

Abnormal Uterine Bleeding

History of Presenting Illness

- Increased volume of blood
- Increased frequency of bleeding
- Irregular timing of periods
- Bleeding between periods
- Unusually painful menstruation
- Passing of clots

NORMAL UTERINE BLEEDING:

YOU ONLY WANT TO MENSTRUATE...

- Every 24 to 35 days (mean 27-28)
- For 2 to 9 days at a time (mean 4-5)
- With only 1 or 2 heavy days
- Totalling less than 60 ml of blood

Differential Diagnoses

- Abortion
- Adnexal Tumors
- Adrenal Adenoma
- Adrenal Carcinoma
- Cervicitis
- Endometrial Carcinoma
- Endometritis
- Hyperprolactinemia
- Hyperthyroidism
- Hypothyroidism
- Pelvic Inflammatory Disease
- Pituitary Microadenomas
- Uterine Cancer
- Vaginitis

**MUST EXCLUDE
PREGNANCY !!
BEFORE YOU DO ANYTHING ELSE**

- Coagulation disorders
- Endometrial polyps
- Genitourinary infection
- Intrauterine device
- Liver disease/failure
- Medications (chemo?...)
- Renal disease/failure
- Steroid hormones
- Uterine fibroids

Are they on any
HORMONE
REPLACEMENT
THERAPY?

Findings on History

- Is this the first time its happened?
- Was it accompanied by pain?
- How much blood was there? →

SEXUAL HISTORY: ask about STDs,
Ask about sexual abuse

Screen for HEMO + ENDOCRINOPATHY:

Has there been galactorrhoea, hirsutism, cold intolerance, easy bruising?

Contraceptive History: recent cessation of the oral contraceptive pill?

- Intrauterine devices ever installed?

AGE- DIRECTED SUSPICION:

Menarche → late teens:

most commonly have anovulatory bleeding

due to the immaturity of their hypothalamic-pituitary axis. If bleeding does not respond to usual therapy in this age group, a bleeding disorder must be considered.

(Undiagnosed von Willebrands Factor Deficiency is the most likely culprit)

IRREGULAR MENSES SINCE MENARCHE? Or... OBESE? → consider anovulation

30 →50 yr olds:

Organic or structural abnormalities.

Fibroids or polyps are frequent anatomical findings.

Organic causes can be anything from thyroid dysfunction to renal failure.

postmenopausal:

any uterine bleeding should receive an immediate workup for **endometrial cancer.**

Endometrial hyperplasia must be considered in women who are obese, aged 70 or older, nulliparous, or have diabetes.

What bleeding is abnormal?

intermenstrual bleeding

bleeding in between normal periods

menorrhagia

excessively heavy episodes (over 80 ml)

prolonged periods (over 7 days)

metrorrhagia

irregular, frequent and variable periods

postmenopausal bleeding (PMB)

postcoital bleeding

(often associated with intermenstrual bleeding)

precocious menstruation

(usually a component of precocious puberty)

breakthrough bleeding

[BTB; unscheduled bleeding with use of hormonal contraception or hormone replacement therapy (HRT)]

Estimates of VOLUME:

average tampon holds 5 mL

average pad holds 5-15 mL of blood

Passing clots? → There must be over 80ml

Relationship to the THYROID GLAND:

- **HYPO = MENORRHAGIA**

- **HYPER = AMENORRHOEA**

Are there any SYMPTOMS OF ANAEMIA?

Findings on Examination

IMPORTANT STUFF TO LOOK FOR:

Signs of severe volume depletion: **ANAEMIC PALLOR?**

Obesity: = independent risk factor for **endometrial cancer** →

Signs of androgen excess (eg, **hirsutism, acne, virilisation**):

This usually points to polycystic ovarian syndrome (PCOS)

Ecchymosis+ Purpura: This also is a sign of trauma or a possible bleeding disorder.

Visual field exam (looking for pituitary bitemporal hemianopia)

Thyroid gland exam (looking for hypothyroid features)

Breast exam (galactorrhoea, or absence of secondary sexual characteristics)

Hepato or splenomegaly (clotting factor undersynthesis or aplastic thrombocytopenic anaemia)

Adipose tissue is a locale for estrogen conversion. Therefore, the larger the patient, the more increased the risk (and the higher the unopposed estrogen level on the endometrium).

