Webinars
Thrombotic Microangiopathies
Hemolytic uremic syndrome and other thrombotic microangiopathies

EuroBloodNet Topic on Focus

TTP in the setting of Pregnancy

Speaker: Professor Marie Scully
Institution: UCLH/UCL, London, UK
ERN-EuroBloodNet subnetwork: TMA
11 June 2021

Co-funded by the Health Programme of the European Union

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Network Hematological Diseases (ERN EuroBloodNet)

Speakers fees and advisory boards:

Takeda, Sanofi, Octapharma, Novartis

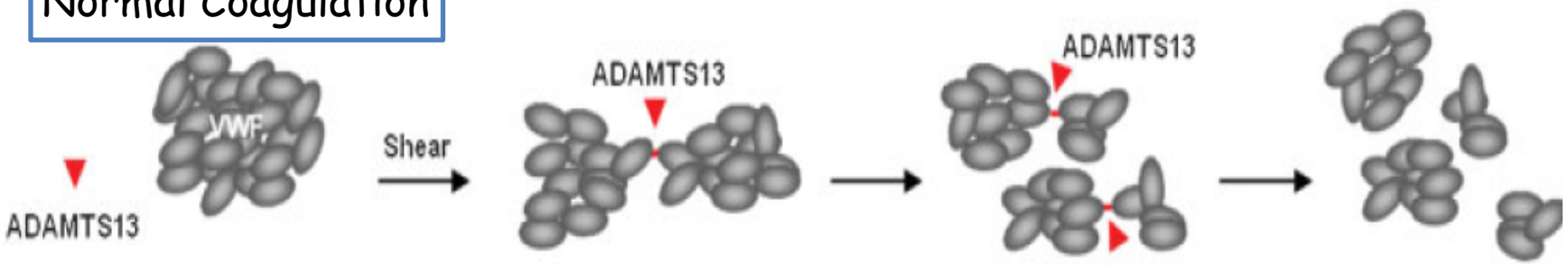
Grants:

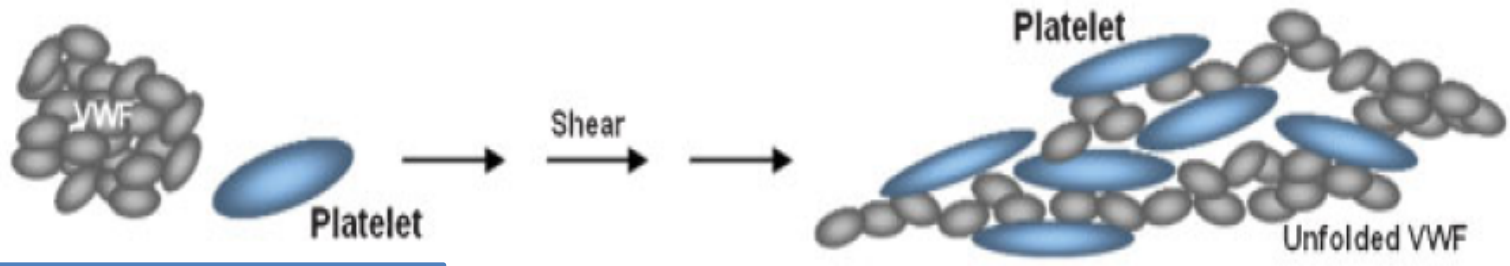
Shire, Novartis

1. TTP may appear as a a pregnancy associated TMA
2. Patients presenting with pregnancy associated TTP more likely have late onset congenital TTP
3. Women with a history of TTP can be supported through further pregnancies

VWF-ADAMTS 13: Pathophysiology in TTP

Normal Coagulation





ADAMTS 13 deficiency

Tsai Sem Throm Hemostasis 2012

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French TMA reference group

592 adult TTP cases

42 Pregnancy onset TTP

10 CONGENITAL TTP

(24%)

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Moatti-Cohen et al Blood 2012

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French TMA reference group

592 adult TTP cases

42 Pregnancy onset TTP

10 CONGENITAL TTP

(24%)

Moatti-Cohen et al Blood 2012

8908 Deliveries

79 women with plts <75000

50 women- ADAMTS 13 assessment

4 women with ADAMTS 13 <10%

3 congenital TTP cases

1 acquired TTP cases

5% women with PLTS <75,000 in pregnancy: Congenital TTP

Delmas et al, BMC Preg 2015

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TTP & women of child bearing years

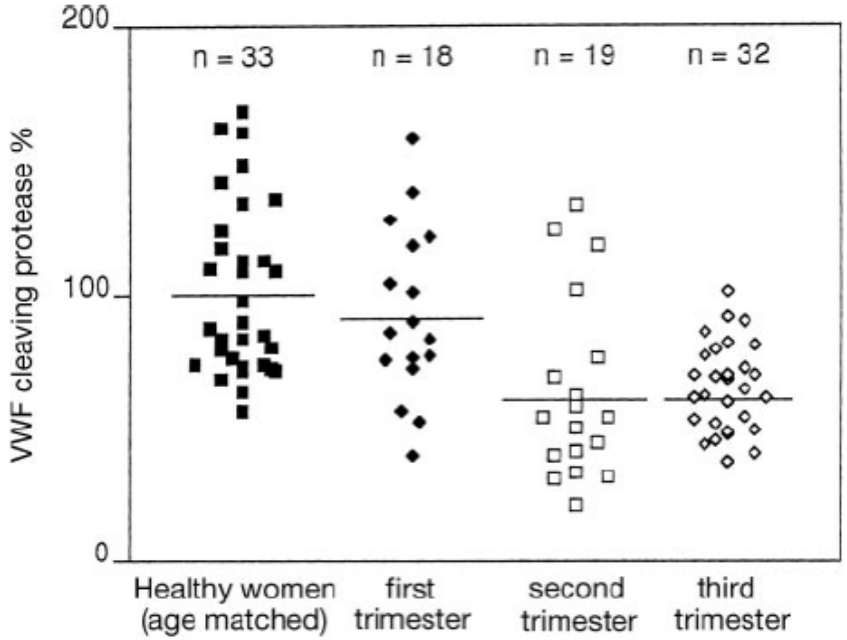
- Median age of presentation of TTP is 3rd-4th decade. More common in women

