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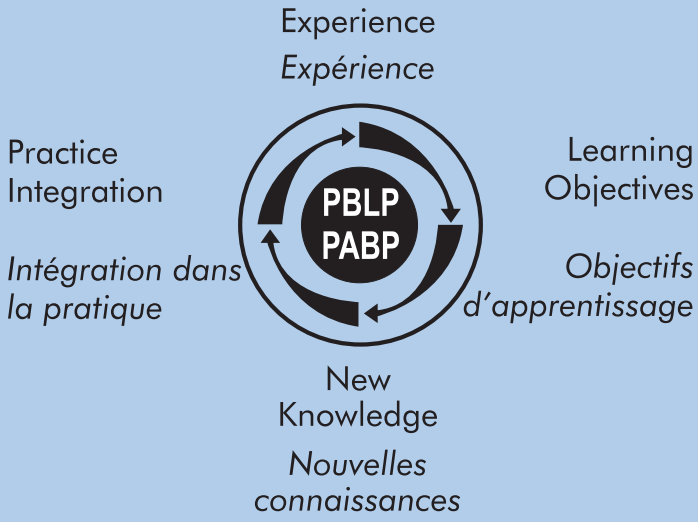

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Practice Based Learning Programs (PBLP)
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McMaster University
1280 Main Street West • DTC Basement
Hamilton • Ontario • Canada L8S 4L8

Tel: 905-525-9140 ext./poste 22219 • 1-800-661-3249
Fax: 905-540-4988
Email: fmpe@mcmaster.ca
Website: www.fmpe.org

ABNORMAL UTERINE BLEEDING: INVESTIGATING AND MANAGING

Abnormal uterine bleeding (AUB) is a relatively common, complex issue in primary care. Differing guidelines, unclear terminology, lack of information about common underlying causes by age group and menopausal status hamper the use of an evidence-based approach.

This module will enable clinicians to:

- identify the cause of abnormal uterine bleeding in premenopausal and postmenopausal women.
- identify 'red flags' and determine appropriate investigations.
- select effective treatment options.

CASES

Case 1: Catherine, age 17

Catherine has been experiencing very heavy periods with bad cramps for the past four months. She tried ibuprofen with her last two periods, but she does not think it has helped. Her periods started at age 12, and they are regular, every 28–29 days. With her most recent period, bleeding on the first day was so heavy that she soaked through both a tampon and a pad almost every hour. During her previous period, Catherine bled through her clothing during a volleyball game, and she is very concerned about this happening again. She wants to know if there is any way to prevent this. She has a steady boyfriend, and he uses condoms as their method of contraception.

What additional information from history would be helpful for identifying the underlying cause for her heavy bleeding?

What physical examination would be indicated?

What investigations would you consider?

How would your approach change if she had a family history of colon cancer?

Part Two

On examination, uterus is normal size and contour. There are no cervical abnormalities, adnexal masses, or cervical motion tenderness. The pregnancy test and other investigations are negative.

What do you think is happening?

What treatment would you consider if the pregnancy test is negative and no anatomical abnormalities are found on investigation?

If symptoms persist after three months, what do you do?

What would you do now?

Case 2: Marie, age 48

After eight weeks of amenorrhea, Marie's last menstrual period was "extremely heavy." She had to change her tampon every few hours during the day and also wear a pad at night. She has no associated dysmenorrhea. Marie's menstrual pattern has become unpredictable over the past two years, with heavy periods occurring at irregular intervals between four and eight weeks. She has put off coming in for this problem as she thought she might be starting menopause.

There is no history of a gynecological problem, and her Pap smear was normal a year ago. She has hypothyroidism for which she takes thyroid replacement hormone. She has no major medical problems and is a nonsmoker. Marie has never been pregnant, and she does not think she could be pregnant now. Her blood pressure is 130/86 mm Hg, her weight is 78 kg, and with a height of 165 cm, her body mass index (BMI) is 29 kg/m^2. Her pelvic examination is within normal limits.

What investigations would you consider given the current information?

Case 3: Cassandra, age 55

Cassandra has been experiencing intermittent painless vaginal spotting for the past nine months. She describes quarter-sized vaginal spotting twice a day for 4–5 days a week. She has not been sexually active for three years and has not had a Pap test since menopause at the age of 52 years. Her past medical history includes hypertension, for which she takes hydrochlorothiazide 12.5 mg po daily, and dyslipidemia. She has been taking acetylsalicylic acid (ASA), 81 mg po daily, for the past two years. Cassandra has no history of bleeding disorders or sexually transmitted infections. Her blood pressure is 134/90 mm Hg, her weight is 77 kg, and her height is 158 cm, making her BMI 31 kg/m^2. Her pelvic examination is within normal limits, with no atrophic vaginal changes or cervical polyps. A Pap test was performed.

What investigations would you consider given the current information?

Part Two

Cassandra's Pap test was within normal limits. Endometrial biopsy revealed fragments of a benign endometrial polyp. Her transvaginal ultrasound showed a heterogeneous endometrium with a 3 mm double-thickness endometrial echo (EE). Her bleeding has stopped.

How would you manage Cassandra at this point?

Part Three – Three months later

Cassandra is now bleeding again intermittently.

How would you proceed?

INFORMATION SECTION

1. *Definition*: The terminology relating to abnormal uterine bleeding (AUB) is inconsistent and confusing. In this module:
   a) *AUB in premenopausal women* is defined as any substantial and persistent change in frequency, duration, or amount of bleeding during or between periods.[1-3]
   b) *AUB in postmenopausal women*, who are not taking hormone replacement therapy (HRT), refers to spontaneous or unexpected uterine bleeding that occurs > 1 year after the last menstrual period.[1]

2. *Quality of life*: AUB may have a substantial impact on a woman's life.[4] Bleeding is associated with significant social embarrassment, due to self-consciousness about perceived odour and fear of staining clothes or furniture. In fact, measuring the quantity of blood loss is not as useful as determining impact on quality of life. Women may alter their lives, avoiding social occasions if no bathroom is available.[1] Severe pain can also reduce quality of life.

PREMENOPAUSAL WOMEN

3. Up to 14% of premenopausal women experience AUB, which may be anovulatory or ovulatory.[5]
   a) *Anovulatory AUB* is irregular or infrequent, and the flow may be light or very heavy. Anovulatory AUB is more common at the extremes of a woman's reproductive life and in obese women.[1]
   b) *Ovulatory AUB* is regular, with a cycle length of 24–35 days, but the duration is greater than seven days or the volume is excessive.[1] Ovulatory cycles are often accompanied by some degree of cramping.

