Living with Atypical HUS

PREGNANCY AND ATYPICAL HUS

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Pregnancy and Atypical HUS

Pregnancy and Kidney Disease (PreKID) Clinic

- Collaborative approach – High Risk OB & nephrology

Patients Counseled >1000

- Number of Pregnancies 65%

> 50 new patients consulted at clinic undergo pregnancy annually

- < 10 have had aHUS

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Pregnancy Counseling

Pregnancy Risk Assessment

Risk of Deterioration in Kidney Function

Risk of Adverse Pregnancy Outcomes

Preeclampsia, Poor fetal growth, Pre-term Delivery

Risk of a Flare

Optimization Strategies

Pregnancy Management

Differentiating aHUS from TTP and Preeclampsia/HELLP Syndrome

Postpartum Care

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Disease Flare

- Pregnancy Exacerbated
  - Lupus
    - Present or Flare in any trimester or early postpartum
    - Nephritis is the biggest risk for a bad outcome
    - Antiphospholipid Antibody Syndrome
    - Severe Morbidity and Mortality reported
      - 6-12 months of disease quiescence recommended
  - ANCA
  - **TTP/ Atypical HUS**
  - Diabetic Nephropathy
    - ? Mechanism
  - ? MCD, FSGS, MN, IgA
    - Deserves further study

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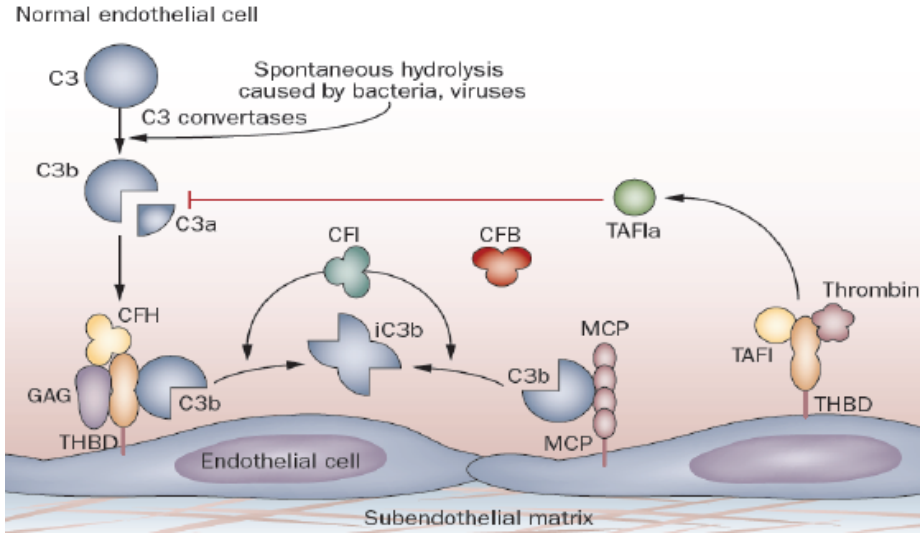
Complement System

- Innate immune system - protect
- 3 distinct pathways (classical, lectin and the alternate)
- Alternate pathway (C3 convertase) can be initiated spontaneously so it is tightly regulated

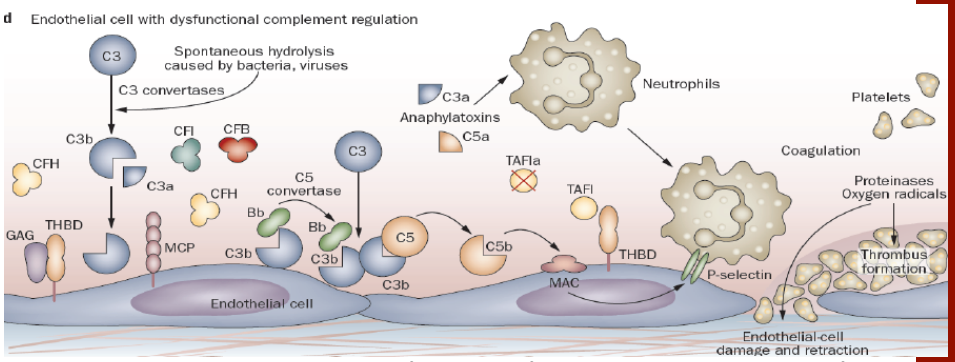


Chiang and Inagi, Nat Rev Immunol 2010

aHUS-associated complement abnormalities

- **Loss of function mutations:**
  - Factor H (*CFH*)
  - Factor I (*CFI*)
  - Membrane cofactor protein (*MCP*/CD46)
  - Thrombomodulin (*THBD*/CD141)

