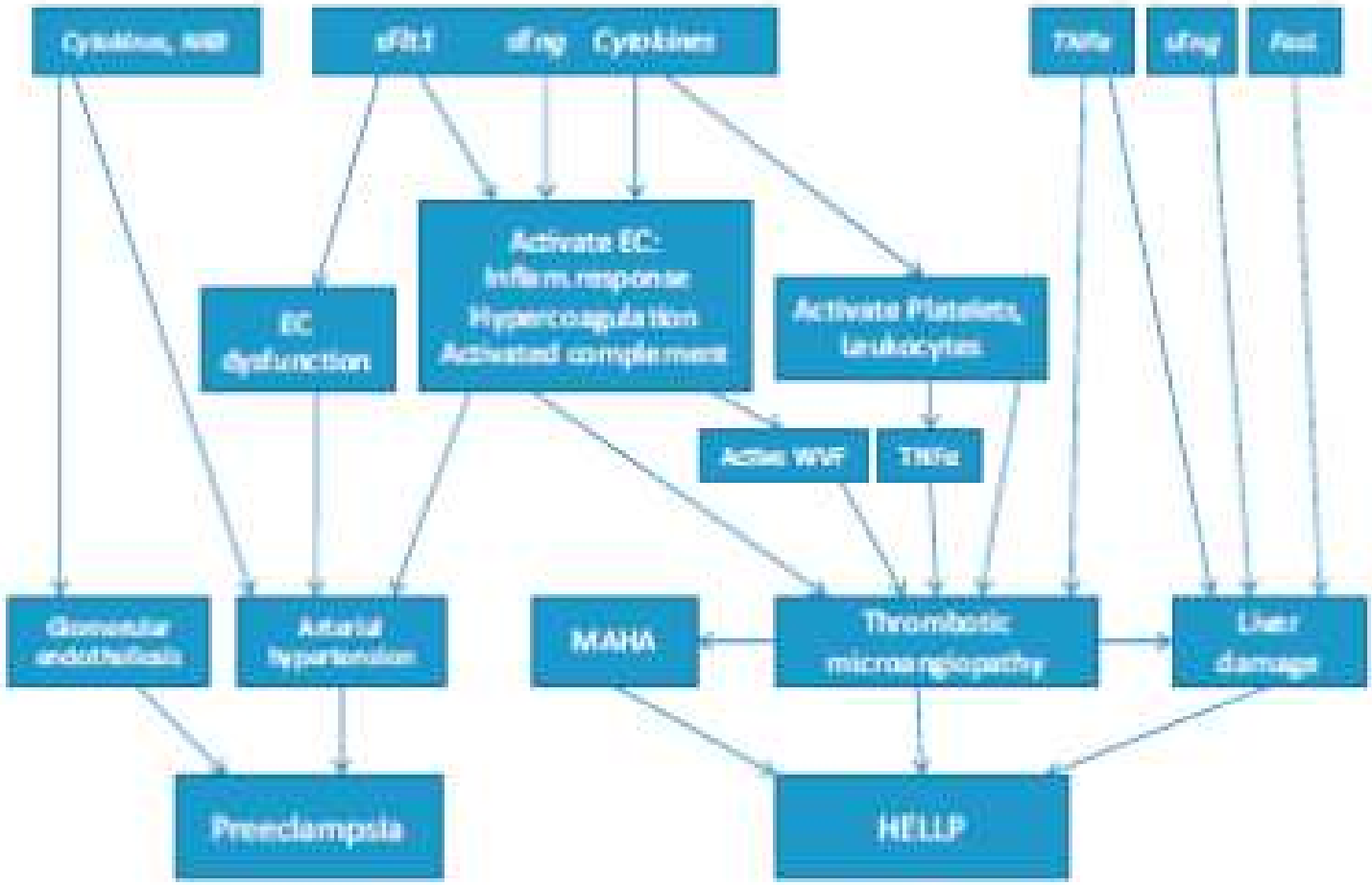

($P < 0.05$). *Conclusion:* Acute endothelial cell activation in HELLP syndrome and decreased ADAMTS13 activity result in increased amounts of active VWF. This might explain the consumptive thrombocytopenia and thrombotic microangiopathy associated with HELLP syndrome. Inhibition of circulating active VWF could be a potential new approach in the treatment of patients with HELLP syndrome.

# *Patogenesi*

European Journal of Obstetrics & Gynecology and Reproductive Biology 166 (2013) 117–123

## Pathogenesis of the syndrome of hemolysis, elevated liver enzymes, and low platelet count (HELLP): a review

Ulrich Abildgaard [a,*], Ketil Heimdal [b]



## MANIFESTAZIONI CLINICHE

- *Dolore addominale in epigastrio e/o ipocondrio destro*
- *Nausea vomito*
- *Ipertensione*

