MICROANGIOPATIE TROMBOTICHE: PATOGENESI/TERAPIA

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Le microangiopatie trombotiche in gravidanza

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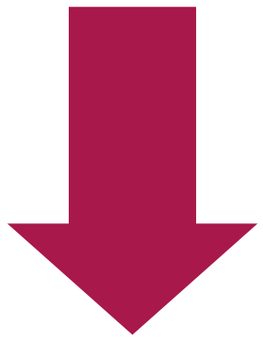
TMA - DEFINITION

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

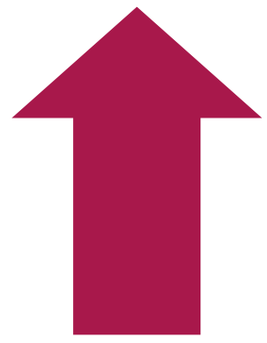
- Pregnancy
- Thrombocytopenia
- Microangiopathic haemolytic anaemia (MAHA)
- Small vessel thrombosis
- Organ injury

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



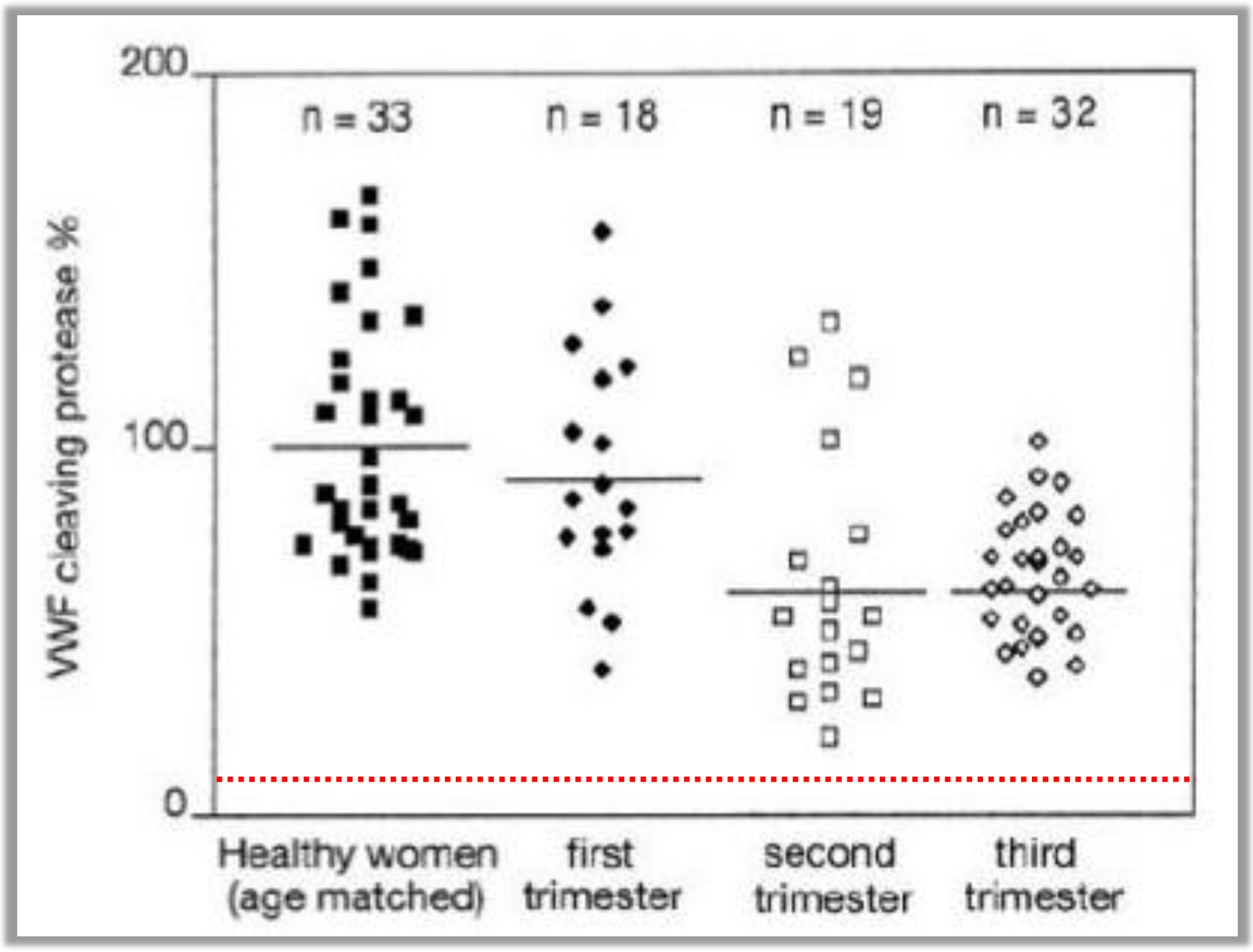
Procoagulant

PREGNANCY IS A HYPERCOAGULABLE STATE

Fibrinogen	Increased from 2.5 g/l to 5 g/l
Factor II	Slightly increased
Factor V	Slightly increased
Factor VII	Increased 10 folds
Factor VIII	Increased 2 folds
Factor XI - X	Increased
Factor XI	Decreased by 70%
Factor XII	Increased by 40%
Factor XIII	Decreased by 40%

and to make things worse...

