Clinical Management of Platelet Disorders in Women

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September 8, 2016
ISTH Advanced Training Course in Thrombosis and Hemostasis

Clinical and Molecular Hemostasis Research Group
## Disclosures for Paula James

<table>
<thead>
<tr>
<th>Disclosures</th>
<th>Details</th>
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<tr>
<td>Research Support/P.I.</td>
<td>CSL Behring, Bayer, Octapharma, Baxalta</td>
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<tr>
<td>Employee</td>
<td>No relevant conflicts of interest to declare</td>
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<td>Consultant</td>
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<td>Scientific Advisory Board</td>
<td>Biogen, Baxter, CSL Behring</td>
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Evidence

and

Clinical Pearls
Menstruation

The Past
160 menstrual cycles
  late periods
  multiple pregnancies
  extended breastfeeding
  early menopause

The Present
450 menstrual cycles
  early periods
  few pregnancies
  short breastfeeding
  late menopause
Menorrhagia = Heavy Menstrual Bleeding (HMB)

• 30% women report at some point

• 10 – 15% have objective menorrhagia

• 5 – 10% seek medical attention

Rees et al, Brit J Haem 1991; 98:327-8
Causes of Menorrhagia

- Undiagnosed: ~50%
- Bleeding disorder: ~25%
- Hormonal: ~10%
- Uterine pathology: ~15%

Kouides et al, Hemophilia 2002; 8:330-338
Frequency of Menorrhagia

Kadir et al, Hemophilia 1998; 4:836-41
Definition of Menorrhagia
(Heavy Menstrual Bleeding)

>80 mls menstrual blood loss (MBL)

Clinically, this is a useless definition
Correlates of > 80 mls MBL

- soaking through pad in 1 hour
- soaking pj’s
- clots > 1 inch
- low ferritin

James et al, Gynecol Reprod Bio 2011;158:124-34
score > 100 = 80 mls MBL

<table>
<thead>
<tr>
<th>Name: Sabine Mustermann</th>
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<tr>
<td>Date: Week</td>
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<tr>
<td>Sanitary towel</td>
</tr>
<tr>
<td>Intensity of bleeding per sanitary towel</td>
</tr>
<tr>
<td>x 1</td>
</tr>
<tr>
<td>x 5</td>
</tr>
<tr>
<td>x 20</td>
</tr>
<tr>
<td>and/or Tampons</td>
</tr>
<tr>
<td>Intensity of bleeding per tampon</td>
</tr>
<tr>
<td>x 1</td>
</tr>
<tr>
<td>x 5</td>
</tr>
<tr>
<td>x 15</td>
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<td>Daily points:</td>
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Vicenza-based BATs

- **Vicenza**
  - 2005: 0 to +3
  - Duration: 40 minutes

- **MCMMDM-1VWD**
  - 2006: -1 to +4
  - Duration: 40 minutes

- **Condensed MCMMDM-1VWD**
  - 2008: -1 to +4
  - Duration: 5-10 minutes

- **PBQ**
  - 2009: -1 to +4
  - Duration: 20 minutes

- **ISTH BAT**
  - 2010: 0 to +4
  - Duration: 20 minutes

- **Self-BAT**
  - 2013: 0 to +4
  - Duration: 5-10 minutes
Impact of Menorrhagia

• missing work and school

• cause of 2/3 hysterectomy in women of reproductive age

• negative impact on QoL

• iron deficiency (anemia)

Treatment of Menorrhagia

differs little between women with a bleeding disorder and without

• Exceptions:
  – DDAVP and platelet transfusion/factor replacement
  – (anti-inflammatories or NSAIDs)
Treatment of Menorrhagia

• individualized
• medical – 1st Line
  – hormonal
  – non-hormonal
• surgical
  – if no plans for future pregnancy
Hormonal

- combined oral contraceptives
  - decrease MBL
  - increase VWF and FVIII levels (50 mcg oestradiol)
  - semi-continuous or continuous
  - pill, ring, patch

- depot medroxyprogesterone acetate (Depo-Provera®)
  - IM injection q 3 monthly
  - irregular bleeding

• Levonorgestrel- IUS (Mirena®)
  – initially irregular bleeding (up to 6 months)
  – decreases MBL by 74 – 97%, improves QoL
  – 56% amenorrhea at 9 months
expulsion + malposition + request for removal in 50% WBD
Non-hormonal

• Antifibrinolytics
  – tranexamic acid (cyclokapron®)
  – reversibly blocks lysine binding sites
  – decreases MBL by ~50%
  – nausea, GI upset
  – concern re: thrombosis
    • 238,000 patient years
      – risk similar to general population
  – recommended dose 1 gm TID - QID

Desmopressin

- **DDAVP** – 1-deamino-8-D-arginine vasopressin
- Endogenous release of VWF and FVIII
  - Platelet disorders
- **IV/SC**
  - 0.3 mcg/kg
- **IN**
  - 150 mcg/spray 1 – 2 sprays
- Days 1 and 2/3 of menses
- Hyponatremia, fluid restrict
- Headache, flushing

