Women’s Issues in Bleeding Disorders
Menorrhagia, pregnancy and delivery

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Women’s Issues

- Menorrhagia in women with bleeding disorders
- Inheritance and genetic counselling
- Symptomatic haemophilia carriers
- Pregnancy and delivery
- Some issues for an affected baby
Women Bleed Too

http://www.womenbleedtoo.org.uk
(UK Haemophilia Society)

www.projectredflag.org
(NHF of USA)

‘Females with von Willebrand disease: 72 years as the silent majority’

(PA Kouides, Haemophilia 1998; 4: 665-676)
Menorrhagia can be defined objectively or subjectively

**Objectively**, menorrhagia is taken to be a total menstrual blood loss = or >80 ml per menstruation

**Subjectively**, menorrhagia is defined as a complaint of excessive menstrual blood loss occurring over several consecutive cycles in a woman of reproductive years
What is menorrhagia?

- Menstrual flow that soaks through one or more sanitary pads or tampons every hour for several consecutive hours
- The need to use double sanitary protection to control menstrual flow
- Soaking through bed clothes
- Menstrual period that lasts longer than 7 days
- Menstrual flow that includes large blood clots
- Associated with low iron stores (ferritin) and anaemia
Menorrhagia in women with bleeding disorders

<table>
<thead>
<tr>
<th>Disorder</th>
<th>Prevalence of menorrhagia %</th>
</tr>
</thead>
<tbody>
<tr>
<td>Von Willebrand Disease</td>
<td>74-92</td>
</tr>
<tr>
<td>Bernard Soulier syndrome</td>
<td>51</td>
</tr>
<tr>
<td>Glanzmann thrombasthenia</td>
<td>98</td>
</tr>
<tr>
<td>Factor XI deficiency</td>
<td>59</td>
</tr>
<tr>
<td>Carriers of haemophilia</td>
<td>57</td>
</tr>
<tr>
<td>Other rare factor deficiencies</td>
<td>35-70</td>
</tr>
</tbody>
</table>

*(Reproductive health in women with bleeding disorders Kadir R and James AH – WFH Monograph 2009)*
<table>
<thead>
<tr>
<th>Tampon</th>
<th>1 pt</th>
<th>5 pts</th>
<th>10 pts</th>
</tr>
</thead>
<tbody>
<tr>
<td>Pad</td>
<td>1</td>
<td>2</td>
<td>3</td>
</tr>
<tr>
<td>1 pt</td>
<td></td>
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<tr>
<td>5 pts</td>
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</tr>
<tr>
<td>10 pts</td>
<td></td>
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</tr>
</tbody>
</table>

Record for each day the number of pads or tampons which match each illustration.
PBAC scores against menstrual blood loss

Pictorial Blood Assessment Chart
score 100 = 80ml blood

Higham et al BJOG 1990; 97: 734-9
Women with inherited bleeding disorders

• 116 women studied at Royal Free Hospital
  – 66 vWd
  – 30 carriers of haemophilia
  – 20 with factor XI deficiency

• Menstrual loss assessed with the PBAC
  – Menorrhagia defined as score >100

• Age matched control group of 69 women

Kadir et al. Haemophilia 1999; 5: 40-48
Menstrual scores in women with bleeding disorders compared with controls

Kadir et al. Haemophilia 1999; 5: 40-48
Frequency of inherited bleeding disorders in women with menorrhagia

- 12% general gynaecology referrals are for menorrhagia
- 208 women attending gynaecology clinic RFH October 1995 – June 1997 screened with bleeding history including PBAC
- 150 women with PBAC score > 100 –
  - APTT; FVIIIIC; VWF AC; and FXIC

