CASE STUDY

MANAGEMENT OF AN OBSTETRIC PATIENT WITH PLASMINOGEN ACTIVATOR INHIBITOR-1 DEFICIENCY

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OBJECTIVES

- Discuss the role of plasminogen activator inhibitor-1 in hemostasis
- Explain how PAI-1 deficiency is diagnosed
- Identify treatment options for PAI-1 deficient patients

PATIENT HISTORY

- 25 year old GI patient at 12 weeks and 2 days
- Referred to MU maternal fetal medicine clinic for further care
- Diagnosed with plasminogen activator inhibitor-1 (PAI-1) deficiency at 18
- Hematology-oncology and Pathology consults requested

PATIENT HISTORY – EXTERNAL RECORDS

- At 18, patient referred to pediatric hematology-oncology for a history of bleeding:
  - Bruises with no history of trauma
  - Excessive bleeding following a piercing at age 18
  - Wisdom teeth extraction with bleeding for 4 days
  - Bleeding for 3 days following nasal polypectomy at age 15
  - Menorrhagia (~ 1 pad/hour, lasting up to 2 weeks)
  - Excessive bleeding with tonsillectomy at age 5
- Family History
  - Mother, maternal grandmother and maternal cousin with history of excessive bleeding
  - Mother had postpartum bleeding for 2 weeks, requiring a hysterectomy to stop the bleeding

PATIENT HISTORY – EXTERNAL RECORDS

- History is highly suggestive of a bleeding disorder
  - Initial testing was normal, including testing for von Wilebrand disease
  - Repeat testing was normal
  - PAI-1 activity level was reported as <6%
  - PAI-1 activity levels repeated at another lab with results <2%
- Given Lysteda (2 tablets TID) to take during menses
  - Patient reported significant improvement
- Mother tested for PAI-1 deficiency with the same results

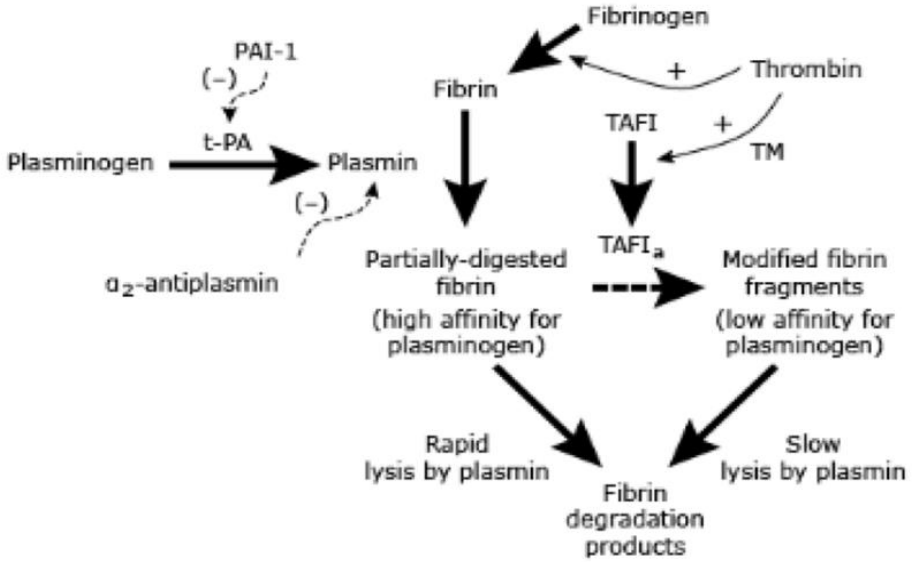
QUESTIONS:

- What is the best intervention to help alleviate potential postpartum hemorrhage in this patient? Continue antifibrinolytics? FFP?
- What treatment options are safe during pregnancy? Delivery? Postpartum?
- Is there a way we can monitor her response to therapy?

