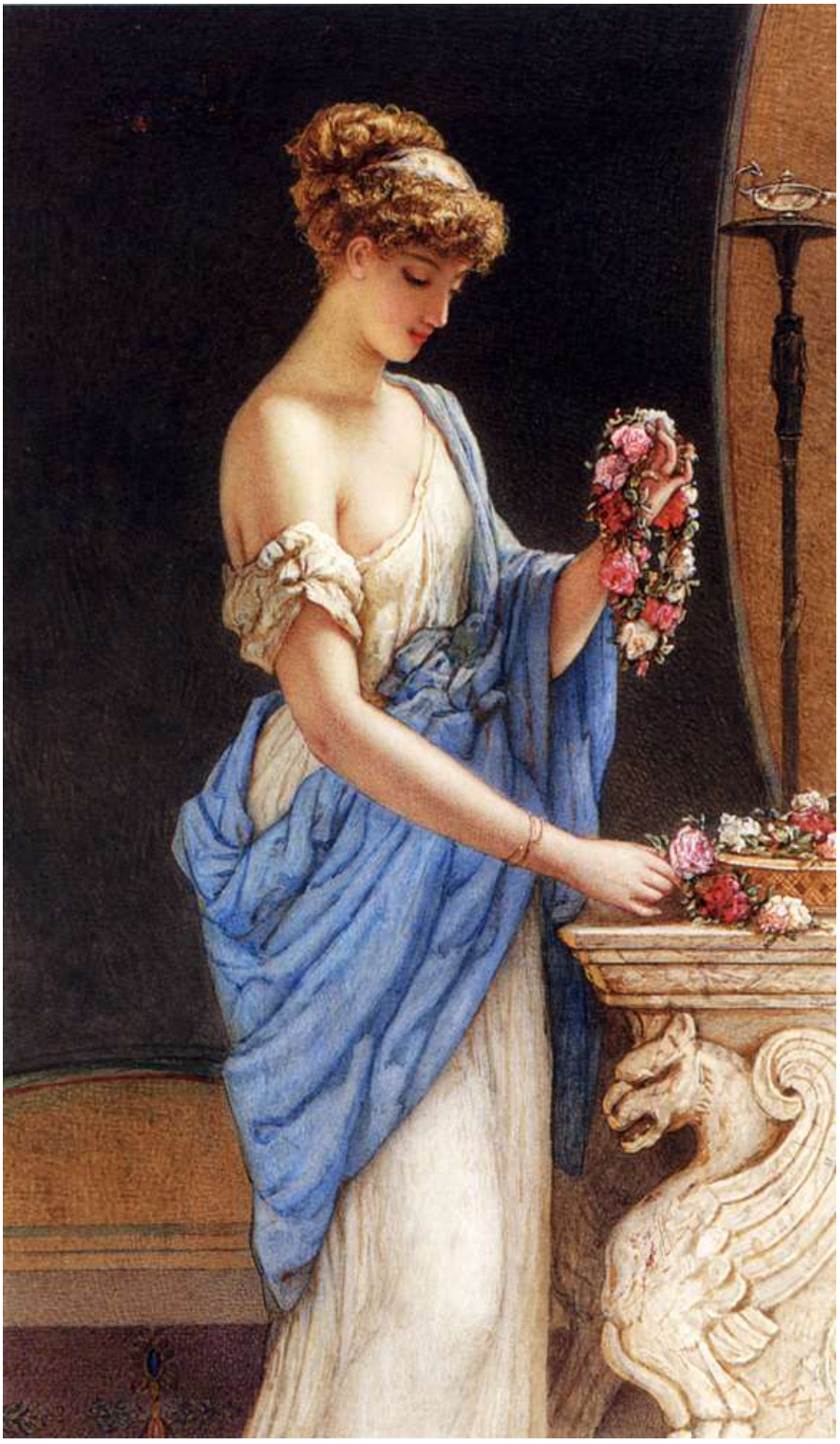
THE NORTHERN HOSPITAL

NON-PREGNANCY RELATED PV BLEEDING



"A Girl in Classical Dress", 1874 Water colour on paper, Auguste Jules Bouvier

"She neither danced nor sung, nor played on the flute, her skill was confined to the pantomime arts; she excelled in buffoon characters, and as often as the comedienne swelled her cheeks, and complained with a ridiculous tone and gesture of the blows that were inflicted the whole theatre of Constantinople resounded with laughter and applause. Her features were delicate and, her complexion though somewhat pale, was tinged with a natural colour; every sensation was instantly expressed by the vivacity of her eyes; her easy emotions displayed the graces of a small but elegant figure; and either love or adulation might proclaim that painting and poetry were incapable of delineating the matchless excellence of her form. But this form was degraded by the facility with which it was exposed to the public eye, and prostituted to licentious desire. Her venal charms were abandoned to a promiscuous crowd of citizens and strangers, of every rank and of every profession: the fortunate lover who had been promised a night of enjoyment was often driven from her bed by a stronger or more wealthy favourite; and when she passed through the streets, her presence was avoided by all who wished to escape either the scandal or the temptation. The satirical historian has not blushed [1] to describe the naked scenes which Theodora was not ashamed to exhibit in the theatre. [2]After exhausting the arts of sensual pleasure [3] she most ungratefully murmured the parsimony of nature [4];but her murmurs, her pleasures, her arts, must be veiled in the obscurity of learned language…

…Her beauty assisted by art or accident soon attracted, captivated, and fixed the patrician Justinian…the treasures of the East were poured at her feet and the nephew of Justin was determined perhaps by religious scruples, to bestow on his concubine the sacred and legal character of a wife.

…the prostitute who in the presence of innumerable spectators, had polluted the theatre of Constantinople, was adored as a queen in the same city by grave magistrates, orthodox bishops, victorious generals, and captive monarchs.

