REVIEW ARTICLE

Abnormal Uterine Bleeding: An Age Based Approach

Shannon C. Scott DO, FACOFP[1], Erin Raney, PharmD, BCPS, BC-ADM[2], Heather Johnston, OMS-IV, OMM National Undergraduate Fellow[1]

1. Midwestern University - Arizona College of Osteopathic Medicine
2. Midwestern University - College of Pharmacy-Glendale

KEYWORDS:

Abnormal Uterine Bleeding

Endometrial Cancer

Endometrial Hyperplasia

PCOS

Women's Health Issue

Abnormal uterine bleeding (AUB) is a concern across the female reproductive lifespan. The initial evaluation focuses on identifying the underlying cause, either related or unrelated to structural abnormalities. Treatment options are then matched to the individual needs of the patient, which vary based upon age and reproductive plans. This article addresses common examples of age-specific issues associated with AUB. A case-based approach will discuss the evaluation and management of AUB issues including anovulation, polycystic ovarian syndrome, endometrial hyperplasia, and postmenopausal bleeding on hormone replacement therapy.

INTRODUCTION

Abnormal Uterine Bleeding (AUB) is the preferred terminology for heavy menstrual bleeding or intermenstrual bleeding.[1] As defined by the Menstrual Disorders Working Group of the International Federation of Gynecology and Obstetrics (FIGO) and endorsed by the American College of Obstetricians and Gynecologists (ACOG), AUB is acute or chronic "bleeding from the uterine corpus that is abnormal in regularity, volume, frequency, or duration and occurs in the absence of pregnancy." Using the acronym PALM-COEIN, both groups support the division of AUB into a classification system based on etiologies "related to uterine structural abnormalities" and "unrelated to uterine structural abnormalities": P- Polyp, A- Adenomyosis, L- Leiomyoma, M- Malignancy and hyperplasia, C- Coagulopathy, O- Ovulatory dysfunction, E-Endometrial, I- Iatrogenic, and N- Not otherwise classified. This system should be used to guide a thorough medical history and physical exam for each patient.[1,2]

In the last 20 years, endometrial cancer incidence has increased by 40%.[3] Endometrial cancer risk factors for women under age 40 include nulliparity, hypertension, body mass index (BMI) greater than 30, irregular menstruation, and family history.[2] Endometrial cancer should be considered in any postmenopausal woman with AUB, particularly since the risk of endometrial cancer increases with age. Postmenopausal women who are not on hormone replacement therapy that experience AUB have a 10% risk of endometrial cancer.[4] Endometrial cancer risk factors can be divided into non-modifiable and modifiable *(Table 1)*.[5]

TABLE 1:

Endometrial Cancer Risk Factors

NON-MODIFIABLE	MODIFIABLE
Increasing age	Obesity
Caucasian race	Hormone Replacement
Early menarche	
Late menopause	
Nulliparity	
Infertility	

CORRESPONDENCE:
Shannon C. Scott DO, FACOFP | sscott1@midwestern.edu

 Print ISSN: 1877-573X

The medical history is very important when considering AUB. It should include age of menarche, bleeding patterns, and severity of bleeding. The terms menorrhagia (menstrual blood loss > 80mL) and metrorrhagia (intermenstrual bleeding) have been replaced with heavy menstrual bleeding (AUB/HMB) and intermenstrual bleeding (AUB/IMB), respectively. Medical history should also include surgeries, medications, and symptoms of hemostatic disorders. The physical exam should include general physical and pelvic examination - external, speculum with pap or human papilloma virus (HPV) test based on age specific screening guidelines,[6] and bimanual exam. Laboratory testing includes a pregnancy test, complete blood count, targeted screening for bleeding disorders (if risk factors present), and thyroid function tests. In addition, testing for Chlamydia trachomatis should be considered. Recommendations for diagnostic imaging and endometrial tissue sampling are based on age and risk factors and will be discussed in separate sections.[7]

This review will use case examples to focus on three age groups of women with AUB: ages 18-35, 35-50, and over 50. Consideration of the medical history, physical exam, and management of common bleeding conditions will be highlighted. Where appropriate, associated co-morbid conditions and the risks of endometrial cancer will be discussed.

