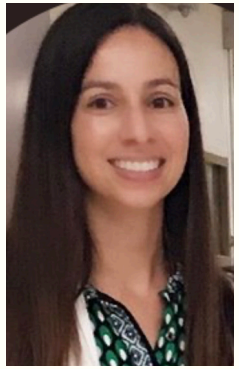
Hematologic Issues in Pregnancy



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UNIVERSITY OF MIAMI
MILLER SCHOOL of MEDICINE

Jackson HEALTH SYSTEM
Miracles made daily.

Disclosures

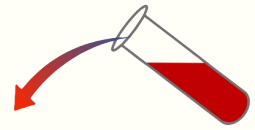
Diana Byrnes, MD, MPH

None

Michael J. Paidas, MD

Commercial Interest	Relationship	Role
BioIncept, LLC	Grant Stock option	Principal Investigator Scientific Advisory Board
UpToDate	Royalty	Contributing Author
GestVision	Grant	Principal Investigator
Progenity	Grant	Principal Investigator

NIH funding related to PreImplantation Factor, BioIncept, LLC:
NIAID- Acute Radiation Syndrome, PI
NICHD- Neonatal Brain Injury, PI



Topics To Cover

- Introduction: Pregnancy & Its Impact on Women's Health
- Venous Thromboembolism
- Thrombocytopenia
- Anemia
- Thrombotic microangiopathy
- Bleeding disorders

Pregnancy as the stress test of life

Susceptibility / vulnerability

- Genetics
- Metabolic syndrome
- Life style factors
- Socioeconomic status

Pregnancy complications

- Hypertensive disorders
- Low fetal growth
- Preterm delivery
- Placental abruption
- Stillbirth
- Gestational diabetes

Mortality / morbidity

- Cardiovascular disease
- Type 2 diabetes
- Autoimmune diseases?
- Cancer?

Sattar N, Greer IA., BMJ 2002

Subsequent thromboembolism following placenta mediated complications

Danish Registries

Follow up: median 14.6 y

Accruing 11,600,945 person-year

Combination	Rate	HR	CI	p
No complications	3.1	1	(reference)	
Preeclampsia	5.0	1.61	(1.39-1.87)	<0.001
Preeclampsia + PTD	4.9	1.62	(0.99-2.65)	0.054
Preeclampsia + SGA	8.5	2.74	(1.93-3.88)	<0.001
Preeclampsia + PTD + SGA	7.9	2.57	(1.72-3.84)	<0.001

Acta Obstet Gynecol Scand. 2012 Sep;91(9):1053-60.
J Thromb Haemost. 2012 Jul;10(7):1320-5.
Acta Obstet Gynecol Scand. 2012 Apr;91(4):503-10
Paediatr Perinat Epidemiol 2010; Jul 1;24(4): 323-30.

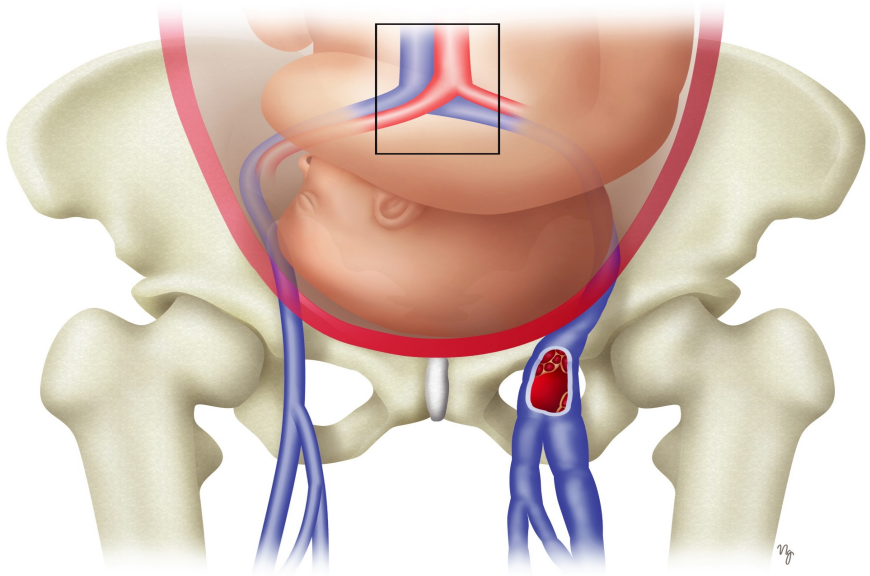
Hypertension. 2009 Jun;53(6):944-51.
BJOG. 2010 Feb;117(3):274-81.
Obstet Gynecol. 2009 Jun;113(6):1217-24.
Semin. Perinatol 2007 Aug;31(4) 219-22

Venous thromboembolism (VTE) in Pregnancy

- VTE complicates ~1.2 of every 1,000 deliveries
- Highest risk is in the 3rd trimester
- Despite the low absolute risks, pregnancy-associated VTE is the leading cause of maternal morbidity and mortality.
  - Bates et al. Blood Adv(2018) 2 (22): 3317–3359

https://utswmed.org/medblog/pulmonary-embolism-pregnancy/

Venous thromboembolism



Virchow's Triad

Stasis
- Compression iliac veins
  - Rt. iliac artery over left iliac vein
  - Gravid uterus
- Hormonally mediated vein dilation
- Immobilization

Vascular Damage
- Vascular compression at delivery
- Assisted or operative delivery

Hypercoagulable Blood
- ↑ **Procoagulant factors:**
  ↑fibrinogen, ↑factor V, IX, X XII and VIII levels
- ↓ **Anticoagulant activity:**
  ↓Protein S levels and ↑activated protein C resistance
- ↓ **Fibrinolytic activity:**
  ↑PAI-1 and 2 and ↓t-PA activity

= more thrombin generation + less clot dissolution

Bourjeily G, Paidas MJ, Khalil H, Rosene-Montella K, Rodger M. Lancet. 2010 Feb 6;375(9713):500-12

Clotting Factor Changes in Pregnancy: Promotes Hypercoagulability

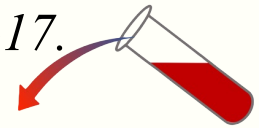
Coagulation Factors:

- **Increased in Pregnancy**:
  Fibrinogen, FVII, FVIII, von Willebrand factor, FX, PAI-1, PAI-2
- **No Change**:
  F II, FV & IX

Anticoagulants:

- **Decreased Pregnancy**:
  Protein S
- **No Change**:
  Protein C
  Antithrombin

Practice bulletin no. 196: thromboembolism in pregnancy. Obstet Gynecol. 2018; July;132 (1):e1-17.



Risk Factors for VTE Associated with Pregnancy

Antepartum & Postpartum VTE	Odds ratio (95% CI)
Thrombophilia	51.8 (38.7-69.2)
Previous VTE	24.8 (17.1-36.0)
Family history of VTE	3.9
Superficial venous thrombosis	10.0 (1.3-78.1)
BMI >25 kg/m^2	1.8 (1.3-2.4)
Antepartum immobilization	7.7 (3.2-19.0)
BMI > 25 kg/m^2 ^ & antepartum immobilization	62.3 (11.5-337.6)

Antepartum VTE	Odds ratio (95% CI)
Assisted Reproduction	4.3 (2.0-9.4)
Smoking	2.1 (1.3-3.4)

Postpartum VTE	Odds ratio (95% CI)
Infection (vaginal)	20.2 (6.4-63.5)
Infection (Cesarean)	6.2 (2.4-26.3)
Pre-eclampsia	3.1(1.8-5.3)
Pre-eclampsia &IUGR	5.8 (2.1-16.0)
Emergency Cesarean	2.7 (1.8-4.1)
Hemorrhage (w/o surg.)	4.1 (2.3-7.3
Hemorrhage (w/ surg.)	12.1 (3.9-36.9)

Other possible Risk factors	Odds ratio (95% CI)
Cesarean	2.1 (1.8-2.4), 1.3 (0.7-2.2)
Age	2.1 (2.0-2.3), 0.8 (0.6-1.1)
Parity	1.1 (0.9-1.4) 1.7 (1.2-2.4)

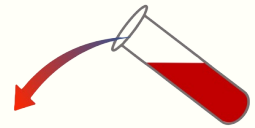
^ BMI at first prenatal visit

Modified from Bourjeily G, Paidas M, Khalil H, Rosene-Montella K, Rodger M.Lancet. 2010 Feb 6;375(9713):500-12.

Inherited Thrombophilias in Pregnancy

ACOG Practice Bulletin, Obstet Gynecol No 132 (1), July 2018; e18-34

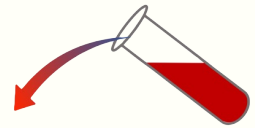
Thrombophilia	Prevalence in General Pop (%)	VTE Risk per pregnancy (No Hx) (%)	VTE Risk per pregnancy (Previous VTE) (%)	Percentage of all VTE
FVL heterozyg	1-15	0.5-1.2	10	40
FVL homozyg	<1	2.2-14.0	17	2
PGM heterozyg	2-5	0.4-2.6	>10	17
PGM homozyg	<1	2-4	>17	0.5
FVL/PGM double heterozyg	0.01	4-8.2	>20	1-3
AT deficiency	0.02	0.2-11.6	40	1
PC deficiency	0.2-0.4	0.1-1.7	4-17	14
PS deficiency	0.03-0.13	0.3-6.6	0-22	3



Thrombophilia & Pregnancy Loss

Factor	Non-recurrent Pregnancy Loss	Late Non-Recurrent Pregnancy Loss	Recurrent First Trimester Loss	Recurrent Pregnancy Loss
FVL	1.52 (1.06-2.19)[b]	2.06 (1.1-3.86)[d]	1.91 (1.01-3.61) [d]	3.04 (2.16-4.3) [a]
PGM	1.13 (0.64-2.01) [b]	2.66 (1.28-5.53) [d]	2.70 (1.37-5.34) [d]	2.05 (1.18-3.54) [a]
PC def	1.4 (0.9-2.2)[c]	2.3 (0.6-8.3) [c]	NA	1.57 (0.23-10.54) [a]
PS def	1.3 (0.8-2.1) [c]	7.39 (1.28-42.83)[a]	NA	14.72 (0.99-218.01) [a]
AT def	2.1 (1.2-3.6) [c]	5.2 (1.5-18.1) [c]	NA	NA

[a] Rey E, et al. Lancet. 2003;361:901–908.meta-analysis.
[b] Rodger MA, et al. PLoS Med. 2010;7:728. systematic review & meta- analysis of prospective cohort studies.
[c] Preston FE, et al. Lancet. 1996;348:913–916.
[d] Robertson L, et al. Br J Haematol. 2006;132:171–196. systematic review.
Pritchard AM, Hendrix PW, Paidas MJ. Hereditary Thrombophilia and Recurrent Pregnancy Loss. Clin Obstet Gynecol. 2016 Sep;59(3):487-97. Table 1



Thrombophilia & Selected Pregnancy Complications

Thr-philia	Preeclampsia	IUGR	Abruption
FVL	1.23 (0.89- 1.7)	1.0 (0.8- 1.25)	1.85 (0.92-3.7)
PGM	1.25 (0.79-1.99)	1.25 (0.92-1.7)	2.02 (0.81-5.02)
PC def	21.5 (1.1-414.4)	NA	5.93 (0.23-151-98)
PS def	2.83 (0.76- 10.57)	10.2 (1.1-91)	0.3 (0-70.1)
AT def	7.1 (0.4-117.4)	NA	4.1 (0.3-49.9)

Rodger MA et al. . PLoS Med 2010; 7(6):728
Robertson L et al. Br J Haematol 2006; 132(2): 171–196.
Alfirevic Z et al. Eur J Obstet Gynecol Reprod Biol 2002;101(1):6–14.

Hendrix PW, Tinelli A, Malvasi and Paidas MJ. Chapter 13: Thrombophilia and Pregnancy. In: "Management and therapy of early obstetric complications:. Editors: Di Renzo, Gian Carlo; Malvasi, Antonio; Tinelli, Andrea, Springer International Publishing, CH-6330 Cham (ZG), Switzerland. p 287-314, 2016.

Thrombophilia Screening: targeted approach

Inherited Thrombophilias in Pregnancy

ACOG Practice Bulletin No 197, July 2018; vol 132 (1) e18-34

When to Consider Ordering an evaluation:

1) Personal history VTE, with or without a recurrent risk factor, and no prior thrombophilia testing.

2) First degree relative with a high- risk thrombophilia.

- In women with VTE: FVL, PGM, AT, PS, PC & acquired thrombophilia testing (anticardiolipin antibodies
  - Remote from VTE event (>6 wks)
  - Not pregnant
  - Not on hormonal therapy
  - Not on anticoagulation

Antiphospholipid Antibodies

- VTE Pts (no RF <70 y) 3.1% pos LAC vs 0.9% con, OR 3.6
- Women <50 stroke: 17% pos LAC vs 0.7 con, OR 43.1
- RAB patients: 10-15% have APAS, obstetric criteria
- For patients with APAS by OB criteria, pos LAC= annual incidence of DVT 1.46%, stroke 0.32%
- Asymptomatic Triple threat patients (LAC pos, ACA pos, B2 GP1 pos) VTE risk 5.3% per year
- APAS: in 20-35% of patients with SLE
- Reported ORs for LAC-associated fetal loss range from 3.0 to 4.8
- Anti-cardiolipin antibodies display a wider range of reported OR's of 0.86 to 20.0

Giannakopoulos and Krilis NEJM 2013
Bas de Laat, Mertens, de Groot Nature 2008
Galli et al Hematol J. 2003; 4:180-6; Greaves Lancet. 1999; 353:1348-53.