PLASMINOGEN ACTIVATOR INHIBITOR-1

- Serine protease inhibitor
  - Inhibits action of tPA and uPA
  - Down-regulates fibrinolysis
- 12.2 kb gene on Chromosome 7 at q21.3-q22 encoding 9 exons
- Produced by endothelial cells and hepatocytes
  - Also present in alpha granules of platelets
  - Present in small amounts in plasma
- Short half-life

Regulation of fibrinolysis by plasminogen activator inhibitor-1 (PAI-1), α2-antiplasmin, and thrombin-activatable fibrinolysis inhibitor (TAFI)



Fay, WP Thrombotic and hemorrhagic disorders due to abnormal fibrinolysis . UpToDate. 20019.

PAI-1 DEFICIENCY

- First reported in 1989 by Schleef et al.
- Epidemiology
  - Exceptionally rare, incidence unknown
  - Reported in a large Older Order Amish kindred in Indiana as well as other parts of North America, Europe and Asia
  - Primarily reported to have autosomal recessive inheritance
- Pathophysiology
  - Results from either qualitative or quantitative defects in PAI-1

PAI-1 DEFICIENCY

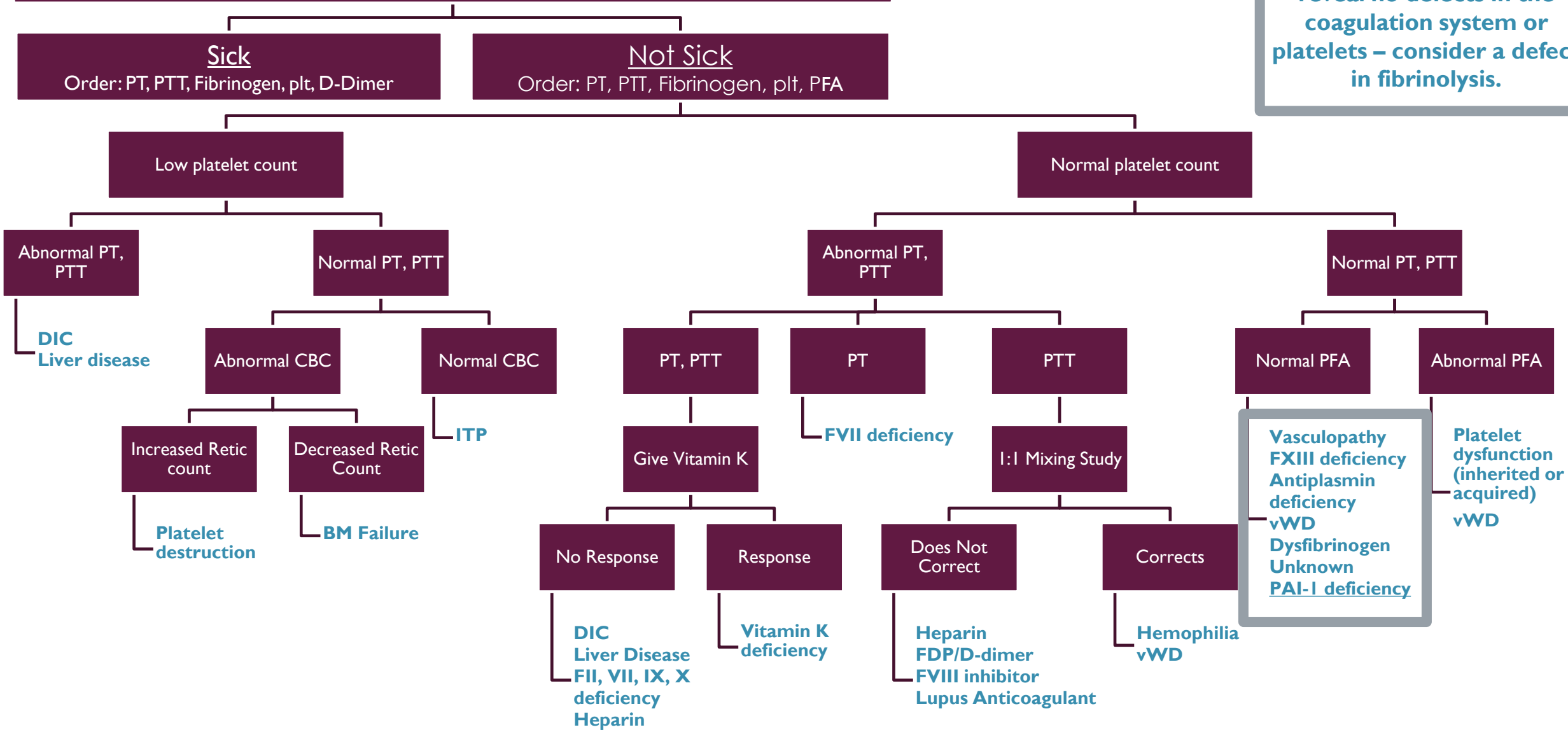
- Clinical presentation
  - Mild to moderate bleeding associated with injury or surgery
  - Menorrhagia, antenatal bleeding, postpartum hemorrhage
  - Epistaxis, easy bruising
- Treatment
  - Antifibrinolytic agents (tranexamic acid and aminocapric acid)