- **Gain of function mutations:**
  - *CFB*
  - *C3*



Chiang and Inagi, Nat Rev Immunol 2010

- **Autoantibodies:**
  - CFH (in combination with *CFHR3/CFHR1* deletion: DEAP-HUS)

Noris and Remuzzi, N Engl J Med 2009

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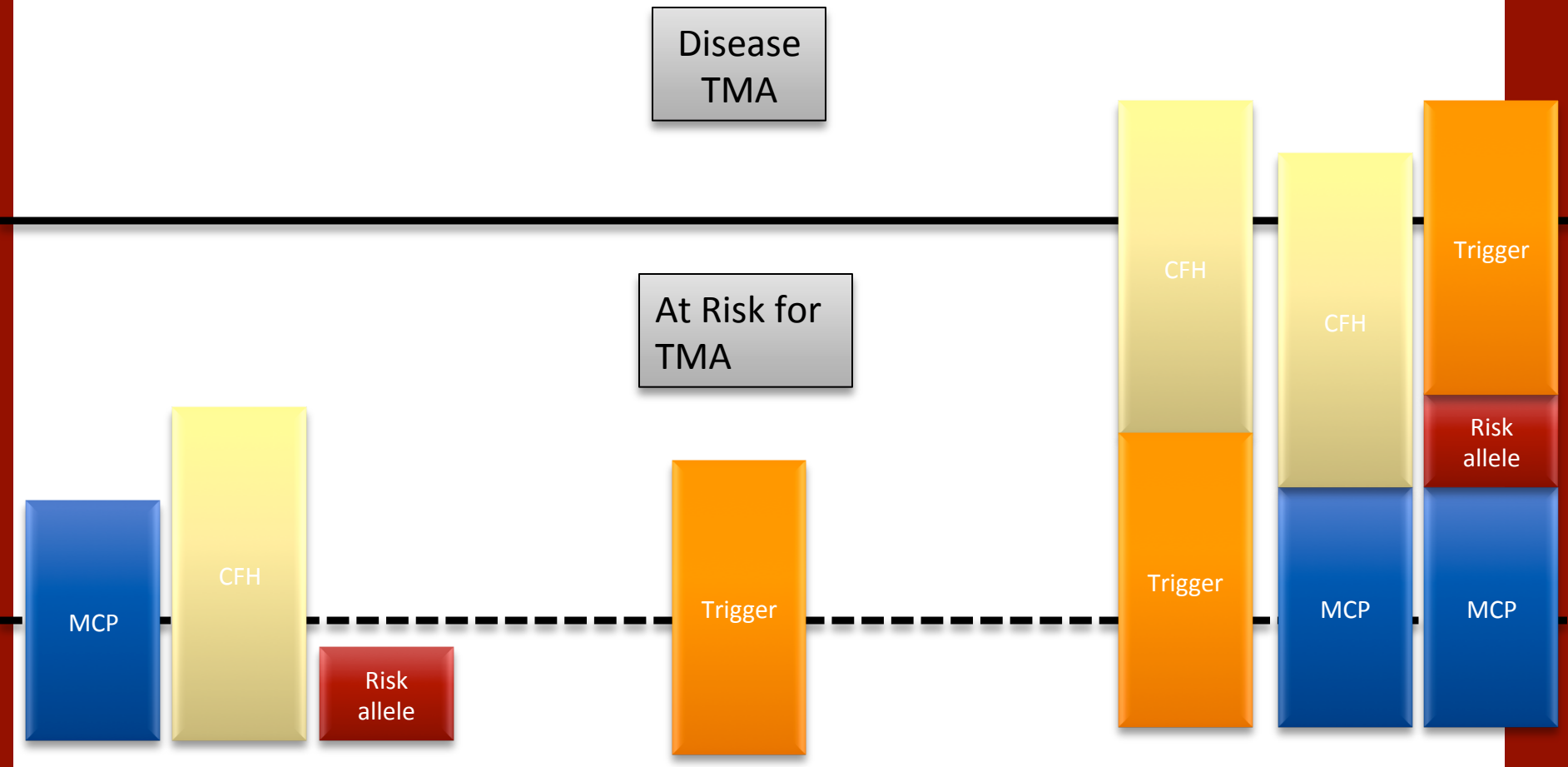
Multiple hit theory of TMA pathogenesis



