COMPARATIVE EVALUATION OF THE EFFICACY OF ORMELOXIFENE AND NORETHISTERONE IN ABNORMAL UTERINE BLEEDING

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CHENNAI

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CERTIFICATE

This is to certify that the dissertation entitled **"COMPARATIVE EVALUATION OF THE EFFICACY OF ORMELOXIFENE AND NORETHISTERONE IN ABNORMAL UTERINE BLEEDING"** submitted by **Dr.SHANMUGA SUNDHARI A V** in the Institute of Obstetrics and Gynaecology (Madras Medical College) Egmore, Chennai, in partial fulfillment of the university rules and regulations for award of MS degree in Obstetrics and Gynaecology under my guidance and supervision during the academic year 2019-2022.

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DECLARATION

I solemnly declare that this dissertation entitled **"COMPARATIVE EVALUATION OF THE EFFICACY OF ORMELOXIFENE AND NORETHISTERONE IN ABNORMAL UTERINE BLEEDING"** was done by me at INSTITUTE OF OBSTETRICS AND GYNAECOLOGY, Madras Medical College during 2019-2022 under the guidance and supervision of, **Prof. Dr. MOHANA, MD. DGO.** This dissertation is submitted to the Tamil Nadu Dr. M.G.R. Medical University towards the partial fulfillment of requirements for the award of M.S. Degree in Obstetrics and Gynaecology.

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CONTENTS

INTRODUCTION

Abnormal uterine bleeding is the most common menstrual disorder among women in all age groups and accounts for 20% of gynaec OPD.[1] It is characterized by heavy, prolonged flow with or without breakthrough bleeding. It is most often the result of endocrinological dysfunction which responds well to conservative treatment. It causes adverse effects which includes Anaemia, reduced quality of life and increased healthcare costs.

AUB can be managed both medically and surgically. Over 7500 hystrectomies were done every year of which 30% of them done for menorrhagia.[2] Though this surgery is relatively safer option, there are long term complications like premature ovarian failure, cardiovascular disease etc. In view of above complications, women nowadays are looking forward to an efficient medical therapy.[3]

The medical treatment of AUB comprises of Combined Oral Contraceptive pills, Progestogens, Danazol, Gonadotrophin releasing hormone agonists, Anti-fibrinolytics, Ethamsylate, Prostaglandin synthetase inhibitor and Levonorgestrel-releasing intrauterine device .

Norethisterone(progestogen) – a 2nd generation 19-nortesterone-derived progestin, is commonly used for this treatment .It was originally intended for use as a drug for irregular menstruation and endometriosis in mexico city in 1951[4] . But being a hormonal drug, it causes various side effects such as stroke, heart disease, fluid retention, breast engorgement, weight gain, breakthrough bleeding, dementia, spotting etc.[5]

Ormeloxifene, a third generation Selective Estrogen Receptor Modulator (SERM) is widely used non-steroidal oral contraceptive. This drug was developed at Central Drug Institute, Luckno in 1967[4]. It acts on estrogen receptors as agonist and antagonist in different tissues. It has anti-estrogenic action on endometrium and breast and estrogenic action vagina, bones, liver, cardiovascular and central nervous system[6] Unlike progesterone, Ormeloxifene does not produce breakthrough bleeding, spotting, breast engorgement, weight gain.

AIM AND OBJECTIVE

- To assess the efficacy of Ormiloxifene in AUB and to compare it with Norethisterone.
- To study the adverse effects of both the drugs

REVIEW OF LITERATURE

AUB is defined by ACOG as bleeding from the uterine cavity that is abnormal in volume, frequency, regularity, duration in the absence of pregnancy. About one third of the women experiences the abnormal uterine bleeding during her extremes of life . [8]

Abnormal uterine bleeding affects the quality of life of many women during their reproductive period. It is the most common cause for many referral into secondary care.it could be acute or chronic.

- ACUTE AUB: it is defines as an episode of heavy bleeding that is of sufficient quantity to require immediate intervention to minimize or prevent further blood loss.[8]
- CHRONIC AUB: it is defined as bleeding from the uterine corpus that is abnormal in duration, volume, frequency and/or regularity, and has been present for the past 6 months duration. [8]

Normal menstrution: menstruation is cyclical shedding of uterine lining as a result of sequence of events occur in a women's body triggered by hormones. Average age of menarche is 12. However some girls begin as early as at the age of 8 or as late as at the age of 16. A sound HPO axis is essential for normal menstruation.

Normal menstruation is described in terms of amount of blood loss, duration of blood loss, Regularity, frequency of the cycle.

1. Amount of blood loss-average blood loss is 80 ml . >80 ml loss is referred as menorrhagia(heavy menstrual bleeding)[8]
2. Duration of blood loss – the menstrual flow last from 2-7 days[8]
3. Cycle length – 21 – 35 days cycle with average of 28 days cycle[8]

   If <21 days cycle it is called polymenorrhoea

   If >35 days cycle it is called oligomenorrhoea
4. regularity- normal menstruation occurs regularly with a deviation of 2-7 days.[8]

Physiology of menstruation:

Menstruation is the end step of cyclical hormonal release from hypothalamus, pituitary gland and ovaries. It is the periodic vaginal bleeding that starts with the shedding of uterine mucosa (menstruation). The length of the cycle is usually variable, but an average figure is 28 days from the start of one menstrual period to the start of next cycle.**[3]** Hormone secretion starts from the hypothalamus as it secrets GnRH (gonadotropin releasing hormone) in pulsatile manner once puberty starts. It is then transported to anterior pituitary gland where it attaches to the 7-transmembrane G- protein coupled receptor and stimulates the secretion of FSH and LH [3]. These two hormones act on the ovaries – particularly

theca cells and granulosa cells in ovarian follicle. LH mediate the theca cells to produce the progesterone and androstenedione from cholesterol by activating the enzyme cholesterol desmolase.[3].

This androstenedione enters into the granulosa cells . FSH mediates the conversion of this androstenedione into testosterone and then into 17- beta-estradiol by activating the enzyme aromatase.[3]]

The granulosa cells in the follicles also produces inhibin and activin. These hormones either inhibit and stimulate the release of FSH from anterior pituitary by downregulating or upregulating the GnRH receptors.[3]

Menstrual cycle is divided into four phases:

- menstrual phase
- follicular phase
- ovulation phase
- luteal phase

Menstrual phase:

- It starts from onset of bleeding and shedding of endometrium. It last for about 3-7 days. It occurs as a result of withdrawal of progesterone . bleeding is chiefly from arterial . menstrual blood contains prostaglandins, tissue debris, fibrinolysin. Because of fibrinolysin, the menstrual blood doesn't clot unless the bleeding is heavy. Menstrual blood contains blood, cells from the endometrial lining and mucus.

Follicular phase:

It starts after the menstruation phase and ends with ovulation. Change in length of menstrual cycle is due to change in length of follicular phase. After the stimuli from hypothalamus , the pituitary starts secreting FSH. This inturn stimulate the ovary to produce oestrogen from the developing follicle.

The predominant hormone during this phase is oestrogen . it causes proliferation of stroma and glands**.**

Ovulation phase:

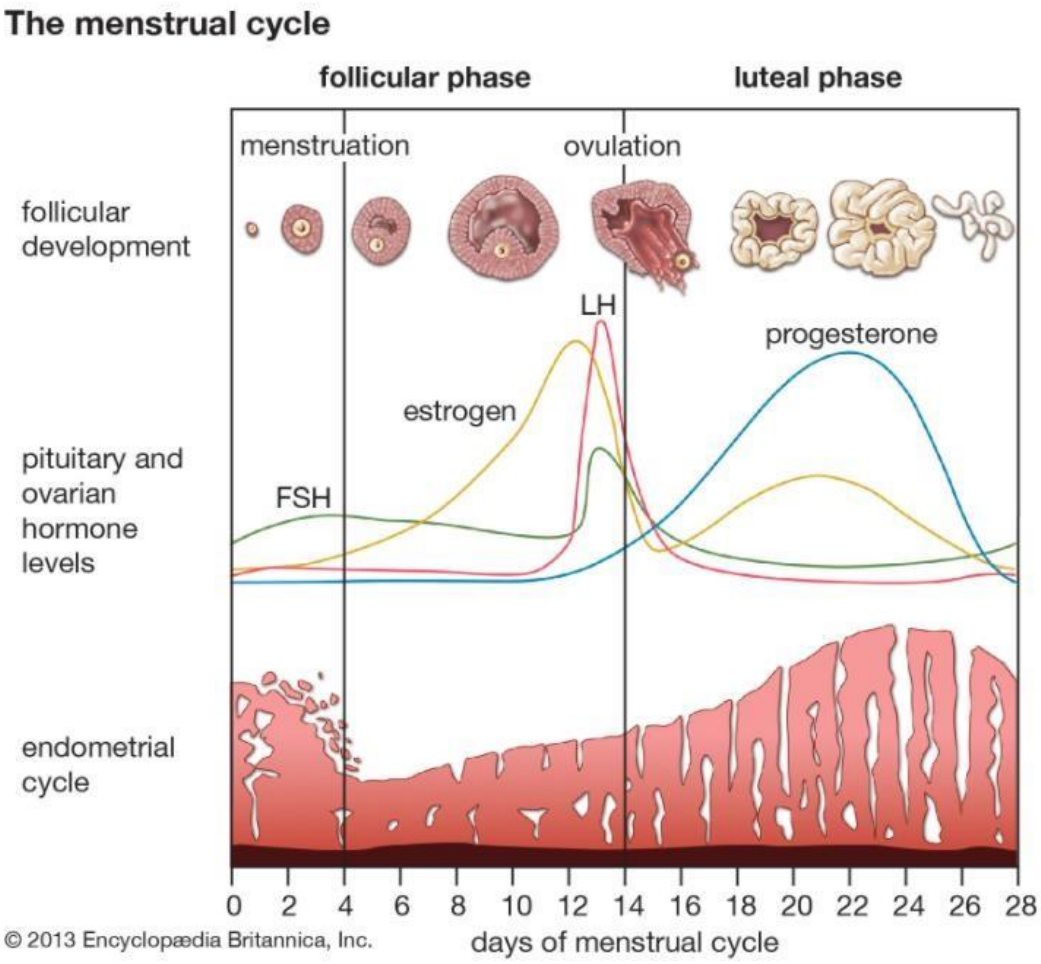
It is the period when ovum releases from the graafian follicle under the influence of LH. It always occurs before 14 days of next

menstruation. High level of estrogen produced from the developing follicle, sends positive feedback mechanism causing FSH and LH to rise causing LH surge. This causes release of oocyte from mature follicle from the surface of the ovary. At the end of ovulation phase, oestrogen level comes down. The egg will be picked up by the fimbrial end of the fallopian tube and move towards the endometrial cavity by ciliary motion of tubal epithelium. The lifespan of the egg is around 24 hours.

LUTEAL PHASE:

It starts from day 14 to day 28. progesterone is the predominant hormone during this phase. Progesterone is produced by corpus luteum (ruptured follicle) under the influence of LH. Corpus luteum also produces small amount of estrogen. Both hormones maintain the thickened lining of the uterus. During this phase the endometrium becomes more secretory, forming more complex glands.

As the cycle goes, the progesterone send negative feedback to anterior pituitary, thus reducing the FSH and LH secretion, thereby decreasing estrogen and progesterone level. Drop in progesterone level causes the endometrium to shed.



Normal control of menstrual bleeding:

When the menstruation starts, the platelet aggregation forms clot in the opened vessels.PGF2α cause the myometrium to contract and constrict the blood vessels in endometrium.

The regeneration of epithelium begin in 3td and 4th day of the menstruation by thegrowth of epithelium from the open endometrial glands.this is facilitated by the growth factors such as the vascular

endothelial growth factor, epidermal growth factor, fibroblast growth factor.

In the setting of excessive bleeding , the H-P-O axis is intact but the endometrial changes get altered.it is found that prostacyclin(PGE_2) , which is a local vasodilator is increased than PGF2α in the endometrium.

OLDER TERMS IN ABNORMAL UTERINE BLEEDING

- Oligomenorrhoea means Cycle length lasting for >35 days
- Polymenorrhoea means Cycle length lasting for <21 days
- Menorrhagia means cycle length (21 to 35 days)but with profuse bleeding (80 ml) or with increased duration (7 days)
- Menometrorrhagia means Irregular bleeding associated with increased flow or duration
- Amenorrhoea- Absence of monthly cyclical bleeding for > 6 months in reproductive age group.
- Metrorrhagia or Intermenstrual bleeding means Intermittent bleeding between cycles.
- Midcycle spotting means Minimal bleeding that occurs around ovulation.
- Postmenopausal bleeding means bleeding in postmenopausal women after cessation of bleeding for >1yr.