- >50% patients are women of child-bearing age

- Normal pregnancy

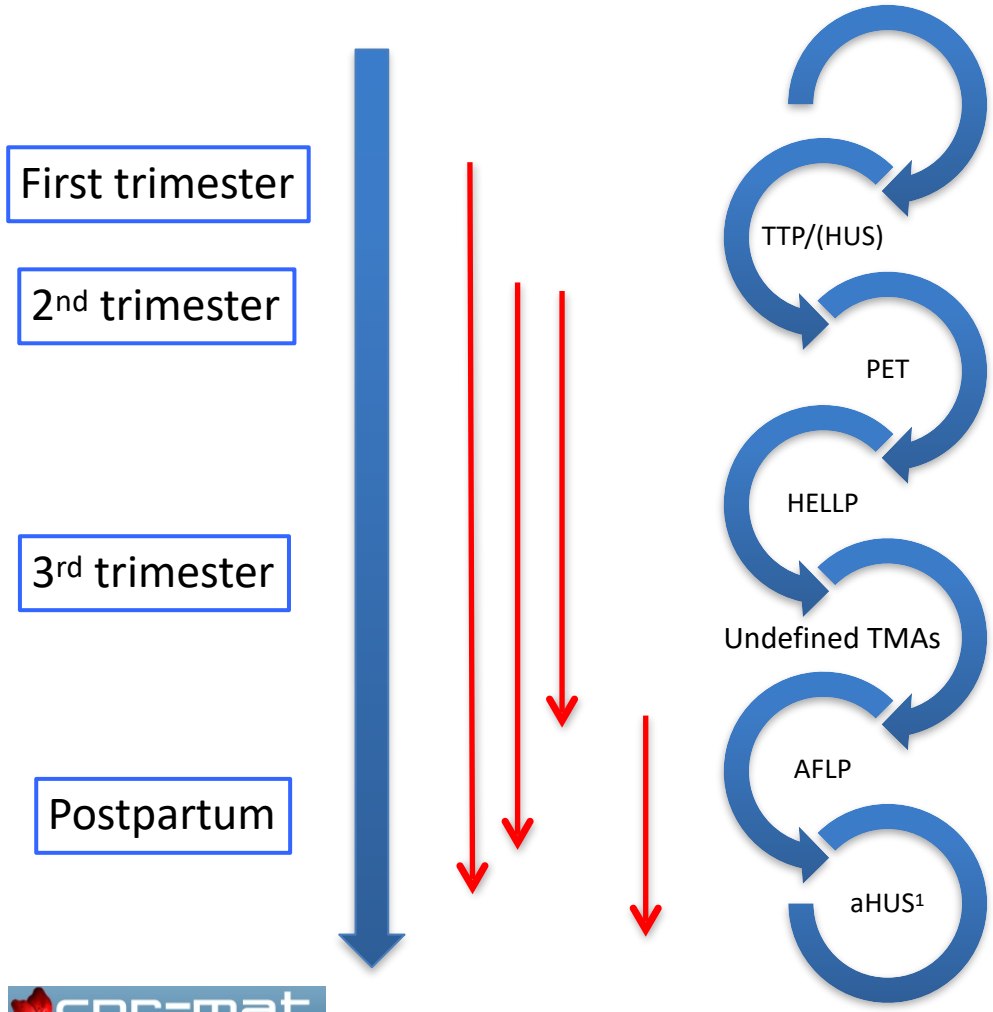
↑ FVIII ↑ VWF

↓ ADAMTS13 activity



Mannucci P et al. Blood 2001;98(9):2730-5

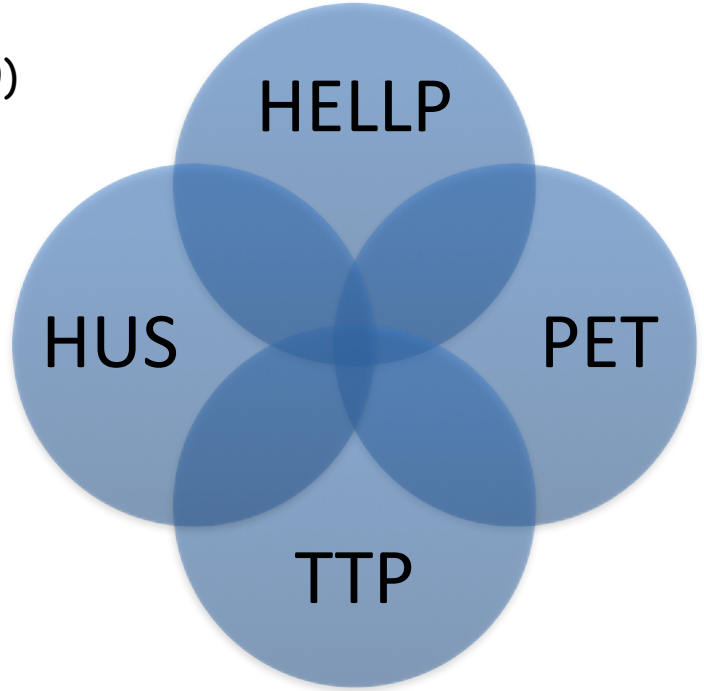
Pregnancy Associated TMAs



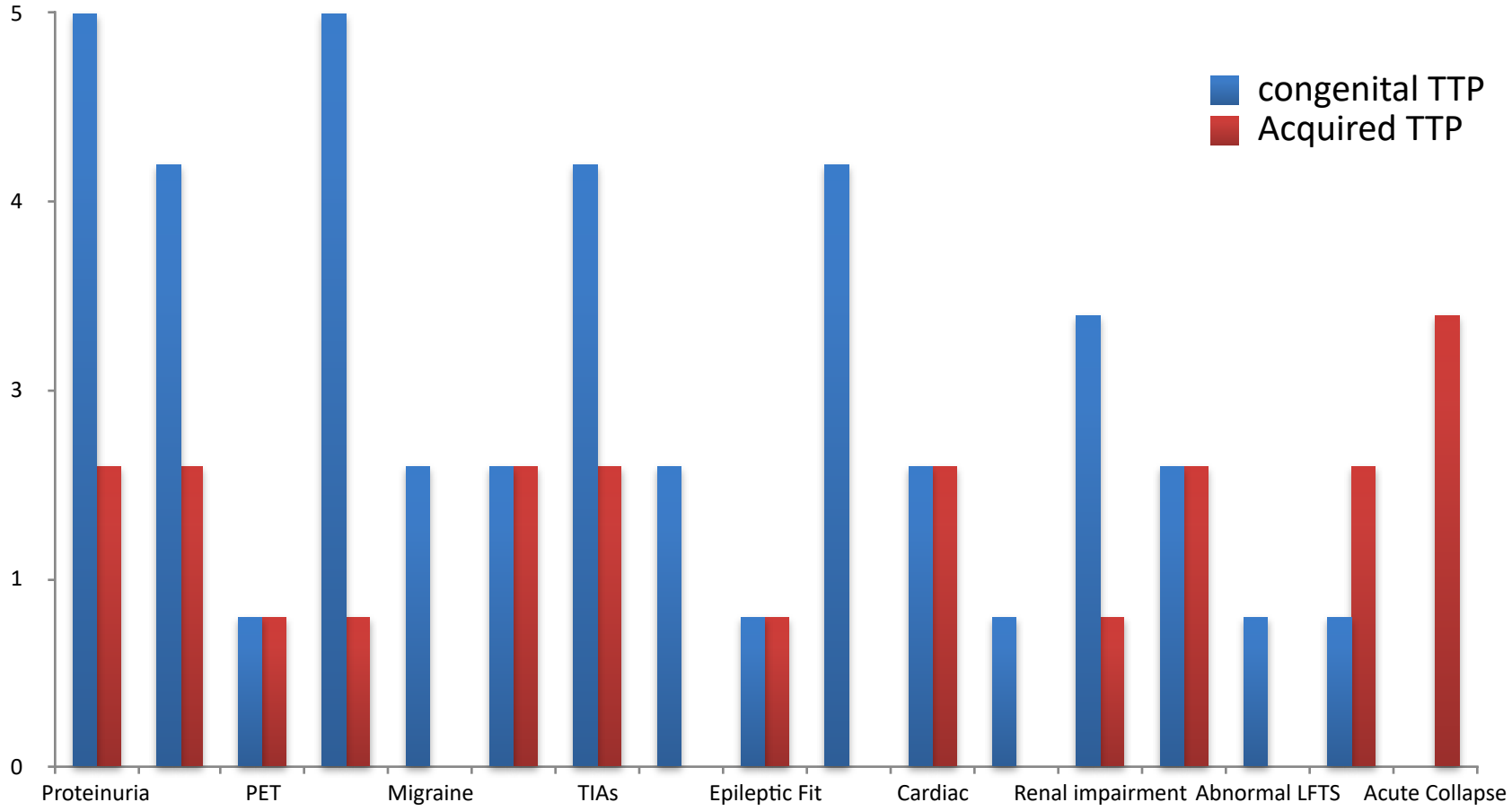
1. Fakhouri F et al. J Am Soc Nephrol 2010;21:859–67

When to treat obstetric TMAs?

