



## Managing Menorrhagia

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Haematologist

Gynaecologist

Woman with bleeding disorder

+



+

## Women with Bleeding Disorders Haematologist v Gynaecologist

### Haematologist- bleeding symptoms

- Menorrhagia 90% women
  - Postpartum haemorrhage
  - Dental bleeding
  - Bruising
  - Epistaxis
  - Postoperative bleeding
  - Bleeding after injury

### Gynaecologist - menorrhagia

- 10-15% of women
- 15% referrals to gynaecologists
- 300,000 hysterectomies done worldwide each year
- Bleeding disorders present in 20% of women

## Definition of Menorrhagia?

Blood loss > 80ml per menstrual cycle

- Based on data from 1960s
- Very subjective
- <50% women referred with menorrhagia have loss >80ml

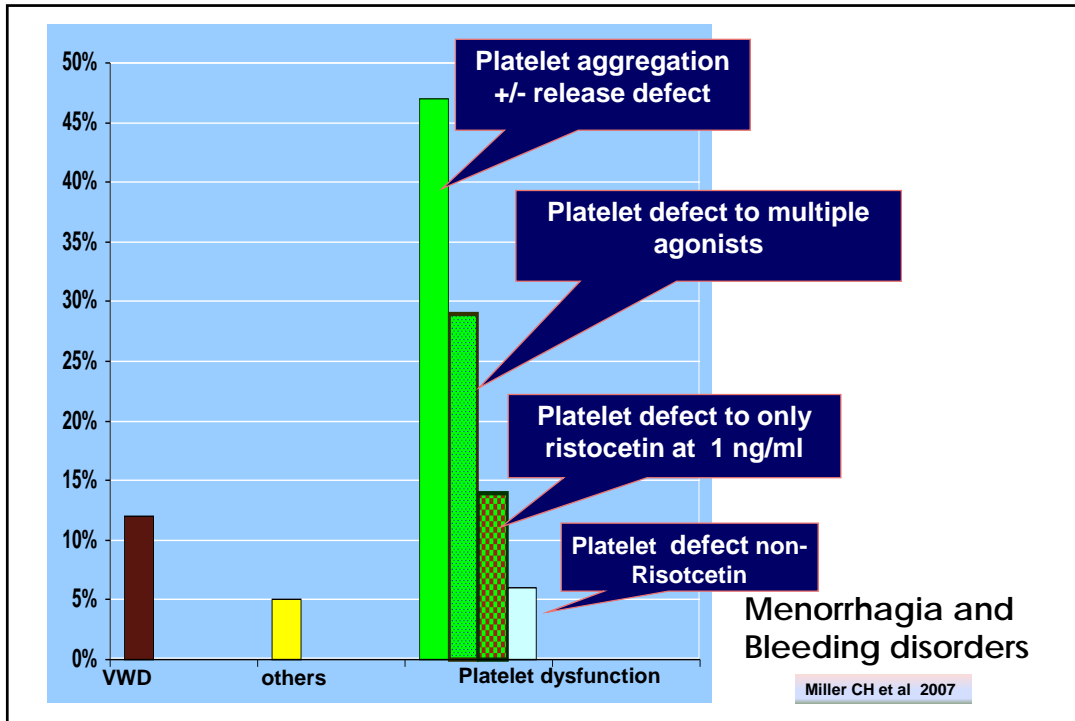


125ml

## + Practical Definitions of Menorrhagia

- Clinical/menstrual history variables associated with blood loss  $\geq 80\text{ml}^*$ 
  - Change in sanitary protection more than hourly at time of full menstrual flow
  - Clots > size of AUS\$ 1 coin (2.6cm)
  - Low ferritin
- Others<sup>§</sup>
  - >30 pads/tampons per cycle
  - Using pad + tampon at same time
  - Requiring super-absorbent pad or tampon
  - Frequent staining of clothes
  - Lost time off from school or work

\*Warner et al. Am JO&G 2004 190:1216-23  
§ Kouides. Haemophilia 2002 8 (3) 330-338