The PELVIC EXAM:

Look for external genital lesions

Look for infectious discharge

Confirm the site of the bleeding

***FOUND SOME SORT OF MASS?
→ immediate ultrasound!***

The UTERINE EXAM:

Uterine size, shape, and contour:

enlarged irregularly shaped uterus = fibroids if you're in the 30-50 age group

enlarged uterus (regular or not) in the elderly = CANCER until proven otherwise

Cervical motion tenderness

= **symptom of pelvic inflammatory disease (PID); gonorrhoea or chlamydia.**

Adnexal tenderness or masses

VERY SCARY if presents in the over-50s:

Ovarian cancer may present with intermenstrual bleeding as its only symptom.

HALLMARK of Dysfunctional Uterine Bleeding (DUB) is a completely NEGATIVE PELVIC EXAM (i.e no pathology → diagnosis by exclusion)

Tests and Investigations

BIOPSY: always the gold standard

Human Chorionic Gonadotropin Blood or Urine Test

Exclude Pregnancy

Full blood count

Exclude ANAEMIA and THROMBOCYTOPENIA

Iron studies

Exclude IRON DEFICIENCY

Imaging of the genital tract:

transvaginal and abdominal ultrasound

sonohysterography

hysteroscopy

endometrial sampling (biopsy or curettage)

Cervical PAP smear

Histology of the cervix may uncover horrible problems

→ but only 40% of the time

Other tests only if indicated by physical + history findings:

Liver function to investigate coagulopathy

coagulation screen to investigate coagulopathy

thyroid function to investigate hypothyroidism

pituitary hormone assay to investigate endocrinopathy

(particularly interested in **PROLACTIN**)

plus LH, FSH if it looks like polycystic ovaries

CT / MRI of abdomen for staging of malignancy

Urine protein, BUN and Creatinine – rule out nephrotic syndrome

SOFT AND FLUFFY MANAGEMENT

Prostaglandin synthetase inhibitors

inhibit the synthesis of prostaglandin

interfere with the myometrial binding of prostaglandin E2 (particularly the **fenamates**)
= 20-40% reduction in menstrual blood loss
= decrease in the number of days of bleeding.

Antifibrinolytic drugs

- act by inhibiting plasminogen activator,

THUS = reduce the accelerated endometrial fibrinolytic activity found in menorrhagic women.

Tranexamic acid reduces menstrual blood loss by about 50% in cases of **DUB**

Cyclical progestogen therapy

- **most effective in cases of anovulatory dysfunctional uterine bleeding**

- has less effect in cases of **ovulatory menorrhagia**.

Agents used include **medroxyprogesterone acetate, norethisterone or dydrogesterone**

- should be used for at least 2 weeks of each treatment cycle

- total treatment duration of about 6 months.

Combined oestrogen-progestogen formulations

= oral contraceptive pill incorporating the synthetic oestrogen ethinylloestradiol

= give a significant decrease in menstrual blood loss of between 40 and 50%.

!! The first cycle may show little change and patients must be encouraged to persist.

= safe in older women up to the age of the menopause *providing that they do not have a history of hypertension, cigarette smoking or venous thromboembolic disorders.*

Danazol, (a derivative of 17 alpha ethinyl testosterone)

= ? inhibits endometrial proliferation

= thus → causes endometrial atrophy

= ALSO reduces pituitary gonadotrophin secretion

= ALSO inhibits enzymes involved in ovarian steroidogenesis. (? Aromatase?)

= **BUT :ANDROGENIC SIDE EFFECTS**

**DANAZOL IS A SQUATTER:
displaces oestrogen
from its own receptors!**

GnRH agonists

= Eg. goserelin and nafarelin

= **initially increases GnRH, but then “exhausts” the pituitary**

= hypogonadotropic hypogonadism resulting in amenorrhoea or oligoamenorrhoea.

= Longterm use is complicated by decreasing bone mass and **should be limited to 6 months**.

Progestogen releasing intrauterine system

= decrease in menstrual loss of 80-90% after 12 months

= not yet licensed in Australia!

HARD AND SCALY MANAGEMENT

Endometrial ablation

= destruction of the endometrium under hysteroscopic visualisation

= an electro-cautery, laser or a microwave technique.

= procedure is performed under general anaesthetic using glycine or similar non-conducting media to distend the endometrial cavity. **MUST DESTROY THE BASALIS LAYER**

= a short stay in hospital and only short term morbidity postoperatively.