PAI-1 DEFICIENCY – DIAGNOSIS

- History
  - Patient and family history of bleeding suggestive of a bleeding disorder
- Bleeding Screen
  - CBC
  - PT
  - PTT
  - (Fibrinogen level, PFA)

Approach to The Bleeding Patient

In a patient with abnormal bleeding, if initial tests reveal no defects in the coagulation system or platelets – consider a defect in fibrinolysis.

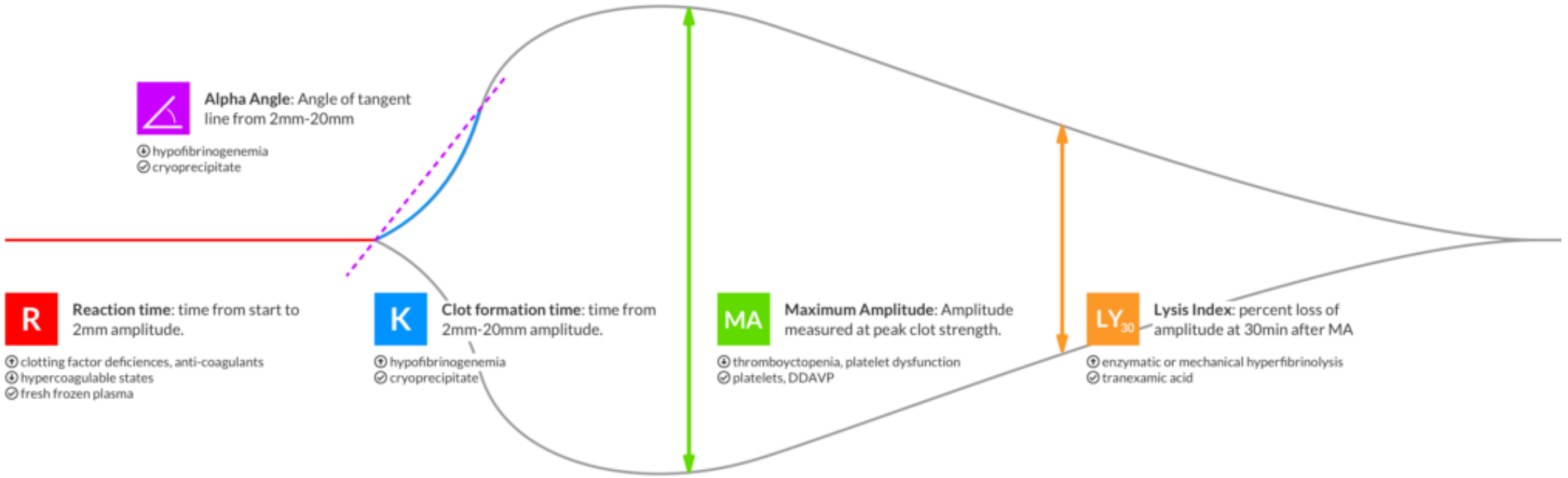


Adapted from: Figure 89.1 Overview of the approach to a bleeding patient based upon screening laboratory tests Abshire, T. C., & Abrams, C. S. (2013). Approach to the Bleeding Patient. In *Transfusion Medicine and Hemostasis: Clinical and Laboratory Aspects* (2nd ed., pp. 593-599). San Diego, CA: Elsevier.

