A STUDY ON ORMELOXIFENE IN MANAGEMENT OF ABDOMINAL UTERINE BLEEDING

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"A STUDY ON ORMELOXIFENE IN MANAGEMENT OF ABNORMAL UTERINE BLEEDING"

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ABBREVATION

AUB	**Abnormal Uterine Bleeding**
RCOG	**Royal College of Obstetrics and Gynaecologists**
HMB	**Heavy Menstrual Bleeding**
GnRH	**Gonadotropin Releasing Hormone**
ER	**Estrogen Receptor**
NSAIDs	**Nonsteroidal Anti-Inflammatory Drugs**
FIGO	**International Federation of Obstetrics and Gynecology**
AVMs	**Arteriovenous Malformations**
AUB-O	**Abnormal Uterine Bleeding-Ovulatory Dysfunction**
PCOS	**Polycystic Ovary Syndrome**
TVUS	**Transvaginal Ultrasonography**
MRI	**Magnetic Resonance Imaging**
SERMs	**Selective Estrogen Receptor Modulators**
SPRMs	**Selective Progesterone Receptor Modulators**
UAE	**Uterine Artery Embolization**
SIS	**Saline Infusion Sonohysterography**
ACOG	**American College of Obstetrics and Gynaecology**
DUB	**Dysfunctional Uterine Bleeding**

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ABSTRACT

INTRODUCTION:

Abnormal uterine bleeding is a significant debilitating clinical condition and effect 14-25% of women. One of the newest designer medications for the treatment of AUB is Ormeloxifene. We sought to determine the effectiveness and potency of Ormeloxifene in the treatment of AUB-O in this longitudinal investigation.

OBJECTIVES:

To study the efficacy and acceptability of Ormeloxifene in management of AUB

METHODOLOGY:

The study was conducted in Department of Obstetrics and Gynecology of Shri B M Patil medical college. In this study 52 patients aged 30-55 years, presenting with heavy menstrual bleeding were enrolled. Patients with Pelvic pathologies, liver dysfunctions or who are in use of IUCDs or oral contraceptives, were excluded from the study. All the participants were subjected for complete menstrual history, medical history, clinical examination and laboratory evaluation done. All cases received Ormeloxifene 60mg twice weekly for the first 12 weeks, followed by once weekly for next 12 weeks. The participants were followed every three months and six months for subjective and objective improvement in menstrual

blood loss by measuring PBAC score, endometrial thickness, hemoglobin concentration. Statistical analysis was performed by using MS Excel and Statistical Package for Social Sciences software version 20.

RESULTS:

The study showed 50 out of 52 study participants had improvement after using Ormeloxifene for 6 months and the side effects was found negligible. There was improvement in hemoglobin concentration, PBAC score, TVS-ET score in all the participants.

CONCLUSION:

Ormeloxifene is effective and safe in patients with AUB-O and this can reduce the burden of surgery in patients suffering from AUB-O.

KEYWORDS: AUB-O, Ormeloxifene, HMBL, Hysterectomy

INTRODUCTION

Abnormal Uterine Bleeding (AUB) is a general term for irregularities in the menstrual cycle that involve regularity, frequency, volume of flow and duration when they don't occur during pregnancy. Up to one-third of women often suffer irregular uterine bleeding at some point in their lives, with menarche and perimenopause being the two times when it happens most frequently. An ideal cycle of 21 to 35 days lasts 3 to 7, and results in blood loss of 5 to 80 millilitres. Any variations in these 4 factors qualify as irregular uterine haemorrhage.[1]

AUB, often referred to as AUB of ovulatory diseases, can be caused by ovulatory abnormalities like oligovulation, anovulation, polycystic ovarian alterations, and corpus luteal dysfunction. The patient has heavy and prolonged menstrual bleeding (HMB) that lasts more than eight days, results in blood loss of more than 80 ml, or both, and causes anaemia. The main causes of AUB are changes in prostaglandin levels or changes in hypothalamic-pituitary-ovarian function. It results in severe, extensive bleeding.[1]

One of the most typical gynaecological symptoms encountered on a daily basis is AUB, which can afflict one-third of women of childbearing age. All civilizations experience significant social and physical morbidity as a result of the vast range of AUB disturbances, which may also be indicative of a serious underlying disease.

10%–30% of menstrual women experience menorrhagia at any given moment, and up to 50% of women may experience it during the perimenopausal transit phase. According to studies, menstrual blood loss averages 60 to 80 ml per month and is linked to iron deficiency anaemia. Any irregularity in the regularity, frequency, duration, or volume of menstrual flow is referred to as AUB, and its underlying cause could be pharmacological, pathological, or physiological.[2]

Even while research into less invasive surgical procedures like endometrial ablation has increased, hysterectomy is still the only viable long-term solution for women who have no further fertility issues. The need for non-surgical methods of lowering menstrual blood loss is still present. The Royal College of Obstetricians and Gynaecologists (RCOG) advises starting therapy with medicinal management before turning to surgical procedures in order to reduce the morbidity associated with hysterectomy.[3]

It is undoubtedly a difficult assignment when there is no general agreement on the drugs that should be provided in this situation. Nonsteroidal anti-inflammatory drugs (NSAIDs), antifibrinolytics, combined oestrogen and progesterone or progesterone alone, high dose oestrogen, gonadotropin releasing hormone (GnRH) agonists, danazol, and levonorgestrel releasing intrauterine system are just a few of the many different medications used to treat AUB. Their main downsides, despite

being efficient in lowering blood loss, are their expense and unfavourable side effects when used frequently.[4]

The most recent designer medicine for the treatment of AUB is ormeloxifene. It is a third-generation selective oestrogen receptor (ER) modulator that has a high affinity for ERs. In some tissues, like the vagina, bone, and central nervous system (CNS), cardiovascular system (CVS), it acts like an oestrogen, whereas in the uterus and breasts, it has an antiestrogenic action. Its pharmacological role in AUB is based on this. The discovery of two distinct types of ER α and ER β as well as knowledge of the intricate nature of ER structure and function provide a significant therapeutic opportunity for discovering a substance with favourable bone, cardiovascular, and neurological profiles without having a negative impact on uterine and breast reproductive tissues. Two receptor isoforms with varying ligand affinities coexist in many tissues, there are at least two activating factors present, and there are an increasing number of coactivators and corepressors. These factors all contribute to the selective ER regulation.[5]

Thus, these are many studies, which have been done on Ormeloxifene for abnormal uterine bleeding with ovulatory dysfunction. But still there is a lacunae in this research field. Hence the present study has been undertaken to study an efficacy of Ormeloxifene in the treatment of AUB-O.

An overview of abnormal uterine bleeding (AUB):

When they don't happen during pregnancy, AUB refers to irregularities in the monthly period that involve frequency, regularity, length, and volume of flow. At some point in their life, all women will have abnormal uterine bleeding; the perimenopausal and menstrual cycles are when these abnormalities most frequently occur. A typical menstruation has a periodicity of 24 to 38 days, lasts between two and seven days, and results in blood loss of 5 to 80 millilitres. Any variations in these 4 factors qualify as irregular uterine haemorrhage. It is preferable to use straightforward terminology to describe the nature of aberrant uterine bleeding rather than outdated ones like menstrual irregularity, amenorrhoea, and dysfunctional uterine bleeding. "The International Union of Gynecology and Obstetrics (FIGO)" updated the nomenclature first in 2007, and then again in 2011 and 2018. The FIGO systems provide an acronym for typical etiologies after first defining abnormal uterine bleeding. These statements are true in nongestational, chronic AUB-O. "In the year 2018, this committee considered menstrual bleeding, and irregular bleeding was deemed to be outside the 75th percentile".[1]

Another distinction that might be noticed is between acute and persistent abnormal uterine bleeding. Acute AUB is profuse bleeding that needs to be treated right away to stop more blood loss. Acute AUB that refers to abnormalities in monthly

bleeding over the majority of the previous six months can happen by itself or superimpose on chronic AUB.[1, 6]

Additionally, in 2018 they released FIGO-AUB SYSTEM 1 and FIGO AUB SYSTEM 2

FIGO SYSTEM 1 includes updates to the terminology and descriptions of the warning signs and symptoms of abnormal uterine bleeding (Figure 1).

Parameter	Normal	Abnormal
Frequency	Absent (no bleeding) = amenorrhea	
	Infrequent (>38 days)	
	Normal (≥24 and ≤38 days)	
	Infrequent (<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: ≥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	

Figure 1: FIGO System 1

The FIGO AUB SYSTEM 2 (PALM-COEIN) includes a revision of the classification of the underlying causes of AUB (Figure 2).

System 2 category	Change
AUB-A	Refined sonographic diagnostic criteria
AUB-L	Inclusion of Type 3 as a submucous leiomyoma Type definitions and distinctions Distinction between Types 0 and 1; 6 and 7 Distinction between Types 2 and 3; 4 and 5
AUB-C	No longer includes AUB associated with pharmacologic agents that impair blood coagulation which are now included in AUB-I
AUB-I	Now includes AUB associated with all iatrogenic processes including the use of pharmacological agents used for anticoagulation and those thought to interfere with ovulation
AUB-O	Diagnostic threshold changes based upon the revisions of System 1, described above No longer includes ovulatory disorders associated with drugs known or suspected to interfere with ovulation
AUB-N	The name of the category has been changed from "Not Yet Classified" to Not Otherwise Classified There is a brief discussion of a potential new cause of AUB the so-called uterine "niche" or isthmocele following lower segment cesarean section

Figure 2: FIGO AUB System 2

Etiology:[7]

In order to classify the underlying causes of irregular uterine bleeding, the International Federation of Obstetrics and Gynecology (FIGO) created the useful term PALM-COEIN. The first part to explore structural problems is PALM. The second section, COEI, goes into great length on non-structural concerns. So to say, the N stands for "Not else classified."

Polyp.

Adenomyosis

Leiomyoma

Hyperplasic and **M**alignant conditions

Coagulopathy

Dysfunction of the **O**varies

Abnormalities of the **E**ndometrium

Iatrogenic

Not otherwise classified

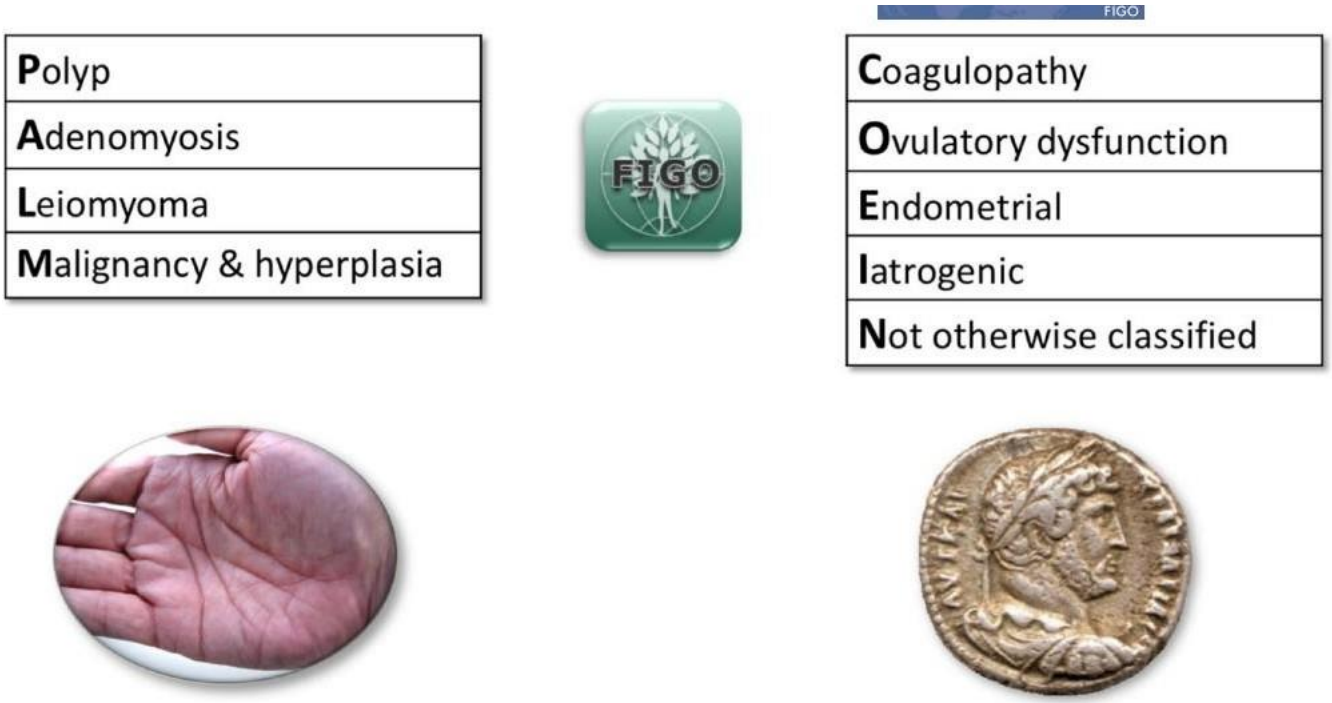


Figure 3: FIGO AUB System 2 PALM COEIN

The participant's unusual uterine bleeding may be caused by the aforementioned problems. Endometrial colonies, endometrial polyps, or leiomyomas are examples of structural disorders that may not be the primary cause of an individual's AUB and instead may be asymptomatic.