Changes in ADAMTS13 during pregnancy



P.M. Mannucci et al. Blood 2001; 98:2730-2735

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%

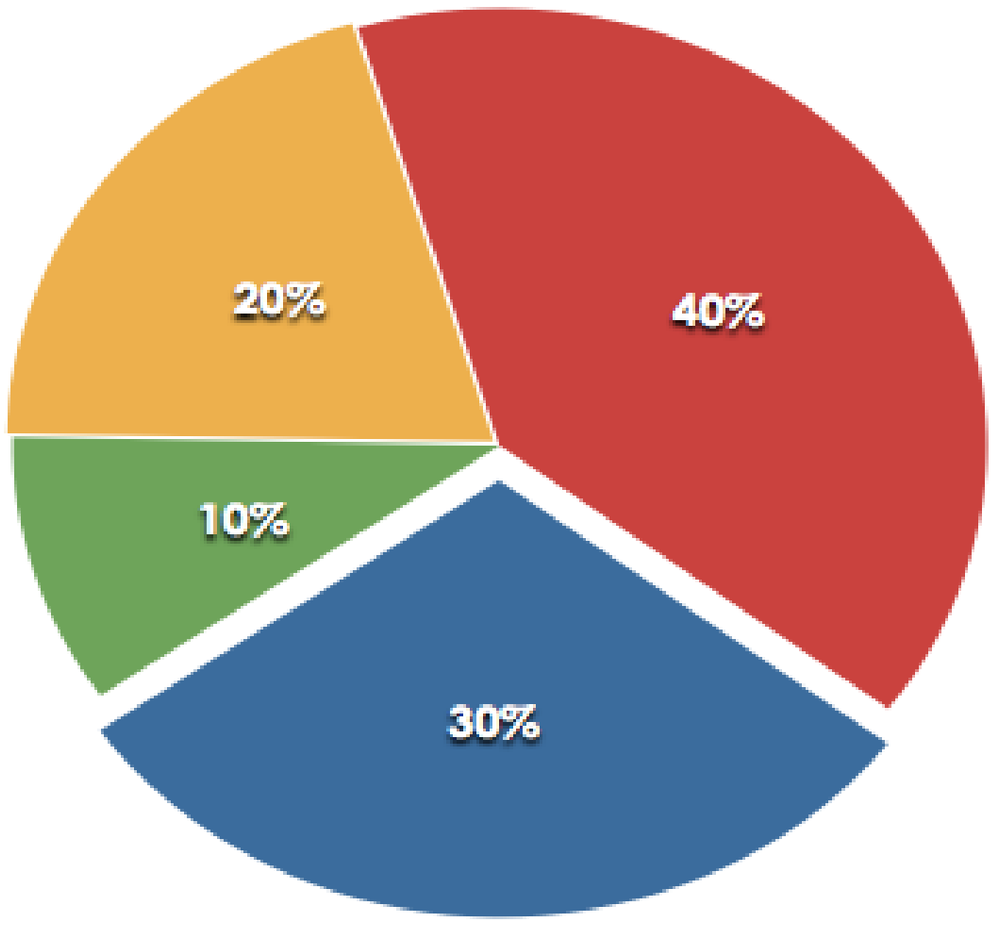
  (55% of PE risk if HELLP < 28 sett)

Am College of Obstetricians and Gynecologists : Hypertension in Pregnancy. 1996
Sibai – Obstet and Gynecol 2004
Weinstein - Am J Obstet & Gynecol 1982
Liszewski MK et al. Hematology Am Soc Hem Educ Program 2011:9-14

PE/HELLP syndrome

epidemiology

> 37 weeks



27 - 37 weeks

< 27 weeks

After delivery