# Frequency of inherited bleeding disorders in women with menorrhagia

<table>
<thead>
<tr>
<th>Disorder</th>
<th>Number</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mild VWD</td>
<td>15</td>
</tr>
<tr>
<td>Moderate VWD</td>
<td>3</td>
</tr>
<tr>
<td>Factor XI deficiency</td>
<td>4</td>
</tr>
<tr>
<td>Combined deficiencies</td>
<td>2</td>
</tr>
<tr>
<td>Carrier of haemophilia A</td>
<td>1</td>
</tr>
<tr>
<td>Platelet disorder</td>
<td>1</td>
</tr>
</tbody>
</table>

*Kadir et al. Lancet 1998; 351: 485-489*
Frequency of von Willebrand disease in women with menorrhagia

- 150 women attending gynaecology clinic with PBAC score of >100
  - 15 Mild VWD
  - 3 Moderate VWD
- Frequency of VWD 13% compared with maybe 0.1 to 1% of the normal population

*Kadir et al. Lancet 1998; 351: 485-489*
VWD in women: a systematic review

- 11 studies including 988 women
- 131 diagnosed with VWD
- Prevalence mean 13% (5-24%)
- Testing for VWD should be included in the investigation of menorrhagia

Shankar et al BJOG 2004; 111: 734-40
Prevalence rates of von Willebrand disease in 988 women presenting with menorrhagia

Shankar et al BJOG 2004; 111: 734-40
The frequency of bleeding symptoms in the normal population compared with 264 Scandinavian patients with VWD


<table>
<thead>
<tr>
<th>Investigated symptom</th>
<th>Frequency</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>normal</td>
</tr>
<tr>
<td>Epistaxis</td>
<td>5-39%</td>
</tr>
<tr>
<td>Bruising</td>
<td>12-24%</td>
</tr>
<tr>
<td>Bleeding from small wounds</td>
<td>0.2-2%</td>
</tr>
<tr>
<td>Gum bleeding</td>
<td>7-51%</td>
</tr>
<tr>
<td>Menorrhagia</td>
<td>23-44%</td>
</tr>
<tr>
<td>Post partum haemorrhage</td>
<td>6-23%</td>
</tr>
<tr>
<td>Bleeding after tooth extraction</td>
<td>1-13%</td>
</tr>
<tr>
<td>Bleeding post tonsillectomy</td>
<td>2.4-11%</td>
</tr>
<tr>
<td>Bleeding after surgery</td>
<td>1.4-6%</td>
</tr>
<tr>
<td>AT LEAST ONE SYMPTOM</td>
<td></td>
</tr>
<tr>
<td>MALE</td>
<td>&gt;25%</td>
</tr>
<tr>
<td>FEMALE</td>
<td>&gt;46%</td>
</tr>
</tbody>
</table>
An underlying bleeding disorder should be suspected when a woman with menorrhagia has:

- Family history of a bleeding disorder
- Personal history of
  - Nose bleeds >10 mins
  - Notable bruising without injury (>2cm)
  - Minor wound bleeding (cuts >5 mins)
  - Excessive bleeding after dental extractions/surgery
  - Bleeding from ovarian cysts or corpus luteum
  - PPH especially delayed >24h
Menorrhagia and quality of life

• Studied in 99 patients with inherited bleeding disorder (vWD 57, haemophilia carriers 24, and FXI deficiency 18) compared with 69 normal controls

• Menorrhagia
  – Prolonged duration
  – Flooding
  – Passage of clots

• Associated with reduced quality of life
  – Interference with work
  – Pain

Kadir et al Haemophilia 1998; 4: 836-841
Predictive value of bleeding symptoms in diagnosis of type 1 VWD (Tosetto et al JTH 2006)
Treatment of Menorrhagia

- Oral iron
- Tranexamic acid 1 g three or four times a day
- Combined oral contraceptive or similar.
- Norethisterone 5-10 mg three times daily for 5 days before or during period (or continuously) (titrate dose)
- Intranasal or subcutaneous desmopressin on day 1 and 3 of period
- Factor replacement therapy
- Levonorgestrel intra-uterine system (Mirena coil)
- Injectable medroxyprogesterone acetate
- If future fertility not required, then endometrial ablation or hysterectomy

James et al. Consensus for management of VWD and other bleeding disorders in women experiencing menorrhagia or PPH. Am J Obs Gyn 2009; 20:12 e1-8
Algorithm of management of menorrhagia

Would the patient like to preserve fertility?