Complement mutations increase risk and some may be more important eg CFH

Additional triggers eg, CNI, toxin, IRI or pregnancy

Disease becomes manifest as risk factors accumulate

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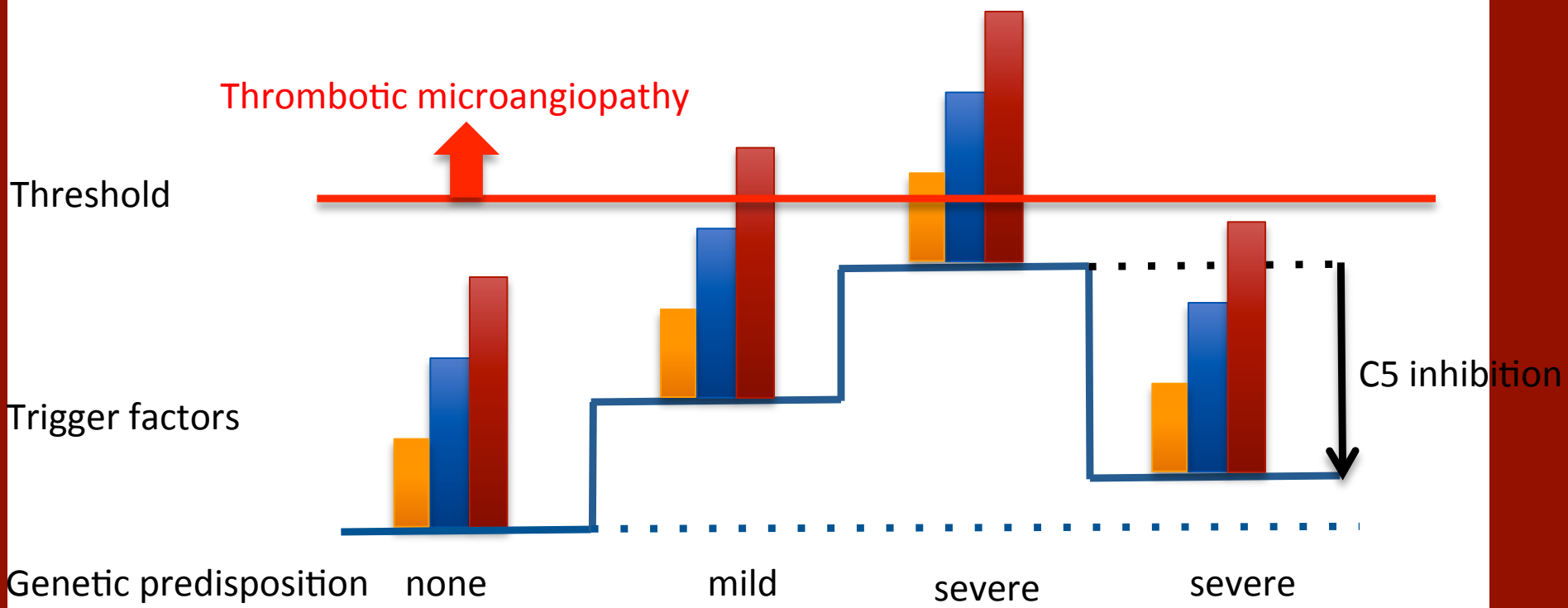
Multiple hit theory of TMA pathogenesis