## *Criteri di Diagnosi*

**Table 1: Main diagnostic criteria of the HELLP syndrome**

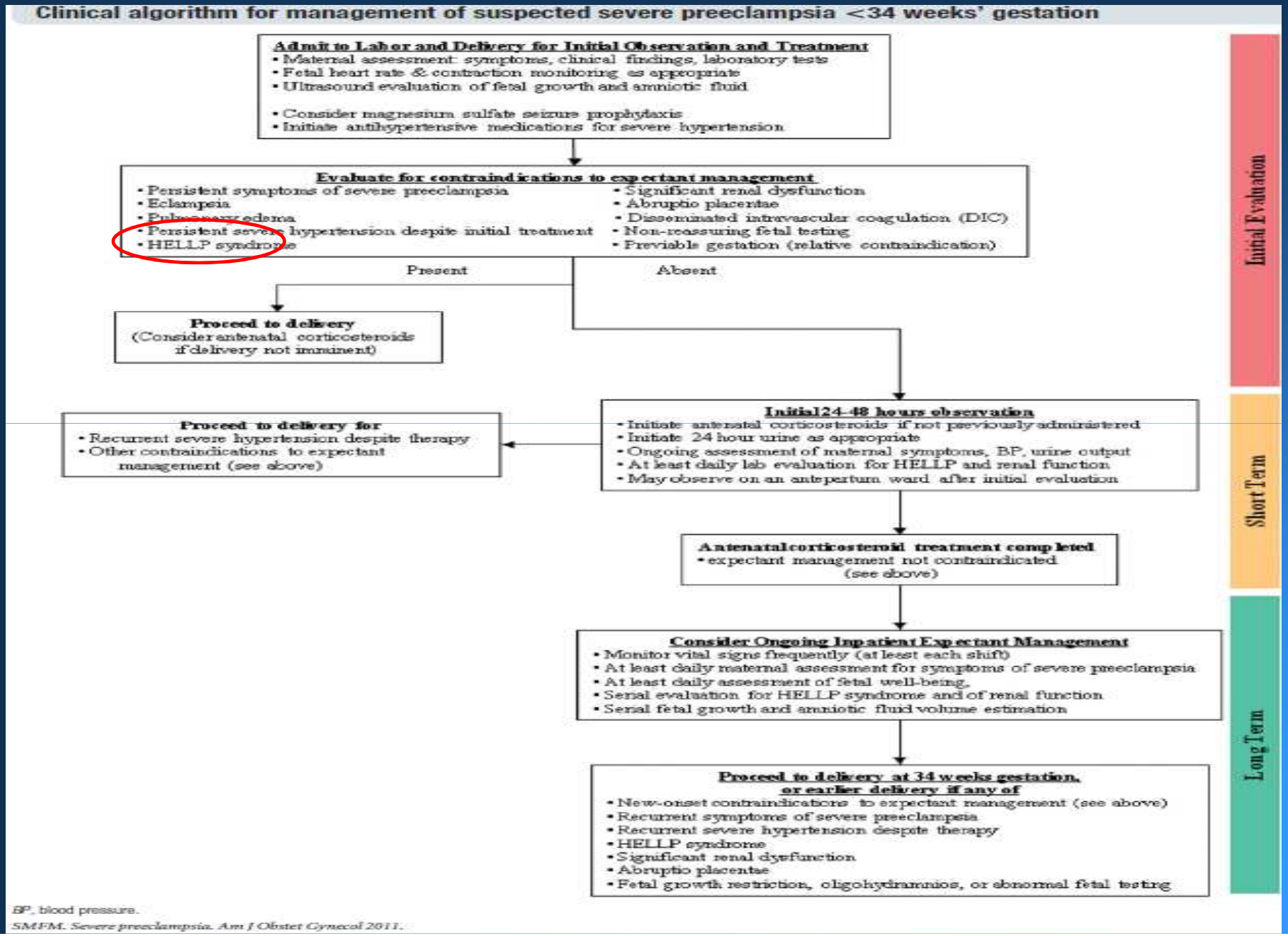
| HELLP class | Tennessee Classification | Mississippi classification |
|---|---|---|
| 1 | Platelets ≤ 100·10⁹/L<br>AST ≥ 70 IU/L<br>LDH ≥ 600 IU/L | Platelets ≤ 50·10⁹/L<br>AST or ALT ≥ 70 IU/L<br>LDH ≥ 600 IU/L |
| 2 | RMN/TC | Platelets ≤ 100·10⁹/L<br>≥ 50·10⁹/L<br>AST or ALT ≥ 70 IU/L<br>LDH ≥ 600 IU/L |
| 3 | | Platelets ≤ 150·10⁹/L<br>≥ 100·10⁹/L<br>AST or ALT ≥ 40 IU/L<br>LDH ≥ 600 IU/L |

## *Diagnosi Differenziale*

**Table 2: Differential diagnosis of the HELLP syndrome.**

1. Diseases related to pregnancy
   - Benign thrombocytopenia of pregnancy
   - Acute fatty liver of pregnancy (AFLP)
2. Infectious and inflammatory diseases, not specifically related to pregnancy:
   - Virus hepatitis
   - Cholangitis
   - Cholecystitis
   - Upper urinary tract infection
   - Gastritis
   - Gastric ulcer
   - Acute pancreatitis
3. Thrombocytopenia
   - Immunologic thrombocytopenia (ITP)
   - Folate deficiency
   - Systemic lupus erythematosus (SLE)
   - Antiphospholipid syndrome (APS)
4. Rare diseases that may mimic HELLP syndrome
   - Thrombotic thrombocytopenic purpura (TTP)
   - Haemolytic uremic syndrome (HUS)

