Case #4: Bleeding Disorders in Pregnancy
Norma, 27yrs ♀

• G1P0
• referred from GP for iron deficiency anemia and a prolonged PTT
  – GP started patient on iron
• You see her in your clinic in her 2nd trimester
  – She tells you she has a diagnosis of \textit{VWD Type 2N}
  – Other past medical history: none
  – Medications: pre-natal vitamins, iron

What would you like to ask her on history?
“Standardized” Bleeding Assessment

• The bleeding history is the **most important predictor** of the presence of a bleeding disorder

• Validated Bleeding Assessment Tools (BAT’s)
  – Improves post test probability of lab tests
  – Facilitates exploration of variability in bleeding severity
  – Informs treatment decisions
  – Allows effective communication

• Her condensed MCMDDM-1 VWD score is 4
  – Epistaxis (1 point)
  – Menorrhagia requiring anti-fibrinolytics and supplemental iron (3 points)
First Trimester Results from GP

Hb 98 g/L (RI 140-180)
MCV 76 fL (RI 80-95)
Plts 480 x 10⁹/L (RI 150-400)
Ferritin < 10 ng/ml (RI 22-275)

PT 14 s (RI 11.5-15.5)
PTT 37 s (RI 26-35)
Fibrinogen 3.0 g/L (RI 1.5-3.5)

What investigations are needed to diagnose VWD?
You order VWD screening and subtyping...
<table>
<thead>
<tr>
<th>Test</th>
<th>1&lt;sup&gt;st&lt;/sup&gt; Trimester</th>
<th>2&lt;sup&gt;nd&lt;/sup&gt; Trimester</th>
<th>Normal Range</th>
</tr>
</thead>
<tbody>
<tr>
<td>Hb</td>
<td>98 g/L</td>
<td>120 g/L</td>
<td>140-180</td>
</tr>
<tr>
<td>MCV</td>
<td>76 fL</td>
<td>82 fL</td>
<td>80-95</td>
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<td>Plts</td>
<td>480 x 10&lt;sup&gt;9&lt;/sup&gt;/L</td>
<td>375 x 10&lt;sup&gt;9&lt;/sup&gt;/L</td>
<td>150-400</td>
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<tr>
<td>PT</td>
<td>14 s</td>
<td>13.8 s</td>
<td>11.5-15.5</td>
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<tr>
<td>PTT</td>
<td>37 s</td>
<td>31 s</td>
<td>26-35</td>
</tr>
<tr>
<td>Fibrinogen</td>
<td>3.0 g/L</td>
<td>4.1 g/L</td>
<td>1.5-3.5</td>
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</table>

<table>
<thead>
<tr>
<th>Test</th>
<th>1&lt;sup&gt;st&lt;/sup&gt; Trimester</th>
<th>2&lt;sup&gt;nd&lt;/sup&gt; Trimester</th>
<th>Normal Range</th>
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</thead>
<tbody>
<tr>
<td>VWF:RCo</td>
<td></td>
<td>0.98 IU/mL</td>
<td>0.50-1.50</td>
</tr>
<tr>
<td>VWF:Ag</td>
<td></td>
<td>1.1 IU/mL</td>
<td>0.55-1.81</td>
</tr>
<tr>
<td>FVIII activity</td>
<td></td>
<td>0.60 IU/mL</td>
<td>0.50-1.50</td>
</tr>
<tr>
<td>Multimers</td>
<td></td>
<td>Normal</td>
<td>Normal</td>
</tr>
<tr>
<td>RIPA (low dose)</td>
<td></td>
<td>No aggregation</td>
<td>No aggregation</td>
</tr>
</tbody>
</table>

**What is your interpretation?**
VWD Classification

Type 1 - mild/moderate quantitative trait ~80%

Type 2 - qualitative traits

- Type 2A
- Type 2B
- Type 2M
- Type 2N

~20%

dominant

recessive

Type 3 - severe quantitative trait ~ 1 per million

Due to auto-correction, a primary diagnosis of VWD during pregnancy may be difficult without molecular techniques
**VWF and Pregnancy**

<table>
<thead>
<tr>
<th>Question</th>
<th>Answer</th>
</tr>
</thead>
<tbody>
<tr>
<td>Does VWF activity and antigen change during pregnancy?</td>
<td>Yes, VWF activity and antigen generally increases (3-5x)</td>
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<tr>
<td>Type 1 VWD, may see changes in type 2</td>
<td></td>
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<tr>
<td>When in pregnancy do you expect this to occur?</td>
<td>Begins in second trimester, peaking at term and returning to baseline postpartum</td>
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<tr>
<td>However, the exact change in VWF profile is unpredictable from patient to patient</td>
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## Factor VIII and Pregnancy

