Hematologic Complications of Pregnancy

Robert S. Siegel, M.D.
Professor of Medicine
The George Washington University School of Medicine and Health Sciences
Director, Division of Hematology/Oncology
GW Medical Faculty Associates
DISCLOSURES

Off-Label Usage
• None

Financial Relationships with Relevant Commercial Interests
• CVS/Caremark….Consulting on their formulary

Research Support
• Janssen
• Celegene
• Bristol Myer Squibb
• Medivation
• Incyte
Discussion

- Anemia
- Thrombocytopenia and other bleeding disorders
- Venous thromboembolism
ANEMIA
Anemia

- Common complication
- Plasma volume increases 40-50%
- Red cell mass increases 20-30%
- At term:
  - Hgb at 10-11 gm/dl
  - HTC at 30-34%
Iron Requirements

- Iron Requirement = 680 – 1000 mg
- Fe deficiency was common in past
- Standard Therapy:
  - Elemental iron 60 – 120 mg/d
  - Parenteral iron therapy rarely needed
Folate Requirements

- B-12 deficiency is rare
- Folate needs 5-10x normal
- Daily prenatal vits up to 1 mg/day
  - avoids maternal megaloblastosis
  - avoids fetal neural tube defects
Folate Requirements

Higher folate doses needed:

- hemoglobinopathy
- patients on anti-convulsants
- multiple gestations
Sickle Cell Disease

Sickle cell mothers suffer increased

- crises
- stillbirth/spontaneous abortions
- infections of all types, esp UTIs
- risk of hypertension
- pulmonary infection
  - Mycoplasma, Haemophilus, Salmonella
Sickle Cell Disease

Infants of sickle cell mothers

- Are often small for gestational age
- Premature delivery is more common
Sickle Cell Disease

Transfusions / exchange transfusions
- not routinely used throughout pregnancy
- may be useful in final weeks
- Individualized therapy

Early & aggressive therapy for:
- Infection
- pain crisis
Immune Hemolytic Anemias

Medications:

• immune mediated hemolysis

• can trigger G6PD hemolysis

• similar evaluation to non-pregnant states
Thrombocytopenia and Other Bleeding Disorders
Thrombocytopenias of Pregnancy

- Gestational Thrombocytopenia
- Immune Thrombocytopenic Purpura
- Human Immunodeficiency Virus
- Preeclampsia/HELLP Syndrome
- SLE/ Various Vasculitides
- TTP/HUS
Gestational Thrombocytopenia

- May be a dilutional issue vs mild ITP
- Platelet count is 70-150,000/dl
- Mothers can be delivered normally
- No assoc with fetal thrombocytopenia
- Occurs in 5-7% of all pregnancies
- Patients should receive routine OB care
Immune Thrombocytopenia

- Occurs in .1 to 1 in 1000 women
- A diagnosis of exclusion
- Platelet count is 20-30,000/dl
- Lower than in gestational thrombocytopenia
- Diagnosis is suggested when a mother with pre-existing ITP develops profound thrombocytopenia
Immune Thrombocytopenia

- Concern for fetal thrombocytopenia
  - among ITP mothers, 10% have plts < 50,000
  - 4% have platelet counts < 20,000
  - Fortunately a rare problem

- Neonatal thrombocytopenia may worsen before improving

- Scalp vein sampling & PUBS are problematic
Immune Thrombocytopenia

- Prednisone/IVIg used for bleeding or platelets less than 20,000/dl
- C-section is often utilized....but improvement in fetal outcome remains unproven
- Platelets rise after delivery
- Splenectomy performed in 2nd trimester
Immune Thrombocytopenia

- Most pregnancies were uneventful
- Bleeding was uncommon and not correlated with platelet count
- No assoc between maternal & infant’s platelet Ct
- 32% required ITP therapy
- Platelet count in 2nd child was predicted by platelet count in first
- Intracranial bleed/fetal loss in ITP mothers = 1-2%
- Retrospective Study by Webert, Blood 2003 102(13);4306-11
Treatment of ITP -