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

PE/HELLP syndrome

PATHOGENETIC MECHANISMS

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

Haram et al: The HELLP syndrome clinical issues and management, BMC pregnancy childbirth, 2009

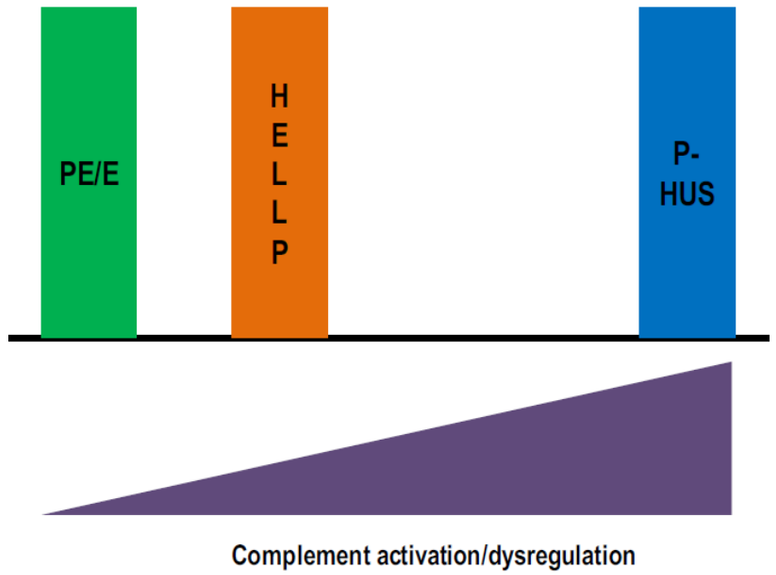
PE/HELLP syndrome

PATHOGENETIC MECHANISMS

The role of inflammatory response

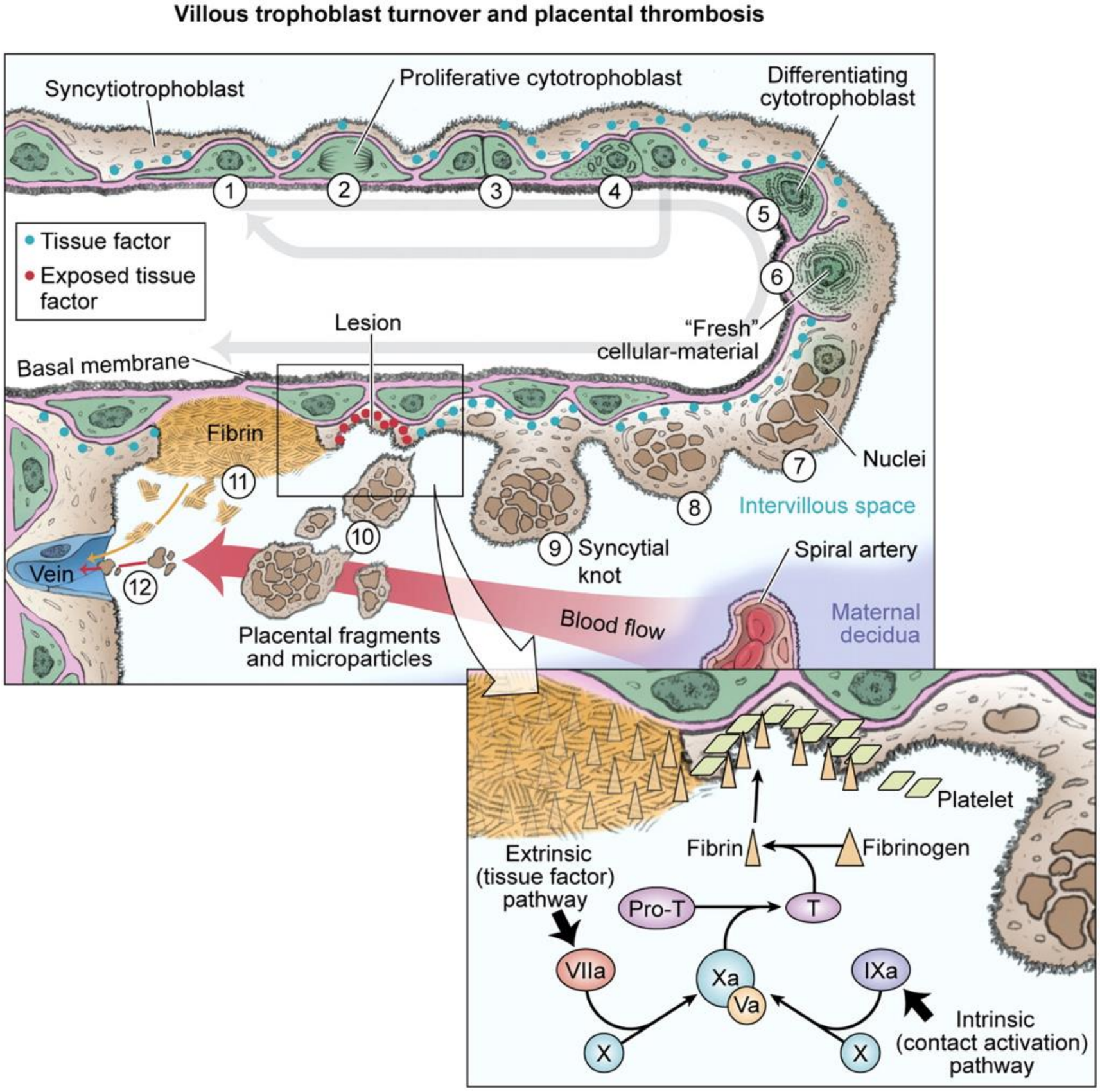
- ✓ release into the maternal blood of syncytiotrophoblast particles (STBM)
- ✓ activation of complement (?)