# Management


Clinical algorithm for management of suspected severe preeclampsia <34 weeks' gestation
Admit to Labor and Delivery for Initial Observation and Treatment
• Maternal assessment: symptoms, clinical findings, laboratory tests
• Fetal heart rate & contraction monitoring as appropriate
• Ultrasound evaluation of fetal growth and amniotic fluid
• Consider magnesium sulfate seizure prophylaxis
• Initiate antihypertensive medications for severe hypertension
Evaluate for contraindications to expectant management
• Persistent symptoms of severe preeclampsia
• Eclampsia
• Pulmonary edema
• Persistent severe hypertension despite initial treatment
• HELLP syndrome
• Significant renal dysfunction
• Abruptio placentae
• Disseminated intravascular coagulation (DIC)
• Non-reassuring fetal testing
• Previable gestation (relative contraindication)
Present
Absent
Proceed to delivery
(Consider antenatal corticosteroids if delivery not imminent)
Proceed to delivery for
• Recurrent severe hypertension despite therapy
• Other contraindications to expectant management (see above)
Initial 24–48 hours observation
• Initiate antenatal corticosteroids if not previously administered
• Initiate 24 hour urine as appropriate
• Ongoing assessment of maternal symptoms, BP, urine output
• At least daily lab evaluation for HELLP and renal function
• May observe on an antepartum ward after initial evaluation
Antenatal corticosteroid treatment completed
• expectant management not contraindicated (see above)
Consider Ongoing Inpatient Expectant Management
• Monitor vital signs frequently (at least each shift)
• At least daily maternal assessment for symptoms of severe preeclampsia
• At least daily assessment of fetal well-being.
• Serial evaluation for HELLP syndrome and of renal function
• Serial fetal growth and amniotic fluid volume estimation
Proceed to delivery at 34 weeks gestation, or earlier delivery if any of
• New-onset contraindications to expectant management (see above)
• Recurrent symptoms of severe preeclampsia
• Recurrent severe hypertension despite therapy
• HELLP syndrome
• Significant renal dysfunction
• Abruptio placentae
• Fetal growth restriction, oligohydramnios, or abnormal fetal testing
Initial Evaluation
Short Term
Long Term
BP, blood pressure.
SMFM. Severe preeclampsia. Am J Obstet Gynecol 2011.

# Complicanze

## Complicanze Materne

## Complicanze Neonatali

**The HELLP syndrome: Clinical issues and management. A Review**
Kjell Haram[1], Einar Svendsen*[2] and Ulrich Abildgaard[3]

**Table 3: Complications reported in the HELLP syndrome**

| Maternal complications | Occurrence (%) |
|---|---|
| Eclampsia | 4–9 |
| Abruptio placentae | 9–20 |
| DIC | 5–56[2] |
| Acute renal failure | 7–36 |
| Severe ascites | 4–11 |
| Cerebral oedema | 1–8 |
| Pulmonary oedema | 3–10 |
| Wound hematoma/infection[2] | 7–14 |
| Subcapsular liver hematoma | Between 0.9% and <2% |
| Liver rupture | >200 cases or about 1.8% |
| Hepatic infarction | >30 cases combined with APS |
| Recurrent thrombosis | Associated with prothrombin gene 20210a mutation |
| Retinal detachment | 1 |
| Cerebral infarction | Few case reports |
| Cerebral Haemorrhage | 1.5–40[2] |
| Maternal death | 1–25 |
| **Foetal/neonatal complications** | |
| Perinatal death | 7.4–34 |
| IUGR | 38–61 |
| Preterm delivery[4] | 70 (15% < 28 gestational weeks) |
| Neonatal thrombocytopenia [1] | 15–50 |
| RDS | 5.7–40 |

**Box 4. Management of patients with documented subcapsular hematoma of the liver**

*General considerations:*

I. Have the blood bank aware of the potential need for large amounts of packed red blood cells, fresh frozen plasma, and platelet concentrate (ie, 30 units of blood, 20 units of fresh frozen plasma, 30–50 units of platelets).
II. Consult a general or vascular surgeon.
III. Avoid direct and indirect manipulation of the liver.
IV. Closely monitor hemodynamic status.
V. Administer intravenous magnesium sulfate to prevent seizures.

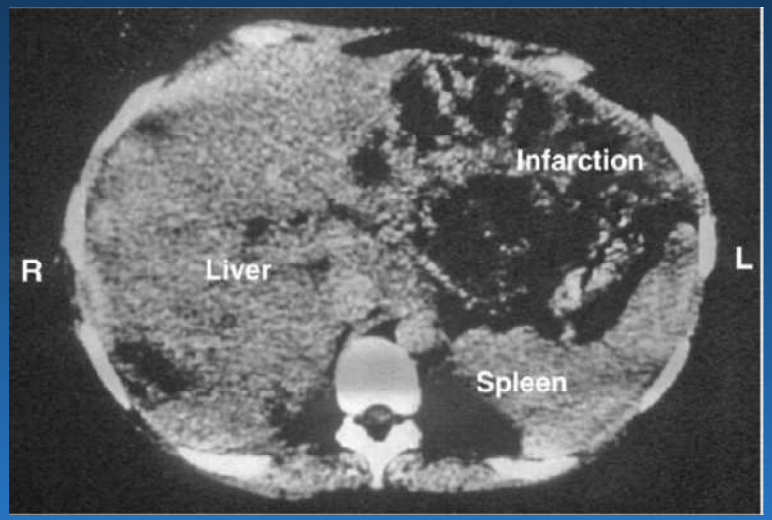
*If the hematoma is unruptured:*

I. Manage conservatively with serial CT scans or ultrasound.

*If the hematoma is ruptured:*

I. Massive transfusions
II. Immediate laparotomy
  A. If bleeding is minimal:
    (1) Observe.
    (2) Drain area with closed suction.
  B. If bleeding is severe:
    (1) Apply laparotomy sponges as packs for pressure.
    (2) Embolize the hepatic artery to the involved liver segment.
    (3) Surgically ligate hemorrhaging hepatic segment.
    (4) Loosely suture omentum or surgical mesh to the liver to improve integrity.