Management of ITP during pregnancy

• **Recommendations:**
  • Pregnant patients requiring treatment receive corticosteroids or IVIg (1C)

Treatment of ITP after labor and delivery

• **Suggestion:**
  • For pregnant women with ITP, the mode of delivery should be based on obstetric indications (2C)

Blood 2011, 117;16:4190-4207
Thrombocytopenia: Preeclampsia

- Affects 6% of all pregnancies after 20 weeks
- Prima-gravidas at increased risk
- BP > 140/90, proteinuria > 0.3 gms/24 hrs
- Platelets low in 15-50%
- Platelet count < 50,000 seen in < 5%
- Treatment - delivery ASAP
Prevention of Pregnancy Complications in Patients at high risk for preeclampsia

- Age < 20 or > 30 yo
- High body mass index
- Hypertension
- History of insulin resistance

Recommendations:

- Low dose ASA throughout pregnancy

Treatment Guidelines, Bates S, et al, Chest 2012; 141(2)(suppl)e691s-736s
Thrombocytopenia: HELLP Syndrome

- Hemolysis (microangiopathic)
- Elevated (Bili>1.2, SGOT>70)
- Liver enzymes (LDH >600)
- Low Platelets (<100,000/dl)
Thrombocytopenia: HELLP Syndrome

- 12% of preeclamptic pts have HELLP
- Typical platelet count < 100,000
- Pts have nausea, malaise, abd pain
- HELLP pts should be delivered ASAP
- HELLP pts may maintain low platelet count for days after delivery
- Plasmapheresis for refractory patients
Thrombotic Thrombocytopenic Purpura

- Seen with pregnancy or post partum
- Thrombocytopenia, microangiopathic hemolytic anemia, impaired renal function, fever, neurologic abnormalities
Thrombotic Thrombocytopenic Purpura

Widespread endothelial damage seen

Therapy:
- Daily plasmapheresis
- Delivery ASAP
- Splenectomy for resistant cases
Thrombocytopenia: Neonatal Alloimmune Thrombocytopenia (NAIT)

- Fetal inheritance of platelet isoantigens not present in the mother

- Fetal thrombocytopenia – when isoantibodies cross placenta

- Most common Ag: HPA-1a & HPA-5b
Thrombocytopenia: (NAIT)

Women at highest risk:
- related to other women with NAIT
- prior pregnancy complicated by NAIT
- lacking HPA-1a and HPA-5b Ag

Dx: a well infant with very low platelet count
- Later pregnancies more affected than first
Thrombocytopenia: (NAIT)

- Most severe complication is intracranial bleeding
- 10-50% occurs in utero
- Tx: washed maternal platelets or from blood bank
- Antenatal Tx: early C-section, IVIg, prednisone, intrauterine platelets
Bleeding Disorders

Von Willebrand Disease:

- Types 1 & 2A patients have safe levels of von Willebrand factor by delivery

- Type 2B patients may have worsening thrombocytopenia during pregnancy because of platelet aggregation

- Type 3 disease is least common, but most severe... VWF levels do not rise through pregnancy... bleeding risk is unchanged
Bleeding Disorders II

Von Willebrand Disease:
Among patients with Types 2B, 2M, 2N, & 3

- Do NOT use DDAVP
- Use Factor replacement until VWF and Ristocetin cofactor levels reach 50 IU/ml
Bleeding Disorders III

Other Bleeding Disorders:

- Bleeding risk for Hemophilia A and B carriers
  - In Factor VIII deficiency..factor levels < 30 IU/dl
    - use DDAVP or recombinant Factor VIII for 3-4 days
    - rarely required by delivery
  - In Factor IX deficiency..factor levels < 50 IU/dl
    - use recombinant factor IX for 3-4 days
    - Factor IX levels typically do not rise during pregnancy
Factor XI Deficiency