Fakhouri, Transfusion and Apheresis Science,2016



- ✓ increase the blood levels of IL-6 and TNFa
- ✓ activation of vascular endothelial cells release of active multimeric vWF
- ✓ platelet aggregation and adherence of platelets to vessel intima

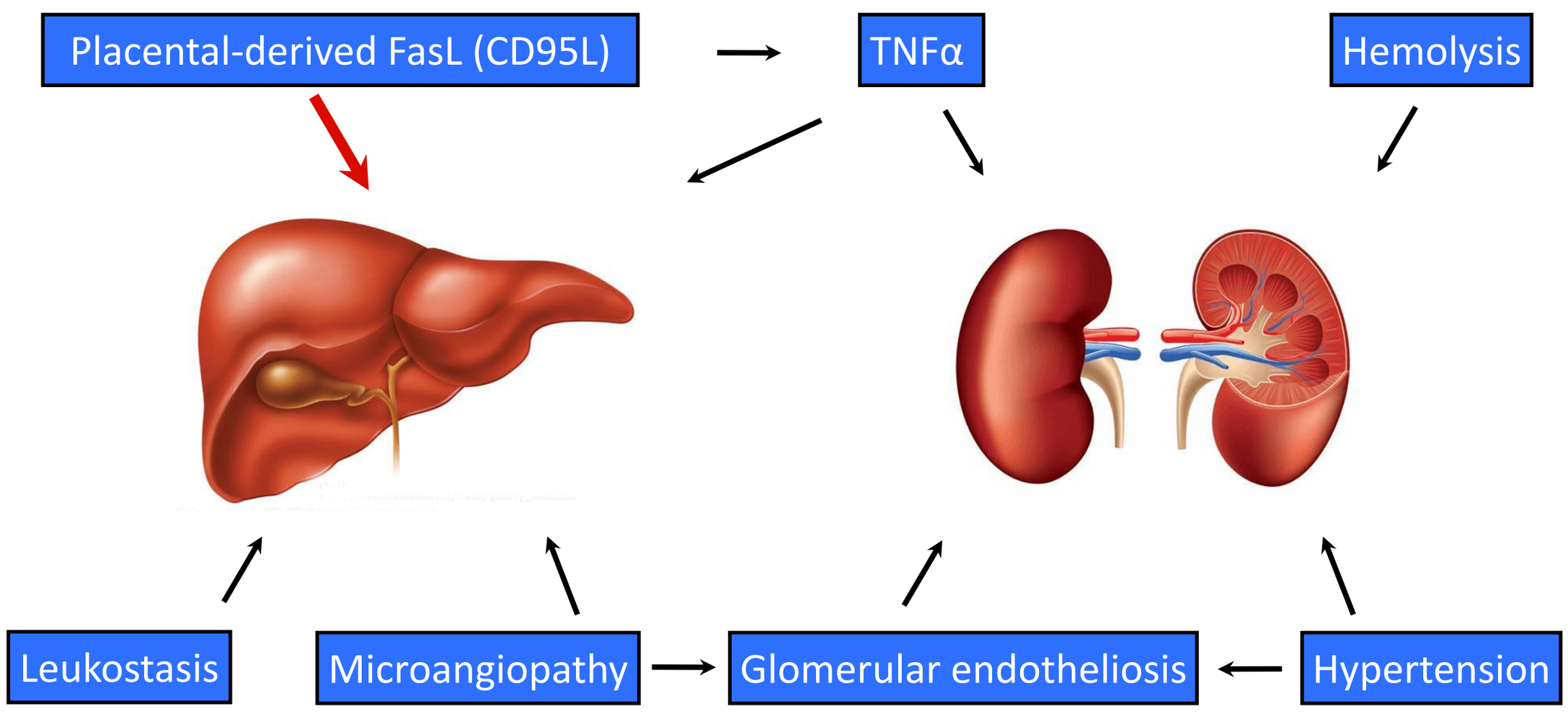
PE/HELLP syndrome pathogenetic mechanisms



PE/HELLP syndrome

PATHOGENETIC MECHANISMS

Liver and kidney dysfunction



PE/HELLP syndrome

CLINICAL SYMPTOMS

Epigastric or right upper abdominal quadrant pain in women with hypertension or PE could be indicative 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

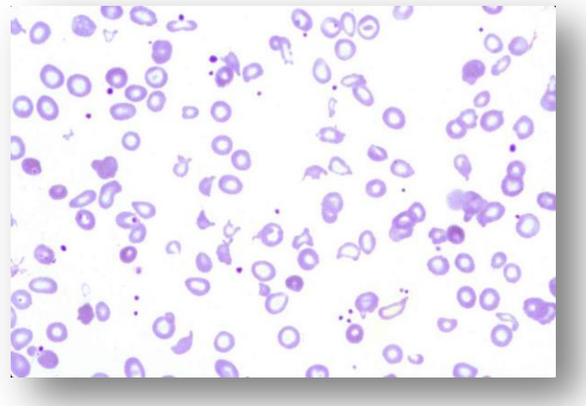
PE/HELLP syndrome

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/HELLP syndrome

	Platelet	LDH	Enzymes	Maternal morbidity
Class I	**< 50.000**	> 600 UI/L	**AST or ALT > 70 UI/L**	40% - 60%
Class II	> 50.000 <100.000	> 600 UI/L	**AST or ALT > 70 UI/L**	20% - 40%
Class III	> 100.000	> 600 UI/L	AST > 40 UI/L	20%