…Her secret apartments were occupied by the favourite women and eunuchs, whose interests and passions she indulged at the expense of justice: the most illustrious personages of the state were crowded into a dark and sultry antechamber, when at last after tedious attendance they were admitted to kiss the feet of Theodora, they experienced, as her humour might suggest the silent arrogance of an Empress or the capricious levity of a comedian…

Perhaps her health had been impaired by the licentiousness of her youth…at length in the twenty fourth year of her marriage and the twenty second year of her reign, she was consumed by a cancer and the irreparable loss was deplored by her husband who in the room of a theatrical prostitute might have selected the purest and most noble virgin of the East."

Edward Gibbon, "The History of the Decline and Fall of the Roman Empire", volume 4 1781.

"Gibbon's fame was now well established. Only the clergy continued their attacks, and indeed extended them; for they found a new front against which to direct them. This was what even Gibbon's defender, the Greek scholar Richard Porson would describe as his "rage for indecency": an indecency which was generally relegated to the footnotes and protected by the "obscurity of learned language". The most notorious of such notes

described the strip-tease act of the Empress Theodora, the wife of Justinian, in her unreformed days as a prostitute on stage. Gibbon leaves the quotation in the original Greek of the Byzantine historian Procopius, from which I shall not presume to release it. The clergy were perhaps particularly irritated by this comment, "I have heard that a learned prelate, now deceased, was fond of quoting this passage in conversation". The prelate is said to have been William Warburton, Bishop of Gloucester, the swashbuckling literary tyrant whose pretensions to scholarship had once been punctured by Gibbon. The Bishop of Norwich was so shocked by this quotation that he went through the whole of Gibbon's work extracting the indecent passages in order to hold them up for execration; but he was forestalled by the edition of "The Gentleman's Magazine", who published such a list, without comment and was duly reproached by a correspondent for printing "filthy extracts from a silly book". I am told that Cecil Rhodes was so stimulated by this note that he hired a classical scholar to translate all Gibbon's Greek and Latin quotations, but was disappointed by the meagre result".