- Mostly seen in Ashkenazi Jewish population
- Heterozygous frequency is 1 in 12
- May bleed heavily during C-section
- Treatment is FFP and possibly DDAVP
Venous Thromboembolism
Essential Thrombocytosis, JAK2 & Pregnancy

63 pregnancies studied in 36 ET women
- 61% live births, 39% fetal loss
- 10/20 patients studies had JAK2 mutation,
- Predictors of outcome

Results:
- No correlation with maternal age, JAK2, WBC, HGB, platelet count
- Only factors that affected results: use of ASA
  - 75% of patients who took ASA had successful delivery

Gangat et al, Eur J Hem 2009, 32(S50-S53)
The Balancing Act

Based on packets of proteins in blood in:

• Platelets
• Vessel walls
• Tissues (brain, heart)
Thrombosis & Pregnancy

Pregnancy & 6 wks postpartum
- 5-6 fold risk of DVT
- 1/1000 pregnancies

Most DVT (90%) involve left iliac vein
- From L iliac vein compression by R iliac artery and ovarian artery
- Iliac VTE more likely to embolize
Pathogenesis of VTE in Pregnancy

Virchow’s Triad
Hypercoagulability, Stasis, Endothelial damage

- Hypercoagulability
  - Increased coagulation factors
  - Acquired resistance to APC, Protein S
  - Impaired Fibrinolysis
    - Increased plasminogen activator inhibitor 1&2
  - High Factor VIII levels
Pathogenesis of VTE in Pregnancy

Virchow’s Triad

Stasis

- Diminished venous flow to lower extremities
  - 50% reduction by end of 2nd trimester
  - Nadir at 36 weeks
  - Full recovery 6 weeks post delivery

Endothelial damage

- Endothelial damage to pelvic vessels
  During vaginal delivery or C-section
Normal Pregnancy & postpartum period as an *Acquired Hypercoagulable State*

- ↑ concentration of coagulation factors II, V, VII, VIII, IX, X, XII, fibrinogen and vWF;

- ↓ levels of free protein S, and ↑ acquired resistance to APC

- ↑ markers of coagulation: D-dimer and Prothrombin fragment F1+2

- ↓ venous flow in the extremities
Thrombophilia and VTE in Pregnancy

- Inherited thrombophilia is present in 15% of Western populations
- Thrombophilia seen in 50% of pregnant VTE pts
- Level of risk dependent on:
  - Underlying thrombophilic effects
  - History of thrombotic events
  - Additional risk factors
Pregnancy-Associated Thrombosis

- PE account for 15% of maternal deaths in developed countries

- In women of reproductive age, > 50% of VTE related to pregnancy

- Incidence rate of VTE = 3.24/1000 women-years (Glasgow retrospective study of > 72,000 deliveries)

- 84% of deep vein thrombosis = left leg

- Highest VTE Risk in 3rd trimester & in first 6 wks post-partum
Pregnancy-Associated Thrombosis

MEGA Study * (population-based; first VTE; subset of 285 pregnant women vs. 857 controls):

- 4 to 5 x increased risk of VTE during pregnancy
- 8.8x increased risk in 3rd trimester
- 52 x increased if patient V Leiden carrier
- 31 x increased if patient II G20210A carrier
- 84 x increased in the first 6 weeks post partum

During pregnancy, levels of the anticoagulants antithrombin (AT) and protein C (PC) are unchanged, but free protein S levels decrease markedly. These changes are interpreted as being due to hormonal changes, especially increased estrogen levels correlated with pregnancy progression. Are these changes pathologic?

