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Management of Common Gynecological Problems

A Guide for Practitioners

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Contents

1. Normal and Abnormal Puberty 1
Chandra Mansukhani, Rashmi Nigam, Divya, Pallavi Sharma

Puberty ***1***
- Mechanism *1*
- Factors Determining Onset of Puberty *1*
- Endocrinology in Puberty *2*
- Thelarche and Adrenarche *4*
- Changes in Genital Organs *4*
- Delayed Puberty or Interrupted Puberty *6*
- Precocious Puberty *9*

2. Menopause: Physiology and Symptomatology 15
Mala Srivastava, Mamta Dagar
- Premature Ovarian Failure *15*
- Physiology *15*
- Lipids and Lipoproteins *17*
- Central Nervous System *17*
- Prediction of Menopause *18*
- Evaluation of the Women *18*
- Sequelae of Ovarian Failure *20*

3. Vaginal Discharge: Normal and Abnormal 24
Mala Srivastava
- Normal Vaginal Discharge *24*
- Natural Defense Mechanism of Vagina *25*
- Flora Normally Present in Vagina *25*
- Organisms Normally Present in the Vagina *25*
- Causes of Vaginal Discharge *26*
- Abnormal Vaginal Discharge *26*
- Bacterial Vaginosis *28*
- Fungal Infection *30*
- Trichomoniasis *31*
- *Neisseria Gonorrhoeae* *32*
- Chlamydiasis *33*
- Summary of Characteristics of Common Vaginal Infections *33*

4. Abnormal Uterine Bleeding 35
Chandra Mansukhani, Anurag Vashista, Rashmi Nigam
- Incidence *35*

- Etiology *35*
- Approach to Abnormal Uterine Bleeding *36*

5. Dysmenorrhea 49
Punita Bhardwaj
- Prevalence *49*
- Types *49*
- Etiology *50*
- Symptoms *54*
- Diagnosis *55*
- Treatment *56*

6. Chronic Pelvic Pain 58
Shweta Mittal Gupta
- History *58*
- Causes of Chronic Pelvic Pain *59*
- Physical Examination *60*
- Diagnostic Test *62*
- Management *63*

7. Urinary Problems in Women: Hush No More 67
Geeta Mediratta
- Urinary Incontinence *67*
- Types of Disorders *67*
- Risk Factors for Urinary Incontinence *69*
- Approach to Patient with Incontinence *69*
- Nonsurgical Treatment *72*
- Surgical Treatment for Stress Incontinence *74*
- Surgical Treatment for Detrusor Overactivity *75*
- Surgical Treatment of Fistula *75*
- Voiding Dysfunction *76*
- Bladder Pain Syndromes *77*

8. Fibroids: A Close Insight 80
Kanwal Gujral, Pramod Yerne, Anurag Vashista
- Risk Factors *80*
- Signs and Symptoms *80*
- Classification *81*
- Diagnosis *81*
- Management of Fibroids *82*

9. When to Intervene in a Case of Ovarian Cyst? 90
Kanika Jain, Kanika Chopra
- Functional Ovarian Cysts *90*
- Benign Ovarian Neoplasm *91*

- Malignant Ovarian Neoplasm *93*
- Approach to the Patient with Ovarian Cyst *94*

10. Pelvic Inflammatory Disease 99
Kanwal Gujral
- Risk Factors for Pelvic Inflammatory Disease *99*
- Acute Pelvic Inflammatory Disease *99*

11. The Enigma of Polycystic Ovarian Syndrome 107
Ruma Satwik
- Definition and Diagnosis *107*
- Criteria in Adolescence *108*
- Management *114*

12. Management of an Infertile Couple..... 124
Abha Majumdar, Neeti Tiwari
- Evaluation of Female Partner *124*
- Evaluation of Male Partner *130*
- Treatment of Specific Disorders *133*
- Unexplained Infertility *139*

13. Contraception: Making the Right Choices..... 141
Mamta Dagar
- Contraceptive Choices and Efficacy *141*

14. Medical Abortion: What a General Practitioner Should Know?.... 156
Sharmistha Garg
- Clinical Care of the Women Undergoing Abortions *161*
- Medical Methods of Abortion—Adapted from World Health Organization Safe Abortion Guidelines 2012 *162*
- Complications of Abortions *163*