# Complicanze Epatiche




*Incidenza 5-10%*
*Ematomi sottocapsulari*
*Infarti epatici*
*Rottura della capsula*

# Utilité de la corticothérapie dans le syndrome HELLP : mythe ou réalité ?

## *Usefulness of corticosteroids in HELLP syndrome: Myth or reality?*

O. Pourrat[a,*], F. Pierre[b]

La Revue de médecine interne 33 (2012) 297–299

**Steroidi????**

*Efficacia nel recupero più rapido dei valori di Piastrine.*

*Non modifica outcome*

***QUALE POSSIBILE AZIONE?***

conclu à l'effet significatif des corticostéroïdes sur la numération plaquettaire. Les auteurs concluaient qu'en définitive il n'y avait à l'heure actuelle pas suffisamment de preuves pour recommander l'usage des corticostéroïdes en routine ; ils notaient toutefois que les corticostéroïdes pouvaient être justifiés dans les situations cliniques dans lesquelles une remontée accélérée du chiffre de plaquettes pouvait avoir une utilité clinique [10]. Il est donc justifié de mettre en place des essais contrôlés multicentriques portant sur des effectifs suffisants pour tenter de répondre à cette interrogation [3].

Un essai multicentrique contrôlé contre placebo (étude PRETIP) a testé chez 70 patientes l'hypothèse selon laquelle l'administration précoce de fortes doses de méthylprednisolone (180 mg sur 36 heures) pourrait limiter la chute des plaquettes au cours de la prééclampsie compliquée d'une thrombopénie ; les résultats sont en cours d'analyse.

### 2. Syndrome HELLP du postpartum

L'accouchement est suivi d'une amélioration rapide des divers paramètres cliniques et biologiques, avec remontée du chiffre de plaquettes au-dessus de 100 000 par millimètre cube en six à huit jours dans 85 % des cas [5]. Cependant, dans 15 % des cas, la situation peut s'aggraver temporairement dans les trois premiers jours et menacer le pronostic vital, notamment en raison du risque de complications hémorragiques ; la transfusion de produits sanguins (plaquettes et globules rouges) peut alors s'avérer indispensable [5].

au-dessus de 70 000 par millimètre cube était constatée dès la 30e heure en moyenne contre 48 dans le groupe témoin [15]. Une autre étude, contrôlée randomisée monocentrique, concluait à l'absence d'efficacité de la dexaméthasone dans un groupe de 71 patientes traitées en postpartum : la durée moyenne de séjour était plus courte dans le groupe sous dexaméthasone (6,8 jours versus 8,2 jours), mais cette différence n'atteignait pas le seuil de réduction fixé par les auteurs pour conclure à une différence statistiquement significative ; la durée médiane de séjour était identique (quatre jours) ; il n'y avait pas de diminution significative des besoins transfusionnels ; la remontée des plaquettes n'était pas accélérée de façon significative [8]. Enfin, une large étude monocentrique de 105 femmes, randomisée et contrôlée par placebo en double insu, n'a pas objectivé d'efficacité de la dexaméthasone à la dose de 12 mg toutes les 12 heures pendant quatre jours, et notamment pas de différence significative de complications hémorragiques : dans le groupe placebo, le pourcentage de transfusions était de 39 contre 29 % dans le groupe traité par dexaméthasone, mais la différence n'était pas statistiquement significative ; la vitesse de remontée des plaquettes, de baisse des transaminases et des LDH était similaire dans les deux groupes [16]. La revue très récente de la Cochrane Database Systemic Reviews citée précédemment a émis pour les essais thérapeutiques portant sur le syndrome HELLP du postpartum des conclusions similaires à celles concernant cette pathologie dans le prepartum [10].

Il serait intéressant de mettre en place des essais contrôlés multicentriques portant sur des effectifs suffisants pour tenter de répondre à cette interrogation [2,3].

maternel de la prééclampsie est lié à une réponse inflammatoire systémique [17]. Les microparticules syncytio-trophoblastiques libérées en grande quantité par le placenta stimulent en effet une production élevée synergique d'interleukine (IL)-12 et d'IL-18 par les mononucléaires circulants, qui entraine une stimulation de la production d'interféron gamma (IFNγ) par les cellules *natural killer* (NK) ; la résultante en est une réponse inflammatoire intense systémique déviée vers l'activation des lymphocytes T helper (Th) de type 1 (Th1), alors que la grossesse normale est caractérisée par une activation prédominante des Th2 (à laquelle on attribue un effet protecteur permettant la poursuite d'une grossesse normale). Dans le syndrome HELLP du prepartum qui s'accompagne d'une élévation de l'IL-6, il a été constaté après administration de prednisolone une réduction des taux de l'IL-6 de façon significative par rapport à un groupe témoin ($p<0,01$) [18].