Suspected Pulmonary Embolism in Pregnancy

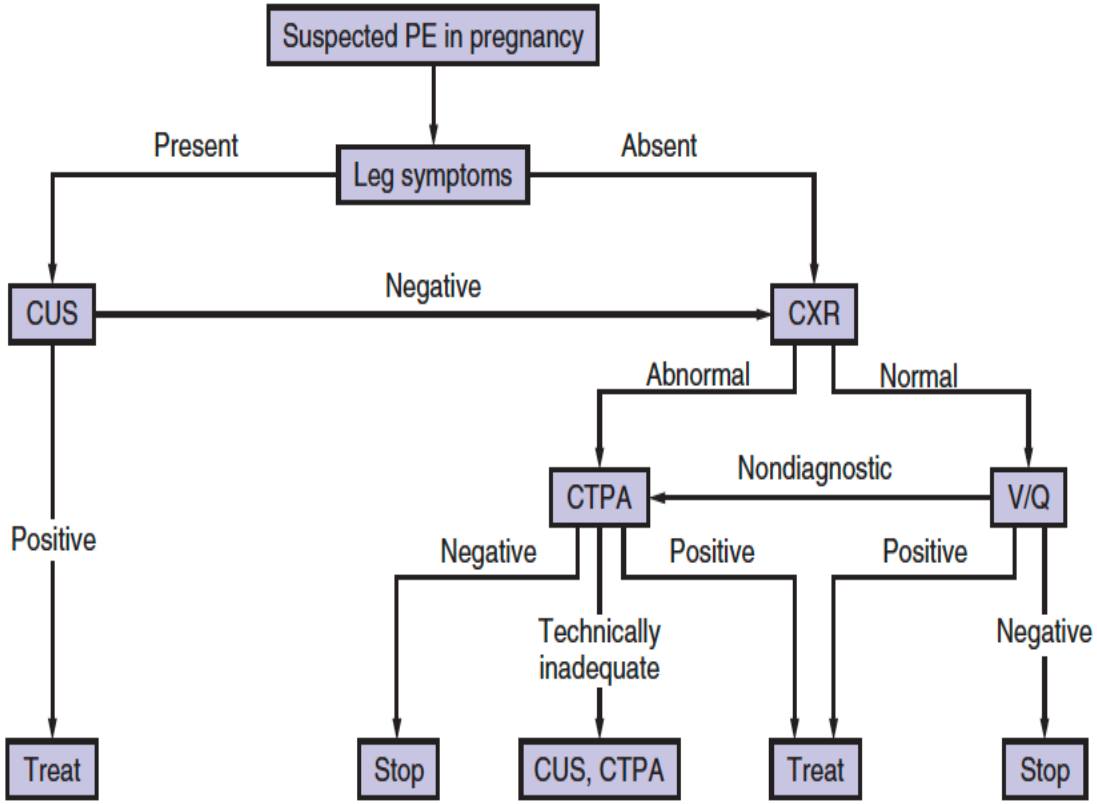


Figure 54.7 Diagnostic algorithm for pregnant patients with suspected pulmonary embolism *(PE)* and concomitant symptoms of deep venous thrombosis. *CTPA*, computed tomographic pulmonary angiography; *CUS*, compression ultrasound; *CXR*, chest radiograph; *V/Q*, ventilation-perfusion scan. *(Reprinted with permission of the American Thoracic Society. Copyright © 2012, American Thoracic Society.)*

Creasy and Resnick Chapter 54 Leung A, Sottile P and Lockwood CJ, 2019

Leung AN, Bull TM, Jaeschke R, Lockwood CJ, Boiselle PM, Hurwitz LM, James AH, McCullough LB, Menda Y, Paidas MJ, Royal HD, Tapson VF, Winer-Muram HT, Chervenak FA, Cody DD, McNitt-Gray MF, Stave CD, Tuttle BD; ATS/STR Committee on Pulmonary Embolism in Pregnancy. American Thoracic Society documents: an official American Thoracic Society/Society of Thoracic Radiology Clinical Practice Guideline--Evaluation of Suspected Pulmonary Embolism in Pregnancy. Radiology. 2012 Feb;262(2):635-46. PMID: 22282185

Suspected DVT in Pregnancy

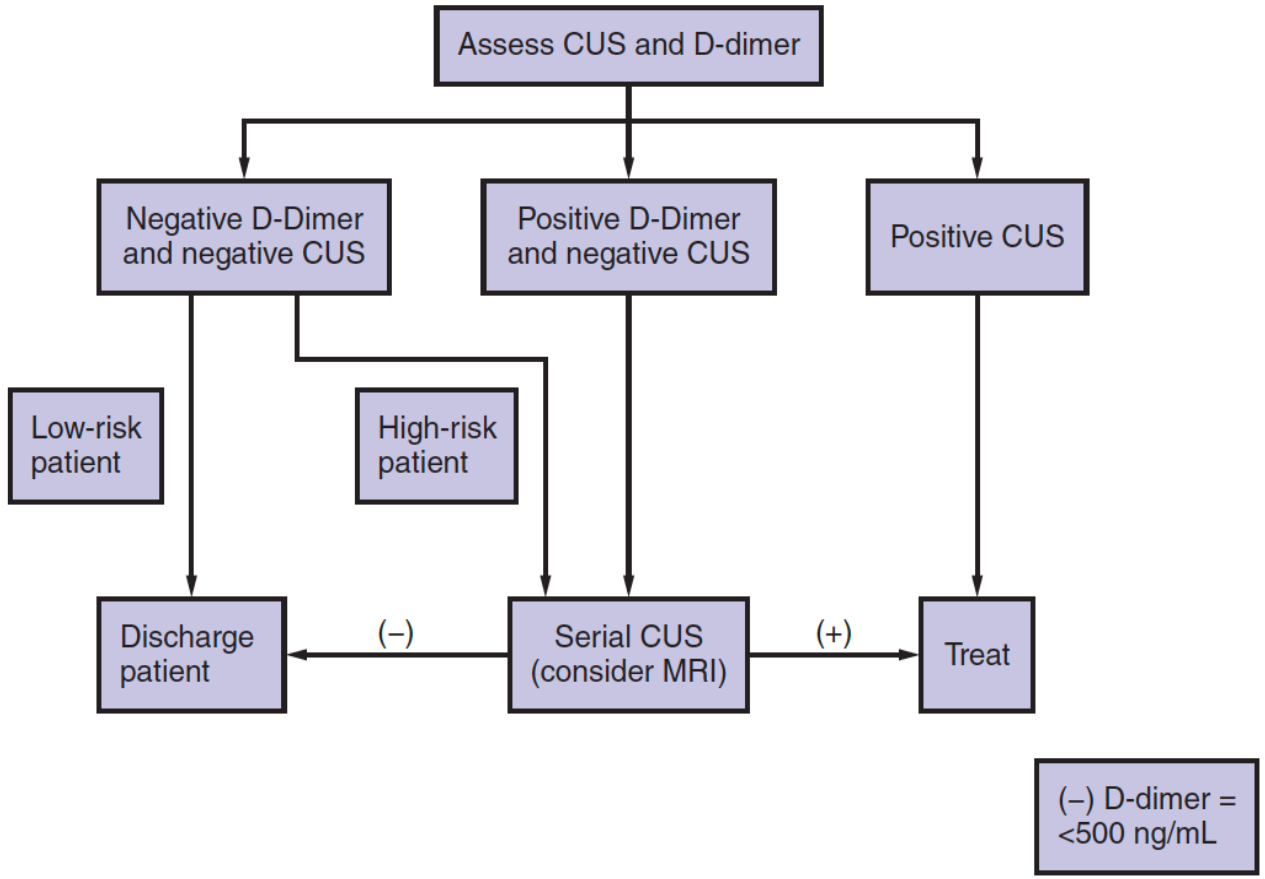
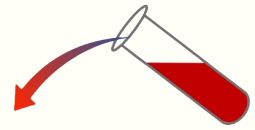


Figure 54.3 Compression ultrasound algorithm with D-dimer assessment. Diagnostic algorithm for patients with suspected deep venous thrombosis combining compression ultrasound *(CUS)* and D-dimer assessment. *D/C*, Discharge; *MRI*, magnetic resonance imaging.

Creasy and Resnick Chapter 54 Leung A, Sottile P and Lockwood CJ, 2019

Treatment of VTE

- Hemodynamically stable patients
  - LMWH- better bioavailability, low risk of bleeding, low rate of HIT and osteopenia
  - Standard dose: 1mg/kg Q12
  - UFH- Used around labor and delivery due to short half life & readily reversible
  - Continue AC for 6 weeks post partum
  - Coumadin can be used post partum – detected in breast milk in small amounts but considered safe



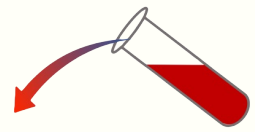
Treatment of VTE

- Hemodynamically unstable or severely hypoxemic patients
  - Thrombolysis if no contraindications
  - t-PA appears to be the best thrombolytic agent.
  - Main risk is maternal bleeding, reported in 8% of patients treated

Recommendation 8

In pregnant women with acute pulmonary embolism and life-threatening hemodynamic instability, the ASH guideline panel *suggests* administering systemic thrombolytic therapy in addition to anticoagulant therapy (conditional recommendation, very low certainty in evidence about effects ⊕◯◯◯).

Bates et al. *Blood Adv*(2018) 2 (22): 3317–3359



Management of Peripartum Anticoagulation

Table 4. Timing of Neuraxial Anesthesia in Relation to Pharmacologic Anticoagulation

Dosage Regimen	Intrapartum, Elective Procedure	Intrapartum, Urgent/ Emergent Procedure	Postpartum
UFH prophylaxis (7,500 units SC twice daily or 10,000 units SC twice daily)	Hold dose for 12 hours and assess coagulation status before administering neuraxial anesthesia	Hold dose for 12 hours and assess coagulation status before administering neuraxial anesthesia. However, in urgent cases with greater competing risks from general anesthesia, placement of neuraxial anesthesia may be appropriate	Wait at least 1 hour after neuraxial blockade and catheter removal before restarting heparin
UFH adjusted-dose (>10,000 units per dose or >20,000 units per day)	Hold dose for 24 hours and assess coagulation status before administering neuraxial anesthesia	If at least 24 hours since last dose and aPTT within normal limits or undetectable anti-Xa, likely low risk for neuraxial blockade	Wait at least 1 hour after neuraxial blockade or catheter removal before restarting heparin
Low-dose LMWH prophylaxis	Wait 12 hours after last dose before neuraxial blockade	Insufficient data to make a recommendation for placement of neuraxial blockade less than 12 hours from last dose of LMWH. In high risk situations in which intervention is needed, risks of general anesthesia may outweigh risks of spinal epidural hematoma	Wait at least 12 hours after neuraxial blockade and at least 4 hours after catheter removal to restart LMWH prophylaxis
LMWH intermediate-dose or adjusted-dose	Wait 24 hours after last dose before neuraxial blockade	If less than 24 hours, insufficient evidence to recommend proceeding with neuraxial blockade	Consider waiting at least 24 hours after neuraxial blockade *and* at least 4 hours after catheter removal to restart LMWH anticoagulation

Abbreviations: LMWH, low-molecular-weight heparin; SC, subcutaneously; UFH, unfractionated heparin.

Data from Leffert L, Butwick A, Carvalho B, Arendt K, Bates SM, Friedman A, et al. The Society for Obstetric Anesthesia and Perinatology consensus statement on the anesthetic management of pregnant and postpartum women receiving thrombo-prophylaxis or higher dose anticoagulants. Members of the SOAP VTE Taskforce. Anesth Analg 2018;126:928–44.

Practice bulletin no. 196: thromboembolism in pregnancy.Obstet Gynecol. 2018; July;132 (1):e1-17.

Management of Peripartum Anticoagulation

Anticoagulant	Recommendation
UFH prophylaxis (≤ 10,000 IU/d)	No contraindication to timing of heparin dose and performance of neuraxial blockade Note: the American Society for Regional Anesthesia and Pain Medicine advises waiting 4–6 h after last prophylactic UFH dose
UFH therapeutic	Wait 6 h after last dose before neuraxial blockade or PTT
LMWH prophylaxis	Wait 12 h after last dose before neuraxial blockade
LMWH therapeutic	Wait 24 h after last dose before neuraxial blockade

- **Patient can be switched to subcutaneous heparin 2-5 weeks before delivery to allow option of regional anesthesia.**
- **From an obstetric perspective, AC can be resumed 4-6hrs after vaginal delivery & 6-12 hours after C-Section. However, regional anesthesia considerations will influence timing of AC resumption.**

Kouides PA and Paidas MJ. Consultative hematology II: women's health issues. ashpublications.org. Published online May 30, 2019.