15. Breast Cancer Surveillance 165
Debasis Dutta, Kanika Chopra
- Breast Anatomy *165*
- Patients History and Physical Examination *165*
- Types of Lesions in Breast *167*
- Breast Cancer *167*

16. Screening of Gynecological Cancers..... 174
Indrani Ganguli
- Cervical Cancer *175*
- Breast Cancer *177*
- Ovarian Cancer *180*
- Endometrial Cancer *183*

- Vulvar Cancer *184*
- Vaginal Cancer *184*

17. Bleeding after Menopause 186
Harsha Khullar
- Causes of Bleeding *186*
- Management of Patients with Postmenopausal Bleeding *189*

18. Hormone Replacement Therapy in Menopause 193
Indrani Ganguli
- Myth of Menopause *193*
- Ancient India *194*
- Crisis of Menopausal Hormone Therapy *194*
- MHT and Urogynecology *197*
- Breast Cancer and MHT *197*
- MHT and Ovarian Cancer *198*
- Rationality of Low-dose MHT *198*
- Estrogen Replacement Therapy Newer Developments *200*
- Individualizing MHT *202*

19. Ovarian Cancer 204
Harsha Khullar
- Incidence *204*
- Classification *204*
- High Risk Factors *205*
- Epithelial Ovarian Tumor *205*
- Current Recommendations for Women at High Risk of Ovarian Cancer *206*
- Management *207*
- Follow-up after Treatment *207*
- Nonepithelial Ovarian Cancer *207*
- Management of Malignant Germ Cell Neoplasm *208*

20. Cervical Cancer 209
Mala Srivastava
- Epidemiology of Cancer Cervix *209*
- Mechanism of Carcinogens *209*
- Local Examination *210*
- Features of Carcinoma Cervix on Colposcopy *210*
- International Federation of Gynecology and Obstetrics (FIGO) Staging of Cancer of the Cervix Uteri (November 2018) *210*
- FIGO Staging of Carcinoma of the Cervix Uteri (2008) *211*
- Types of Cancer Cervix *212*
- Management of Invasive Cancer of the Cervix *213*

21. Cancer of Endometrium 221
Mamta Dagar
- Epidemiology *221*
- Histopathology *221*
- Risk Factors *222*
- Staging and Treatment *222*
- Pattern of Recurrence *225*
- Follow-up Care *227*
- Prognosis *227*

22. Management of Breast Cancer: An Overview 230
Rakesh Kumar Koul
- Symptoms *230*
- Evaluation of Breast Malignancy *230*
- Histology *231*
- Further Clinical Staging *232*
- Breast Cancer Staging *233*
- Molecular Profiling Assays *237*
- Management of Preinvasive Breast Tumors (Stage 0) *238*
- Treatment of Early Stage Invasive Breast Cancer *239*
- Locally Advanced Breast Cancers *244*
- Inflammatory Breast Cancer *244*
- Principles of Preoperative Systemic Therapy *244*
- Breast Reconstruction Following Surgery *245*
- Metastatic/Recurrent Breast Cancer *246*
- Fertility and Birth Control *248*

Index 251

CHAPTER

4

Abnormal Uterine Bleeding

Chandra Mansukhani, Anurag Vashista, Rashmi Nigam

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INTRODUCTION

Abnormal uterine bleeding (AUB) is defined as bleeding from uterine corpus that is abnormal in regularity, volume, frequency or duration in the absence of pregnancy.

It is a common gynecologic complaint that may affect females of all age groups.

INCIDENCE

Abnormal uterine bleeding affects 10–30% of reproductive aged women and up to 50% of perimenopausal women.

Factors that influence incidence are age and reproductive status.

ETIOLOGY

It mainly depends on the age group to which the woman belongs:

Childhood

- Bleeding prior to menarche should be investigated as abnormal finding.
- Vagina rather than the uterus is the most common source of bleeding.
- Vulvovaginitis is the most frequent cause but dermatologic conditions, neoplastic growths or trauma by accident, abuse or foreign body may also be reasons.
- In case of true uterine bleeding, precocious puberty, accidental exogenous hormone intake or ovarian neoplasms should be considered in these children.
- Adequate evaluation may warrant examination under anesthesia with or without vaginoscopy.