CASE 1: YOUNG ADULT – AGE 18-35

A 22-year-old female presents with abnormal menses. For the past 3 years, she has had 2-3 periods per year and the last one was 6 months ago. Each bleeding episode is heavy with cramping for about 7 days. She does not smoke or take any medications, and denies pregnancy or history of sexually transmitted diseases. First menses reported at age 13 with normal childhood and sexual development. Sexual history includes one lifetime partner and she is currently single. Family history is negative. Physical exam pertinent findings include normal vitals except for BMI of 35 and waist circumference of 36 inches. She has moderate to severe facial acne and sparse coarse hairs on her chin. Pelvic exam shows no clitoromegaly, uterus and ovaries are not palpable. Laboratory studies performed include negative urine pregnancy, normal prolactin, TSH, FSH, LH, high-density lipoprotein (HDL) 40 mg/dL, triglycerides (TG) 180 mg/dL, and elevated fasting blood sugar (FBS) 108 mg/dL. A free testosterone was 38 pg/mL (normal range, 1-21 pg/mL). Pelvic ultrasound was performed showing endometrial stripe 4 mm and normal ovaries.

The causes of AUB in adolescents and young adults overlap in pathology. Adolescent (ages 13-18) AUB is commonly caused by anovulation and an immature hypothalamic-pituitary-ovarian axis.[7] Unrelated to the age at first menses, 60- 80% of cycles become regular (21-34 days apart) within three years after the start of menarche. Most patterns of irregular bleeding in adolescence are considered physiologic and benign. Adolescent obesity has also been reported to play an increasing role in anovulatory cycles.[2]

Up to 20% of patients with heavy bleeding that occur within the first few menstrual cycles may have an associated coagulation disorder. Reported risk factors include bleeding during dental work, surgery-related bleeding, frequent bruising, epistaxis, or bleeding gums with tooth brushing, and family history of bleeding. Laboratory testing for coagulation issues include partial thromboplastin time, prothrombin time, activated partial thromboplastin time, fibrinogen, von Willebrand factor antigen, ristocetin cofactor assay, factor VIII, serum iron, total iron binding capacity, ferritin, and liver function testing. For any abnormal coagulation factor test, a hematology consultation should be considered.[8]

In young adults (19-39 years) the most common causes of all AUB include pregnancy, structural lesions, anovulatory cycles, hormonal contraception, and hyperplasia.[7] Our patient had a negative pregnancy test, ultrasound, and medication history. In reproductive age women, polycystic ovarian syndrome (PCOS) is the most common cause of anovulatory ovarian dysfunction (AUB-O). Menstrual cycles are determined anovulatory (AUB-O) if they are greater than 35 days from the previous one.[9] Our patient also had last menses 6 months ago, which is considered anovulatory amenorrhea and brings into consideration polycystic ovarian syndrome.

The diagnosis of PCOS has been debated by specialty societies and criteria agreement includes the presence of 2 out of the 3 categories: hyperandrogenism, chronic anovulation (oligo- or amenorrhea), and polycystic ovaries (one or both ovaries on ultrasound with 12 or more follicles measuring 2-9 mm in diameter or increased ovarian volume greater than 10cm3).[9] The Androgen Excess Society requires the presence of hyperandrogenism, either physical or chemical signs, whereas the Rotterdam criteria requires any 2 of the 3 criteria. In our case, she has 2 of 3 criteria with amenorrhea and hyperandrogenism (acne, hirsuitism, elevated testosterone). A pelvic ultrasound is not indicated to make the diagnosis of PCOS.[10]

Our patient also has metabolic syndrome, 3 out of 5 criteria needed: increased waist circumference greater than 35 inches, FBS greater than or equal to 100 mg/dL, HDL cholesterol less than or equal to 50 mg/dL, TG levels greater than or equal to 150 mg/dL, and blood pressure greater than 130/85.[11] ACOG recommends a two-hour oral glucose tolerance test for diagnosis of insulin resistance in patients with PCOS.[10]

Insulin resistance is directly linked to the pathology of PCOS. The mechanisms proposed include direct stimulation of ovarian steroidogenesis, reduction in sex hormone-binding globulin, and disruption of the hypothalamic-pituitary axis which lead to hyperandrogenism and ovarian dysfunction.[12] Insulin resistance further exacerbates weight gain that perpetuates the anovulatory cycle of PCOS.