## PBAC Score: Pictorial Blood Assessment Chart

- Score >185 sensitive + specific
  - Prospective assessment
  - Subjective
  - choice of hygiene product
- Mean PBAC score
  - vWD 374 (28-1600)
  - Haemophilia carriers 289 (28-832)
  - Rare BD 257 (47-745)

The numbers 1-8 represent the consecutive days of your menstrual period. Please record for each day the number of pads you used to match each illustration

Pad	1	2	3	4	5	6	7	8
1 pt/pad								
5 pts/pad								
20 pts/pad								
Clots (Yes/No)								

The numbers 1-8 represent the consecutive days of your menstrual period. Please record for each day the number of tampons you used to match each illustration

Tampon	1	2	3	4	5	6	7	8
1 pts/tampon								
5 pts/tampon								
10 pts/tampon								
Clots (Yes/No)								

**Name: M.V.B.**  
**LMP: 15/1/97** **SCORE: 204**

TOWEL	1	2	3	4	5	6	7	8
CLOT FLOODING	1P X2	50P X2						

TAMPON	1	2	3	4	5	6	7	8
CLOT FLOODING								

**Women with bleeding disorders**

**Early detection**  
**Severity & associated morbidity**  
**Assessment tool - treatment efficacy**

## + Causes

50% unknown

- Anovulation
  - Menarche
  - Thyroid disease
  - Polycystic ovarian disease
  - Menopause
- Exogenous hormones
- Fibroids
- Polyps
- Endometrial hyperplasia
- Cancer

## + Question

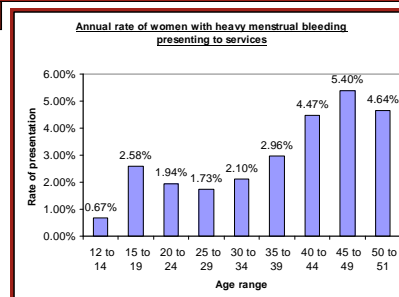
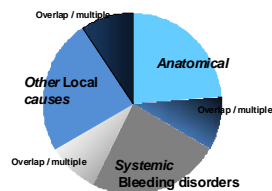
- There is a 50% risk that the son of a female carrier of haemophilia will have haemophilia.
  - What percentage of obstetricians surveyed in the UK could correctly answer this question?
- a) 20%
  - b) 50%
  - c) 70%
  - d) 90%

Chi et al. Haemophilia 2006; 5: 2619

## Menorrhagia – Heavy Menstrual Loss

**Definition - ?**  
Excessive menstrual blood loss affecting quality of life  
Physical, emotional, Social  
Commonly occurs with other symptoms

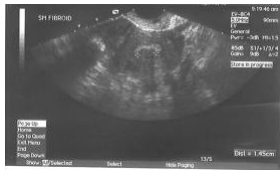
**Affects ~ 880,000 women in England**  
**18 million women world wide**



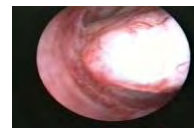
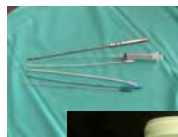
➤ **50% cause is unknown – Dysfunctional**  
➤ **Within a year - 50% surgical intervention**  
➤ **Majority with no anatomical abnormality**

➤ **Bleeding disorders - under-estimated**  
➤ **In the presence of other causes ?**

## Pelvic Ultrasound structural abnormalities



**Endometrial biopsy**  
 intermenstrual bleeding  
 Failure of medical tx women >45 y  
**Hysteroscopy + biopsy**  
 ultrasound inconclusive  
 therapeutic



## Heavy menstrual bleeding

**NHS**  
 National Institute for  
 Health and Clinical Excellence

Hormonal or non-hormonal treatments are acceptable

- LNG-IUS
- TA or NSAID or CHC
- norethisterone or injected long-acting progestogens

Hormonal treatment is not acceptable, woman wishes to conceive

- Tranexamic acid
- NSAID

**In clinical practice**  
 often women are not known/not sufficiently investigated for bleeding disorder

### NSAID

- inhibit platelet aggregation
- increase the risk of bleeding
- exacerbate menstrual loss in

NICE clinical guideline 44

January 2007



+ Menorrhagia Treatment

Preservation of fertility ✓

Pregnancy now?