Adolescence

- Abnormal uterine bleeding mainly results from anovulation or coagulation defects as compared with older reproductive aged women.

- Importantly, sexually transmitted diseases and sexual abuse should not be ignored in this age group.

Reproductive Age

- The hypothalamic-pituitary axis matures by this age and anovulatory bleeding is encountered less frequently.
- The rates of bleeding related to pregnancy and sexually transmitted diseases rise.
- The incidence of leiomyomas and endometrial polyps also increase with age. Bleeding from these lesions becomes common in older women within this age group.

Perimenopause

- Abnormal uterine bleeding is responsible for 70% of all gynecologic visits in this age group.
- Anovulatory bleeding from hypothalamic-pituitary-ovarian dysfunction is a more common finding.
- With aging, risks of benign and malignant neoplastic growths also rise.

APPROACH TO ABNORMAL UTERINE BLEEDING

The systematic approach to AUB has become more simplified and easy after the International Federation of Gynecology and Obstetrics (FIGO) nomenclature of AUB in 2011—The PALM-COEIN approach which includes structural as well as functional causes.

Previously various terms were used in literature to define pattern of AUB. However, they were inconsistently defined and it was difficult to compare results of various studies.

As per FIGO nomenclature, AUB has become universally accepted and there is consistency in defining the condition amongst various bodies. This has simplified the approach to the management with considerable uniformity and comparing the results based on various studies that are conducted at different places.

Based on the etiologies of AUB, FIGO in 2011 introduced the PALM-COEIN nomenclature that included structural (PALM) and functional etiologies (COEIN).

The structural causes include:

- **P**-Polyp
- **A**-Adenomyosis
- **L**-Leiomyomas (submucosal and others)
- **M**-Malignancy.

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These are detectable through various imaging modalities and/or histopathology.

The functional causes include:

- **C**-Coagulopathy
- **O**-Ovulatory dysfunction
- **E**-Endometrial
- **I**-Iatrogenic
- **N**-Not defined that includes DUB (dysfunctional uterine bleeding).

The approach to case of AUB can be divided as:

Evaluation: History and examination.

Investigations: Laboratory, imaging, histopathology.

Management: Correction of anemia and as per PALM-COEIN classification.

Evaluation

History and Examination

- A detailed menstrual history must be taken including age at menarche, last menstrual period date and methods of birth control. The timing of her bleeding, bleeding amount and associated symptoms should be determined. Length of menstrual cycle, regularity and amount of bleeding estimated by number of pads changed per day should be noted.
- Screening for coagulopathies must be done especially in premenarcheal and adolescent age group.

Positive screen for coagulopathies include:

- History of heavy bleeding starting at menarche.
- One of the following:
  - Bleeding during surgery.
  - Bleeding during dental procedure.
- At least two of the following:
  1. Bruising more than or equal to 1 episode/month.
  2. Epistaxis more than or equal to 1 episode/month.
  3. Frequent gum bleeding.
  4. Family history of bleeding symptoms.

Examination includes measuring height, weight and body mass index (BMI); assess pallor and examination of thyroid, breasts and look for acne. In case of hirsutism, Ferriman-Gallwey (FG) scoring should be assigned.

The importance of thorough per abdominal, per speculum and per vaginal examination cannot be stressed upon.