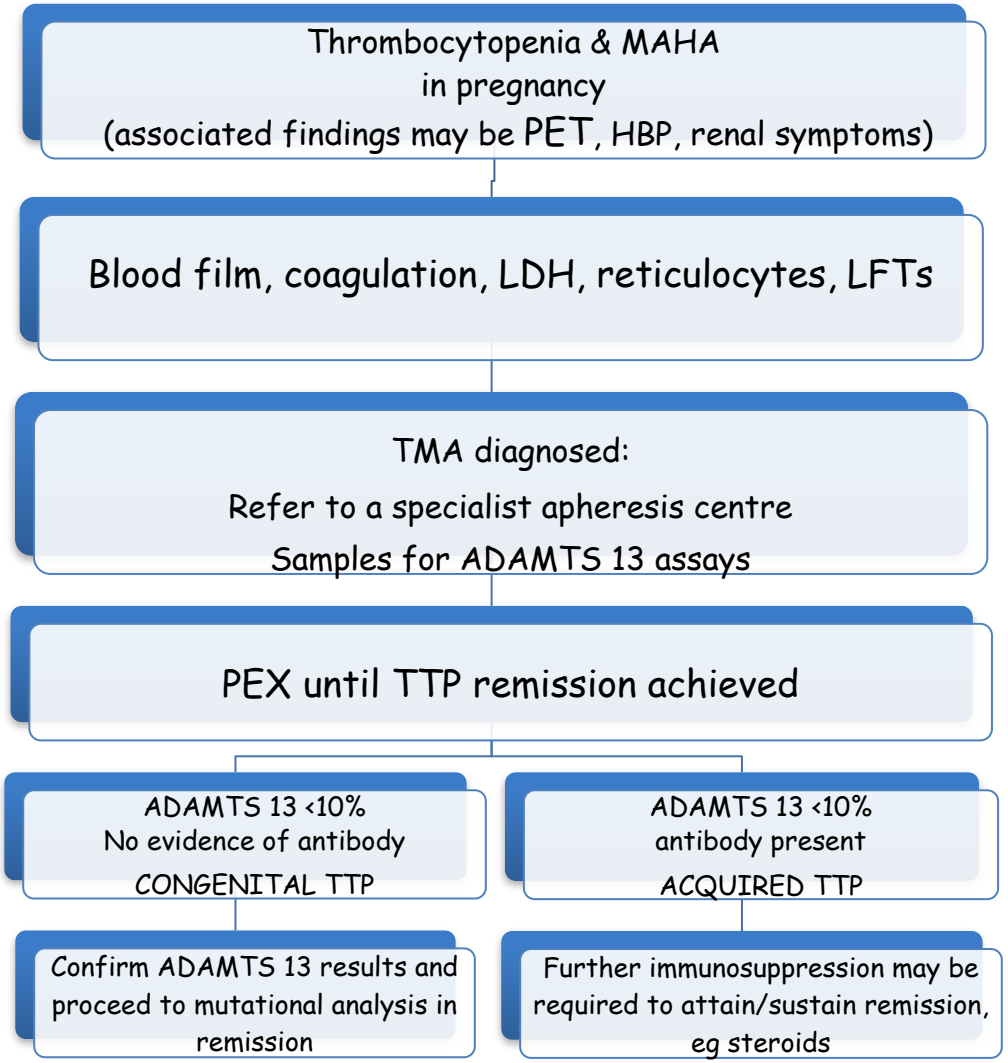
- **TTP**: PEX ASAP!
- **PET/HELLP**: difficult!
  - Monitor/supportive care
  - Delivery
    - Decreasing platelet count (especially <50,000)
    - Deterioration clinically
    - Exclude TTP/aHUS
  - PEX
- **HUS**
  - PEX
  - Eculizumab



Maternal symptoms/ presentation in congenital and acquired TTP



Summary of the management of a patient presenting with acute TTP in pregnancy



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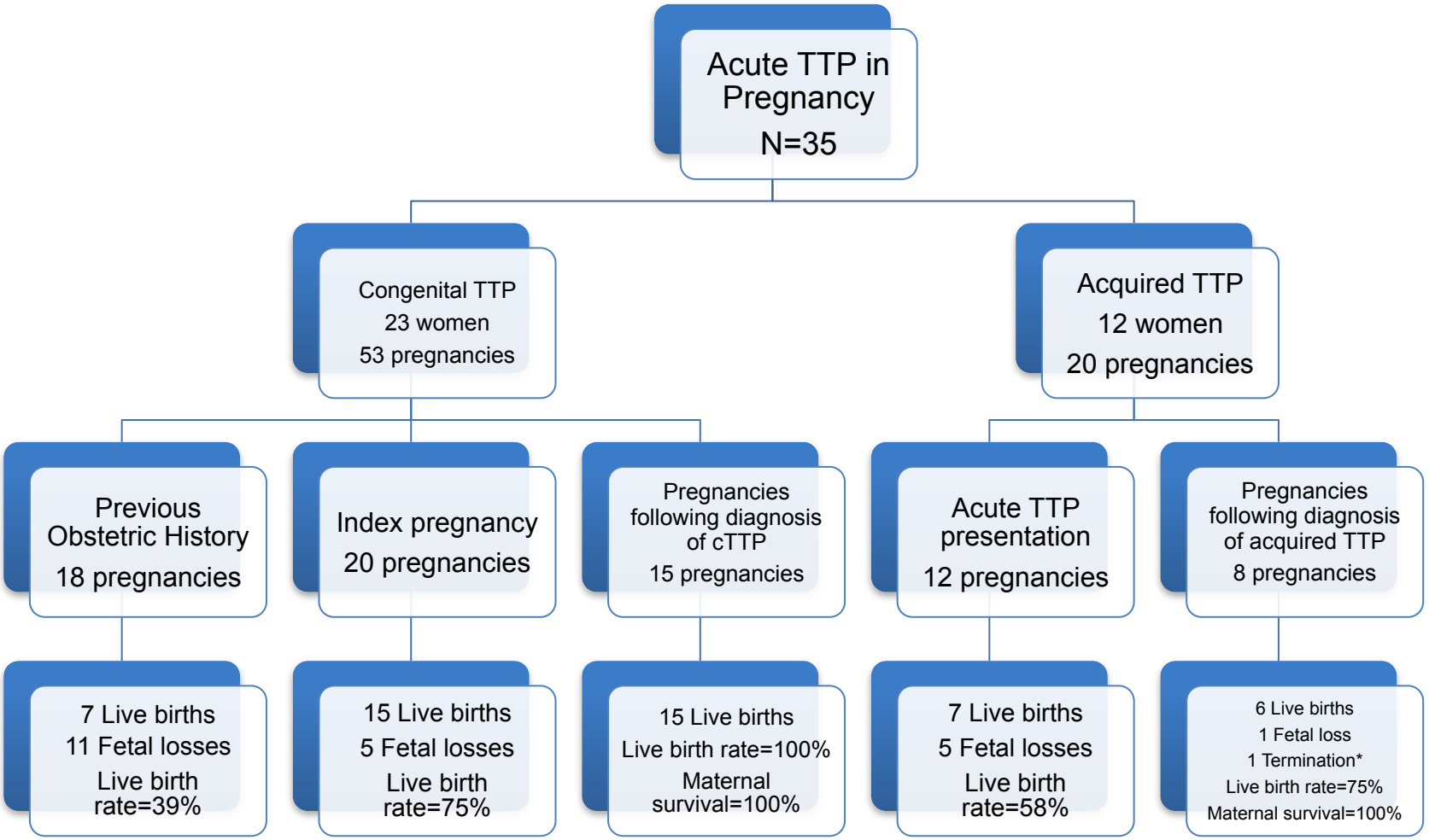
Summary of patients presenting with TTP in Pregnancy