*Rodeghiero et al, Thromb Haemost 1996; 76: 258-66*
n=116
TAA > decrease MBL than IN-DDAVP
both improved QoL
NSAIDS

• avoid in women with severe disorders
• use with caution in patients with mild disorders
• can reduce MBL
• menstrual pain

*Lethaby et al. Cochrane Database Syst Rev, 2000*
Platelet Transfusion/Factor Replacement

very rarely required

- when other treatments fail
- Platelet Transfusions
  - vCJD
  - alloantibodies

Surgical Management

• Endometrial Ablation
  – 70 women, 25 WBD, success > 90%
  – 3/7 successful outcome at 4 years
  – should not become pregnant after

Surgical Management

• Hysterectomy
  – requires multidisciplinary management
  – WBD increased risk of intra-operative bleeding and delayed blood loss at 7-10 days
  – if required, high patient satisfaction

James et al. Obstet & Gynecol 2004; 104:381-388
### Hysterectomy

<table>
<thead>
<tr>
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<th>WBD (n=102)</th>
<th>Normal (n=88)</th>
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</thead>
<tbody>
<tr>
<td>Hysterectomy</td>
<td>26%</td>
<td>9%</td>
</tr>
<tr>
<td>Surgical Bleeding</td>
<td>61%</td>
<td>8%</td>
</tr>
<tr>
<td>Transfusion</td>
<td>46%</td>
<td>9%</td>
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*Kirtava et al, Haemophilia 2003; 9:282-7*
Adolescents with Menorrhagia

• acute menorrhagia should be investigated for bleeding disorder
• if known family history pre-menarchal testing and counselling
  – prior to institution of COCP

Algorithm for Management

Would the patient like to preserve fertility?

Would the patient like to become pregnant now?

Hormonal measures (in order of efficacy):
1. Levonorgestrel IUS
2. Combined oral contraceptives
3. Progestins

Can also consider:
Hysterectomy
Endometrial ablation

Hemostatic agents
Anti-fibrinolytic therapy
  a) tranexamic acid
  b) aminocaproic acid
DDAVP
  a) intranasal
  b) subcutaneous
Definitive therapy
Coagulation factor replacement
e.g. VWF/FVIII concentrate

James A et al, AJOG 2009; 201: 12.e1-12.e8
Other Gynecologic Issues

<table>
<thead>
<tr>
<th>Condition</th>
<th>WBD (n=102)</th>
<th>Normal (n=88)</th>
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<tbody>
<tr>
<td>Ovarian Cyst</td>
<td>52%</td>
<td>22%</td>
</tr>
<tr>
<td>Endometriosis</td>
<td>30%</td>
<td>13%</td>
</tr>
<tr>
<td>Fibroids</td>
<td>32%</td>
<td>17%</td>
</tr>
<tr>
<td>Endometrial hyperplasia</td>
<td>10%</td>
<td>1%</td>
</tr>
<tr>
<td>Polyps</td>
<td>8%</td>
<td>1%</td>
</tr>
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*Kirtava et al, Haemophilia 2003; 9:292-7*
Pregnancy

important issues to consider
Hemostatic Changes in Pregnancy

↑ fibrinogen
↑ factor VII
↑ factor VIII
↑ factor X
↑ VWF
↓ platelet count

↔ factor II
↔ factor V
↔ factor IX
↔ factor XI
↓ factor XIII
?
platelet function

Labour and Delivery

• measure levels at ~32 weeks
  – correct if not normalized for 3 – 5 days
• proceed as obstetrically indicated
• ?regional anaesthesia
  – not contraindicated if factor levels have normalized
  – “No investigations demonstrating values of a platelet function test for the safe placement of regional anaesthesia”

Labour and Delivery

• minimize perineal trauma
  – avoid forceps

• consider risks to baby
  – avoid vacuum, forceps, scalp electrode
    • male or unknown

• written plan in place
  – provide a copy to the patient

Post-partum

- increased risk of early (~10%) and late post-partum (>25%) hemorrhage

- counsel woman to seek medical attention immediately if excessive post-partum bleeding

Demers et al. SOGC Clinical Practice Guidelines 2005; 163:707-718
Post-partum PBAC scores

increased bleeding at 3 – 4 weeks in treated VWD

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

James A, Haemophilia 2015;21:81
Post-partum Management of WBD

n=33 women, 62 pregnancies

Hawke et al, Haemophilia, 2016
Support for Multidisciplinary Care

UKHCDO:
“Management of women with inherited bleeding disorders should be provided by a multidisciplinary team including a haematologist and gynaecologist.”

SOGC/AHCDC:
“The ideal management of women with IBD who suffer menorrhage is through multidisciplinary clinics”
Pre-menarchal girls: “Early introduction to the multidisciplinary team is important”

Demers et al. SOGC Clinical Practice Guidelines 2005; 163:707-718
Women with inherited bleeding disorders, including platelet disorders, face particular gynecologic and obstetrical challenges.
Acknowledgements

Lisa Thibeault
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Julie Grabell
Wei Sim
Key References


1 in 1000 Canadians has a bleeding disorder but most don't know it

Could you be one of them?

Are You Concerned
You May Have Abnormal Bleeding?

Take the Test Now