SCREENING TESTS FOR FIBRINOLYSIS

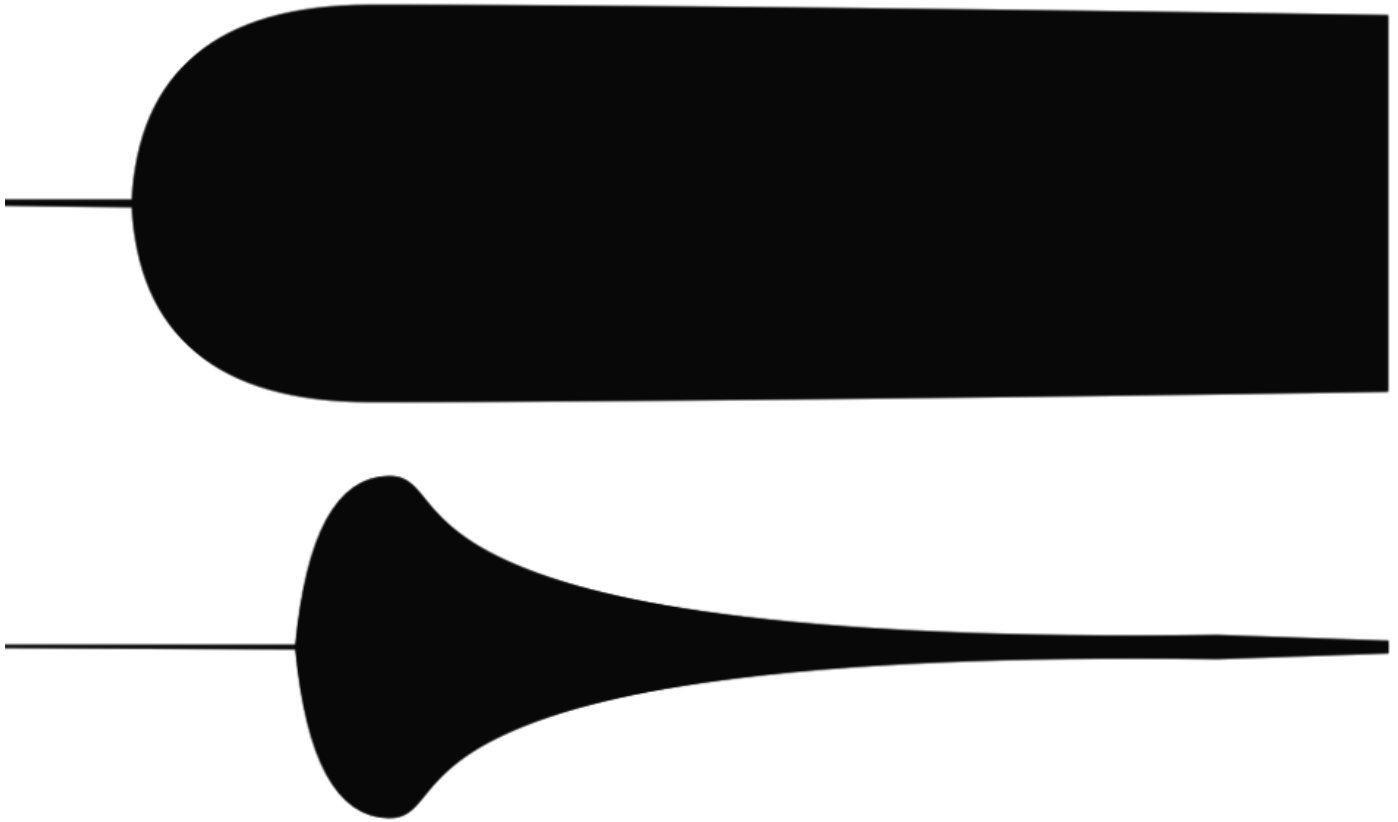
- Euglobulin lysis time (ELT)
  - Historical test
  - Positive when clot is dissolved prematurely (<60-120 min)
- Thromboelastometry/Thromboelastography (TEG)
  - Has largely replaced ELT as screening in acute settings
  - Global hemostasis screen
  - Extent of fibrinolysis = difference between maximum viscosity after clot formation (MA) and clot viscosity at 30 and 60 minutes