* termination <12 weeks because of severe refractory TTP

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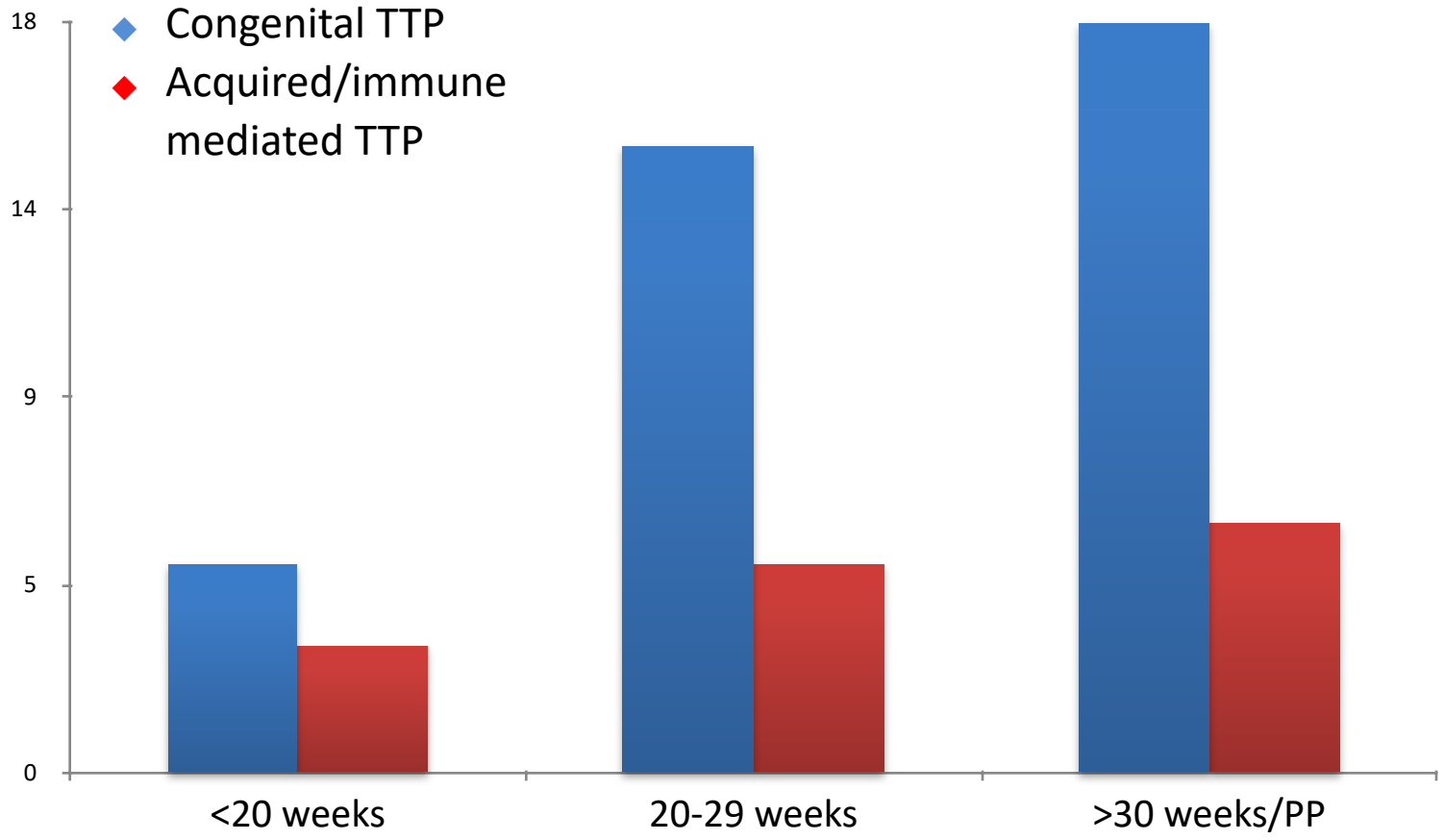

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Scully et al Blood 2014

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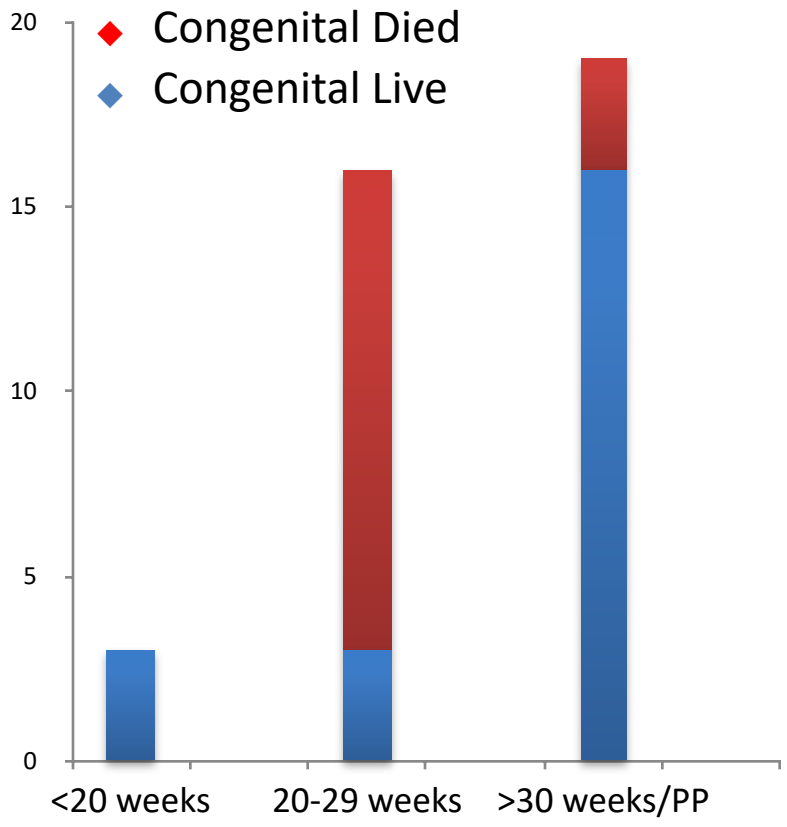
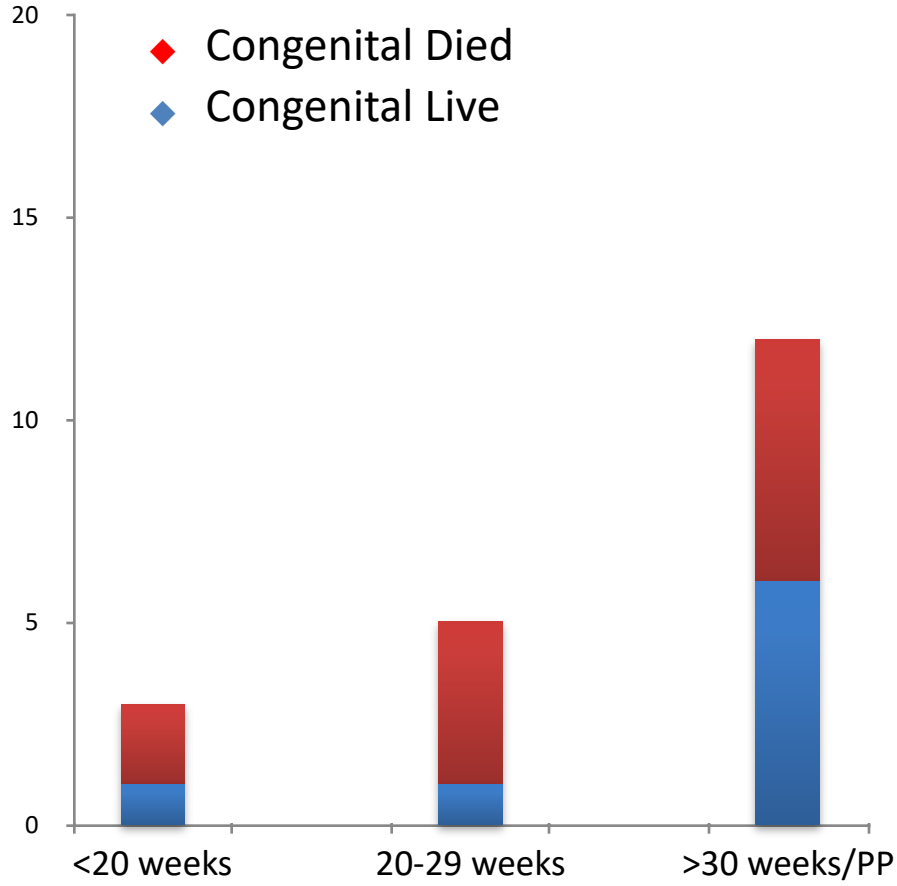
Congenital TTP pregnancy outcomes pre diagnosis