- Dysfunctional uterine bleeding means Any abnormal uterine bleeding without any identifiable local or systemic causes

Causes of menorrhagia:

General causes:

1) Blood dyscrasia
2) Coagulopathy
3) Thyroid dysfunction
4) Genital TB

Pelvic Causes:

1. PID, pelvic adhesions
2. Uterine fibroids, endometrial hyperplasia
3. Adenomyosis
4. Feminizing tumour of the ovary
5. Endometriosis
6. Pelvic congestion, varicose veins in the pelvis

Contraceptive use:

1. IUCD
2. Progesterone only pills
3. Post-tubal sterilization

Hormonal causes:

1. Ovuloatory- irregular ripening/ irregular sheding
2. Anovulatory – resting endometrium

TERMINOLOGIES IN AUB:

Previously used terminologies like dysfunctional uterine bleeding, menorrhagia, oligomenorrhoea, polymenorrhoea, hypomenorrhoea , metorrhagia were no longer in use. New nomenclature of symptoms of normal and abnormal uterine bleeding in the reproductive age were described by FIGO in 2011.

Table showing different parameters of menstrual cycle:

Quality	Normal	Abnormal		Prior Terms
Volume	5–80 mL	Light (<5 mL)	Heavy (>80 mL)	hypomenorrhea, menorrhagia
Duration	≤8 d	Prolonged (>8 d)		hypomenorrhea, menorrhagia
Frequency: days between menses				
	24–38 d	Frequent (<24 d)	Infrequent (>38 d) Amenorrhea (>90 d)	polymenorrhea, oligomenorrhea
Regularity: numbers of days by which cycle lengths vary				
	≤7–9 d	Irregular ≥10 d		

1) **HEAVY MENSTRUAL BLEEDING** : it was formerly called as menorrhagia.it is described as menstruation with excessive flow. Objectively, this is defined as >80 mL of blood loss per menstrual period.[9]

2) **PROLONGED BLEEDING:** lasting >8 days per menstrual period. Most women may complain of both, which is described as heavy ,prolonged menstrual bleeding.[9]

3) **FREQUENT BLEEDING** : It describes menses with <24 days intervening.[9]

4) **IN FREQUENT BLEEDING**: It previously called as oligomenorrhea, is defined by menses with >38 days intervening.[9]

5) **AMENORRHOEA:** Absence of menstrual bleeding in a 90~day period is defined as amenorrhea.[9]

6) **REGULARITY**: If cycle lengths varies from cycle to cycle by more than 10 days, they are considered irregular. As an example, one cycle length is 28 days, but the next is 60 days.[9]

7) **INTERMENSTRUAL BLEEDING** : Intermenstrual bleeding defines bleeding, usually brief, that occurs between fairly normal menses. This term replaces metrorrhagia.[9]

8) **Post coital bleeding**: it is prompted by vaginal intercourse [9]

9) Pre and post menstrual spotting[9]

10) **Break through bleeding and unscheduled bleeding** - they are associated with hormone administration. [9]

11) **Withdrawal bleeding:** it refers to the predictable bleeding that results from an abrupt decline in progesterone levels.[9]

AUB is of 2 types-

1) OVULATORY AUB(20%)

2) ANOVULATORY AUB(80%)

FIGO AUB SYSTEM-1

Parameter	Normal	Abnormal	☑
Frequency	Absent (no bleeding) = amenorrhea		☐
	Infrequent (>38 days)		☐
	Normal (≥24 to ≤38 days)		☐
	Frequent (<24 days)		☐
Duration	Normal (≤8 days)		☐
	Prolonged (>8 days)		☐
Regularity	Normal or "Regular" (shortest to longest cycle variation: ≤7-9 days)*		☐
	Irregular (shortest to longest cycle variation: ≥8-10 days)*		☐
Flow Volume (patient determined)	Light		☐
	Normal		☐
	Heavy		☐

Intermenstrual Bleeding (IMB) Bleeding between cyclically regular onset of menses	None		☐
	Random		☐
	Cyclic (Predictable)	Early Cycle	☐
		Mid Cycle	☐
		Late Cycle	☐

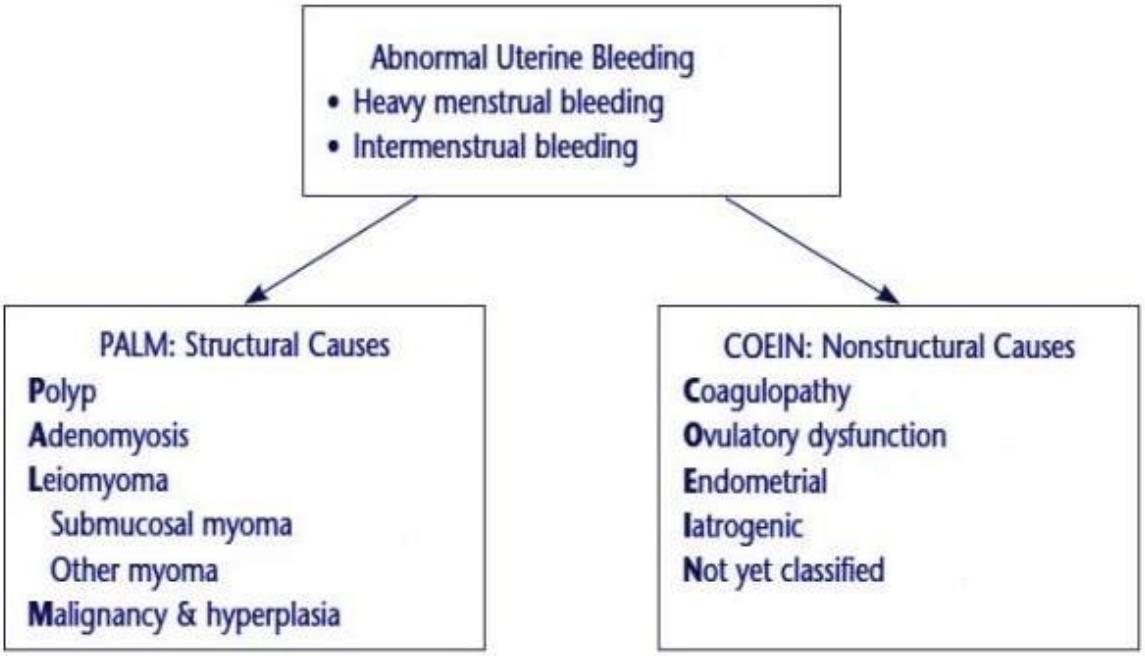
Unscheduled Bleeding on Progestin ± Estrogen Gonadal Steroids (birth control pills, rings, patches or injections)	Not Applicable (not on gonadal steroid medication)	☐
	None (on gonadal steroid medication)	☐
	Present	☐

Causes of AUB:

FIGO AUB SYSYTEM -2:

FIGO developed a classification system for causes of AUB as follows –

–PALM COEIN –



Structural causes:

P - polyp - endometrial / endocervical tissue proliferation that is vascular, glandular, fibromuscular, connective tissue in nature. prevalence – 12%

A - Adenomyosis – based on the depth of endometrial tissue at the interface of endometrium and myometrium , measured post hysterectomy. Prevalence – 5%- 70%

L - Leiomyoma – benign myometrial tumour with fibromuscular component. Prevalence – 70%

M - Malignancy and hyperplasia – atypical hyperplasia, malignancy , premalignant hyperplastic process. It is further classified by WHO or FIGO.

- These causes can be diagnosed and assessed by imaging modalities, histopathology.[9]

Functional causes:

C - Coagulation factor deficiencies- von Willebrand disease, hemophilias, platelet function disorders. Prevalence – 13%

O - Ovulatory dysfunction – seen in PCOS, hypothyroidism, hyperprolactinemia, stress, obesity, anorexia, weight loss, extreme exercise.

E - Endometrial – refer to AUB occur with predictable/ cyclical pattern. Dysfunction of mechanism that affect endometrial hemostasis like infection, inflammation.

I - Iatrogenic – drugs like oral/injectable anticoagulants, intrauterine system, gonadal steroids like estrogen, progestin, androgen, medication

affecting dopamine metabolism(phenothiazines, TCA, antidepressants, herbals (ginseng, ginkgo)

N - Not yet classified – chronic endometritis, A-V malformations, myometrial hypertrophy .[9]

- The above functional causes are evaluated by investigating the underlying medical disorders (hematological/ endocrinological) work up[9]

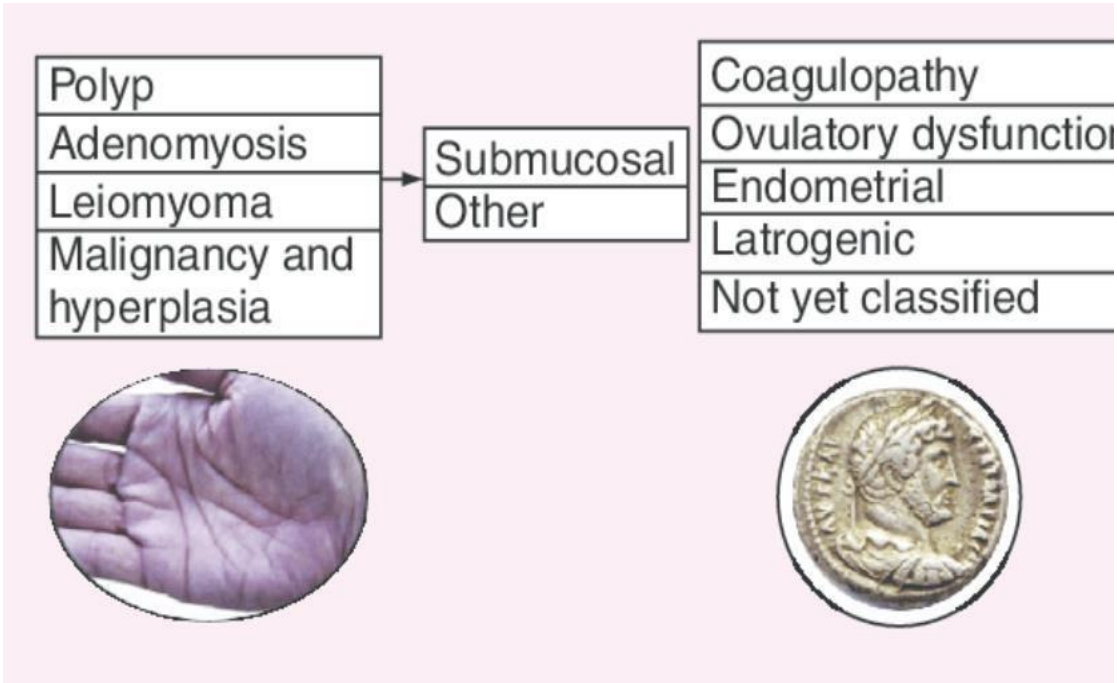


Figure shows FIGO AUB SYSTEM -2

Management of AUB:

History:

- Thorough history must be collected and general and local examination should be done to diagnose the structural cause of AUB.

- Ovulatory status can be identified by cyclical mensus . AUB with ovulatory dysfunction will be irregular in timing and flow and is interspersed with period of amenorhoea. If uncertain ,measuring serum progesterone during mid-luteal phase may help in confirming ovulation.

- In patients with AUB, any of the following criteria should be considered a positive screen for coagulopathies .
    - History of heavy bleeding starting at menarche
    - One of the following:
        - Postpartum hemorrhage
        - Surgery-related bleeding
        -Bleeding associated with dental work

- At least two of the following symptoms:
    - At least one episode of bruising per month
    - At least one episode of epistaxis per month
    - Frequent gum bleeding
    - Family history of bleeding symptoms

Examination:

Any women presenting complaints of bleeding per vaginum, pregnancy must be ruled out and confirmed that bleeding is from cervical canal rather that another location like vagina, vulva, perineum, anal canal. Most of the chronic AUB can be managed in Outpatient basis. An acute episode may need medical emergency.

Investigations: always rule out pregnancy by urine pregnancy test

- To quantify the anaemia- complete blood count , sr.feritin, sr. iron, total iron binding capacity,
- To detect coagulopathies
- Prothrombin time, partial thromboplastin time, activated partial thromboplastin time, sr. fibrinogen, von Willebrand factor antigen, Ristocetin Cofactor Assay, factor VIII
- To do cervical assay for chlamydial infections

- Other test like blood grouping and cross matching, liver function tests, thyroid function tests.

Imaging:

- Transvaginal ultrasound should be considered early in evaluation to identify the structural causes like fibroid, adenomyosis
- Doppler ultrasound : in case of suspected A-V malformations, malignancies .