4. *Anovulatory AUB*: The main causes of anovulatory AUB are the following:
   a) *Adolescence and perimenopause*: Irregular anovulatory cycles can be seen for 2–3 years after menarche and for up to eight years before menopause.[5] Recurrent irregular anovulatory cycles are considered abnormal during the rest of a woman's reproductive years.
   b) *Polycystic ovary syndrome (PCOS)*: About 6–10% of women with anovulation have PCOS.
   c) *Interference with the hypothalamic-pituitary-ovarian axis:*
      - *Hypothyroidism or hyperthyroidism*
      - *Uncontrolled diabetes mellitus*
      - *Hyperprolactinemia*
   d) *Anticonvulsants*: These agents may cause hyperandrogenism and anovulation.
   e) *Antipsychotics*: These medications may contribute to anovulation by raising prolactin levels.[5]

   The risk of endometrial carcinoma increases if ovulation does not occur.[5]

> ***Practice Tip***: Despite limited evidence, more than four withdrawal bleeding cycles per year are recommended to protect the endometrium from hyperplasia.[6] Intrauterine devices[21] and hormonal contraceptives, including use in extended-cycle regimens,[7] decrease the risk of endometrial hyperplasia.[8] See Appendix 3 for medication options.

5. *Ovulatory AUB*: Underlying causes of ovulatory AUB include the following:
   a) *Bleeding disorders*: von Willebrand disease, the most common inherited bleeding disorder, is seen in about 13% of women with AUB. It often presents in adolescents as extremely heavy AUB that occurs at the onset of menses or at regular intervals.[9] Other suggestive symptoms include postpartum hemorrhage, surgery-related bleeding, and bleeding associated with dental procedures; or frequent bruising, epistaxis and bleeding gums. Investigations include: CBC, platelet count, PTT, INR, von Willebrand factor and ristocetin cofactor (For more details, refer to the NIH guidelines[A], Chapter on Diagnosis and Evaluation or pages 198-200 in 2012 ACOG Practice Bulletin on Diagnosis of Abnormal Uterine Bleeding in Reproductive-Aged Women).[10]
   b) *Symptomatic hypothyroidism*
   c) *Structural changes*: submucosal fibroids or endometrial polyps
   d) *Late-stage liver disease*

   With regular ovulation and endometrial sloughing, the risk of endometrial carcinoma decreases.[5]

[A] NIH guidelines - http://www.nhlbi.nih.gov/guidelines/vwd/vwd.pdf

6. One-quarter of endometrial carcinomas occur in premenopausal women.[11] Appendix 1 lists risk factors for endometrial hyperplasia and carcinoma. A history of endometrial or colorectal cancer in a first-degree relative significantly increases the risk. For example, women carrying the mutation for hereditary non-polyposis colorectal cancer have a 42–60% lifetime risk of endometrial carcinoma, and they tend to develop it before menopause.[12]

Investigating AUB in premenopausal women

7. *Cause*: The cause of AUB in premenopausal women is identified in 50–60% of cases (Appendix 2).[1] More than one cause may be present concurrently, so comprehensive investigation is important.
   a) History should determine whether bleeding is anovulatory, ovulatory, anatomic, associated with medications, systemic conditions, or a coagulation problem.[1]
   b) The acronym PALM–COEIN (polyp, adenomyosis, leiomyoma, malignancy and hyperplasia, coagulopathy, ovulatory dysfunction, endometrial, iatrogenic, and not yet classified) was introduced in 2011 by the International Federation of Gynecology and Obstetrics (FIGO) and supported by ACOG as a guide for assessment based on the combination of bleeding pattern and underlying etiology.[10]
   c) Appendix 3 provides an overview of items to explore in history taking.[13]

Practice Tips:
- If treatment for bleeding is required during investigation, use tranexamic acid (Cyclokapron®) or a nonsteroidal anti-inflammatory drug (NSAID).[4]
- For acute bleeding in a hemodynamically stable patient, use a high-dose hormonal contraceptive (e.g., 35 mcg ethinyl estradiol) 2–4 pills/day x 7 days, then 1 pill/day x 14 days.[3]

8. *Laboratory investigations*:
   a) Pregnancy: Rule out pregnancy and pregnancy-related complications if sexually active.[5]
   b) Pap smear: Ensure cervical cytology results are both current and normal if sexually active.[1]
   c) Infections: Perform testing for gonorrhea and chlamydia with *polymerase chain reaction (PCR)* or cultures of urine or swabs.[3;13;14]
   d) Blood work:
      - *Complete blood count* (CBC): All guidelines recommend, if bleeding heavy (Low level of evidence).
      - *Ferritin*: The National Institute for Health and Clinical Excellence (NICE) does <u>not</u> recommend ferritin levels as a routine test, as no evidence indicates ferritin levels provide any more information than a CBC for managing heavy uterine bleeding (Moderate level of evidence). However, if anemia is identified, ferritin is the most accurate method to confirm iron deficiency.
      - *Thyroid function*: There is limited evidence about the association of menstrual irregularities and thyroid disease. NICE recommends TSH only if women have other symptoms or signs of thyroid disease (Low level of evidence), while ACOG indicates that screening for thyroid disease with a TSH is "reasonable and inexpensive."[10]

9. *Investigations for structural and histological abnormalities:*
   a) *Endometrial biopsy*: The Society of Obstetricians and Gynecologists of Canada (SOGC)[15] recommends endometrial biopsy for women > 40 years of age with AUB or increased risk of endometrial carcinoma (Moderate to low level of evidence), while NICE[4] recommends this for women ≥ 45 years of age or women with treatment failure (Low level of evidence).
   b) *Transvaginal ultrasound*: This is recommended for women in whom structural abnormalities, such as fibroids or polyps, are suspected.[1;4;12] Endometrial pathology is more accurately assessed with transvaginal than transabdominal ultrasound.[12] Transvaginal ultrasound has 80% sensitivity and 69% specificity to detect fibroids and polyps.[1] ***Note:*** In premenopausal women, no correlation has been identified between endometrial thickness on ultrasound and endometrial cancer.[1]
   c) *Hysteroscopy*: This is recommended when biopsy or ultrasound is inconclusive and after failure of medical therapy (High level of evidence).[4]
   d) *Saline infusion sonography*: Not a first-line diagnostic tool (High level of evidence)[4] but helpful if intrauterine polyps or fibroids are suspected.
   e) *Magnetic resonance imaging*: Not a first-line diagnostic tool (Moderate level of evidence)[4] but usually required before uterine artery embolization for fibroids
   f) *Dilatation and curettage (D&C)*: Not to be used alone as a diagnostic tool (Moderate to low level of evidence).[1;4]