Antepartum dalteparin versus no antepartum dalteparin for the prevention of pregnancy complications in pregnant women with thrombophilia (TIPPS): a multinational open-label randomised trial

Marc A Rodger, William M Hague, John Kingdom, Susan R Kahn, Alan Karovitch, Mathew Sermer, Anne Marie Clement, Suzette Coat, Wee Shian Chan, Joanne Said, Evelyne Rey, Sue Robinson, Rshmi Khurana, Christine Demers, Michael J Kovacs, Susan Salymoss, Kim Hinshaw, James Dwyer, Graeme Smith, Sarah McDonald, Jill Newstead-Angel, Anne Mc.eod, Meena Khandelwal, Robert M Silver, Gregoire Le Gal, Ian A Greer, Erin Keely, Karen Rosene-Montella, Mark Walker, Philip S Wells, for the TIPPS Investigators

Lancet. 2014 Jul 24

No Benefit to antepartum anticoagulation

Antepartum Prophylaxis for women at risk for pregnancy related VTE

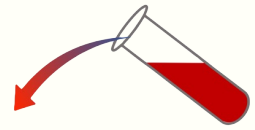
Clinical history	Anticoagulation
➢ Multiple prior VTE ➢ Prior VTE with high-risk thrombophilia ➢ Prior VTE with acquired thrombophilia	Treatment-dose LMWH or UFH
➢ Idiopathic prior VTE ➢ Prior VTE with pregnancy or oral contraceptive ➢ Prior VTE with low-risk thrombophilia ➢ Family history of VTE with high-risk thrombophilia ➢ High-risk thrombophilia (including acquired)	Prophylactic-dose LMWH or UFH
➢ Low-risk thrombophilia ➢ Prior VTE provoked (eg, non- hormonal-trauma or postoperative) ➢ Low-risk thrombophilia and family history of VTE	No treatment

Kouides PA and Paidas MJ. Consultative hematology II: women's health issues. ashpublications.org. Published online May 30, 2019.

Prophylaxis for women at risk for pregnancy related VTE

Scenario	Postpartum Management
No VTE hx, No thrombophilia	**Surveillance or proph w mult RF**
VTE in preg	Adjusted Dose LMWH/UFH 6 wks+
1 Provoked VTE (trans RF, no thrombophilia)	**Surveillance, or proph w addit RF**
Hx 1 unprovoked VTE (no long term AC)	Proph, interm, or adjusted dose LMWH/UFH 6wks
Low Risk thrombophilia, No VTE	**Surveillance, or proph w addit RF**
Low Risk thrombophilia & Fam hx VTE	Proph or interm dose LMWH/UFH
Low Risk thrombophilia & Single VTE (no long term AC)	**Proph or interm dose LMWH/UFH**
High Risk thrombophila & No VTE	Proph or interm dose LMWH/UFH
High Risk thrombophilia & Single VTE or Fam hx VTE (no long term AC)	**Proph, interm dose, or adjusted dose LMWH/UFH (= to AP level)**
2 or more VTE (no long term AC), regardless of thrombophilia	Interm or adjusted dose LMWH/UFH (= to AP level)
2 or more VTE on long term AC, regardless of thrombophilia	**Resume long term AC**

Practice bulletin no. 196: thromboembolism in pregnancy. Obstet Gynecol. 2018; July;132 (1):e1-17.



PATIENT SAFETY BUNDLE

Maternal Venous Thromboembolism Prevention

READINESS

Every Unit

- Use a standardized thromboembolism risk assessment tool for VTE during:
  - Outpatient prenatal care
  - Antepartum hospitalization
  - Hospitalization after cesarean or vaginal deliveries
  - Postpartum period (up to 6 weeks after delivery)

RECOGNITION & PREVENTION

Every Patient

- Apply standardized tool to all patients to assess VTE risk at time points designated under "Readiness"
- Apply standardized tool to identify appropriate patients for thromboprophylaxis
- Provide patient education
- Provide all healthcare providers education regarding risk assessment tools and recommended thromboprophylaxis

RESPONSE

Every Unit

- Use standardized recommendations for mechanical thromboprophylaxis
- Use standardized recommendations for dosing of prophylactic and therapeutic pharmacologic anticoagulation
- Use standardized recommendations for appropriate timing of pharmacologic prophylaxis with neuraxial anesthesia

REPORTING/SYSTEMS LEARNING

Every Unit

- Review all thromboembolism events for systems issues and compliance with protocols
- Monitor process metrics and outcomes in a standardized fashion
- Assess for complications of pharmacologic thromboprophylaxis

Consensus Statement

National Partnership for Maternal Safety

Consensus Bundle on Venous Thromboembolism

Mary E. D'Alton, MD, Alexander M. Friedman, MD, Richard M. Smiley, MD, PhD, Douglas M. Montgomery, MD, Michael J. Paidas, MD, Robyn D'Oria, MA, RNC, APN, Jennifer L. Frost, MD, MPH, Afshan B. Hameed, MD, Deborah Karsnitz, CNM, DNP, Barbara S. Levy, MD, and Steven L. Clark, MD

Obstet Gynecol. 2016 Sep 5. PMID: 27607857

COUNCIL ON PATIENT SAFETY IN WOMEN'S HEALTH CARE

safe health care for every woman

Anemia in Pregnancy

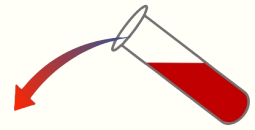
- During normal pregnancy, plasma volume expands by 40-60%
- Red cell mass expands by 20-50%
- Anemia definition according to ACOG and CDC:

Trimester	Hemoglobin	Hematocrit	Prevalence
1st	<11	<33	8%
2nd	<10.5	<32	12%
3rd	<11	<33	33%

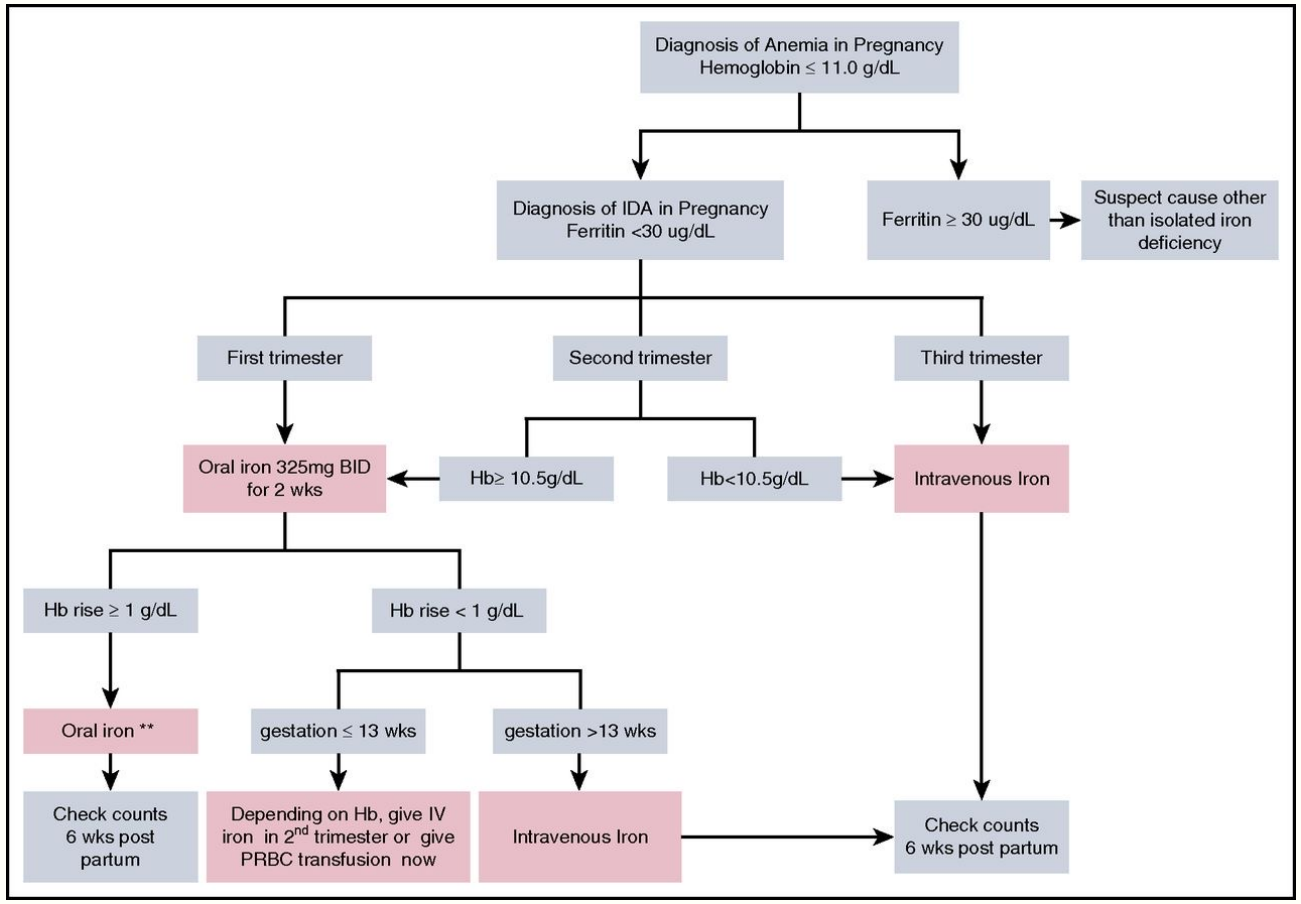
Source: Kouides PA, Paidas M. Consultative hematology II: women's health issues. *ashpublicationsorg*. Published online May 30, 2019.

Iron requirements in pregnancy

- 300-350mg for the fetus and placenta
- 500mg for the expansion of the maternal RBC mass
- 250mg associated with blood loss during labor and delivery
- Requirement for iron increases with trimester: 0.8mg/day in the 1st trimester, 7.5mg/day in the third
- Average absorption of iron from western diets is 1-5mg
- CDC recommends women begin 30mg per day iron supplement at 1st prenatal visit. WHO recommends 60mg/day



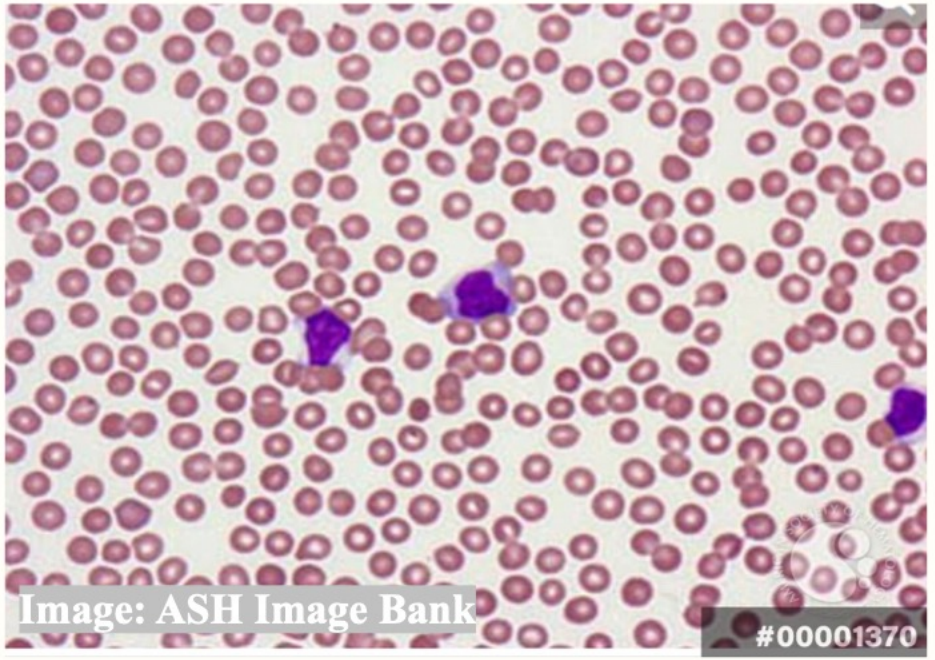
How I treat anemia in pregnancy: iron, cobalamin, and folate



Achebe MM and Gafter-Gvili A. How I treat anemia in pregnancy: iron, cobalamin, and folate, Blood, 2017.