PE/HELLP syndrome

Maternal complication	OCCURRENCE (%)
Eclampsia	4-9
Abruptio placentae	9-20
DIC	4-56
Acute renal failure	7-36
Severe ascites	4-11
Cerebral oedema	1-8
Pulmunary oedema	3-10
Subcapsular liver hematoma	1-2
Liver rupture	<2%
Retina detachment	1
Cerebral infarction	Few case report
Cerebral haemorrhage	1.5-40
Maternal death	1-25

PE/HELLP syndrome

TREATMENT AND MANAGEMENT

Hypertension control

- a-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)

COHELLP: collaborative randomized controlled trial on corticosteroids in HELLP syndrome

Leila Katz[1*], Melania Amorim[2], João P Souza[3,4,5], Samira M Haddad[6], José G Cecatti[6] and COHELLP 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)

	Platelet	LDH	Enzymes	Maternal morbidity
Class I	**< 50.000**	> 600 UI/L	**AST or ALT > 70 UI/L**	40% - 60%
Class II	> 50.000 <100.000	> 600 UI/L	**AST or ALT > 70 UI/L**	20% - 40%
Class III	> 100.000	> 600 UI/L	AST > 40 UI/L	20%

Complemento TMA e gravidanza

HELLP

- Crovetto F, et al. 2012
  - 2/33 pz presentavano mutazione di geni del complemento
- Haeger M, et al. 1990
  - 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
- Ari E, et al. 2009
  - 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

Placenta 34 (2013) 201–203

Contents lists available at SciVerse ScienceDirect

Placenta

journal homepage: www.elsevier.com/locate/placenta

Case report

Eculizumab for the treatment of preeclampsia/HELLP syndrome

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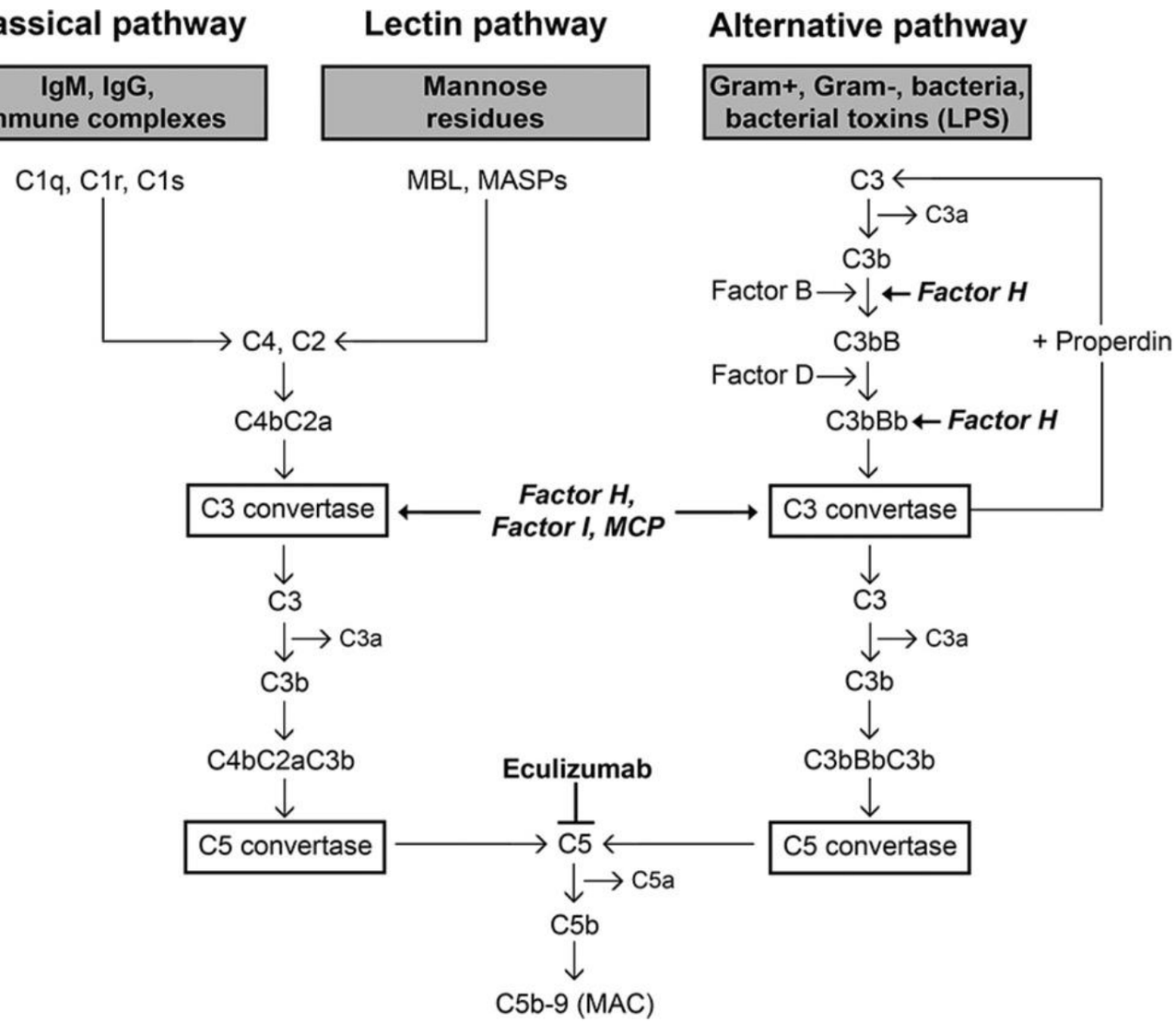
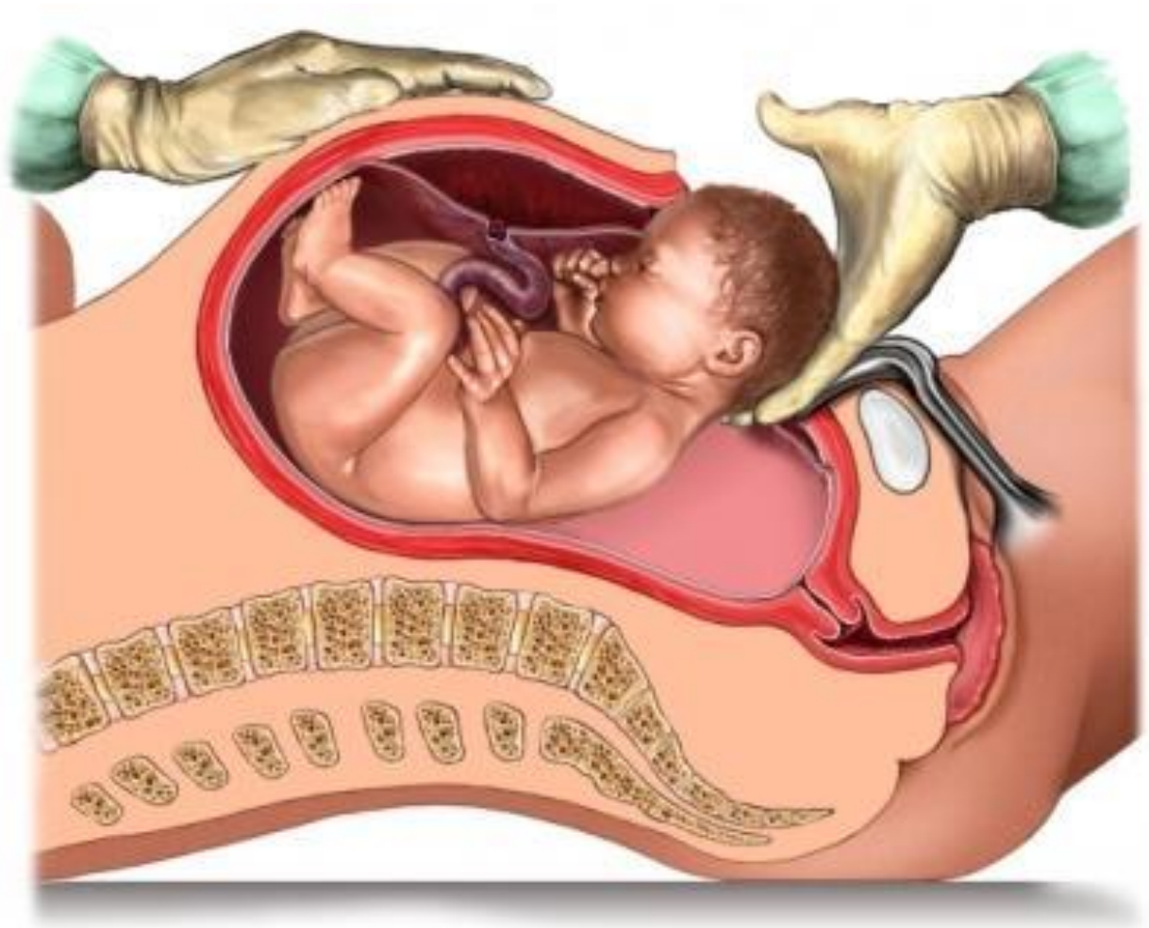