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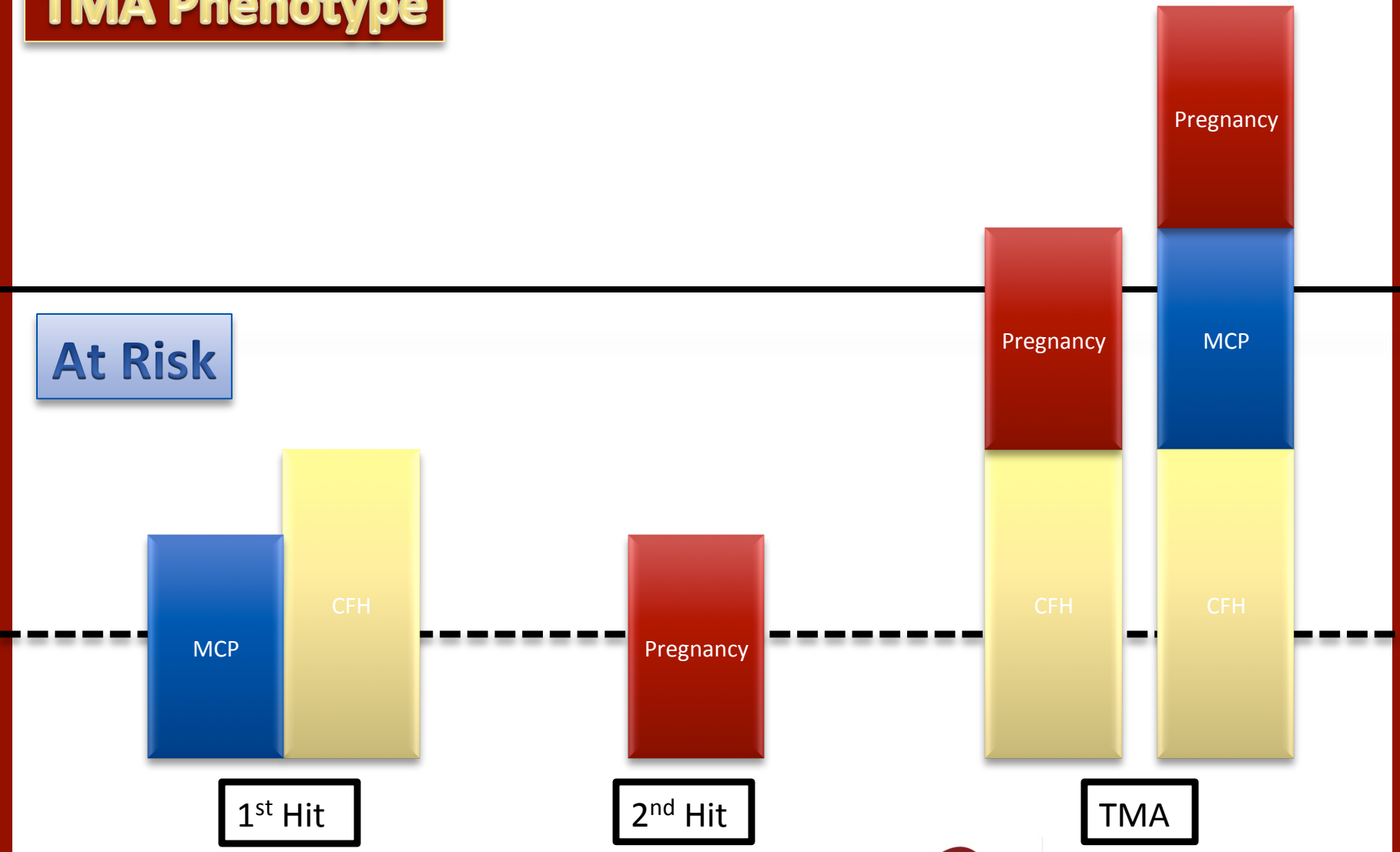
TMA Phenotype



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Pregnancy and Atypical HUS

- Series of 21 pregnancies/100 women with aHUS
- Pregnancy is the trigger in ≈ 20% of women with aHUS
- Most commonly presented in the second pregnancy