Managing AUB in premenopausal women

10. Depending on the diagnosis, several treatment options are available (Appendix 3). It is important to discuss the options with the patient, including side effects and effect on fertility.[4]

11. For all pharmacological treatment options (Appendix 4), a trial of at least 3–6 months is appropriate before deciding if the selected therapy is ineffective. It is important to explain the length of the treatment trial before starting any agent. Any of the following treatments can be tried first and all non-hormonal therapies can be combined with hormonal.

12. *Anovulatory AUB*:
    a) Combined oral contraceptive pills are appropriate before considering other diagnostic or treatment options.[14]

       If a low-dose oral contraceptive pill is ineffective or breakthrough bleeding occurs, consider a higher-dose oral contraceptive pill, a pill with a higher progestin dose, or continuous use of a monophasic pill (back-to-back 21 day packages) with no break for menstruation.[16] Also consider the possibility of an additional underlying cause (e.g., *Chlamydia trachomatis*).[9]

    b) The levonorgestrel-releasing intrauterine system (Mirena®) should be used for at least 6 months before concluding it is ineffective.[4;16] Mefanamic acid 500 mg twice daily for five days can be added to reduce the length of uterine bleeding.[17]
    c) Cyclic progestins such as medroxyprogesterone acetate (Provera®): 5–10 mg PO for 14 days, started initially at any time in the cycle.[16] The dose can be doubled if bleeding occurs before the patient completes a 14-day course. If the patient is bleeding when treatment is begun, increase the dose every two days (maximum 20 mg) as needed to stop the bleeding. Subsequently, the medication should be given 14 days on/14 days off.
    d) Depot medroxyprogesterone acetate (e.g., Depo-Provera®): If bleeding continues after the first shot, the next shot can be given earlier, or a 7-day course of a conjugated estrogen, such as Premarin® 1.25 mg/day, can be given and repeated.[16]

13. *Ovulatory AUB*:
    a) NSAID: Instruct the patient to start taking it 24 hours before the onset of her menstrual flow (e.g., mild cramps) and take it regularly for the duration of menses.[4]
    b) Tranexamic acid: 500 mg–1500 mg q 6-8 h prn for 1–4 days during menstruation
    c) Combined oral contraceptive pills: an alternative therapy, although the evidence for effectiveness (one small randomized controlled trial and several non-randomized studies) is not as strong as NSAIDs or tranexamic acid.[4]
    d) The levonorgestrel-releasing intrauterine system.[4;16]
       Note: A trial should last for > 6 months as irregular bleeding may last this long.[4]
    e) A progestin only: Medroxyprogesterone acetate 10 mg per day for 21 days per month.[5]
       Note: To be effective in reducing bleeding, course must be longer than the 14 days used for treatment of anovulatory AUB.

14. If medical management for premenopausal AUB is ineffective, it is appropriate to further investigate (endometrial biopsy, saline infused sonohysterogram, etc.) or to consider a surgical option (Appendix 3).[14]
    a) If fertility retention is important, hysteroscopy with guided D&C may provide both diagnosis and treatment of underlying pathology.[18]
    b) If fertility retention is not important, and medical treatment fails or is contraindicated, endometrial ablation is a satisfactory and minimally invasive option.[4;18]
    c) If endometrial ablation fails, laparoscopic hysterectomy is an option with a shorter hospital stay and fewer days off work than an open hysterectomy.[4;18]
    d) D&C alone is no longer recommended as a treatment option for AUB since it has no long-term benefit[1;4]

POSTMENOPAUSAL WOMEN

15. Evaluate spontaneous or unexpected AUB in postmenopausal women, using a transvaginal ultrasound and/or endometrial biopsy as the initial investigation(s) (Appendix 5). Risk factors for endometrial hyperplasia and carcinoma are listed in Appendix 1.

16. It is unnecessary to discontinue HRT before investigating AUB with ultrasound or endometrial biopsy.[12]

17. *Endometrial biopsy*: This blind technique has largely replaced D&C as the preferred diagnostic test for histology, as sensitivity and specificity are high and the procedure itself is less invasive.[4]

a) The specificity of endometrial biopsy for detecting endometrial carcinoma is 98–100%, and sensitivity ranges from 67%–96%, with inadequate specimens obtained in 8%–40% (usually 10–20%) of postmenopausal women.[4;11;13] When an adequate specimen is obtained, sensitivity exceeds 90%.[19]
b) Operator experience is important, but a certain percentage of failures are expected in women with an atrophic endometrium.

> ***Clinical Note***: On ultrasound, the normal endometrium is visualized as a thin echogenic layer on both sides of the anechoic endometrial cavity. Endometrial thickness is the sum of the anteroposterior width of both the anterior and posterior endometrial layers. Thus, endometrial thickness is sometimes referred to as "double thickness endometrial echo (or EE)". For simplicity in this module, the term "endometrial thickness" will be used. However, the other term may appear on ultrasound reports. The usual unit of measurement is millimetres (mm), not centimetres (cm).