Other causes of hyperandrogenism were ruled out in this case. Our patient had a normal FSH, LH, TSH, and prolactin that rule out primary ovarian failure, thyroid disease, and prolactin disorders. Free testosterone is recommended over total testosterone in the diagnosis of androgen excess, but physical exam findings are considered equally diagnostic. A 17-hydroxyprogesterone level should be done to rule out congenital adrenal hyperplasia. Unless rapid virilization is present, DHEA is not recommended. Cushing syndrome is extremely rare and screening is not recommended unless other criteria are present.[9]

were regular and lasted around 27 days. She also reports heavier menstrual bleeding, with a length of 7 to 9 days. She reports no other complaints, such as hot flashes or sleep disturbances. She has a history of hypothyroidism, treated with levothyroxine 88 mcg once daily. She is a non-smoker, and is currently sexually active with one partner for 6 months and uses condoms for contraception. She previously used combined oral contraceptives from age 19 to 34 without adverse effects. Her physical exam reveals a BMI of 27 kg/m2 and blood pressure of 118/70 mmHg. Her pelvic exam is normal and her TSH and CBC are within normal limits. A urine pregnancy test is negative. An endometrial biopsy is negative and transvaginal ultrasound shows no structural abnormalities.

Nearly all women experience changes in menstrual bleeding patterns for 4 to 8 years preceding menopause due to declining ovarian function.[16] Although common, complaints of abnormal uterine bleeding during this time must be fully evaluated to rule out other potential causes. The hormone imbalance between estrogen and progesterone that occurs during this time increases risk for endometrial hyperplasia or cancer. Uterine leiomyomas, adenomyosis, thyroid disorders, and coagulopathies are additional examples of pathology associated with abnormal bleeding.[7] Transvaginal ultrasound, hysteroscopy, and saline infusion hysterography can facilitate the detection of anatomic pathology. Endometrial sampling is a key procedure in women with AUB who are 45 years or older. It is also indicated for women who are younger than 45 years if they have a history of unopposed estrogen exposure such as in PCOS, family history of hereditary nonpolyposis colorectal cancer or endometrial cancer or have persistent AUB that fails medical management.[7] In addition to these studies, it is important to assess for iron deficiency anemia and to rule out pregnancy prior to considering treatment options.

The endometrial biopsy for our patient is negative and her normal CBC indicates no need for iron replacement. As anatomic causes are ruled out, the management of AUB-O during perimenopause should focus on a woman's individual concerns related to quality of life. While medical and surgical options exist, either hormonal or non-hormonal pharmacologic strategies are typically considered first-line.

Hormonal options:

Hormonal contraceptives are a viable option for perimenopausal women who are sexually active. Combined hormonal contraceptives (CHCs), containing estrogen and progestin, regulate the menstrual cycle and reduce both the length and volume of menstrual bleeding. If acute management of bleeding is needed, a monophasic oral product containing 35 mcg of ethinyl estradiol may be administered three times daily for 7 days.[8] For non-acute bleeding, the use of a low-dose monophasic preparation is preferred and products that either shorten the hormone-free interval to 4 days instead of 7, or those that offer 3 months of extended use or 12 months of continuous use, provide additional choices that limit the bleeding phase.[17] The combined vaginal ring and contraceptive patch are advantageous for those wishing to avoid daily use, and can be used in a cyclical (monthly withdrawal bleed) or continuous pattern.[17]

The estrogen component of CHCs provides additional benefit for women experiencing vasomotor symptoms, another common symptom during the menopausal transition. However, estrogen-associated precautions and contraindications such as tobacco use, uncontrolled hypertension, history of stroke or venous thromboembolism (VTE), migraine, estrogen dependent cancer, and gallbladder disease may be more common in this age group than younger women, and may prevent the use of an estrogen-containing product.[18] The contraceptive patch has additional warnings regarding thromboembolic risk, and should be avoided in women with VTE risk factors.[19]

Progestin-only contraceptives are often selected for women who are not candidates for estrogen. Unlike combined estrogen-progestin products that provide a regular withdrawal bleed, many women experience amenorrhea after months of progestin-only product use. Unfortunately, unpredictable spotting is common as they are initiated, with a gradual reduction in bleeding episodes over time.[20] There are four levonorgestrel IUDs available in the US providing between 3 to 5 years of contraception depending on the product. The 52 mg LNG-IUS (Mirena) has an FDA-approved indication for menorrhagia, and has been shown to reduce menstrual blood loss, with high acceptability.[20, 21] The etonogestrel subdermal implant provides contraception for up to 3 years and is associated with variable menstrual bleeding patterns, with more than half of women either experiencing infrequent bleeding or amenorrhea.[20] The depo medroxyprogesterone acetate injection, administered every 3 months, produces amenorrhea in the majority of women after 1 year of use. It also has been shown to improve hot flashes associated with perimenopause. However, its use is associated with decreased bone density, which is concerning as a woman approaches menopause.[17, 19]