Congenital TTP pregnancy outcomes in index case



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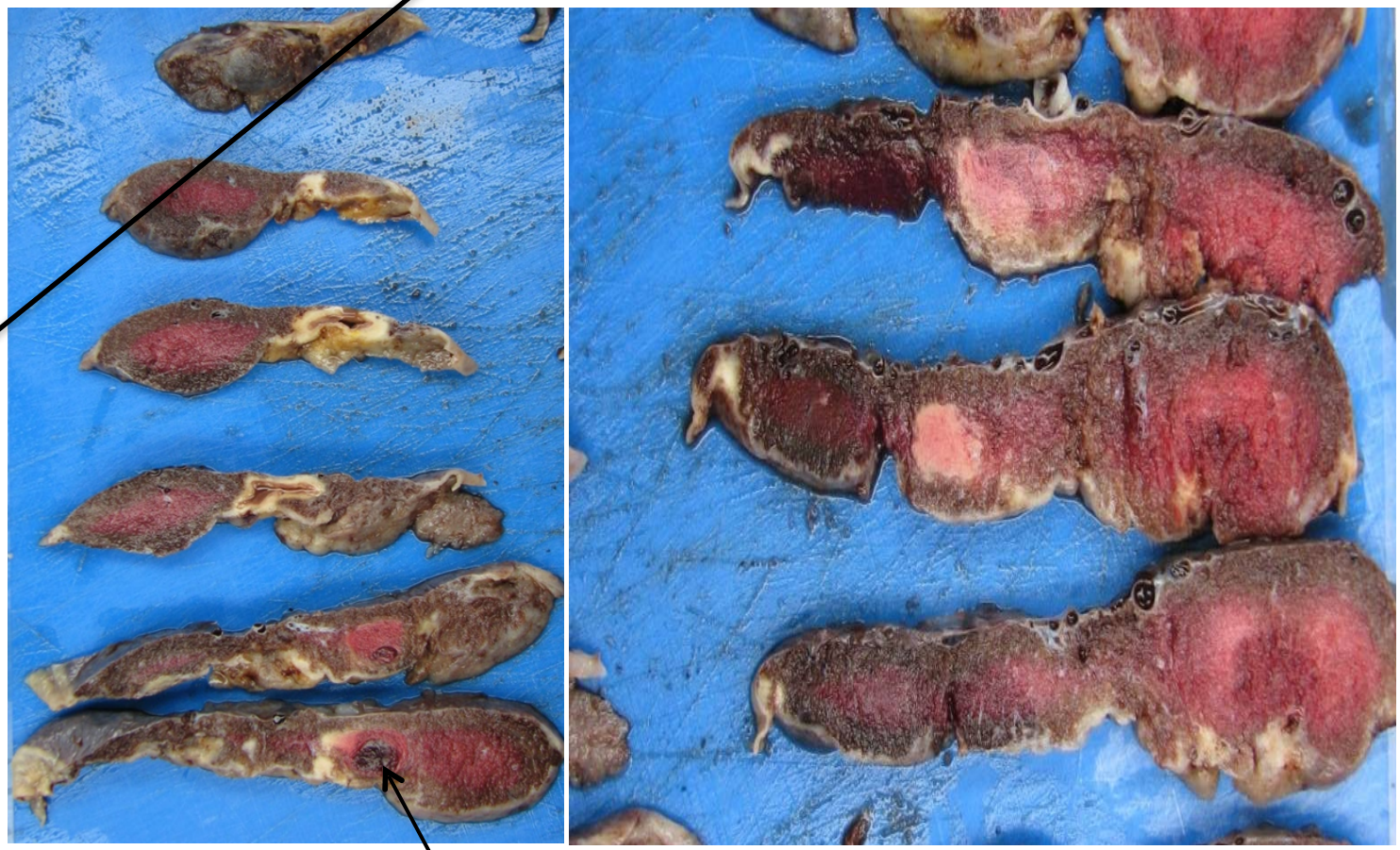
Untreated congenital TTP in Pregnancy – many infarcts, different ages

