Available online at www.jmpas.com

ISSN NO. 2320–7418 DOI: 10.22270/jmpas.V10I2.1007

Review Article

AN OVERVIEW OF ENDOMETRIAL HYPERPLASIA

Gokula Priya M*, Bargavi E, Julega K S

Arulmigu Kalasalingam College of Pharmacy, Srivilliputhur, Tamil Nadu, India

ABSTRACT

Endometrial Hyperplasia is referred as the endometrial cells of uterus, which keep on growing or multiplying instead of shedding because of high levels of estrogen and low or insufficient levels of progesterone. It is a pre-malignant condition but which are not invasive in nature. EH usually occurs in women between 50 – 55 yrs. Endometrium being a hormone dependent tissue depends on estrogen and progesterone for proliferation and shedding. Endometrial thickness gradually increases day by day. EH is caused by PCOS and chronic anovulation in premenopausal women. Obesity, lynch syndrome are other causes of EH. In 1994, WHO classified this EH into four groups. In 2014, WHO revised this classification into two types, one is endometrial Hyperplasia (without atypia) and second one is atypical endometrial hyperplasia or EIN. Patient with EH experiences abnormal uterine bleeding, bleeding in between periods etc… Age, nulliparity, obesity, smoking, diabetes mellitus are the risk factors and is diagnosed by endometrial biopsy, dilation and curettage, transvaginal ultrasound, hysteroscopy. Management of EH is based on it's types. Hyperplasia without atypia is managed by levonorgestrel-releasing intrauterine system (LNG-IUS), oral progestogens and surgery. Atypical EH is managed by surgery hysterectomy.

Keywords: EH (Endometrial Hyperplasia), Estrogen, Progesterone, Hysterectomy, D and C (Dilation and Curettage).

Duration: **Received-** 06/01/2021, **Reviewed-** 10/02/2021, **Revised/ Accepted**- 15/03/2021

Correspondence

Gokula Priya M* ✉ gokulapriya17111999@gmail.com

Address - Doctor of Pharmacy, Arulmigu Kalasalingam College of Pharmacy, Krishnankoil, Srivilliputhur, Tamil Nadu, India

INTRODUCTION

Endometrial Hyperplasia [EH] is a disordered proliferation of the endometrial layer lining of the uterus [1].This pathologic condition is characterized by the hyperplastic changes (cells that undergo abnormal changes before becoming a cancerous cell) in the endometrial gland and stromal structures lining the uterine cavity [2]**.** Mild or simple hyperplasia has a low risk of becoming cancer; complex hyperplasia has a high risk to become as a cancer [3]**.** EH is a premalignant condition, non-physiological, but which are not invasive in nature that results in the increased mass of endometrial tissue with alternations in size and shape [4]. Endometrial Hyperplasia occurs rare in women those who are less than 30 years and increased incidence of EH occur in women between the ages of 50-54 years [1]. The incidence of atypical hyperplasia is greatest in 60-64 years old women. EH incidence in simple - 142 per 1 lakh woman years, complex- 213 per 1 lakh women years[5].

HORMONES AND ENDOMETRIUM

The inner layer of the uterus is known as endometrium, which contains numerous glands submerged within a supportive stroma. It is a hormone dependent tissue. In the presences of steroid (sex) hormones, endometrium undergoes changes throughout the menstrual cycle. During the first half of the cycle, FSH stimulates ovarian follicles to produce estrogen hormone. Estrogen causes the endometrial lining to become thick in order to make the uterus to carry pregnancy. During the second half of the cycle, LH triggers ovulation and stimulates the development of corpus luteum to secrete progesterone hormone. The role of progesterone is to make the endometrium to oedematous and provide nourishment to the fertilized egg. The levels of estrogens and progesterone decreases if the ovum doesn't fertilized by a sperm. Hence the decrease in the progesterone triggers menstruation (shedding of endometrial lining). New menstrual cycle begins after the complete shedding. Usually endometrial hyperplasia occurs, after menopause, or, when ovulation stops, or, progesterone is not produced. It can also occur during the perimenopause, when ovum is not produced regularly. High levels of the estrogen and low or insufficient levels of progesterone cause thickening of endometrium [6]**.**

ISSN NO. 2320–7418 DOI: 10.22270/jmpas.V10I2.1007

ENDOMETRIAL THICKNESS

The thickness of endometrium generally varies from time to time of person's life, from childhood, fertile years, sexual maturity, and after menopause.