18. *Transvaginal ultrasound:* A global endometrial thickness > 15 mm is highly suggestive of endometrial carcinoma (> 50%).[20-22] However, controversy remains regarding a cut-off level for the exclusion of endometrial carcinoma in postmenopausal women with AUB,[23] as "there is no consensus in the literature about what the cut-off value for endometrial thickness should be"[11] and "no endometrial thickness threshold completely excludes possible early endometrial carcinoma."[12]
    a) A 2010 systematic review and meta-analysis by Timmermans and colleagues[24] found that a 3 mm cut-off yielded a sensitivity of 97.9% and specificity of 35.4%, a 4 mm cut-off a sensitivity of 94.8% and a specificity of 46.7%, and a 5 mm cut-off a sensitivity of 90.3% and a specificity of 54%.
    b) The American Congress of Obstetricians and Gynecologists (ACOG)[18] recommends a 4 mm cut-off, as several large studies found a sensitivity of 96–98%, a specificity of 36–68%, a false positive rate of 44–56%, and a false negative rate of 99.4–100%.[18]
    c) Timmermans et al.[24] and the Scottish Intercollegiate Guidelines Network (SIGN)[12] recommend a 3 mm cut-off, weighing the consequences of a false negative result missing endometrial carcinoma versus the harm of a false-positive result (High level of evidence). *Note*: For women taking sequential combined HRT, SIGN recommends a 5 mm cut-off to exclude the risk of endometrial carcinoma,[12] given a post-test probability of endometrial cancer of 2–5% in these women with endometrial thickness > 5 mm.
    d) A limitation of all these recommendations is the failure to take into account the pre-test probability of endometrial carcinoma for an individual woman.[25] Patients with postmenopausal bleeding typically have 10–15% risk of endometrial carcinoma, but certain groups of patients have an incidence reported to be as high as 29%. Patient characteristics can significantly alter the probability of endometrial carcinoma (Appendix 1), especially obesity and diabetes.[26]
    e) Ultimately, clinicians must consider both individual risk factors and endometrial thickness to assist their patients in making an informed choice about the need for more invasive interventions versus continued monitoring.

19. *Transabdominal ultrasound* is a *complementary* evaluation, used to assess an enlarged uterus or obtain a broader view of the pelvic and abdominal areas.[12]

20. *Hysteroscopy*: This technique, which allows direct visualization and biopsy of the endometrium, can be performed as an outpatient procedure or under general anaesthesia.[12] Little research evidence is available.
    a) SIGN recommends hysteroscopy plus biopsy to detect polyps and other benign lesions.[12]
    b) The SOGC guideline for the management of AUB recommends hysteroscopic biopsy for women with persistent bleeding, failure of medical therapy, apparent focal intrauterine pathology, and negative investigations with persistent bleeding.[15]

21. *Dilatation and curettage*: D&C is also a blind procedure, and it is not recommended as a first-line diagnostic method (Moderate level of evidence).[4;12] Sensitivity has not been well studied, but appears to vary widely.[4;27] Results of D&C and endometrial biopsy agree > 80% of the time for findings of endometrial hyperplasia and carcinoma, but biopsy is usually reported to be more sensitive.[4;19] A critical review of 33 reports (13,598 D&Cs and 5,851 office endometrial biopsies) found a similar specimen adequacy, but a higher complication rate with D&C.[11]

22. *Recurrent or persistent postmenopausal bleeding*: There is no evidence to support a specific time frame for reinvestigating persistent or recurrent

postmenopausal bleeding, but it is important to remember all diagnostic methods have a false negative rate.[12]

Managing AUB in postmenopausal women

23. If initial diagnostic tests are negative, and symptoms resolve, it may be appropriate to follow the woman clinically.[3] If bleeding persists, endometrial evaluation is definitely indicated, refer if necessary.

24. Once premalignant or malignant endometrial disease has been treated or excluded, benign lesions can be treated if bleeding remains a problem (Appendix 5).

THE BOTTOM LINE

- Diagnosis and appropriate management of AUB depends on a comprehensive structured approach to investigation.
- Investigation of premenopausal AUB requires eliminating pregnancy, medications, and systemic causes and classifying bleeding as ovulatory or anovulatory *before* performing specific investigations of uterine causes.
- The major objective in investigating postmenopausal uterine bleeding is identifying any premalignant or malignant uterine changes.

CASE COMMENTARIES

Case 1: Catherine, age 17

What additional information from history would be helpful for identifying the underlying cause for her heavy bleeding?

It is appropriate to take a thorough menstrual and sexual history; medical history, including bleeding from other sites and any family history of bleeding problems; a list of current medications including OTC and herbal; and a psychosocial history (Info points 3, 7; Appendices 2, 3). If the patient had extremely heavy but regular periods at menarche, this could increase your suspicion of a bleeding diathesis (Info point 5a).

What physical examination would be indicated?

Physical examination should include vital signs, weight, height, BMI, signs of anemia, examination of the thyroid, and external genital examination for any lesions. A pelvic examination, including assessment of the cervix for friability and motion tenderness, and the presence of cervical polyps, erosions, uterine size and contour, or any signs of pelvic inflammatory disease would be appropriate (Appendix 3).

What investigations would you consider?

Appropriate investigations would include urine human chorionic gonadotropin to check for pregnancy and a CBC (Info point 8, Appendix 3). Depending on the personal and family history and other clinical findings, von Willebrand's screen, ferritin and TSH might be performed (Info points 5,8). It may also be appropriate to screen for chlamydia and gonorrhea and perform a Pap test (Info point 8).

Part Two

What do you think is happening?

Catherine's problem appears to be ovulatory excessive bleeding. Given her youth, an underlying bleeding disorder is possible, especially if her periods have been heavy since menarche (Info point 5a). Other possibilities include chlamydia endometritis, adenomyosis, and pregnancy or retained products of conception.

What would you do now?

The psychological consequences and fear of embarrassment due to heavy bleeding are significant for most women (Info point 2), and it is important to provide both reassurance and treatment. An NSAID would help manage the pain and reduce bleeding, but it needs to be taken early and used regularly (Info point 13a). A combined monophasic oral contraceptive pill also could help with both the bleeding and the pain; clinical experience suggests a benefit, but good-quality evidence is lacking (Info point 13c). Extending the cycle (bi-cycling or tri-cycling) offers the additional benefit of avoiding periods during competitions. Tranexamic acid may be an alternative to reduce bleeding (Info point 13b). Ultimately, treatment selection may depend on using a combination of medications and consideration of patient preferences (Info points 10,11; Appendix 3).

Case 2: Marie, age 48

What investigations would you consider given the current information?

As Marie's pelvic examination is normal, the main diagnostic possibilities are anovulation (Info points 3, 4), adenomyosis, and possibly endometrial adenocarcinoma (Info point 6, Appendix 1).

See Appendix 2 for potential causes of AUB in perimenopause.

Potential investigations include CBC, TSH to determine whether her level is in the therapeutic range (Info point 8d), endometrial biopsy and pelvic ultrasound (Appendix 3). It is also important to perform a pregnancy test (Info point 8a).