Hugh Trevor-Roper, Introduction to 1994 Everyman's edition of volumes 4-6 of Edward Gibbon, "The History of the Decline and Fall of the Roman Empire"

The greatest scandal of the early Byzantine (or latter Eastern Roman) Empire of the Sixth century AD was the marriage of probably their greatest emperor Justinian I, to a common theatre prostitute, to whom he was hopelessly enslaved. So powerful was Justinian however no subject in the land would dare to oppose the union. Any word against her would have meant instant death. Not only did he marry Theodora, but he elevated her to co-empress of the empire. The highest citizens of the land, "grave magistrates, orthodox bishops, victorious generals, even captive monarchs", who required her audience, where forced to approach her on bended knee and to kiss her feet, before being either ignored or ridiculed. Her early life and reputation was so scandalous and shocking that Edward Gibbon felt himself unable to provide translation of the original ancient Greek descriptions of her given by Procopius. He did however include some of the original Greek in a series of footnotes to his great work, "Decline and Fall of the Roman Empire", resulting in a great scandal upon its publication. The only English he did provide within one of his footnotes was the rather cryptic, "…she wished for a fourth altar on which she might pour libations to the god of love".

After she married Justinian however she remained faithful to him to her death and he to her. She predeceased Justinian who was devastated by his loss. He never took another Empress. The ancient sources are vague on her cause of death, Procopius saying only that she was "consumed by a cancer". From what we know of Theodora's early life, however, cancer of the cervix would be a fair bet. In the mid-Sixth century AD there was nothing that could have been done for her even though she was the second most powerful person of the Empire. Only 21st century medical science in the form of Gardasil, could have prevented the consuming cancer of the infamous Empress, provided she had received it before she embarked on her career as a "performer" in the seedy theatres of Sixth century Constantinople. Happily women of the 21st century may be readily protected against the "consuming cancer" not only by Gardasil but also by PAP smear. Although most will not carry quite the same risk profile as Theodora, it is nonetheless very important that this message should be given to young women, and when we provide this message it must be delivered in plain English and not be "veiled in the obscurity of learned language".

NON PREGNANCY RELATED PV BLEEDING

Introduction

Vaginal bleeding can be thought of as **pregnancy related** or **non-pregnancy related.**

The following relates to vaginal bleeding in the non-pregnant patient

Of the causes of non-pregnant related bleeding, the causes can be thought of as:

- Primary or abnormal uterine bleeding.
- Secondary genital tract bleeding.

Primary or abnormal uterine bleeding is the most common cause.

All women of childbearing age with PV bleeding must be assumed to be pregnant until proven otherwise.

All postmenopausal women with PV bleeding must be assumed to have carcinoma (vaginal, cervical or endometrial) till proven otherwise.

See also separate documents on:

- **Vaginal Bleeding in Early Pregnancy - Threatened Miscarriage**
- **Vaginal Bleeding in Early Pregnancy - Miscarriage**

Terminology

Menorrhagia:	Menstrual cycles that are either excessive or prolonged A strict definition of menorrhagia is defined as a loss of more than 80 mL per menstrual cycle (about 6 tampons per day for 4 to 5 days).[1]
Metromenorrhagia:	Excessive or prolonged bleeding that occurs at irregular intervals.
Oligomenorrhoea:	Interval between uterine bleeding from 35 days to 6 months.
Polymenorrhoea:	Regular bleeding that occurs at intervals shorter than 21 days.
Amenorrhoea:	The absence of bleeding for more than 6 months
Intermenstrual bleeding:	Bleeding that occurs between otherwise regular menstrual periods.

Physiology

The Normal menstrual Cycle:

In general terms, a normal menstrual cycle is characterized by: [1]

- An intermenstrual length of 24 to 35 days
- A luteal phase length of 14 ± 1 days
- Vaginal mucus which changes at the time of ovulation to become more copious, clear and stretchy
- Breast and abdominal swelling in the late luteal phase
- Menstrual bleeding of under 80 mL over 4 to 7 days.