Before puberty: Endometrium is smaller.

Menstruation: According to Radiological Society of North America [RSNA], the endometrium is very thin during menstruation, measures 2-4 mm in thickness. During the first half of the proliferative phase [6-14 days], endometrium becomes thicken and measures 5-7 mm. When the cycle progresses to ovulation and the endometrium becomes thicker upto 11 mm. During the secretory phase, endometrium reaches its maximum thickness of 16 mm.

Menopause: RSNA states that a postmenopausal person has the endometrial thickness less than 5 mm [7].

Endometrial hyperplasia: EH is considered whatever the endometrial thickness is greater than 10 mm especially in the menopausal patients [8].

ETIOLOGY

1. **Premenopausal**

- Polycystic Ovarian Syndrome [PCOS]: Increasing circulating androgens peripherally converted to estrogens (estrogen is responsible for the proliferation for the proliferation of endometrium)
- Chronic anovulation/Infertility: deregulated without opposing the progesterone secretion.

2. **Pre and Post-menopausal** Estrogen supplementation:

- Systemic therapy to reduce symptoms of menopause leads to endometrial proliferation.
- Tamoxifen has partial agonist action and can induce endometrial proliferation.

3. Women with hereditary nonpolyposis colonic cancer(lynch syndrome),develop increased risk of complex atypical EH.

4. Postmenopausal nulliparous women are having high chance to develop endometrial hyperplasia.

5. Obesity→Aromatase (enzyme converting circulating androgens to estrogens) found in adipose tissue leads to peripheral hyperestrogenism.

6. Stromal hyperplasia and Hyperthecosis:
Stromal luteinization→ hyperandronism→ hyperestrogenism[9,10]

CLASSIFICATION

The old WHO classification in 1994,

1. Simple hyperplasia without atypical: Without normal architecture change, the glands number may increase, progression rate to cancer-1%
2. Simple hyperplasia with atypia: Simple hyperplasia associated with remarkable changes in nuclear level (nuclear shape and size and prominent nucleoli); progression rate to cancer-8%.
3. Complex hyperplasia without atypia: Irregular glands become more crowded, progression rate to cancer-3%.
4. Complex hyperplasia with atypia: Complex hyperplasia associated with atypical features, progression rate to cancer-29% [11].

Revised WHO classification (2014):

This is the widely used classification in the world.

- Hyperplasia without atypia
- Atypical hyperplasia or EIN

Mutter classification

Later the pathologists and clinicians led to the formation of new classification.

- Benign hyperplasia
- Endometrial Intraepithelial Neoplasia (EIN)[12]

CLINICAL PRESENTATION

- Abnormal uterine bleeding
- Menorrhagia
- Intermenstrual bleeding
- Post-menopausal uterine bleeding
- Hormone replacement therapy or tamoxifen leads to irregular bleeding [4]
- In some rare causes they occur asymptomatic.[9]
- Menstrual bleeding that is heavier or longer than usual or that are shorter than 21 days.[13]
- Bleeding in between periods.[14]

RISK FACTORS

- Age greater than 35 years.
- Nulliparous woman.
- Personal history of certain conditions such as Diabetic Mellitus, Polycystic Ovarian Syndrome, Gall bladder disease or Thyroid disease.
- Obesity.
- Family history of ovarian, colon or uterine cancer [8]
- Smoking.
- Genetic mutations.
- Caucasian origin.
- Lynch syndrome [15].