Fakhouri F et al *JASN* 2010;21:859-867

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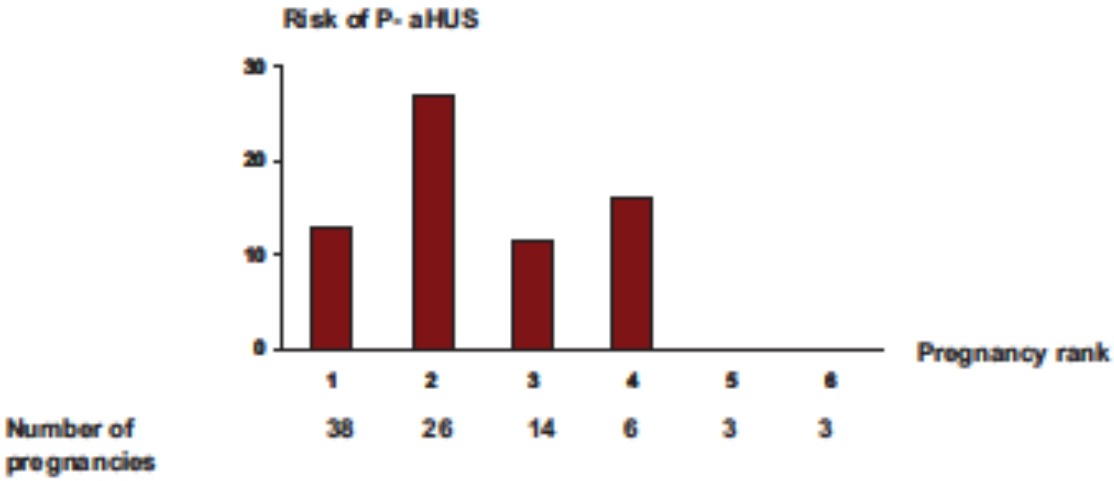
Pregnancy and Atypical HUS

- 74% with documented complement abnormalities had at least one pregnancy before the pregnancy related aHUS



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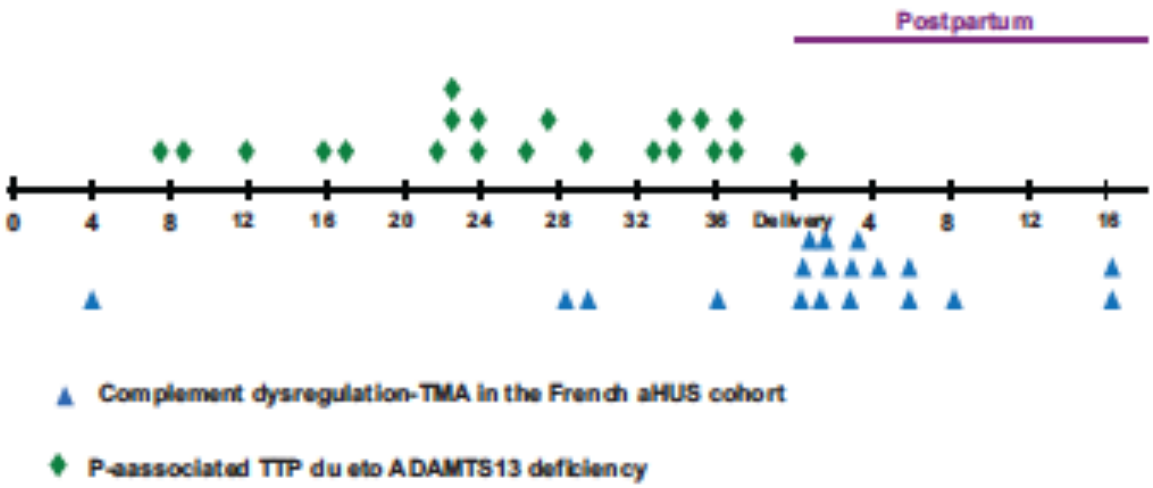
Pregnancy and Atypical HUS

- 79% presented postpartum
  - Presumed the complement system is activated to help cleanup placental debris



