Peripartum Management of Von Willebrand Disease

Barbara A. Konkle, M.D.
Director, Clinical and Translational Research
Director, Hemostasis, Platelet Immunology and Genomics Laboratory
Bloodworks Northwest
Professor of Medicine/Hematology
University of Washington
Seattle, WA
Disclosures

• Research Support
  – Baxalta, Octapharma

• Consultancy
  – Baxalta, CSL Behring
Presentation Outline

• VWF changes in pregnancy
• Bleeding risks in pregnancy, delivery and postpartum
• Treatment approaches
Patient Presentation

• Ms. Smith, a 23 year old female, has Type 1 VWD (VWF:Ag 29%, VWF:Act 28%, FVIII 40%):
  – She is 12 weeks pregnant with her first pregnancy
  – She has a history of menorrhagia, bleeding after dental extraction and easy bruising
  – She asks about bleeding during pregnancy and management of delivery

• How would your advice differ is she had
  – Type 3 VWD?
  – Type 2B VWD?
VWF Synthesis
# VWD Classification

<table>
<thead>
<tr>
<th>Type</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>Partial quantitative deficiency of VWF</td>
</tr>
<tr>
<td>2</td>
<td>Qualitative Defects in VWD</td>
</tr>
<tr>
<td>2A</td>
<td>Abnormal VWF multimer formation or increased proteolysis</td>
</tr>
<tr>
<td>2B</td>
<td>Increased affinity for platelet GpIb</td>
</tr>
<tr>
<td>2M</td>
<td>Decreased VWF-dependent platelet adhesion without HMWM loss</td>
</tr>
<tr>
<td>2N</td>
<td>Markedly decreased binding affinity for FVIII</td>
</tr>
<tr>
<td>3</td>
<td>Virtually complete deficiency of VWF</td>
</tr>
</tbody>
</table>

Sadler et al J Thromb Haemost 2006;4:2103-2114; Figure from NHLBI VWD Guidelines 2007
VWF in Normal Pregnancy

N=46 normal pregnancies

Drury-Stewart D, et al, PLOS One 2014
The VWF Increase in Pregnancy is from both increased production and half-life prolongation.

<table>
<thead>
<tr>
<th></th>
<th>Baseline</th>
<th>3rd Trimester</th>
<th>Fold Increase</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Expected vs. Observed VWF</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Calculated VWF production (U/hr)</td>
<td>1202</td>
<td>2194</td>
<td>1.8</td>
</tr>
<tr>
<td>Observed VWF concentration (U/dL)</td>
<td>80</td>
<td>191</td>
<td>2.4</td>
</tr>
<tr>
<td>Expected VWF concentration (U/dL)</td>
<td></td>
<td>101</td>
<td>1.3</td>
</tr>
<tr>
<td><strong>VWF(_{t/2}) which would account for observed VWF excess</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>VWF:Ag(_{t/2}) (hours)</td>
<td>12*</td>
<td>24</td>
<td>2.0</td>
</tr>
</tbody>
</table>

***ref

Drury-Stewart D, et al, PLOS One 2014
Type 1 VWD and Pregnancy

• VWF and FVIII levels increase during pregnancy
  – Wide variation in values
• In most women with Type 1 VWD values normalize with pregnancy and fall post-partum although prospective longitudinal data limited.
• However, by history many women with Type 1 VWD report bleeding symptoms with childbirth.

VWF and FVIII levels in Pregnancy: Cross-sectional Analysis

### Prospective Study In Type 1 VWD

<table>
<thead>
<tr>
<th></th>
<th>n</th>
<th>VWF:Ag (%)</th>
<th>VWF:RCo (%)</th>
<th>FVIII (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Baseline</strong></td>
<td>11</td>
<td>41.1 (7.1)</td>
<td>34.4 (8.4)</td>
<td>76.4 (70.8)</td>
</tr>
<tr>
<td><strong>Labor</strong></td>
<td>11</td>
<td>136.4 (50.8)</td>
<td>128.9 (47.8)</td>
<td>134.2 (42.7)</td>
</tr>
<tr>
<td><strong>6 weeks PP</strong></td>
<td>10</td>
<td>57.8 (22.8)</td>
<td>52.1 (25.4)</td>
<td>80.9 (32.2)</td>
</tr>
<tr>
<td><strong>Infant cord blood</strong></td>
<td>9</td>
<td>97.9 (35.8)</td>
<td>96.2 (34.8)</td>
<td>67.7 (22.6)</td>
</tr>
</tbody>
</table>

Sood et al, 2014
Pregnancy in VWD: VWF Ag Levels

Sood et al, manuscript submitted
Predictors of EBL/Hgb drop

• 2 women with PPH
  – One with uterine atony (highest VWF values)
  – One woman treated at home with Stimate 3 days PP

• Predictors of increased EBL
  – C-section (r=0.76; p=0.02)
  – Manual placental delivery (r=0.76, p=0.04)

• Predictors of hemoglobin drop 36 wks gestation to 6 wks postpartum
  – Episiotomy (r=0.75, p=0.03)
  – Degree of tear (r=0.99, p=0.02)

Sood et al, 2016
### Hemorrhagic Complication of Pregnancy in VWD

U.S Nationwide Inpatient Sample, 2000-2003, 16,824,897 deliveries\(^1\)

<table>
<thead>
<tr>
<th>Complication</th>
<th>With VWD (n=4067) c/w Unaffected women</th>
<th>Odds Ratio (95% CI), (p) value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Antepartum Bleeding</td>
<td></td>
<td>10.2 (7.1, 14.6), &lt;0.01</td>
</tr>
<tr>
<td>Postpartum Hemorrhage (PPH)</td>
<td></td>
<td>1.5 (1.1, 2.0), &lt;0.01</td>
</tr>
<tr>
<td>Perineal Hematoma</td>
<td></td>
<td>3.3 (0.8, 13.4), 0.09</td>
</tr>
</tbody>
</table>