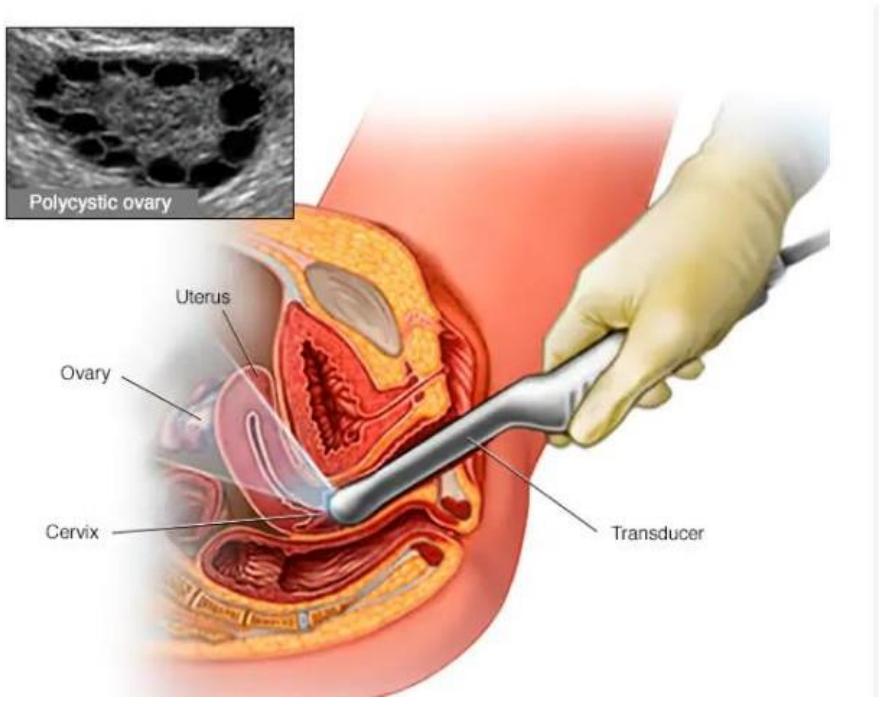


Figure shows trans vaginal ultrasound

- 3dimensional TVUS or MRI may be helpful in evaluation of myometrium to distinguish between adenomyosis from fibroid and in myoma mapping

- Saline sonography is better than hysterosalphingography to rule out endometrial polyp , submucous lesions

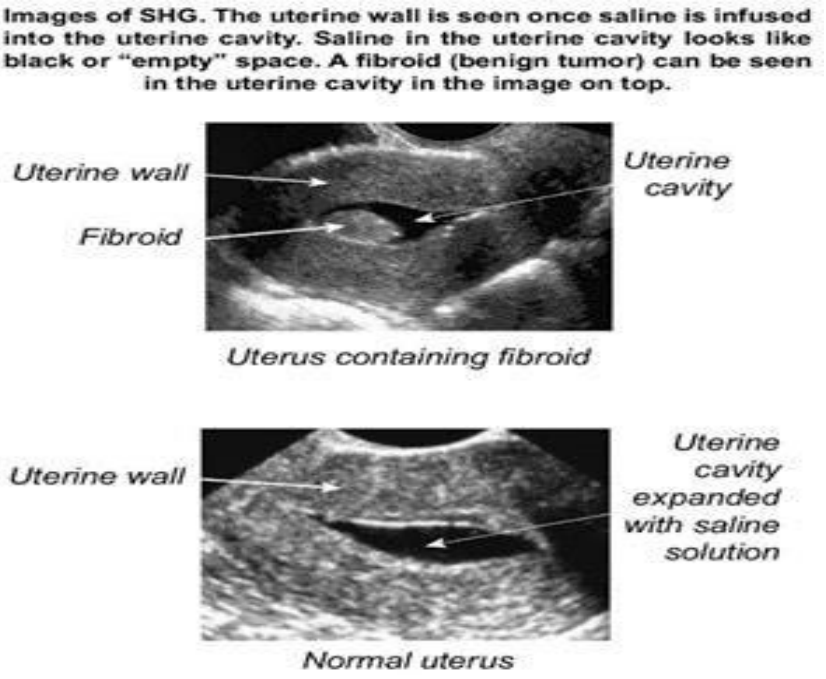


Figure shows saline infusion sonogram showing polyp within the endometrial cavity and a normal endometrial cavity.

-Hysteroscopy – to detect intrauterine abnormalities.

Endometrial sampling:

It is not mandatory for all patients. It will wise to consider for all women around 45 years , if possible under hysteroscopic guidance. Selection of patients requiring endometrial biopsy includes combination of risk factors for premalignant and malignant lesion comprising of age, genetic(lynch syndrome) and personal risk factor like (obesity, tamoxifene therapy) and TVS for endometrial thickness.

Device selection depends on the type of endometrial lesion either focal or global.

Dilatation and curettage (D&C) has sensitivity of >90% to detect endometrial hyperplasia/cancer.blind sampling can miss the pathology in case of focal lesion. Such patients benefits from D&C with hysteroscopy. Office techniques includes metal curette like novak and Kevorkian curette were used earlier. Endometrial sample taken using these curette shows positive correlation with histological report obtained from the hysterectomy specimen. However they are associated with patient discomfort and rarely uterine perforation and infection. To overcome these complications flexible plastic samplers (pipelle device) is used.

Limitations:

- Inadequate sampling. Patients with inadequate sample who carries high risk of cancer, must be planned for D&C with hysteroscope.
- Inability to access the cavity in cervical stenosis

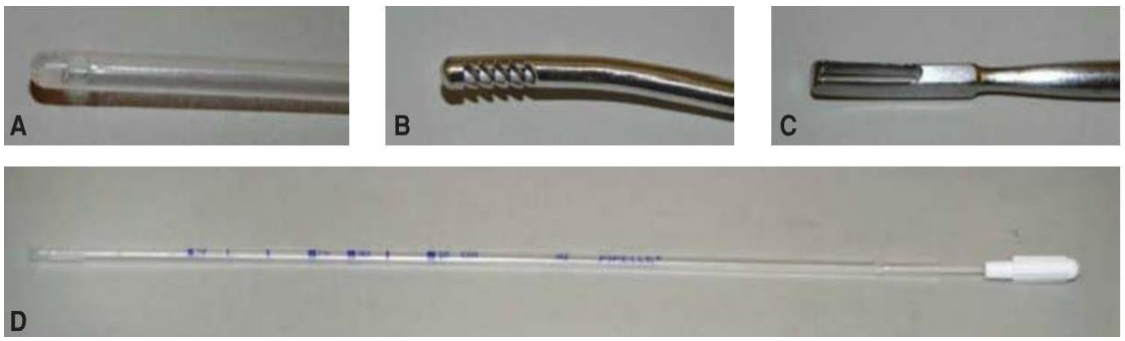


Figure shows Endometrial sampling devices. A. Pipelle fluted tip. B. Novak curette tip. C. Kevorkian curette tip. D. Pipe lie suction device.

Treatment of AUB:

AUB is treated according to the underlying causes:

AUB – P:

- Hysteroscopic polypectomy is done for younger women who are willing to preserve fertility.

- In women ,who completed family, hysteroscopic polypectomy can be performed ,followed by LNG- IUS insertion after confirmation of benign nature of lesion on histopathology .If histopathology suggests malignancy, further management should be as AUB-M.

AUB – A:

- In women with AUB-A, desirous of preserving fertility but unwilling for immediate conception, progestogens especially

LNG-IUS can be used as first-line therapy and gonadotropin releasing hormone (GnRH) agonists with add-back therapy is recommended as second-line therapy.

- Combined oral contraceptives, danazol, NSAIDs, and progestogens can be offered for symptomatic relief where LNG-IUS and GnRH agonists cannot be used.

- In case of failed medical management, vaginal or laparoscopic hysterectomy can be done.

AUB – L:

- Women with intramural or subserosal myomas , desirous of preserving fertility, can be managed with tranexamic acid or combined oral contraceptives (COCs) or NSAIDs as second-line therapy . LNG-IUS can be used other medical treatment fails and patient is not trying to conceive for at least 1 year.

- If treatment fails, or if myoma is causing infertility, myomectomy is recommended by abdominal (open or laparoscopic)/ hysteroscopic route depending on myoma location.

- For sub-mucosal myomas Grade 0-1, hysteroscopic resection (for 4 cm diameter) is the recommended treatment.

- In women above 40 years of age, not desirous of continued fertility, hysterectomy is the definitive treatment; however medical management including LNG-IUS may be used.

AUB-M (Malignancy and Endometrial Hyperplasia) :

- In AUB-M with endometrial malignancy, standard protocol for management of malignancy should be followed.

- In AUB-M with endometrial hyperplasia with atypia, hysterectomy is the standard treatment.

- In AUB-M with endometrial hyperplasia without atypia, LNG-IUS (as first line), oral progesterones can be used.

AUB-C (Coagulopathy)

1. In AUB-C, tranexamic acid as primary option and hormonal treatment with COCs/LNG-IUS as secondary option* are recommended in consultation with a haematologist .

2. If bleeding is uncontrolled with medical management, specific factor replacement should be done or desmopressin in refractory cases has to be given

3. NSAIDs are contraindicated as they can affect platelet function and interact with drugs that might affect liver function and production of clotting factors.

4. Injectables drugs like GNRH agonist are contraindicated

AUB – O:

1. In women not desiring conception ,COCs can be used as first-line therapy for 6-12 months

2. Cyclic luteal-phase progestins should not be used as a specific treatment in women with AUB-O

3. Norethisterone cyclically (for 21 days) is given as initial therapy in acute episodes of bleeding

4. Assess response after 1 year of medical management and then decision to continue / discontinue the treatment should be made.

5. LNG-IUS is recommended if COC is contra indicated.

6. Both hormonal and non-hormonal therapies can be prescribed for adolescents.

AUB – E:

Endometrial causes are very rare.placental site nodule is also belong to this category.

Acute endometritis in the postpartum or postabortal period can cause heavy menstrual bleeding from infection like Chlamydia trachomatis infections, pelvic tuberculosis, and pelvic inflammatory disease.

AUB – I:

Drug causing AUB should be stopped and alternative for that drug should be given.

LNG-IUS can also be used.

AUB – N: .

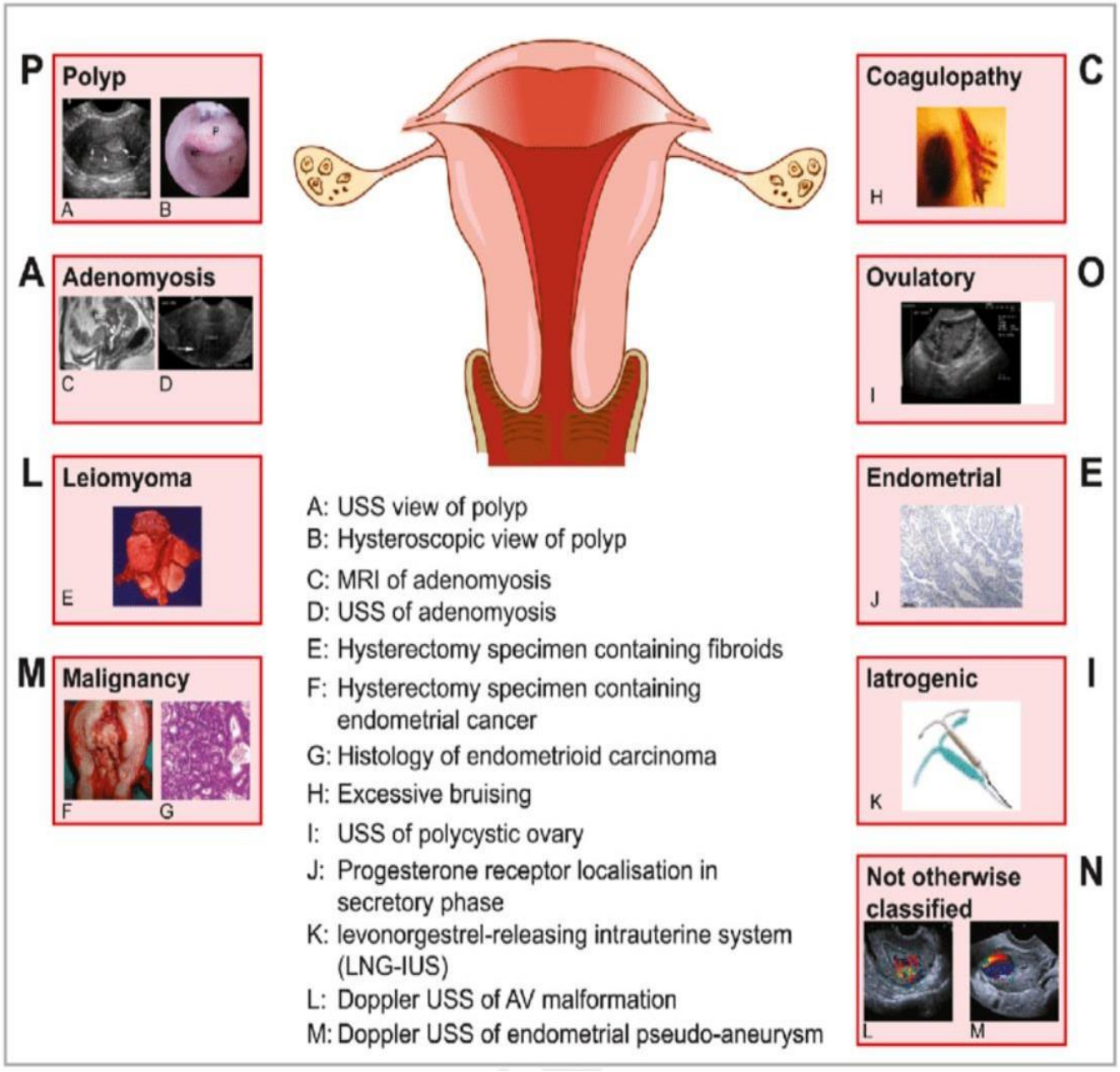
- LNG-IUS is recommended as first-line therapy to reduce menstrual bleeding

- In patients who desirous of continued fertility, COC is used as second line therapy

- For cyclical / predictable AUB ,non-hormonal options such as NSAIDs and tranexamic acid are recommended

- When medical or conservative surgical treatments (such as ablation) have failed or are contraindicated, and GnRH agonists along with add-back hormone therapy are recommended to reduce idiopathic AUB, while hysterectomy is suggested as last option.