Thrombocytopenia in Pregnancy

- Most common hematologic abnormality in pregnancy
- Affects ~10% of pregnant women



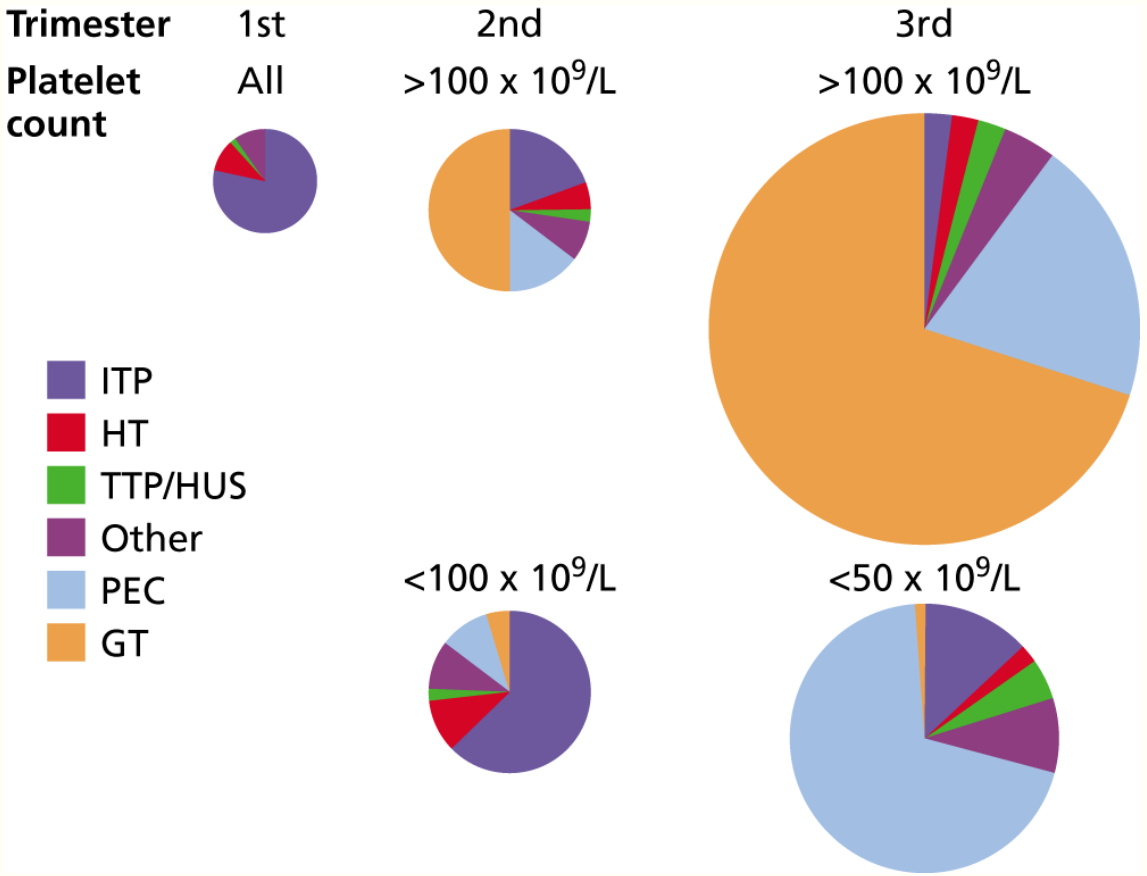
Cines et al. Blood 2017. 130(21):2271-2277

Gestational Thrombocytopenia

- Defined as platelet count below 150K
- 4.4-11.6% of pregnancies
- Does not become apparent before the mid-second trimester
- Only 1-5% of women develop plt count below 100K
- No biomarkers to provide affirmative dx
- Fetal thrombocytopenia is uncommon
- Does not respond to IVIG or steroids
- If does not resolve withing 1-2 months of delivery, consider dx of ITP or hereditary thrombocytopenia.

Cines et al. Blood 2017. 130(21):2271-2277

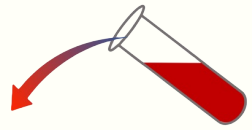
Consultative Hematology II: Women's Health Issues



Peter A. Kouides, Michael Paidas, 2019, Consultative Hematology II: Women's Health Issues, American Society of Hematology Self-Assessment Program, Seventh Edition, Figure 3-1

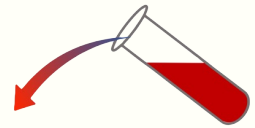
Immune Thrombocytopenia

- Accounts for ~3% of all cases of thrombocytopenia in pregnancy
- Most common cause of platelet count <50K
- Diagnosis of exclusion
- Should be suspected when otherwise healthy mother who is taking no medications presents with plt count <70K in 1st or 2nd trimester



ITP Management (1)

- Treatment initiated when platelet count falls <20-30K, and for procedures and delivery
- Hematomas following neuraxial anesthesia are rare in patients with ITP and platelet count >50K and no concomitant coagulopathy or exposure to antithrombotic agents
- Most guidelines suggest minimum plt count of 80K for neuraxial anesthesia
- Plts should be measured more frequently starting 32-34 weeks, repeated weekly in unstable patients
- Care needs to be coordinated with experienced obstetrician and neonatologist
- Mainstay of treatment is steroids and IVIG

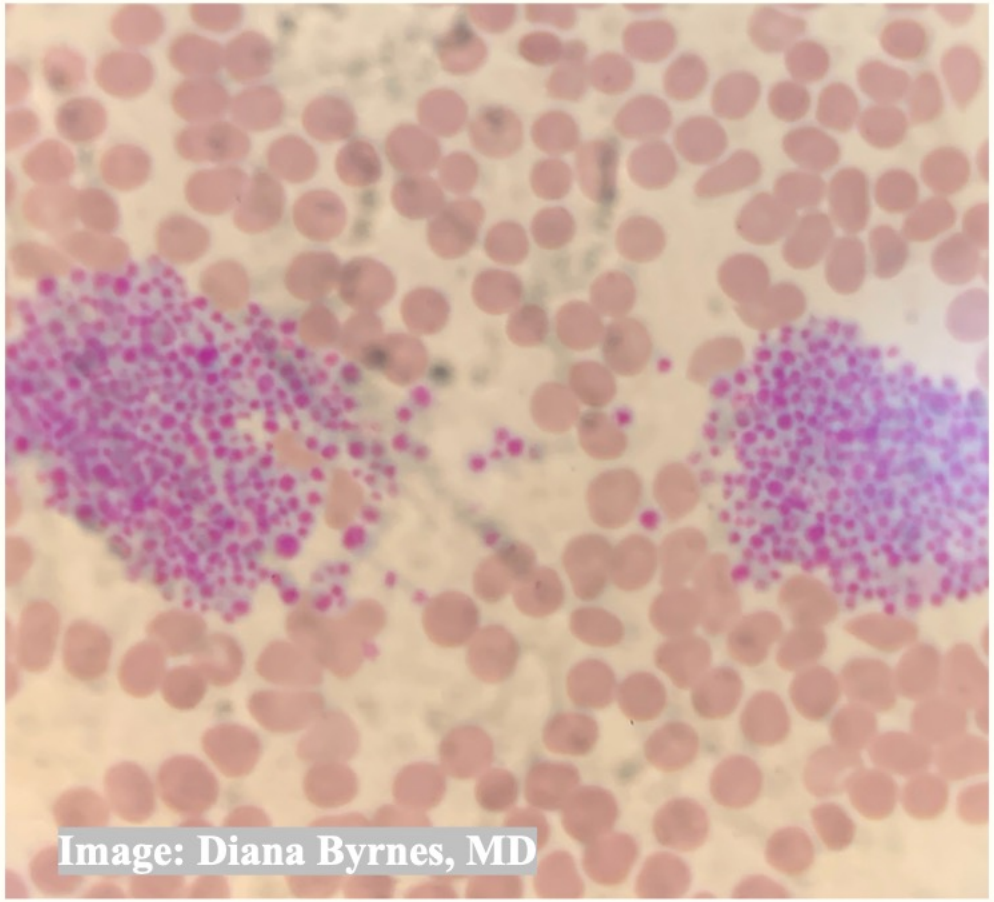


ITP Management (2)

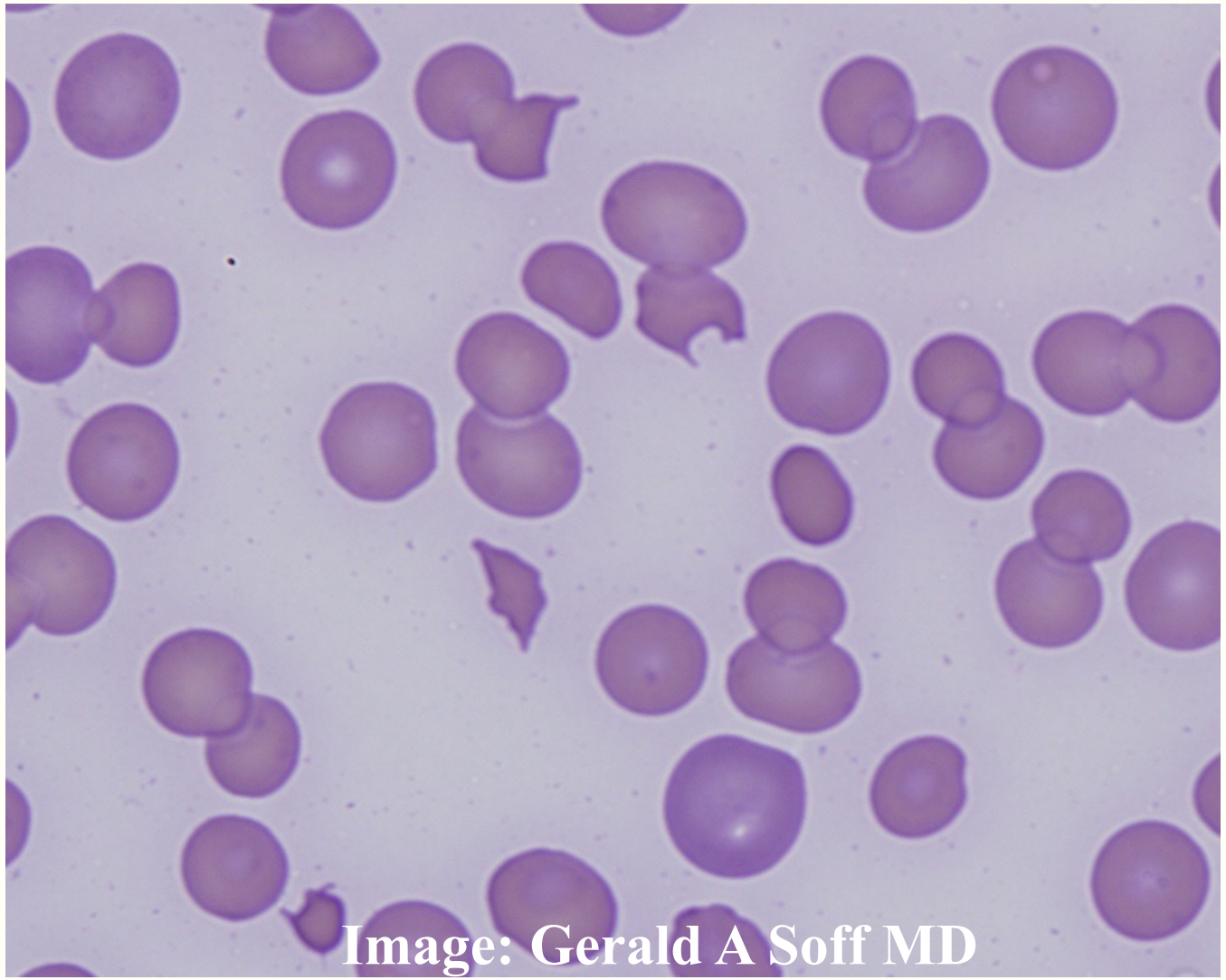
- Corticosteroids
  - Oral prednisone preferred over pulse dexamethasone
  - Persistent exposure to high dose steroids in 1st trimester is associated with small increased risk of cleft palate
  - Exposure throughout gestation may increase risk of preterm birth and gestational diabetes
- IVIG 1g/kg used if corticosteroid therapy fails or maternal intolerance
- Splenectomy has been performed safely in 2nd trimester
- TPO agonists & SYK inhibitors are not recommended in pregnancy
- Rituximab is not teratogenic, but associated with prolonged B-cell depletion and need to delay neonatal vaccines.

Don’t forget to look at the smear!

Platelet Clumping



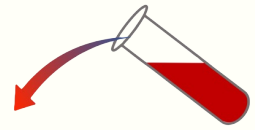
Microangiopathic disorders in pregnancy



Schistocytes and Thrombocytopenia

Differential Diagnosis

Pregnancy-specific TMA	Non-pregnancy specific TMA
➢ Preeclampsia ➢ Hemolysis, Elevated Liver enzyme levels, and Low Platelet (HELLP) ➢ Acute fatty liver of pregnancy (AFLP)	➢ Thrombotic thrombocytopenic purpura (TTP) ➢ Atypical hemolytic uremic syndrome (aHUS)



Preeclampsia (PEC)

- Most common cause of thrombocytopenia associated with TMA
- Occurs late in 2nd or 3rd trimester, rarely during first week post-partum

Cines et al. Blood 2017. 130(21):2271-2277

TABLE E-1. Diagnostic Criteria for Preeclampsia

Blood pressure	• Greater than or equal to 140 mm Hg systolic or greater than or equal to 90 mm Hg diastolic on two occasions at least 4 hours apart after 20 weeks of gestation in a woman with a previously normal blood pressure • Greater than or equal to 160 mm Hg systolic or greater than or equal to 110 mm Hg diastolic, hypertension can be confirmed within a short interval (minutes) to facilitate timely antihypertensive therapy
and	
Proteinuria	• Greater than or equal to 300 mg per 24-hour urine collection (or this amount extrapolated from a timed collection) or • Protein/creatinine ratio greater than or equal to 0.3* • Dipstick reading of 1+ (used only if other quantitative methods not available)
Or in the absence of proteinuria, new-onset hypertension with the new onset of any of the following:	
Thrombocytopenia	• Platelet count less than 100,000/microliter
Renal insufficiency	• Serum creatinine concentrations greater than 1.1 mg/dL or a doubling of the serum creatinine concentration in the absence of other renal disease
Impaired liver function	• Elevated blood concentrations of liver transaminases to twice normal concentration
Pulmonary edema	
Cerebral or visual symptoms	

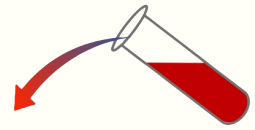
*Each measured as mg/dL.