Yes

Would the patient like to become pregnant now?

Yes

Hemostatic measures*
- Antifibrinolytic drugs (tranexamic acid and aminocaproic acid)
- DDAVP (intranasal or subcutaneous)
- Clotting factor replacement

*can also be used in women who do not wish to get pregnant, either alone or in combination with hormonal therapies

No

No

In women with pelvic pathology or for whom other measures have failed, can also consider surgical options*:
- Endometrial ablation
- Hysterectomy

*Consider hemostatic evaluation prior to surgery

Hormonal measures
- Levonorgestrel IUS
- Combined oral contraceptives
- Progestins
- GnRH therapy

Kadir and James WFH 2009
Haemorrhagic ovarian cysts

- Multiple case reports (9/136, 7% women with vWD in one series)
- Can be severe
- Bleeding into peritoneal cavity or retroperitoneum
- Correct the bleeding disorder
- Ovulation is not normally accompanied by any clinically significant bleeding
- Increased risk of endometriosis
Review of pregnancy and childbirth in vWd

- 4067 deliveries in women with vWd between 2000-2003 (USA)
- Diagnosis of vWd 1 in 4000 women
- Increased risk of antepartum bleeding odds ratio 10.2
- Increased risk of PPH odds ratio 1.5
- Higher risk of transfusion odds ratio 4.7
- 5 maternal deaths, a rate 10 fold higher than normal women but rate still very low – 1 in 1000 women

James A and Jamison MG, JTH 2007; 5: 1165-1169
Rare Bleeding Disorders
Average rates of marriages between first cousins among Arabs

Gynaecological and obstetric problems in women with different bleeding disorders

<table>
<thead>
<tr>
<th>Comparison</th>
<th>Normal Women</th>
<th>114 Women with Bleeding Disorders</th>
</tr>
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<tbody>
<tr>
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<tr>
<td></td>
<td></td>
<td>48 vWd</td>
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<tr>
<td></td>
<td></td>
<td>31 haemophilia carriers</td>
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<tr>
<td></td>
<td></td>
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<tr>
<td></td>
<td></td>
<td>15 with normal levels</td>
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<tr>
<td></td>
<td></td>
<td>15 mild deficiency</td>
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<td></td>
<td></td>
<td>1 moderate deficiency</td>
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<tr>
<td></td>
<td></td>
<td>35 rare bleeding disorders</td>
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</tr>
<tr>
<td></td>
<td></td>
<td>14 FVII</td>
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<tr>
<td></td>
<td></td>
<td>10 FXI</td>
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<tr>
<td></td>
<td></td>
<td>4 V+VIII</td>
</tr>
<tr>
<td></td>
<td></td>
<td>7 others (fibrinogen, XIII, V and X)</td>
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<tr>
<td></td>
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<tr>
<td></td>
<td></td>
<td>10 severe (&lt;1%)</td>
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<td></td>
<td></td>
<td>8 moderate (2-10%)</td>
</tr>
<tr>
<td></td>
<td></td>
<td>17 mild (11 to LLN)</td>
</tr>
</tbody>
</table>

Siboni et al. Haemophilia 2009 (online June 2009)
Siboni et al. Haemophilia 2009
Factor VII deficiency and menstruation

- 14 women with FVII deficiency (2 severe)
- 23 healthy women
- PBAC and quality of life questionnaire
- Menorrhagia = PBAC score >100
  - FVII deficient 8/14 (57%) and 6 (43%) anaemia
  - healthy women 4/23 (17%) 2 (9%) anaemia
- Significantly worse quality of life scores in women with FVII deficiency

Adolescents
Acute menorrhagia in adolescents

- 9-year case review January 1971-80
- Admissions to hospital excluding genital tract pathology
- Primary coagulation disorder
  - 20% of total 59 patients
  - 25% of those with HB < 10g/dl
  - 33% of those requiring transfusion
  - 50% of those presenting at the menarche

Menorrhagia in adolescents

- Adolescents < 20 years admitted to University of Michigan hospital 1979-95.
- 37 adolescents with 46 admissions.
- Menarche, average 12.9y.
- Admission, average 15.9y.
- 15/46 (33%) haematological disease.