Sarig et al 2008
The same results were obtained with PT 1+2 levels during pregnancies.
<table>
<thead>
<tr>
<th>Inherited</th>
<th>Acquired</th>
</tr>
</thead>
<tbody>
<tr>
<td>• Protein S and C Deficiency</td>
<td>• Antiphospholipid Ab</td>
</tr>
<tr>
<td>• APC Resistance</td>
<td>• Ovarian Hyperstimulation</td>
</tr>
<tr>
<td>• AntiThrombin Deficiency</td>
<td>• Obesity</td>
</tr>
<tr>
<td>• Factor V Leiden</td>
<td>• Immobilization</td>
</tr>
<tr>
<td>• Prothrombin G20210A</td>
<td>• Age &gt; 35</td>
</tr>
</tbody>
</table>
### Typical prevalence rates for congenital thrombophilia in European populations

<table>
<thead>
<tr>
<th>Thrombophilic defect</th>
<th>Prevalence (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Antithrombin deficiency</td>
<td>0.25 – 0.55</td>
</tr>
<tr>
<td>Protein C deficiency</td>
<td>0.20 – 0.33</td>
</tr>
<tr>
<td>Factor V Leiden heterozygotes</td>
<td>2 - 7</td>
</tr>
<tr>
<td>Prothrombin G20210A heterozygotes</td>
<td>2</td>
</tr>
<tr>
<td>MTHFR C677T homozygotes</td>
<td>10</td>
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</table>
# VTE Risk in Thrombophilic Patients

<table>
<thead>
<tr>
<th>Thrombophilia*</th>
<th>Odds ratio for VTE**</th>
</tr>
</thead>
<tbody>
<tr>
<td>AT III Deficiency (quant)</td>
<td>282</td>
</tr>
<tr>
<td>AT III Deficiency (qual)</td>
<td>28</td>
</tr>
<tr>
<td>Factor V Leiden (heterozygous)</td>
<td>4.5</td>
</tr>
<tr>
<td>Prothrombin gene mutation</td>
<td>4.4</td>
</tr>
<tr>
<td>MTHFR C677T (homozygous)</td>
<td>No change (pregnancy only)</td>
</tr>
</tbody>
</table>

**Gerhardt A et al. NEJM 2000;342:374-380
Acquired conditions which cause thrombophilia in pregnant women

- Thrombophilic defect
  - Ovarian hyperstimulation syndrome
  - Antiphospholipid antibody syndrome
- Obesity
- Immobilization
- Age > 35
- C-section
- Hyperemesis
Assisted Reproductive Tx & DVT Risk

Ovarian Hyperstimulation Syndrome (OHSS)
- Increased Risk of DVT, esp after tx cycle that results in pregnancy
- Of 54 cases reviewed by Stewart et al,
  - 6 had a history of prior thrombosis
  - 2 had a strong family history of thrombosis.
- Prophylaxis indicated for high risk women
Assisted Reproductive Tx & DVT Risk

- Estradiol levels > 10x normal
- Polycystic ovaries increase risk
- Thrombi occur at 7 to 10 weeks
- Mechanism(s) for thrombosis is unclear
- Underlying thrombophilia generally has not been detected in these women
- Prophylactic anticoagulation is not recommended

1. Treatment Guidelines, Bates S, et al, Chest 2012; 141(2)(suppl)e691s-736s
Assisted Reproductive Tx & DVT Risk

Literature Review of 54 cases

- 75% had DVT
  - internal jugular or neck veins
  - Upper extremities

- 25% suffered arterial clots, often intracerebral

Managing patients at risk for VTE

- Risk of VTE must be established
- No evidence to support universal screening for inherited thrombophilia in pregnant patients
- Use of thromboprophylaxis is often a judgment decision
Risk of a First VTE

Multiplicative effect of OCs and FVL

Incidence per 10,000 women-years of OC use

- OC- FVL-
- OC+ FVL-
- OC- FVL+
- OC+ FVL+

Safety of withholding heparin in pregnant women with a history of VTE

Previous VTE is a risk factor for recurrence

- 125 pregnant women with prior VTE were prospectively followed
- Antepartum heparin was held
- Labs for thrombophilia sent on 95 women
- Warfarin or other anticoagulant given for 6 weeks post partum

Brill-Edwards et al, NEJM 2000; 343(20) 1439-44.
Safety of withholding heparin in pregnant women with a history of VTE