THROMBOELASTOGRAPHY (TEG)



Differential Diagnosis of Thromboelastography. (2018, August 16). Retrieved April 1, 2019, from https://ddxof.com/thromboelastography-teg

THROMBOELASTOGRAPHY (TEG)



Differential Diagnosis of Thromboelastography. (2018, August 16). Retrieved April 1, 2019, from https://ddxof.com/thromboelastography-teg

ADDITIONAL TESTS

- Citrate anticoagulated blood should be drawn in the morning with minimal tourniquet time
- Evaluate:
  - PAI-1 activity → undetectable
  - PAI-1 antigen → undetectable or low
  - tPA antigen → low
    - Free tPA in the absence of PAI-1 is cleared faster than normal

TREATMENT OF PAI-1 DEFICIENCY

- Antifibrinolytic agents - Prevent binding of plasminogen to fibrin, inhibiting fibrinolysis and stabilizing the fibrin clot
  - Tranexamic acid (TXA)
  - Epsilon-aminocaproic acid (EACA)
  - Can be used to treat bleeding or for prophylaxis prior to invasive procedures.

OBSTETRIC PATIENTS WITH PAI-1 DEFICIENCY

- Diagnosed at 47 years old with complete PAI-1 deficiency
- Pregnancies:
  1) Age 26
     - Bleeding started at 16 weeks and FFP was given 2x/week
     - 19 weeks: massive bleeding, no fetal heartbeat
  2) Age 27
     - Minor bleeding at 11 weeks and FFP started at 2-3x per week
     - 32 weeks: placental abruption and emergency C-Section – live female infant
     - **Perioperative blood loss of 4500 mL with 42 U FFP**
  3) Age 29
     - FFP administration started at 8 weeks prior to any bleeding
     - 27 weeks: placental abruption and uterine contractions; C-section – live female infant
     - Blood loss estimated 1037 mL

- Large amounts of FFP were needed in this case:
  - Limited quantities of PAI-1 are present in FFP
  - PAI-1 has a very short half-life

Iwaki T, Nagahashi K, Kobayashi T, Umemura K, Terao T, Kanayama N. The first report of uncontrollable subchorionic and retroplacental haemorrhage inducing preterm labour in complete PAI-1 deficiency in human. Thromb Res 2012; 129: e161–3.

OBSTETRIC PATIENTS WITH PAI-1 DEFICIENCY

- 21 year old G1 at 39 weeks scheduled for induction of labor
- Diagnosed with PAI-1 deficiency at age 15 after tonsillectomy with postoperative hemorrhage
- Aminocaproic acid administered for 7-14 days following delivery
  - 9 grams over 1st hour following delivery
  - 9 grams q8h during hospitalization and for 14 total days
- Uneventful hospital course without postpartum hemorrhage, discharged on POD#3

Smith S, Thornton YS. Pregnancy complicated by Plasminogen activator inhibitor type 1 deficiency 2010; Southern Medical Journal; 103:1259-1260.

OBSTETRIC PATIENTS WITH PAI-1 DEFICIENCY

- Largest report of PAI-1 deficient patients is from Heiman et al (2014)
  - 10 patients in a large Older Order Amish kindred with complete absence of PAI-1 antigen
  - 7 of the patients were women and two of those women had been pregnant

Table 2. Details of obstetric history of complete PAI-1-deficient patients.