- Uterine Artery embolization is the option for A-V malformations


P
Polyp
A
B
A
Adenomyosis
C
D
L
Leiomyoma
E
M
Malignancy
F
G
C
Coagulopathy
H
O
Ovulatory
I
E
Endometrial
J
I
Iatrogenic
K
N
Not otherwise classified
L
M
A: USS view of polyp
B: Hysteroscopic view of polyp
C: MRI of adenomyosis
D: USS of adenomyosis
E: Hysterectomy specimen containing fibroids
F: Hysterectomy specimen containing endometrial cancer
G: Histology of endometrioid carcinoma
H: Excessive bruising
I: USS of polycystic ovary
J: Progesterone receptor localisation in secretory phase
K: levonorgestrel-releasing intrauterine system (LNG-IUS)
L: Doppler USS of AV malformation
M: Doppler USS of endometrial pseudo-aneurysm

TREATMENT OF DYSFUNCTIONAL UTERINE BLEEDING

A. Conservative management:

I. Non-hormonal drugs

a. NSAID

b. Tranexamic acid

c. Ethamsylate

II. Hormonal treatment

a. Progestogens

b. oc pills

c. Danazol

d. GnRH analogues

III. Levonorgestrel-releasing intrauterine system

lV. SERM - ormiloxifene

B. Minimally invasive surgery :

Abalative technique

a. 1 st generation

b. 2nd generation

C. Surgical management

I. Hysterectomy

DRUGS IN AUB:

NSAIDs :

- They act by inhibiting the production of prostaglandin, by binding to the cyclooxygenase enzyme.

- Commonly used for acute episodes of AUB.

- These are most effective when initiated just prior to or with menses onset and continued throughout the menstruating days making it an advantage.

- Another advantage is that it relieves dysmenorrhea.

- The conventional NSAIDs nonspecifically inhibit both cyclooxygenase-1 (COX-1), an enzyme essential to normal platelet function, and cyclooxygenase--1 (COX-2), which mediates inflammatory response mechanisms.

- Thus, conventional NSAIDs such as ibuprofen and naproxen may not be ideal because of their inhibitory effects on platelet function and hemostasis.

- Although NSAIDs require only temporal dosing, are costeffective, and are well tolerated, they often are only moderately effective for AUB-E and reduce menstrual bleeding by approximately 25 % only.

- If further control of blood loss is needed, other agents may be needed.

- Routinely used NSAIDS for AUB:-
    - Mephenemic acid
    - Ibuprofen
    - Naproxen
    - Flurbiprofen
    - Meclofenamic acid
    - Diclofenac
    - Indomethacin
    - Acetylsalicyclic acid

Side effects:

- Gastric mucosal damage
- Bleeding: inhibition of platelet function
- Asthma and anaphylactoid reactions in susceptible individuals

TRANEXAMIC ACID:

- Tranexamic acid belongs to anti-fibrinolytic drug.
- It is more potent than Epsilon amino caproeic acid.
- It is a lysine analogue which combines with the lysine binding sites of plasminogen and plasmin so that the plasmin is no longer able to bind to the fibrin thus stabilizing the fibrin strand thereby preventing the lysis of clot and bleeding.

Dose: 10–15 mg/kg 2–3 times a day or 1–1.5 g TDS oral, 0.5–1 g TDS by slow i.v. infusion.[11]

Ethamsylate:

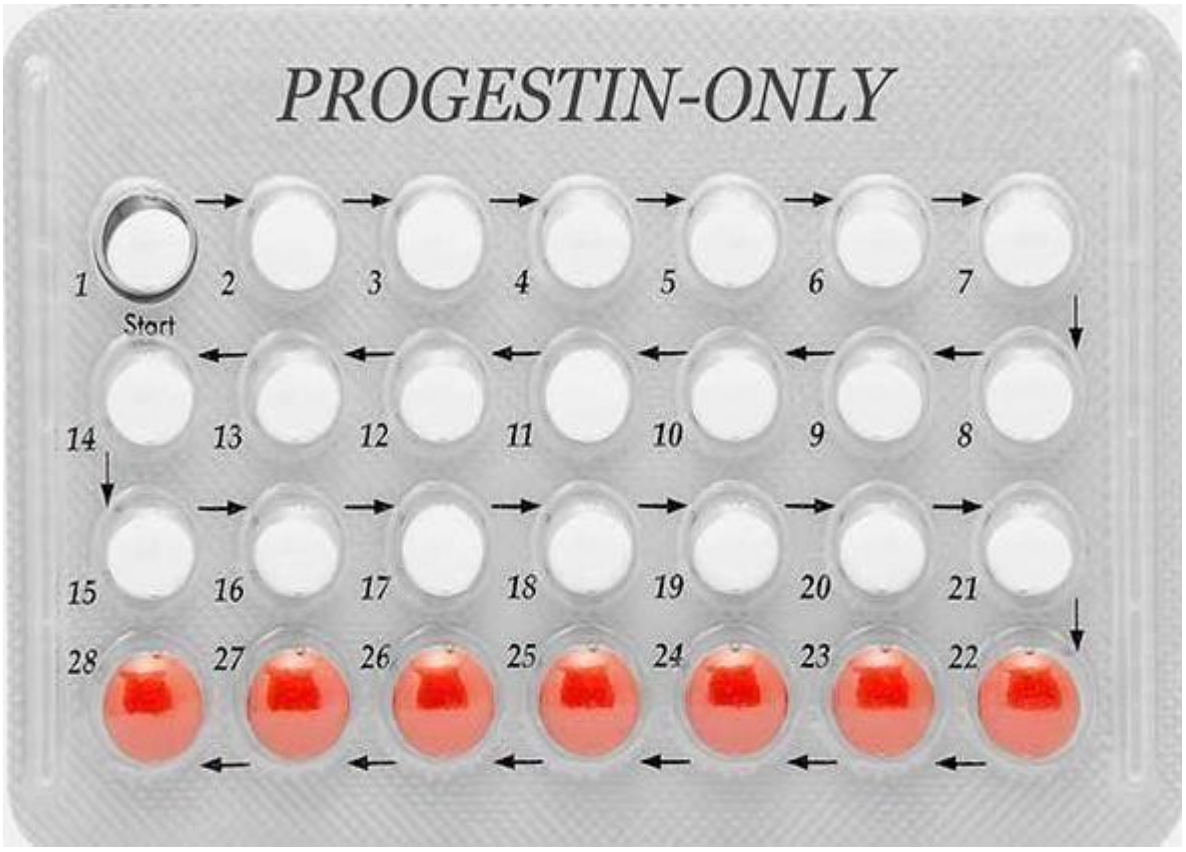
- It is also an anti-fibrinolytic drug and mechanism of action is similar to that of tranexamic acid.

- It is a specific antidote for fibrinolytic agents

- Initial dose is 5 g oral/i.v., followed by 1 g hourly till bleeding stops (max. 30 g in 24 hrs).[11]

PROGESTINS:

- They are secreted in secretory phase of menstruation which convert proliferative endometrium into secretory endometrium.



It is of 2 types:

- Progesterone derivatives: medroxyorogesterone acetate, megestrol acetate, dydrogesterone, hydroxyprogesterone caproate , nomegestrol acetate.

- 19- nortestosterone derivatives:
    - older compounds:-norethindrone, lynestrenol, allyestrenol, levonorgestrel.
    - newer compounds:- desogestrel, norgestimate, gestodene.

Actions:

On uterus: brings about secretory changes on estrogen primed endometrium. The glands enlarges and become tortuous and increased secretion. Continuous use of progesterone brings about deciual changes like stroma enlarges and becomes spongy, glands atrophy and reduce the sensitivity of myometrium to oxytocin .

On cervix: the watery cervical secretion due to estrogen action is converted to viscid, scanty and cellular. It prevent sperm penetration.

On vagina: leucocyte infiltration of epithelium.

On breast:- proliferation of acini in glands

On CNS: high concentration on circulatin have sedative effect.

On body temperature:- a rise in body temperature due to resetting the hypothalamic thermostat.(0.5 c)

On respiration: stimulation of respiration.

On metabolism: - impairs the glucose tolerance , raise LDL and lower HDL cholesterol levels.

On pituitary : it has weak inhibitory action on gonadotropin secretion from pituitary. Administration of progesterone during the follicular phase suppress the LH surge and inhibits ovulation.

For abnormal uterine bleeding, associated with anovulatory cycles , progesterone can be given in large doses to reduce the profuse bleeding. (medroxyprogesterone acetate/ norethindrone 10-20 mg/day) . cyclical treatment at low doses will normalize the mensutral flow and regularize the cycle. progesterone with inherent oestrogenic action or OC pills can be given cyclically for 3-6 months.

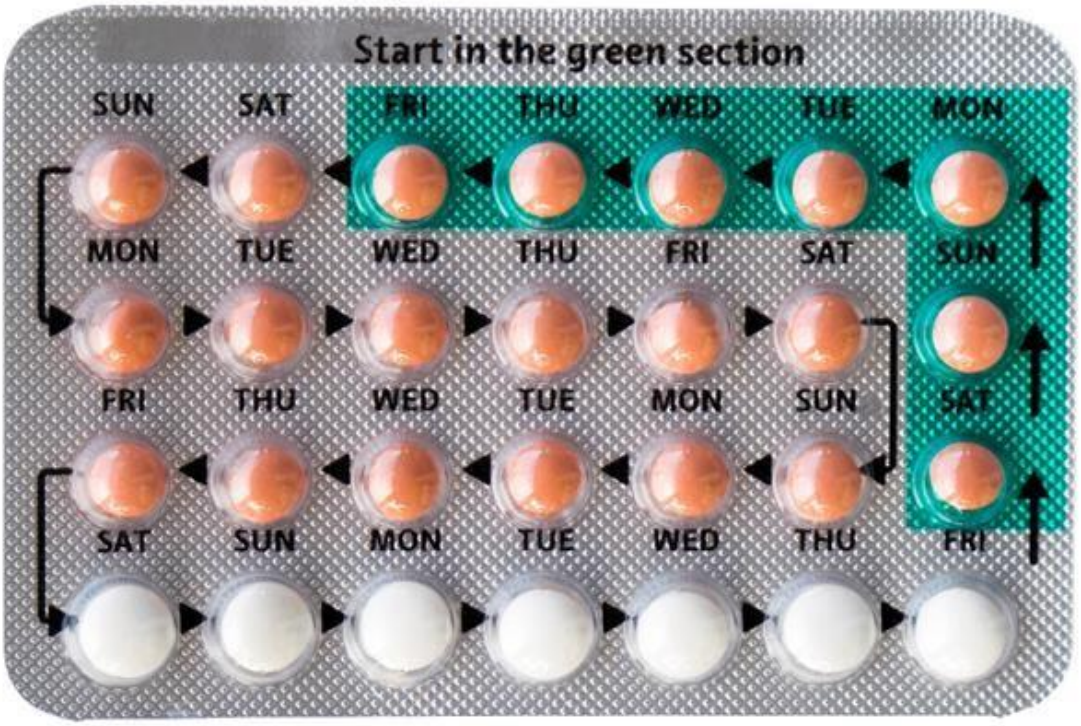
Side effects:

- Intermenstrual Bleeding
- Fatigability
- Mood swings
- Bloating
- Pedal edema
- Headache
- Depression
- Loss of libido
- Atherogenic lipid profile

COMBINED ORAL CONTRACEPTIVE PILLS:

It contains both estrogen and progestin.

- It is of monophasic, biphasic, triphasic depends on the dose of progesterone thoughout the cycle while the estrogen dose remains the same for contraceptive purpose.
- They act by negative feedback mechanism on anterior pituitary , reducing the release of FSH and LH . This prevents the follicle development and ovulation.



Absolutely Contraindications:

1. H/O Thromboembolism
2. H/O coronary and cerebrovascular disease
3. Moderate-to-severe hypertension
4. Hyperlipidaemia
5. Active liver disease, hepatoma or h/o jaundice during past pregnancy.
6. Suspected/overt malignancy of genitals/ breast.
7. Prophyria.
8. Impending major surgery—to avoid excess risk of postoperative thromboembolism.

Relative contraindications :

1. Diabetes
2. Obesity
3. Smoking
4. Undiagnosed vaginal bleeding
5. Uterine leiomyoma
6. Mentally ill
7. Age above 35 years
8. Mild hypertension
9. Migraine
10. Gallbladder disease

DANAZOL:

- It is an ethisterone derivative, have weak androgenic, anabolic and progestational activity.
- It acts by suppression of gonadotropin release form anterior pituitary.
- It causes endometrial atrophy thereby amenorrhoes occurs.