Pathophysiology

Causes of abnormal vaginal bleeding in the non-pregnant patient include:

1. **Primary or abnormal uterine bleeding:**
    - Associated with ovulatory cycles:
        - ♥ Most common cause of abnormal uterine bleeding
        - ♥ It presents as **regular** and **heavy** bleeding, which can lead to anemia.
        - ♥ Menstrual blood has been shown to have increased **fibrinolytic activity and/or increased prostaglandins.**
    - Associated with non-ovulatory cycles (also known as **Dysfunction Uterine Bleeding**):
        - ♥ Less common cause of abnormal uterine bleeding
        - ♥ It presents as **irregular bleeding** of variable heavy volume.
        - ♥ In anovulatory cycles, (and other high estrogen states), there is a **relative lack of progesterone** to oppose the estrogenic stimulation of the endometrium.

          This results in excessive endometrial proliferation (and occasionally hyperplasia/ metaplasia). The endometrium becomes unstable and prone to irregular shedding.

          Anovulatory cycles are due to immaturity of disturbances of the hypothalamic - pituitary axis, and so tends to be seen at the extremes of reproductive ages:

♥♥ In the first decade after menarche

♥♥ In premenopausal women.

Also in:

♥♥ PCOS

♥♥ Physical / emotional stress

2. **Secondary genital tract bleeding:**

- Anatomical causes:

  Examples include:

  ♥ Malignant disease (uterine, cervical, vaginal).

  ♥ Fibroids

  ♥ Endometriosis/ adenomyosis.

  ♥ Polyps

  ♥ Varices

  ♥ AVMs

- Infection
- Trauma
- Systemic disease:

  Endocrine disease:

  ♥ Thyroid disorders

  ♥ Hyperprolactinemia

  ♥ Polycystic Ovarian Syndrome (PCOS).

  Hematological disease:

  ♥ Coagulopathies

- Iatrogenic causes:

  ♥ IUDs

- ♥ Drugs:
  - ♥♥ Anticoagulants/

Clinical Assessment

Important Points of history

1. The differentiation of anovulatory bleeding from ovulatory bleeding may be made on history.
   - Ovulatory bleeding follows the usual cyclic periodicity, but is heavy in nature.
   - Anovulatory bleeding is irregular in timing and amount.
2. Bleeding suggestive of a secondary cause:
   - Here bleeding may occur with either regular cycles or, more frequently, with *inter-menstrual or post-coital bleeding.*
3. The presence of clots is abnormal and usually suggests heavy bleeding.
4. Check for any significant symptoms of anemia.
5. Take a general history for possible secondary causes.

Important Points of Examination:

1. Assess for any hemodynamic compromise.
2. Look for signs of anaemia
3. Look for evidence of an endocrinopathy:
4. PV examination to look for any local pathology/ trauma.

Investigations

These will be guided by the clinical situation and the degree of suspicion for any given pathology

The following may need to be considered:

Blood tests:

1. FBE:
   - Anaemia
   - Infection

- Haematological disorders

2. CRP if infection is suspected.

3 **Beta HCG**:

- **This is essential in all women of child bearing age and should be done in all cases to rule out pregnancy related PV bleeding.**

4. Iron studies, if a hypochromic, microcytic blood film is seen

5. Coagulation profile if there is a clinical suspicion for a coagulopathy or the patient is on warfarin.

6. Group and save or cross match blood as clinically indicted.

7. Tests for endocrinopathy

   These are not routinely indicated, but rather should be done where there is reasonable clinical suspicion.

   - TFTs
   - Pituitary hormones.
   - Oestrogen/ progesterone levels

8. Vagina/ cervical swabs for M&C, if infection is suspected.

Ultrasound:

- Especially for fibroids/ adenomyosis/ polyps.
- A limited assessment of the endometrium.

EUA and D&C:

- This may ultimately be needed, especially to rule out malignancy and especially in cases of post menopausal bleeding.

Management

Attend to any immediate resuscitation issues:

- Transfusion may be required in cases of severe/symptomatic anemia.