	Total number of pregnancies	Bleeding onset in the ante-natal period	Infant birth weight (g)	Gestation (weeks)	Gender	Treatment used by mother	Complications for mother	Complications for infant	Infant/child growth and development
Patient 1	3	1–19 weeks	1644	31 3/7	F	EACA	Anaemia	RDS, hyper-bilirubinemia	normal
		2 weeks–miscarriage	n/a	6	n/a	EACA	none	n/a	n/a
		3–12 weeks	1736	31 5/7	M	EACA	pelvic haematoma	RDS	normal
Patient 2	4	1–12 weeks	1900	31 6/7	F	EACA	none	RDS	normal
		2–17 weeks	1345	30 3/7	F	EACA	none	RDS	normal
		3–12 weeks	2238	34 4/7	M	EACA	none	none	normal
		4–8 weeks	2409	36	F	TA	none	hyper-bilirubinemia	normal

EACA, epsilon-aminocaproic acid; RDS, respiratory distress syndrome; TA, tranexamic acid.

Heiman M, Gupta S, Shapiro A.D. The obstetric, gynecological and fertility implications of homozygous PAI-1 deficiency: single-center experience. Hemophilia 2014: 20; 407—412

OBSTETRIC PATIENTS WITH PAI-1 DEFICIENCY

- Recommendations
  - Menorrhagia
    - 1 week prior to onset:
      - Low dose TXA (25 mg/kg or maximum 1300 mg/dose) once daily or
      - EACA (100 mg/kg per dose or maximum 3 g) once daily
    - Day 1 of menses → minimum of 5 days
      - TXA 25 mg/kg per dose (maximum 1300mg) 3-4x daily
      - EACA 100 mg/kg per dose (maximum 3 g) 4x daily
  - Iron supplements

Heiman M, Gupta S, Shapiro A.D. The obstetric, gynecological and fertility implications of homozygous PAI-1 deficiency: single-center experience. Hemophilia 2014: 20; 407—412

OBSTETRIC PATIENTS WITH PAI-1 DEFICIENCY

- Recommendations
  - Pregnancy
    - Intermittent bleeding in 1st or 2nd trimester
      - TXA 25 mg/kg per dose (maximum 1300 mg) 3-4x daily
      - EACA 100 mg/kg per dose (maximum 3 g) 4x daily
    - Prophylactic continuous use of antifibrinolytics recommended from 26th week onwards
      - Continuous vaginal bleeding frequent close to end of 2nd trimester
    - Continue for at least 2 weeks postpartum

Heiman M, Gupta S, Shapiro A.D. The obstetric, gynecological and fertility implications of homozygous PAI-1 deficiency: single-center experience. Hemophilia 2014: 20; 407—412

ANTIFIBRINOLYTICS IN PREGNANCY

- FDA rates EACA as a category C drug
  - No reported use of EACA use during lactation
  - The molecular weight of the drug is low enough that excretion into breast milk is expected
- FDA rates TXA as a category B drug
  - No adverse fetal effects have been seen in reproductive toxicity testing in animal models
  - Several case reports of TXA used in pregnancy, none with adverse effects on the fetus or newborn
  - Able to cross the placental barrier and is excreted in breast milk
    - Breastfeeding is acceptable when using TXA for prophylaxis of hereditary angioedema
  - The effects of TXA on the fetus when given just prior to delivery are unknown

WOMAN TRIAL

- TXA has been shown to reduce risk of death in bleeding trauma patients (CRASH-2 trial).
- WOMAN trial collaborators studied the effect of early administration of TXA in women with post-partum hemorrhage.
- Conclusions
  - TXA reduces death due to bleeding in women with post-partum hemorrhage
  - Adverse events did not differ significantly in TXA vs placebo group

CRASH-2 trial collaborators, Shakur H, Roberts I, et al. Effects of tranexamic acid on death, vascular occlusive events, and blood transfusion in trauma patients with significant haemorrhage (CRASH-2): a randomised, placebo-controlled trial. Lancet 2010; 376:23.

WOMAN Trial Collaborators. Effect of early tranexamic acid administration on mortality, hysterectomy, and other morbidities in women with post-partum haemorrhage (WOMAN): an international, randomised, double-blind, placebo-controlled trial. Lancet 2017.