DIAGNOSIS

Ultrasound (transvaginal ultrasound)

Imaging the endometrium on 5-10 days of cycle reduces the variability in endometrial thickness.

Pre-menopausal

ISSN NO. 2320–7418 DOI: 10.22270/jmpas.V10I2.1007

1. The stage of menstrual cycle plays a key role in the thickness of endometrial cells. In the secretory phase, thickness of normal endometrial lining may exceed beyond 15mm.
3. If the patients having less than 8mm endometrium thickness, hyperplasia can be excluded.

Postmenopausal

If the thickness of endometrium is greater than 5 mm it is considered abnormal.

Appearance of endometrium in ultrasound

- Nonspecific.
- Asymmetric / surface irregular focal thickening.
- Cystic changes.
- Heterogenous and irregular endometrial thickening.
- Polypoid mass lesion.
- Intrauterine fluid collection.
- Frank myometrial invasion [16]

Endometrial biopsy

Abnormal uterine bleeding can be evaluated by this endometrial biopsy method. It is a quick and cost effective way to evaluate the histopathology of endometrium. [17]

Hysteroscopy

1. Diagnostic hysteroscopy is conducted using miniature hysteroscopy and there is no need for anesthesia or vaginal instrumentation. It is the direct visualization method.[18]
2. If the premenopausal woman having regular menstrual cycles, the hysteroscopy studies are taken at the follicular phase of the menstrual cycle.[19]

Dilation and Curettage

Dilation → opening (dilation) of the cervix (lower part of uterus) that opens into vagina. To promote dilation MISOPROSTOL (cytotec) is given vaginally or orally.

Vaginally – 200, 400 mcgs [20]

Curettage → scrapping or removal of tissue of endometrium that lines the uterine cavity with a surgical instrument called a curette.

Reason for D & C:

- Obtain samples of endometrium
- Abnormal uterine bleeding

Anaethesia

The procedure is done by using general, regional or local anesthesia. The type of anaethesia depends upon medical history and reason for the procedure.

Complications: Usually it is very safe.

- Perforation of uterus

Surgical instrument makes a perforation in uterus. Usually healing occurs itself without treatment. Two potential problems may occur during perforation, one is bleeding from injury and another one is injury to internal organs.

- Cervical injury

- It occurs during dilation or using the curette Infections.
- Intrauterine adhesions :

In rare cases, in the area of scar tissue, adhesions can occur in the uterus.

Side effects: Spotting of blood

Diagnostic D&C is sometimes done in combination with hysteroscopy; this involves the dilation of the cervix and inserting a narrow camera to examine the uterus inner parts.[21]

CT Scan and MRI

There is insufficient evidence evaluating computerized tomography (CT), diffusion-weighted magnetic resonance imaging (MRI).

Accurate diagnosis, which depends on the frequency of the sample examined is important for the choice of treatment.[22]

MANAGEMENT

A. **Management of endometrial hyperplasia without Atypia:**

Initial management

i. Chance to develop as an endometrial malignant is less than 5%.

ii. It will retrogress spontaneously during follow up in majority of cases.

iii. Obesity and effects of HRT can be identified and discussed.

iv. Endometrial biopsies are followed up to ensure regression.

v. Progestogen treatment indicates that abnormal uterine bleeding and patients who fail to regress. (Treatment with Progestogen has higher regression rate).

First-line treatment

- Oral and Intrauterine [levonorgestrel-releasing intrauterine system (LNG-IUS)] progestogens are effective.
- The LNG-IUS can be used as the first-line medical treatment. Because it is most effective with few adverse effects.
- Cyclical progestogens are less effective, so it should not be used.

ISSN NO. 2320–7418 DOI: 10.22270/jmpas.V10I2.1007

- Progestogens can be given continuously (Medroxy progesterone 10-20 mg/day or Norethisterone 10-15 mg/day) for woman who declines the LNG-IUS.