= long term amenorrhoea is achieved in 50% of patients

= significant reduction of blood loss in another 40% of patients.

= **this is not for people with painful menorrhagia (DYSMENORRHOEA)**

Myomectomy

= may be performed as an open procedure or laparoscopically to resect submucous myomas from within the endometrial cavity, as a separate procedure or as part of endometrial ablation.

Hysterectomy: major operation with all the risks thereof **Most often performed operation!**

= provides definitive cure for menorrhagia.

= The mortality rate ranges from 0.1-1.1 cases per 1000 procedures.

= The morbidity rate usually is 40%.

Disease Aetiology

Intermenstrual bleeding:

Usually the result of benign or malignant lesions of the inner surfaces of the genital tract (especially cervix and endometrium)

Menorrhagia:

pelvic pathology

[eg myomata (fibroids); adenomyosis; polyps; endometriosis, endometrial carcinoma;

generalised medical diseases

- RARE (coagulation disorders; SLE; hypothyroidism; etc)

dysfunctional uterine bleeding:

(definition of DUB: excessive uterine bleeding which is not due to complications of pregnancy or to pelvic pathology or generalised medical diseases)

- anovulatory or ovulatory

Metrorrhagia:

hypothalamic - pituitary effects on ovarian function

surface lesions of the genital tract

polycystic ovarian disease

Postmenopausal:

- BTB with HRT
- **atrophic vaginitis**
- endometrial adenocarcinoma

Table 24-2. CAUSES OF ABNORMAL UTERINE BLEEDING BY AGE GROUP

Age Group	Causes
Prepuberty	Precocious puberty (hypothalamic, pituitary, or ovarian origin)
Adolescence	Anovulatory cycle
Reproductive age	Complications of pregnancy (abortion, trophoblastic disease, ectopic pregnancy) Organic lesions (leiomyoma, adenomyosis, polyps, endometrial hyperplasia, carcinoma) Anovulatory cycle Ovulatory dysfunctional bleeding (e.g., inadequate luteal phase)
Perimenopausal	Anovulatory cycle Irregular shedding Organic lesions (carcinoma, hyperplasia, polyps)
Postmenopausal	Organic lesions (carcinoma, hyperplasia, polyps) Endometrial atrophy

Menorrhagia is the most common cause of anaemia in premenopausal women

Epidemiology

Frequency:

- menorrhagia = leading reason for gynecologic office visits
- BUT only 10-20% of all menstruating women experience blood loss severe enough
- DUB is a common diagnosis, making up 5-10% of cases in the outpatient clinic setting.

Mortality/Morbidity:

Loss of more than 80 mL of blood = serious medical sequelae.

→ iron-deficiency anemia

→ patients may experience shortness of breath, fatigue, palpitations

Age: Any woman of reproductive age who is menstruating may develop menorrhagia.

Most patients with menorrhagia are older than 30 years.

This is because the most common cause of heavy menses in the younger population is anovulatory cycles, in which bleeding does not occur at regular intervals.

ADOLESCENTS may present with a disorder of haemostasis masquerading as menorrhagia (in up to 20% of cases)

DIRE PREDICTIONS:

About 1-2% of women with improperly managed anovulatory bleeding eventually might **develop endometrial cancer.**

Women who use estrogen HRT for 5 years or longer have approximately a 3.5-fold increase in risk compared with that of women who have never used such therapy

Uterine bleeding in menstruation: the ENDOMETRIAL CYCLE

first day of bleeding is described as day 1 of the menstrual cycle.

Pre ovulation = **proliferative phase (thickening endometrium)**

Post Ovulation: **Secretory phase : glands dilate, become tortuous;
→ begin secreting glycogen rich mucus)
Stroma cells become oedematous**

No fertilised ovum to care for? That means...

The thick blood-rich nutrient-crammed endometrium is USELESS

Thus;

- The endometrium shrinks in height.
- The spiral arterioles supplying the endometrium go into spasm causing ischaemia and stasis.
- There is an influx of inflammatory white blood cells initiating release of prostaglandins of the F series and E series.
- Finally the tissue collapses leading to bleeding and shedding of the spongiosum layer of the endometrium.

The average volume of menstrual blood loss during menstruation is 30mL with a range of 10 to 80mL.

Normal menstrual blood does not clot because of the presence of fibrinolytic substances.