“AUB-O due to anticoagulants were transferred from of the coagulopathy group to the iatrogenic category” in the 2018 FIGO system.

Cervicitis, chronic liver disease, and pelvic inflammatory disease are among the illnesses that fall within the group of illnesses that are not otherwise categorised.

Rare etiologies for AUB not previously characterised include myometrial hyperplasia, endometritis, and arteriovenous malformations (AVMs).

Epidemiology:

Between 3% to 30% of reproductive-aged women worldwide are thought to experience abnormal uterine bleeding, with menarche and perimenopause having the highest incidences. The prevalence climbs to 35% or more when menstruation and unexpected bleeding are taken into account. Many studies solely consider periods with Heavy Menstrual bleeding (HMB). It is difficult to pinpoint the precise prevalence since many women do not seek medical attention for their symptoms and because some diagnostic criteria are factual while others are arbitrary.[8]

Pathophysiology:

One of the most frequent problems affecting women of all reproductive ages, from puberty through menopause, as well as occasionally post-menopausal women, is dysfunctional uterine hemorrhage (DUB).It is described as abnormal uterine bleeding that cannot be explained by pregnancy, inflammation, or tumour, meaning that no genital organ lesions are found during a careful bimanual pelvic examination. The two key clinical indicators for determining the presence of dysfunctional uterine bleeding are

- Acyclical, unpredictable, variable, and possibly accompanied or unaccompanied by systemic symptoms, abnormal uterine bleeding from the uterus.
- Verify there are no local or systemic pathologies that could induce menstrual irregularities.

The term "DUB" has been changed to "AUB," and is now classified as AUB-O. The most common causes of abnormal uterine bleeding are uterine diseases (PALM-COEIN categories are indicated parenthetically), including endometrial polyps (AUB-P), adenomyosis (AUB-A), uterine leiomyomas (AUB-L), and endometrial hyperplasia or cancer. Systemic disorders including genetic coagulopathies like von Willebrand disease and acquired coagulopathies like

AUB-C and ovulatory dysfunction is additional potential etiologies (AUB-O). More people experience ovulatory AUB than ovulatory dysfunction related AUB.

A spectrum of illnesses known as ovulatory dysfunction (AUB-O) includes amenorrhea and irregular heavy menstrual cycles. Cycles are painless. Typically, endocrinopathies such polycystic ovary disease causes them (PCOS). The causes of abnormal bleeding in these AUB instances are connected to unopposed oestrogen. In ovulatory AUB, the hypothalamic-pituitary-ovarian system is intact, and the levels of steroid hormones are typical. Ovulatory AUB accounts for the majority of instances once regular menses have been established throughout adolescence. The aberrant prostaglandin synthesis and receptor over-expression, elevated local fibrinolytic activity, and elevated local plasminogen activator activity are all contributing factors to ovulatory AUB.[6-8]

One thing that has to be stressed in this situation is the value of D&C and endometrial studies in perimenopausal women to rule out endometrial malignancy. When medical treatment fails in younger women, D&C is performed. A specific type of anovulatory AUB, known as Metropathica hemorrhagica, is observed in women between the ages of 40 and 45. Nothing to do with parity. The signs are common symptoms. The woman begins to have ongoing, painless bleeding, which may begin at the start of menstruation or be preceded by 6–8 weeks of amenorrhea. The woman occasionally discusses her past menorrhagia.

Palm-Coein classification

Polyps

Up to 67% of premenopausal women with endometrial polyps experience intermenstrual bleeding, often known as AUB.A few millimetres to a few centimetres in size, polyps can be single or many, sessile or pedunculated, and of any number. They frequently extend from the fundus of the uterus and into the internal os and have vascular centres surrounded by localised hyperplastic endometrial gland and stroma developments. Despite the fact that the exact cause of polyps is unknown, genetic, metabolic, and hormonal factors could be to blame. Age seems to be associated with an increase in the occurrence of polyps in females, which ranges from 8 to 35%. Although benign endometrial polyps predominate, premenopausal women have a 1.7% chance of malignancy and postmenopausal women have a 5.4% risk, according to a new survey of more than 10,000 women. Age, tamoxifen use, high oestrogen levels, obesity, and Lynch syndrome are all risk factors for developing polyps (hereditary nonpolyposis colorectal cancer).[9]

Cervical polyps seldom exceed 3 cm in size, are often benign, are typically simple to remove in the clinic, and should be referred for a pathologic analysis. "It is important to remember that cervical polyps can develop in conjunction with

endometrial intraepithelial neoplasia (EIN) or endometrial hyperplasia and endometrial polyps and may be mistaken for a prolapsing leiomyoma".[10]

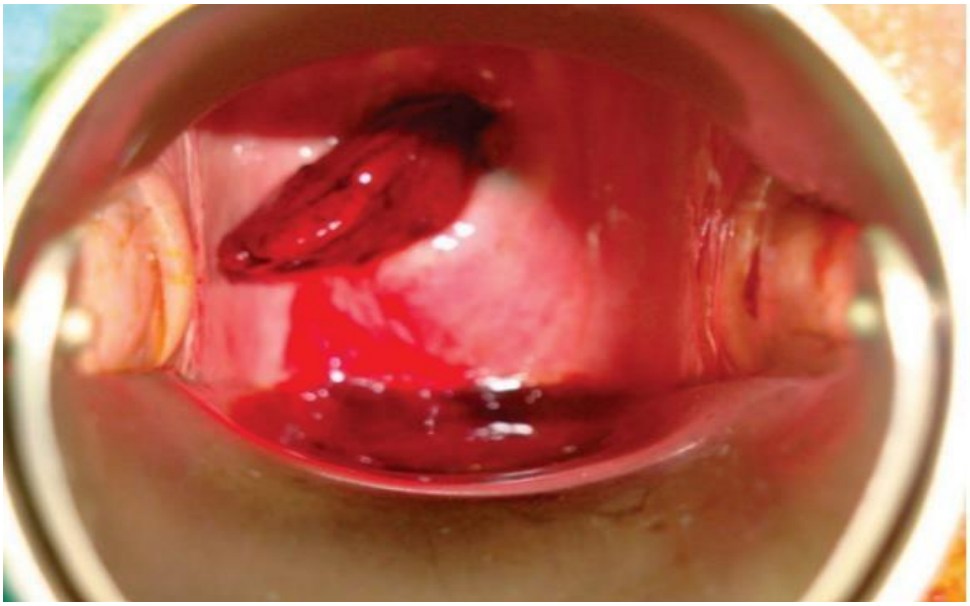


Figure 4: Polyp

Adenomyosis

Endometrial stroma and glands invades locally or more widely across the uterine musculature in a condition known as adenomyosis, which causes the myometrium around them to enlarge. It is anticipated that 5% to 70% of women would be affected. In their quartet to fifth years of life, multiparous women experience the majority of instances. HMB, irregular bleeding, dysmenorrhea, or dyspareunia can occur in female patients, in contrast to the one-third of cases where it is asymptomatic. According to the available data, "The pathologic features of

adenomyosis are all related to abnormal gene expression, increased angiogenesis and multiplication, decreased apoptosis, impaired cytokine expression, in-regional oestrogen production, progesterone resistance, increased nerve density, and immunologic oxidative stress".

Although particular TVUS and magnetic resonance imaging (MRI) criteria also contribute to the diagnosis, the ultimate diagnosis is made through hysterectomy histologic evaluation. Transvaginal ultrasound (sensitivity: 89%; specificity: 89%) may detect myometrial heterogeneity that interferes with the delineation of the endometrial-myometrial interface, echogenic striations, myometrial cysts, a spherical uterus, or asymmetrical myometrial thickening. Due to fact that adenomyosis makes the uterus more vascular, colour Doppler ultrasound can identify the pattern of penetrating arteries.

Criterion For Diagnosing Adenomyosis[1,6]

The MUSA committee's eight TVUS requirements are graphically represented.

(A) Asymmetrical myometrial thickness

(B) Myometrial cysts,

(C) Hyperechoic islands,

(D) Fan-shaped shadowing,

(E) Echogenic subendometrial buds and lines,

(F) Translesional vascularity,

(G) When present, an uneven junctional zone

(H) Interrupted junctional zone are some of these.

Junctional zone can be identified and assessed most effectively using three-dimensional ultrasonography.

At least for the time being, a diagnosis of adenomyosis is strongly associated with the fulfilment of two or more of these criteria.

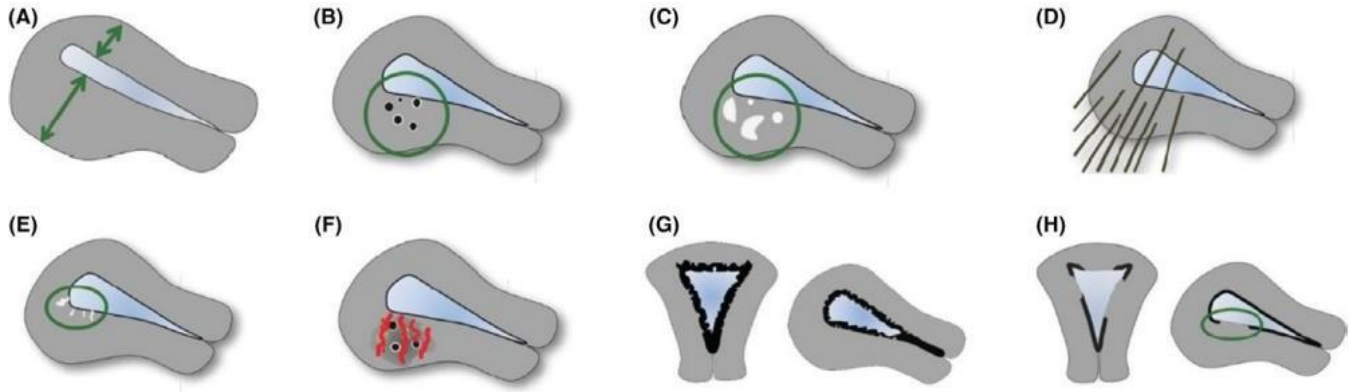


Figure 5: Adenomyosis Diagnostic Criteria

T2-weight MRI scans may show "Punctate hyperintense bleeding foci, islands of heterotopic endometrial tissue, cystic enlargement of heterotopic glands, and diffuse or focal widening of the endometrial myometrial junctional zone of 12 mm or more (sensitivity, 86%; specificity, 86%)". Adenomyosis can be successfully treated medically with suppressive hormonal therapies, including "long-term use of gonadotropin receptor hormone (GnRH) agonists and short-term use of continuous contraceptive hormones, high-dose progestins, selective oestrogen receptor modulators (SERMs), selective hormone receptor modulators (SPRMs), the 52-mg

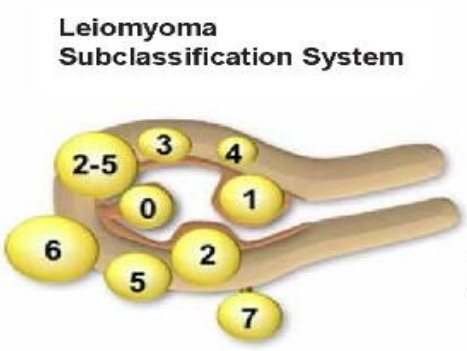
LNG IUS, aromatase inhibitors, and danazol". According to the study, "if amenorrhea was achieved, there was no statistically significant difference in pain reduction across pharmacological therapies". The price and side effects of various therapies, however, differ greatly.

According to the authors, the LNG IUS is by far the most attractive medical treatment because of its efficiency and discreet side effects. After endometrial ablation, adenomyosis, which has a 20% failure risk, "is a predictor of therapeutic failure due to bleeding. Uterine artery embolization (UAE) and MRI-guided targeted ultrasound (MgFUS), which were initially approved by the Food and Drug Administration for the treatment of leiomyoma, seem to be promising treatments for adenomyosis in nonrandomized trials". In a variety of brief studies utilising UAE that were followed for one or more years, Taran et al. found that 50% to 90% of the women had lessened symptoms. Women with adenomyosis who used MgFUS had a 25% to 66% decrease in bleeding over the course of a year. When a woman fails medical treatment, hysterectomy remains the only option.[11-15]

Leiomyoma

Leiomyomas are benign monoclonal tumours that form in the myometrium throughout the reproductive years and are also known as myomas or fibroids. "They are the most common pelvic tumours, with lifetime prevalence estimates for white women of 70% and black women of over 80%". Early menarche, oral

contraceptive use before the age of 18, poor parity, nutrition (greater meat intake, higher glycemic index or load, alcohol consumption), hypertension, African American ethnicity, and family history are risk factors for developing leiomyomas. Menstrual cramps or HMB are among the symptoms, as are those linked to mass such pelvic pressure, incessant urination, digestive problems, "or reproductive dysfunction (infertility or obstetrical complications such as adverse outcomes related to leiomyoma location)". The medical diagnosis may be identified "based on the results of a pelvic examination, with pelvic ultrasound serving as the usual confirmatory test (although normal findings need not rule out the existence of submucosal leiomyoma as a cause of AUB). The FIGO classification of leiomyoma location establishes the relationship between leiomyomas and the endometrium or visceral peritoneum (serosal layer)".