Based on her age alone, it is important to rule out endometrial carcinoma, although the risk is higher in women with additional risk factors (Info point 4, Appendix 1). An endometrial biopsy is an appropriate initial investigation to assess the endometrium (Info point 9a). Transvaginal ultrasound is useful to identify anatomic abnormalities such as endometrial polyps, but endometrial thickness is not helpful in premenopausal or perimenopausal women (Info point 9b, Appendix 3).

How would your approach change if she had a family history of colon cancer?

Although a family history of colon cancer could further increase Marie's risk of endometrial carcinoma (Info point 6, Appendix 1), she already has met the criteria for investigation with an endometrial biopsy due to multiple risk factors for endometrial hyperplasia (age > 45, nulliparity, and possible infertility).

What treatment would you consider if the pregnancy test is negative and her endometrial biopsy and transvaginal ultrasound are normal?

Marie's problem is most likely anovulatory perimenopausal bleeding (Info point 3a). Potential treatments include progestins alone (levonorgestrel intrauterine system, depo-Provera, oral progestins - cyclic or continuous) or a combined oral contraceptive (Appendix 3). Treatment choice is determined by the patient after discussing effectiveness, side effects, and effects on fertility (Info points 10, 12; Appendix 4).

If symptoms persist after three months, what would you do?

Consider ordering a saline infusion sonohysterogram to detect submucosal fibroids or polyps (Info point 9d). You can also repeat the endometrial biopsy as false negative rate is about 10% when an adequate specimen is obtained (Info point 17). If normal, consider gynecology consultation (Appendix 3).

Case 3: Cassandra, age 55

What investigations would you consider given the current information?

Postmenopausal spotting is most commonly atrophic in origin and unlikely to indicate a serious problem (Appendices 2 & 5). However, endometrial carcinoma is the cause in 10-15% of patients with postmenopausal bleeding, so this possibility is important to exclude (18d). Appropriate initial investigations are endometrial biopsy and/or a transvaginal ultrasound to evaluate the endometrium (Info points 15, 17, 18; Appendix 5).

Part Two

How would you manage Cassandra at this point?

As Cassandra's endometrium (double thickness EE) is 3 mm and her bleeding has stopped, it could be appropriate to follow her clinically (Appendix 5). Because Cassandra's elevated BMI increases the possibility of endometrial carcinoma (Appendix 1), some practitioners may prefer to refer her to a gynecologist for further evaluation (Appendix 5).

Part Three – Three months later

How would you proceed?

Consider ordering a saline infusion sonohysterogram to assess the polyp. Some practitioners may repeat the endometrial biopsy and transvaginal ultrasound to evaluate the endometrium (Info points 17,18) and then refer to a gynecologist for further evaluation if needed (Appendix 5).

Author: **Joanne Opsteen, NP-PHC, BScN, MSc**
Nurse Practitioner
Toronto, Ontario

Reviewers: **Risa Bordman, MD CCFP FCFP**
Family Physician
Toronto, Ontario

Gillian Graves, MD, FRCSC
Obstetrician and Gynecologist
Halifax, Nova Scotia

Medical Editor: **Jacqueline Wakefield, MD, CCFP, FCFP**
Family Physician
Tobermory, Ontario

Medical Writer: **Joanna Gorski, BSc (Hons), BEd, DVM**
Niagara-on-the-Lake, Ontario

Module Development Coordinator: **Dawnelle Hawes, BA, BKin, MEd**
Hamilton, Ontario

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Web-based resources cited within the module were active at the time of publication.

LEVELS OF EVIDENCE

Evidence Level	Type of evidence Included
High	• Systematic reviews/meta-analyses that include a wide range of well-designed studies (few limitations/risk of bias, directly applicable to target population); summary estimate has a narrow confidence interval. • Large, well designed RCTs, Study conclusions are unlikely to be strongly affected by information from future studies.
Moderate	• Systematic reviews/meta-analyses of studies with more limitations/risk of bias (less well designed RCT's, cohort, case control studies), or when the summary estimate has a wide confidence interval. • Single moderate sized well-designed RCTs. • Well-designed, consistent, controlled but not randomized trials; • Large cohort studies Study conclusions could change with additional information from future studies.
Low	• Small RCT's with a high risk of bias • Controlled or cohort studies with significant limitations/risk of bias or significant variation between study results Evidence from well-designed studies in representative populations is lacking or insufficient.
Very Low	• Expert Opinion • Individual case reports or series

Sources: 1) Scottish Intercollegiate Guidelines Network-(SIGN) http://www.sign.ac.uk/guidelines/fulltext/50/annexb.html. Accessed Oct, 2012; **2)** U.S. Preventive Services Task Force Grade Definitions. May 2008. http://www.uspreventiveservicestaskforce.org/uspstf/grades.htm accessed Oct, 2012; **3)** Balshem H, Helfand M, Schunemann HJ, Oxman AD, Kunz R, Brozek J et al. GRADE guidelines: 3. Rating the quality of evidence. J Clin Epidemiol 2011; 64(4):401-406. PM:21208779

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APPENDIX 1. Risk Factors for Endometrial Hyperplasia and Carcinoma

Premenopausal women*

Risk factor	OR	95% CI
Family history: Endometrial carcinoma Colorectal cancer (HPNCC/Lynch syndrome†)	 5.8 5.0	 1.1–28.6 1.3–19.1
Obesity: Weight ≥ 90 kg	5.5	2.9–10.6
Infertility	3.6	1.3–9.9
Age: ≥ 45 years	3.1	1.5–6.1
Nulliparity	2.8	1.1–7.2

OR, odds ratio; CI, confidence interval

* Independent risk factors, multivariate analysis (n=1,033)

† Lynch syndrome is another term for hereditary nonpolyposis colorectal cancer, an inherited condition that increases risk of colon, endometrial, and a number of other cancers. This is the most common of the genetic syndromes linked with increased risk of colon cancer (estimates of about 3% of all colon CA).

Sources: (1) Farquhar CM, Lethaby A, Sowter M, Verry J, Baranyai J. An evaluation of risk factors for endometrial hyperplasia in premenopausal women with abnormal menstrual bleeding. *Am J Obstet Gynecol* 1999;181(3):525-529.; **2)** Guido RS, Kanbour-Shakir A, Rulin MC, Christopherson WA. Pipelle endometrial sampling: sensitivity in the detection of endometrial cancer. J Reprod Med 1995;33:76-8. **3)** Vilos GA, Lefebvre G, Graves GR. Guidelines for the Management of Abnormal Uterine Bleeding. JOGC 2001;106(August):1-6.