Primary or abnormal uterine bleeding:

There are 4 principle pharmacological treatments for abnormal uterine bleeding:

1. The progestins

2. Anti-fibrinolytic agents

3. Anti-prostaglandin agents

4. Combined oral contraceptive pill (COCP)

Considerations for these options include:

- **All** these agents may be used for ovulatory or non-ovulatory abnormal uterine bleeding.

- **Ovulatory bleeding** will benefit relatively more than non-ovulatory bleeding by treatment with:

    - ♥ An antifibrinolytic agent - Tranexamic acid.

    - ♥ An antiprostaglandin agent - Ibuprofen/ naproxen/ mefenamic acid

- **Non-ovulatory bleeding** will benefit relatively more than ovulatory bleeding by treatment with:

    - ♥ Progestins

Options for mild to moderate bleeding:

The progestins: [1]

- **Norethisterone**:

    - ♥ **5 mg b.d or tds; on days 1- 21 of a 28 day cycle for up to 6 months (for ovulatory cycles)**

      5 mg orally, once daily for the same 12 days of each calendar month (for anovulatory cycles)

Or

- **Medroxyprogesterone acetate**. [1]

    - ♥ **10 mg 1-3 times a day (depending on degree of bleeding) on days 1- 21 of a 28 day cycle for up to 6 months (for ovulatory cycles)**

      10 mg orally, once daily for the same 12 days of each calendar month (for anovulatory cycles).

Anti-fibrinolytic agents: [1]

- **Tranexamic acid:**

- ♥ **1 - 1.5 gram 6-8 hourly for the first 3 to 5 days of menstruation.**

Anti-prostaglandin agents: [1]

- Mefenamic acid:
  - ♥ **500 mg orally, 3 times daily.**
- Ibuprofen:
  - ♥ **200 to 400 mg orally, 3 to 4 times daily. Maximum daily dose 1600 mg.**
- Naproxen:
  - ♥ **500 mg orally initially, then 250 mg every 6 to 8 hours. Maximum daily dose 1250 mg.**

LNG-IUS Device:

If **long term** treatment is required then a Levonorgestrel-releasing intrauterine system (**LNG-IUS)** device may be used, which is placed into the uterus.

The levonorgestrel-releasing intrauterine system (LNG-IUS) releases levonorgestrel at an initial rate of 20 micrograms daily, and provides effective contraception for 5 years.

An LNG-IUS should only be inserted by a trained practitioner.

Combined oral contraceptive pill (COCP): [1]

- The COCP produces a thinner endometrium, and has a high degree of patient acceptability and convenience.

  It is the most widely used first-line drug in primary care for controlling heavy menstrual bleeding, whether cycles are ovulatory or anovulatory.

  There are many preparations available - but one with at least **30 micrograms of ethinyloestradiol** should be used.

Options for acute emergency heavy menstrual bleeding: [1]

High dose regimens may be necessary for the short term control of heavy bleeding.

Tranexamic acid:

In the acute setting, **tranexamic acid** is considered first-line treatment.

It can be given orally or IV in more serious situations:

- **Tranexamic acid 1 to 1.5 g orally, 6 to 8 hourly until bleeding stops.**

Or

- **Tranexamic acid, 10 mg/kg IV, every 8 hours until bleeding stops.**

Hormonal treatment:

If tranexamic acid is unavailable or not tolerated, hormonal treatments may be used:

- **Norethisterone 5 to 10 mg orally, every 4 hours until bleeding stops.**

Or

- **Medroxyprogesterone 10 mg orally, every 4 hours until bleeding stops. Maximum daily dose 80 mg**

Or

- **An ethinyloestradiol 30 to 35 micrograms combined oral contraceptive pill orally, every 6 hours until bleeding stops. Re-evaluate after 48 hours**

  *Occasionally if the bleeding still doesn't stop, a **high dose oestrogen** may be required, (though this nausea can become a significant problem)*

  Use an ethinyloestradiol 50 micrograms combined oral contraceptive pill orally, every 6 hours until bleeding stops. Re-evaluate after 48 hours.