S – Submusosal	0	Pedunculated intracavitary
	1	< 50% intramural
	2	≥ 50% intramural
O – Other	3	Contacts endometrium; 100% intramural
	4	Intramural
	5	Subserosal ≥ 50% intramural
	6	Subserosal < 50% intramural
	7	Subserosal pedunculated
	8	Other (specify e.g. cervical, parasitic)

Hybrid leiomyomas (impact both endometrium and serosa)	Two numbers are listed separated by a hyphen. By convention, the first refers to the relationship with the endometrium while the second refers to the relationship to the serosa. One example is below	
	2-5	Submusocal and subserosal, each with less than half the diameter in the endometrial and peritoneal cavities, respectively.

Figure 6: FIGO Leiomyoma Sub classification System

SIS or hysteroscopy can be used to determine whether a leiomyoma is submucous (sub endometrial) or of type 0, 1, or 2. By disrupting the uterine cavity's close proximity, submucosal fibroids induce heavy menstrual bleeding that results in anaemia. According to clinical research, the bleeding will be reduced if the submucosal fibroid is removed. The relationship between leiomyomas and the endometrium and visceral peritoneum can also be seen via MRI. MRI may assist doctors in determining whether to perform uterine-sparing treatments, and gadolinium can be used to detect devascularized (degenerated) leiomyomas. Although a leiomyosarcoma diagnosis cannot be made with certainty, an MRI may reveal characteristics that increase the possibility of the rare cancer.[16-19]

Malignancy and Premalignant Conditions

Cervical or vaginal cancer might result in unusual bleeding. It is vital to identify "the cause of any AUB by evaluating the vulva, uterus, and cervix with Pap preview screening or tissue collection, as advised by the American Obstetricians and Gynaecologists Association". AUB may be less crucial than EIN in older premenopausal and menopausal women (subtype: simple or benign hyperplasia vs [the more worrisome] subtype: atypical hyperplasia with progression to or concurrent with endometrial malignancy). 63,000 new instances of endometrial cancer are recorded each year in the United States, with a lifetime risk of 2.8%. Given that the majority of female cancer patients (between 75 and 90 percent)

present with AUB, it is fortunate that 70% of cases are discovered at an early stage. Less frequent but more dangerous endometrial cancers include papillary serous, clear cell, mucinous, and carcinosarcoma.

Endometrioid (adenocarcinoma) is a most common type of cancer. Oestrogen that is unopposed with only an intact uterus, obesity, type 2 diabetes, hypertension, nulliparity, and tamoxifen use are risk factors for EIN and cancer. Due to the 27% to 71% lifetime risk of endometrial cancer in women with Lynch syndrome, vigilant endometrial surveillance is required up until risk-reducing hysterectomy. The American College of Obstetricians and Gynecologists advises collecting endometrial samples from all female patients with AUB who are over 45 or under 45 and also have additional EIN risk factors.

Endometrial samples examined with the Pipelle instrument had an endometrial cancer detection sensitivity of 91% in premenopausal women and an EIN detection sensitivity of 81%. (subtype: atypical endometrial hyperplasia). In a thorough research, the sensitivity and specificity of hysterectomy for the diagnosis of endometrial cancer were 86% and 99%, respectively; for the detection of EIN, they were 78% and 96%.Endometrial malignancy and atypical endometrial intraepithelial neoplasia (EIN) are effectively treated by hysterectomy; benign hyperplasia without atypia-type EIN can be handled with oral progestins or LNG IUS and maintained with endometrial surveillance.[20-23]

Coagulopathy

Between 5% and 24% of women with HMB may have inherited bleeding disorders, most notably von Willebrand disease (vWF). Women who frequently bruise easily, develop epistaxis, gum or tooth bleeding, postpartum haemorrhage, or have severe surgical bleeding should be tested for coagulopathy. Factor deficits (factors VIII and IX are more frequent, whereas factors VII and XI are less frequent) and platelet abnormalities may be associated with heavy menstrual bleeding. Leukemia, aplastic anaemia, renal or liver disease or failure, septicemia, disseminated intravascular coagulopathy, and women who are taking medications that affect coagulation or platelet function, like NSAIDs, herbal remedies, anticoagulants, and chemotherapy drugs should all be taken into account when diagnosing an acquired coagulopathy.[24-26]

Ovulatory Dysfunction

Amenorrhea can develop from irregular or infrequent ovulation, but irregular bleeding is more common. Anovulations are more common early in a woman's menstrual phase and late in the perimenopausal years. Bleeding episodes can range in severity from mild and infrequent for two or more periods to sudden and severe HMB occurrences that require immediate medical intervention. The absence of luteal progesterone, which is a necessary element for successful endometrial hemostasis when HMB is associated with anovulation, results in chronically

proliferative endometrium. This condition appears to be accompanied by lower local prostaglandin F2a levels.

A separate disorder known as the luteal-out-of-phase event may afflict ovulating women and typically manifests in later reproductive years. These women ovulation, but they start developing follicles prematurely in the late stages of pregnancy, which results in high blood levels of estradiol and the associated HMB. Although the origin of ovulatory dysfunction is unknown, polycystic ovarian syndrome, obesity, hypothyroidism, hyperprolactinemia, anorexia, strenuous exercise, and drastic weight loss may be factors.[27-29]

Endometrial Disorders

The major malfunction of the local endometrial hemostasis is the cause of endometrial diseases. Women with HMB exhibit with regular, cyclic menstruation that is suggestive of normal ovulation. The aetiology is unknown; however it is most likely brought on by vasoconstriction defects (endothelin-1, prostaglandin F2a), which speed up clot breakdown, and enhanced plasminogen production. Given its antifibrinolytic properties, tranexamic acid may be used to treat this later problem. NSAIDs, the 52-mg LNG IUS, oral, intramuscular, and subcutaneous progestins, oral or ring or patch combination contraceptives (monophasic or monthly, or extended cycle), danazol, and, where necessary, surgical procedures

including endometrial ablation or hysterectomy are also available as therapies for HMB.[30-32]

Unclassified (AUB-N):

Includes uncommon causes that are poorly understood or recognised, such as myohyperplasia, uterine varicose veins, and arteriovenous malformations. Others lack a discernible reason, according to current investigations. They are all grouped together as members of this unclassified AUB. Better studies may be allocated in new categories in the future as they become available.

THE CLINICAL APPROACH TO ABNORMAL UTERINE BLEEDING

Evaluation of the "amount" of blood loss during menstruation and its effects on the patient are the initial steps in the diagnostic workup. There are several graphs, surveys, and patient-reported treatment outcomes (PROMs) that are disease-specific available. However, there is little proof that they change patient outcomes, hence they are not frequently utilised in clinics. While research is being done to provide validated PROMs and hemorrhage scores that are clinically effective, in reality, the physician must rely on an individual evaluation to look into AUB.[33]

The clinical approach to assessing a patient with AUB can be taken in several steps.

When a patient complains of menstruation, the doctor should get a thorough history from them. Some of the past facts are as follows:

Menstrual history, including:

- Menarche age
- Last period
- Menstrual cycle regularity, frequency, length of period, and flow rate
    1. Regularity (with a range of +/- 2 to 7 days) might be absent, erratic, or consistent. (difference of over 20 days)
    2. Frequency is divided into three categories: irregular (less than 24 days), typical (between 24 and 38 days), and infrequent (less than 24 days) (greater than 38 days)
    3. It is possible to categorise the length as protracted (days more than 8), typical (about 4 - 8 days), or abbreviated (days less than 4)
    4. The flow can be classified as heavy (more than 80 mL), ordinary (5-80 mL), or light depending on its volume (less than 5 mL of blood loss)

Since it is challenging to estimate exact volume measurements outside of research settings, it is crucial to ask specific questions about how often you change your sanitary products throughout the day, how big any clots are, whether you need to change them at night, and whether you ever feel like you're being "flooded."

- Post-coital and intermenstrual haemorrhage
- Past sexual and reproductive behaviour

- o Prior obstetric experience, including the number of pregnancies and manner of delivery
- o Subfertility and desire for conception
- o Modern contraception
- o Previous sexually transmitted diseases (STIs)
- o History of PAP smears

- Symptoms that are connected to other symptoms or systemic symptoms
  - o Any weight loss
  - o Pain abdomen
  - o Discharge Per vagina
  - o Bowel or bladder symptoms
  - o Anemia symptoms or signs
  - o Bleeding disorders symptoms or signs
  - o Endocrine problems symptoms or signs
- A history of coagulopathies, cancer, and endocrine diseases in the family
- Occupational history; the effect of symptoms on quality of life; Social history, including cigarette, alcohol, and drug use
- Any surgical history in past

Physical examinations includes:

- Vital indicators, includes blood pressure and body mass index (BMI)
- Pallor-related symptoms, such as mucosal / skin pallor

Endocrine-related symptoms:

- Checking for thyroid enlargement or discomfort
- Unusual or excessive hair growth patterns, clitoromegaly, and acne may be signs of hyperandrogenism.
- Moon-like features, unusual fat distribution, and striae that may be signs of Cushing syndrome
- Abdominal exam to feel for any pelvic / abdominal tumours
- Symptoms of coagulopathies, such as bruising / petechiae
- Speculum and bimanual examination of the pelvis
- Pap smear, if necessary
- STI testing (for gonorrhoea and chlamydia, for example), and wet preparation as needed
- Endometrial biopsies if required.[34-36]

MEASUREMENTS FOR MENSTRUAL BLOOD LOSS

1. ALKALINE HEMATIN TEST

Using spectrophotometry to measure the end result after extracting the haemoglobin from the sanitary napkins and converting it to hematin. It is not recommended above other procedures and is only sometimes employed.

2. [PBAC]Pictorial Blood Loss Assessment Charts

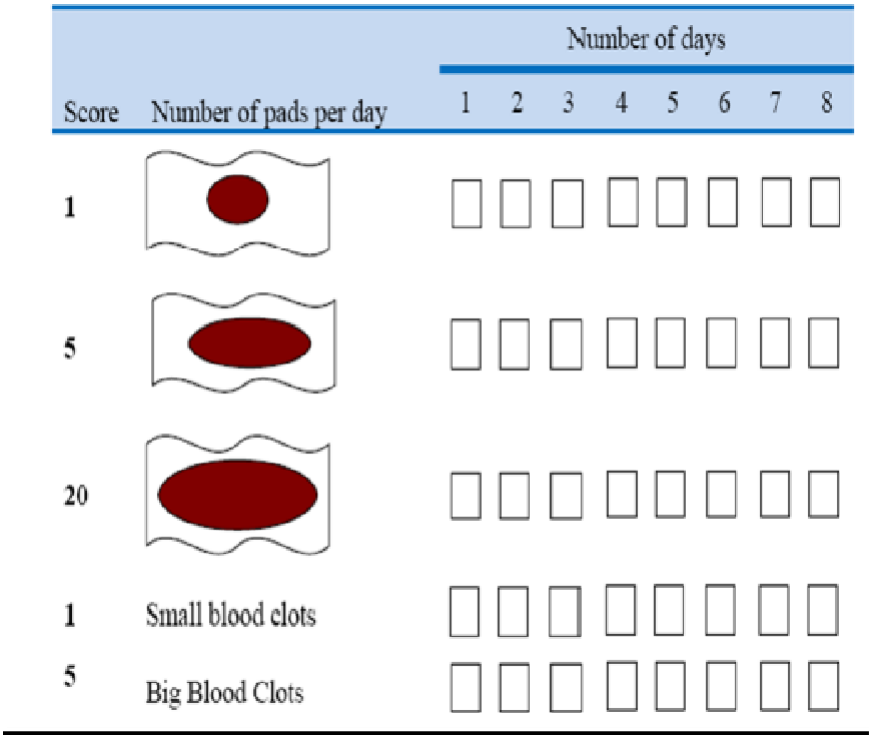


Figure 7: [PBAC] Pictorial Blood Loss Assessment Charts

Higham had developed scoring system to determine how much blood is lost throughout a period. Heavy menstrual bleeding is defined as a PBAC Score of 100, which is comparable to more than 80 ml of monthly blood loss. Its among the most precise ways to determine the precise blood loss.