Postmenopausal women

Risk factor	OR/RR*	95% CI	Comment
Family history of endometrial cancer or colorectal cancer			Definite risk, but detailed information not available for postmenopausal women
Overweight: BMI ≥ 26 kg/m^2 Obesity: BMI ≥ 35 kg/m^2	2.0 4.4–4.7	1.05–3.7 3.12–7.07	Epidemiologic studies consistently show that obesity increases risk
Age: Per year older than 55 years	1.03	0.99–1.03	Risk steadily increases with age
Diabetes	2.2	1.09–4.6	
Nulliparity	2.1	0.9–4.8	
Tamoxifen[(1)]	Treatment > 5 years increases risk at least fourfold		Higher treatment dose and longer duration increase risk

*OR, odds ratio; CI, confidence interval; *RR, rate ratio.*

[Note: at prevalence rates of about 10%, these statistics produce essentially the same values

Sources: **1)** Scottish Intercollegiate Guidelines Network. 61. Investigation of Post-Menopausal Bleeding. A national clinical guideline. Royal College of Physicians. 2002; **2)** Opmeer BC, van Doorn HC, Heintz AP, Burger CW, Bossuyt PM, Mol BW. Improving the existing diagnostic strategy by accounting for characteristics of the women in the diagnostic work up for postmenopausal bleeding. BJOG 2007 Jan;114(1):51-8. PMID: 17233860; **3)** McCullough ML, Patel AV, Patel R, Rodriguez C, Feigelson HS, Bandera EV, Gansler T, Thun MJ, Calle EE. Body mass and endometrial cancer risk by hormone replacement therapy and cancer subtype. Cancer Epidemiol Biomarkers Prev 2008 Jan;17(1):73-9. Epub 2008 Jan 9. PMID: 18187388; **4)** Zocchetti C, Consonni D, Bertazzi PA. Relationship between prevalence rate ratios and odds ratios in cross-sectional studies. Int J Epidemiol 1997 Feb;26(1):220-3. PMID: 9126523

APPENDIX 2. Potential Causes of Abnormal Uterine Bleeding by Reproductive Status

Early postmenarche	Anovulatory cycles: related to immaturity of the hypothalamic-pituitary-ovarian axis Hypothalamic suppression: stress, weight loss, heavy exercise, eating disorder Bleeding diathesis Pregnancy Pelvic infection
Reproductive years	Pregnancy and pregnancy-related conditions Structural disease: polyps, adenomyosis, leiomyoma/fibroids Malignancy and hyperplasia/premalignant conditions Coagulopathy/bleeding diathesis Ovulatory dysfunction/anovulation Endocrine dysfunction: polycystic ovary syndrome, thyroid dysfunction, pituitary adenoma Pelvic infection Systemic disease: renal, hepatic
Perimenopause	Anovulation Structural disease: polyps, adenomyosis, leiomyoma/fibroids Malignancy and premalignant lesions
Menopause	Atrophy Malignancy and premalignant lesions Structural disease: polyps, fibroids, adenomyosis
All ages	Medications: contraceptives, antidepressants, thyroid hormone replacement, anticoagulants, nonsteroidal anti-inflammatory, acetylsalicylic acid, antipsychotics, antiepileptics, tamoxifen, and estrogen therapy Herbal preparations: ginko, ginseng, motherwort, soy

Sources:

1) Telner D, Jakubovicz D. Approach to diagnosis and management of abnormal uterine bleeding. Can Fam Physician 2007;53:58–64;

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6) Practice bulletin no. 128: diagnosis of abnormal uterine bleeding in reproductive-aged women. American College of Obstetrics and Gynecology. Obstet Gynecol. 2012 Jul;120(1):197-206. PMID: 22914421.

APPENDIX 3. Stepwise Approach to Premenopausal Abnormal Uterine Bleeding (AUB)

Step 1 – Presentation/History

- Amount of blood loss, flooding, fatigue, pain, impact on lifestyle and activities
- Ovulatory or anovulatory cycles
- Sexual history
- *Pregnancy*: explore current possibility & desire for future pregnancy
- *Psychosocial issues*: especially stress, depression
- *Family history*: bleeding disorder, blood clots
- *Medications causing bleeding*: contraceptives, anticoagulants, herbs (ginseng, gingko, soy products), phenothiazines, SSRIs/TCAs, corticosteroids, thyroxine, tamoxifen (requires endometrial sampling)
- Intrauterine device
- *Systemic causes*: PCOS, diabetes, thyroid dysfunction, pituitary or hypothalamic conditions, hepatic or adrenal problems

Step 2 – Physical Examination

- *Weight, Height, BMI, Vital signs*
- *Thyroid*
- *Skin*: pallor, ecchymosis, petechiae, abdominal striae, acne, hirsutism, acanthosis nigricans
- *Speculum exam*: Pap + swabs; friable cervix associated with infection or dysplasia
  - Reassess or refer if abnormal Pap smear
- *Pelvic/bimanual exam*: detect genital tract pathology (fibroids, polyps, adnexal masses, tenderness, etc.)
  - If abnormal, consider transvaginal U/S
  - If fibroids or polyps, refer

Step 3 – Investigation

- Rule out pregnancy and related bleeding ***first***
- *CBC*: consider ferritin
- *TSH*: *if* symptoms/signs suggest thyroid dysfunction
- *Coagulopathy work-up*: if family history or bleeding dyscrasia
- *Pelvic Ultrasound*: transvaginal preferred
- *Endometrial biopsy*: if increased risk of endometrial hyperplasia, atypia, carcinoma

Endometrial cancer risk factors

- BMI > 40 or weight >90 kg
- Age ≥ 45
- Diabetes
- Anovulatory cycles/Polycystic ovary (PCOS)†
- Family history of endometrial or colon cancer
- Tamoxifen use

Approach to results:

- *Hyperplasia without atypia*: medroxyprogesterone acetate (Provera®) 10 mg, 5–90 days; repeat biopsy in 3–6 months
- *Atypia/carcinoma*: refer to gynecologist