<table>
<thead>
<tr>
<th>Question</th>
<th>Answer</th>
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</thead>
<tbody>
<tr>
<td>Does FVIII activity change during pregnancy?</td>
<td>Yes, FVIII increases (acute phase reactant), 3–5x</td>
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</tbody>
</table>

Like VWF:RCo, the exact change in FVIII activity is unpredictable from patient to patient.
Norma’s 2\textsuperscript{nd} Trimester VWD Profile:

- VWF activity – 0.98 IU/mL (normal)
- VWF antigen – 1.1 IU/mL (normal)
- FVIII activity – 0.60 IU/mL (normal)

Is further monitoring of VWF profiles required?

General principle: Regardless of VWD sub-type, \textbf{monitoring is essential}

When and how often do you want to monitor?

Minimally, VWF:RCo, VWF:Ag and FVIII activity checked once per trimester
How could you confirm the diagnosis of VWD Type 2N?
Molecular Testing

- homozygous R854Q
  - Most common **VWD type 2N** mutation
Norma wants to know...

“Can I deliver at my community hospital?”

What is the criteria for referral to a tertiary care center for VWD and pregnancy?
Referral to Hemophilia or High-risk Obstetrics Centre

• Regardless of VWD type, referral recommended when 3rd trimester values:
  – FVIII < 0.50 IU/mL
  – VWF:RCo < 0.50 IU/mL
  – Or history of severe bleeding
Norma also asks...

“Is my baby going to have von Willebrand’s disease too? Can we find out?”

How can you check the baby’s VWD status? Is it warranted?
VWD Genetic Counseling

- To know baby’s VWF status requires an invasive procedure
  - Amniocentesis or chorionic villous sampling
- Imperative to know VWF subtype before testing
  - Genotype-phenotype correlations are inconsistent with Type 1
    - Prenatal testing not recommended
  - Genotype-phenotype correlation more consistent with Type 2
    - Prenatal testing of potential value
    - Type 2N VWD inheritance is autosomal recessive
  - Given severity of disease, testing for Type 3 disease can be justified

Provide Patient Choice
Would testing change management?
Would pregnancy be terminated depending on the results?
VWD and Invasive Procedures

- Check FVIII activity and VWF:RCo before procedure
- Prophylaxis indicated when:
  - VWF:RCo < 0.50 IU/mL

Examples:
- Chorionic villous sampling
- Amniocentesis
- Cervical cerclage

You explain an invasive procedure is needed for genetic testing and prophylactic treatment might be needed.
She also wants to know...

“If I need an invasive procedure, what can you give me to prevent bleeding? Are these drugs safe for the baby?”

What are your therapeutic options during pregnancy?
Therapeutic Options

- **Tranexamic acid**
  - Oral (500 mg tablets): 2-3 tabs, TID
    - 15-25 mg/kg TID
  - IV: 10 mg/kg TID
  - Topical: 5% w.v. QID

- **DDAVP (if responder)**
  - SC 0.3 μg/kg
  - IV 0.3 μg/kg over 30 min
  - Intranasal (150 μg/single spray)
    - 2 sprays for adult
    - 1 spray for child

- **VWF/FVIII concentrate (Humate-P, Wilate)**
  - For epidural, delivery or c-section:
    - RCoF: 30-60 U/kg IV q12-24h (depends on patient levels, product and specific procedure)
    - Dosing calculator for humate-P: [www.humate-P.com](http://www.humate-P.com)
Tranexamic Acid (TA)

- Anti-fibrinolytic agent
- TA crosses the placenta
- Pregnancy category B drug
  - No mutagenic effect in animal studies but human data lacking
- Given in short durations, not associated with increased thromboembolic complications
- Very low concentrations in breast milk (~1% of peak)

- Regularly used without any adverse sequelae
DDAVP (desmopressin)

- Synthetic derivative of antidiuretic hormone
- Increases VWF and FVIII transiently
  - Most effective in type 1 VWD with normal VWF
    - However type 1 VWD tend to correct the most during pregnancy and rarely require DDAVP
    - Response typically poor in type 2 and absent in type 3

- DDAVP test dose is needed to ascertain responsiveness
  - Check all VWF parameters at time 0, 1, 2 and 4 hours after DDAVP