3.Self-evaluation tools

Self-evaluation tools includes

1. Unusually heavy bleeding

2. Bleeding for more than 7 days

3. Pad flooding

4. Related transit of clots more than 3 cm.

Evaluation:

Laboratory setting:

A pregnancy test, CBC, assessment for cervical cancer and thyroid-stimulating hormone (TSH) levels should all be part of the laboratory evaluation for AUB. Particularly in individuals who are at high risk for infection, screening for Chlamydia trachomatis must be taken into consideration. Cyclical menses are often a good indicator of ovulatory state.[37]

If the patient has anaemia or thrombocytopenic haemorrhage will be shown by a CBC. The initial indication of von Willebrand disease is frequently the development of excessive menstrual bleeding at menarche. All adults with a screening test history for bleeding conditions and all teenagers with heavy menstrual bleeding should undergo laboratory testing. Prothrombin time, partial thromboplastin time, a CBC with platelets, and fibrinogen or thrombin time are all

recommended as first testing; bleeding time would be neither specific nor sensitive and is not recommended. Depending on the results of early tests or if a patient's medical history implies underlying bleeding disorders, special tests for von Willebrand disease or other coagulopathies, such as von Willebrand-ristocetin cofactor activity, von Willebrand factor antigen, and others, may be advised.[38]

AUB is linked to both hypothyroidism and hyperthyroidism, however hypothyroidism is more typical. It's possible that AUB and subclinical hyperthyroidism go along In a study of women with what looked to be normal thyroid function, those who had heavy monthly bleeding had significantly lower TSH levels and greater levels of total triiodothyronine, free triiodothyronine, free thyroxine, and total thyroxine than those who did not. Women with AUB can reasonably and cheaply be screened for thyroid illness by measuring their TSH levels.[39]

Clinical Screening for a Hemostasis Disorder in a Patient with Excessive Menstrual Bleeding

Based on their medical history and the presence of any of the following, patients with severe menstrual bleeding should have an initial evaluation for an underlying hemostasis disease:

1. Bleeding heavily ever since menarche

2. Either one of the following:

- Bleeding after delivery
- Bleeding following surgery
- Connected with dental work bleeding

3.At least two of the following signs:

- One or two times a month, you get bruises
- One or two times per month, epistaxis
- Bleeding gums frequently
- Bleeding symptoms run in the family

*Patients who have positive screen should be given consideration for additional testing, which may include seeing a haematologist and getting their von Willebrand factor and ristocetin cofactor levels checked.[40-45]

Abnormal Uterine Bleeding Diagnostic Evaluation

Medical history includes:

Menarche and Menopause Ages

Menstrual cycle patterns

Menstrual severity (clots or flooding)

Pain (intensity and management)

Medical conditions

Surgical history

Usage of drugs

Symptoms and signs of potential hemostatic disorders.

Physical Examination:

- General physical examination:
- Abdominal examination:
- Pelvic Examination includes

—Per speculum- cervical erosion, a polyp, or a lesion or growth

—If needed, Pap smear test,

—Bimanual examination-

Unusual uterine growth

Firm to the touch Fibroid

Non tender

consistently enlarged uterus

Soft to the touch Adenomyosis

tenderness

Discovering a PID-adnexal lump and discomfort in the cervical motion.

Laboratory Tests:

- Urine or blood test for Pregnancy
- Complete blood parameters
- Screening for bleeding disorders (if indicated)

- TSH level

Diagnostic or imaging procedures accessible (when indicated):

- Transvaginal ultrasound
- Magnetic resonance imaging
- Saline infusion sonohysterography

Various Tissue Sampling Techniques (when indicated)

- Endometrial aspiration /Office endometrial biopsy
- Hysteroscopy directed endometrial sampling (office or operating room)

Endometrial sampling warning signs

- Age greater than 40 and any trend of irregular bleeding
- If ET-12mm, Tamoxifen use, endometrial cancer in the family, and a known genetic mutation are present, it is possible to proceed sooner.
- Multiple AUB-M risk factors
- History of repeated anovulatory cycles
- Unsuccessful medical management.

Adding a coagulation panel for people in their twenties and thirties with suspected bleeding issues.[40-45]

Imaging:

Transvaginal ultrasound, hysteroscopy and MRI are a few examples of imaging tests. Transvaginal Ultrasonography does not exposing the patients to radiation and can reveal ovarian abnormalities, endometrial thickness, adenomyosis, uterine size and form, and leiomyomas (fibroids). It is a crucial instrument that should be acquired as soon as irregular uterine bleeding is being investigated. Although MRI is more expensive than other scanning options and is not usually used on patients with AUB, it can provide detailed images that are useful for planning surgeries. If endometrial polyps are discovered, transvaginal ultrasound images are cloudy, or submucosal leiomyomas are visible, hysteroscopy and sonohysterography (transvaginal ultrasound with intrauterine contrast) are effective treatments. Although more intrusive, hysteroscopy and sonohysterography are frequently done in offices.[46]

Testing of endometrial tissue is advised for AUB patients who have a high chance of developing hyperplasia or cancer, even though it may not always be necessary. Although MRI is more expensive than other scanning options and is not usually used on patients with AUB, it can provide detailed images that are useful for planning surgeries. If endometrial polyps are discovered, transvaginal ultrasound images are cloudy, or submucosal leiomyomas are visible, hysteroscopy and

sonohysterography (transvaginal ultrasound with intrauterine contrast) are effective treatments.[47]

Management:

The cause of abnormal uterine bleeding, desire for fertility, medical stabilization of the patients, and other associated complications are only a few of the variables that affect how to treat AUB. Based on these variables, treatment should be tailored to the patient. For first AUB therapy, medicinal methods are typically favoured.[48]

Hormonal therapies are the primary line of treatment for severe abnormal uterine bleeding. Treatment options for acute AUB include oral progestins, combination oral contraceptive pills (OCPs), and intravenous (IV) conjugated equine oestrogen. When treating acute AUB, tranexamic acid can stop the breakdown of fibrin. The tamponade of uterine haemorrhage with a Foley bulb is a mechanical approach to the management of acute AUB. It's crucial to assess the patient's clinical stability and restore lost volume with fluid resuscitation and blood products while attempting to stop the acute abnormal uterine bleeding. Desmopressin can be used to treat acute AUB brought on by the coagulopathy von Willebrand disease. It can be given intravenously, subcutaneously, or intranasally. Dilation and curettage can be needed for some patients.

The list of specific treatments for each classification is provided below, based on the term PALM-COEIN for the causes of chronic AUB:

The clinical features of cervical polyps have a significant impact on how they are treated. Asymptomatic polyps often don't require treatment, although there are occasional exceptions. Removal is typically necessary for polyps that are symptomatic, big, or unusual. When managing polyps, some techniques include polypectomy, which entails grasping the base of the polyp with a ring forceps and twisting and rotating it until it comes off; punch biopsy forceps are used for smaller polyps; and polyps with a thick stalk typically require electrosurgical excision or hysteroscopic removal. Every removed polyp should undergo further histological testing to rule out cancer. In postmenopausal and women with recurrent polyps, further hysteroscopy examination of the cervical canal and uterine cavity is important to rule out any endometrial disorders (polyps or malignancy).

- Endometrial polyps can coexist with cervical polyps in up to 25% of female patients.
- Cervical polyps are present in 10.9% of postmenopausal women and 7.8% of premenopausal women with any endometrial illness, respectively.

Treatment for adenomyosis involves:

Prostaglandin inhibitors (anti-inflammatory medications) decrease menorrhagia and pain in one-third of patients. Menorrhagia is reduced by tranexamic acid by half.

Menorrhagia and pain can both be decreased with the help of progestin and combined oral contraceptive pills. Up to 90% of patients who use an intrauterine device (IUD) that releases levonorgestrel experience less menstrual bleeding and pain. A gonadotropin-releasing hormone (GnRH) agonist will cause amenorrhea and a hypo-oestrogenic condition, which will end menorrhagia and discomfort and reduce the size of the foci (unfavourable effects include menopausal symptoms if oestrogen/progestogen is not given as add-back therapy). Uterine artery embolization reduces the amount of menorrhagia and bleeding days brought on by adenomyosis. A localised adenomyoma can be surgically removed. Adenomyomectomy is carried out less frequently. The best and only choice for older women with severe symptoms whose previous therapy alternatives have failed is to get a hysterectomy.

Leiomyomas (fibroids) may be treated medically or surgically depending on the patient's desires conception, medical conditions, pressure complaints, and uterine cavity deformation. Surgery options includes hysterectomy, endometrial ablation,

and embolization of the uterine artery. One option for medical therapy is the use of an intrauterine device (IUD) that releases levonorgestrel, as well as GnRH agonists, tranexamic acid and systemic progestins in combination with non-steroidal anti-inflammatory drugs (NSAIDs). In the endometrium, mifepristone has a lesser affinity for oestrogen receptors than progesterone receptors. A direct action of mifepristone is to decrease the number of progesterone receptors, which helps to reduce the size of the fibroid. Mifepristone results in early follicular hormonal milieu and ovarian acyclicity, which may suppress fibroid growth that is steroid dependent. Amenorrhea is a side effect of mifepristone, which also inhibits ovulation. The menstrual blood loss may be reduced by mifepristone's direct suppressive effects on the endometrial vasculature and reduction of stromal vascular endothelial growth factor (VEGF).[49]

Radiation therapy, surgery, adjuvant therapy, high doses of progestins in the absence of surgery, or huge dosages of progestins are all possible treatments for malignancy or hyperplasia, depending on the stage.

Desmopressin or tranexamic acid can be used to treat coagulopathies that result in AUB (DDAVP).

By altering a woman's lifestyle, ovulatory dysfunction can be treated when anovulatory cycles are found in women with obesity, PCOS, or other disorders.

Endocrine disorders should be handled with the appropriate medications, such as cabergoline for hyperprolactinemia and levothyroxine for hypothyroidism. Since the underlying processes of endometrial problems are unclear, there is no specific treatment available.

According to the offending drug or collection of drugs, iatrogenic causes of AUB should be treated. Other methods, such the levonorgestrel-releasing IUD, combination oral contraceptive tablets (in monthly or prolonged cycles), or systemic progestins, may be taken into account if an oral contraceptive method is suspected to be the primary cause of AUB. The aforementioned techniques can also aid in controlling AUB if other drugs are suspected but cannot be stopped. Based on the patient's goals regarding reproduction and any coexisting medical conditions, individual therapy should be customised.

Entities like endometritis and AVMs are not otherwise specified causes of AUB. Gentamicin 1.5 mg/kg IV every 8 hrs or 5 mg/kg IV every 24 hours are two antibiotics that can treat endometritis, along with clindamycin 900 mg IV every 8 hours. When compared to TID, QD gentamicin dose has been proven to be equally efficacious and to be related with a shorter length of hospital stay. Piperacillin-tazobactam and ampicillin-sulbactam may be utilised for patients with endometritis caused by GBS resistance to clindamycin and embolization can treat AVMs.[50, 51]

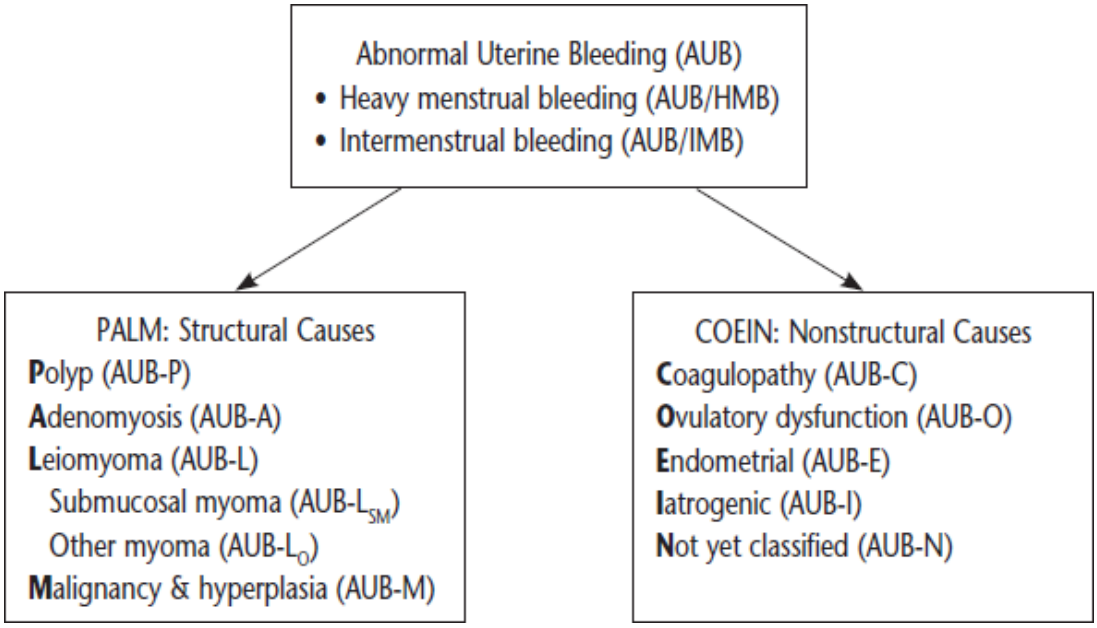


Figure 8: AUB causes of PALM-COEIN

The Basic PALM-COEIN approach is used to classify the causes of irregular uterine bleeding in menstruating women who are not pregnant in the table above. The International Federation of Gynaecology and Obstetrics has endorsed this method, which use the name AUB along with words that characterise related bleeding patterns.