PE/HELLP syndrome

TIMING OF DELIVERY



- > 34 weeks: immediate delivery after maternal stabilization
- 24-34 weeks: corticosteroids, after maternal stabilization, and delivery after 24 hours

TTP

DEFINITION

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

Antepartum	Postpartum
87,3% (n= 145)	12,7% (n= 21)

< 14 weeks	14-28 weeks	> 28 weeks
11,7%	55.5%	32.8%

Pregnancy-Associated TTP

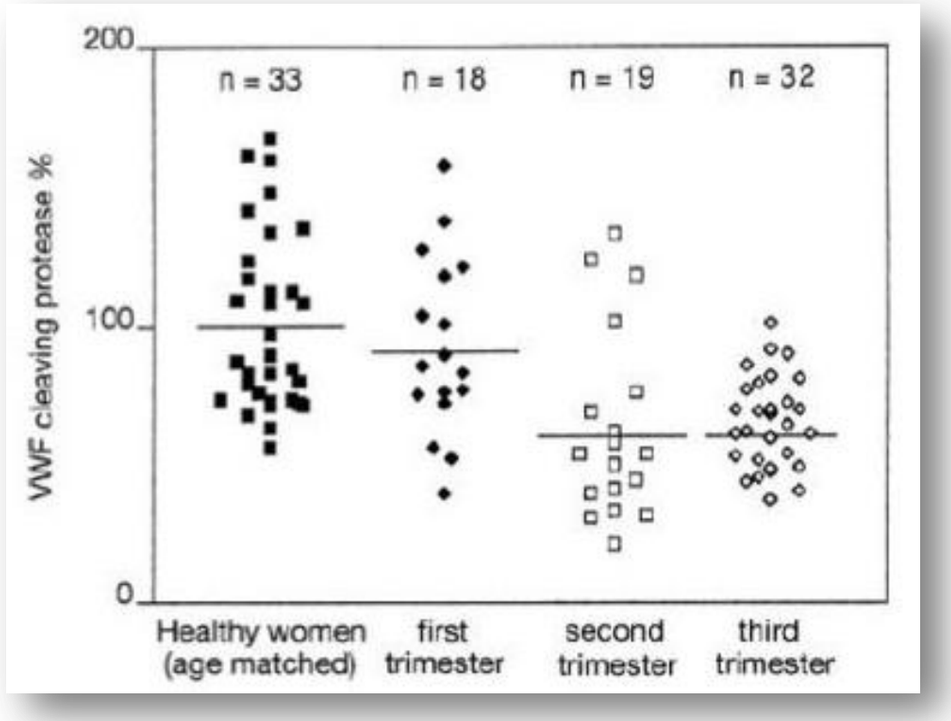
PATHOGENETIC MECHANISMS

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**

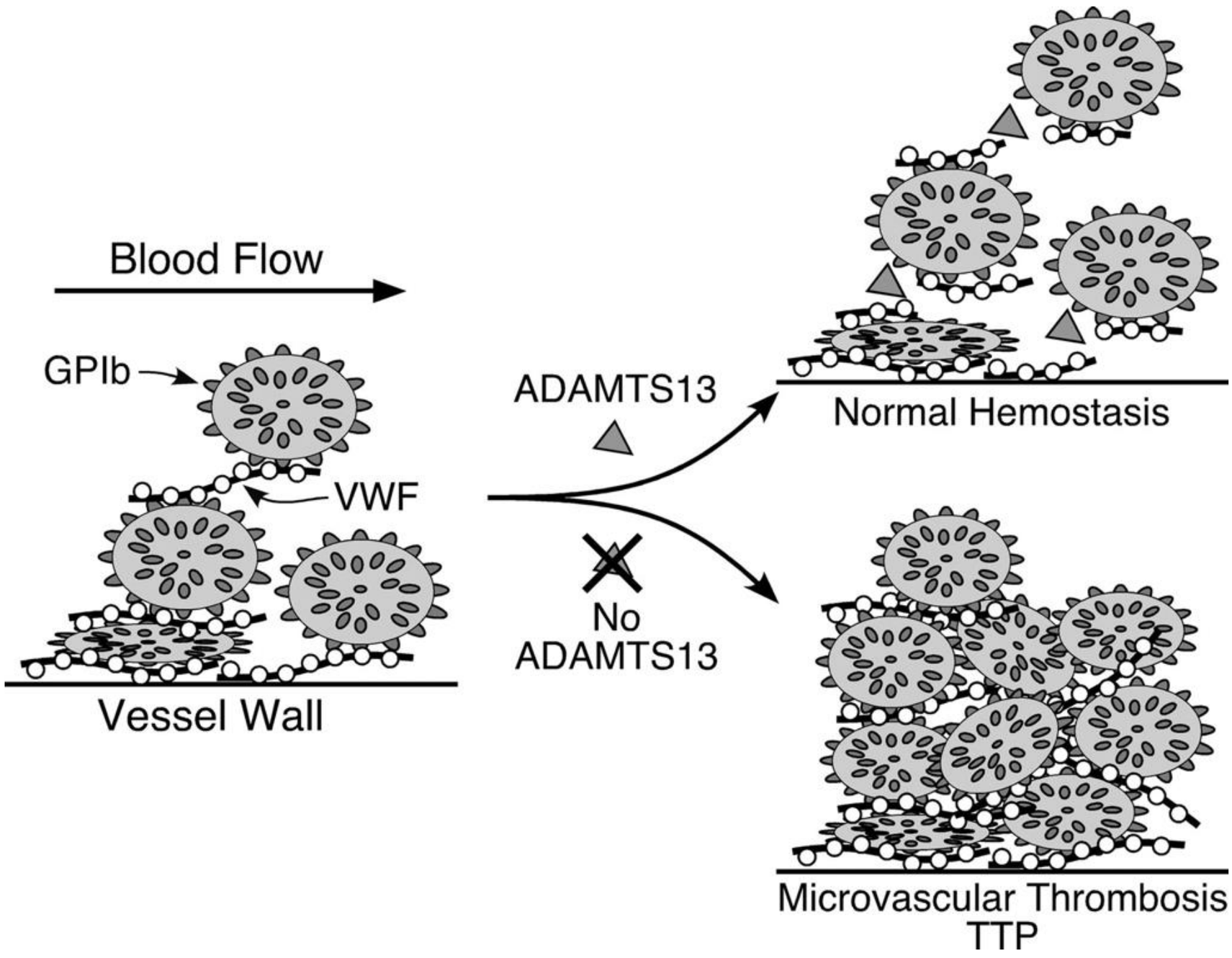
ADAMTS13



vWF levels

Pregnancy-Associated TTP

PATHOGENETIC MECHANISMS



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

DIFFERENTIAL DIAGNOSIS	Congenital TTP (n=10, 24%)	Acquired TTP (n=32, 76%)
Nulliparity	100%	62.5%
ADAMTS13 <10% at onset	100%*	100%**
Anti-ADAMTS13 at onset	0% (0/10)	72% (23/32)

*ADAMTS13 remained undetectable in remission

**9 patients recovered ADAMTS13 >30% in remission and were diagnosed as aTTP

M. Moatti-Cohen et al. On behalf of the French Reference Center for Thrombotic Microangiopathies.

Blood: 2012 .vol 119 n 24

Pregnancy-Associated TTP

TREATMENT AND MANAGEMENT: Before 24 weeks'

LABORATORY STUDIES

CLINICAL PROFILE

Plasma exchange every 2 weeks

If platelet count is < 150.000, increase weekly or Rituximab

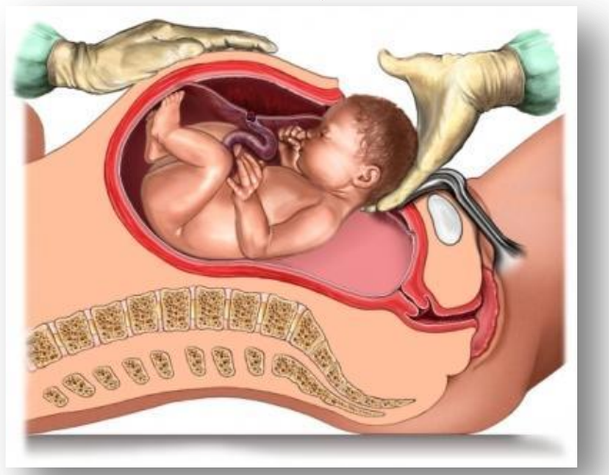
Pregnancy-Associated TTP

TREATMENT AND MANAGEMENT: After 24 weeks'

LABORATORY STUDIES

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**

aHUS

HISTORY AND DEFINITION

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)