  Dose is 200- 600 mg/day.

GnRH analogues:

This category includes leuprolide, goserelin, nafarelin, triptorelin

Mechanism of action: naturally GnRH secreted in pulsatile manner while continuous exposure (with GnRH analogues) desensitizes GnRH receptors result in inhibition of release of FSH and LH secretion .

They can be given as depot injections(3.6mg given monthly for maximum 6 months), GnRH implants.

Adverse effects:

- Menopausal symptoms
- Osteoporosis.

SERM:

This category of drugs acts on estrogen receptors and exerts agonistic action on few organs and antagonistic action on other few organs.

- Drugs under this class includes- tamoxifen, raloxifene, ormiloxifene, ospemifene, lasofoxifene, toremifene**,bazedoxifene.**

These drugs were used for treatment of breast cancer,osteoporosis and postmenopausal symptoms. They are primarily used in postmenopausal women of younger age and it is recommended if there is family history of breast carcinoma.

1st generation- tamoxifene

2nd generation- raloxifene

3rd generation- ormiloxifene, bazedoxifene, lasofoxifene

Ormiloxifene-

Also known as centchroman [3,4-trans-2,2-dimethyl-3-phenyl-4-p-(b-pyrrolidinoethoxy) phenyl-7-methoxy chroman][24]

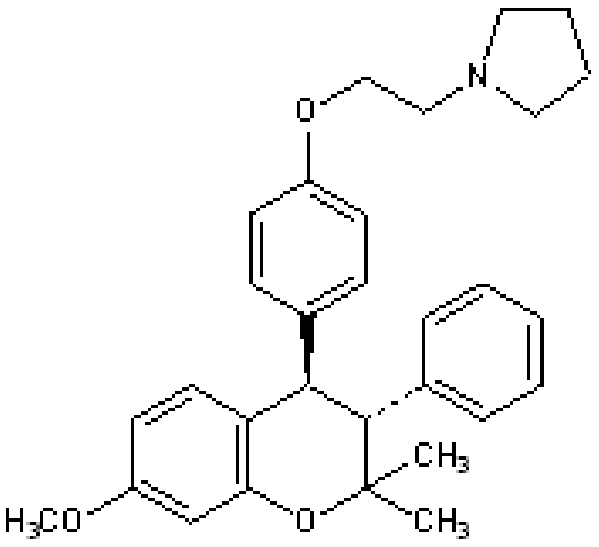


Figure shows chemical structure of ormiloxifene

- It is a non-steroidal, non-hormonal synthetic SERM , first developed by central drug research institute(CDRI) in lucknow , delhi in July 1991 and sold under brand name Saheli**.**

- It is approved for use in India and multiple other countries including Thailand, Bangladesh, Russia, New Zealand, United Kingdom and some North and South American countries[25]

Mechanism of action:

- It exerts both estrogenic action (bones) and anti-estrogenic action (uterus, breast)

- It causes an asynchrony in the menstrual cycle between ovulation and the uterine lining development thus act as a contraception.

- In clinical trials, it caused ovulation to occur later than it normally would in some women, but did not affect ovulation in the majority of women, while causing the lining of the uterus to build more slowly.[12]

- It speeds the transport of any fertilized egg through the fallopian tubes more quickly than is normal , this combination of effects creates an environment such that if fertilization occurs, implantation will not be possible.[12]

- Thus Centchroman inhibits implantation via inhibition of endometrial receptivity to blastocyst signals by antagonism of action of estrogen, without changing the concentration or secretion pattern of estrogen and progesterone, hypothalamo-pituitary-ovarian axis, follicle maturation, ovulation, gamete

transport or fertilization, and preimplantation development of embryos [24]

- Ormiloxifene suppresses the receptors in the reproductive organs like the ovaries, uterus and breasts but it stimulates the estrogen receptors of other organs like the bones. while it acts as a birth control pill , it also may prevent breast cancer [27] and may be therapeutically effective for other clinical conditions such as osteoporosis , restenosis, dermatitis, endometriosis and uterine fibroids[26]

- Centchroman inhibits osteoclast degradation by 30%, calmodulin-dependent cyclic nucleotide phosphodiesterase and the effects are calcium dependent [25]
- Centchroman, in addition to its competitive antagonism at the estrogen receptor level, promotes the conversion of intracellular estradiol (E2) to estrone (E1), a biologically less active form, by activating 17-β-hydroxysteroid dehydrogenase II, thus decreasing the estrogen receptor pool[26]

- Ormiloxifene also causes indirect anti-progestational effects in the uterus by its anti-estrogenic effect rather than by blocking the progesterone receptors

Dose:

For AUB :- 60mg twice a week for 1st 12 weeks followed by 60 mg every week there onwards

For contraception:- 30mg twice a week for 1st 12 weeks followed by 30 mg every week from 13th week .

Uses:

- As a oral contraceptive pills
- For abnormal uterine bleeding
- For treatment of mastalgia and fibroadenoma

Side effects: delayed menstruation.

LNG -IUS:

It is a T- shaped device containing 52 mg of LNG. it slowly releases the hormone at a rate of 20 mcg every day and slowly decreased to 11 mcg per day at the end of 5 years. On an average 14 mcg per day get released.

Mechanism of action: it suppresses the endometrial proliferation and causes thinning of endometrium. This low serum level doesn't inhibit ovulation.

- it can be used upto 5 years.

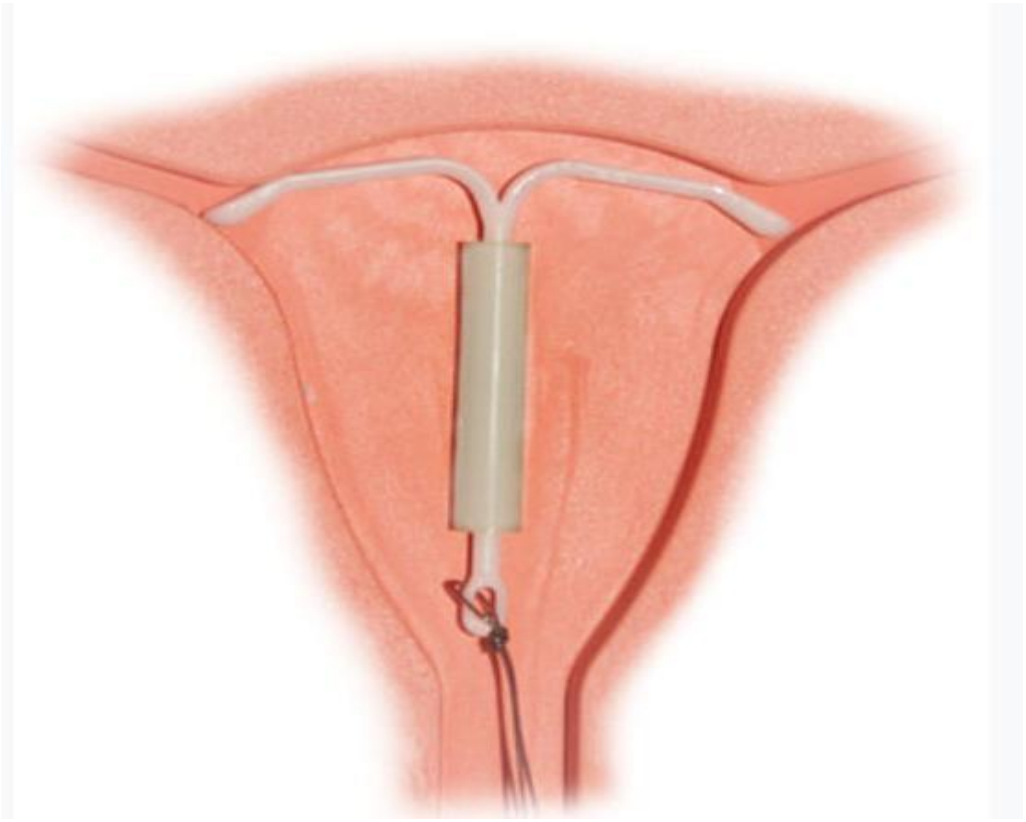


Figure showing a properly positioned LNG-IUD.

ENDOMETRIAL ABALATION:

1st generation:

- Rollerball electro surgical desiccation
- Endometrial resection by resectoscope

- This technique requires a general anaesthetic. A **resectoscope** (operating hysteroscope) is used to destroy the endometrium using diathermy energy (usually monopolar).

  Either a small electrical **wire loop** is used to shave off the endometrium, or a ball is used to burn/destroy the endometrium.
- Endometrial vaporization by the neodymium:yttrium-aluminum-gamet (Nd-YAG) laser.

2nd generation:

- Radiofrequency induced thermal ablation
- Cavaterm balloon therapy – a small diameter catheter requires minimal cervical dilatation which inflates the balloon with hot liquid that fills the endometrial cavity
- Microwave endometrial abaltaion – it consists of 8 mm diameter reusable probe which is inserted into uterus.

Microwaves are short high frequency radio waves. They are part of electromagnetic spectrum with wave length of 0.3-30cm and a frequency of 300-300000 MHz.

- Laser Therapy
- Photodynamic Therapy

- Electrode Mesh - novasure – requires very short treatment time (maximum 2 min)
- Hydro Therm abalator -
- Cryotherapy – this system is a compressor driven and uses a new mixed gas coolant to generate temperature of -90 to -100 C.

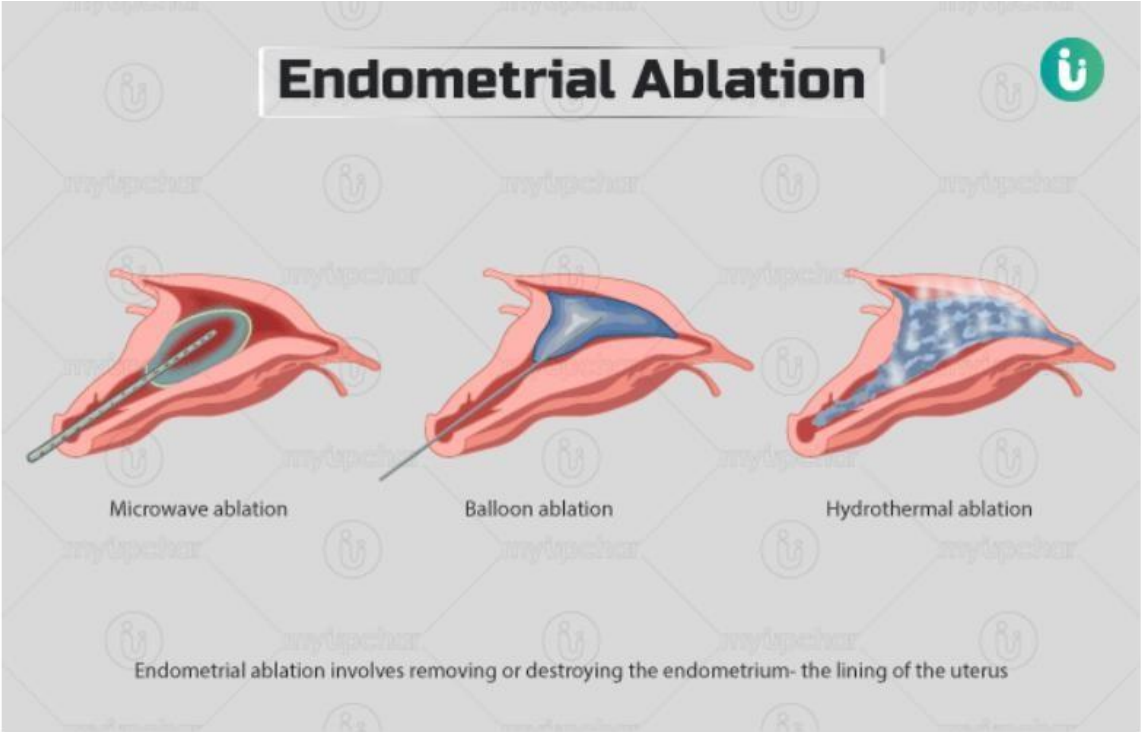


Figure shows various endometrial ablation techniques

Advantages:

- Lower Morbidity
- Short Hospital Stay
- Fast Recovery
- Reduced Treatment Costs

Studies Related to this Topic

- Neha Agarwal et al conducted a comparative study of efficacy of ormeloxifene and norethisterone in dysfunctional uterine bleeding and concluded that ormeloxifene is superior to norethisterone in reducing menstrual loss.

- Biswarup Tah et la conducted a study to evaluate the effect of ormeloxifene in dysfunctional uterine bleeding and dysmenorrhea in women in reproductive age group and concluded that ormiloxifene is superior than medroxyprogesterone acetate with better therapeutic efficacy, convenient dosage schedule, lesser side effects and cost effective.

- Ravibabu komaram et al conducted a study of efficacy of ormiloxifene in the pharmacological management of dysfunctional uterine bleeding and concluded that ormeloxifene, a non-hormonal agent, provides effective and favourable outcome by increasing the mean hemoglobin level of1.3 gm/dl in post treatment level.