Obstetrics & Gynecology. 122(5):1122-1131, November 2013

HELLP and ALFP

- HELLP
  - Variant of PEC characterized by more severe thrombocytopenia, more fulminant MAHA, and more profoundly elevated liver function tests
  - DIC may be present in 10% of women

- AFLP
  - Occurs in 1 in 5,000-10,000 pregnancies. More common in multiple gestations
  - Nausea, vomiting, abdominal pain
  - Coagulopathy disproportionately severe relative to liver function
  - Hypoglycemia in severe cases
  - Reduction in antithrombin III
  - DIC
  - Encephalopathy

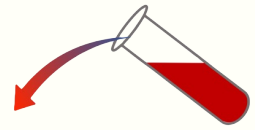


Management of HELLP/AFLP

- Urgent Delivery
- Supportive care and resuscitation of mother with transfusion of red cells, platelets, and coagulation factors as needed
- Steroids in HELLP <34 weeks

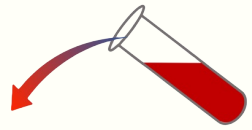
TTP

- 1 in 200,000 pregnancies
- 10% of women with aTTP & 25-50% of women with cTTP present for the first time in pregnancy
- Maternal mortality can be reduced by 80-90% with prompt recognition and initiation of treatment
- Abundance of schistocytes and nucleated red cells on smear, markers of hemolysis, ADAMTS13<10%
- Management
  - Plasmapheresis and corticosteroids
  - Little published data on use of Rituximab, azathioprine, or other modalities in pregnancy
- Risk of recurrence in subsequent pregnancy exceeds 50% if persistently reduced ADAMTS activity, therefore, measure in 1st trimester to identify women at high risk



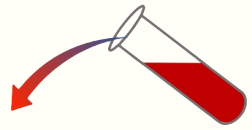
Atypical HUS

- 10-20% of women with aHUS present for the 1st time in pregnancy.
- May reflect stress of compliment activation that develops normally during pregnancy
- Presentation: progressive renal failure, thrombocytopenia, platelet count>50K, MAHA, normal ADAMTS13 levels
- Consumption of plasma C3 and C4 and generation of soluble C5b-9 complexes are seen but not diagnostic
- Genetic testing can be done but long turn around time
- 1—30% risk of recurrence in subsequent pregnancies



Atypical HUS - Management

- Plasmapheresis until TTP excluded
- Eculizumab
  - Used safely in pregnancy
  - Not detected in breast milk
  - No fetal harm reported
  - Patients need to vaccinated against meningococcus
- Delivery does not alter outcomes
- Risk of fetal loss is 10-20%



MAHA in Pregnancy Summary

Table 1. Clinical and laboratory features of pregnancy-associated microangiopathies

	Preeclampsia/HELLP	TTP	HUS	AFLP
Elevated blood pressure	+++	+	+	++ (50% of cases)
Neurological symptoms	+/++ (headache)	+++ (numbness, weakness, aphasia, mental status)	+	+
Abdominal symptoms	+ (RUQ pain)	++ (unspecific/diffuse)	+	+++ (unspecific/diffuse)
Fever	−	−/+	−/+	−
Easy bruising	−	−/+	−	−
Thrombocytopenia	+/++ (>50 × 10^9/L)	+++ (<20 × 10^9/L)	+ (<100 × 10^9/L)	+
Renal impairment (elevated creatinine; > ~2 mg/dL)	+/++	+/++	+++	++/+++
Hepatic dysfunction and inflammation (AST/ALT)	+	−/+	−/+	+++ (and bilirubin)
Coagulopathy	−/+	−	−	+++
LDH	+	+/+++	+/++	+++
Microangiopathic hemolytic anemia	+	+/+++	+/++	+
Hypoglycemia	−	−	−	+
ADAMTS13 activity	Normal	<10%*	>20%-30%†	>30%

Estimated prevalence of clinical signs and symptoms and laboratory features in women with TMAs during pregnancy. Reference ranges in healthy pregnancy must be taken into consideration.

+, prevalence; −, not usually present; ALT, alanine aminotransferase; AST, aspartate transaminase; LDH, lactate dehydrogenase; RUQ, right upper quadrant.

*Some investigators require that the ADAMTS13 activity level in plasma be below 10% of normal to make the diagnosis of TTP, whereas others use this solely as providing confirmation of a clinical diagnosis.

†ADAMTS13 activity is generally above 30% of normal in patients with a clinical diagnosis of aHUS, but there are no guidelines that exclude this diagnosis based on activity levels per se.

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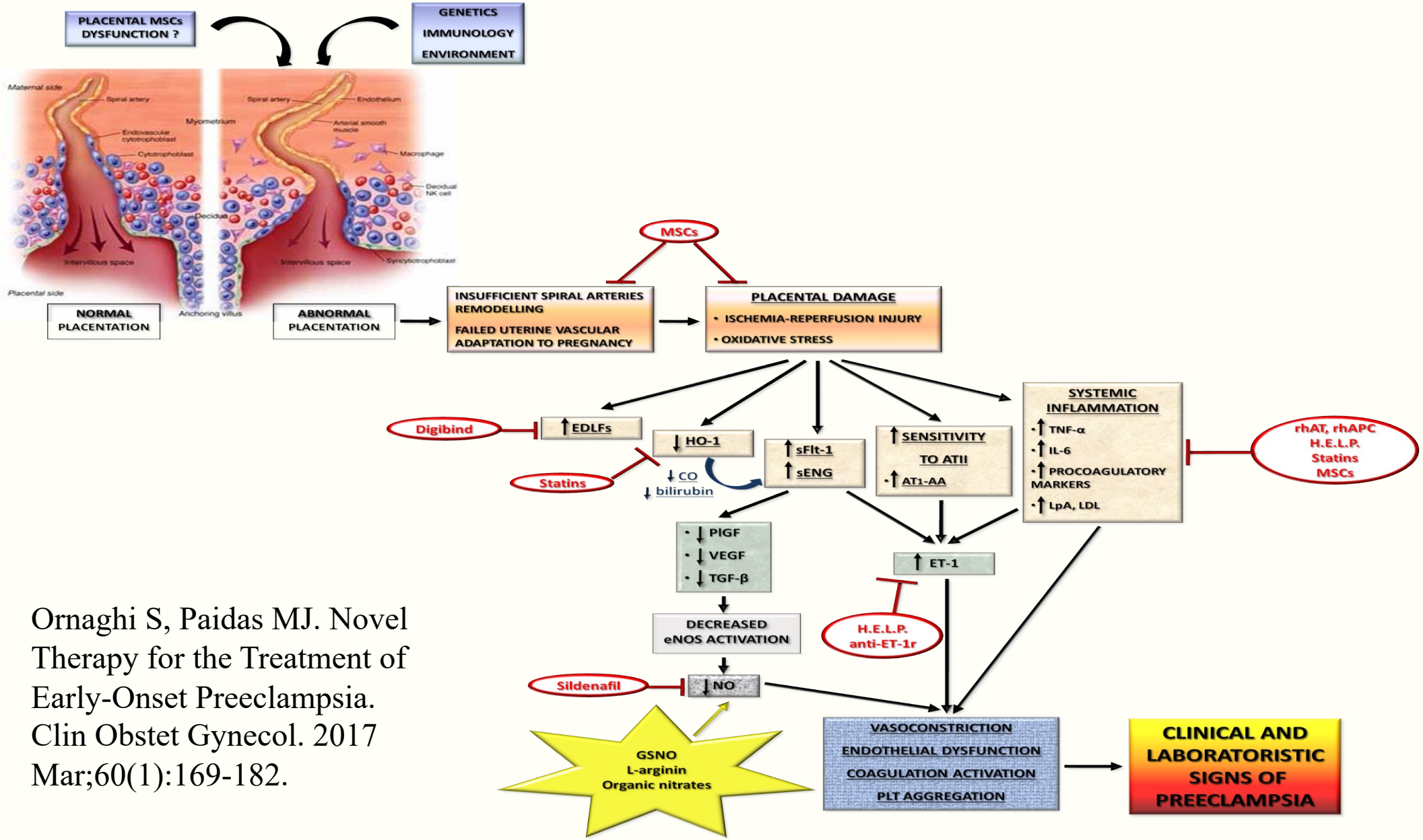
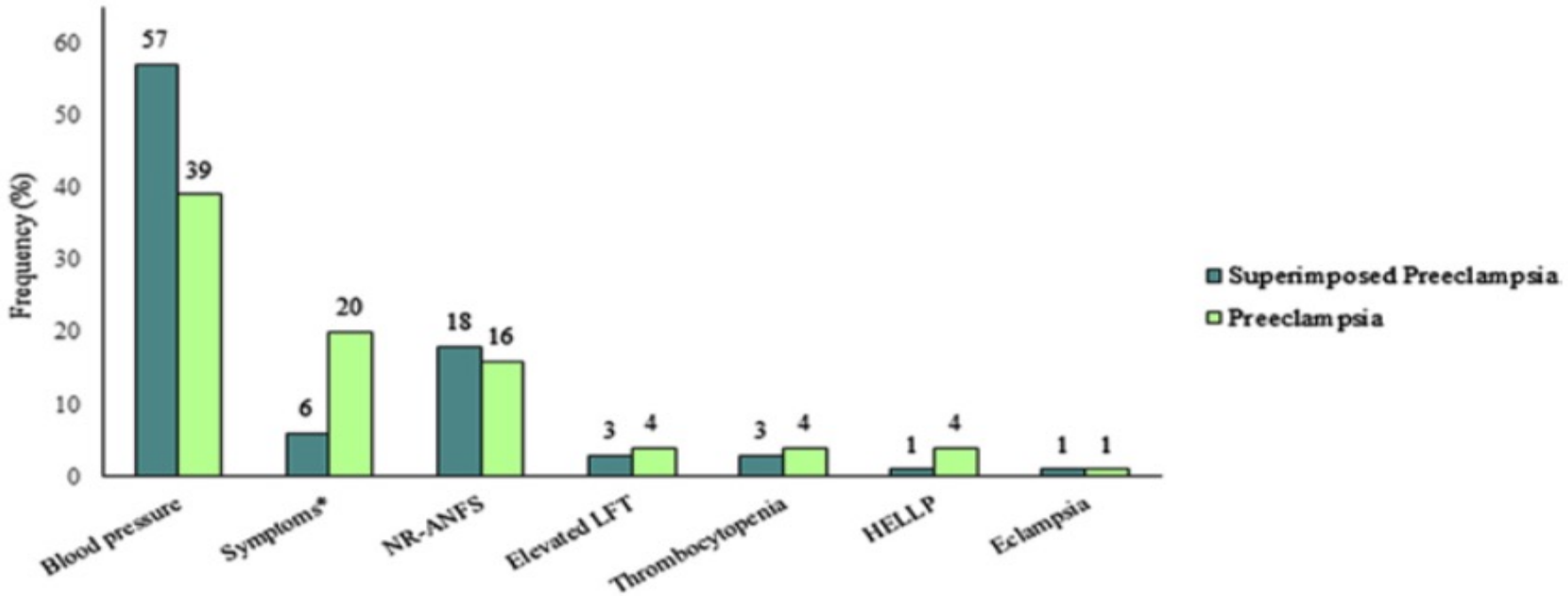


Ornaghi S, Paidas MJ. Novel Therapy for the Treatment of Early-Onset Preeclampsia. Clin Obstet Gynecol. 2017 Mar;60(1):169-182.

Preterm Preeclampsia <37 wk

FIGURE

Indications for delivery



Bar graph representing common indications for delivery in pregnancies complicated by superimposed preeclampsia (*blue*) and preeclampsia (*green*) expectantly managed in hospital setting. The frequencies do not add up to 100% due to missing or other indications for delivery.

LFT, liver function testing; *HELLP*, hemolysis, elevated liver enzymes, and low platelet count; *NR-ANFS*, nonreassuring antenatal fetal surveillance.

*Persistent neurological or gastrointestinal symptoms.

Valent. Expectant management of preeclampsia. Am J Obstet Gynecol 2015.