aHUS

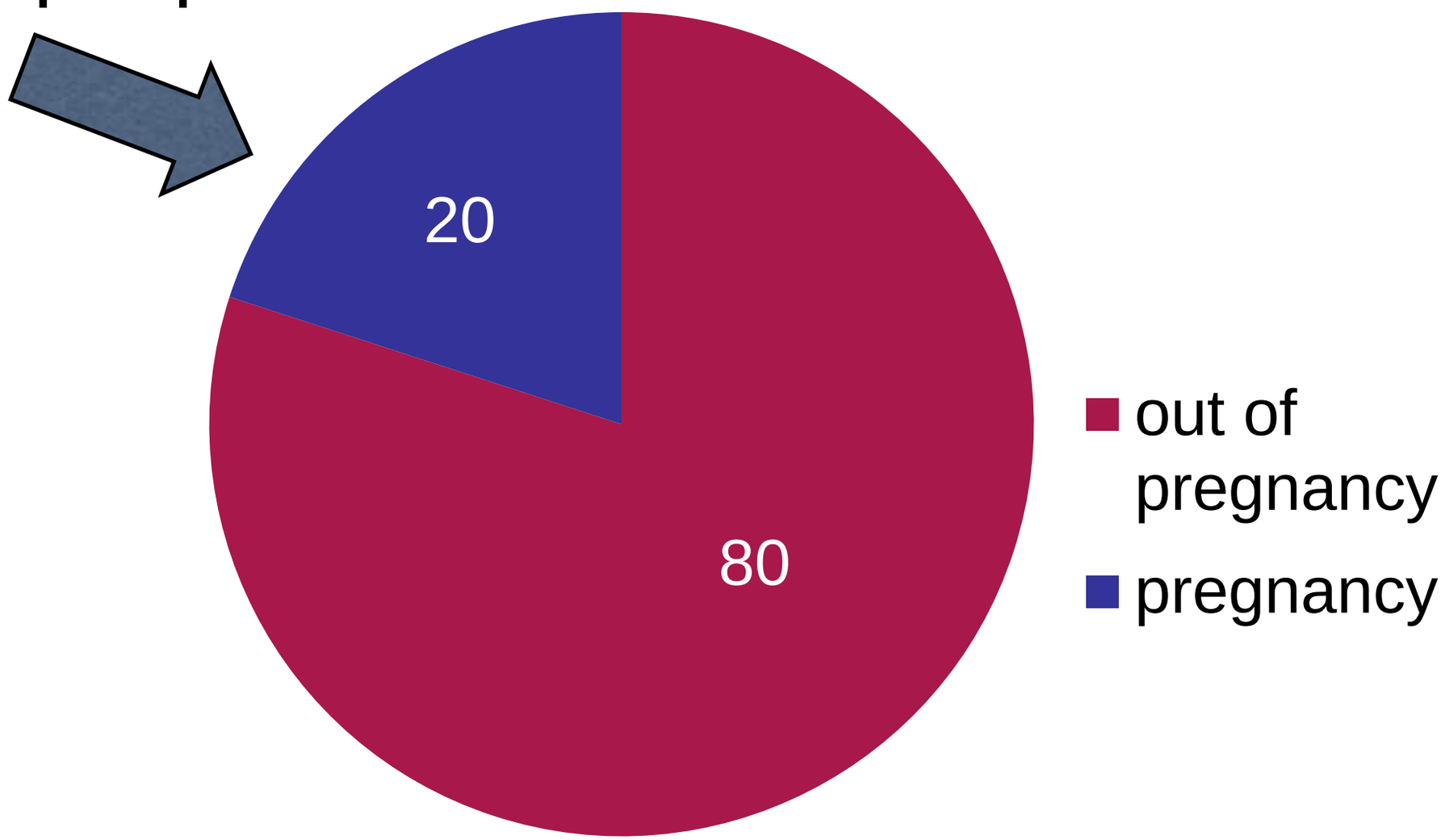
EPIDEMIOLOGY

- 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

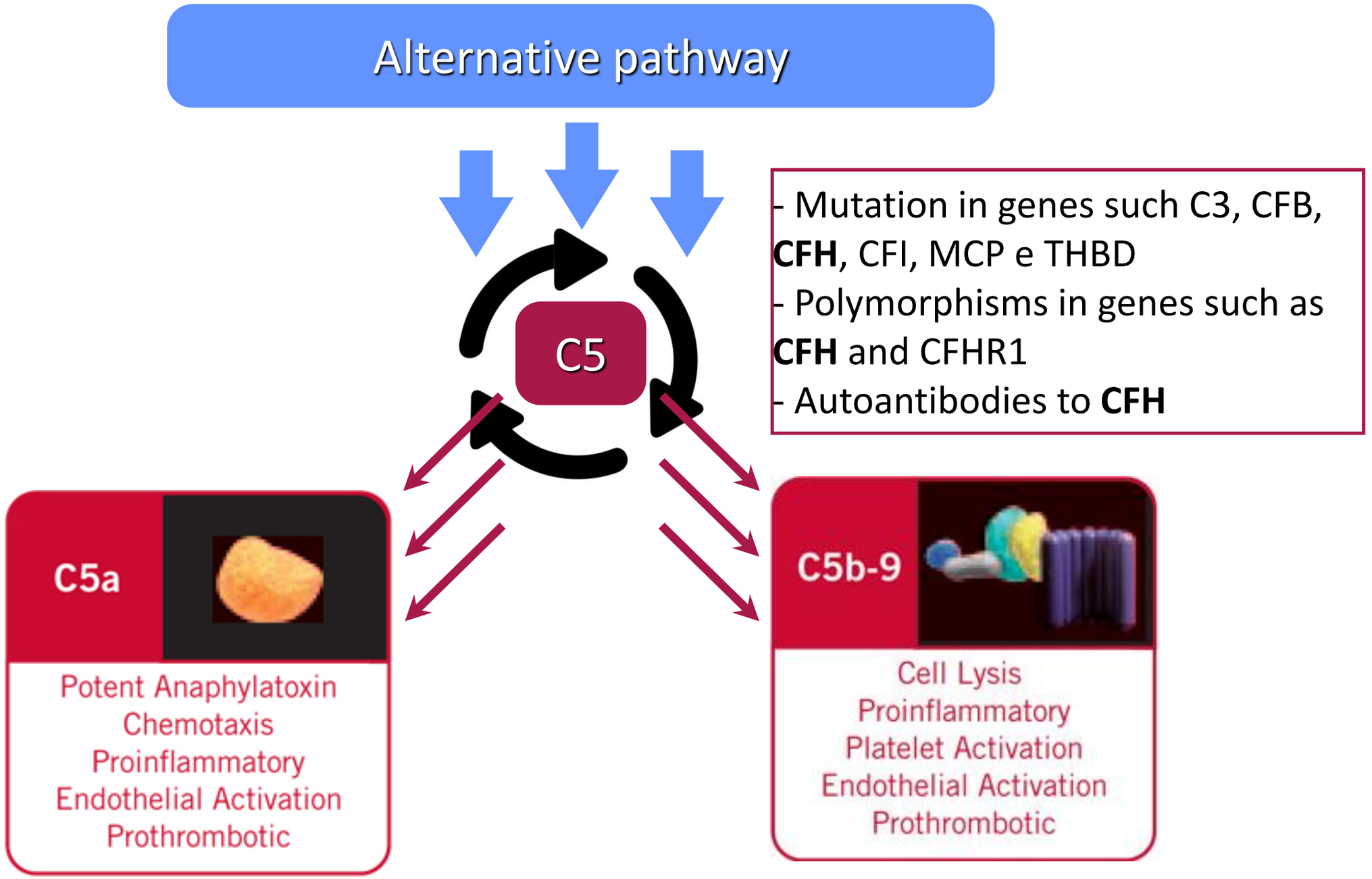
80% during the post-partum



Fakhouri et al, Pregnancy associated aHUS revisited in the era of comp lent gene mutation, J Am Soc Nephrol, 2010

Pregnancy-Associated aHUS

PATHOGENETIC MECHANISMS



Pregnancy-Associated aHUS

PATHOGENETIC MECHANISMS

- Mutation in genes such 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%)