† Note: Long-term risk of endometrial hyperplasia or carcinoma exists with anovulatory cycles and PCOS. Protect endometrium with either hormonal contraceptives, Mirena®, or cyclic progestins, progesterone (Prometrium®) 200-300 mg/d; norethindrone acetate (Norlutate®) 5-10 mg/d; or megestrol acetate (Megace®) 30 mg/d (Appendix 4)

Step 4 – Medical Therapy

Ovulatory AUB

- *NSAIDs*: start 24 hrs before and for duration of menses
- *Tranexamic acid (Cyclokapron®)*: antifibrinolytic that reduces blood loss; take 500-1500mg q 6-8 hours, day 1-4 only when bleeding
- *Cyclic progestin* (Provera®) 10 mg/day x 21 days/month *or*
- *Levonorgestrel-releasing intrauterine system* (Mirena®)

Anovulatory AUB without atypia/cancer

- *Combination oral contraceptive*: with ethinyl estradiol ≤ 35 mcg, *or*
- *Cyclic progestin: (e.g., Provera® 5-10 mg/day x 14 days/month) or*
- *Depo-Provera®, or*
- *Levonorgestrel-releasing intrauterine system* (Mirena®)

Step 5 – Further Evaluations/Surgical Treatments if Failed Medical Therapy

If not previously done:

- Transvaginal ultrasound
- Endometrial biopsy
- Saline infusion sonohysterogram
- Gynecology consult
  - Hysteroscopy
  - Endometrial ablation
  - Hysterectomy

Note: D&C is no longer a treatment option for AUB since it has no long-term benefit [Sources (1) and (2) below]

The management of acute bleeding in hemodynamically stable patients includes high-dose hormonal contraceptive (i.e., 35 mcg ethinyl estradiol) **2–4 pills/day x 7 days, then 1 pill/day x 14 days** [Sources (1) and (5) below].

Sources: **1)** Bordman R, Telner D, Jackson B, Little D, Gamache N. An approach to the diagnosis and management of benign uterine conditions in primary care. 2010. Centre for Effective Practice and Ontario College of Family Physicians. http://machealth.ca/programs/buc/m/resources/26.aspx Accessed Oct, 2012; **2)** Heavy menstrual bleeding. Clinical practice guideline 44. 2007. London, UK, National Institute for Health and Clinical Excellence (NICE). http://guidance.nice.org.uk/CG44 Accessed Oct, 2012; **3**) Albers JR, Hull SK, Wesley RM. Abnormal uterine bleeding. Am Fam Physician 2004; 69(8):1915-1926. PM:15117012; **4)** Sweet MG, Schmidt-Dalton TA, Weiss PM. Evaluation and management of abnormal uterine bleeding in premenopausal women. Am Fam Physician 2012; 85(1):35-43; **5)** Zacur HA. Managing an episode of acute or prolonged uterine bleeding. In: Barbieri RL, Falk SJ, editors. UpToDate. Waltham, MA: UpToDate; 2012. ; **6**) Practice bulletin no. 128: diagnosis of abnormal uterine bleeding in reproductive-aged women. American College of Obstetrics and Gynecology. Obstet Gynecol. 2012 Jul;120(1):197-206. PMID: 22914421

APPENDIX 4. Medications Commonly Used for Treatment of Abnormal Uterine Bleeding

Medication/Agent	Dose	How it works	Side effects*	Contraindications	Approximate monthly cost
Non-steroidal anti-inflammatory drugs (NSAIDs) • Mefenamic acid • Naproxen (Naprosyn®, Anaprox®) • Ibuprofen (Advil®, Motrin®) • Sodium Diclofenac (Voltaren®)	Mefenamic acid 500 mg q 6-8 h Naproxen 250-500 mg q6-12h Ibuprofen 400 mg q4-6h Sodium diclofenac 50 mg tid	Reduces production of prostaglandin	*Common*: indigestion, diarrhea *Uncommon*: dizziness, headache, rashes *Rare*: worsening of asthma in sensitive individuals, ulcer with possible bleeding	Acute peptic ulcers or hx of ulcers, active IBD, hypersensitivity to NSAIDs Caution in patients with asthma, nasal polyps, renal disease, liver disease, CHF, HTN	Varies depending on type and brand used and amount needed per month Ibuprofen (Advil®, Motrin®) & Naproxen sodium 220 mg (Aleve®) are OTC Cost per dose for generic over-the-counter ibuprofen and naproxen ranges from $0.25 to $1.00
Tranexamic acid (Cyklokapron®)	500-1500 mg q6-8h prn (Note: 6 gm is maximum daily dose)	Anti-fibrinolytic agent	*Uncommon*: indigestion, diarrhea, headache	History, risk or active thromboembolic disease (DVT, PE) Acquired colour vision disturbance	500 mg is ~$40
Combined Oral Contraceptive Pill (COCP)	As per package	Prevents proliferation of endometrium	*Common*: mood change, headache, nausea, fluid retention/bloating, breast tenderness, weight gain, breakthrough bleeding *Very rare*: DVT, stroke, heart attack	Hx/active thromboembolic disorder, cerebrovascular disorder, CAD, DVT, acute liver disease, breast cancer, migraine with aura, undiagnosed abnormal vaginal bleeding, pregnancy, uncontrolled HTN, smoker > 35 years old	~ $15-$35 depending on brand
Progestin: Oral • *Medoxy- progesterone* (Provera®) • *Norethindrone* (Norlutate®) • Norethisterone (Micronor®) • *Progesterone* (Prometrium®)	***Ovulatory AUB:*** 21 days/month •Provera® 5-10 mg •Norlutate® 2.5-10 mg ***Anovulatory AUB:*** Provera®5-10 mg 10 - 14d /month Norlutate® 2.5-10 mg day days 5-25 Micronor® 0.35 mg daily	Prevents proliferation of endometrium	*Common*: weight gain, bloating, breast tenderness, headaches, acne (but usually minor and transient) *Uncommon*: nausea, headaches *Rare*: depression	Undiagnosed vaginal bleeding/ breast disease (including CA), pregnancy, severe liver disease, depression Prometrium®: peanut allergy	Medoxy-progesterone 5 mg = $6 -$15 Micronor® 0.35 mg = $30-$35 Norlutate® 5 mg = $60 Prometrium® 100 mg = $30
Progestin: Injectable Medoxy- progesterone (Depoprovera®)	150mg IM q 3 months Monitor BMD if use > 2 years	Prevents proliferation of endometrium	*Common*: weight gain, irregular bleeding, amenorrhea, bloating/ fluid retention, breast tenderness *Less common*: bone density loss	Same as for oral progestins (above)	at $30-$45 per injection equals about $10-$15 per month
Progestin: Intrauterine Levonorgestrel- releasing system (LNG-IUS) (Mirena®)	Device lasts 5 years, then insert new device	Device which slowly releases progestogen to prevent proliferation of endometrium	*Common*: irregular breakthrough bleeding (may last for 6 months), *Less common*: amenorrhea *Rare*: uterine perforation, expulsion, progesterone side effects from systemic absorption	Pregnancy, PID, undiagnosed uterine bleeding, uterine abnormalities that distort cavity, uterine/cervical malignancy, acute liver disease, immunodeficiency, leukemia	At $350-$375 per device equals about $7 per month
* *Common*=about 1 in 100 chance; *uncommon*=about 1 in 1000 chance; *rare*=about 1 in 10,000 chance; *very rare*=about 1 in 100,000 chance					