Surgical options

The ultimate treatment option will be **surgical**.

Endometrial ablation or **hysterectomy** may be preferred to drug therapy in women who:

- No longer wish to be able to conceive
- Are perimenopausal
- Have poorly controlled symptoms
- Have adverse effects from the drugs
- Have significant uterine pathology.

Hysterectomy is preferred to drug therapy for women with endometrial hyperplasia with atypia where endometrial ablation is not appropriate.

Secondary genital tract bleeding:

Treatment in these situations is, of course, primarily directed to the **underlying cause.**

Preventive Measures

It is important to emphasize to women that preventive measures that are available that reduce the risk of one of the most important causes of non-pregnancy related PV bleeding, **cervical carcinoma.**

These measures include:

- **Papanicolaou** (**PAP) smear** screening.
- **Gardasil vaccination**:
    - ♥ For the Human Papilloma Virus, a major cause of cervical carcinoma.

Disposition:

Admission to hospital will be necessary for those with:

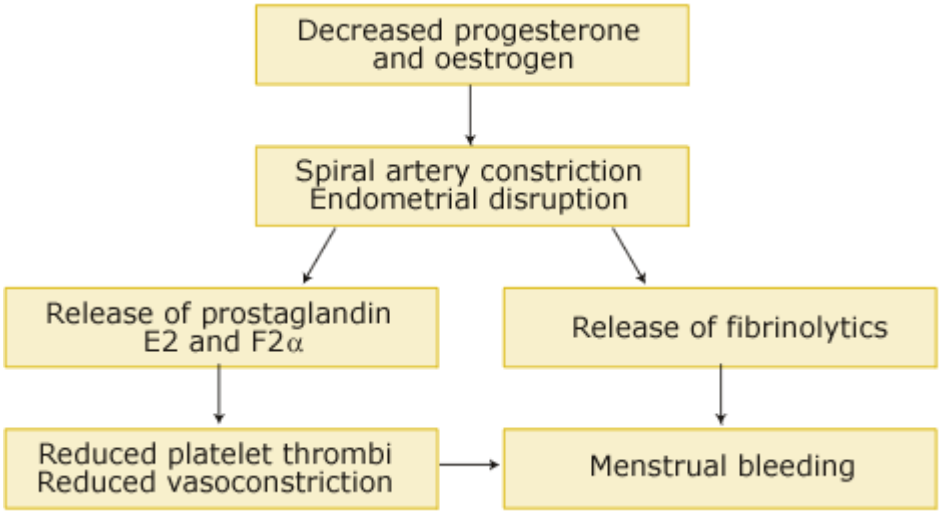
- Hemodynamic compromise.
- Clinically significant or severe anaemia
- Significant systemic illness requiring investigation and/ or stabilization.

If the patient is not unwell then referral to Gynaecology outpatients should be made. **This is urgent for women with postmenopausal bleeding.**

Appendix 1

The Pathophysiology of Menorrhagia: [1]

- The endometrium undergoes proliferation and thickening during the follicular phase under the influence of oestrogen produced by the ovary.
- A normal endometrial thickness, as measured by ultrasound, is between 6 and 12 mm.
- After ovulation, the endometrium is exposed to progesterone produced by the corpus luteum.
- Biochemically, the cycle is confirmed as being ovulatory if the serum progesterone is above 20 nmol/L during the midluteal phase (5 to 10 days before menses).
- Menorrhagia is favoured by endometrial development that is not followed by ovulation, excessive local production of prostaglandins, or excessive fibrinolysis of clot



The physiology of menstrual bleeding. [1]

References

1. eTG - March 2015:

    - Endocrine Therapeutic Guidelines, 5th ed 2014.

2. Bryan S, Brown F.T. Abnormal Vaginal Bleeding in the Non-Pregnant Patient: in Cameron et al. Textbook of Adult Emergency Medicine, 4th ed 2015.

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Reviewed June 2015.