***Corticosteroids for HELLP (hemolysis, elevated liver enzymes, low platelets) syndrome in pregnancy.***

*Woudstra DM, Chandra S, Hofmeyr GJ, Dowswell T.*

***Cochrane Database Syst Rev 2010 Sep 8;(9)***

*"Those receiving steroids showed significantly greater improvement in platelet counts which was greater for those receiving* ***dexamethasone than those receiving betamethasone.*** *The use of corticosteroids may be justified in clinical situations in which increased rate of recovery in platelet count is considered clinically worthwhile."*

# *Trombofilie ereditarie e HELLP syndrome*

*Acta Obstetricia et Gynecologica*. 2008; 87: 635–642

**Maternal factor V Leiden mutation is associated with HELLP syndrome in Caucasian women**

SABINE MUETZE[1,2], BRIGITTE LEENERS[1,3], JAN R. ORTLEPP[4], SABINE KUSE[5], CARMEN G. TAG[6], RALF WEISKIRCHEN[6], AXEL M. GRESSNER[6], SABINE RUDNIK-SCHOENEBORN[2], KLAUS ZERRES[2] & WERNER RATH[1]

In summary, our data confirm that Caucasian women carrying a heterozygous factor V Leiden mutation have an increased risk of developing HELLP syndrome (OR 4.45). In contrast, no significant association was found for prothrombin 20210G>A mutation and MTHFR 677C>T polymorphism. No further differences were detected when thrombophilic genotypes were related to the clinical features of HELLP syndrome and perinatal outcome. Moreover, there was no evidence for a fetal genetic influence on the mother's risk of developing HELLP syndrome. We further may conclude from our study that gene–gene interactions do not have a major impact on the role of thrombophilic mutations in the etiology of HELLP syndrome.

Table IV. Studies on genetic thrombophilias and risk of HELLP.

| Ref. (Year) | Country (Ethnicity) | Cases | Controls | FVL | MTHFR (homozygous) | Prothrombin |
|---|---|---|---|---|---|---|
| Krauss et al. (1998) (17) | Germany | 21 HELLP | – | 19% (4/21) were heterozygous FVL carriers | – | – |
| Rigo et al. (2000) (22) | Hungary (Caucasian) | 18 HELLP | 101 Healthy pregnant women matched for age and parity | pos (OR 2.83 [95% CI 1.24–6.48], $p=0.015$) | neg | – |
| von Tempelhoff et al. (2000) (25) | Germany (Caucasian) | 32 HELLP | 61 Women with normal pregnancies, primiparous | pos (OR 4.5 [95% CI 1.2–16.5], $p=0.04$) | – | – |
| Zusterzeel et al. (2000) (26), Raijmakers et al. (2001) (21) | Netherlands (Caucasian) | 95 HELLP | 405 Population-based controls | – | neg (OR 1.5 [95% CI 0.8–2.6], $p=0.17$) | – |
| Bozzo et al. (2001) (14) | Italy | 18 HELLP | – | No FVL carriers | | |
| Livingston et al. (2001) (19) | USA (White, African American) | 21 HELLP | 97 Normotensive controls | neg (OR 1.71 [95% CI 0.46–6.36])* | neg | neg |
| van Pampus et al. (2001) (24) | Netherlands (89% Caucasian) | 114 Severe PE/HELLP | General Dutch population | neg (OR 2.4 [95% CI 0.23–120]) | – | neg (OR 1.5 [95% CI 0.35–5.29]) |
| Benedetto et al. (2002) (13) | Italy | 32 HELLP | 111 Normal pegnant women matched for age and parity | neg (OR 2.29 [95% CI 0.56–9.32]) | – | neg (OR 6.03 [95% CI 0.65–47.54] |
| Schlembach et al. (2003) (23) | Germany (Caucasian) | 36 HELLP | 27 Women without HELLP syndrome | neg ($p=0.282$) | – | neg ($p=0.251$) |
| Gerhardt et al. (2004) (16) | Germany | 97 Severe PE including 41 HELLP | 277 Women with normal pregnancy | neg (OR 0.9 [95% CI 0.4–2.2], $p=1.0$) | neg (OR 0.8 [95% CI 0.4–1.8], $p=0.69$) | neg (OR 1.94 [95% CI 0.5–7.0], $p=0.29$) |
| Demir et al. (2006) (15) | Turkey | 100 PIH including 20 HELLP | 102 Women with normal pregnancies | neg ($p=0.115$) | pos ($p=0.041$) | neg ($p=0.275$) |
| Nagy et al. (2007) (20) | Hungary (Caucasian) | 63 HELLP | 73 Healthy pregnant controls | – | pos ($p=0.003$) | – |
| Larciprete et al. (2007) (18) | Italy | 108 Adverse pregnancy aoutcomes (HELLP, severe PE, DIC, FGR, AP, fetal death) | 176 Controls | – | neg | neg |

*OR+CI are given for all thrombophilias combined.
CI, confidence interval; *neg*, negative; *pos*, positive; OR, odds ratio; AP, abruption placentae; DIC, disseminated intravascular coagulopathy; FGR, fetal growth restriction; PE, preeclampsia; PIH, pregnancy-induced hypertension.
If available OR, 95% CI and/or *p*-value are given in brackets.