Differential diagnosis:[52]

Any gastrointestinal (GI) or genitourinary (GU) bleeding might resemble abnormal uterine bleeding. As a result, it is necessary to rule out bleeding from other sources, which is included in the differential diagnosis.

On the basis of anatomical location or system, the treatment options for genital tract bleeding is:

- Vulva: benign growths or cancer
- Vagina: Unwanted growths, vaginitis, STDs, cancer, trauma, and foreign objects
- Cervix: Malignancies, sexually transmitted diseases, and benign growths
- Ovaries and fallopian tubes: Pelvic inflammatory illness, cancer
- Urinary tract: Malignancy, infections
- Inflammatory bowel illness and Behçet syndrome affect the digestive tract.
- Ectopic pregnancy, spontaneous abortion, and placenta previa affect the reproductive system.

Uterus: The acronym PALM-COEIN lists the causes of bleeding from the uterine corpus.[52]

Prognosis:

The aetiology will also affect the outcome for abnormal uterine bleeding, which is often good. In addition to improving the patient's overall quality of life, the major objectives of treating and diagnosing chronic AUB are to rule out severe illnesses like cancer as well as to evaluate and treat other concomitant medical disorders that may have an influence on therapy or symptoms. The prognosis varies depending

on whether surgical or medicinal therapy is used. Anti-fibrinolytic and non-steroidal anti-inflammatory drug therapy has been shown to reduce blood loss during menstruation by up to 50%.There is a dearth of randomised trial evidence, despite the fact that oral contraceptives can be effective. Women with severe monthly bleeding as their primary symptom of AUB have demonstrated to respond better to the levonorgestrel-releasing IUD than to other medical therapies, which also improves the patient's quality of life. Up to 50% and 90% of women, respectively, may experience amenorrhea when using injectable progestogens and GnRH agonists. Due to its negative effects in producing a low oestrogen state, GnRH agonists are normally only used for a 6-month course, and injectable progestogens might cause breakthrough bleeding as a side effect.

Endometrial ablation used in surgical procedures was shown to control bleeding more successfully at 4 months after surgery in randomised clinical studies and reviews, but after 5 years there had been no difference from medicinal care. The hysterectomy group showed superior outcomes at 1 year in studies comparing hysterectomy to levonorgestrel-releasing IUD. By ten years, many of the women who used levonorgestrel-releasing IUDs had undergone hysterectomies, but there had been no difference in the quality of life at five or ten years.[53]

Complications:

Anemia, infertility, and endometrial cancer are possible side effects of persistent irregular uterine bleeding. If immediate treatment and supportive care are not started, severe anaemia, hypotension, shock, and even death might occur.[53]

ORMELOXIFENE:

The central drug research centre in Lucknow initially created ormiloxifene/centchroman as a contraceptive pill. Saheli is its commercial name in India. It has Novex-DS, Centchroman, and Sevista licences Ormeloxifene has been used as an oral contraceptive since the 1990s, although its most well-known application is as a non-hormonal, non-steroidal, once-weekly pill. [5, 54]

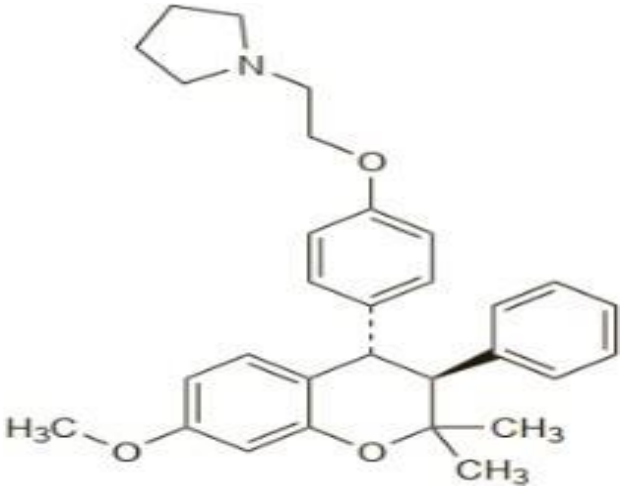


Figure 9: Structure of Ormeloxifene

Researchers' interest in selective oestrogen receptor modulators (SERM) has grown recently as a result of their tissue-specific pharmacology. One such orally administered once-weekly contraceptive available in India is ormeloxifene, a multipurpose nonsteroidal SERM. It possesses powerful estrogen-antagonistic and modest estrogen-agonistic actions. By preventing the production and activation of osteoclasts, it reduces bone loss brought on by ovariectomy. [54]

Dosage**:**

Ormeloxifene (30 mg/week) given to women for a year did not result in excessive platelet aggregation. The fact that ormeloxifene had no effect (up to 80 mg/kg) on the vascular cycloxygenase activity in rats at concentrations that prevented the production of malonaldehyde suggests that ormeloxifene has a sparing effect that may lower the risk of thrombotic episodes by tipping the scales in favour of more advantageous anti-aggregatory prostaglandin.

Despite having only a few trials, a SERM has shown promise in new pharmacological therapies including ormeloxifene. A third generation non-steroidal, non-hormonal SERM called ormeloxifene has an anti-estrogenic impact on the breast and uterus and an estrogen-like action in the vagina, bones, central nervous system, and cardiovascular system. By acting on the endometrial oestrogen receptor, it also minimises dysmenorrhea and premenstrual syndrome (ER).[55]

Side effects:

The negative side effects include headaches, nausea, and missed periods. As previously mentioned ormeloxifene has fewer and more tolerable side effects.

Uses:

Menorrhagia and endometriosis improved when it was taken as a contraceptive, which prompted control studies for the treatment of menorrhagia when it was approved for this purpose. By regulating ER expression on the endometrium, it also lessened premenstrual symptoms, mastalgia, and dysmenorrhea while normalising uterine cavity haemorrhage. Trans7methoxy2, 2dimethyl3phenyl4 (4(2pyrrolidinoethoxy) phenyl (chromanhydrochloride) is the chemical name for ormeloxifene. Ormeloxifene binds to cytosol receptors in a competitive manner, blocking them as well as causing protracted depletion, prolonging the duration of its effects even after drug removal. Its terminal halflife is 170 hours, and it is quickly taken first from GI tract, reaching a maximum level in 4 hours. Plasma proteins have limited affinity for it.[56]

According to its mode of action, ormeloxifene is a selective oestrogen receptor modulator, or SERM.

1. It is an oestrogen antagonist in the uterus and ovaries but an oestrogen agonist in the bones.

2. It does not hinder ovulation.

3. It prevents the endometrium's priming and growth in response to oestrogen.

4. The fertilised egg is transported through the fallopian tubes faster than usual.

5. The fertilised egg enters a non-conducive endometrium too quickly, which prevents implantation from taking place.

Contraindications include:

- Drug allergy
- PCOD
- Dysplastic cervix
- Liver illness
- Kidney disease and other conditions.

Pharmacokinetics:

- Absorption: When taken orally, it is quickly absorbed through the mesentery and reaches the peak serum concentration in 240 minutes.
- Distribution: Plasma proteins are not bound.
- Excretion: The terminal half-life lasts about 170 hours.[57,58]

LITERATURE REVIEW

Bhalla H et al(2010) did a study Systemic hemodynamic effects of a once-weekly oral contraceptive dose of ormeloxifene, a nonsteroidal medication. This investigation was carried out with a clear objective in mind. On systemic hemodynamics, coagulation capability, and serum antioxidant activity in vivo, the short-term effects of ormeloxifene and raloxifene were studied. In 19 groups of 10 adult female Colonybred Sprague-Dawley rats, ormeloxifene or raloxifene (0.25, 1.25, or 3 mg/kg/day) were administered orally for 7, 15, or 30 days. Simple gum acacia in distilled water was used as therapy on the animals in the control group. We measured systemic hemodynamics and serum total antioxidant activity 24 hours after the last dose. They obtained outcomes as only an increase in R wave amplitude in rats at a dose of 3 mg/kg/day for 30 days was the only significant effect of ormeloxifene at these doses and regimens on antioxidant activity or hemodynamic parameters. Just seven days after treatment at this dosage, this raloxifene impact became apparent. However Overall, both agents' responses were, nevertheless, quite comparable. They came to the conclusion that the results show that ormeloxifene and raloxifene have similar pharmacological profiles when administered to rats over a short period of time. Long-term studies could enable a fair comparison of the advantages and disadvantages of ormeloxifene and

raloxifene in terms of cardiovascular outcomes based on changes in the ECG (R wave).[59]

Nandhini G. M., (2022) did a study on a review of ormeloxifene's effectiveness in treating ovulatory disorders' abnormal uterine bleeding. For the first 12 weeks, they took 60 mg of ormeloxifene twice weekly; for the next 12 weeks, they took it once weekly to treat 40 instances of heavy menstrual bleeding (HMB) with ovulatory dysfunction in women between the ages of 40 and 52. Before and after therapy, the patients' haemoglobin levels, pictorial blood loss assessment chart (PBAC) scores, and endometrial thickness were assessed. They got results because they saw a substantial decline in endometrial thickness and PBAC score. Additionally, it is discovered that the amount of haemoglobin considerably rises from 8.40.8 to 9.90.7. In this study, 90% of cases experienced noticeable changes in their symptoms after 6 months of ormeloxifene medication, but 10% of the individuals needed surgical intervention, such as a hysterectomy. Amenorrhea and hypomenorrhea were found in 7.5% and 5% of patients, respectively. In light of these findings, they came to the conclusion that ormeloxifene would be the best option for patients with AUB because it is extremely safe and has tolerable side effects. This straightforward drug-based therapy has improved compliance, tolerability, and a discernible decrease in symptoms, leading to satisfaction with the course of treatment.[60]

Dhananjay BS et al (2012) did a research participants included those who had been given a DUB diagnosis. After clearing out other potential reasons of the irregular uterine bleeding, DUB was identified, and ormiloxifene therapy was initiated. There were 35 instances in all. The efficiency of the ormeloxifene treatment was evaluated by contrasting the endometrial layer before and after 3 months of sevista medication. A 60 mg pill of ormeloxifene was administered twice weekly for three months, then once per week for an additional three months. They discovered that there was a statistically significant increase in Hb g/dl (p 0.001) and a statistically significant decrease in endometrial thickness after treatment with ormeloxifene (p 0.001). They arrived at this judgement that ormeloxifene is a useful medication for the management of dysfunctional uterine haemorrhage.[61]

KomaramRavibabu.et.al. (2013) conducted a prospective study of 24 weeks on 50 women with dysfunctional uterine bleeding to determine the effectiveness of ormeloxifene in the pharmacological management of DUB. They discovered that ormeloxifene is effective in reducing menstrual blood loss while having little to no negative effects on normal endocrinal and physiological parameters. It also demonstrated effective therapeutic efficacy and had fewer side effects.[62]

Neha Agarwal.et.al. (2013) did a prospective study on sixty patients on Efficacy and the Safety of Ormeloxifene in Dysfunctional Uterine Bleeding in which they

found the drug was effective and quick-acting and appeared as a promising approach for the medicinal management of DUB. They also found the drug oncologically protective to the breast and endometrium. [63]

Hari Om Singh. et.al. (2015) did a Study on 172 patients aged 25-45 years, with complaints of heavy menstrual bleeding. Ormeloxifene was administered orally twice a week for 12 weeks and then once a week for next 12 weeks. Menstrual blood loss was measured using Pictorial blood loss assessment chart and haemoglobin level. The frequency of clots during post-treatment was significant compared to pre-treatment and it's also cost-effective therapy.[64]

Nikita Gandotra.et.al. (2017) did a descriptive study on 30 patients of Dysfunctional Uterine Bleeding (DUB) on the role of Ormeloxifene in the management of dysfunctional uterine bleeding, in which they found that Controlling dysfunctional uterine bleeding with ormeloxifene is quite effective and also, they found mean haemoglobin concentration increased by 1.4gm/dl and endometrial thickness also decreased after treatment and also found that most common side effect was amenorrhea.[65]

OBJECTIVES

1. To study the efficacy of Ormeloxifene in management of Abnormal Uterine Bleeding (AUB-O).
2. To explore the acceptability of Ormeloxifene in the treatment of Abnormal Uterine Bleeding (AUB-O).