Duration and Follow up:

i. To induce histological regression, oral progestogens or LNG-IUS can be given for minimum 6 months.
ii. If the patients tolerate the adverse effects and fertility not desired, LNG-IUS can be used upto 5 years.
iii. After diagnosis, endometrial biopsy can be advised.
iv. Endometrial surveillance can be done for atleast 6 months once.
v. Advise should be given regarding the visit to hospital in case of any abnormal vaginal bleeding after completion of treatment.
vi. Patient those who are having BMI greater than 35 or those who are taking oral Progestogen are at high risk of relapse. In such cases, 6 months once patients are advised to take endometrial biopsies.

Surgery:

i. Hysterectomy cannot be advised as a first-line treatment.
ii. Hysterectomy is indicated in woman who does not want to preserve their fertility.
iii. Postmenopausal woman should be offered bilateral-salpingo-oophorectomy along with total hysterectomy.[17]

Current Progestin therapies [23]

ROUTE	FORMULATION (DRUG)	DOSE
Oral	Medroxy progesterone Megestrol Norethindrone	5-10 mg/day 40-320 mg/day 2.5-10 mg/day
Intramuscular	Medroxy progesterone	150 mg once every 3 months
Vaginal	Progesterone gel Progesterone tablet	4% or 8% , 45-90 mg/day 100-200 mg/day
Intrauterine	LNG-IUS	52 g ; replace every 5 years

***B.* Management of atypical hyperplasia or endometrial hyperplasia with atypia:**

Initial management:

i. Total hysterectomy is done because of the risk of malignancy.
ii. Laparoscopic approach to total hysterectomy is preferable because of less pain, shorter hospital stay and quick recovery.
iii. Postmenopausal woman should be offered Bilateral Salpingo Oophorectomy (BSO) together with total hysterectomy. [17]
iv. BSO – is an operative method to remove both the ovaries and fallopian tubes. [24]

Types of Hysterectomy

Total hysterectomy

Removal of uterus and cervix but not the ovaries. It is the common type of hysterectomy.

Radical hysterectomy

Removal of uterus, cervix, top portion of vagina, cervix surrounded tissues and pelvic lymph nodes. It is used as a treatment option for cancer.

Hysterectomy with oophorectomy

Removal of uterus with any one of the ovary or both the ovaries and fallopian tube.

Supracervical hysterectomy

Removal of body of uterus, leave the cervix untouched. It is used for the treatment of non-cancerous conditions. [25]

CONCLUSION

Endometrial Hyperplasia is the abnormal condition of the endometrium. The lining of the endometrium becomes thick due to increased proliferation of the cells (hyperplasia). It is not a cancer but it is a pre-cancerous condition that may lead to cancer. This condition of endometrial proliferation is caused by certain medical conditions such as PCOS (polycystic ovarian syndrome), lynch syndrome (hereditary non-polyposis colorectal cancer), chronic anovulation, obesity etc. Sometimes in rare cases it is asymptomatic or symptomatic such as abnormal uterine bleeding with or without pain, bleeding between periods, menorrhagia etc. On experiencing these symptoms, endometrial samples are collected from the patients. Before collection of samples trans vaginal ultrasound is preferred in order to ensure the endometrial thickness. Endometrial samples are collected by Biopsy, D&C. EH is treated based on the type. Surgery is not considered as the first-line treatment for endometrial hyperplasia without atypia. Progestogen and LNG-IUS are the first-line management of EH without Atypia. But whereas surgery is considered as the first-line treatment option of Atypical Hyperplasia. Hysterectomy or hysterectomy combined with BSO is the treatment option for Atypical Hyperplasia.