More recent infarct

Very old white infarct with central cavity



Infarct with central haemorrhage

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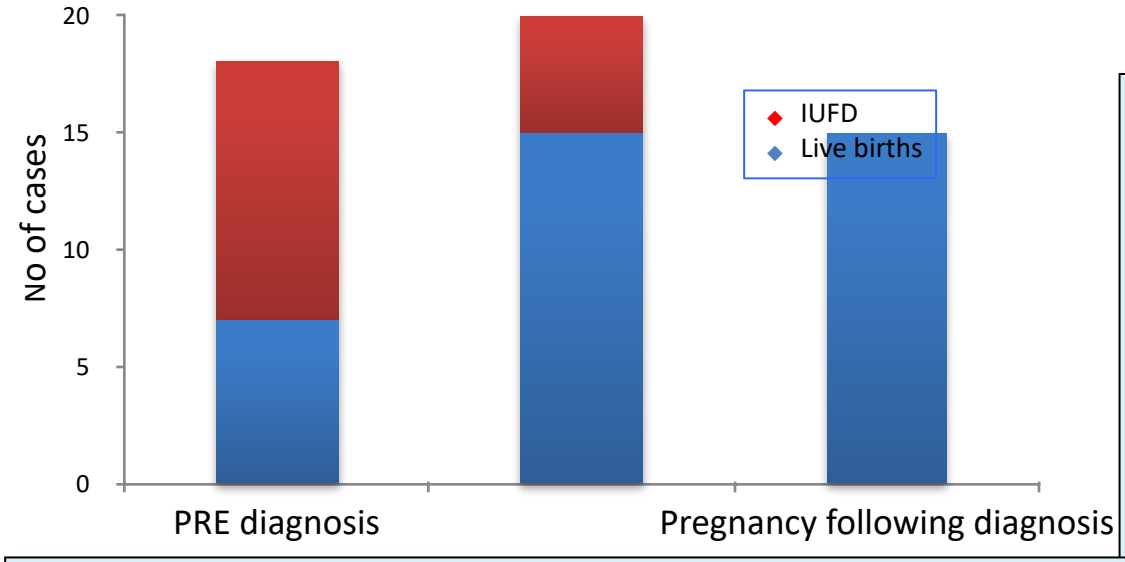


Untreated/presenting pregnancy:

Maternal complications

- Neurological
- Cardiac
- Hypertension
- Renal Abruption

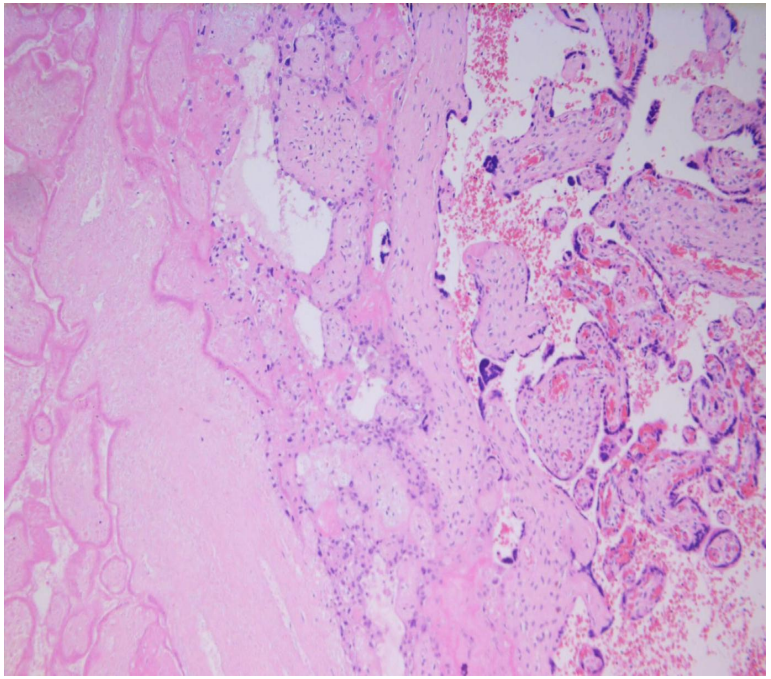
Fetal complications

- Preterm
- IUGR

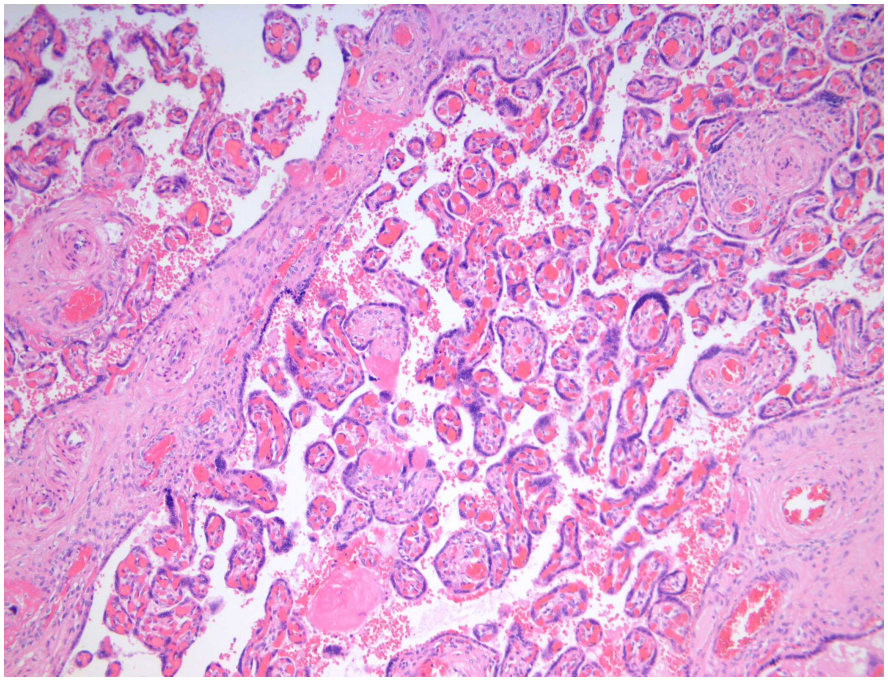
Treatment of subsequent pregnancies

- Regular plasma Infusion:
  - 2 weekly from 1st trimester
  - Weekly from end 2nd/3rd Trimester-guided by FBC/LDH
- PEX/intermediate-purity FVIII (BPL 8Y)
- Low dose aspirin
- +/-Prophylactic low molecular weight heparin (LMWH)
- Monitoring in a specialist obstetric unit
- Planned delivery
- PP monitoring/PI