<table>
<thead>
<tr>
<th>Risk Factors for PPH in Women with VWD* (n=666)</th>
<th>With PPH N=28 (%)</th>
<th>W/O PPH N=478</th>
<th>(p) value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Anemia</td>
<td>8 (27.6)</td>
<td>78 (14.2)</td>
<td>0.05</td>
</tr>
<tr>
<td>Caesarean section</td>
<td>7 (24.1)</td>
<td>201 (36.5)</td>
<td>0.23</td>
</tr>
<tr>
<td>Age (mean, +/- SD)</td>
<td>25.4 +/- 6.2</td>
<td>27.8 +/- 5.9</td>
<td>0.03</td>
</tr>
</tbody>
</table>

*Prevalence of PPH 5.5%

\(^1\)James AH and Jamison MG. J Thromb Haemost. 2007;5:1165,

VWD: Postpartum Focus

Table 1. Characteristics of pregnancies in women with and without von Willebrand disease (VWD).

<table>
<thead>
<tr>
<th></th>
<th>With VWD (n = 35)</th>
<th>Without VWD (n = 40)</th>
<th>Significance</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mean age</td>
<td>28.8</td>
<td>30.6</td>
<td>NS</td>
</tr>
<tr>
<td>Race/ethnicity</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>White</td>
<td>28 (80%)</td>
<td>29 (73%)</td>
<td>NS</td>
</tr>
<tr>
<td>African American</td>
<td>6 (17%)</td>
<td>7 (17%)</td>
<td></td>
</tr>
<tr>
<td>Hispanic</td>
<td>1 (3%)</td>
<td>1 (3%)</td>
<td></td>
</tr>
<tr>
<td>Asian</td>
<td>0</td>
<td>3 (7%)</td>
<td></td>
</tr>
<tr>
<td>Parity</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Nulliparous</td>
<td>15 (43%)</td>
<td>9 (23%)</td>
<td>NS</td>
</tr>
<tr>
<td>Multiparous</td>
<td>16 (46%)</td>
<td>29 (72%)</td>
<td></td>
</tr>
<tr>
<td>Unknown</td>
<td>4 (11%)</td>
<td>2 (5%)</td>
<td></td>
</tr>
<tr>
<td>Mode of delivery</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Vaginal</td>
<td>21 (60%)</td>
<td>29 (72%)</td>
<td>NS</td>
</tr>
<tr>
<td>Caesarean</td>
<td>13 (37%)</td>
<td>11 (28%)</td>
<td></td>
</tr>
<tr>
<td>Unknown</td>
<td>1 (3%)</td>
<td>0</td>
<td></td>
</tr>
</tbody>
</table>

James et al, Haemophilia 2015;21:81
Postpartum Bleeding by PBAC

Fig. 2. Pictorial blood assessment chart scores by week postpartum.

James et al, Haemophilia 2015;21:81
VWF Levels Postpartum

James et al, Haemophilia 2015;21:81
Management of Pregnancy in VWD

• Check VWF levels at beginning of 3rd trimester

• If levels > 50%
  – Treat as normal pregnancy without VWD-specific treatment
  – Alert to postpartum hemorrhage
  – Question if goal should be higher

• If level < 50%
  – Continue to monitor
  – Plan for VWF-containing factor support
  – Role of desmopressin
Desmopressin in Pregnancy

• Concerns about fluid shifts peripartum
• Systematic review of 30 studies of use for treatment and prophylaxis of bleeding in pregnancy\textsuperscript{1}
  – Overall safe
  – 2 cases of symptomatic hyponatremia in 172 women
  – Included 51 patients in 1\textsuperscript{st} or 2\textsuperscript{nd} trimester
• My concern, is there the same response at parturition vs. pre-pregnancy?

\textsuperscript{1}Trigg DE et al, Haemophilia 2012;18:25.
OB Anesthesia

• Recommended for any anesthesia
  – VWF: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 3rd trimester

Prevention of 2° PPH

• Patient education
  – Weekly follow-up recommended\textsuperscript{1}
  – Average time of hemorrhage 15.7 +/- 5.2 days\textsuperscript{2}

• Monitor factor levels as needed

• Factor and/or antifibrinolytic therapy
  – Pre-emptive or as needed

More Severe VWD and Pregnancy

• Requires factor support
  – Length of treatment depends on severity and mode of delivery
    • Females with hemophilia B, 5 with levels <20%, 2 <5%\(^1\)
      – Increased PPH with factor coverage < 4 days, none with > 6 days

• Type 2B
  – Decrease in platelet count as pregnancy progresses
    • The role of platelet transfusion is controversial\(^2\)
  – VWF-containing factor support at delivery/PP usually required

\(^1\)Yang MY and Ragni MV. Haemophilia 2004;10:483,
Biguzzi E, et al, Haemophilia 2015;21:e70..
Return to Patient: My Approach

• Ms. Smith, a 23 year old female, has Type 1 VWD (VWF:Ag 29%, VWF:Act 28%, FVIII 40%):
  – Check values at beginning of 3rd trimester
    • If normal, letter to OB and patient: Treat as normal, alert for PPH
    • Consider Rx for tranexamic acid at home
    • If low, recheck closer to delivery
      – Factor replacement if remains low

• How would your advice differ is she had
  – Type 3 or 2 B VWD?
    • Follow levels throughout pregnancy
    • Planned delivery with factor +/- platelets for delivery and postpartum
    • Tranexamica acid postpartum
Thank You