Fakhouri F et al *JASN* 2010;21:859-867

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Pregnancy and Atypical HUS

- Outcomes were poor for mom
  - 62% reaching ESRD by one month
  - 76% reaching ESRD by last follow-up
  - Despite majority receiving PLEX
- Outcomes were reasonable for baby

Table 5. Pregnancy outcome in 44 women with aHUS and genetic defects (*CFH* = 23, *CFI* = 9, *MCP* = 4, *C3* =3, *CFB* = 2, more than one mutation = 3) and in 10 patients with aHUS and no detectable genetic defect

	Number of Pregnancies	Fetal Loss	Preeclampsia	P-aHUS	Uneventful Pregnancy
Patients with genetic abnormality (n = 44)	103	5 (4.8%)	8 (7.7%)	18 (17.4%)	77 (74.7%)
Patients with no genetic abnormality (n = 10)	15	0 (0%)	0 (0%)	3 (20%)	12 (80%)

Fakhouri F et al *JASN* 2010;21:859-867

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Pregnancy and Atypical HUS

Table 4. Frequency of P-aHUS according to the type of complement dysregulation

Patients	Number of Pregnancies	P-aHUS (%)
CFH mutations (n = 23)*	49	10 (20%)
Mutations in SCR19-20 (n = 6)	10	1 (10%)
Mutations in other SCR (n = 17)	38	9 (24%)
CFI mutations (n = 8)	26	3 (11%)
MCP mutations (n = 4)	6	1 (17%)
C3 mutations (n = 3)	7	2 (28%)
CFB mutations (n = 2)	7	0 (0%)
More than one mutation (n = 4)†	5	3 (60%)
No mutation (n = 10)	15	3 (20%)

*Three patients with two mutations in *CFH* (SCR 9 and 19)—in *C3/CFH* and in *MCP/CFH*—were excluded from the analysis.
†Patients with two mutations in *CFH* (SCR 9 and 19)—in *C3/CFH* (patient 8), in *MCP/CFH* (P3), and in *CFI/CFI* (patient 4)

1st pregnancy presentation 4/7 CFH Mutation

Fakhouri F et al *JASN* 2010;21:859-867

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Pregnancy Counseling

- Women with a history of aHUS or a genetic preponderance ≈ 20%
- CFH mutation may be the worst to have
- Subsequent Pregnancies potentially more dangerous than the 1st pregnancy
- Disease is aggressive

PREGNANCY MANAGEMENT

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Characteristics and Outcomes of AKI treated with Dialysis During Pregnancy

- Analyzed data from 1.9 million pregnancies in ON over 15 years (1997 to 2011)
- Incidence of AKI treated with dialysis: 1 in 10,000 pregnancies (95% CI 0.8 to 1.1) (N=188)
- Women treated with acute dialysis in pregnancy were older, had a lower neighborhood income, fewer prenatal visits, and were more likely to have preexisting hypertension or chronic kidney disease compared with the general population
    - Preexisting medical condition (RR 2.24, 95% CI 1.42-3.52)
    - Medical complication of pregnancy (RR 5.55, 95% CI 4.16-7.38)