- Typically DDAVP challenges are not performed during pregnancy
DDAVP Safety

• Systematic review of DDAVP in diabetes insipidus and pregnancy found no association with:
  – Maternal hypertension, uterine hyperstimulation, prematurity or low birth weight

• Case reports of maternal seizures warrant monitoring of:
  – Fluid balance, hyponatremia especially during delivery

• DDAVP does not cross the placenta

• Pregnancy category B drug
  – Safe in animal reproduction studies but not evaluated in pregnant women

• Generally considered to be safe
VWF:FVIII Concentrate

• Humate-P, Wilate
• Purified from pooled human plasma
  – Viral reduction procedure
  – Safer source of VWF:FVIII than cryoprecipitate
• Pregnancy category C drug
  – No studies in animals or humans

• Case reports have safely supported pregnancy and delivery without adverse fetal outcome
Pre-Delivery Planning

• You are unable to obtain previous DDAVP challenge results

• You discuss a plan to re-check her VWF:RCo and FVIII activity later in 3rd trimester

• You coordinate with OB for planned delivery at center with hemophilia experience, laboratory + blood bank support

• Mode of delivery as per OB
Then One Saturday Night...

• You are paged by anesthesiology
• Norma has been admitted (earlier than planned), awaiting epidural
  – 8 cm dilated
  – Mom and baby stable
  – 37 weeks gestation
• Patient informed staff of VWD type 2N status

They want to know if epidural safe to proceed
Norma’s 3rd Trimester VWF Profile

• Fortuitously, you had drawn VWF profile a few days ago:

<table>
<thead>
<tr>
<th>Test</th>
<th>Result</th>
<th>Normal Range</th>
</tr>
</thead>
<tbody>
<tr>
<td>VWF:RCo</td>
<td>1.35 IU/mL</td>
<td>0.50-1.50</td>
</tr>
<tr>
<td>VWF:Ag</td>
<td>1.60 IU/mL</td>
<td>0.55-1.81</td>
</tr>
<tr>
<td>FVIII</td>
<td>0.78 IU/mL</td>
<td>0.50-1.50</td>
</tr>
</tbody>
</table>

What is your management plan?
VWD and Delivery

3rd trimester: VWF:RCo and FVIII activity

> 0.50 IU/mL

Yes

Safe for delivery + neuraxial anesthesia

No or unknown

Humate-P: R:CoF 60 units/kg IV q12h
Wilate: R:CoF 40 units/kg IV q12h

Humate-P dosing calculator available online: www.humate-p.com
24 hours later...

- Uncomplicated vaginal delivery
- Baby is well
  - Peds heme evaluating
- Blood loss ~350 cc
- Mother stable, presently no active bleeding

Any further risk of bleeding post-delivery?
Delayed Post-Partum Hemorrhage (PPH) in VWD

• Delayed PPH occurs in ~25% of VWD (15-20x more common)
  – VWF and FVIII fall with decreasing estrogen
  – Baseline reached 7-21 days (mean presentation 15 days)

VWF Monitoring
• Type 1 VWD – generally not necessary, unless severe deficiency
• Type 2 and 3 VWD – maintain VWF:RCo and FVIII activity >0.50 IU/mL for 3-5 days post-partum
  – May need 2 weeks prophylaxis or more
  – Consider discharge with oral TA x 7-10 days
  – Educate about PPH signs and symptoms
  – *Early follow up with clinical assessment is recommended*

*practice varies*
Summary

• VWF/FVIII activity
  – Often increase with pregnancy
  – Check at presentation, before invasive procedures and at least once per trimester

• Increase VWF:RCo and FVIII activity when < 0.50 IU/mL
  – DDAVP
  – VWF:FVIII concentrate

• Use anti-fibrinolytics

• Delayed post-partum hemorrhage
  – VWF:FVIII rapidly drops post-parturition
  – Early follow up and close clinical monitoring is warranted