ANOTHER OPTION – APHERESIS PLATELETS

- PAI-1 is present within alpha granules of platelets
- Study from Brogren et al (2004) showed that platelets produce large amounts of active PAI-1
  - Platelets were found to contain abundant translationally active PAI-1 mRNA
- Apheresis platelets could provide PAI-1 to a patient with a deficiency

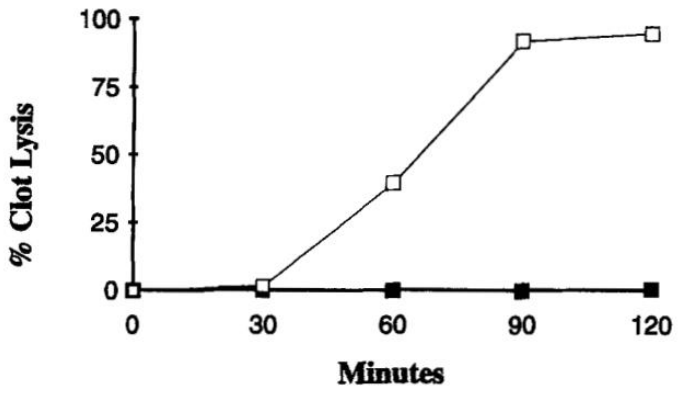


Fig 1. Inhibition of t-PA–mediated clot lysis by platelets. A mixture of fluorescein-labeled fibrinogen (1 mg/mL), Glu-plasminogen (20 μg/mL), and t-PA (0.6 U/mL) was clotted in the absence (□) or presence (■) of platelets (2.5 × 10^8/mL), and the percentage of clot lysis was determined at the indicated time points, as described in Materials and Methods. Note the marked inhibition of fibrinolysis in clots containing platelets.

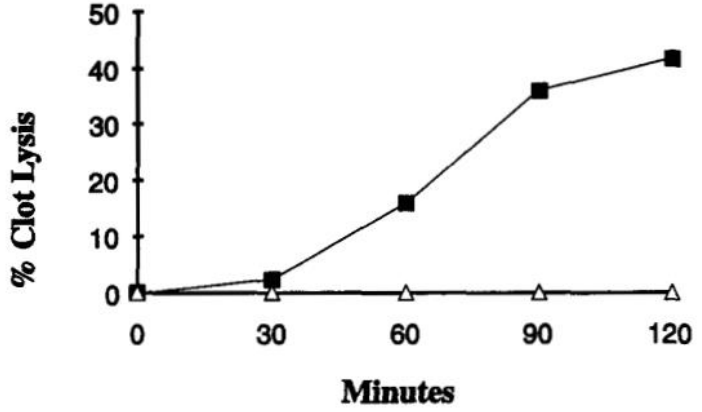


Fig 2. Comparison of effects of normal versus PAI-1–deficient platelets on clot lysis. Fibrin clots were formed in the presence of t-PA (0.67 U/mL) and washed platelets (2.5 × 10^8/mL) prepared from an individual with homozygous PAI-1 deficiency (■) or a normal control (△). At the indicated time points, the percentage of clot lysis was determined.

Brogren, H., Karlsson, L., Andersson, M., Wang, L., Erlinge, D., and The fixed cells were then rinsed with sodium cacodylate and post- Jern, S. (2004). Platelets synthesize large amounts of active plasminogen activator inhibitor 1. Blood 104, 3943–3948.

Fay WP, Eitzman DT, Shapiro AD, Madison EL, Ginsburg D. Platelets inhibit fibrinolysis in vitro by both plasminogen activator inhibitor-1-dependent and -independent mechanisms. Blood. 1994;83: 351-356.