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Investigations

- *Ultrasonography (USG):* It should be done in all cases of AUB assessing uterus, adnexa and endometrial thickness (ET). It can be omitted in females less than 40 years of age up to 6 months of medical treatment.
- *3D USG:* It can be used as noninvasive alternation to hysteroscopy in selected cases like intramyometrial lesions or for fibroid mapping.
- *Doppler USG:* It is of help in cases of suspected arteriovenous (AV) malformations and malignancy. It can also be used to differentiate between fibroid and adenomyosis.
- *Magnetic resonance imaging*: It is of use in cases to differentiate between fibroids and adenomyosis, mapping of fibroids while planning conservative surgery and prior to therapeutic embolization of fibroids.
- *Saline infusion sonohysterography (SIS):* It is used in cases of suspected intracavitary lesions when hysteroscopy is not available.
- *Hysteroscopy:* It allows for direct visualization of intracavitary lesions and facilitates directed biopsies. The indications of hysteroscopy include:
  - Intermenstrual spotting
  - Intracavitary lesions
  - Ambiguity between symptoms and histopathology
  - Thick endometrial thickness (ET) on transvaginal scan (TVS) but HPE is inadequate or atrophic. No response to medical management.
- *Endometrial sampling:* This is recommended in all cases of age more than 40 years and in cases of age less than 40 years with high risk factors like:
  - Irregular bleeding.
  - Obesity, hypertension, polycystic ovary syndrome (PCOS), diabetes.
  - Unopposed estrogen therapy.
  - Endometrial thickness more than 12 mm.
  - Family history of cancer (CA) ovary or breast or endometrium or colon or hereditary nonpolyposis colon cancer (HNPCC).
  - Tamoxifen therapy for hormone replacement therapy (HRT) or breast cancer.
  - Persistent AUB, unresponsive to medical treatment.
- *Endometrial aspiration (EA):* This is one preferable technique. Dilatation and curettage is not recommended. *Hysteroscopy-guided sampling* has advantage over EA in that it can determine location of focal lesions found on USG. It can also serve as diagnostic as well as therapeutic benefit in the same session.

Management

Management of AUB can be either medical or surgical as shown in the flow chart followed by the detailed discussion of various aspects of medical as well as surgical management (Flowcharts 4.1 and 4.2).

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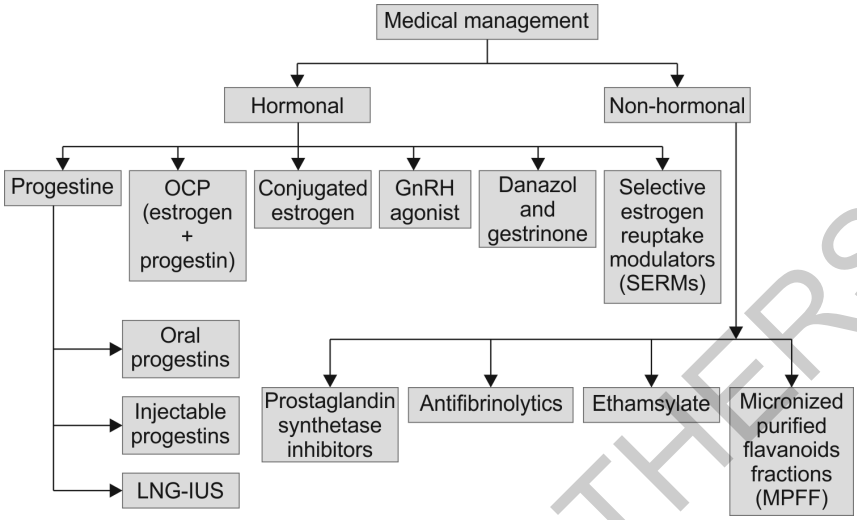
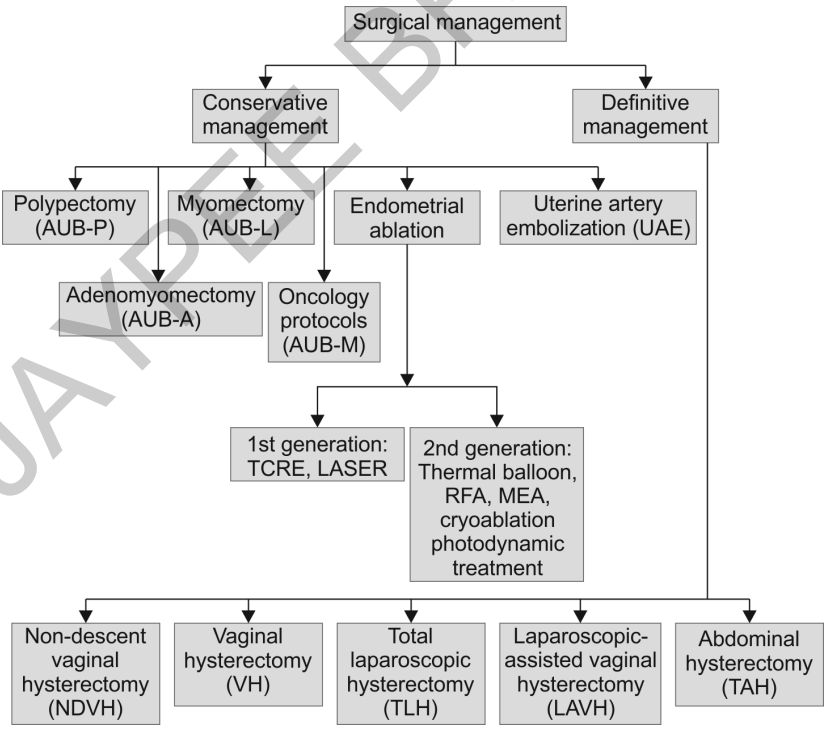
Flowchart 4.1: Medical management of abnormal uterine bleeding.