Hildebrand, Hladunewich and Garg JASN 2015

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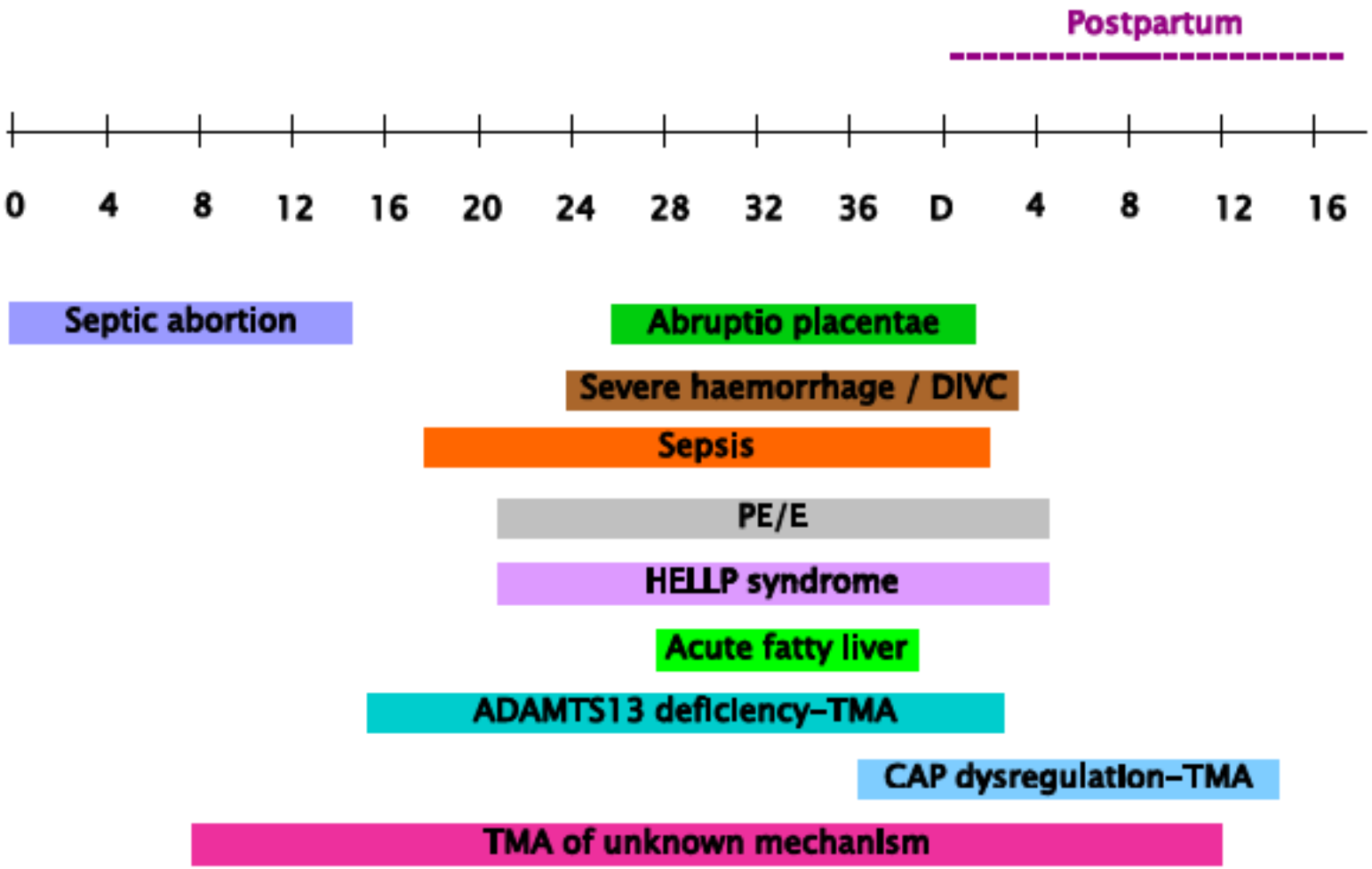
Diagnosis