Results:
- 3/125 women had recurrent VTE
- No VTE in 44 women with
  - No evidence of thrombophilia
  - Prior VTE associated with temporary risk factor
- In 51 patients with:
  - Positive lab evaluation for thrombophilia
  - And/or idiopathic prior VTE
  - 5.9% had VTE

**Gerhardt A et al. NEJM 2000;342:374-380
Women on Vit K antagonists contemplating pregnancy

- Frequent checks for pregnancy
- Change to LMWH when pregnancy is achieved
- Limit use of fondaparinux or parenteral direct thrombin inhibitors to pts with HIT who can not receive danaparoid
- Avoid oral direct thrombin inhibitors and anti-Xa inhibitors

Treatment Guidelines, Bates S, et al, Chest 2012; 141(2)(suppl)e691s-736s
Use of anticoagulants in nursing women

During Breastfeeding, the following can continue:

- Warfarin
- UFH
- LMWH
- danaparoid
- r-hirudin
- low dose aspirin

- Avoid fondaparinux, oral thrombin and anti Xa inhibitors

Treatment Guidelines, Bates S, et al, Chest 2012; 141(2)(suppl)e691s-736s
VTE Prophylaxis after C-Section

- Pre-op risk DVT risk assessment to determine need for prophylaxis
  - In absence of VTE risk factors, use only early mobilization
- For women at increased risk because of 1 major risk factor or 2 minor risk factors:
  - Prophylactic LMWH or UFH or compression stockings
- For women with > 2 risk factors & at high risk for VTE:
  - Prophylactic LMWH + compression stockings and/or INT pneumatic compression
  - High risk pts should continue prophylaxis for 6 wks post discharge

Treatment Guidelines, Bates S, et al, Chest 2012; 141(2)(suppl)e691s-736s
VTE Prophylaxis in Pregnancy: Single past VTE with temporary risk

Antenatal: clinical surveillance, no therapy

Postpartum: Anticoagulant tx for 6 weeks

- Enoxaparin 40 mg qd
- Dalteparin 5000 IU qd
- Warfarin (INR 2-3)

Treatment Guidelines, Bates S, et al, Chest 2012; 141(2)(suppl)e691s-736s
Single past idiopathic VTE associated with higher risk thrombophilia, No long term anticoagulants

Long term conditions
- Anti thrombin deficiency
- Antiphospholipid antibody
- Prothrombin gene mutation
- Factor V Leiden
- Homozygosity for these conditions

Antenatal
- Prophylactic or INT dose LMWH

Postpartum:
- Therapeutic anticoagulation x 6 weeks

Treatment Guidelines, Bates S, et al, Chest 2012; 141(2)(suppl)e691s-736s
VTE Prophylaxis in Pregnancy: ≥ 2 VTE, no thrombophilia, no anti-coag tx

Antenatal: LMWH
Prophylactic or INT or ADJ dose LMWH

Postpartum---Treat for 6 weeks
Prophylactic or INT or ADJ dose LMWH
OR
Warfarin with INR 2-3

Treatment Guidelines, Bates S, et al, Chest 2012; 141(2)(suppl)e691s-736s
VTE Prophylaxis in Pregnancy: Previous VTE episodes, patient receiving long term anticoagulation

- Stop Oral anticoagulants, Make change to:
  - ADJ dose LMWH
  - 75% of therapeutic dose of LMWH

- Resume long term anticoagulation post partum

Treatment Guidelines, Bates S, et al, Chest 2012; 141(2)(suppl)e691s-736s
Acute VTE Diagnosed in Pregnancy

Antenatal
- ADJ dose LMWH
- S.Q. Therapy should continue through pregnancy
- Hold for 12 -24 hours before delivery

Postpartum: continue for at least 6 weeks after delivery for total duration of therapy at least 3 months

Choices
- LMWH
- Warfarin (INR 2-3)