Placental Histology

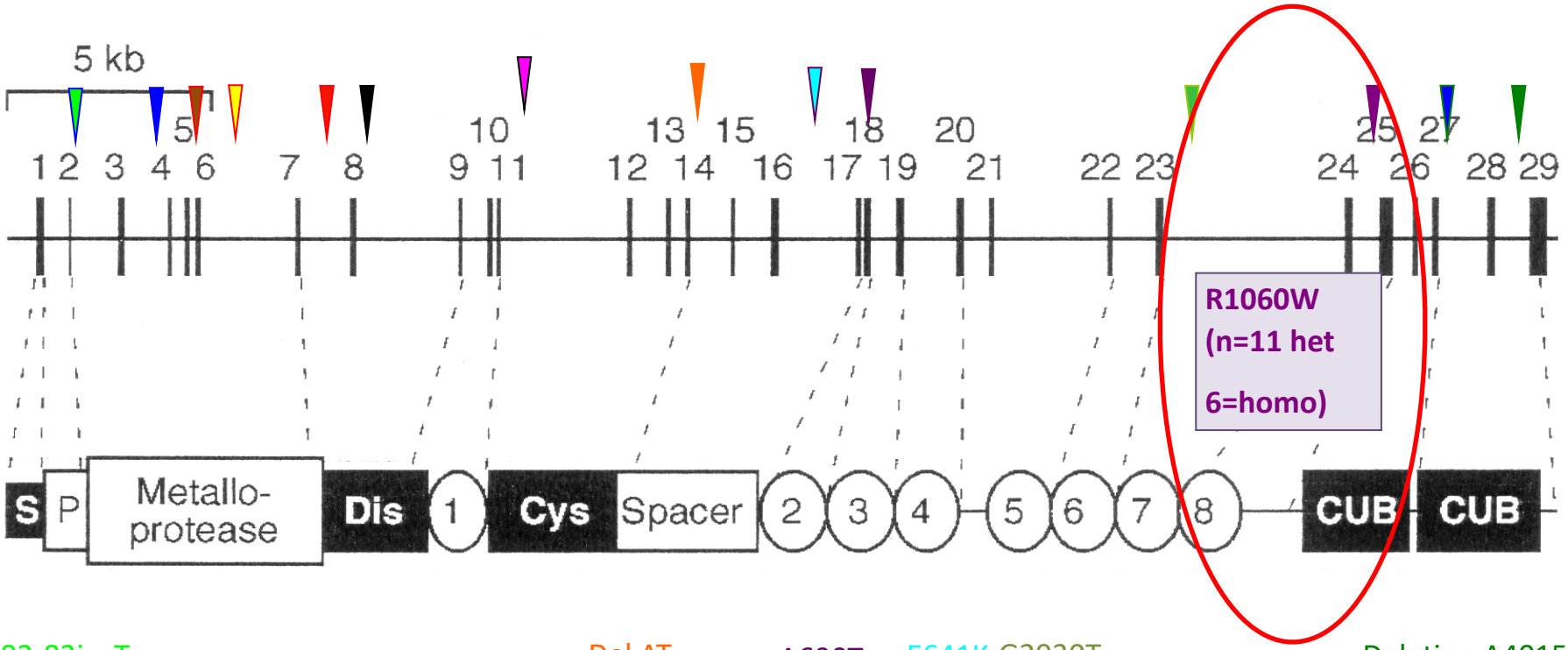


Distal villous hypoplasia and infarction at 27 weeks' gestation in untreated congenital TTP and associated IUFD.



Normal villi in the subsequent delivery from the same mother after treatment

Congenital TTP presenting in pregnancy - genetic abnormalities in UK cohort



82-83insT N=1

G241-C242 del (n=2)

R102H

C265S, Deletion 719-724 N=2

Del AT, M486, R497C N=3

G401R N=1

A690T, Deletion N667T N=2

E641K A596V N=2

G2930T N=1

Deletion A4015 R1206X, R12190Q N=2

N=1

Deletion A111Q N=1

D217H N=1

Scully et al, Blood 2014

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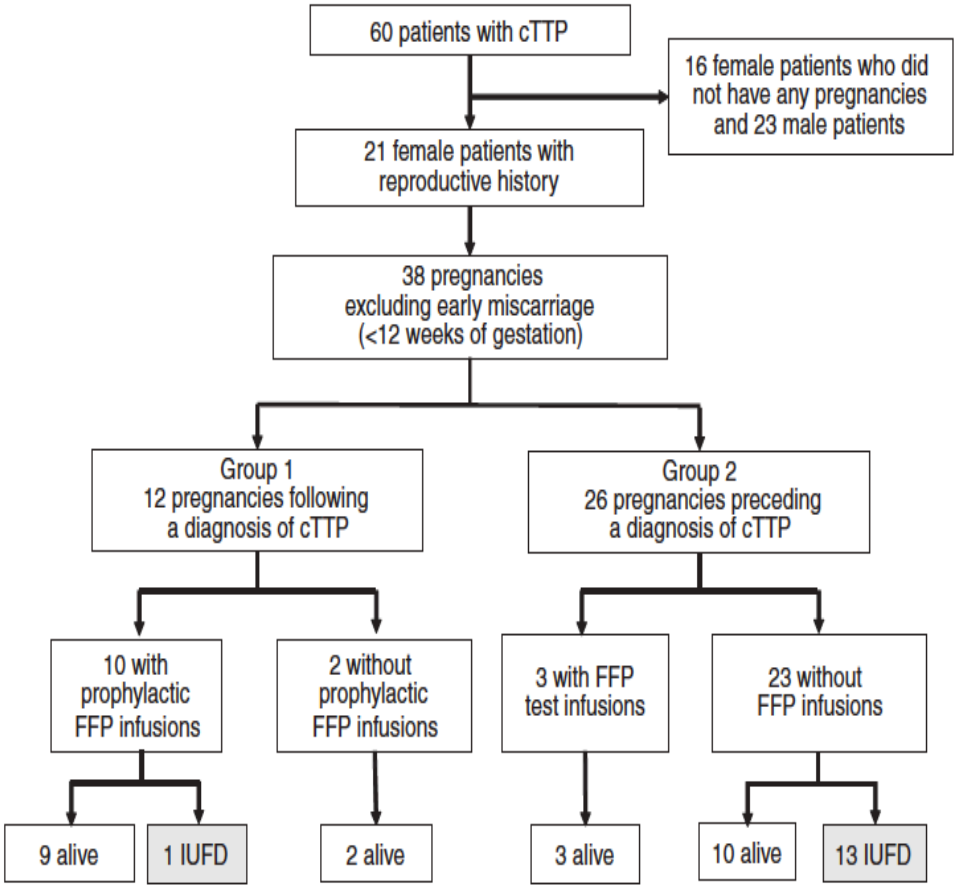
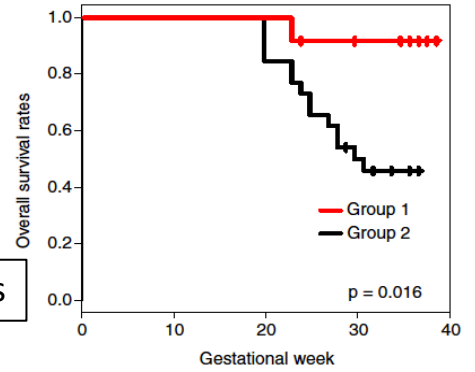
Congenital TTP in pregnancy – Japanese Experience