✓

X

Tranexamic acid  
DDAVP  
FVIII/FIX  
VWF conc

Hormonal  
Levonorgestrel IUD  
Combined OC  
Progesterone only pill

+ Menorrhagia Treatment

Preservation of fertility X

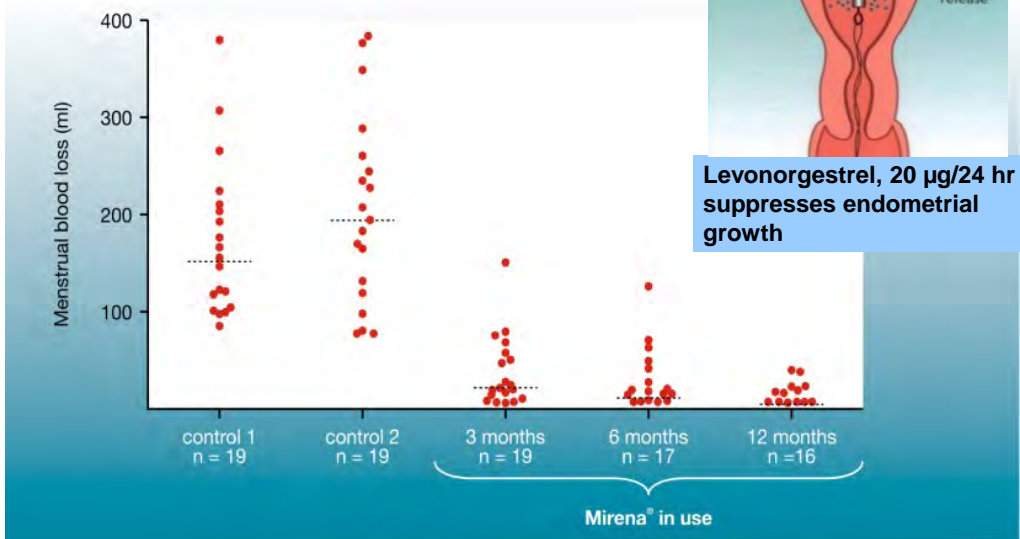
Tranexamic acid  
DDAVP  
FVIII/FIX  
VWF conc

Hormonal  
Levonorgestrel IUD  
Combined OC  
Progesterone only pill

Hysterectomy  
Endometrial ablation

## LNG-IUS (Mirena)

Most effective reversible contraceptive – 5 y



## LNG-IUS (Mirena)

- Duration - ≤ 1 day at 12 months
- Amenorrhoea - 17% first year  
- 75% five years
- Continuation - 81% at 3 years

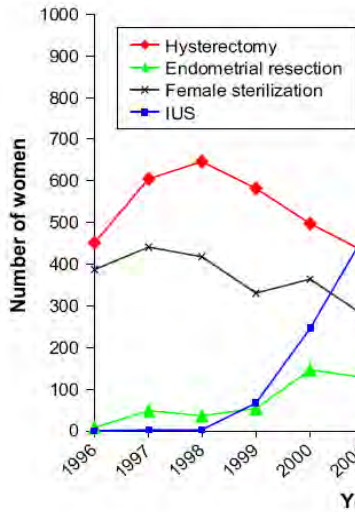


Figure 2. Fall in gynaecology surgery with associated rise in use of the Newcastle upon Tyne.