(GnRH: gonadotropin-releasing hormone; LNG-IUS: levonorgestrel-intrauterine system; OCP: oral contraceptive pill).

Flowchart 4.2: Surgical management of abnormal uterine bleeding.



(AUB: abnormal uterine bleeding; LASER: light amplification by stimulated emission of radiation; MEA: microwave endometrial ablation; RFA: radiofrequency ablation; TCRE: transcervical resection of the endometrium).

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Medical Management

Nonhormonal:

- Prostaglandin synthetase inhibitors (mefenamic acid):
  - It is usually the first-line of management for DUB in adolescent and reproductive age group. There is 30% reduction in menstrual blood loss and additional improvement in associated dysmenorrhea.
  - *Mode of action*: It inhibits cyclooxygenase (COX) enzyme and causes blockage of myometrial prostaglandin E2 (PGE-2) receptors.
  - *Regimen*: From the beginning of menstrual cycle, 500 mg thrice daily for 5 days.
  - Caution should be exercised in prescribing prostaglandin synthetase inhibitors, especially COX-2 inhibitors, to women with history of myocardial infarction, stroke and heart failure.
- *Antifibrinolytics (tranexamic acid)*:
  - These also constitute the first-line of management of AUB in adolescent and reproductive age group females, bringing about 50% reduction in menstrual blood loss. They are also useful in managing AUB related to IUCD (intrauterine contraceptive device).
  - *Mode of action*: They cause blockage of lysine-binding sites on plasminogen thereby reducing plasmin levels. This brings a reduction in fibrinolytic activity in endometrium. Thus the fibrin plug formed is not broken and this prevents and arrests the bleeding.
  - *Regimen*: Around 1–2 g per day in form of 650 mg thrice daily for 5 days starting from the beginning of menstrual cycle.
  - Antifibrinolytics have dose-dependent insignificant side effects like gastrointestinal (GI) upset. There is no alteration of coagulation parameters. However, they may not be effective or may have adverse reactions in women with history or risk of thromboembolism.
- *Ethamsylate*:
  - *Mode of action*: It maintains capillary integrity, has antihyaluronidase activity and inhibits prostaglandins. This causes platelet aggregation and adhesions resulting in formation of platelet plug.
  - *Regimen*: 500 mg QID starting from 5 days before anticipated onset of menstruation and continue for 10 days.
  - Ethamsylate is currently not approved by American College of Obstetricians and Gynecologists (ACOG) or Royal College of Obstetricians and Gynecologists (RCOG) and is still under trial for management of AUB.
- *Micronized purified flavonoid fractions (MPFF)*:
  - They cause increase in venous tone, lymphatic drainage and normalize capillary permeability.
  - Currently there is no evidence regarding their efficacy in treatment of AUB.