# Trombofilie ereditarie e HELLP syndrome

doi:10.1111/j.1447-0756.2010.01397.x J. Obstet. Gynaecol. Res. Vol. 37, No. 6: 527–533, June 2011

## Frequency of hereditary thrombophilia, anticoagulant activity, and homocysteine levels in patients with hemolysis, elevated liver functions and low thrombocyte count (HELLP) syndrome

Ovgu Ozkan Dogan[1], Yavuz Simsek[2], Sevki Celen[1] and Nuri Danisman[2]

In conclusion, AT-III deficiency and homocysteine levels were significantly higher in the study group compared with the control group, whereas thrombophilic mutations of FVL, the prothrombin gene, and the MTHFR gene of the two groups were similar. Of note, screening for AT-III deficiency might be considered as a component of a genetic screening test for obstetric complications, despite its relatively low prevalence in the general population. Measurement of homocysteine levels could be used to assess the risk of HELLP syndrome in patients with pre-eclampsia, in addition to other clinical and laboratory measures. We believe that increased coagulation activity has an important role in the pathogenesis of HELLP syndrome, but this relationship needs clarification via valuable data established from larger prospective controlled studies.

***Deficit di ATIII e omocisteina ↑ aumento dell'incidenza di HELLP***

***Mutazioni FVL, protrombina, MTHFR Nessuna relazione***

# Outcome

Gynécologie Obstétrique & Fertilité 38 (2010) 166–172

Incidence et facteurs de risque d'une complication vasculaire lors de la grossesse suivant un antécédent de prééclampsie et/ou de HELLP syndrome

*Subsequent pregnancy outcome in women with a history of preeclampsia and/or HELLP syndrome*

S. Cathelain-Soland [a], C. Coulon [a], D. Subtil [a,b], V. Houfflin-Debarge [a,b], P. Deruelle [a,b,*]

- *Rischio di ricorrenza di complicanze vascolari:*
  *Ipertensione gestazionale 12-29%*
  *HELLP syndrome 2-27%*
  *Pre-eclampsia 15-55%*

- *Fattori predittivi di ricorrenza di complicanze vascolari:*

*Parto < 32 s.g.*
*peso alla nascita < 3° centile,*
*BMI elevato*
*ipertensione arteriosa cronica*

***Monitoraggio intensivo della gravidanza: ecografie, laboratorio, PAO, BMI***

*Obstet Gynecol 2008 Aug 112 359-72*
*Prediction and prevention of recurrent pre-eclampsia.*
*Barton JR. Sibai BM.*

# Outcome

OCTOBER 2009 American Journal of Obstetrics & Gynecology

## Long-term maternal and subsequent pregnancy outcomes 5 years after hemolysis, elevated liver enzymes, and low platelets (HELLP) syndrome

Mounira Habli, MD; Nahid Eftekhari, MD; Emily Wiebracht, MD; Annette Bombrys, DO; Maram Khabbaz, MD; Helen How, MD; Baha Sibai, MD

TABLE 3
**Outcomes of subsequent pregnancies in women with HELLP syndrome**

| Outcome (n = 53) | n (%) |
|---|---|
| Spontaneous abortion (<20 wks) | 5 (9) |
| Preterm (<37 wks) | 26 (49) |
| Preeclampsia | 15 (28) |
| HELLP | 13 (24.5) |
| Birthweight <10th percentile | 2 (4) |
| Abruptio placentae | 1 (1.8) |

*HELLP*, hemolysis, elevated liver enzymes, and low platelets.

*Habli. Long-term 5-year maternal and pregnancy outcomes after HELLP syndrome. Am J Obstet Gynecol 2009.*

TABLE 5
**Subsequent pregnancy and long-term outcome based on gestational age at onset of HELLP**

| Factors | Gestational age at index ≤28 wks (n = 34) | Gestational age at index >28 wks (n = 94) | *P* value |
|---|---|---|---|
| Subsequent pregnancy outcome (n = 53) | | | |
| Preterm (<37 wks), n (%) | 7/13 (54) | 19/40 (48) | .75 |
| Preeclampsia, n (%) | 5/13 (39) | 10/40 (25) | .47 |
| HELLP, n (%) | 3/13 (23) | 10/40 (25) | > .99 |
| Long-term outcome (n = 123) | | | |
| Depression, n (%) | 8/30 (27) | 31/93 (33) | .65 |
| New-onset essential hypertension, n (%) | 14/30 (47) | 26/93 (28) | .07 |
| Anxiety, n (%) | 8/30 (27) | 24/93 (26) | > .99 |

Lancet 2007; 369: 1791–98

## Antiplatelet agents for prevention of pre-eclampsia: a meta-analysis of individual patient data

Lisa M Askie, Lelia Duley, David J Henderson-Smart, Lesley A Stewart, on behalf of the PARIS Collaborative Group*