OUR PATIENT – PLAN FOR DELIVERY

- Give 1g of TXA at time of delivery
- Large bore IV access
- Blood Bank:
  - Type and cross
  - Apheresis platelets available
  - Fresh frozen plasma available (4 units will be thawed)
  - Massive transfusion protocol, if necessary
- Follow patient with TEG
- Post-partum
  - TXA 2 tablets 3 times daily for 2 weeks after delivery
  - Keep the patient in the hospital at least 48 hours after delivery

OUR PATIENT – CLINICAL COURSE

- Admitted for induction of labor at 39 weeks
- Patient suffered arrest of dilation for 6 hours → proceeded with cesarean delivery
- 1g TXA administered prior to entering OR
- Female infant born with Apgar scores of 9 at one minute and 9 at 5 minutes
- Blood loss estimated at 1000 mL with no products transfused
- TXA 1,300mg 2 tablets oral TID in hospital
- No acute bleeding complications following delivery or after discharge

TEG RESULTS

Prior to Delivery

	Value	w/hep-ase	Units	Reference Range
R (Reaction Time)	5		minute(s)	5.0-10.0
K (Kinetics)	1.3		minute(s)	1.0-3.0
Angle	70.5		degrees	53.0-72.0
MA (Maximum Amplitude)	70.5		mm	50.0-70.0
G (Clot Firmness)	12.0		dynes/cm2	4.5-11.0
EPL (Estimated Percent Lysis)	6.4		%	0.0-15.0
LY30 (% Lysis 30 min. after MA)	6.4		%	0.0-8.0
AA (Arachidonic Acid)			% inhib	<=20
ADP (Adenosine Diphosphate)			% inhib	<=20

Delivery Day, After TXA

	Value	w/hep-ase	Units	Reference Range
R (Reaction Time)	3.4		minute(s)	5.0-10.0
K (Kinetics)	1.6		minute(s)	1.0-3.0
Angle	71.4		degrees	53.0-72.0
MA (Maximum Amplitude)	60.4		mm	50.0-70.0
G (Clot Firmness)	7.6		dynes/cm2	4.5-11.0
EPL (Estimated Percent Lysis)	0		%	0.0-15.0
LY30 (% Lysis 30 min. after MA)	0		%	0.0-8.0
AA (Arachidonic Acid)			% inhib	<=20
ADP (Adenosine Diphosphate)			% inhib	<=20

Delivery Day, After TXA

	Value	w/hep-ase	Units	Reference Range
R (Reaction Time)	6.7		minute(s)	5.0-10.0
K (Kinetics)	1.8		minute(s)	1.0-3.0
Angle	67.6		degrees	53.0-72.0
MA (Maximum Amplitude)	68.8		mm	50.0-70.0
G (Clot Firmness)	11.0		dynes/cm2	4.5-11.0
EPL (Estimated Percent Lysis)	0		%	0.0-15.0
LY30 (% Lysis 30 min. after MA)	0		%	0.0-8.0
AA (Arachidonic Acid)			% inhib	<=20
ADP (Adenosine Diphosphate)			% inhib	<=20

Postpartum, No longer on TXA

	Value	w/hep-ase	Units	Reference Range
R (Reaction Time)	8.5		minute(s)	5.0-10.0
K (Kinetics)	1.2		minute(s)	1.0-3.0
Angle	72.6		degrees	53.0-72.0
MA (Maximum Amplitude)	69.9		mm	50.0-70.0
G (Clot Firmness)	11.6		dynes/cm2	4.5-11.0
EPL (Estimated Percent Lysis)	13.7		%	0.0-15.0
LY30 (% Lysis 30 min. after MA)	13.7		%	0.0-8.0
AA (Arachidonic Acid)	NA		% inhib	<=20
ADP (Adenosine Diphosphate)	NA		% inhib	<=20

SUMMARY

- PAI-1 deficiency is a very rare inherited bleeding disorder
- Clinical manifestations include easy bruising, menorrhagia and moderate to severe bleeding following surgery or trauma
- Diagnosis should be considered in patients with a history suggestive of a bleeding disorder, but normal initial testing.
  - Follow up with tests for fibrinolysis, PAI-1 activity and PAI-1 antigen aid in diagnosis
- Patients should be treated with antifibrinolytic agents such as TXA or EACA
- Transfusion support with plasma or MTP may be required

RESOURCES

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THANK YOU!