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Hormonal

- *Progesterones*:
  - Progesterones bring a halt to endometrial growth and thus result in organized sloughing of the endometrium following withdrawal.
- *Oral progesterones*:
  - Two main progesterones used orally are norethisterone (NE) 5 mg and medroxyprogesterone acetate (MDPA) 10 mg.
  - *For acute heavy bleeding*: Superthreshold regimen is used to arrest an acute event of uncontrolled DUB. NE 5 mg is administered 4–6 times per day till bleeding stops and then twice daily for 2–3 weeks.
  - *For cyclical heavy menstrual bleeding*:
    - *Ovulatory cycles*: Ovulatory AUB is not usually due to progesterone deficiency but due to altered prostaglandin synthesis or hemostatic disruption. For ovulatory AUB, NE (5 mg) thrice daily or MDPA (10 mg) thrice daily is administered from 2nd to 25th day of each cycle.
    - *Anovulatory cycles*: Norethisterone (5 mg) twice or thrice daily or MDPA (10 mg) once daily is administered for 10 days. Withdrawal bleeding usually occurs 3–5 days following the 10 day course. It may also occur during or before the duration of course is over. This is followed by same dose taken from day 16 to day 25 following first day of withdrawal cycle for at least 3–6 cycles.
  - It is recommended to rule out endometrial carcinoma before starting progesterone therapy. Side effects of oral progesterones include mood alterations, weight gain, bloating, headache and atherogenic changes in lipid profile.
- *Injectable progesterone (Depo-Provera)*:
  - Depo-Provera (depot medroxyprogesterone acetate) 150 mg administered intramuscularly (IM) every 3 months is useful in managing AUB. There is additional benefit of contraception offered by the treatment. Prolonged use of Depo-Provera however, may cause a loss in bone mineral density and prolonged amenorrhea.
- *Levonorgestrel-intrauterine system (LNG-IUS; Mirena)*:
  - It effectively suppresses endometrial proliferation and lasts for 5 years from the time of insertion. There is decreased expulsion rate, added benefit of contraception and reduction in menstrual blood loss to an extent of 74–97%.
  - It can be used as first-line of management of AUB in reproductive and perimenopausal age group patients.
  - It is more effective in decreasing the blood loss as compared to mefenamic acid. The therapeutic effect of LNG-IUS is similar to endometrial ablation for up to 2 years of therapy. There is also

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equal improvement in health status, quality of life and social well-being of women opting for LNG-IUS compared to those undergoing hysterectomy at 1 year and 2 years for management of AUB.

- *Contraindications to LNG-IUS are*:
  - Pregnancy (confirmed or suspected)
  - Uterine anomalies distorting the cavity (congenital or acquired)
  - Acute pelvic inflammatory disorder (PID) or history of acute PID
  - Postpartum endometritis or infected abortion in past 3 months
  - Abnormal pap smear or known or suspected uterine or cervical neoplasia
  - Genital bleeding of unknown etiology
  - Untreated acute vaginitis or cervicitis
  - Acute liver disease or benign or malignant hepatic tumor
  - Increased susceptibility to pelvic infection
  - Previously inserted IUCD that has not been removed
  - Known or suspected breast carcinoma
  - Previous ectopic gestation
  - Hypersensitivity to any component of mirena.

- *Combined oral contraceptive (COC) pills*:
  - Combined oral contraceptives bring about endometrial atrophy along with reduced endometrial fibrinolysis.
  - At least 30 μg of estrogen containing preparations are recommended.
  - Initially one pill every 8 hours is recommended till bleeding stops or reduced. The regimen continues for next 24 hours of stoppage of bleeding. The dose is then reduced to one pill every 12 hours for 3–7 days followed by one pill per day for next 21 days. This regimen is recommended for adolescent AUB and can also be used in peri-menopausal age group patients.
  - There is additional benefit of contraception and reduction in associated dysmenorrhea.
  - Thus abnormal uterine bleeding associated with ovulatory dysfunction as defined by PALM-COEIN classification can be managed by nonhormonal and hormonal treatment with progesterones and COCs.
  - *Recommendations for abnormal uterine bleeding due to ovulatory dysfunction (AUB-O) management thus are*:
    - Both hormonal and nonhormonal therapies can be prescribed.
    - Combined oral contraceptives are first-line management for 6–12 months if fertility not desired.
    - Cyclic luteal phase progestins (D10-D14) are specific management.
    - If patient is not willing for COCs and wishes symptom free interval of at least 1 year, LNG-IUS is the choice of treatment.
    - Response is reassessed annually in such cases.