- Godha Z et al conducted a comparative study of ormeloxifene and medroxyprogesterone acetate abnormal uterine bleeding and concluded that ormeloxifene should be considered the first choice in the management of AUB, especially in the perimenopausal age group where amenorrhea is acceptable.

- Nanda SK et al conducted a study on the role of sevista in the management of dysfunctional uterine bleeding and concluded that ormeloxifene can be used as an effective drug in treatment of dysfunctional uterine bleeding.

- Kriplani A et al from All India Institute of Medical Sciences conducted a study on Efficacy of ormeloxifene versus oral contraceptive in the management of abnormal uterine bleeding due to uterine leiomyoma and concluded that Ormeloxifene with its convenient twice-weekly dosage schedule was effective in treating AUB-L, with 72% of patients responding to 6-month treatment compared with 8% with COC, even though leiomyoma volume increased insignificantly with both ormeloxifene and COCs.

- Hari Om Singh et al conducted a study on effect of ormeloxifene for management of dysfunctional uterine bleeding and found that the median difference between pretreatment and post-treatment PBAC score was found to be significant. Similarly, It was also same with the difference in mean hemoglobin between pretreatment and post-treatment levels. The frequency distribution of clots during post treatment was significant as compared to pretreatment. Ormeloxifene is a cost- effective therapy.

- Sharda B. Ahmed et al conducted a study on role of ormeloxifene in the management of dysfunctional uterine bleeding and concluded that ormeloxifene is very effective and safe as has good acceptability and compliance due to its minimal side effects low cost and simple dosage.

- Dr.Umesh Sawarkar et al conducted a study on Efficacy of Ormeloxifene in management of dysfunctional uterine bleeding and found that after the intervention, 76.8% of women achieved a duration of bleeding of 4–5 days, and in 87% of women, menstrual cycle became regular. Passage of clots was reduced by 71.83%. Mean Hb concentration of study participants increased by 0.5 g/dl at the end of the study. Thus, ormiloxifene is effective alternative and appears to be

a promising option for medical management of dysfunctional uterine bleeding.

- Debasmita Mandal et al conducted a Comparative study of low-dose oral contraceptive pill and ormeloxifene in the treatment of dysfunctional uterine bleeding and found that Hb rise in both groups was almost similar, OCP group revealed an improvement in mean Hb concentration of 0.65 g%, whereas ORM showed a rise of 0.72 g%. Secondary outcomes were adverse reactions, satisfaction level, and poor responders in both groups and concluded that Ormeloxifene is effective in treating DUB in almost in all aspects and can be considered as nonsteroidal option of therapy.

- Swati Gett et al did a comparative study between Ormeloxifene and Norethisterone in reducing menorrhagia in dysfunctional uterine bleeding and concluded that : Ormeloxifene is a new modality and is found to be a better option in reducing menorrhagia in DUB in respect to a greater success rate, better compliance and cost effectiveness.

METHODOLOGY

Study Participants:

All women with abnormal uterine bleeding attending the out-patient department fulfilling the inclusion criteria are enrolled in the study.

Study Design: Randomized controlled study

Inclusion criteria:

All women presenting with excessive, prolonged or frequent interval of bleeding in out -patient department without any evidence of any systemic, pelvic organ pathology.

Exclusion criteria:

- Postmenopausal bleeding
- Fibroid uterus/adenomyosis/cervical polyp/endometrial polyp
- Severe cervical dysplasia or carcinoma of cervix
- Atypical endometrial hyperplasia or malignancy
- Pregnancy

Number of groups studied: Two groups

Sampling:

A. Population: all women presenting with abnormal uterine bleeding without any evidence of systemic, pelvic organ pathology.

Sampling method: A single blinded randomized sampling

Sampling size: Using Open Epi version 3.01, the minimum sample size was calculated to be 120

60 in each arm with an alpha error of 5% and power of 80%

Randomization details: Randomized controlled study

Method of study:

After getting approval from the Institutional Ethical Committee, over 120 women presenting with abnormal uterine bleeding without any organic, systemic or iatrogenic cause will be recruited in this study. They will be allocated in to two groups A and B, 60 in each group using proper randomization method.

Informed consent will be taken. A detailed history of menstrual complaints will be taken. General examination will be done to assess the Anemia. Pelvic examination will be done to rule out pregnancy, fibroid, adenomyosis or any other pelvic pathology. Baseline Investigations will

be done for Hb%, Total count, Differential count, bleeding time, clotting time, platelet count, thyroid profile to rule out any bleeding disorders and subclinical hypothyroidism. Ultrasound examination will be done for endometrial thickness and to rule out other pathology.

Group A will be administered with Ormeloxifene tablet 60mg twice a week for 12 weeks followed by 60mg once a week for next 12 weeks. Group B will be administered with Norethisterone tablet 5mg twice a day for 21 days followed by 7 days withdrawal for 6 cycles. Both groups will be followed up at 1,3,6 months. All subjects will be asked to maintain a menstrual diary recording the episodes of bleeding, the days of bleeding, number of sanitary pads used, degree of soiling of used pads, number and size of clots passed, presence of menstrual cramps and any other symptoms they experienced. The pictorial blood loss assessment chart (PBAC) scoring will be done on each visit to assess menstrual blood loss. This PBAC method correlates well with the alkaline hematin test. A PBAC score ≥ 100 indicates a menstrual loss of ≥ 80ml and will be considered diagnostic for menorrhagia.

The outcome parameters are amount of menstrual blood loss (assessed by fall in PBAC score), amount of hemoglobin concentration, endometrial thickness using ultrasound to be measured at each visit.

Statistical analysis will be performed using Microsoft Excel and SPSS software.

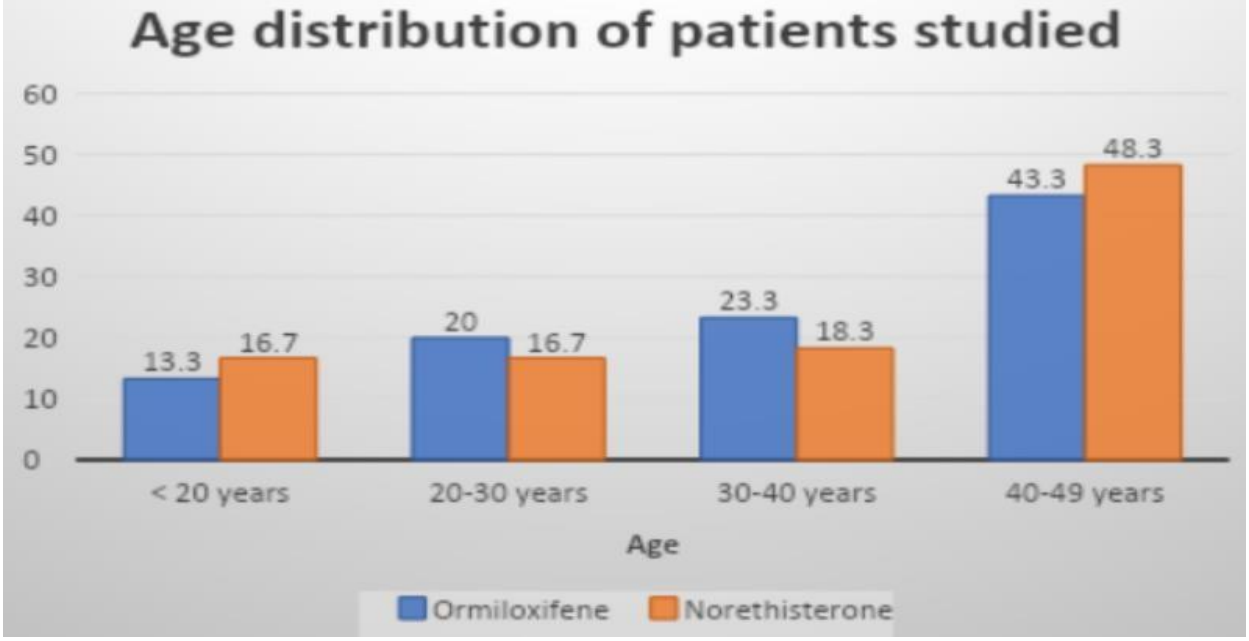
RESULTS

		a			
		Ormiloxifene N=60		Norethisterone N=60	
		n	%	n	%
age	<20 years	7	11.6%	10	16.7%
	20-30 years	13	21.6%	10	16.7%
	30-40 years	14	23.3%	11	23.3%
	40-49 years	26	43.3%	29	48.3%
	Total	60	100.0%	60	100.0%

Table shows age distribution of the patients in this study

This is a analytical cross-sectional study consisting of 120 patients divided into two groups. Group A consisted of 60 patients who were given Ormiloxifene and group B consisted of 60 patients who were given Norethisterone.

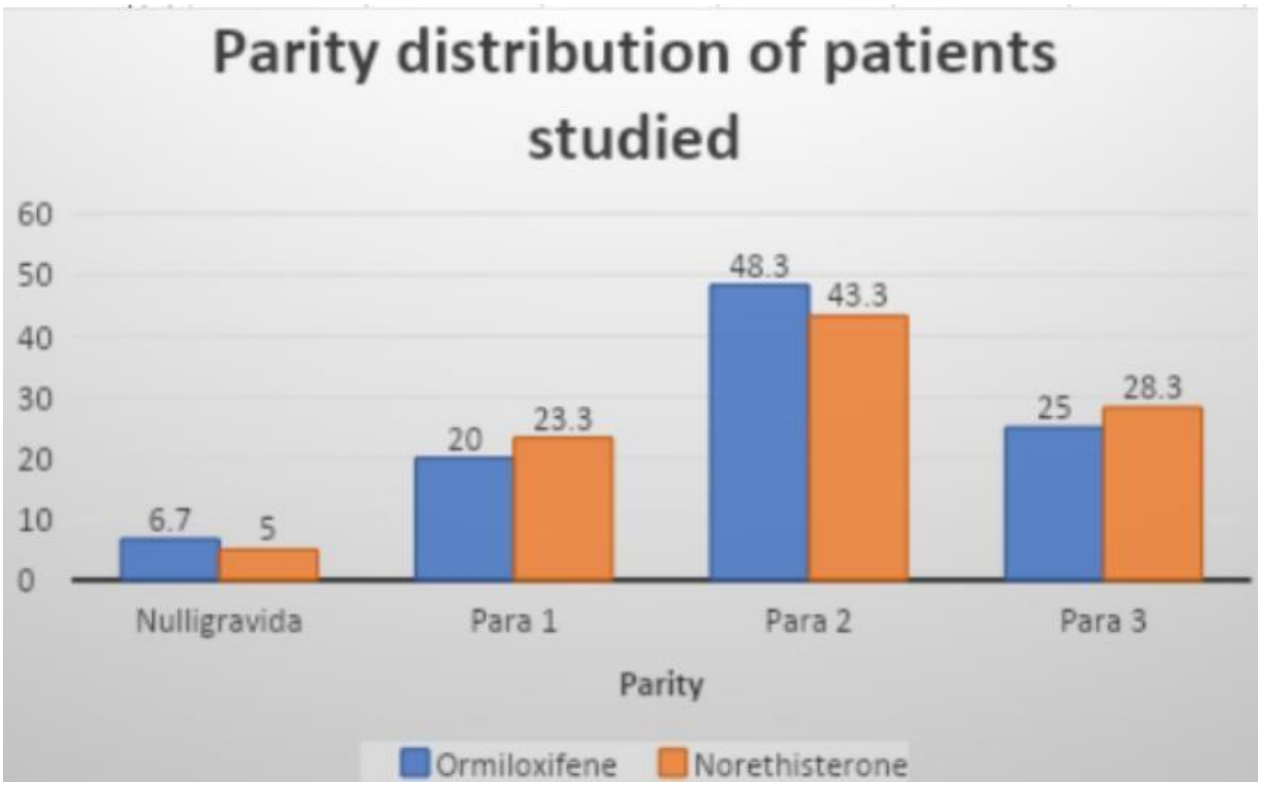
Data is entered using Microsoft excel and analysed using statistical software spss version 16. Descriptive statistics is given by frequency, percentage, graphs and mean±sd. Students t-test is used to check the mean difference between the groups and fishers excat test is used to find the relation ship between categorical outcome. P-value<0.05 is considered to be significant through out the study.