**Menstrual pain & PMS**  
**Endometrial hyperplasia**  
**Endometriosis**  
**? Adenomyosis /fibroid**

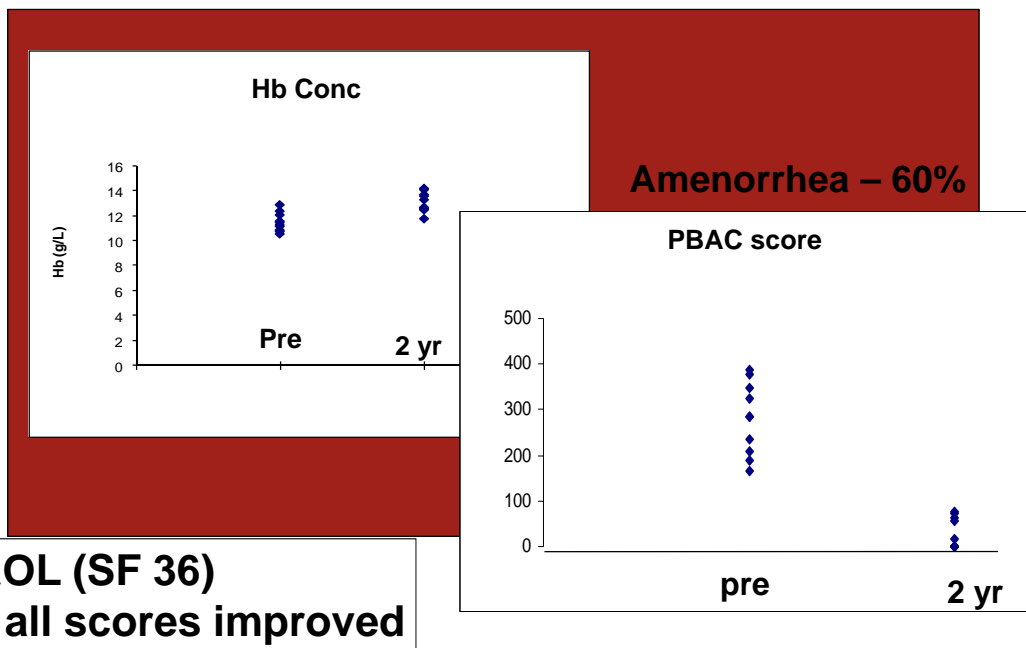
LNG-IUS (Mirena)

**Menstrual irregularity  
prolonged bleeding/spotting**

Side effects	Three months <small>% of women rep. side effects</small>	Fifth year <small>% of women rep. side effects</small>
Lower abdominal pain	10.5	2.0
Acne or other skin problems	3.5	1.8
Back pain	3.1	1.0
Mastalgia	3.1	1.0
Headache	2.8	1.6
Mood changes	2.5	0.6
Nausea	2.4	0.3

**Uterine perforation – 1/1000  
Expulsion rate – 1/20 women in 5 year**

LNG-IUS (Mirena)-**Women with bleeding disorders**

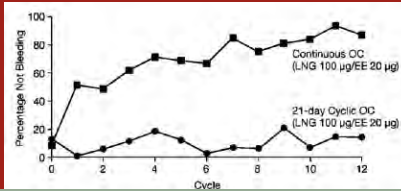


## Hormonal Treatment

Combined hormonal contraceptives  
Oral, Transdermal, vaginal rings

- Contraception
- Good cycle control
- control ↓ Pain and PMS

### Extended use CHC



- Less bleeding episodes/spotting
- Fewer menstrual symptoms
- No difference to traditional regimens
- Return to fertility
- Change in BP, weight, biochemistry

Machado 2004, Wiegatz 2004, Edelman et al 2006

### Women with bleeding disorders

- ↓ MBL – effective (24-88%)
- Prevention of ovulation bleeding
- Risk of thrombosis in very small

### Others

- Progestogens
- Oral
- Other long acting

**Jadelle**

Foster 1995, Jarvis 2002

## Haemostatic non-hormonal Treatment

### DDAVP nasal/subcut

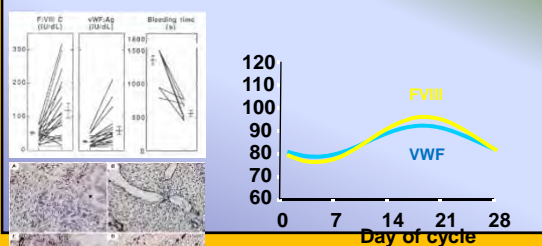


### Tranexamic acid

Fibrinolytic activity  
Increased in menorrhagia  
positive correlation with MBL

TA - 40-50% Reduction in MBL

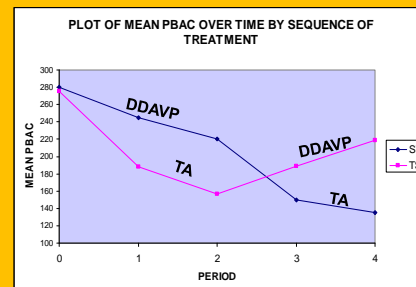
Lethaby 2000



VWF – Endometrium

Kadir 1999

Lethagen, Blut 1990



Kouides 2007

## Haemostatic non-hormonal treatment

### DDAVP and TA

#### Adverse effect – Fluid Retention

- Female 78% (Vs 59% male) more SE  
5/8 for treatment of menorrhagia
- 2/3 serious SE reported in women treated  
for menorrhagia