Treatment Guidelines, Bates S, et al, Chest 2012; 141(2)(suppl)e691s-736s
Deep Venous Thrombosis: Making the Diagnosis

- Compression ultrasonography:
  - Difficult in calf and iliac vein DVT
- MRI is useful for iliac vein DVT.....
  - CT causes radiation exposure to fetus
- Negative D-Dimers are helpful
- Limited venography is acceptable
- For suspected PE, CT or Ventilation/perfusion scan
- Making the correct diagnosis is critical
Thrombophilia and Pregnancy Complications and Loss

- A woman should be screened for Antiphospholipid Antibodies when she has:

  recurrent pregnancy loss (≥3) before 10 weeks

Treatment Guidelines, Bates S, et al, Chest 2012; 141(2)(suppl)e691s-736s
Anti-phospholipid Antibodies (APLA)

- Occur in association with:
  - systemic lupus
  - drugs
  - without explanation in an otherwise healthy woman

- APLA is associated with increased risk of thrombosis and pregnancy loss
Prevention of Pregnancy Complications in Women with Thrombophilia

Patients with APLAs and:
• recurrent pregnancy loss (>3)

Recommendations:
• Prophylactic or INT dose UFH or LMWH +
• Aspirin 75 to 100 mg qd

Treatment Guidelines, Bates S, et al, Chest 2012; 141(2)(suppl)e691s-736s
### Gestational Outcome in 50 Women with Thrombophilia and Recurrent Fetal Loss

<table>
<thead>
<tr>
<th>Antithrombotic Treatment</th>
<th>Gestations</th>
<th>Live Born</th>
<th>%</th>
<th>P</th>
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<tbody>
<tr>
<td>None</td>
<td>193</td>
<td>38</td>
<td>20</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>Enoxaparin</td>
<td>61</td>
<td>46</td>
<td>75</td>
<td></td>
</tr>
</tbody>
</table>

Brenner (*Thromb Haemost* 2000)
ASA + Heparin alone in women with Recurrent Miscarriage (ALIFE)

364 pts with a hx of unexplained recurrent miscarriage (>2)...all were < 6 weeks pregnant

Patients were enrolled into 3 arms

- ASA 80 mg qd + open label LMWH
- ASA 80 mg alone
- Placebo

Primary measure: measure was live births.

Kaandorp et al: NEJM 2010;362: 1586-1596
ASA + Heparin alone in women with Recurrent Miscarriage (ALIFE)

Proportions that gave live birth by group

- ASA..... 50.8%
- ASA + LMWH .......54.5%
- Placebo.....57%

Even patients with thrombophilia didn’t benefit
- Subgoups were small

Conclusion: Neither ASA .....nor ASA + LMWH improved the live birth rate

Kaandorp et al: NEJM 2010;362: 1586-1596
The Scottish Pregnancy Intervention Study (SPIN)

294 participants, presenting at <7 weeks gestation, with a history of 2 consecutive previous pregnancy losses at or before 24 weeks gestation

Patients were excluded if they had APLA, LAC, ACA, hx DVT or hx of arterial thrombosis

Randomized to

- Enoxaparin 40mg sq (start at 6 wks)+ 75mg ASA qd
- Surveillance only

Clark P et al, Blood 2010; 115:4162-4167
The Scottish Pregnancy Intervention Study (SPIN)

RESULTS

- 147 participants randomized to pharmacological intervention, 32 (22%) pregnancy losses occurred
- 147 participants with surveillance only:
  - 29 losses (20%)

Conclusion: No evidence to support pharmacologic intervention on the basis of miscarriages alone.

Clark P et al, Blood 2010; 115:4162-4167
Many investigators don’t treat until 3 miscarriages. More data is needed in this group

Anticoagulation was not started until 6 weeks after conception

Many assisted-conception units prescribe LMWH immediately after embryo transfer

So...with 1 or 2 miscarriages and no dx of APLA, pharmacologic intervention is not recommended

Ian Greer NEJM editorial 2010; 362:1630-1631