Fakhouri F et al *CJASN* 2012

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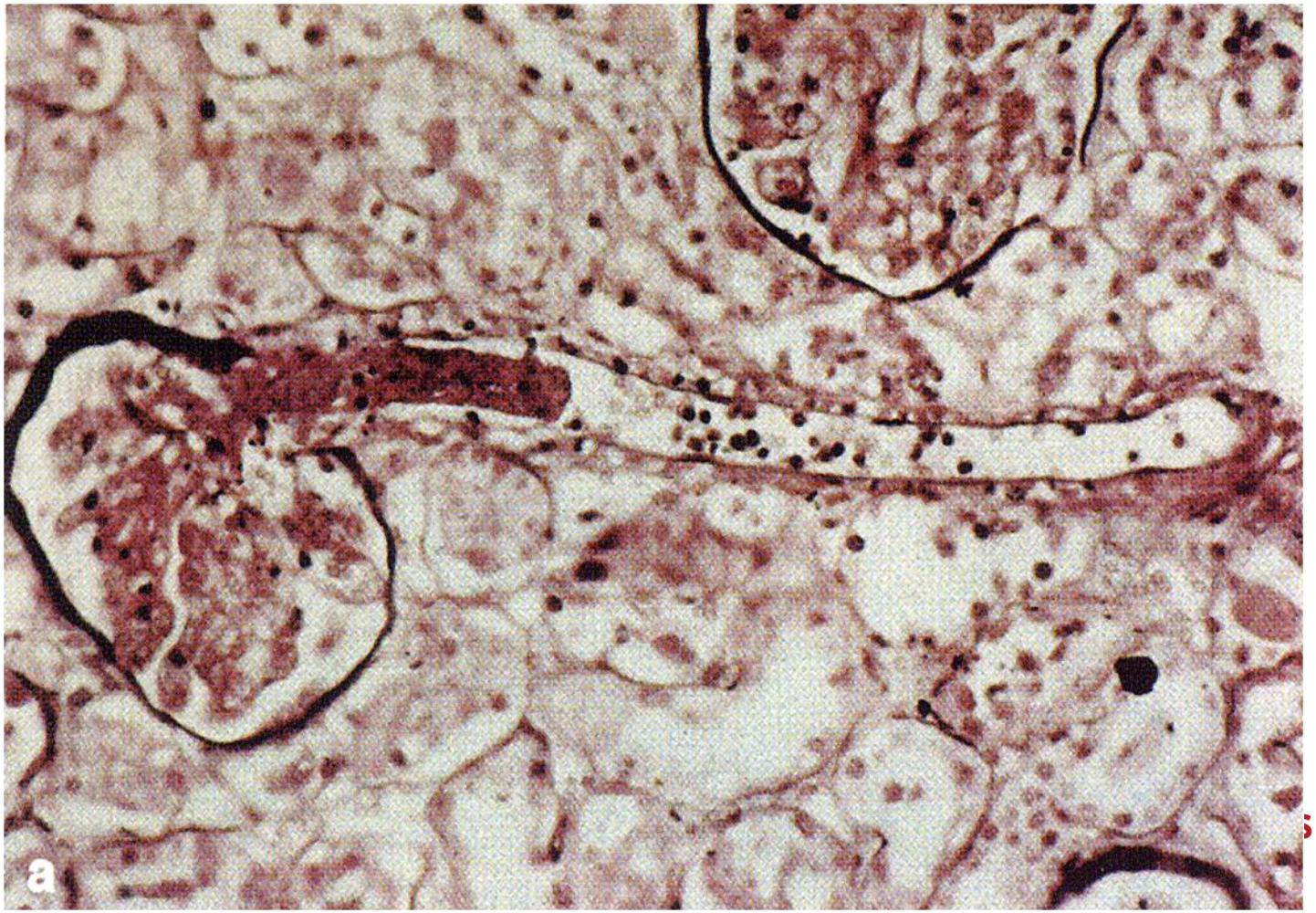
THROMBOTIC MICROANGIOPATHY

A pathology that results in thrombosis in capillaries and arterioles due to an endothelial cell injury



Diagnosis

- Preeclampsia/ HELLP Syndrome
  - Disease of the placenta
- TTP
  - Estrogen effect on ADAMTS13
    - Decreases throughout pregnancy to nadir in postpartum
    - Pro-coagulant state
- Atypical HUS
  - genetic mutations activation or regulation of the alternative complement pathway triggered by pregnancy

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Treatment

- Preeclampsia/HELLP Syndrome
  - Delivery
- TTP
  - PLEX
- aHUS
  - PLEX
  - Eculizumab

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Treatment

- Eculizumab
  - Has been used during pregnancy in PNH
  - Does not appear to cross the placenta
  - Does not appear to enter breast milk
  - Case report in pregnancy of a women with a homozygous mutation in Factor H treated from 26 weeks onward
    - 38 weeks gestation
    - 3650 g baby

Ardissino et al ACOG 2013

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In Summary

- Patients need to be aware of their potential risks entering a pregnancy
- Clinicians need to be educated as this is a difficult clinical diagnosis to make
- Availability of Eculizumab will make child bearing a safer potential for patients with aHUS

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