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  - Cyclic norethisterone for 21 days is used as initial therapy for acute episodes and should be continued for 3 months.
  - Surgical treatment is not recommended unless AUB persists or is not responsive to medical therapy.
- *Conjugated estrogens (premarin)*:
  - In superthreshold doses, they stabilize endometrium and arrest bleeding. They also stimulate clotting at capillary level and promote vasoconstriction of spiral vessels.
  - They are used as hemostat for acute AUB episodes.
  - However, they are alone not recommended for treatment of AUB for long term as they can cause unopposed endometrial hyperplasia.
  - The recommended dose is 25 mg intravenously (IV) every 4 hours for up to 3 doses followed by 2.5 mg pill every 6 hours.
- *Selective estrogen receptor modulators (SERMs)*:
  - They are useful in case of perimenopausal DUB with hormonal deficiency. There is 60% reduction in menstrual blood loss.
  - The recommended dose is 60 mg twice daily for 12 weeks followed by 60 mg per week.
- *Gonadotropin-releasing hormone agonists (leuprolide)*:
  - They are helpful in short term to induce amenorrhea and allow women to rebuild their hemoglobin levels and red blood cell (RBC) mass. They are indicated in women awaiting natural menopause, surgery, young patients with medical disorders, anemia or immunosuppression.
- *Danazol and gestrinone*:
  - They cause hypoestrogenism and hyperandrogenism thus causing endometrial atrophy.
  - Danazol is given as 100–200 mg/day for 3–6 months and gestrinone is prescribed as 2.5 mg daily every 3–4 days.
  - They bring about a 60% reduction in blood loss. However, because of androgenic side effects, they are not used and are not recommended.
- *Abnormal uterine bleeding related to coagulopathy (AUB-C)*:
  - Around 13% of heavy menstrual bleeding (HMB) cases have systemic disorders of hemostasis.
  - The inherited ones include Von Willebrand disease (VWD), factor VIII, IX, XI deficiencies and platelet function defects.
  - Von Willebrand disease is commonest coagulation disorder presenting as HMB.
  - Nonhormonal treatment like tranexamic acid is used as primary line of management.
  - Hormonal therapy includes COCs and LNG-IUS.
  - In refractory cases, hematology consultation is needed.

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- Specific factor replacement is to be done wherever possible.
- *Desmopressin is used as treatment for VWD*: When surgical intervention is indicated, appropriate preoperative, postoperative and intraoperative management is to be done with hematologist.

Surgical Management

- *Endometrial polyps and abnormal uterine bleeding (AUB-P):*
  - Polyps are localized tumors of columnar epithelium of endocervix or endometrial epithelium. They contain both glandular and stromal elements and are usually benign.
  - Hysteroscopic polypectomy is recommended in young women who wish to preserve fertility.
  - In women with multiple or recurrent polyps, the polyps should be sent for histopathology. If benign, LNG-IUS or endometrial ablation is the option. If it comes malignant, the treatment protocol is followed as per oncology.
- *Abnormal uterine bleeding associated with adenomyosis*:
  - Adenomyosis is estrogen dependent entity usually presenting as HMB and dysmenorrhea.
  - The cases must be individualized based on age, symptoms, associated pathology like leiomyomas, polyps or endometriosis and desire for fertility.
  - If fertility preservation is desired and immediate conception is not wished for:
    - Levonorgestrel-intrauterine system is first-line of treatment.
    - Gonadotropin-releasing hormone agonists with add back therapy are used for those unwilling for LNG-IUS.
    - Nonsteroidal anti-inflammatory drugs, combined pills and progestogens are used for symptomatic treatment.
    - Adenomyomectomy is reserved for selected cases.
  - If fertility preservation is not desired, LNG-IUS or GnRH agonist with add back therapy is used for medical management.
  - Hysterectomy is reserved for those not responding to medical treatment and not wishing for fertility preservation.
- *Abnormal uterine bleeding associated with leiomyomas (AUB-L)*:
  - Leiomyomas are the benign fibromuscular tumors of the myometrium.
  - They are classified from Type 0 to type 8 by FIGO based on their relation to endometrium.
  - The treatment is individualized based on age, parity, symptoms and desire for fertility or menstrual function preservation.
  - Usually, type 0–1 with size less than 4 cm is resorted to hysteroscopic myomectomy. Abdominal myomectomy is recommended for size greater than 4 cm.