Sources: 1) Bordman R, et al. An Approach to the Diagnosis and Management of Benign Uterine Conditions in Primary Care. Center for Effective Practice, University of Toronto, 2005.; **2)** NICE clinical guideline 44. Table 1. Pharmaceutical treatment proven to reduce menstrual bleeding. Available at www.nice.org.uk/CG44 (accessed October 2012).

APPENDIX 5. Stepwise approach to postmenopausal abnormal uterine bleeding (AUB)

Step 1 – Presentation/History

- Amount/frequency of blood loss
- Medications causing bleeding: HRT, anticoagulants, ASA, tamoxifen
- Risk factors for endometrial CA: obesity, diabetes, family history of CA, etc.

Differential Diagnosis & Frequency

Atrophic vaginitis	59%	Hormonal effect	7%
Endometrial polyp	17%	Cervical cancer	2%
Endometrial hyperplasia	10%	Other	< 1%
Endometrial carcinoma	10%	*Source: Karlsson 1995*	

Step 2 – Physical Examination

- General examination:
  - Height, Weight, BMI
  - Stigmatae of liver disease
  - Ecchymosis
- Pap if not current or history of abnormality
- Pelvic examination:
  - External genitalia
  - Atrophic/infectious vaginitis
  - Uterine size/contour
- Cervical swabs or urine for PCR testing if at risk

Step 3 – Investigation/Treatment Principles

CBC

INR, PTT, bleeding time, von Willebrand screen *if* evidence of coagulopathy (bruising, bleeding elsewhere)

TSH *if* symptoms or signs of thyroid disease

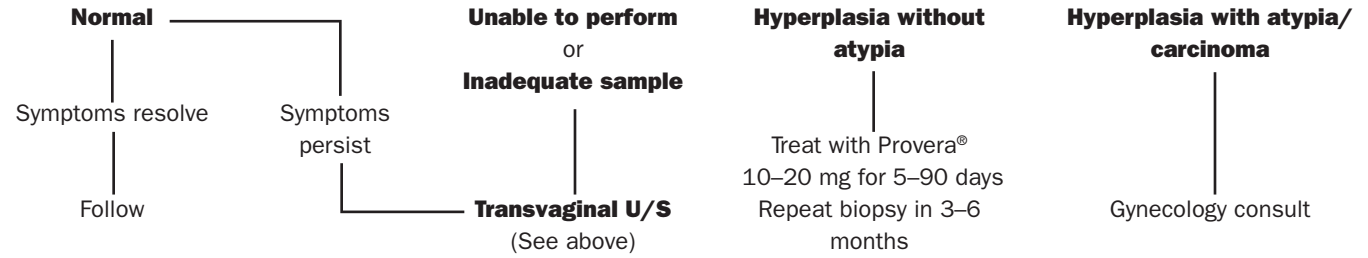
Evaluate the endometrium/uterine cavity

- Endometrial biopsy, transvaginal U/S, or both initially to assess endometrium
- Base choice of first investigation on patient preference, physician experience with procedure, U/S availability

Transvaginal U/S

- If double-thickness EE below cut-off* (≤ 3mm) ***and*** symptoms resolve » watch
- If double-thickness EE above cut-off* (> 3mm) ***or*** symptoms persist » need endometrial evaluation
- *See Info point 18 re cut-off controversy.

Endometrial biopsy and results



Step 4 – Medical Therapy after investigations

- Topical estrogen therapy for vaginal atrophy: creams, tablets, vaginal ring
- If taking systemic HRT, adjust meds by trial and error after ruling out pathology
  - Increase estrogen and/or decrease progesterone if endometrial thickness ≤ 5 mm
  - Decrease estrogen and/or increase progesterone if endometrial thickness > 5 mm
  - Vary dosing schedule: cyclic vs continuous

Step 5 – Further Evaluations/Surgical Treatments

- Saline infusion sonohysterogram
- Hysteroscopy
- Removal of polyp
- Hysterectomy

Sources:

1) Bordman R, Telner D, Jackson B, Little D, Gamache N. An Approach to the diagnosis and management of benign uterine conditions in primary care. second. 2010. Centre for Effective Practice and Ontario College of Family Physicians. http://machealth.ca/programs/buc/m/resources/26.aspx Accessed Jan, 2012; **2)** Heavy menstrual bleeding. Clinical practice guideline 44. 2007. London, UK, National Institute for Health and Clinical Excellence (NICE). http://guidance.nice.org.uk/CG44 Accessed Jan, 2012; **3)** Albers JR, Hull SK, Wesley RM. Abnormal uterine bleeding. Am Fam Physician 2004; 69(8):1915-1926. PM:15117012; **4)** Sweet MG, Schmidt-Dalton TA, Weiss PM. Evaluation and management of abnormal uterine bleeding in premenopausal women. Am Fam Physician 2012; 85(1):35-43.; **5)** Opmeer BC, van Doorn HC, Heintz AP, Burger CW, Bossuyt PM, Mol BW. Improving the existing diagnostic strategy by accounting for characteristics of the women in the diagnostic work up for postmenopausal bleeding. BJOG. 2007 Jan;114(1):51-8. BJOG. 2007 Jan;114(1):51-8. PMID: 1723386