ASA ↑

# Profilassi ?

Our data show that antiplatelet agents produce moderate but consistent reductions in pre-eclampsia and its consequences, but there is no clear evidence that such agents are any more or less effective in reducing the relative risk for any particular subgroup. This

congenital abnormalities in infants.[53] Our analyses showed no change in the risk of post-partum or ante-partum haemorrhage between women who received antiplatelet agents and those who did not, nor was there an effect on infant bleeding (table 1). Our analyses highlight the problem of measuring and defining post-partum haemorrhage. Two trials were excluded

BLOOD, 5 APRIL 2012 • VOLUME 119, NUMBER 14

## Heparin in pregnant women with previous placenta-mediated pregnancy complications: a prospective, randomized, multicenter, controlled clinical trial

*Ida Martinelli,[1] *Piero Ruggenenti,[2,3] Irene Cetin,[4] Giorgio Pardi,[5] Annalisa Perna,[2] Patrizia Vergani,[6] Barbara Acaia,[3] Fabio Facchinetti,[7] Giovanni Battista La Sala,[8] Maddalena Bozzo,[8] Stefania Rampello,[10] Luca Marozio,[11] Olimpia Diadai,[2] Giulia Gherardi,[2] Sergio Cominetti,[2] Giuseppe Remuzzi,[2,3] and Pier Mannuccio Mannucci,[12] for the HAPPY Study Group

EBPM ↓

Antithrombotic prophylaxis with low-molecular-weight heparin in addition to medical surveillance failed to decrease the number of late pregnancy complications compared with medical surveillance alone in 135 women with a previous history of preeclampsia, eclampsia, HELLP syndrome, intrauterine fetal death, FGR, or placental abruption. Baseline characteristics of study participants were similar in the 2 study arms, so that failure to detect any

events because of previous HELLP syndrome or preeclampsia. In the meantime, antithrombotic prophylaxis should not be routinely administered to prevent recurrences of placenta-mediated pregnancy complications and should be restricted to women who have a proven benefit from this intervention, such as those with previous thromboembolic events[6] and perhaps those with previous placental abruption without fetal loss.[8]

*J Thromb Haemost* 2012; **10**: 64–72.

## Low-molecular-weight heparin added to aspirin in the prevention of recurrent early-onset pre-eclampsia in women with inheritable thrombophilia: the FRUIT-RCT

J. I. P. DE VRIES,* M. G. VAN PAMPUS,† W. M. HAGUE,‡ P. D. BEZEMER,§ J. H. JOOSTEN* and ON BEHALF OF FRUIT INVESTIGATORS

# *Profilassi ?*

***ASA e EBPM***

This randomized trial has shown that adding LMWH to aspirin before 12 weeks gestation reduces recurrent HD in women with previous early-onset HD and/or SGA, in the context of an inheritable thrombophilia without antiphospholipid antibodies. This reduction affects recurrent early-onset HD, and in particular pre-eclampsia, before 34 weeks gestation, with a highly favorable NNT. It results in longer gestation and less need for corticosteroid therapy for fetal lung maturation. No such difference was seen in the overall recurrence of HD irrespective of gestational age.

