Hemostasis During the Menstrual Cycle

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Uterine Hemostasis Colloquium
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References

• Trigg
Case

- 30 year-old female with history of heavy menstrual bleeding, postpartum hemorrhage, and bleeding after wisdom tooth extraction
- A comprehensive hemostatic evaluation was non-diagnostic
- Is there a role for repeat, menstrual cycle specific testing in this woman?
• Hormonal Changes During Menstrual Cycle
• Hemostatic Changes During Menstrual Cycle
  – VWF
  – Platelet function
  – Coagulation factors
  – Fibrinogen
  – Fibrinolytic

• What are the implications?
  – Testing
  – Increase or decrease in thromboembolic or bleeding risks
HORMONAL CHANGES
Hormonal Changes During Menstrual Cycle

Follicular phase D1-14
Luteal phase D14-28

Hormones During Follicular and Luteal Phases

*Giardina, et al. J Clin Endocrinol Metab. 2004; 89:6179-6184*

<table>
<thead>
<tr>
<th>Hormone</th>
<th>Follicular</th>
<th>Luteal</th>
<th>p</th>
</tr>
</thead>
<tbody>
<tr>
<td>Estradiol (pg/ml)</td>
<td>59.1 ± 30.2</td>
<td>87.6 ± 36.7</td>
<td>&lt;0.01</td>
</tr>
<tr>
<td>FSH (mIU/ml)</td>
<td>4.5 ± 1.5</td>
<td>3.7 ± 2.2</td>
<td>&lt;0.05</td>
</tr>
<tr>
<td>Progesterone (ng/ml)</td>
<td>0.8 ± 0.7</td>
<td>7.1 ± 2.9</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>LH (mIU/ml)</td>
<td>3.5 ± 1.9</td>
<td>5.7 ± 9.7</td>
<td>NS</td>
</tr>
</tbody>
</table>
VON WILLEBRAND FACTOR
Changes in Endometrial VWF with Menstrual Cycle

Changes in Endometrial VWF with Menorrhagia

Grp 1: menorrhagia + VWD
Grp 2: menorrhagia (no VWD)
Grp 3: nl menstrual loss

Changes in Plasma VWF and Factor VIII (n=175)

Miller. Thromb Haemost. 2002; 87:1082-3
VWF Cyclical Variation vs No Cyclical Variation

Cyclical Variation
• Miller et al, 2002
• Kadir et al, 1999
• Blomback et al, 1997
• Roell et al, 2007
• Jern et al, 1991

No cyclical variation
• Onundarson et al, 2001
• Koh et al, 2005
• Feuring et al, 2002
• Giardina et al, 2005
• He et al, 1999

VWF levels approximately 10% (range 2-24%) lower in menstrual/early follicular phase compared to luteal phase
PLATELET COUNT AND FUNCTION
<table>
<thead>
<tr>
<th>Cycle</th>
<th>Day 1-3</th>
<th>Day 5-9</th>
<th>Day 10-14</th>
<th>Day 21-26</th>
<th>p</th>
</tr>
</thead>
<tbody>
<tr>
<td>Plt ct</td>
<td>299 ± 61.4</td>
<td>301.2 ± 66</td>
<td>318.9 ± 61.9</td>
<td>305.5 ± 63.2</td>
<td>0.62</td>
</tr>
</tbody>
</table>

No statistically significant variation with menstrual cycle
Platelet Function:
PFA100 in Premenopausal Women—No OC (n=18)

Collagen/Epi Cartridge:
*Shorter CT in Luteal Phase → ↑ Plt Fn*
($\Delta = -34.6 \pm 50.1$ sec; $p=0.0095$)

Collagen/ADP Cartridge:
*NS $\Delta$ CT*

COAGULATION FACTORS
Changes in Endometrial Tissue Factor Expression During Menstrual Cycle

• TF is primary initiator of hemostasis in endometrium
• Progesterone initiates decidualization of endometrial stromal cells during mid-luteal phase
• TF expression increased by progesterone in decidualized stromal cells late luteal phase

Effects of Progesterone and Thrombin on TF Expression in Decidual Cells


P<0.05 *vs E2; **vs E2 +MPA, ** vs E2 +Th
Factor VIIa: 20% lower FVIIa luteal phase (-18% midcycle) vs follicular men 46% higher than women (follicular) phase
Factor XIII

Sharief et al, Blood Coag Fib 2016;27:786-790
Coagulation Factors

• XI- no menstrual cycle variation
  – Kadir et al, Thromb Haemost 1999;82;1456-61

• VII-lowest mid-cycle and luteal phase

• II, X- no significant menstrual cycle variation
  – Blomback et al, JTH 2007;5:855-858

• XIII-lowest menstrual (d1-5) and peri-ovulatory (d13-15)
  – Sharief et al, Blood Coag Fib 2016;27:786-790
FIBRINOGEN
Fibrinogen: Cycle variation (No OC) Lowest Day 11

Non-pill: 11% lower d11 vs d1

Fibrinogen

6/20 lowest follicular phase; 2/20 lowest luteal phase

FIBRINOLYTIC PARAMETERS
PAI-1 in Decidual Cell Cultures Treated with Progesterone

PAI-1

Difference follicular/luteal phase

Inverse relationship estradiol and PAI-1 over 4 week cycle

Δ 10± 14 ng/ml; p<0.01

Fibrinolytic Parameters in Plasma Cyclical Variation

- **PAI-1** 2/11 studies

- **tPA** 1/10 studies

- **uPA** 2/3 studies

- **D-dimer** 2/5 studies

*Knol, et al. 2012; 107:22-29*
Thrombin Generation:
*Nl Menstrual Cycle (n=102)*

- Higher during luteal phase than follicular phase ($1524 \pm 283$ vs. $1609 \pm 343$; $p=0.027$)
- *No strong correlation between TG and hemostatic parameters*
- *Progesterone highest in luteal phase*

Summary: Cyclical Variation Hemostatic Parameters

- **VWF**-lowest menstrual/early follicular phase
- **Platelet function**—longer CT follicular phase
- **Coagulation factors**
  - **VII**-lowest mid-cycle and luteal
  - **XIII**- lowest menstrual and peri-ovulatory
  - **XI, II, X**- no cyclic variation
- **Fibrinogen**
  - Lowest follicular phase
- **Fibrinolytic** parameters
  - Conflicting data
- **Thrombin generation**
  - Highest luteal phase
  - Poor correlation with hemostatic parameters
Implications

- Testing—potential implications borderline results

- ? variation in bleeding or thrombotic risks
References

References (cont’d)