Valent *et al* 2015 AJOG

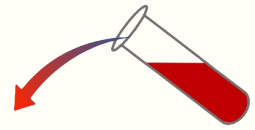
Low Dose Aspirin Therapy

Low dose aspirin therapy for the prevention of preeclampsia was studied by the US Preventive Services Task Force in a systematic evidence review and published in September 2014. Initiation of therapy is recommended by both USPSTF and ACOG between 12 weeks and 28 weeks of gestation for the following high risk indications:

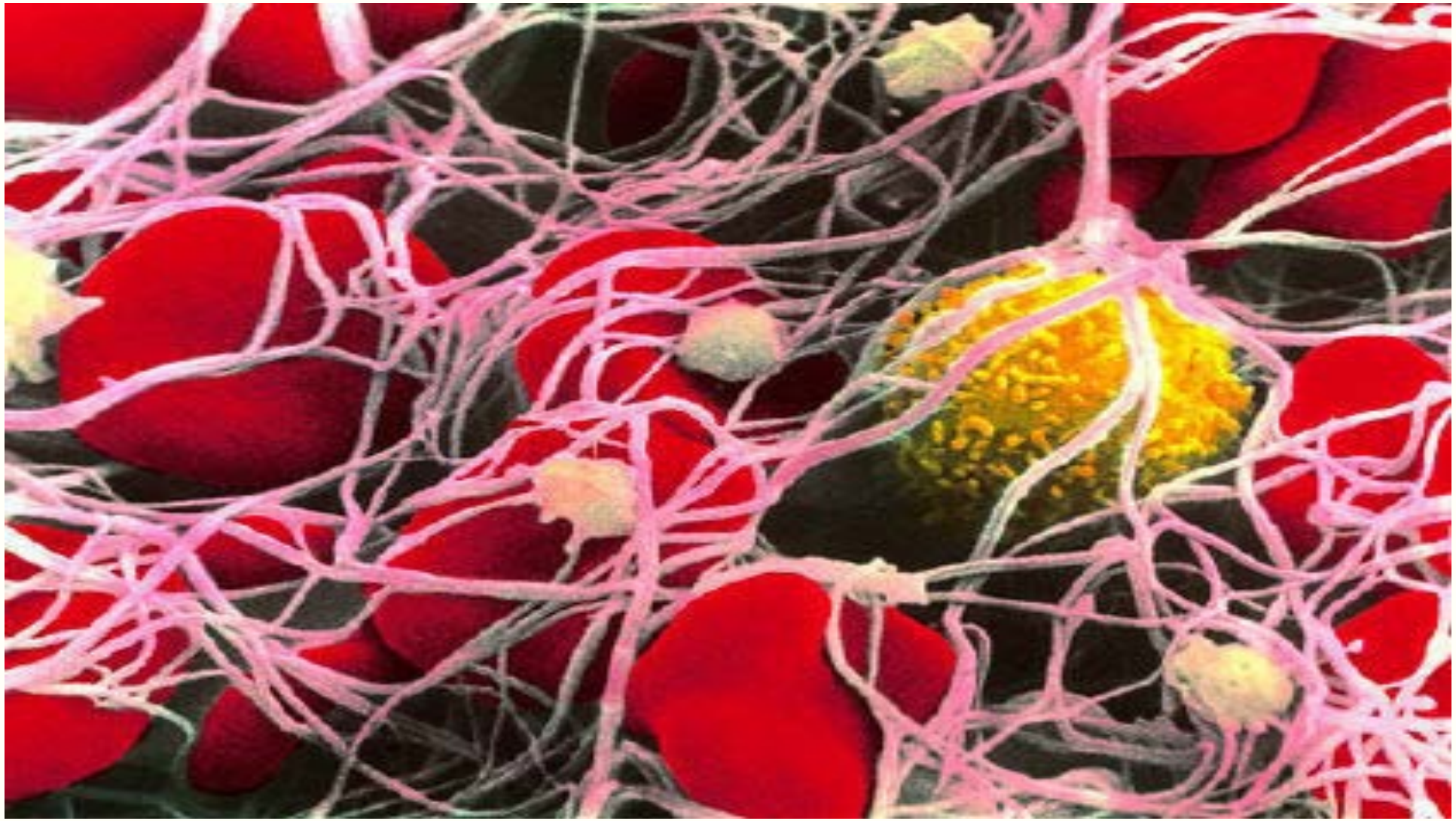
- History of preeclampsia, especially if accompanied by an adverse outcome
- Multifetal gestation
- Chronic hypertension
- Diabetes (Type 1 and Type 2)
- Renal disease
- Autoimmune disease (such as SLE, antiphospholipid syndrome)

The presence of ≥ 2 moderate risk factors may also be an indication for the use of low dose aspirin.

- Nulliparity
- Obesity (body mass index >30 kg/m2)
- Family history of preeclampsia (mother or sister)
- Sociodemographic characteristics (African American race, low socioeconomic status)
- Age ≥ 35 y
- Personal history factors (e.g., low birthweight or small for gestational age, previous adverse pregnancy outcome, >10-y pregnancy interval)



Bleeding Disorders & Pregnancy



Surveillance of female patients with inherited bleeding disorders in US Hemophilia Treatment Centers (Universal Data Collection, UDC) n= 319 participants/20 HTCs Sept 2009-Dec 2010

Disorder	N (%)
vWD Type 1	195 (61.1)
vWD Type 2	25 (7.8)
vWD Type 3	14 (4.4)
vWD Type unknown	49(15.4)
FVIII	40 (12.5)
Platelet disorders	15 (4.7)
Factor VII	11 (3.4)
Factor IX	11 (3.4)
Connective tissue disorders	10(3.1)
Hereditary hemorrhagic telangiectasia	4 (1.3)
Factor XI deficiency	3 (0.9)
PAI-1	3 (0.9)
Fibrinogen deficiency	2(0.6)
Factor V deficiency	2 (0.6)
Factor X deficiency	2 (0.6)
Factor XIII deficiency	2 (0.6)
Missing diagnoses	22 (6.9)

Byams VR et al. Haemophilia 2011; 17(suppl 1): 6-13.

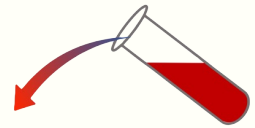
von Willebrand's Disease

- Prevalence 0.6 to 1.3%, but estimated prevalence of von Willebrand's disease is approximately 1 case per 10,000 persons (HTCs)
- Autosomal inheritance (clinically more common in females
- Disease is diagnosed in more females because of female-specific hemostatic challenges
- vWF estimated normal range is generally between 50 and 150 IU per deciliter

Type	Classification
1	Partial quantitative deficiency of vWF
2	Qualitative vWF defects
2A	Decreased vWF- dependent platelet adhesion & a selective deficiency of high molecular weight vWF multimers
2B	Increased affinity for platelet glycoprotein Ib
2M	Decreased vWF- dependent platelet adhesion without a selective deficiency of high molecular weight vWF multimers
2N	Markedly decreased binding affinity for factor VIII
3	Virtually complete deficiency of vWF

Leebeek FWG, Eikenboom JCJ. N Engl J Med 2016;375:2067-2080

Sadler LE et al. J Thromb Haemost 2006; 4: 2103-14



Heavy Menstrual Bleeding in Women with Bleeding Disorders

Disorder	Prevalence of Heavy Menstrual Bleeding, %
von Willebrand Disease (Type I)	79-93
Carriers of hemophilia	57
Factor XI (FXI) deficiency	59
Factor VII (FVII) deficiency	47
Glanzmann's thrombasthenia	13-98

George JN et al. *Blood.* 1990;75(7):1383-1395.
Kadir RA et al. *Haemophilia*. 1999;5(1):40-48.
Kouides PA et al. *Haemophilia*. 2000;6(6):643-648
Napolitano M et al. *Haemophilia.* 2016;22(5):752-759
Peyvandi F et al. *J Thromb Haemost.* 2011;9(suppl 1):236-245.
Ragni MV et al. *Haemophilia*. 1999;5(5):313-317.
Toogeh G et al. *Am J Hematol.* 2004;77(2):198-199.

Coagulation Disorder	Platelet Count	PT	aPTT
Congenital hemophilia	Normal	Normal	**Prolonged**
Acquired hemophilia	Normal	Normal	**Prolonged**
FVII deficiency	Normal	**Prolonged**	Normal
Glanzmann's thrombasthenia	Normal	Normal	Normal
vWD	Normal (low)	Normal	Normal or **Prolonged**

Collins P et al. *BMC Res Notes*. 2010;3:161. doi: 10.1186/1756-0500-3-161.
Kessler CM. In: Kitchens CS et al, eds. *Consultative Hemostasis and Thrombosis*. 3rd ed. Phil, PA: Saunders Els; 2013:16-32.
Mumford AD et al. *Br J Haematol.* 2014;167(3):304-326.
Srivastava A et al. *Haemophilia*. 2013;19(1):e1-e47.
Rajpurkar M et al. *J Pediatr Adolesc Gynecol.* 2016;29(6):537-541.

Management of patients with bleeding disorders

-replace deficient or defective proteins

- provide adjunctive medications at time of bleeding or prior to invasive procedures

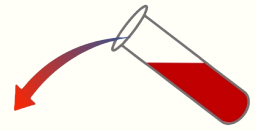
General Strategies:

1) Antifibrinolytics
2) Oral Contraceptives (HMB)

Specific Strategies

1) Blood products
    - Fresh frozen plasma
    - Cryoprecipitate
    - Platelets
- Desmopressin
- Factor replacement products
    - Plasma-derived or recombinant
- Bypassing agents

NHF
WHF



vWF levels postpartum in patients with and without vWD

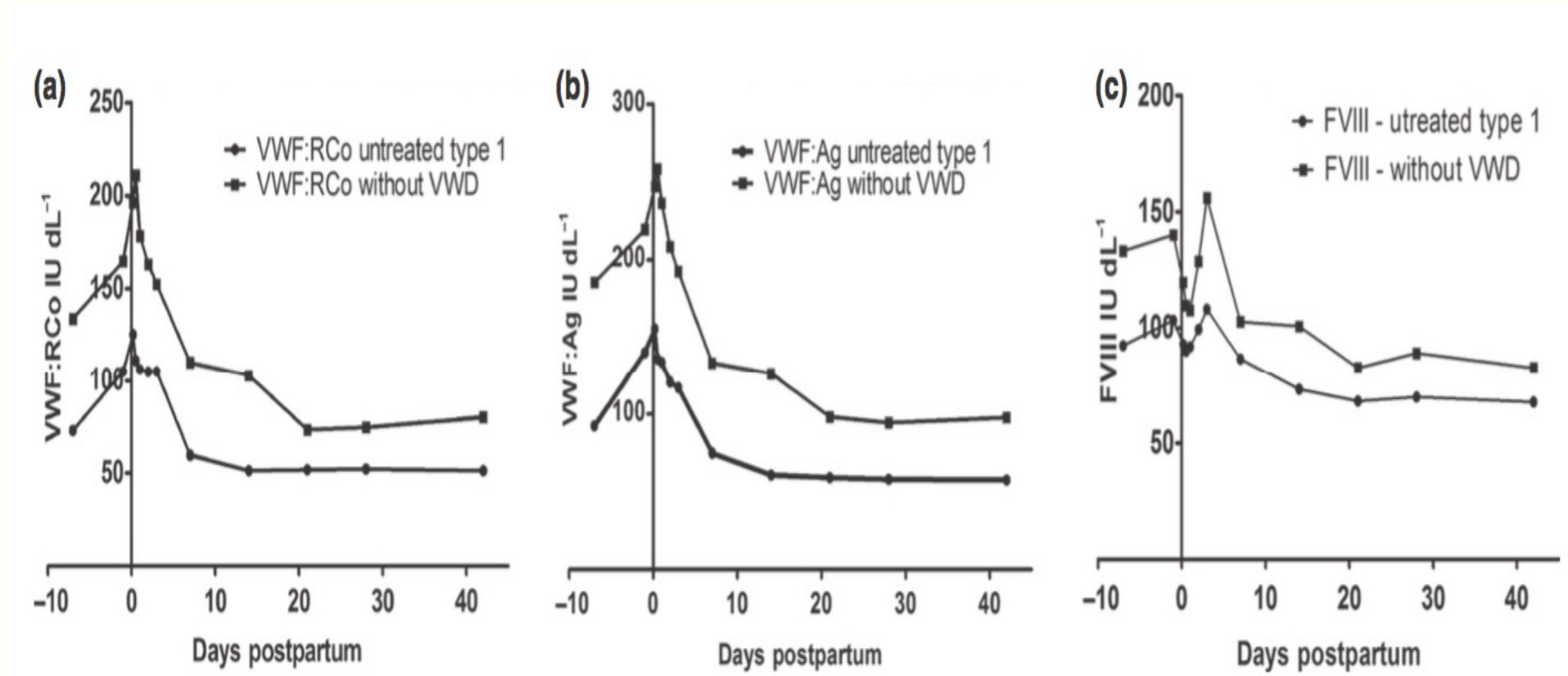


Fig. 3. VWF:RCo, VWF:Ag and FVIII levels among women with untreated type 1 VWD compared to those among women without VWD.

The vWF increase during pregnancy is from both increased production and half-life prolongation.