METHODOLOGY

Study Setting:

The study was conducted Department of Obstetrics and Gynecology, Shri B.M. Patil Medical College, Hospital and Research Centre B.L.D.E. (Deemed to be University).

Sample size: 52.

Type of study: Longitudinal study.

Study Period: January 2021 to June 2022

Inclusion Criteria:

- Women of 30-55 years of age group
- Women diagnosed with AUB-O presenting with heavy menstrual bleeding (i.e. abnormally heavy or prolonged period)

Criteria for Exclusion:

Pelvic diseases include

- Adenomyosis
- Endometrial hyperplasia with atypia
- Uterine fibroids

- Cancers of the uterus, cervix, ovary, vagina, and uterus
- Illnesses like coagulopathy, hepatic dysfunction, heart disease, stroke, renal ailments, and platelet abnormalities
- Previous thrombosis history
- Thyroid disorders
- Pregnancy related bleeding
- Using oral contraceptives or IUCDs
- Ormeloxifene hypersensitivity

METHOD:

All participants after giving informed consent were taken according to the declaration of Helsinki and after considering inclusion and exclusion criteria. Then the participants were subjected for complete menstrual history, medical history, clinical examination and laboratory evaluation as follows:

- Complete Blood Count
- BT, CT
- TSH, T3, T4.
- Transvaginal Scan
- Endometrial Thickness

All cases received ormeloxifene 60mg twice weekly for the first 12 weeks, followed by once weekly for the next 12 weeks.

Figure 10: Ormeloxifene treatment schedule

Every three months, every six months, or earlier if necessary, follow-up was conducted.

Menstrual blood loss by haemoglobin concentration and proliferative endometrial thickness by transvaginal sonography were the main outcome indicators (TVS).

Ormeloxifene's acceptance and side effects were the secondary outcome indicators.

The Pictorial Blood Loss Assessment Chart (PBAC), which correlates with the alkaline hematin test, was used to objectively measure menstrual blood loss.

The improvement of symptoms was also evaluated subjectively. The participants were instructed on how to perform PBAC grading based on the quantity and size of

clots that have passed, as well as the extent of sanitary napkin soiling.

An 80ml menstrual blood loss is equivalent to a PBAC score of 100, which is used to diagnose heavy menstrual bleeding.

PBAC Scoring

Pads	Minimally soiled Moderate soiled Saturated	1 5 20
Clots	Small (size of Rupee coin smaller) Large (larger than a rupee coin)	1 5

Before starting therapy, during the third and sixth months, endometrial thickness, haemoglobin concentration, and PBAC score were all measured. At each appointment, a thorough menstrual history was taken, including information on the number of sanitary napkins used, the passage of clots, and dysmenorrhea. Any negative impacts were supposed to be highlighted. Ormeloxifene's acceptability and subjective symptom improvement were evaluated.

Sample size calculation:

Assuming that 26% of the subjects in the population have the factor of interest, the study would require a sample size of 52. For estimating the expected proportion with 12% absolute precision and 95% confidence with the anticipated Proportion

of Dysmenorrhea among women with dysfunctional uterine bleeding [4] of 26%, the study would require a sample size of 52 patients with a 95% level of confidence and 12% absolute precision.

Formula used:

- $\mathbf{n=\frac{z^2\ p*q}{d^2}}$

Where Z = Z statistic at α level of significance

d^2= Absolute error

p = Proportion rate

q= 100-p

Statistical analysis:

The data obtained was entered in a Microsoft Excel sheet, and statistical analysis was performed using SPSS (Version20). Results were depicted in Mean ± SD, counts and percentages, and diagrams. The Wilcoxon signed-rank test was used to compare two groups' differences in continuously distributed continuous data that were normally distributed. We compared categorical variables using the Mac Nemer's chi-square test. Statistical significance was set at $p<0.05$. Two-tailed statistical tests were used for each test.

RESULTS

Details of the study patients who were enrolled and lost contact are shown in Figure 11. Due to noncompliance, 2 patients lost track of their treatment and choose hysterectomy.

FIGURE NO.11

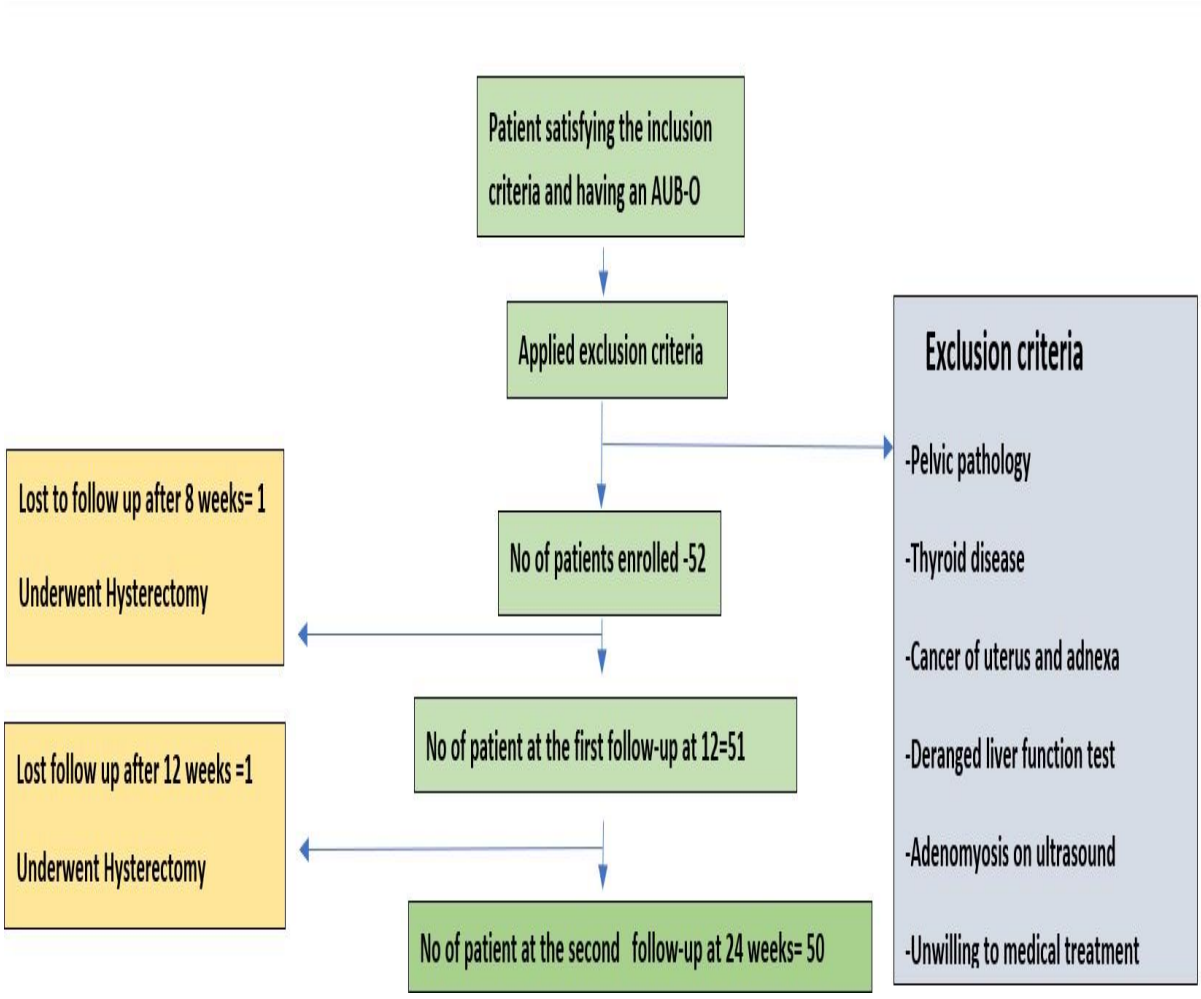
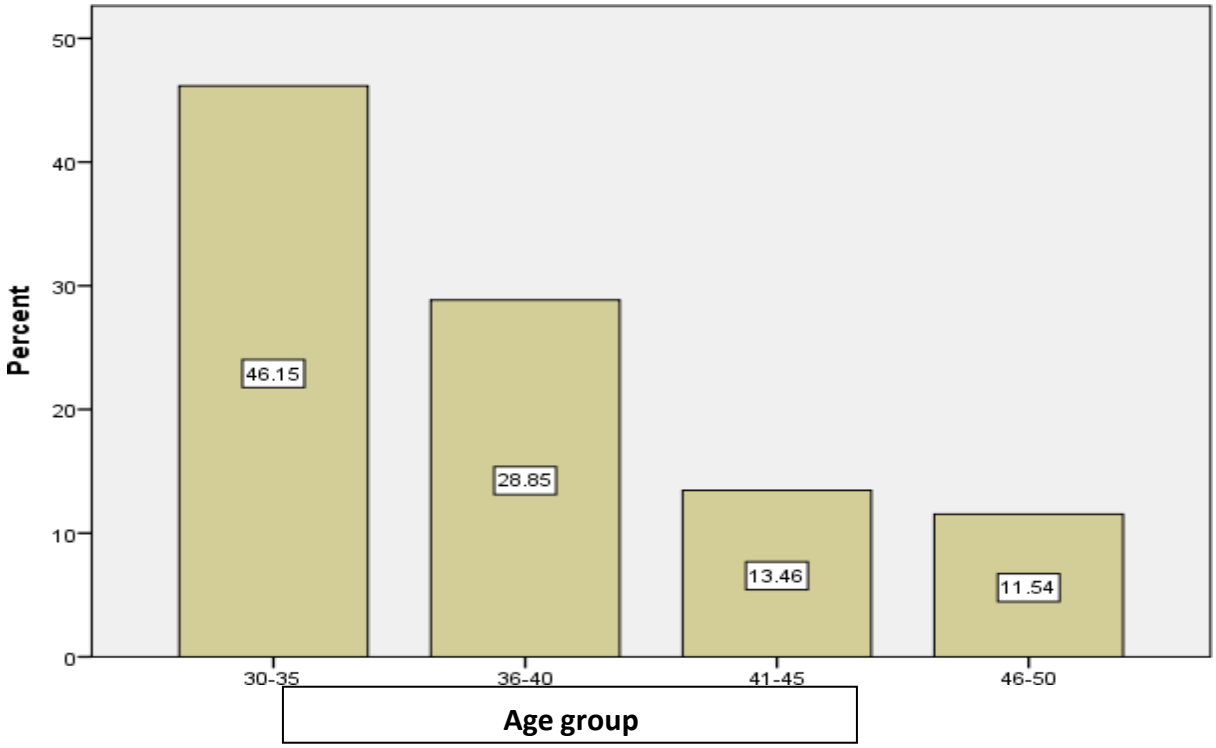


Table 1: Age-Specific Case Distribution:

Age Group (Years)		Frequency	Percent
Valid	30-35	24	46.2
	36-40	15	28.8
	41-45	7	13.5
	46-50	6	11.5
	Total	52	100

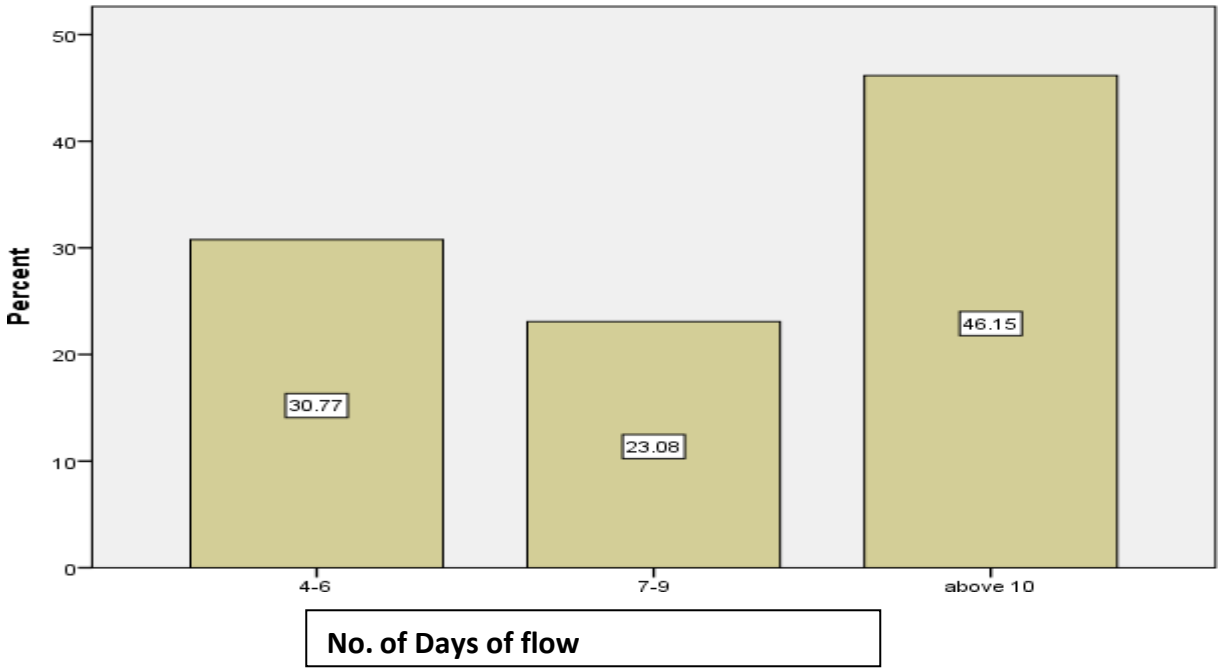


According to Table 1 and the bar graph above, the majority of participants in our study (46.2%) were between the ages of 30 and 35, while 28.8% were between the ages of 36 and 40. It suggests, to a point, that middle-aged women are most

commonly affected by abnormal uterine bleeding brought on by ovulatory dysfunction.