### VWD Subtypes

#### TABLE 2
Common laboratory findings in von Willebrand disease

<table>
<thead>
<tr>
<th>Subtype&lt;sup&gt;a&lt;/sup&gt;</th>
<th>von Willebrand factor antigen</th>
<th>von Willebrand factor ristocetin cofactor activity</th>
<th>von Willebrand factor ristocetin cofactor activity/ von Willebrand factor antigen</th>
<th>Factor VIII</th>
<th>Low dose ristocetin-induced platelet aggregation</th>
<th>Multimer assay</th>
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</thead>
<tbody>
<tr>
<td>Type 1</td>
<td>Low</td>
<td>Low</td>
<td>&gt;0.5-0.7</td>
<td>Low or normal</td>
<td>No reaction</td>
<td>Normal</td>
</tr>
<tr>
<td>Type 2A</td>
<td>Low</td>
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<td>&lt;0.5-0.7</td>
<td>Low or normal</td>
<td>No reaction</td>
<td>Decrease in large multimers</td>
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<tr>
<td>Type 2B</td>
<td>Low</td>
<td>Low</td>
<td>&lt;0.5-0.7</td>
<td>Low or normal</td>
<td>Positive</td>
<td>Decrease in large multimers</td>
</tr>
<tr>
<td>Type 2M</td>
<td>Low</td>
<td>Low</td>
<td>&lt;0.5-0.7</td>
<td>Low or normal</td>
<td>No reaction</td>
<td>Normal</td>
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<tr>
<td>Type 2N</td>
<td>Normal to low</td>
<td>Normal to low</td>
<td>&gt;0.5-0.7</td>
<td>Low</td>
<td>No reaction</td>
<td>Normal</td>
</tr>
<tr>
<td>Type 3</td>
<td>Absent</td>
<td>Absent</td>
<td>&gt;0.5-0.7</td>
<td>Low</td>
<td>No reaction</td>
<td>Absent</td>
</tr>
</tbody>
</table>

<sup>a</sup> See Table 1 for explanations of each subtype.

## VWD Subtypes

<table>
<thead>
<tr>
<th></th>
<th>Normal</th>
<th>Type 1</th>
<th>Type 2A</th>
<th>Type 2B</th>
<th>Type 2M</th>
<th>Type 2N</th>
<th>Type 3</th>
<th>PLT-VWD*</th>
</tr>
</thead>
<tbody>
<tr>
<td>VWF:Ag</td>
<td>N</td>
<td>L, ↓ or ↓↓</td>
<td>↓ or L</td>
<td>↓ or L</td>
<td>↓ or L</td>
<td>N or L</td>
<td>absent</td>
<td>↓ or L</td>
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<tr>
<td>VWF:RCo</td>
<td>N</td>
<td>L, ↓ or ↓↓</td>
<td>↓↓↓ or ↓↓↓</td>
<td>↓↓</td>
<td>↓↓</td>
<td>N or L</td>
<td>absent</td>
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<tr>
<td>FVIII</td>
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<td>N or ↓</td>
<td>N or ↓</td>
<td>N or ↓</td>
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<td>1-9 IU/dL</td>
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<td>RIPPA</td>
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</tbody>
</table>
Peripartum Management

Type 1 VWD:
- DDAVP if FVIII or VWF:RCo <50 IU/dL. Follow FVIII and VWF:RCo daily (titrate infusions accordingly).
- Maintain levels of both >50 IU/dL during labor, delivery, and up to 5 days postpartum.

If prolonged treatment with DDAVP, consider adding VWF concentrates.

Type 2 VWD:
- DDAVP if response documented on test dose (mainly 2A)
- VWF concentrates (if FVIII or VWF:RCo <50 IU/dL). Follow FVIII and VWF:RCo daily (titrate infusions accordingly).
- Maintain levels of both >50 IU/dL during labor, delivery, and up to 5 days postpartum.

Continue close follow-up of FVIII and VWF:RCo levels for up to 2 weeks postpartum (especially if cesarean section) and provide prophylaxis accordingly to avoid late postpartum hemorrhage.

Type 3 VWD:
- VWF concentrates (if FVIII or VWF:RCo <50 IU/dL). Follow FVIII and VWF:RCo daily (titrate infusions accordingly).
- Maintain levels of both >50 IU/dL during labor, delivery, and up to 5 days postpartum.

Operative vaginal delivery only if necessary. Avoid pudendal blocks and episiotomies if possible.

Avoid hypotonic solutions at time of delivery if using DDAVP in order to prevent hyponatremia.

# Humate-P Dosing

## Humate-P® von Willebrand Disease Dosage Calculator

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### These calculations are to be used only with Humate-P® and are applicable to all VWD types

**General Rule:** Doses are calculated based on an expected in vivo recovery of 2.0 IU/dL rise in VWF:RCo activity per every IU/kg of VWF:RCo administered.

See attached Prescribing Information for full dosing recommendations.