The above table shows age distribution of patients in both the group. 43.3% of patients in group A and 48.3% of patients in group B were between 40-49 years .. Looking at the graph we can conclude that mean age is similar in both the groups

		treatment group			
		Ormiloxifene N=60		Norethisterone N=60	
		N	%	n	%
parity	Nulligravida	4	6.7%	3	5.0%
	Para 1	12	20.0%	14	23.3%
	Para 2	29	48.3%	26	43.3%
	Para >= 3	15	25.0%	17	28.3%
	Total	60	100.0%	60	100.0%

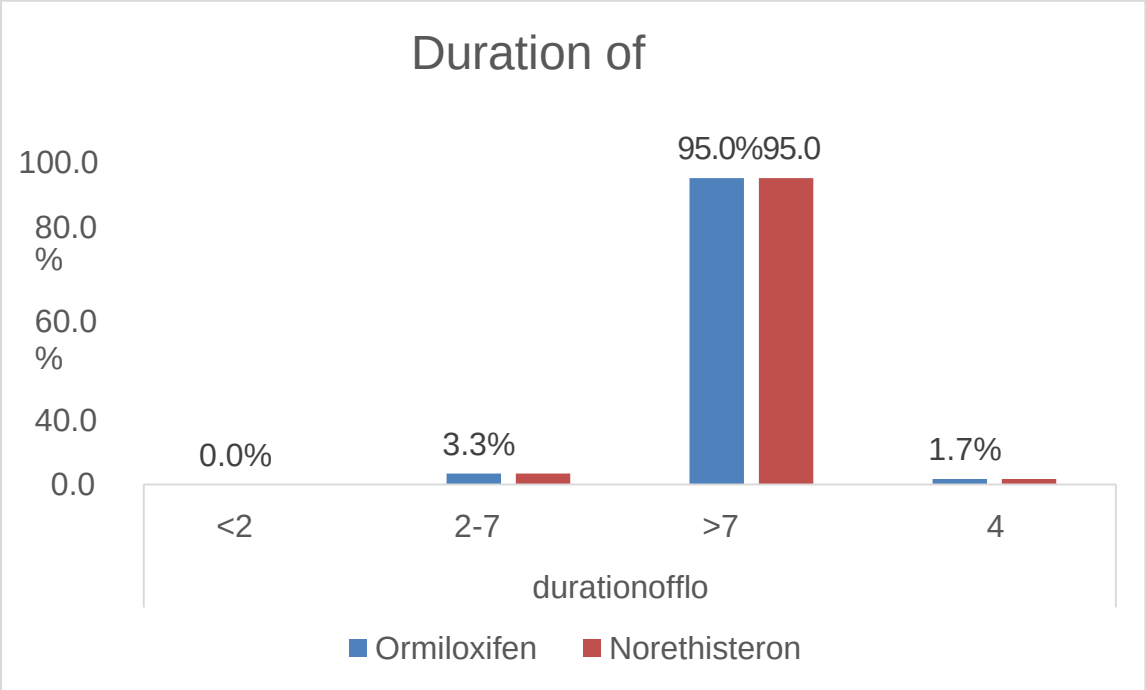
Table shows the parity distribution of patients in this study



The above table shows the gravida distribution of the patients in study population under consideration in each group. Parity is almost equally distributed in each group showing no difference.

		Treatment group			
		Ormiloxifene		Norethisterone	
		N	%	n	%
Duration of flow	<2 days	0	0.0%	0	0.0%
	2-7 days	2	3.3%	2	3.3%
	>7 days	57	95.0%	57	95.0%
	4	1	1.7%	1	1.7%
	Total	60	100.0%	60	100.0%

Table shows the duration of the cycle in both treatment groups



The above table gives us detailed information about duration of blood flow among women's in both the group. Patients who are under Ormiloxifene 95% of them had duration of flow for >7 days and same frequency was found among women who were under treatment of norethisterone.

Table shows the durations of AUB in both study groups

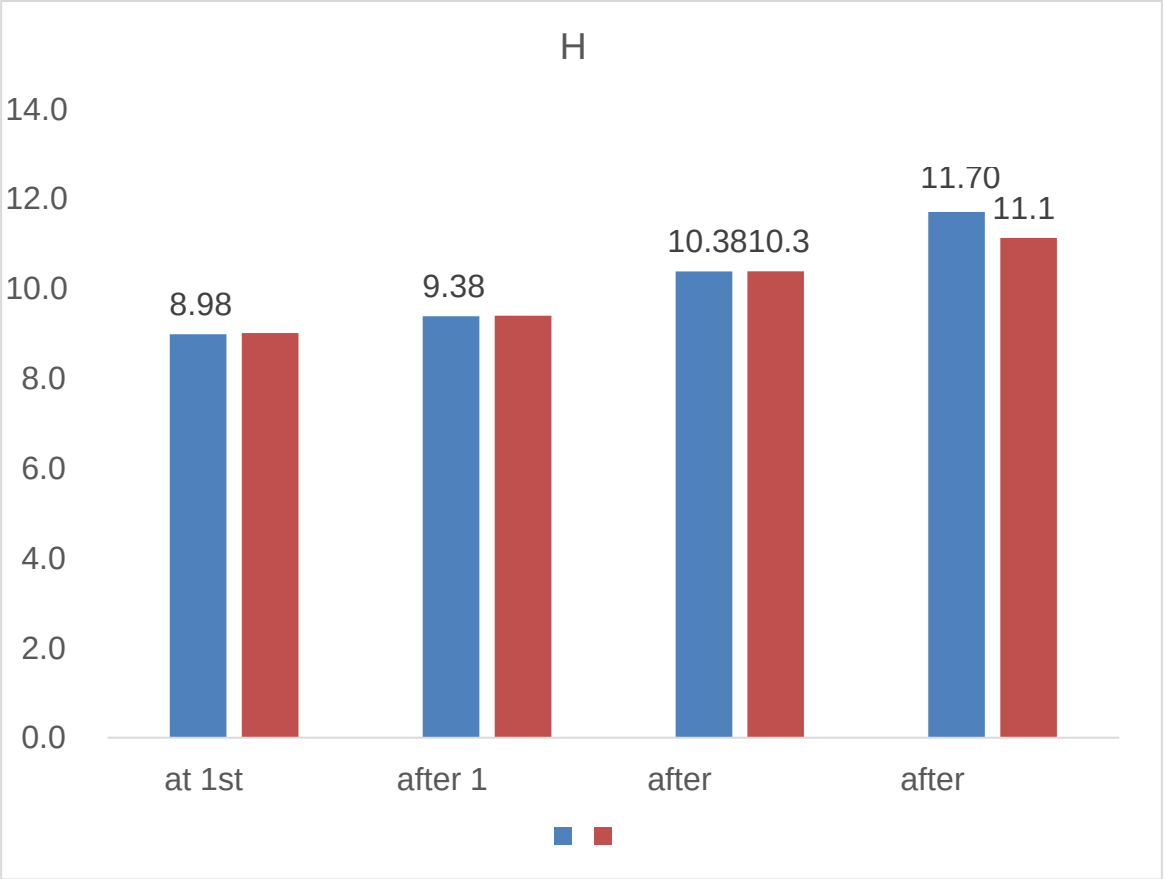
	Ormiloxifene (n=60)		Norethisterone (n=60)	
	Mean	sd	Mean	sd
Duration of complaint in months	9	3	8	2

Mean duration of complaints in month of patients who are under Ormiloxifene is 9±3 and Patients who are under norethisterone is 8±2.

Table shows comparison of hemoglobin levels in both study group at 1, 3, 6 months of the study

HB	Ormiloxifene (n=60)		Norethisterone (n=60)		Mean Difference	95% Confidence Interval of the Difference		P value
	Mean	Sd	Mean	sd		Lower	Upper	
baseline	8.98	0.68	9.01	0.67	-0.03	-0.28	0.21	0.787
at 1	9.38	0.71	9.40	0.66	-0.01	-0.26	0.23	0.915
at 3 months	10.38	0.58	10.38	0.61	0.00	-0.22	0.21	0.976
at 6 months	11.9	1.54	11.1	0.59	0.58	0.15	1.00	0.008*

P value is calculated using students t test;
level of significance at 5%;
* Statistically significant



Mean haemoglobin level in group A is 8±0.68 and at 6 months is 11.9±1.5 and in group B mean haemoglobin is 9.0±0.6 and at 6 months is 11.1±0.59 there is statistically significant reduction between two groups from base line to 6 months with p-value<0.05 i.e., 0.008. From baseline to 6 months HB increases by 0.58 units. Group A to Group B there is rise in HB level by 0.58 units by which we can infer that woman in treatment group A will have better rise in HB level than in treatment Group B from baseline to 6 months.

Table shows comparison of endometrial thickness in both groups at 1,3,6 months of the study.

Table:

Endometrial thickness in mm	Ormiloxifene (n=60)		Norethisterone (n=60)		Mean Difference	95% Confidence Interval of the Difference		P value
	Mean	sd	Mean	sd		Lower	Upper	
baseline	11.18	0.93	11.46	0.96	-0.28	-0.62	0.06	0.108
at 1 weeks	10.27	0.83	10.42	0.86	-0.15	-0.45	0.16	0.339
at 3 months	9.27	0.78	9.58	0.82	-0.30	-0.59	-0.01	0.040*
at 6 months	7.43	0.72	8.17	0.94	-0.75	-1.05	-0.44	0.001*

P value is calculated using students t test;
level of significance at 5%;
* Statistically significant

Mean endometrial thickness in group A(Ormiloxifene) is 11.18±0.93 and at 6 months 7.43±0.72 and meanendometrial thickness in group B(Norethisterone) is 11.46±0.96 at baseline and 8.17±0.94 at 6 months which is significant with p-value 0.001. There is significant decrease in the endometrial thickness from baseline to 3 months which is significant with p-value 0.04. There is significant reduction in endometrial from group A to Group B by 1.05 units where as reduction is 0.59 from group

A to group B in 3 months but if we see the baseline there is significant increase in thickness from group A to group B which is not significant with p-value 0.108

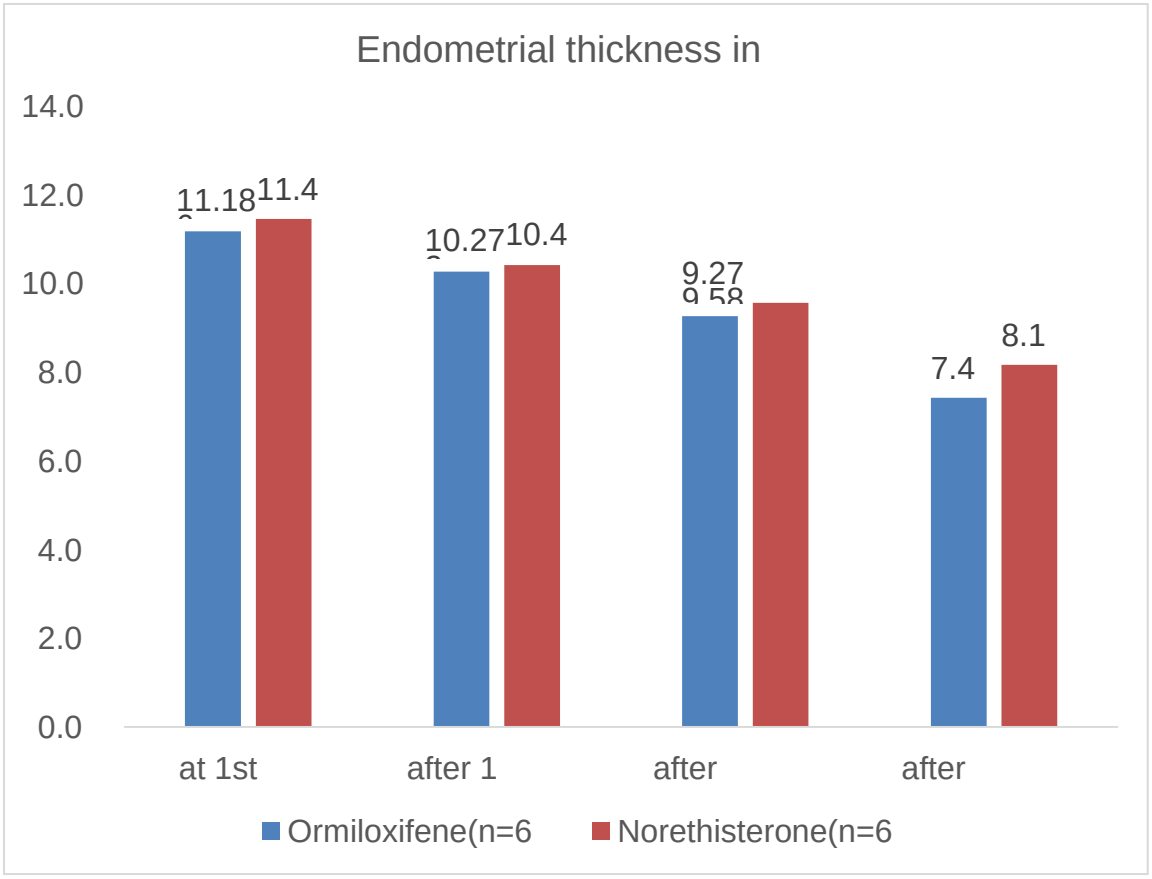
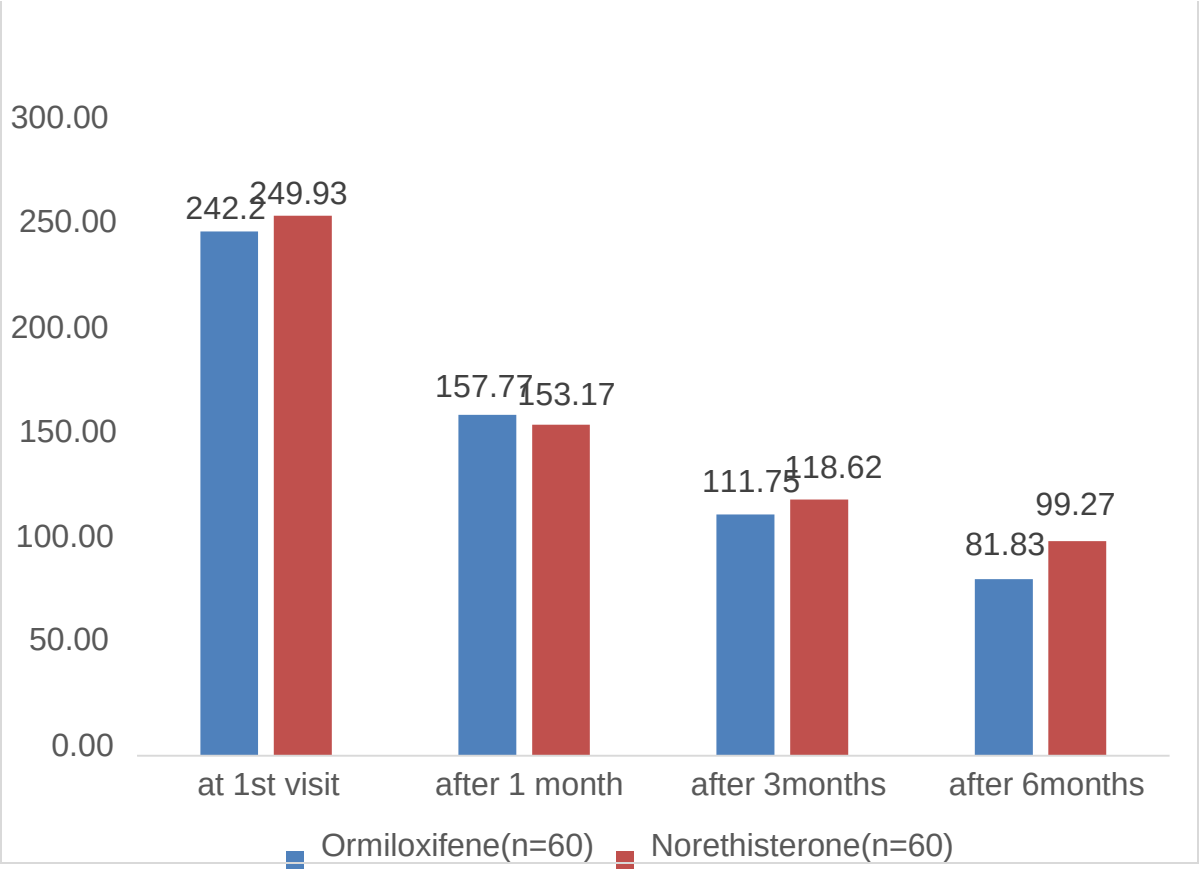