Women not desiring contraception can be treated with cyclical progesterone regimens, which result in a withdrawal bleed after the completion of each cycle. If managing an acute bleeding event, oral medroxyprogesterone may be given as 20 mg three times daily for 7 days.[8] For chronic management, oral medroxyprogesterone acetate 10 mg daily is given for 10-14 days per month. An additional non-contraceptive hormonal option is a GnRH agonist, which down regulates the hypothalamic, pituitary, ovarian axis and leads to a "pseudomenopause." These are generally not recommended as a first-line approach due to the lack of data in AUB-O and the risk for hot flashes and reduced bone density.[22]

Non-hormonal options:

Women with contraindications to hormone products may be candidates for non-hormonal options. Nonsteroidal anti-inflammatory drugs (NSAIDs) such as mefenamic acid, naproxen, and ibuprofen are effective for the management of AUB through uterine vasoconstriction resulting from decreased prostaglandin synthesis.[23] Because of the unique mechanism, NSAIDs can be used in conjunction with other medical options, such as hormonal contraceptives. Women with an aspirin/NSAID allergy, bleeding disorders or who are taking other anticoagulant or antiplatelet medications should avoid this option.

TABLE 2:

Management of Hirsutism

HIRSUTISM MANAGEMENT	PROS	CONS	SIDE EFFECTS
Laser Therapy	Well tolerated	Cost Short term effect Dark hair better results	None – but adding eflornithine to laser had better effects
Eflornithine HCL Facial Cream	Well tolerated Combined with laser therapy improves effect	Cost Short term effect, use recommended for 6 months	Local stinging, burning, redness, rash
Spironolactone-aldosterone antagonist	BID dosing Cost Improves acne	Do not use in pregnancy	Hyperkalemia Orthostatic hypotension
Flutamide-androgen receptor agonist	Combined with lifestyle/ metformin- additive effects[13]	Do not use in pregnancy	Dry skin Hepatitis (rare)
Finasteride - 5-alpha reductase inhibitor	Better tolerated than other anti-androgens Better if combined with OCPs	Do not use in pregnancy	Rare
Combined Hormonal Contraception	Cost Improves acne	Do not use in pregnancy	May increase insulin resistance
Metformin	Cost	Results vary Not first line for hirsutism or acne[12]	GI upset, diarrhea

Hyperandrogenism also causes hirsutism, acne, and alopecia. Hirsutism involves substantial growth of terminal hairs over the chin, neck, lower face, and sideburns. This hair growth typically has gradual onset and worsens with weight gain.[9] Any patient with a rapid onset of hirsutism and clitoromegaly should be evaluated for an androgen secreting tumor.[10] Management of hirsutism is discussed in *Table 2.*[9, 10]

The further management of PCOS is multifocal. Both exercise and weight loss have proven cardiovascular reduction in morbidity and mortality. As little as a 5% reduction in weight has been reported to restore ovarian function and fertility in PCOS. The addition of pharmacotherapy with metformin (Glucophage) will improve ovulation, increase weight loss, and decrease insulin and androgen levels. Metformin may also prevent the conversion of insulin resistance to Type 2 diabetes.[12] A common skin finding of insulin resistance and PCOS is acanthosis nigricans that is described as hyperpigmented, verrucous skin patches in the neck folds or axillae.

Patients with PCOS are at increased risk of endometrial hyperplasia and endometrial cancer. Our patient had a normal transvaginal ultrasound; however, endometrial thickness in premenopausal women is not helpful in the determination of endometrial hyperplasia.[7] Prevention of endometrial hyperplasia in PCOS is achieved with hormonal contraception, either combined hormonal contraception (CHC) or progestin-only derivatives. The levonorgestrel-releasing intrauterine system is also acceptable. There have been no studies suggesting that one hormonal contraceptive is superior to another. Progestin-only therapy may include side effects of irregular bleeding. Contraindications and tolerability of various hormonal contraceptives is further discussed in Case 2. According to the AACE, the optimal number of induced cycles per year have not been determined.[12]

A large Australian retrospective study by Hart and Doherty in 2015 determined that PCOS increases the risk of many conditions. These include obesity, endometrial cancer, mortality, adult-onset diabetes, hypertension, ischemic heart disease, asthma, and mood disorders.[14] Other studies have discussed an increased risk of sleep apnea.[15] In addition to screening our patient for these co-morbid conditions, follow up monitoring of weight loss, insulin resistance, and cholesterol is recommended.