Dunn et al 2000, Leissenger et al 2001

#### Premenstrual phase – anti diuretic phase

#### To minimise adverse effects

- Day 1-2 omit or give only one dose
- Use of adjuvant therapy to avoid prolonged use

Kadir et al 2008

**20 women with prolonged bleeding time**

**MBL- significant reduction**

- DDAVP – during days of administration
- DDAVP + TA – overall MBL

Edlund et al 2002

## Factor Replacement

**During menstrual bleeding**  
**Regularly - severe disorders**  
**Recurrent ovulation bleeding**  
**Excessive/frequent breakthrough bleeding**

**Multi-disciplinary management**  
**Home treatment with close liaison with haemophilia centre**

**Main problem – availability and cost**

## Surgical management

### Hysterectomy



Failed medical treatment  
-Bleeding disorders  
-Haematological assessment

	No VWD n=1,357,588	VWD n=545	P value
Thrombosis	0.20%	0	1.000
Infection	0.38%	0.73%	0.159
Transfusion	2.13%	7.34%	<0.001
Bleeding	0.86%	2.75%	<0.001
Wound compl.	0.15%	0.37%	0.192
Length of stay	3.49 days	3.68	0.0877
Cost	\$13,225	\$19,584	<0.001
Died	0.13%	0.18%	0.515

\*James et al, unpublished data from the NIS

Complication rate 8.7%  
Readmission 6%

Abdominal v vaginal  
higher complication rate

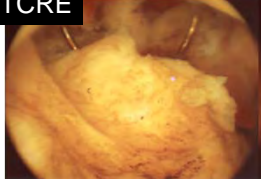
Spilsbury et al 2008

## Endometrial ablation

2<sup>nd</sup> generation



TCRE



- Uterus – 10/52, fibroids < 3 cm
- Less complications, hospital stay but retreatment required
- Not contraceptive