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- First generation ablation like transcervical resection of the endometrium (TCRE) are useful in selected cases undergoing hysteroscopic myomectomy but not desirous of pregnancy.
- Type 2–4 is usually managed medically with symptomatic management like tranexamic acid, COCs, nonsteroidal anti-inflammatory drugs (NSAIDs).
- If concurrent contraception is desired, LNG-IUS is the option.
- Myomectomy is reserved for the cases with associated infertility or failure of medical management.
- Hysterectomy is resorted to cases with age more than 40 years, symptomatic myomas and not desiring fertility.
- Levonorgestrel-intrauterine system can be given for type 3–4 myomas, selected type 2 myomas and contraindicated in type 0 and type 1.
- Selective progesterone receptor modulators (SPRMs) like ulipristal acetate or mifepristone are emerging as promising agents for the management.
- Gonadotropin-releasing hormone agonists with add back therapy is used as short term treatment for improving anemia, prior to myomectomy to reduce size and selected perimenopausal women to tide over menopause.
- Endometrial ablation is useful in cases of HMB with small uterine fibroids (<3 cm), uterus <10 weeks. Second generation ablative therapies should be used.

- *Abnormal uterine bleeding associated with malignancy (AUB-M):*
  - Follow-up of standard oncology protocol is recommended for AUB-M category women.
  - In case of hyperplasia with atypia, hysterectomy is the standard treatment.
  - If woman is young desiring fertility and has good compliance for regular follow-up, conservative treatment with high dose progesterones is an exceptional treatment.
  - In cases of hyperplasia without atypia, LNG-IUS is first-line therapy. Alternate option is oral progesterones. Endometrial aspiration should be repeated every 6 months.
  - Ablative therapy is not recommended because complete destruction is not ensured and histological follow-up is difficult.
- Conservative surgery (endometrial ablation).

Principles of Conservative Surgery

- To bring about destruction of endometrium in menorrhagia.
- Usually reserved for the cases following failure of medical management and before resorting to extirpative procedures.

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- The endometrium has immense power to regenerate and the basal layer is responsible for regeneration.
- To bring about therapeutic Asherman's syndrome so as to arrest bleeding.
- The destruction should always occur from fundus to cornua to upper endocervical canal.
- The endomyometrial surface is irregular and must be destroyed.
- The burns can spill through oviducts and also affect serosa. Therefore caution is recommended and surgical expertise is desired to perform the procedure.

Choice of Patients

- Normal uterus with at least 3 months history of heavy menstrual flow.
- No intrauterine pathology including normal endometrial biopsy and pap smear.
- No evidence or suspicion of pregnancy, malignancy or infection.
- Endometrial carcinoma should be ruled out.
- Completed family is desirable.
- Normal endometrial cavity.

Food and Drug Administration (FDA) Guidelines for Conservative Procedures

Inclusion criteria:

- Uterine bleeding from benign causes.
- Failed medical management.
- Uterocervical length as measured by uterine sound should be less than 12 cm.

Exclusion criteria:

- Pelvic inflammatory disease
- Coagulopathy
- Abnormal pap smear
- Malignancy
- Pregnancy
- Previous ablation
- Previous uterine surgeries.

Preprocedure Counseling

- The main aim is to return the bleeding to normal levels or lesser. Amenorrhea is not the desired result.
- The woman may experience vaginal discharge which may be bloody during the first few days, serosanguineous after 1 week and profuse and watery thereafter.

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Management of

Common Gynecological Problems

A Guide for Practitioners

From the onset of puberty to the cessation of periods and beyond, women suffer from several unique problems. These may arise out of disturbed physiology at various periods in their lives or because of a desire to bear children or limit fertility. The problems arising after the reproductive lifespan ends also offer a different challenge to the treating physician. Additionally, treatments on offer for several such problems are many and follow the classic example of "one size does not fit all".

This book brings together contributions from experts on commonly encountered gynecological conditions, presenting pathophysiology, symptomatology and management in an easy-to-comprehend manner. All chapters liberally employ tables, original pictures/diagrams to enlist and explain important concepts.

It is hoped that, through this effort, the general practitioners would find a readily usable reference book for common gynecological problems.

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