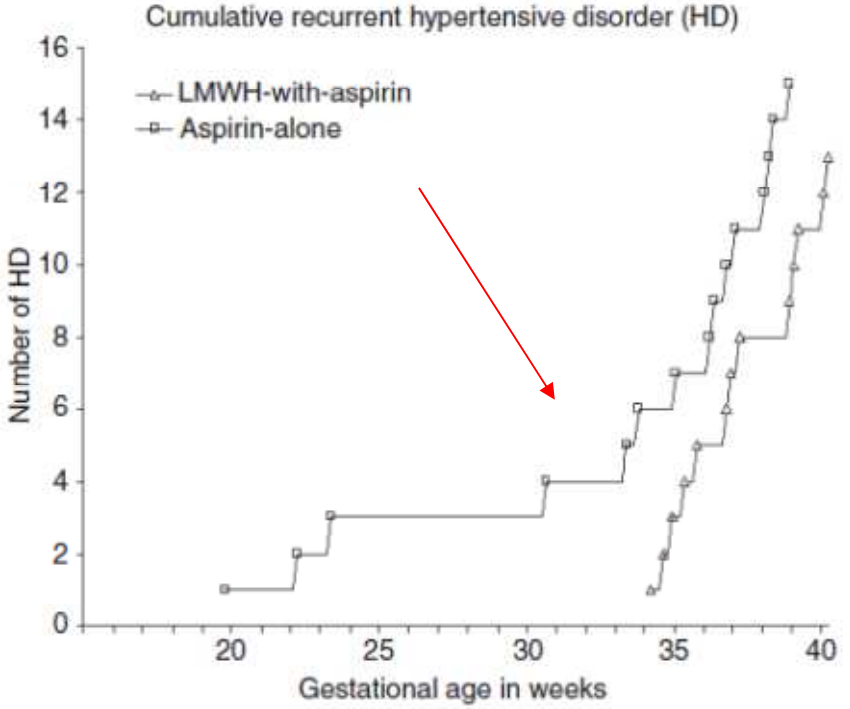


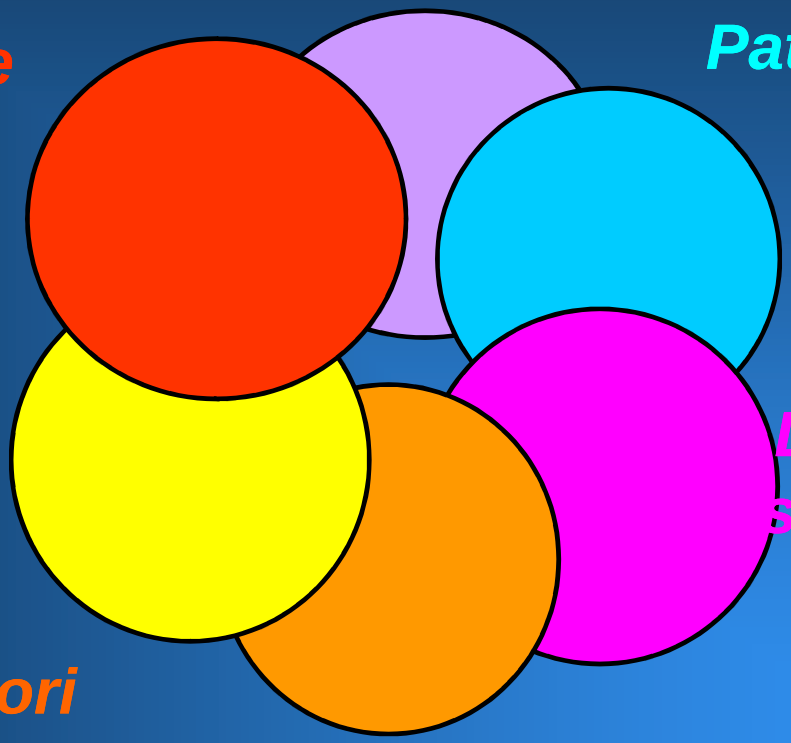

**Fig. 2.** Recurrence of hypertensive disorders (HD) per week in each study arm.

Hypertens Pregnancy. 2006;25(2):115-27.

**Prophylaxis of** recurrent preeclampsia**: low-molecular-weight heparin plus low-dose** aspirin **versus low-dose** aspirin **alone.**

Sergio F, Maria Clara D, Gabriella F, Giorgia S, Sara De Carolis, Giancarlo P, Alessandro C

# *HELLP Syndrome*



***Fattori di Rischio***

***Patogenesi***

***Diagnosi e severità***

***Fattori Predittivi di ricorrenza***

***Profilassi***

***Outcome***

*Scuola di Specializzazione*
*in*
*Ginecologia ed Ostetricia*

Università degli Studi di Padova
Direttore: Prof. G.B.Nardelli

# *CASO CLINICO*

*Specializzanda: Dr.ssa Cristiana Nardi*

**The fibrinogen/CRP ratio as a new parameter for the diagnosis of disseminated intravascular coagulation in patients with HELLP syndrome and as a predictive factor for neonatal outcome**

Karin Windsperger, MD; Rainer Lehner, MD

*Rapporto Fibrinogeno/PCR*

TABLE 5
**Mean ranks of the classical parameters within the groups overt and no overt DIC**

| Coagulation parameters | Mean ranks: Nonovert DIC (n = 98) | Mean ranks: Overt DIC (n = 13) | *P* value |
|---|---|---|---|
| Platelet count | 60.41 | 22.77 | < .05 |
| Fibrinogen | 56.12 | 46.73 | > .05 |
| Antithrombin | 55.02 | 27.42 | < .05 |
| Thrombin time | 54.05 | 53.65 | > .05 |
| aPTT | 53.73 | 73.08 | < .05 |
| PT | 57.66 | 43.50 | > .05 |

*aPTT*, activated partial thromboplastin time; *DIC*, disseminated intravascular coagulation; *PT*, prothrombin time.

*Windsperger. The fibrinogen/CRP ratio as a new parameter for the diagnosis of DIC. Am J Obstet Gynecol 2013.*

TABLE 7
**Mean ranks of the fibrinogen/CRP ratio within the groups overt and no overt DIC**

| Variable | Mean ranks: Overt DIC | Mean ranks: No overt DIC | *P* value |
|---|---|---|---|
| Fibrinogen/CRP ratio | 31.77 | 58.15 | < .05 |

*CRP*, C-reactive protein; *DIC*, disseminated intravascular coagulation.

*Windsperger. The fibrinogen/CRP ratio as a new parameter for the diagnosis of DIC. Am J Obstet Gynecol 2013.*

# Management

Clin Perinatol 31 (2004) 807–833

## Diagnosis and management of hemolysis, elevated liver enzymes, and low platelets syndrome

John R. Barton, MD[a,b,*], Baha M. Sibai, MD[b]

1. *Assessing and stabilizing the maternal condition*

*(a) Correction of coagulopathy if DIC is present*
*(b) Antiseizure prophylaxis with magnesium sulfate*
*(c) Treatment of severe hypertension*
*(d) Transfer to tertiary care center, if appropriate*
*(e) CT or ultrasound of the abdomen if subcapsular hematoma of the liver is suspected*

*2. Evaluation of fetal well-being*

*(a) Nonstress testing*
*(b) Biophysical profile*
*(c) Ultrasonographic biometry to rule out intrauterine growth restriction*

*3. Evaluation of gestational age*

If >34 weeks' gestation, or non reassuring test of fetal status or presence of several maternal disease (DIC, renal failure, abruptio placenta…): DELIVERY

If < 34 weeks' gestation, glucocorticosteroids: DELIVERY