HEMNOSTASIS IS ACHIEVED BY:

- the **partial occlusion of spiral arterioles with platelet and fibrin plugs;**
- the predominance of **F series prostaglandins (vasoconstrictors)** over E series prostaglandins (vasodilators) during menstruation;
- normal **ovarian follicle growth supplying oestrogen to regenerate the endometrium.**

Uterine action of sex hormones

**In the glands of the endometrium,
progesterone is
antagonistic to oestrogen.**

Sex Steroids in General:

oestrogen receptor = activated by **oestradiol**, (E2) by various synthetic oestrogens to a lesser extent, by oestriol

progesterone receptor= activated by **progesterone**, by various synthetic progestogens

androgen receptor = activated by **dihydrotestosterone** to a small extent the progestogens (of the 19-nortestosterone type).

Oestrogen @ endometrium:

- **Increases mitosis**
- **UPREGULATES ITS OWN RECEPTORS AND PROGESTERONE RECEPTORS**
- **Thus oestrogen is needed to prime the uterus for the secretory phase (else it wont respond to the progesterone from the corpus luteum)**
-

Progesterone @ endometrium:

- **INHIBITS mitosis**
- **DOWNREGULATES ITS OWN RECEPTORS**
- **Downregulates oestrogen receptors**
- **Stimulates cell differentiation**
- **→ leads to a well-ordered sequence of cessation of mitosis, subnuclear vacuolation, supranuclear vacuolation and glandular secretion, stromal edema and stromal cell decidualisation**

WITHDRAWAL OF PROGESTERONE @ ENDOMETRIUM

→ activates **LYSOSOMES**→ the endothelium dies and is shed

TOO MUCH OF PROGESTERONE @ ENDOMETRIUM:

→ the endothelium **STILL DIES!** It inhibits its own receptors, so after a while the endothelium wont detect it **AS IF IT HAD BEEN WITHDRAWN**

SO: THE ENDOCRINE BASIS OF ORAL CONTRACEPTION: you give progesterone EARLY in the proliferative phase to STOP THE OESTROGEN-INDUCED THICKENING

...a thin under-developed endometrium wont bleed as much, or harbour a foetus.

Risk factors for uterine cancer

Causal risk factors

- Late menopause
- Nulliparity
- Prolonged
- Unopposed
- Estrogen exposure
- Obesity
- Other cancers
- Familial Cancer Syndromes
- Polycystic ovarian disease

Casual risk factors

- Hypertension
- Diabetes
- Mellitus

Factors associated with decreased disk

- Oral Contraceptive Pill
- Alcohol
- Progestogens

Hormone Replacement Therapy: *Why would anyone ever do that to a patient?*

Acute oestrogen withdrawal?

- *hot flushes,*
- *night sweats,*
- *insomnia,*
- *difficulty in concentration,*
- *loss of short term memory,*
- *lethargy,*
- *depression,*
- *anxiety,*
- *loss of libido,*
- *skin itchiness,*
- *dry vagina*
- *superficial dyspareunia?*

Then you need HRT!

* Loss of libido may also require *testosterone*

If you're a **HYPOGONADAL MAN**

If you're **MENOPAUSAL WOMAN**

If you've **HAD BOTH YOUR OVARIES REMOVED**

**HRT: Oestrogen orally or transdermally
+ Progesterone cyclically**

(cant just give oestrogen, or the endometrium will not know when to stop growing!)

...of course, if you have no uterus its OK to give oestrogen alone.

Supplemental vaginal oestrogen (tablets or creams) can be given to women with symptoms of vaginal atrophy.

the only way to sensibly stop HRT is to gradually reduce the dose over 4-6 months (or symptoms recur - often dramatically)

WHAT ELSE DOES IT DO:

prevents loss of calcium salts from bone (with reduction in risk of osteoporotic fractures),

slows development of arteriosclerosis (with reduction in risk of myocardial infarction),

reduces changes in large bowel mucosa (with reduction in risk of colon cancer),

reduces changes in brain function (with reduction in risk of Alzheimer's dementia)

prevents a number of adverse changes...

in the pelvic floor, bladder and vagina, joints (osteoarthritis), skin, teeth, hair and eyes.

!! WARNING !! → causes slight increase in breast cancer risk;

→ causes small increase in the risk of (non-fatal) venous thrombo-embolism and of some arterial thrombosis in the first year of use of HRT

Many other reproductive and lifestyle factors have a much greater influence on breast cancer risk than HRT.