CASE 2: ADULT – AGES 35-50

A 46-year-old woman presents to clinic with complaints of irregular menstrual bleeding. She states that over the past year, her menstrual cycles are ranging from 20 to 36 days. Before that time, her cycles

Tranexamic acid is a fibrinolytic that reduces the volume of uterine bleeding, and is an option to manage acute bleeding in an oral dose of 1300 mg three times daily for 5 days.[8] It can be used to manage chronic bleeding, although it does not address the underlying cause. Caution is advised due to its associated risk for VTE, which is exacerbated by concomitant use of estrogen-containing contraceptives.

Surgical options of endometrial ablation and hysterectomy are typically reserved for use after pharmacologic strategies fail or in women who are not candidates for medical management.[24]

Our patient is sexually active and does not appear to have contraindications to estrogen or progesterone containing contraceptive products. She is not experiencing hot flashes, so a combined hormonal or progestin-only contraceptive may be used. The decision may be made based upon whether she would prefer a predictable withdrawal bleeding pattern, or a progestin-only method that would likely lead to amenorrhea after several months of use. She is not a candidate for an NSAID due to her aspirin allergy, so this should be avoided as an adjunctive measure.

CASE 3: OLDER ADULT, POST-MENOPAUSAL – AGE 50+

A 62-year-old, obese, nulligravida, female presents for a well-woman examination. She has never married and used condoms for contraception when she was sexually active. She has no significant past medical history and has not seen a doctor in the last 10 years. She believes that she has never had an abnormal pap smear. Her first menstrual period was at age 11 and she experienced menopause 6 years ago. She has never been on any hormone replacement therapy. She denies hot flashes or mood swings. The patient does mention however, an episode of vaginal spotting 2 weeks ago. The bleeding was managed by a pantiliner and lasted about 2 days. Her blood pressure and pulse are stable and BMI is 33kg/m^2. The results of a transvaginal ultrasound (TVUS) are indeterminate with poor visualization.

Any AUB in postmenopausal women should be further evaluated given the increased risk of endometrial cancer. Other non-malignant causes of postmenopausal bleeding include, but are not limited to: atrophic vaginitis, endometrial atrophy, fibroids, simple endometrial hyperplasia, and endometrial or cervical polyps.[25]

Our patient had an initial TVUS reflecting poor visualization. The next step in management includes an endometrial biopsy, hysteroscopy with dilation and curettage, or sonohysterography. The ACOG supports endometrial biopsy or transvaginal ultrasound (TVUS) for the initial evaluation of AUB in postmenopausal women.[26, 27] Either method is sufficient in most cases. The benefits of TVUS include less invasive, less expensive testing with a high negative predictive value. TVUS will allow visualization of structural polyps and fibroids. If the endometrial thickness on TVUS is less than 4 mm, the probability of endometrial cancer is 1%,28 and endometrial biopsy is not recommended. If the endometrial thickness is greater than 4 mm, endometrial biopsy, hysteroscopy with dilation and curettage, or sonohysterography is advised.[27,28]

Classification of endometrial tissue and risk categories include both hyperplasia with atypia and hyperplasia without atypia.[28] Hyperplasia with atypia has a greater risk for progression to carcinoma over 20 years, compared to hyperplasia without atypia.[29] If our patient's endometrial biopsy reflects hyperplasia with atypia or carcinoma, definitive treatment includes a total hysterectomy and staging of the disease. If diagnosed early, endometrial carcinoma is usually confined to the uterus in 75% of cases. Early detection affords lower mortality rates and favorable prognoses.[30] Non-surgical management may be considered in some patients who are younger and desire fertility or are not surgical candidates. If our patient's endometrial biopsy reflects hyperplasia without atypia, treatment with an oral progestin or LNG-IUD can be considered.[28] Newer drugs in research have included metformin.[29]