Table 2: Days of Flow in the Cases Under Study:

No. of Days of flow		Frequency	Percent
Valid	4-6	16	30.8
	7-9	12	23.1
	Above 10	24	46.2
	Total	52	100.0

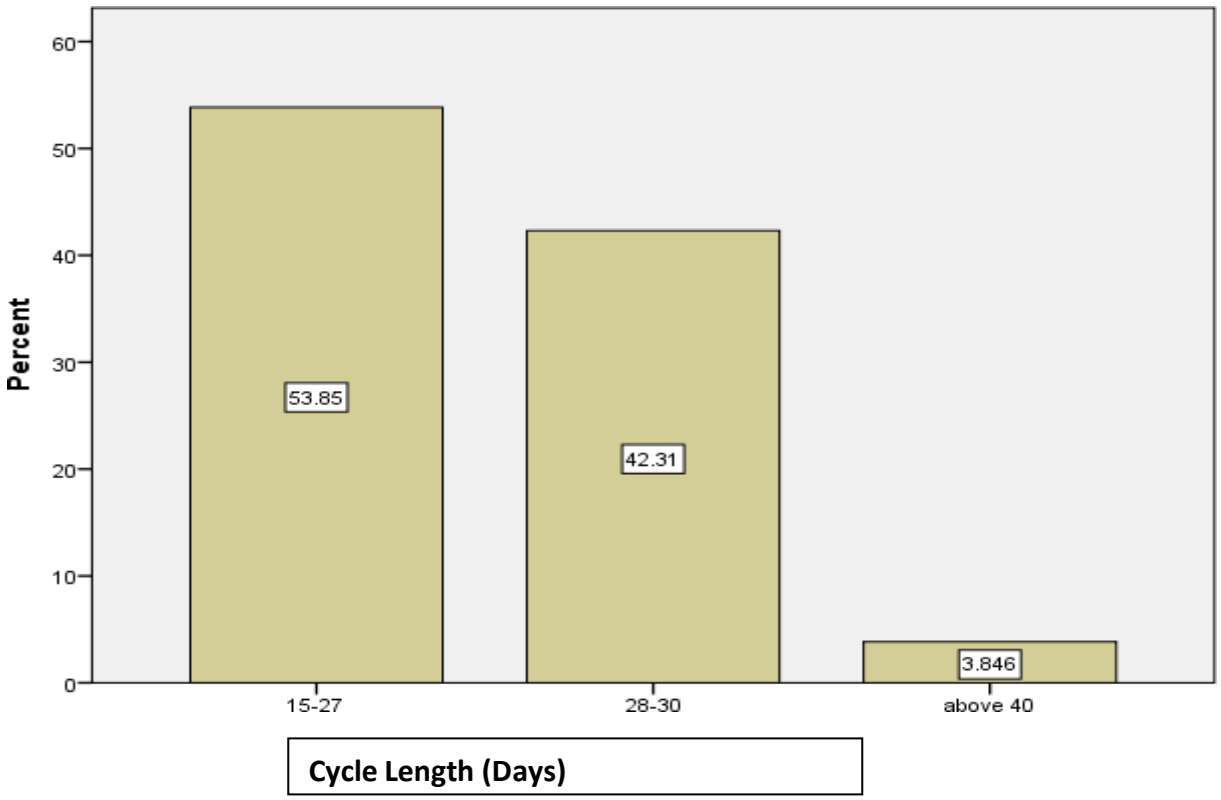


The number of days of flow was depicted in Table 2 and above Bar chart which show that 46.2% of the participants were having a flow of more than 10 days and

30.8% of the study population had a flow of 4-6 days. This shows that maximum participants had a prolonged cycle.

Table 3: Length of cycle in cases under study:

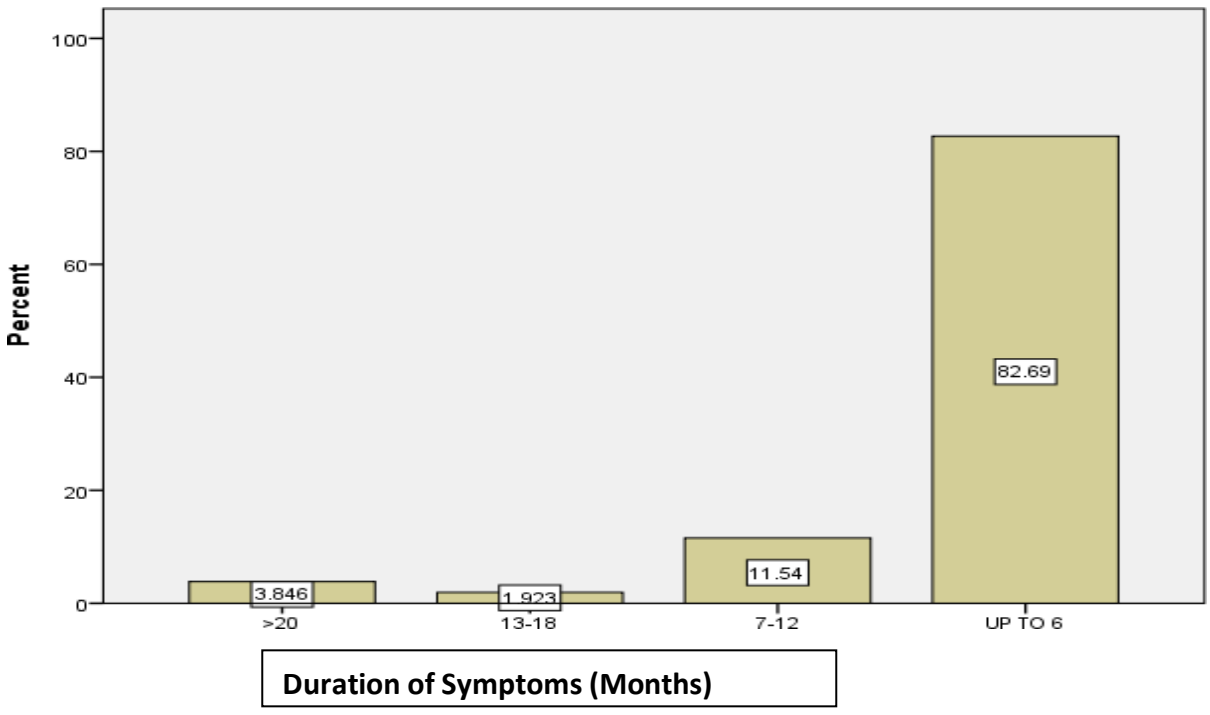
Cycle Length (Days)		Frequency	Percentage
Valid	15-27	28	53.8
	28-30	22	42.3
	Above 40	2	3.8
	Total	52	100.0



Cycle length of the cases under study was shown in Table 3 and above Bar chart which denotes that more than 96% of the study population is having a cycle length of 15-30 days. This indicates that most of the study participants bleed frequently.

Table 4: Duration of Symptoms of Cases under Study:

Duration of Complaints (Months)		Frequency	Percent
Valid	>20	2	3.8
	13-18	1	1.9
	7-12	6	11.5
	Up to 6	43	82.7
	Total	52	100



Most of the study participants (82.7%) presented to hospital seeking medical advice within 6 months of the appearance of symptoms whereas there were some participants (3.8%) seeking medical advice were bearing the complaints for more than 20 months, shown in Table 4 and above Bar chart.

Table 5: Duration of Treatment:

Duration of Treatment (Months)		Frequency	Percent
Valid	2	1	1.9
	4	1	1.9
	6	50	96.2
	Total	52	100.0

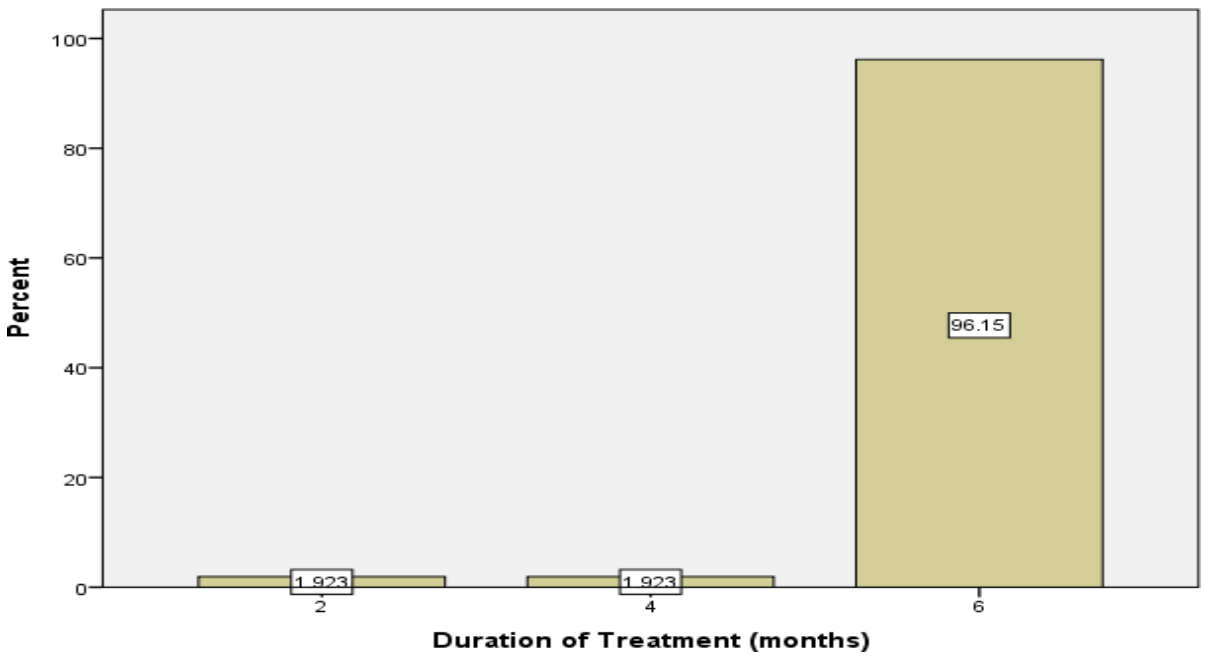


Table 5 and above Bar chart shows that 100% of the study participants received the Ormeloxifene, in that only 96.15% received total 6 months and 1.923% participants received treatment only for 2 months and other 1.923% received treatment for 4 months and discontinued and underwent hysterectomy

Table 6: Previous Treatment Taken (other than Ormeloxifene) or Not:

Previous Treatment Taken or Not		Frequency	Percent
Valid	No	48	92.3
	Yes	4	7.7
	Total	52	100.0