Table shows comparison of PBAC score of both study groups at 1,3,6 months of the study

Table								
PBAC score	Ormiloxifene (n=60)		Norethisterone (n=60)		Mean Difference	95% Confidence Interval of the Difference		P value
	Mean	sd	Mean	sd		Lower	Upper	
baseline	242.72	33.74	249.93	31.21	-7.22	-18.97	4.53	0.226
at 1 weeks	157.77	22.81	153.17	19.89	4.60	-3.14	12.34	0.241
at 3 months	111.75	15.09	118.62	18.00	-6.87	-12.87	-0.86	0.025*
at 6 months	81.83	12.93	99.27	14.75	-17.43	-22.45	-12.42	0.001*
P value is calculated using students t test; level of significance at 5%; * Statistically significant								

This table shows PBAC score from baseline to 6months. Mean has reduced by 81.8±12.93 from baseline in group A and 99±14 in group B with p-value 0.01. The mean PABC score at the end of study period is 81.22 and 99.22 in group a and group B, reporting an overall reduction blood loss by 17.43 units.


300.00
250.00
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242.2
249.93
157.77
153.17
111.75
118.62
81.83
99.27
at 1st visit
after 1 month
after 3months
after 6months
Ormiloxifene(n=60)
Norethisterone(n=60)

		Treatment group			
		Norethisterone (n=60)		Ormiloxifene (n=60)	
		n	%	n	%
AMENORRHOEA	yes	0	0%	6	10.0%
	no	60	100%	54	90.0%
	Total	60	100.0%	60	100.0%
Intermenstrual bleeding	yes	5	8.3%	2	3.3%
	no	55	91.6%	58	96.6%
	Total	60	100.0%	60	100.0%
Weight Gain	yes	5	8.3%	1	1.7%
	no	55	91.6%	59	98.3%
	Total	60	100.0%	60	100.0%
headache	yes	2	3.3%	3	5.0%
	No	58	96.6%	57%	95%
	Total	60	100.0%	60	100.0%
Nausea	yes	7	11.6%	3	5.0%
	No	53	88.3%	57	95%
	Total	60	100.0%	60	100.0%

When comparing the two groups, side effects like nausea, weight gain, intermenstrual bleeding are more common in norethisterone group compared to ormiloxifene group.

Amenorrhoea , one of the side effect occurred in the ormiloxifene group which may be beneficiary for the patients in the perimenopausal group. Hence it can be concluded that Ormiloxifene is a better treatment drug that can be used to reduce the side effects in patients.

drug	Time period	Passage of clots	Dysmenorrhea
Ormiloxifene	Pre-treatment	52(86.7%)	34(56.7%)
	Post-treatment	8 (13.3%)	5(8.3%)
Regesterone	Pre-treatment	56(93.3%)	31(51.7%)
	Post-treatment	16(26.6%)	17(28.3%)

Table shows the effect of each drug on symptoms of AUB.

When comparing the two groups, Patients in group A were observed better reduction of symptoms than group B.

DISCUSSION

Menstrual disorder are the second most prevalent obstetrics and gynaecological problem that leads to hospitalisation. Abnormal uterine bleeding (blood loss of more than 80 ml every cycle) affects 10-33% of women at some point in their life. Abnormal uterine bleeding occurs more commonly in the first five years after a women attains menopause and around menopausal transition, but it can occur at any time of reproductive period. Anovulation is responsible for 90% of abnormal uterine haemorrhage, while ovulatory cycles account for 10%. Only half of the women who complained of heavy menstrual bleeding met the clinical criteria of losing more than 80ml every cycle. This problem can be treated medically as well as surgically.[13]

The following study is a randomized control study conducted to compare the efficacy and safety of ormeloxifene with Norethisterone in treating abnormal uterine bleeding.

In this study, 120 patients are considered of which each group consists of 60 patients each. Group A received ormeloxifene and rest 60 i.e., Goup B received norethisterone . Most of the patients were falling in 40-49 years of age in both the treatment groups. Age, Parity of patients,

duration of flow, complaints had no significant difference between the groups. Hence both the treatment had equal distribution.

When compared to Norethisterone, Ormeloxifene is certainly superior. The findings in the Norethisterone group are consistent with Fraser,1990[14] and Irvine et al,1998[15] There have been few clinical trials on the use of ormeloxifen in abnormal uterine bleeding. Biswas et al. found comparable results in the ormeloxifen group in a research published in 2004[16]

The pictorial blood assessment chart(PABC) score is used to assess blood during the menstrual cycle. In this study, the reduction in mean PABC score with ormeloxifene (242.2 to 81.2) was significantly more that seen with norethisterone(249 to 99.1) after 6 months of therapy($p<0.05$).

However at the end of 1st week of treatment, mean PABC score was 157 for group A and 153 for group B respectively which is not significant with p-value >0.05. But at the end of 3rd month PABC score of group A reduced to 111.2 and 118.6 in group B which was statistically significant with p-value 0.0025.

According to a study by Agarwal N,singh & manocha(2013) also concluded that ormeloxifene was more effective than norethisterone in reducing blood loss, the study showed the findings as mean PABC score with ormeloxifene (277.33 to 70.11) which is significantly more than norethisterone(246 to 108.5). There was increase in hemoglobin level and reduction in endometrial thickness was also find with ormeloxifene than norethisterone(9.68% vs 11.07% vs 10.17%, p value <0.05) and no major side effects were reported in any group.[13]

One more study by kriplain A. et al[17] also proved that PACB score is significantly more in group A than group b. Results of our study is comparable with Battacharryya TK et al and Jyotsan Shravage et al.

One more study had corresponding results like this study Devi LT et [18]al showed that ormeloxifene is better drug as compared to Norethisterone for menstural symptoms. The results proved that there was significant reducation in the passage of clots with group A drugs when compared with Group B drugs.

Menorrhagia was reduced by 80% to 87% in studies conducted in the year 2000 on 70 patients using ormeloxifene at a dose of 30mg twice weekly for 6 months. Another trial conducted in 2004 on 80 women

found that using ormeloxifene at a dose of 60mg twice weekly for three months followed by 60mg once weekly for another three months reduced menorrhagia by 85.7% after 6 months.

In this study the results obtained were very similar to above quoted studies. The mean haemoglobin count was 8 in group A from baseline and was increased up to 11.9 and in group B the mean HB was around 9 and at end of 6 months mean Hb in group 2 increases up to 11 which is significant with p-value< 0.05. It is clear that ormeloxifene is better drug compared to norethisterone in managing DUB. Most of the study justified with same results showing that group A treatment drug has more efficacy compared to group B treatment drugs.

Mean endometrial thickness in group A(Ormiloxifene) is 11.18±0.93 and at 6 months 7.43±0.72 and mean endometrial thickness in group B(Norethisterone) is 11.46±0.96 at baseline and 8.17±0.94 at 6 months which is significant with p-value 0.001. There is significant decrease in the endometrial thickness from baseline to 3 months which is significant with p-value 0.04. There is significant reduction in endometrial from group A to Group B by 1.05 units where as reduction is 0.59 from group A to group B in 3 months but if we see the baseline there is significant increase in thickness from group A to group B which is not

significant with p-value 0.108 this results corresponds with Devi LT et al[18], Agharwal(2013) where in the results concluded Ormeloxifene group was associated with statistically significant reduction in endometrial thickness after 6 months of therapy and three months of follow-up.

Ormeloxifene has anti-Oestrogenic activity in the endometrium, limiting endometrial growth, and is more effective since it blocks oestrogen receptors directly, preventing oestrogen's mitogenic activity.[19]

A perfect medication for perimenopausal women would be one that avoids bone loss, improves cardiovascular health, and eliminates the chance of breast or uterine cancer, Ormeloxifene, in particular, fits this description of selective oestrogen receptor modulators. The goal of this study was to determine the efficacy of ormeloxifene and compare it to Norethisterone in the treatment of DUB.

Ormeloxifene is a superior medicine for relieving menstruation problems than Norethisterone. Both Ormeloxifene and Norethisterone were found to considerably alleviated dysmenorrhoea symptoms.

More clinical trials are required to validate the side effects. Apart from these side effects group A treatment drugs has been found to have a favourable effect compared to group B treatment drug.

We believe that ormeloxifene is a better medicine than norethisterone for the treatment of patients with abnormal uterine bleeding. More trials in a younger age group should be conducted to prove or disprove the negative effects of genital prolapse and urinary incontinence due to stress before taking the drug and recommended to be used. Sometimes the drug is recommended to be used by women who has completed child bearing in the perimenopausal age group after through investigation. The medication can be used as a first-line treatment. In that case, treatment is used in the medical management of AUB in this subgroup of patients.

The study consisted of smaller number of sample size. For more reliable outcome, larger study groups with RCT and more statistical tests may be used. Patients must be followed for a long time. The effect of estrogen receptors on other organs has not been studied, however it is strongly suggested.

CONCLUSION

Nearly 20-30% of reproductive aged women and 50% of perimenopausal women are affected by AUB which affects her quality of life in terms of anaemia, cost of sanitary pads and interference with day - to-day activities. Hysterectomy is the ultimate method to halt the abnormal uterine bleeding, however it, in most cases is usually accompanied by removal of ovaries causing surgical menopause and its ill effects that necessitate the HRT. Conservative Medical management should always be recommended to avoid the morbidity of surgery. For women with AUB who wish to retain fertility, conservative medical management is the only currently available options. Among the other pharmacological agents, some are effective only for anovulatory AUB, some are useful only for ovulatory AUB, and still others may be effective for both.

Among the medical management like NSADS, Oral contraceptive pills, danazol, GnRH agonist, anti-fibrinolytic drugs which is non steroidal should be preferred. However they can be used only for limited period of time.

Ormeloxifene, a selective estrogen receptor modulator, reduce the blood loss in patients with AUB that is evidenced by decrease in PBAC score , decrease in endometrial thickness along with significant rise in haemoglobin levels. Amenorrhea/ hypomenorrhea were the desirable side effects in the perimenopausal age group and in women who are unfit for surgery without affecting the normal endocrine and physiological functions. It is non-steroidal , non-hormonal drug protective to both breast and endometrium. The easier administration of the drug facilitates patient compliance and acceptability and the marked relief of symptoms results in greater satisfaction. There is no need of taking drug every single day making it more convenient. Ormeloxifene should be the drug of choice in patients with AUB in all age groups with effective therapeutic efficacy and lesser side effects