Inheritance and genetic counselling in the bleeding disorders
A person’s sex is determined by the X and Y chromosomes.
The diagnosis was a shock initially both for me and for the rest of the family. In fact my mum still has trouble coming to terms with the fact that it could be her fault that I have haemophilia.
Congenital bleeding disorders

• Too often unprepared in a family with known bleeding disorder
• Screen family members
• Counselling about risks
• Antenatal diagnosis
Haemophilia and inheritance

- Carriers of haemophilia A or B may be at risk of excessive bleeding and need levels measuring early in life
- A normal level does not exclude carrier status
- Implications of inheritance should ideally be discussed well in advance of pregnancy
- Education needs to begin early
- Reproductive choices
Information about carrier status

• 1990 a study of 549 obligate and potential carriers found that
  – 41% had never been tested and were not informed that they might be at risk
  – 19% of women had never discussed the inherited nature of the disease in the home

• Ideally:
  – Age 1 yr check FVIII or IX level
  – Teenage – undertake genetic testing
  – Adult woman and partner – pre-pregnancy counselling

• Problems with discovery of carrier status – stigmatisation, guilt
Management of Haemophilia A and B Carriers

- Average factor level in carriers is 60% (range 5 to 219) compared to 100% in normal women (range 45 to >250)
- 8% carriers HA have a level <50% at delivery
- 50% carriers HB have a level <50%
- Cut off for treatment of carriers for surgery or delivery:
  - >60 no bleeding so no interventions required
  - <60 be careful – there is evidence of excessive bleeding after surgery with levels 40-60%
  - <30 treat

Genetic counselling in the haemophilia centre - constraints

- It is essential that those seeking genetic counselling are free to make decisions that are not constrained by their commitment to existing family members.
- Haemophilia specialists are highly committed to the success of treatment and may or may not be conscious of the potential impact of this on their ability to remain neutral in the counselling situation.
- Can issues of paternity be discussed in the haemophilia centre where staff and patients know each other so well?

Genetic testing – the process

- Informed consent with presentation of written material
- Provide the opportunity for questions
- Keep a copy of the signed consent form in the notes, and give one to the person
- Make clear the arrangements for delivery of results
- Ensure the information has been understood
What information?

• The potential clinical effects of being a carrier or affected person
• Current treatment and implications of the condition
• The mode of inheritance and the individual’s genetic risk
• The rationale for identifying the genetic defect
Genetic counselling and genetic testing

- The rare bleeding disorders are autosomal recessive disorders
- Often the parents are consanguineous
- Parents should be advised of the risk of having further affected children
- Antenatal diagnosis and termination of pregnancy may be available
Challenges of Genetic Counseling in Developing Countries

- Inadequate diagnostic, management, rehabilitation facilities, burden of inherited disorders are great
- Social, culture, educational and religious background differs
- Availability of prenatal diagnosis

Data courtesy of Shirin Ravanbod, Iran
Why consanguineous marriage is favoured

- Easy acceptance of genetic disorder or carrier status in close relatives
- No religious and social division
- Family economic considerations

Data courtesy of Shirin Ravanbod, Iran
The Meaning of Carrier Status
giving birth to unhealthy children

- Intense emotions;
  - Fear, anxiety, sadness, anger, guilt
- Stigma (discrimination around sisters)
- Society and in-laws pressure
- Marriage (vulnerable situation)
- Abortion

Slide courtesy of Shirin Ravanbod, Iran
Contacting relatives

• Generally it is the responsibility of the affected person to inform members of the family