Current recommendations consider systemic hormone therapy (HT) appropriate for management of common menopausal symptoms, including vasomotor and urogenital symptoms.[31] Postmenopausal women with AUB who are currently using HT require unique consideration. It is well-established that unopposed systemic estrogen therapy in women with a uterus causes a substantial excess risk for endometrial cancer, which increases with time.[31, 32] Therefore, only women without a uterus should receive systemic estrogen alone for menopausal symptoms. All other women should receive a combination of estrogen and progestogen, which when given in a cyclic or continuous regimen, reduces the excess risk of endometrial cancer.[31] Current research points to greater endometrial cancer risk reduction with a continuous use pattern.[32] Daily continuous administration of estrogen plus progestogen is often associated with a variable and unpredictable bleeding pattern for several months, usually resulting in amenorrhea after that time. If the bleeding persists after 6 months, further endometrial evaluation is recommended. In contrast, the cyclic pattern (estrogen daily plus 12-14 days of progestogen per month) should result in a withdrawal bleed as the progestogen is stopped each cycle. Bleeding occurring outside this expected time should be evaluated.[31]

Women with a uterus who cannot tolerate a progestogen may be a candidate for estrogen plus bazedoxifene (a tissue-selective estrogen complex), which provides endometrial protection.[31] Women who experience bothersome bleeding patterns on HT can also consider nonhormonal options for vasomotor symptoms, such as clonidine, gabapentin or pregabalin, or serotonergic antidepressants.[33] Notably, women without other endometrial cancer risk factors receiving local vaginal estrogen therapy for genitourinary symptoms alone typically do not require additional progestogen for endometrial protection. However, safety has not been studied beyond one year. Any uterine bleeding experienced by a women receiving low dose, local vaginal estrogen should be investigated further.[31]

SUMMARY

Clinical evaluation of abnormal uterine bleeding requires careful consideration of age-specific factors. Identification of the underlying causes, whether structural or otherwise, allows the clinician to determine whether a surgical or medical approach is most appropriate. All decisions must be individualized to a patient's risk and reproductive plans.

AUTHOR DISCLOSURES:
No relevant financial affiliations

REFERENCES:

1. Munro MG, Critchley HO, Broder MS, Fraser IS. FIGO classification system (PALM-COEIN) for causes of abnormal uterine bleeding in nongravid women of reproductive age. FIGO Working Group on Menstrual Disorders. Int J Gynaecol Obstet 2011;113:3-13.
2. ACOG Practice Bulletin No. 136: Management of abnormal uterine bleeding associated with ovulatory dysfunction. American College of Obstetricians and Gynecologists. Obstet Gynecol 2013;176-185.
3. Mackintosh ML, Crosbie EJ. Obesity-driven endometrial cancer: is weight loss the answer? BJOG. 2013; 120(7):791–4.
4. Fazio SB, Ship AN. Abnormal uterine bleeding. South Med J. 2007; 100:376-382.
5. Ali AT. Reproductive factors and the risk of endometrial cancer. Int J Gynecol Cancer. 2014; 24: 384-393.
6. US Preventive Services Task Force. Cervical Cancer: Screening. Available at: https:/www.uspreventiveservicestaskforce.orgPage/Document/UpdateSummaryFinal/cervical-cancer-screening?ds=1&s=cervical%20cancer%20screening. Accessed December 13, 2017.
7. ACOG Practice Bulletin No. 128: Diagnosis of abnormal uterine bleeding in reproductive-aged women. American College of Obstetricians and Gynecologists. Obstet Gynecol 2012;120(1):197-206.
8. ACOG Committee Opinion No. 557: Management of acute abnormal uterine bleeding in nonpregnant reproductive-aged women. American College of Obstetricians and Gynecologists. Obstet Gynecol 2013;121:891-6.
9. Goodman NF, Cobin RH, Futterweit W, Gluek JS, Legro RS, Carmina E. American Association of Clinical Endocrinologists, American College of Endocrinology and Androgen Excess and PCOS Society disease state clinical review: Guide to the best practices in the evaluation and treatment of polycystic ovary syndrome - part-1. Endocrine Practice 2015; 1291-1300.
10. ACOG Practice Bulletin No. 108: Polycycstic Ovary Syndrome. American College of Obstetricians and Gynecologists. Obstet Gynecol 2009 (reaffirmed 2015); 114: 936-948.
11. National Heart, Lung, and Blood Institute. Metabolic Syndrome. Available at: https://www.nhlbi.nih.gov/health-topics/metabolic-syndrome. Accessed December 13, 2017.
12. Goodman NF, Cobin RH, Futterweit W, Gluek JS, Legro RS, Carmina E. American Association of Clinical Endocrinologists, American College of Endocrinology and Androgen Excess and PCOS Society disease state clinical review: Guide to the best practices in the evaluation and treatment of polycystic ovary syndrome - part-2. Endocrine Practice 2015;1415-1426.
13. Naderpoor N, Shorakae S, Courten B, Misso ML, Moran LJ, Teede HJ. Metformin and lifestyle modification in polycystic ovary syndrome: systematic review and meta-analysis. Human Reproduction Update 2015;21,(5):560-574.
14. Hart R, Doherty DA. The potential implications of a PCOS diagnosis on a woman's long-term health using data linkage. J Clin Endocrinol Metab 2015;100(3):911-9.
15. Helvaci N, Karabulut E, Demir AU, Yildiz BO. Polycystic ovary syndrome and the risk of obstructive sleep apnea: a meta-analysis and review of the literature. Endocrine Connections 2017;6:437-445.
16. The North American Menopause Society recommendations for clinical care of midlife women. Available at: http://www.menopause.org/docs/default-source/2014/nams-recomm-for-clinical-care.pdf. Accessed November 30, 2017.
17. ACOG Practice Bulletin No. 110: Non-contraceptive uses of hormonal contraceptives. American College of Obstetricians and Gynecologists. Obstet Gynecol 2010;115:206-18.
18. Curtis KM, Tepper NK, Jatlaoui TC, et al. U.S. medical eligibility criteria for contraceptive use. MMWR Recomm Rep 2016;65(No. RR-3):1-103.
19. Hatcher RA, Trussell J, Nelson AL, Cates W, Kowal D, Policar MS. Contraceptive technology. 20th Ed. Atlanta, GA: Ardent Media, Inc., 2011.
20. ACOG Practice Bulletin No. 186: Long-acting reversible contraception: implants and intrauterine devices. American College of Obstetricians and Gynecologists. Obstet Gynecol 2017;130:e251-69.
21. Lethaby A, Hussain M, Rishworth JR, Rees MC. Progesterone or progestogen-releasing intrauterine systems for heavy menstrual bleeding. Cochrane Database Systematic Reviews. 2015;4:CD002126.