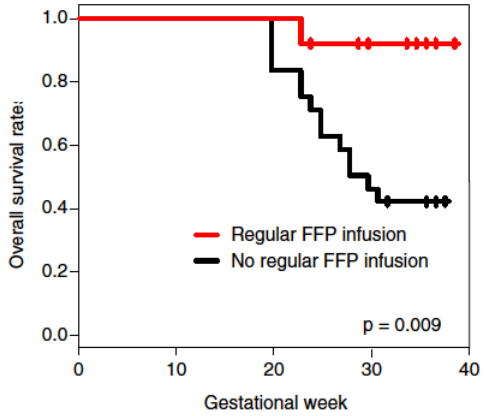


Fetal survival rates



Number at risk

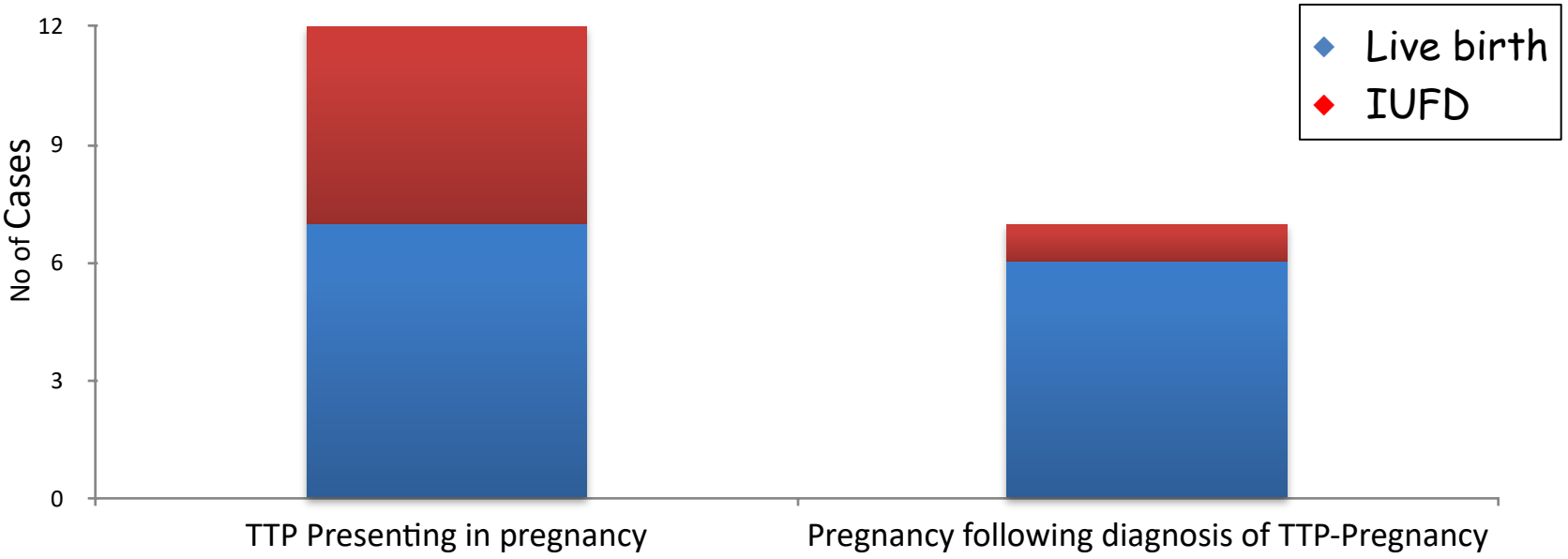
Group 1	12	12	12	10	0
Group 2	26	26	26	12	0



Number at risk

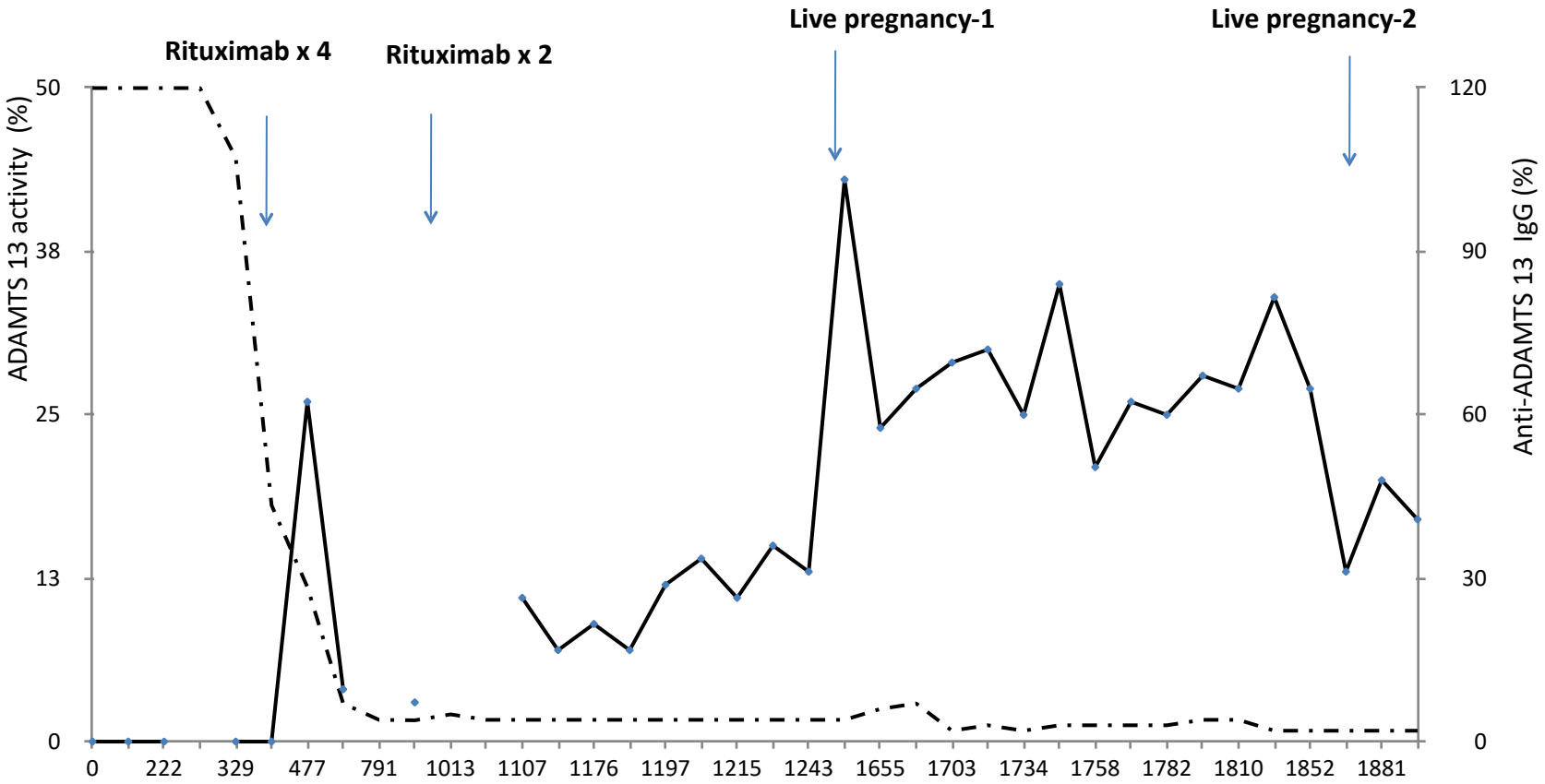
With FFP	13	13	13	10	0
No FFP	25	25	25	12	0

Sakai et al. JTH 2020



- Counselling pre-pregnancy
  - ADAMTS 13 activity/antibody levels
- Planned pregnancy
- Regular review at tertiary referral centre for TTP
- Shared care with specialist obstetrician
- Low dose aspirin from pre-conception
- +/-Prophylactic LMWH in high risk patients

Pregnancy loss and iTTP in Pregnancy



- 2 x 2nd trimester losses
- Low ADAMTS 13 activity and high Anti-ADAMTS 13 IgG in non pregnant state

Potentially impacts a significant proportion of women with TTP

- Baseline ADAMTS13 activity & IgG
- Regular fetal US +/- uterine artery dopplers
- Regular monitoring of ADAMTS13 activity & IgG
- Labour: depends on ADAMTS 13 levels/routine lab parameters/ treatment in pregnancy
- PP monitoring

<u>If ADAMTS 13 activity is <NR at beginning/during</u>

- LDA
- ?Azathioprine/steroids
- ?PEX

?? Use of rituximab

Conclusions : TTP presenting in pregnancy

- Late onset congenital TTP presenting de novo in pregnancy appears more common than acquired antibody-mediated TTP

  Fetal outcome depends on prompt diagnosis and treatment
- Successful outcomes possible in both acquired and congenital TTP
- Management by a specialist centre

- <u>In acquired TTP:</u>
  - Baseline ADAMTS13 activity and antibody status may identify likely relapse
  - Elective PEX should be considered in women with reduced ADAMTS13 activity (<10-15%) and/or raised IgG

- <u>In congenital TTP</u>
  - Regular plasma throughout pregnancy

- Low dose aspirin +/- prophylactic LMWH used to reduce complications related to placental thrombosis

Discussion