Lethaby 1999

2<sup>nd</sup> generation  
Simple, quick, outpatient procedure

Lethaby 2002



## + Impact of bleeding disorders for women

### Work and school performance

- 39% lost time
- 47% accomplished less

Kadir et al 1998

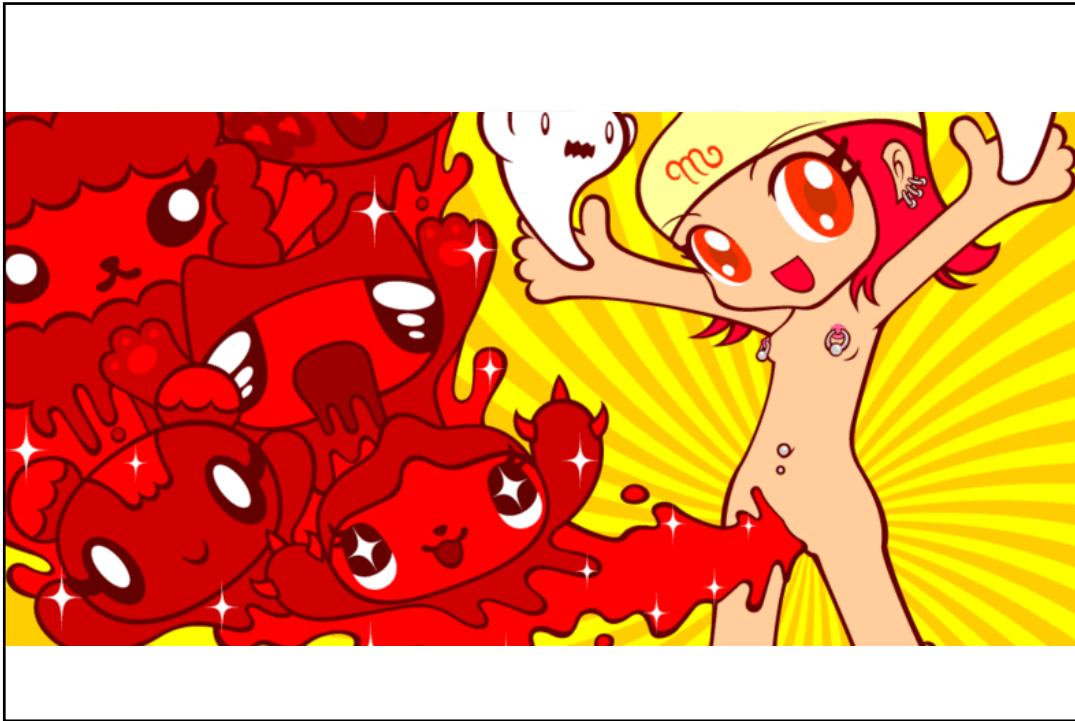
### College or university education

- VWD - 5.5 % Female Vs 35% Male

Barr et al 2003

## + Useful references

- C. A. Lee, C. Chi, S. R. Pavord, P. H. B. Bolton-Maggs, D. Pollard, A. Hinchcliffe-Wood, and R. A. Kadir **The obstetric and gynaecological management of women with inherited bleeding disorders - review with guidelines produced by a taskforce of UK Haemophilia Centre Doctors' Organization.** Haemophilia 12 (4):301-336, 2006.
- Nichols WL, Hultin MB, James AH et al: **von Willebrand disease (VWD): evidence-based diagnosis and management guidelines, the National Heart, Lung, and Blood Institute (NHLBI) Expert Panel report (USA)** Haemophilia 2008;14:171-232
- Andra H James, Kouides, P. A., Abdul-Kadir, R., Edlund, M., Federici, A. B., Halimeh, S., Kamphuisen, P. W., et al. (2009). **Von Willebrand disease and other bleeding disorders in women: consensus on diagnosis and management from an international expert panel.** American journal of obstetrics and gynecology, 201(1), 12.e1-8. doi:10.1016/j.ajog.2009.04.024



### Uterine Artery Embolisation

**Uterine fibroids  
Post operative bleeding**

**Agrawal et al 2008**

### Anti progesterone

Mifpristone RU486

**Reduction MBL**  
60-70% suppress ovulation  
65-90% amenorrhea

**Adverse effects**  
6% hot flushes

**Brown et al 2002**

**Asoprisinil J867**

BEST Clinical Oncology and Gynaecology  
ISSN 1746-2091  
http://www.bestjournal.com

**Future research into abnormal uterine bleeding**

In contrast to progesterone antagonists, selective progesterone receptor modulators (SPRMs) exhibit varying degrees of both progesterone agonistic and antagonistic properties. Although SPRMs do not suppress ovulation, they can induce an antiproliferative effect on the endometrium, although the mechanism for this is unclear. One SPRM showing promise for clinical application is asoprisinil. Preliminary clinical studies of asoprisinil in healthy volunteers demonstrated a dose-dependent suppression of menstruation, irrespective of the effects on ovulation, with no change in basal oestrogen concentrations and no breakthrough bleeding.<sup>24</sup> The drug has also been used to treat fibroid-associated menorrhagia and was found to induce amenorrhoea as well as reduce the volume of the dominant fibroids in a dose-dependent manner without altered basal oestrogen and without symptoms of oestrogen deficiency.<sup>25</sup> Importantly, the safety and tolerability profiles of asoprisinil have been favourable to date. More research is needed into dosages, duration of use, indications for use (fibroids, dysfunctional uterine bleeding, dysmenorrhoea, endometriosis-associated pelvic pain), long-term effectiveness etc.