22. Bradley LD, Ndeye-Aicha G. The medical management of abnormal uterine bleeding in reproductive-aged women. Am J Obstet Gynecol 2016;214(1):31-44.

23. Lethaby A, Duckitt K, Farquhar C. Non-steroidal anti-inflammatory drugs for heavy menstrual bleeding. Cochrane Database Systematic Reviews. 2013;1:CD000400.

24. ACOG Practice Bulletin No. 136: Management of abnormal uterine bleeding associated with ovulatory dysfunction. American College of Obstetricians and Gynecologists. Obstet Gynecol 2013;122:176-85.

25. Oriel K, Schrager S. Abnormal uterine bleeding. American Family Physician 1999;60(5):1371-1380.

26. ACOG Committee Opinion No. 440: The role of transvaginal ultrasonography in the evaluation of postmenopausal bleeding. American College of Obstetricians and Gynecologists. Obstet Gynecol. 2009; 114(2 Pt 1):409–11.

27. ACOG Committee Opinion No. 631: Endometrial intraepithelial neoplasia. American College of Obstetricians and Gynecologists. Obstet Gynecol. 2015; 125:1272–1278.

28. Trimble CL, Method M, Leitao M, Lu K, Ioffe O, Hampton M, Higgins R, Zaino R, Mutter G. Management of endometrial precancers. Obstet Gynecol. 2012; 120(5)1160-1175.

29. Clement N, Oliver T, Shiwani, Snaer J, Mulvaney C, Atiomo W. Metformin for endometrial hyperplasia a Cochrane protocol. BMJ Open 2016;6:1-10.

30. Brasileira F. Endometrial carcinoma: treatment. Rev Assoc Med Bras. 1992; 58(3):281-6.

31. The North American Menopause Society. The 2017 hormone therapy position statement of The North American Menopause Society. Menopause 2017;24(7):728-753.

32. American Association of Clinical Endocrinologists and American College of Endocrinology position statement on menopause-2017 update. Endocrine Pract 2017; 23(7): 869-880.

33. The North American Menopause Society. Nonhormonal management of menopause-associated vasomotor symptoms: 2015 position statement of the North American Menopause Society. Menopause 2015;22(11):1155-1174.