• It is recommended that a post-consultation letter be sent indicating the genetic risks, options available and the offer of genetic counselling to other at-risk relatives
Genetic testing in children

- Males with haemophilia should have their genotype established
  - Inhibitor risk
  - Helpful to identify other affected family members
  - Must send written information about results
Genetic testing in children

- Females who are potential carriers
  - Assay factor because it might affect clinical management (low in a third of carriers)
  - Genetic testing deferred until girl can give informed consent (usually aged 12 years upwards)
Management of pregnancy and delivery
Haemostasis in Pregnancy

**Unchanged:**
- Factors II, V, IX, XIII

**Increased:**
- Fibrinogen (x2), factor VII, Factor VIII (x2), VWF (x3-4), factor X

**Decreased:**
- Factor XI (?)
- Platelets in 3rd trimester.
Reproductive choices

• Male fetus
  – Is he affected?
  – Termination or not
• Adoption
• Avoid children altogether
• Preimplantation genetic diagnosis
  – Selection of unaffected embryos
  – Many questions and concerns
Pregnancy and the Haemophilia Carrier

- Pre-pregnancy counselling and genetic analysis
- Fetal sexing by
  - Fetal DNA analysis from maternal blood at 8-9 wks
  - ultrasound in second trimester
- Antenatal diagnosis
  - Preimplantation genetic diagnosis – creation of embryos by IVF and selection of unaffected one
  - Chorionic villus sampling (1% risk of miscarriage), performed at 10.5 wks, termination by 13 wks
  - Ultrasound guided fetal blood sampling at 18-20 weeks for coagulation testing – greater risk of miscarriage, rarely performed now
Good communication between specialists is vital – joint clinics

- Obstetrician
- GP
- Fetus at risk of inherited bleeding disorder
- Mother at risk of bleeding
- Paediatrician
- Haemophilia Specialists
Management of pregnancy and delivery

- Monitor VIIIIC in mid trimester.
- Formulate delivery plan in final trimester.
- Correct VIIIIC at the beginning of labour.
- Umbilical sample at birth for urgent VIIIIC.
- Affected males given prophylactic treatment with concentrate at birth?
- No IM injections (give vitamin K orally)
**Pre-conceptual Counselling** Joint Consultation

- Book early. Dating scan. Levels FVIII/FIX
  - Fetal sexing: Fetal DNA from maternal blood at 8-9 week
    - PND - CVS between 11-13 weeks (if severe disease)
      - +/- Prophylaxis if FVIII or FIX < 50IU/dl
  - Re-affirm fetal sex at Anomaly Scan. Review in ANC
  - Review at 32 weeks.
    - Assess FVIII/FIX levels (if not normal at booking)
  - Review at 36 weeks. Joint consultation
    - Formulate **Delivery Care Plan**
      - based on levels at 32 weeks.
  - Aim for spontaneous vaginal delivery
    - **Prophylaxis if FVIII or FIX < 50IU/l**
      - Desmopressin/VIII concentrate or FIX concentrate at start of labour
      - Regional analgesia if FVIII/FIX > 50IU/dl
Pregnancy and VWD:

- Most type I VWD corrects completely to normal values
- Type II and III do not correct.
- Type IIb get worse with progressive thrombocytopenia
- Correct haemostasis at the start of labour
- Monitor RiCof post-partum since VWF may decline quite rapidly
- Post-partum, type II and III may require replacement therapy, and type I may need Desmopressin
Pregnancy and bleeding disorders: General

- Planned delivery with a delivery plan.
- No ventouse or scalp electrodes.
- ? Forceps.
- Increased risk of operative delivery.
- Correct bleeding disorder in mother at the start of labour.
- Severe deficiencies may require correction for seven days post-partum.
Women at risk of excessive bleeding at delivery