James AH et al. Haemophilia (2015), 21 81-87

Drury-Stewart DN et al. PLoS One 9(11): e112935, 2014

Population based study of prevalence & risk factors for severe obstetric hemorrhage (Norway)

All women giving birth from Jan1, 1999- April 30, 2004 (n= 307,415)

Risk Factor	Number (%)	Percent with severe hemorrhage	Adjusted OR (95% CI) multivariate
Emergent CD	26, 099 (8.50)	3.40	3.61 (3.28-3.95)
vWD	65 (0.02)	4.60	3.31 (1.01-10.85)
Elective CD	16, 268 (5.30)	2.20	2.47 (2.18-2.80)

Al-Zirqi I et al. BJOG 2008; 115:1265-1272

Odds of various medical conditions at time of childbirth among women with vWD (n= 4067) compared to women without vWD

Nationwide Inpatient Sample from the Healthcare Cost and Utilization Project (HCUP) of the Agency for Healthcare Research and Quality (AHRQ)
2000 to 2003 16 824 897 deliveries

Medical Condition	Number of cases	Odds ratio (95% CI)	P value
Hypertension	54	2.2 (1.1, 3.8)	**0.03**
Cardiomyopathy	9	6.8 (1.7, 27.5)	**0.01**
Anemia	551	2.1 (1.7, 2.6)	**< 0.01**
Thrombocytopenia	63	2.5 (1.4, 4.7)	**< 0.01**
Diabetes	34	1.0 (0.4, 2.5)	0.99
Obesity	31	0.6 (0.2, 1.6)	0.31
Alcohol & Substance abuse	40	0.9 (0.5, 1.7)	0.73
Smoking	220	1.9 (1.4, 2.7)	**< 0.01**

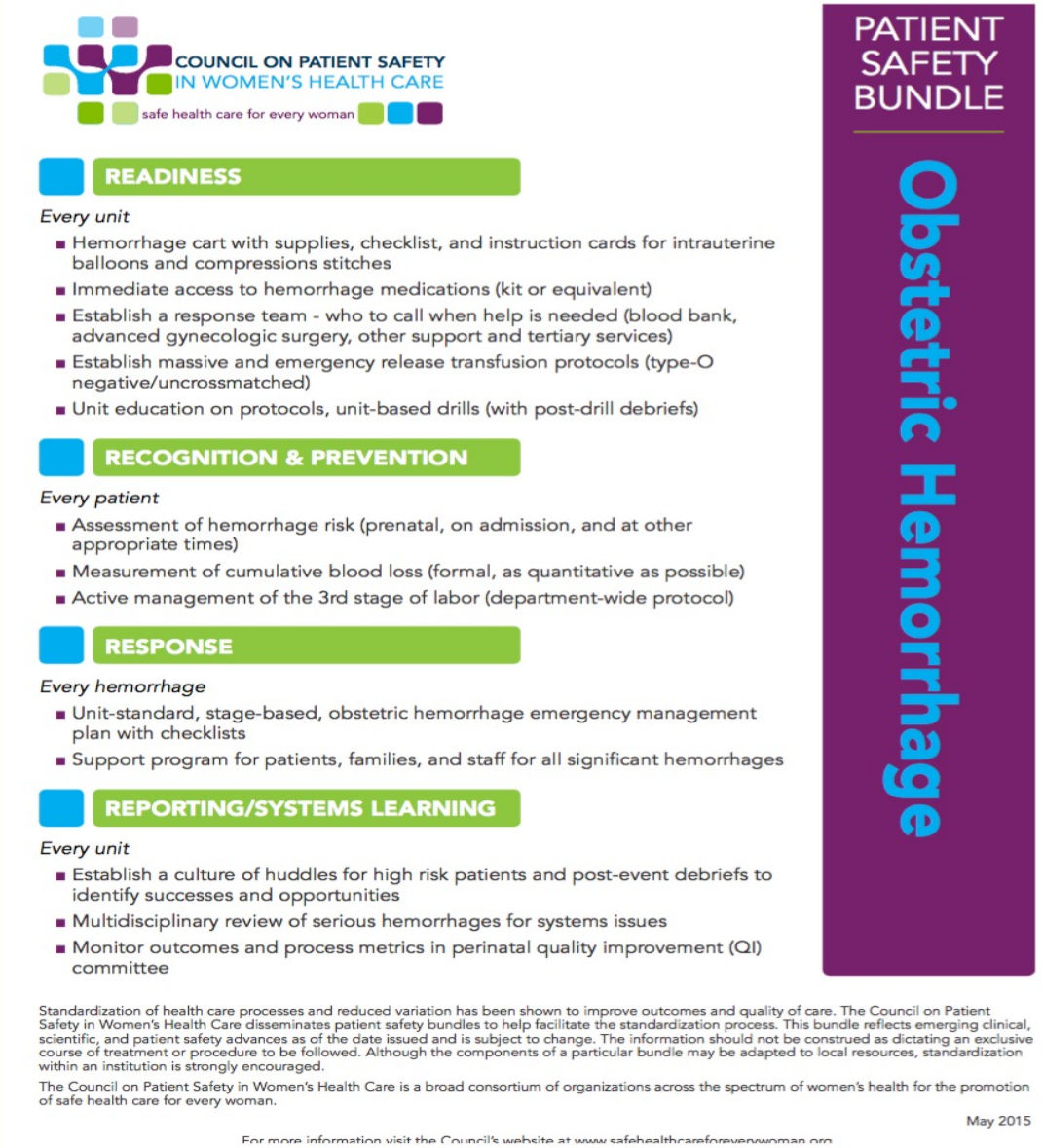
James AH, Jamison MG. Thromb Haemost 2007; 5:11765-9.

Odds of various medical conditions at time of childbirth among women with vWD (n= 4067) compared to women without vWD

Nationwide Inpatient Sample from the Healthcare Cost and Utilization Project (HCUP) of the Agency for Healthcare Research and Quality (AHRQ)
2000 to 2003 16 824 897 deliveries

Obstetric Complication	Number of cases	Odds ratio (95% CI)	P value
Preeclampsia & GHTN	327	0.9 (0.7, 1.20)	0.51
Abruption	53	1.0 (0.5, 1.8)	0.80
Antepartum bleeding	280	10.2 (7.1, 14.6)	**< 0.01**
Cesarean delivery	1158	1.2 (1.0, 1.4)	**0.03**
PPH	261	1.5 (1.1, 2.0)	**< 0.01**
Postpartum infection	54	1.0 (0.5, 1.9)	0.98
Perinatal hematoma	10	3.3 (0.8, 13.4)	0.09

James AH, Jamison MG. Thromb Haemost 2007; 5:11765-9.

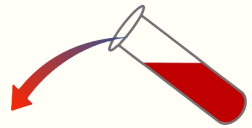


http://www.safehealthcareforeverywoman.org

Pregnancy Management in Women with vWD

- Check vWF levels (FVIII and vWF:Rco) at beginning of third trimester
- If levels are >50%:
  - Treat as normal without vWD- specific treatment
  - Preparation for PPH
- If levels are < 50%:
  - Continue to monitor
  - Plan for vWF-containing factor support
  - Caution with desmopressin due to risk of hyponatremia
  - Tranexamic acid 1gram immediately and every 6 hrs is an option

Nichols WL et al. Haemophilia 2008; 14:171-232
James AH et al. Am J Obstet Gynecol 2009; 201:12. e.1-8.



Pregnancy & Severe vWD

- Requires factor support
  - length of treatment depends on severity & mode of delivery
- Type 2B
  - Decrease in platelet count as pregnancy progresses
  - Role of platelet transfusion is controversial
  - vWF containing factor support at delivery/postpartum usually required

Biguzzi E et al, Haemophilia 2015; 21: 370

Obstetric Anesthesia Management in Women with vWD

- Recommended for any anesthesia
  - vWF:Rco activity and FVIII >50%
  - No report of bleeding complications with anesthesia at this level
- In general, no indication to repeat vWD levels at arrival in labor if normal in third trimester

Nichols WL et al. Haemophilia 2008; 14: 171, Vaughese J and Cohen AJ, Haemophilia 2007; 13:270

Postpartum management in patients with vWD

- Weekly follow up
- Check vWF levels (FVIII and vWF:Rco) weekly
- Average time of hemorrhage is 15.7 +/- 5.2 days
- Factor replacement or antifibrinolytic therapy
  - Preemptive or as needed

Roque H et al. J Matern Fetal Med 2000; 9:257
Neff AT and Sidonio Jr RF. Hematology Am Soc Hematol Educ Program. 2014 Dec 5;2014(1):536-41.

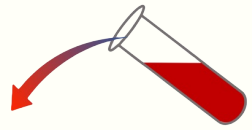
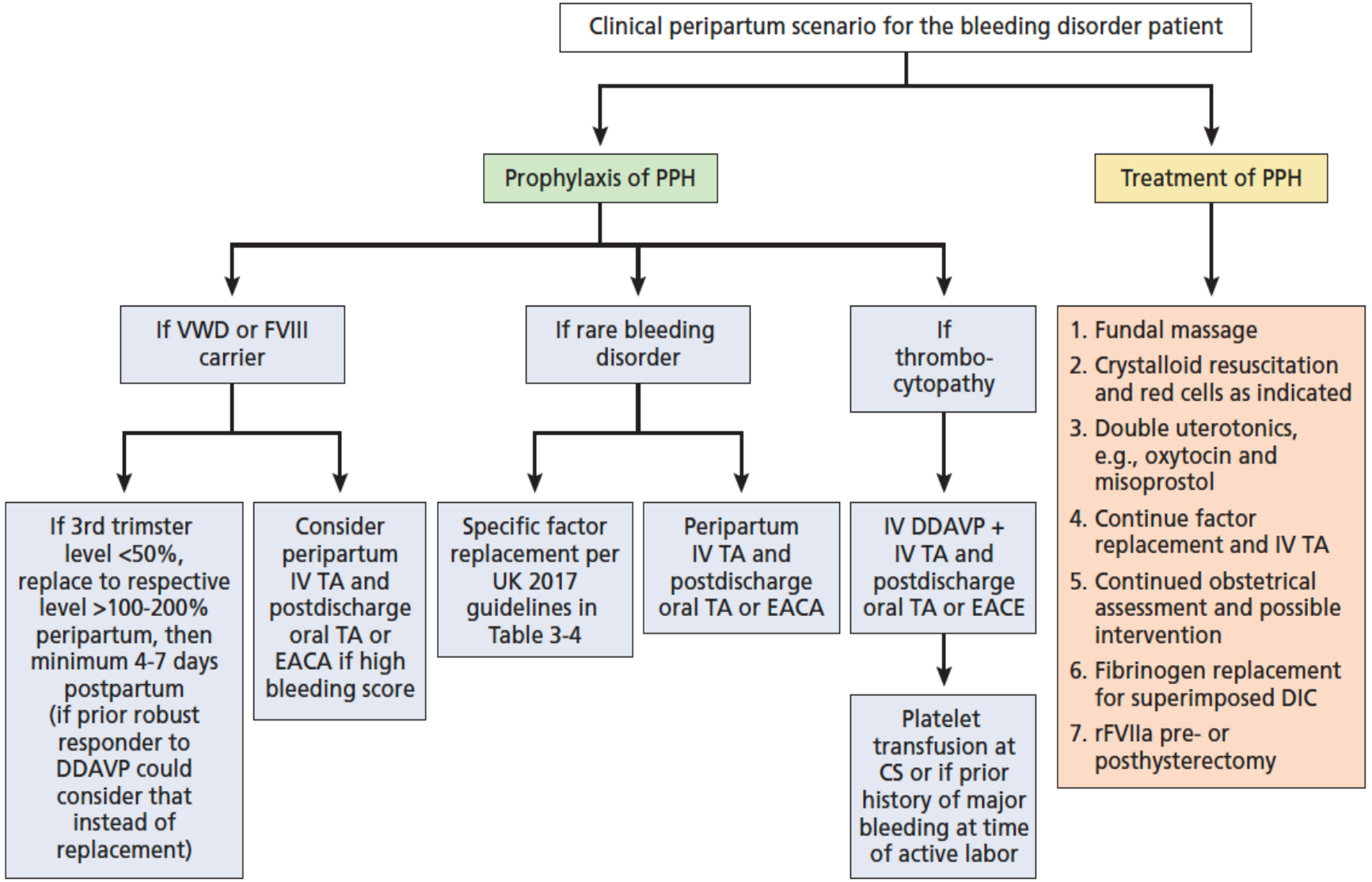


Figure 3.3. Prevention and Management of PPH in patients with bleeding disorders



Kouides PA and Paidas MJ. CHAPTER 3 Consultative hematology II: women's health issues. ASH- SAP, 7th edition. American Society of Hematology. Editor: Cuker, Adam. Pages 61-95. June 2019.

What is Postpartum Hemorrhage?