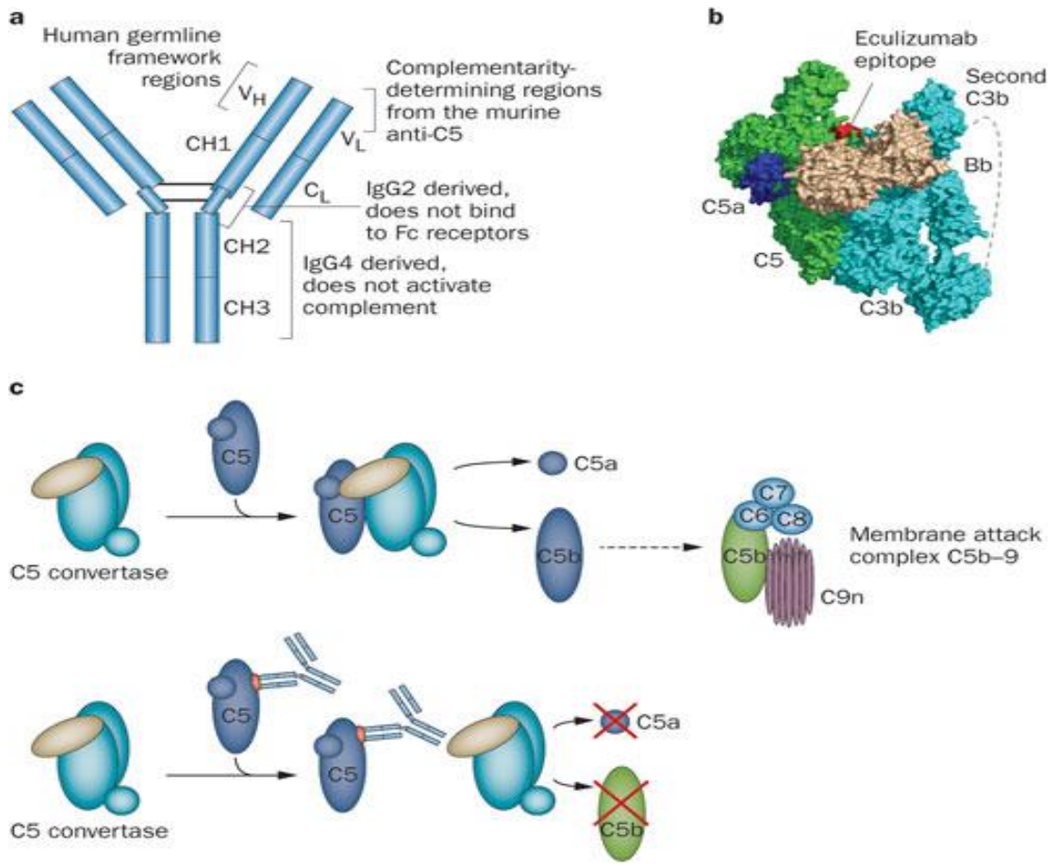
- Most cases of p-aHUS occur during **postpartum** period with severe acute onset associated with **MAHA**

- In contrast, thrombocytopenia is moderate and neurological impairment is uncommon

Pregnancy-Associated aHUS

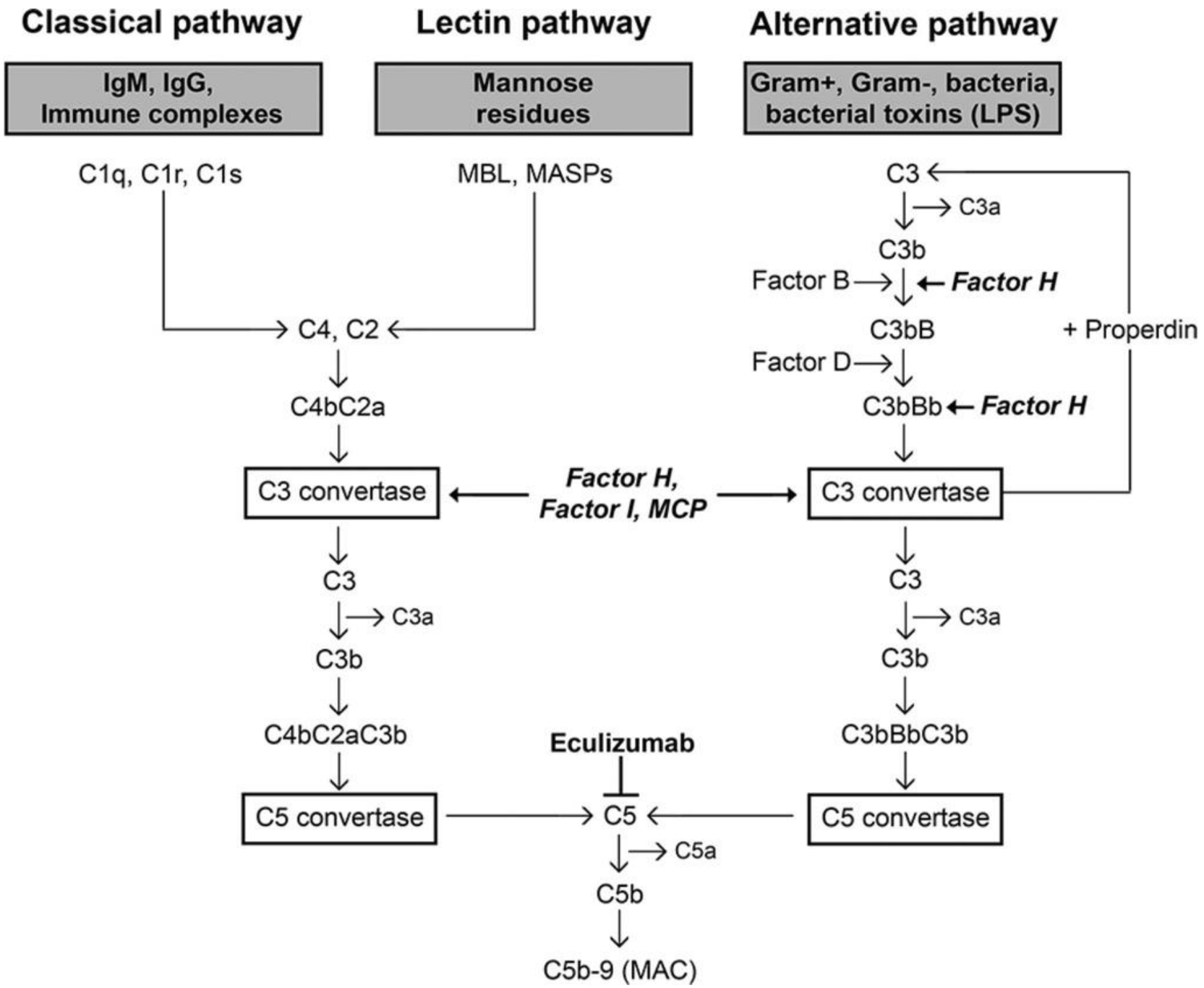
TREATMENT AND MANAGEMENT

- plasma infusions and plasma exchange (to start rapidly because of the high risk of ESRD)
- Complement activation modulators (**eculizumab**) represents 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!