**Chwalisz 2005    Clark 2007**

## +Acute Adolescent Menorrhagia

### Resuscitation and volume replacement Haemostatic agent

- Factor replacement - specific if available
- Platelet transfusion
- DDAVP
- Tranexamic acid

### High doses of hormones

- IV premarin – 40mg IV 4-6 hourly 48 hr + concomitant use of OC pill
- Progestagens – e.g. 40mg medroxyprogesterone acetate for 10 days followed by cyclical 21 day use or OC pill

- Consider uterotonic - Misoprostol
  - Consider rFVIIa
  - UAE – last resort
- Case report in 12 year old with PAI deficiency

Bowkley et al 2007



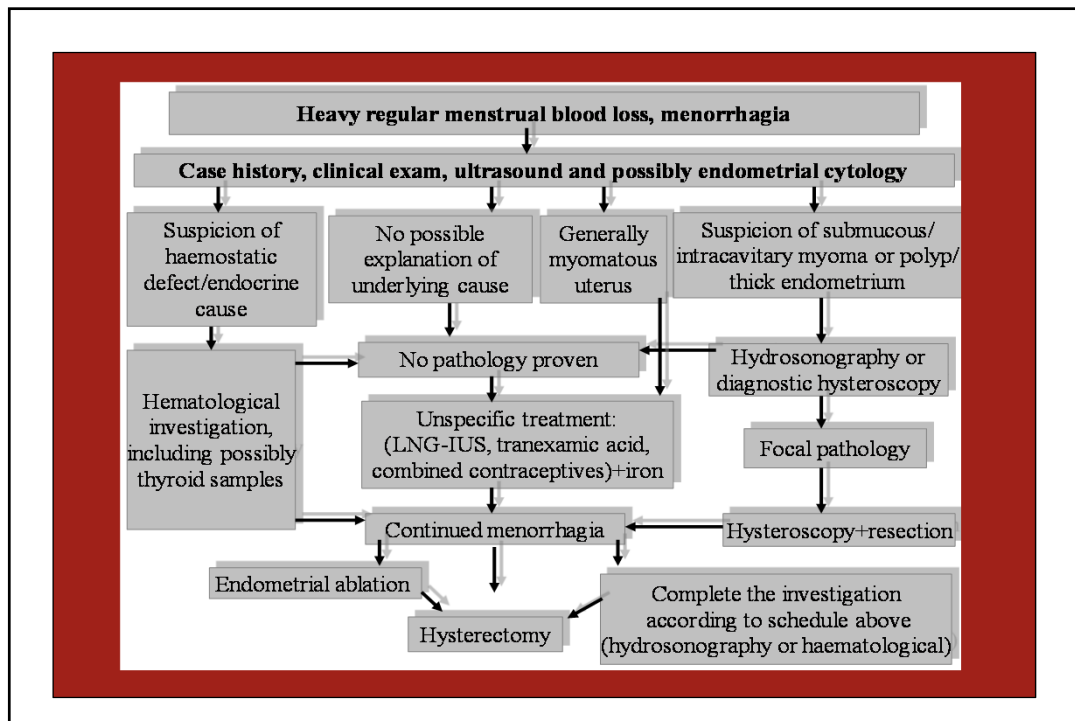
EUA – evacuation of clots and D&C  
Tamponade the uterus -Foley's catheter

Canadian study of 31 girls (mean age 14 years)

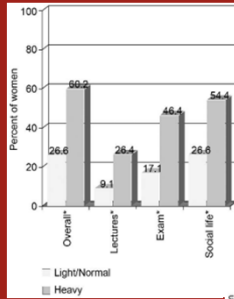
### Complete cessation of bleeding

- Medical Rx – 87% (27/31)
- D&C – required in 4(13%)

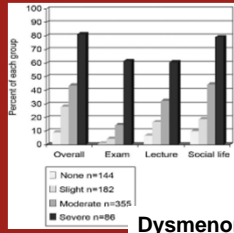
Fleming et al 2007



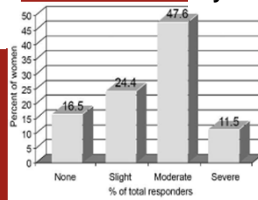
## Menstrual Problems in 767 University Students



Menstrual loss



Dysmenorrhoea



Anastasakis et al 2008