- Management plan prepared in advance
  - Several copies including to the woman
- Joint management with haemophilia specialists (joint clinic)
- Correct the bleeding disorder prior to delivery
- Discuss constraints on epidural anaesthesia in advance
- Aim for natural labour to reduce risks of operative delivery
- Constraints due to risk of birth of affected baby
Obstetric pain relief in women with bleeding disorders

- Study of 80 pregnancies in 63 women
  - 19 FXI deficiency
  - 16 Haemophilia A carriers
  - 15 von Willebrand disease
  - 7 platelet disorders
  - 2 other
- 72 women seen in a joint clinic

Chi et al. Thromb Haemostas 2009; 101: 1104-11
Obstetric pain relief in women with bleeding disorders

- Regional block performed in 41 pregnancies
  - 35 known to have a bleeding disorder
    - 10 given treatment
    - 25 not given because normal coagulation at term (vWD and HA carriers)
  - FXI deficiency mostly managed with tranexamic acid
    - 4 with history of bleeding received concentrate
- Platelet disorders received platelet transfusions and TA at delivery
Use of regional block during labour and delivery

Regional block was used in 41 (37)* pregnancies

35 (32)* pregnancies – women known to have a bleeding disorder

10 (9)* pregnancies – low factor levels at term
  5 (5)* FXI deficiency
  3 (2)* FVII deficiency
  1 (1)* Carrier HB
  1 (1)* Platelet fn disorder

Prophylactic cover given

25 (23)* pregnancies – normal clotting screen and factor levels at term

12 (11)* VWD
  10 (9)* Carrier HA
  2 (2)* Carrier HB
  1 (1)* FVII deficiency

2 (2)* VWD
  1 (1)* Carrier HA
  2 (1)* FVII deficiency
  1 (1)* Platelet fn disorder

6 (5)* pregnancies – status unknown during pregnancy

No prophylaxis required
Regional anaesthesia

• Advantages
  – Pain relief
  – Permits CS without GA
  – Earlier mobilisation
  – Earlier breastfeeding
  – Better for baby

• Disadvantages
  – Low blood pressure
  – Failure of block
  – Side effects including urinary retention
  – Bleeding with resultant paralysis (rare)
# Regional anaesthesia at Royal Free Hospital

The complication rate was slightly higher in the bleeding disorder group.

<table>
<thead>
<tr>
<th></th>
<th>All women</th>
<th>Bleeding disorder group</th>
</tr>
</thead>
<tbody>
<tr>
<td>Regional anaesthesia</td>
<td>45%</td>
<td>33%</td>
</tr>
<tr>
<td>Caesarian sections under regional block</td>
<td>93%</td>
<td>81%</td>
</tr>
</tbody>
</table>
Postpartum haemorrhage

- Primary – i.e. within first 24 hours
- Secondary – later, can occur after discharge from hospital.
  - Women with inherited bleeding disorders should be warned
  - Tranexamic acid is often helpful
- Von Willebrand levels drop rapidly after delivery, some within 6h
Management of the child with a bleeding disorder
Risk of bleeding into the head in haemophilia

- Risk of intracranial bleeding in first 4 weeks about 4% haemophilic babies
- Normal babies 1 in 860 (vacuum extraction) to 1 in 1900 (normal deliveries)
Management of infants with haemophilia

• Prospective study of 580 babies diagnosed aged 0-2 yrs
• USA 135 haemophilia centres
• Birth and delivery – 68% vaginally, 32% CS
• Factor therapy at birth 45 (8%), 26 as prophylaxis (controversial) and 19 for bleeding events
• Head bleeding events as initial bleeding event
  – 28 ICH (71% in infants with no known family history)
    • 27 at less than 1 month of age, 17 of these associated with delivery
    • 5 events aged 1-6 months
• Bleeding after circumcision
• Bleeding after heel sticks

Kulkarni et al. Haemophilia 2009
How can we identify the women at risk?

- Target the women through advocacy organisations.
- Remind GPs and gynaecologists that menorrhagia is symptom of a bleeding disorder.
- Remind haematologists that women with a bleeding disorder may have menorrhagia.
Hope to see you there