ISSN NO. 2320–7418 DOI: 10.22270/jmpas.V10I2.1007

REFERENCE

1. Moore E, Shafi M, 2013. Endometrial hyperplasia. *Obstetrics, Gynaecology & Reproductive Medicine, 23*(3), 88-93.
2. Sobczuk K, Sobczuk A, 2014. New classification system of endometrial hyperplasia WHO 2014 and its clinical implications. *Przeglad menopauzalny = Menopause review, 16*(3), 107-111. doi-10.5114/pm.2017.70589.
3. American Cancer Society, 2019. Endometrial Cancer Risk Factors. 1.800.227.2345.
4. Chandra V, Kim JJ, Benbrook DM, Dwivedi A, Rai R, 2016. Therapeutic Options for Management of Endometrial Hyperplasia. J*ournal of Gynecologic Oncology, 27*(1), 1-25. doi-10.3802/jgo.2016.27.e8.
5. Reed SD, Newton KM, Clinton WL, Epplein M, Garcia R, Allison K, Voigt LF, Weiss NS, 2009. Incidence of endometrial hyperplasia. *American journal of obstetrics and gynecology,200*(6), 678-e1. doi: 10.1016/j.ajog.2009.02.032.
6. Dr Joel Thomas, Dr Joshin Sara Cherian , Dr Juliyana Joseph , Dr Greeshma Paul , Dr Ashby Benny , Dr Megha Philip , Dr Vijay M C, 2018. Diagnostic measures of cancer at different stage. Jou. Of med. Pharm. & allied sci., v7 - i3, 757, 1028-1035. Doi - 10.22270/jmpas.v7i3.757.The American College of Obstetricians and Gynaecologists, 2012. Endometrium Hyperplasia.
7. Nalaboff KM, Pellerito JS, Ben-Levi E, 2001. Imaging the endometrium: disease and normalvariants.*Radiographics,21*(6):1409-1424. Doi:10.1148/radiographics.21.6.g01nv211409.
8. Palmer JE, Perunovic B, Tidy JA, 2008. Endometrial hyperplasia. *The Obstetrician & Gynaecologist. 10*(4):211-216. doi-10.1576/toag.10.4.211.27436.
9. Thomas L, 2019. What is Endometrial Hyperplasia? *News-Medical Life Sciences.* https://www.news-medical.net/health/Types-of-endometrial-hyperplasia.aspx.
10. Royal College of Obstetricians & Gynaecologists, Green-top Guideline No 67, 2016. Management of Endometrial Hyperplasia.
11. The Use of Hysteroscopy for the Diagnosis and Treatment of Intrauterine Pathology: ACOG Committee Opinion, Number 800, 2020. *Obstetrics & Gynecology.* Doi: 10.1097/ AOG. 0000000000003712.
12. Eakta Kandpal, Aman Mittal, 2016. Stem cell & their role in diabetes. Journal of Medical Pharmaceutical and Allied Sciences; 117-131.
13. Ngai SW, Chan YM, Tang OS, Ho PC, 1999. The use of misoprostol for pre-operative cervical dilatation prior to vacuum aspiration: a randomized trial. *Human reproduction, 14*(8):2139-2142 Doi: 10.1093/humrep/14.8.2139.
14. Marsden DE, Hacker NF, 2003. The classification, diagnosis and management of endometrial hyperplasia. *Reviews in Gynaecological Practice, 3*(2), 89-97. Doi: 10.1016/S1471-7697(03)00046-7.
15. Armstrong AJ, Hurd WW, Elguero S, Barker NM, Zanotti KM, 2012. Diagnosis and management of endometrial hyperplasia. *Journal of minimally invasive gynecology, 19*(5), 562-571. Doi: 10.1016/j.jmig.2012.05.009.

How to cite this article

Gokula Priya M, Bargavi E, Julega K S, 2021. An overview of endometrial hyperplasia. Jour. of Med. P'ceutical & Alli. Sci. V 10 - I 2, 1007. P-2676-2680. DOI: 10.22270/jmpas.V10I2.1007.