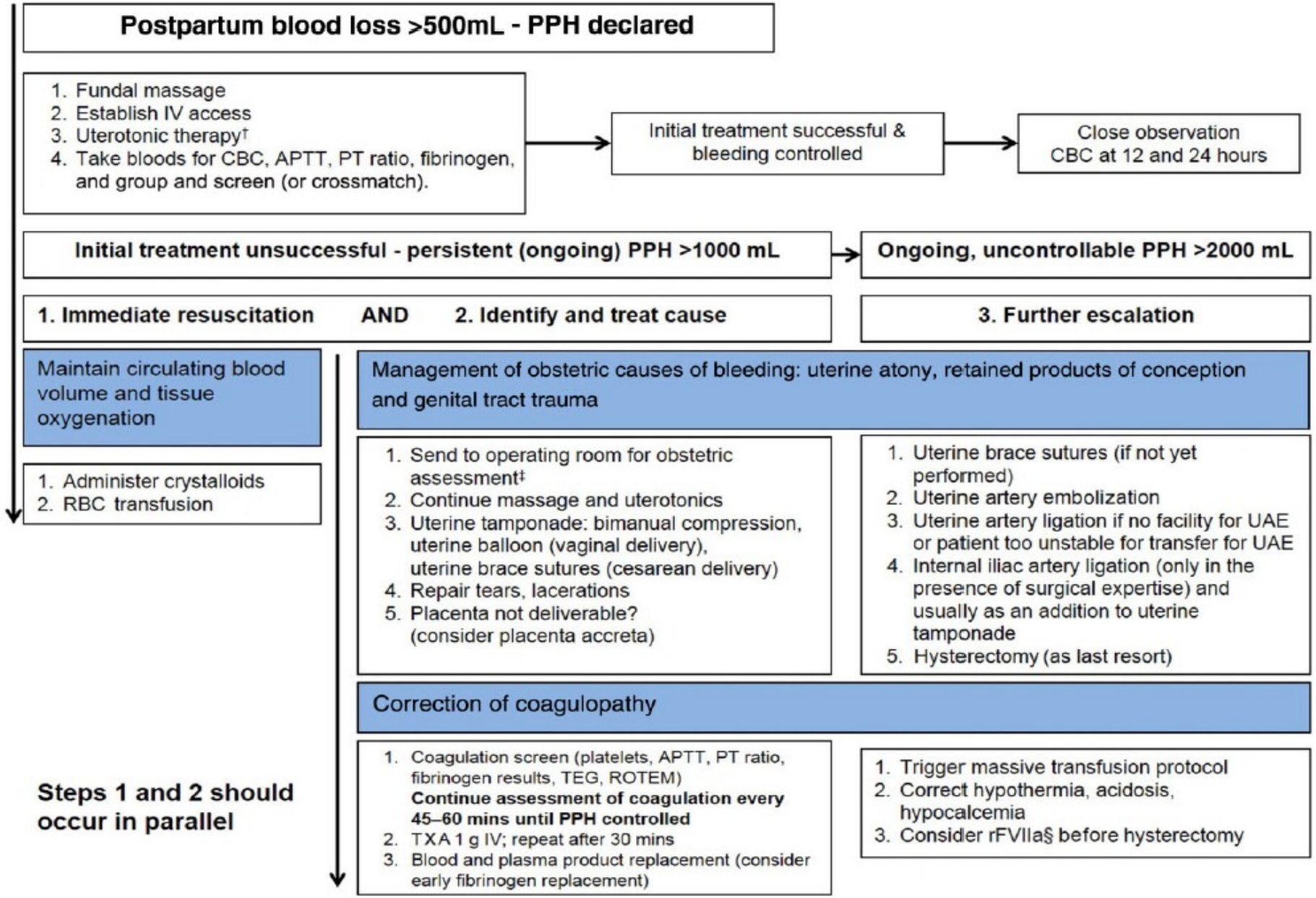
Persistent (ongoing) PPH is active bleeding

- >1000 mL within the 24 hours following birth that continues despite the use of initial measures including first-line uterotonic agents and uterine massage."

Evaluation and management of postpartum hemorrhage: consensus from an international expert panel

Rezan Abdul-Kadir,[1] Claire McLintock,[2] Anne-Sophie Ducloy,[3] Hazem El-Refaey,[4] Adrian England,[5] Augusto B. Federici,[6] Chad A. Grotegut,[7] Susan Halimeh,[8] Jay H. Herman,[9] Stefan Hofer,[10] Andra H. James,[11] Peter A. Kouides,[12] Michael J. Paidas,[13] Flora Peyvandi,[14] Rochelle Winikoff[15]

Transfusion 2014 Jul;54(7):1756-68.



Rezan Abdul-Kadir et al Transfusion 2014 Jul;54(7):1756-68.

Hemostatic Levels for invasive procedures during pregnancy and for delivery

Bleeding Disorder	Clotting Factor	Haemostatic levels (IU/dl) Suggested	Normal range (nonpregnant) (IU/dl)	Comment
vWD	vWF	50	50-175	
Carrier of hemophilia a	FVIII	50	50-150	
Carrier of hemophilia b	FIX	50	50-150	
Fibrinogen deficiency	Fibrinogen	1.0—1.5 g/L	1.5-4.0	To maintain >1.0g/L in pregnancy
Factor II deficiency	FII	20-30	50-150	
Factor V deficiency	FV	15-25	50-150	
Factor VII deficiency	FVII	10-20	50-150	
Factor X deficiency	FX	10-20	50-150	
Factor XI deficiency	FXI	20-70	70-150	
Factor XIII deficiency	FXIII	20-30	70-150	To maintain >3 IU/dL in pregnancy

Kadir RA et al. Haemophilia 2013; 19(suppl 4): 1-10.

Specific Factor Replacement in inherited bleeding disorders peripartum

Factor deficiency	Patients' factor level (normal)	Desired level	Recommendation
VWD type 1	<50%	>100%	VWF concentrate 40–60 IU/kg, then 20–40 IU/kg q 12 h, then daily 3–5 days if vaginal delivery, 5–7 days if cesarean
VWD types 2, 3	<50%	>100%	VWF concentrate 60–80 IU/kg, then 40–60 IU/kg q 12 h, then daily 3–5 days if vaginal delivery, 5–7 days if cesarean
FI (fibrinogen)	<0.5 g/L	1–1.5 g/L × 3 days	Pregnancy prophylaxis: fibrinogen concentrate 50–100 mg/kg twice a week to maintain level at >1 g/L (more during labor) × 3 days. Cryoprecipitate 15–20 mL/kg, SD-FFP 15–30 mL/kg. TXA 15–20 mg/kg IV, then 1 g po tid.
FII	<20% (50%–150%)	20%–40%	PCC 20–40 U/kg, then PCC 10–20 IU/kg q 48 h to maintain levels for at least 3 days
FV	<20% (50%–150%)	20%–40%	FFP 15–20 ml/kg, later FFP 10 ml/kg q 12 h for at least 3 days. For severe bleeding or cesarean, give platelet transfusion (FV+VIII give DDAVP, FFP).
FVII	<20% (50%–150%)	>40%	rFVlla 15–30 µg/kg q 4–6 h for at least 3–5 days
FVIII, FIX	<50% (50%–150%)	>100%	FVIII carrier: FVIII concentrate 20–40 IU/kg; FIX carrier: 40–50 IU/kg
FX	<30% (50%–150%)	>40%	PDFX concentrate 1500 U (18.8–25 U/kg), PCC 10–20 U/kg qd × 3 days, FFP
FXI	<15%–20% (70%–150%)	>30%–40%	If bleeding phenotype or prior h/o PPH-FXI concentrate 15–20 U/kg if available; FFP, TXA alone at 1 g qtg. rFVlla for inhibitors
FXIII	<30% (70%–150%)	>20%	Pd-FXIII 20–40U/kg × 1, rFXIII-A 35U/kg, cryoprecipitate, FFP

Adapted from Pavord S et al, *BJOG* 2017;124:e193–e263. It should be recognized that these represent expert opinion recommendations, and treatment duration and intensity are based on not only the factor level but historical assessment of the bleeding phenotype.

DDAVP, 1-desamino-8D-arginine vasopressin; FFP, fresh frozen plasma; PCC, prothrombin complex concentrate; PDFX, Plasma-derived FX; PdFXIII, Plasma-derived FXIIII; PPH- FXI, Post-partum hemorrhage-FXI concentrate; rFXIII-A, recombinant FXIII; SD-FFP, Solvent detergent Fresh Frozen Plasma;TXA, tranexamic acid;VWD, von Willebrand disease;VWF, von Willebrand factor.

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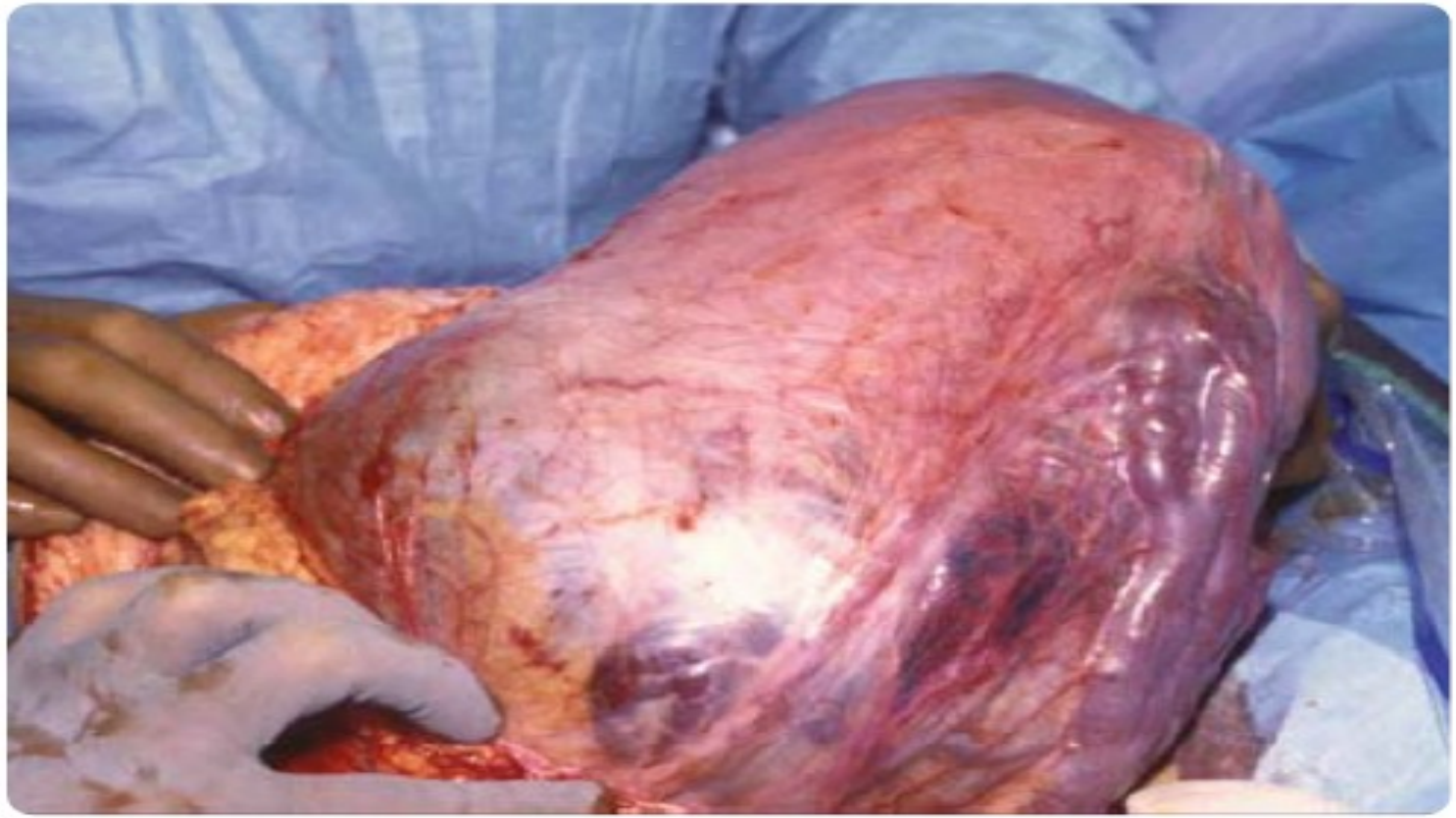
FIGURE 2

Placenta percreta with bladder invasion at cesarean delivery



Lower uterine segment is bulbous with areas of hemorrhage beneath visceral peritoneum and prominent distended vessels. Fundal and posterior hysterotomy was performed to avoid disruption of placenta before hysterectomy was completed.

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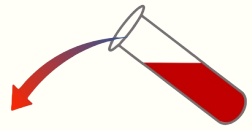
SMFM. Placenta accreta. Am J Obstet Gynecol 2010.

Thank You!



Paidas Laboratory

Arumugam R. Jayakumar, PhD

Assistant Professor

Biochemist & Neuroscientist, Laboratory Director

"We work in a highly collaborative, interdisciplinary research environment and are focused on a range of health complications across the lifespan. We focus on common & rare reproductive/pregnancy conditions."

Our expertise:

- Translational, preclinical (in vitro and animal) and clinical studies and human trials, therapeutics.
- Advanced imaging, molecular & cellular biology, and theoretical modeling.
- Our research has a strong neuroscience and immune basis, targeting brain injury, preeclampsia/fetal growth restriction, pregnancy loss and viral infection.

NEWS@TheU

Researchers develop a 'net' to prevent the coronavirus from entering cells

Dr. Michael Paidas and research professor Arumugam Jayakumar work to develop a compound that could block the SARS-CoV-2 virus from being able to enter human cells. *Photos Jorge Perez/University of Miami*

By Janette Neuwahl Tannen

11-10-2021

An obstetrician gynecologist and a biochemist at the Miller School of Medicine have devised a new therapeutic to stop COVID-19 from overpowering patients who are struggling to survive.