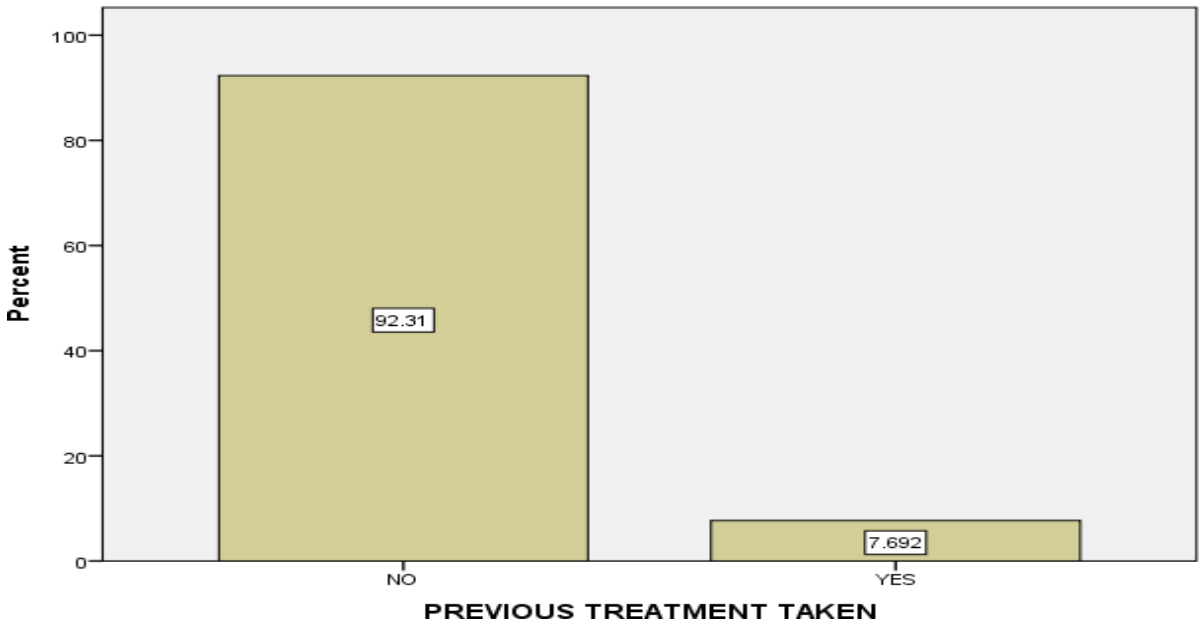
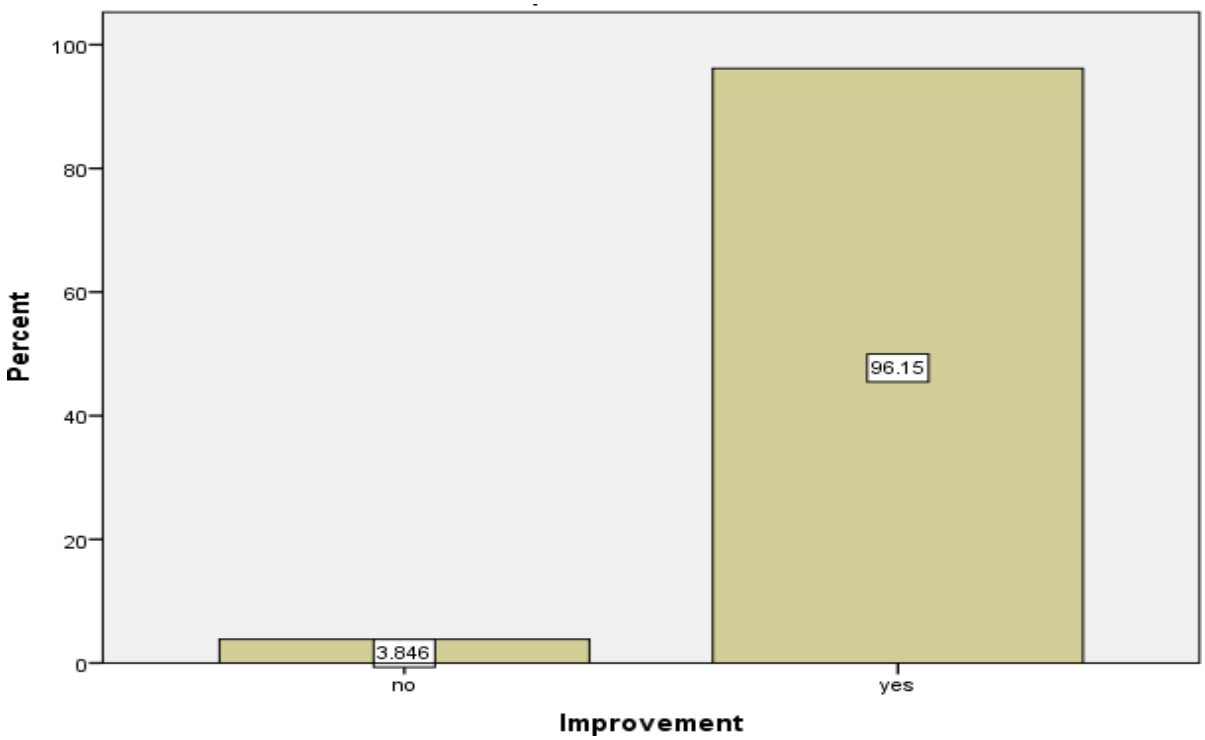


Table 5 and Table 6 with their respective Bar chart show that more than 96% of the study participants received the Ormeloxifene treatment whereas more than 92% did not have any treatment history.

Table 7: Improvement with usage of Ormeloxifene Treatment:

Improvement		Frequency	Percent
Valid	Yes	50	96.2
	No	2	3.8
	Total	52	100



More than 96.2% of the study population showed improvement after the treatment with Ormeloxifene in our study, 3.8% underwent hysterectomy due to noncompliance shown in Table 7 and above Bar chart.

Side Effects with Ormeloxifene Treatment:

Less than 4% of the study participants showed hypomenorrhea after treatment with Ormeloxifene whereas no participants was found to be having amenorrhea and 18% of the study participants have been presented with headache which is depicted in Table 8, Table 9 and Table 10 respectively.

Table 8:

Hypomenorrhea		Frequency	Percent
Valid	Yes	2	3.8
	No	50	96.2
	Total	52	100.0

Table 9:

Amenorrhea		Frequency	Percent
Valid	No	52	100.0

Table 10:

Headache		Frequent	Percentage
Valid	No	43	82.7
	Yes	9	17.3
	Total no.	52	100

Table 11: Descriptive Statistics (n=52):

	Minimum	Max	Mean	Standard Deviation
Age (Years)	30	50	37.19	5.901
Parity	1	6	2.83	0.985
No. of Days of flow	4	24	9.77	4.626
Cycle Length (Days)	15	60	25.58	7.209
Duration of Symptoms (Months)	1	24	4.81	5.022
Pulse (Beats/minutes)	68	106	86.85	9.549
Platelet Count (lakh cells/cu. mm)	1	3	2.15	0.500
TC (cells/cu. Mm)	4	11	7.96	1.793
TSH (mg/dl)	1	3	1.96	0.625
Duration of Treatment (Months)	2	6	5.88	0.615

The comparison of Haemoglobin concentration, PBAC, TVS-ET between pre and post-treatment with Ormeloxifene is shown in Figure 12, Figure 13, and Figure 14 respectively where it is shown that there is a significant improvement seen in these parameters post-treatment with Ormeloxifene. The descriptive statistics of the parameters checked pre-treatment and post-treatment with Ormeloxifene is depicted in Table 12.

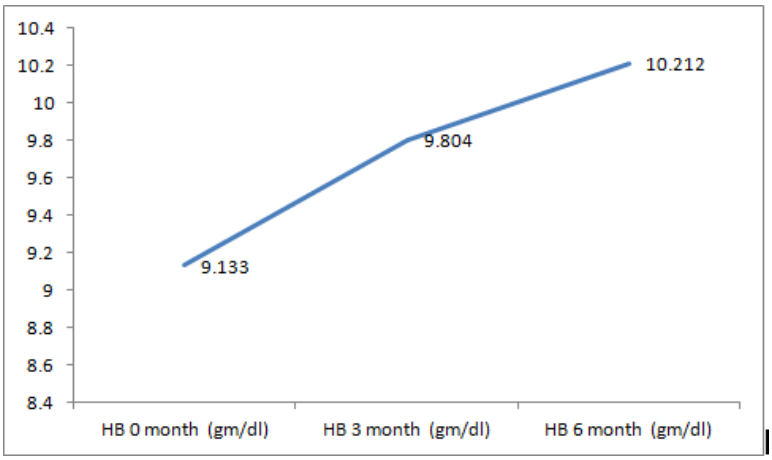


Figure 12: Comparison of Hemoglobin Pre-Treatment and Post-Treatment

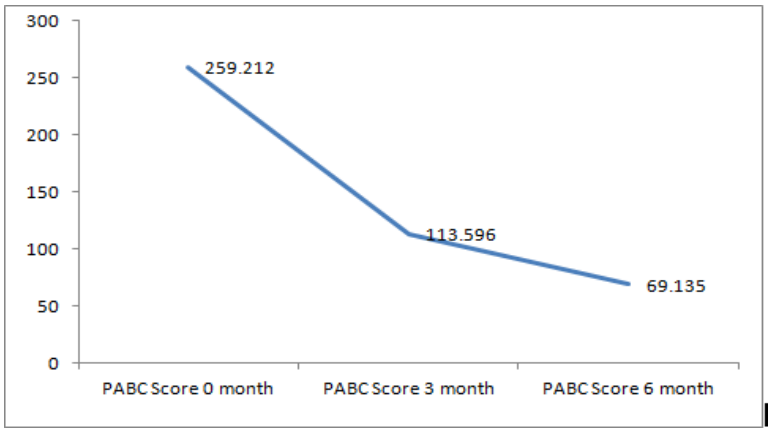


Figure 13: Comparison of PBAC Pre-Treatment and Post-Treatment

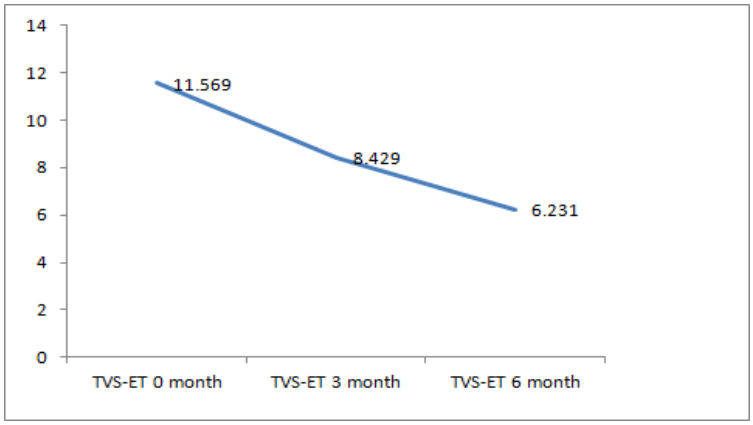


Figure 14: Comparison of TVS-ET Pre-Treatment and Post-Treatment

Table 12: Descriptive Statistics of Pre and Post Treatment (N=52):

	Maximum	Minimum	Mean	Std. Deviation
PBAC Score 0 month	480	152	259.21	76.236
PBAC Score 3 month	330	0	113.60	38.694
PBAC Score 6 month	95	0	69.13	18.556
Hb 0 month (gm/dl)	12	7	9.13	1.253
Hb 3 month (gm/dl)	12	0	9.75	1.619
Hb 6 month (gm/dl)	13	0	10.15	2.182
TVS-ET 0 month	17	8	11.56	2.421
TVS-ET 3 month	12	0	8.40	1.785
TVS-ET 6 month	10	0	6.21	1.719

The Wilcoxon signed-rank test of the PBAC score, Hemoglobin concentration, TVS-ET at 0 month, 3 month, and 6 month is shown in Table 13 showing a significant difference in which normality was checked using Shapiro-Wilk test as shown in Table 14. $p<0.05$ was considered as statistically significant.

Table 13: Wilcoxon Signed-rank test:

Measure 1	**Measure 2**	**W-value**	**Z**	**P**
PBAC Score 0 month	PBAC Score 3 month	1378.000	6.275	<0.001
PBAC Score 0 month	PBAC Score 6 month	1378.000	6.275	<0.001
Hb 0 month (gm/dl)	Hb 3 month (gm/dl)	52.000	-5.801	<0.001
Hb 0 month (gm/dl)	Hb 6 month (gm/dl)	103.000	-5.337	<0.001
TVS-ET 0 month	TVS-ET 3 month	1378.000	6.275	<0.001
TVS-ET 0 month	TVS-ET 6 month	1378.000	6.275	<0.001

Table 14: Test for Normality (Shapiro-Wilk):

		W	**P**
PBAC Score 0 month	PBAC Score 3 month	0.902	<0.001
PBAC Score 0 month	PBAC Score 6 month	0.924	0.003
Hb 0 month (gm/dl)	Hb 3 month (gm/dl)	0.503	<0.001
Hb 0 month (gm/dl)	Hb 6 month (gm/dl)	0.583	<0.001
TVS-ET 0 month	TVS-ET 3 month	0.782	<0.001
TVS-ET 0 month	TVS-ET 6 month	0.816	<0.001

Note: Significant results suggest a deviation from normality.

DISCUSSION

Abnormal Uterine Bleeding owing to Ovulatory Dysfunction (AUB-O), the most prevalent monthly illness in women of reproductive age, is characterised by abnormal uterine bleeding without a clinically discernible organic, systemic, or iatrogenic cause.

As in our study, maximum participants belongs to middle age group (30-35 years), indicates ovulatory dysfunction is common mostly in middle age group (Table 1). So, the conventional treatment option like hysterectomy might not be suitable for these patients.

In our study, we observed the flow rate is more than 10 days for most of the participants (Table 2) indicating towards the altered hemodynamic status of the patients suffering from AUB-O. This might be due to increase in demand of red cells resulting into alteration of the homeostatic mechanisms of the body, which may precipitate if hormonal mechanisms are not providing the required optimal feedback.

We also observed the presentations of complaints of our participants are almost within 6 months which shows the awareness of the disease in society (Table 4).

We also found that almost all participants showed improvement after receiving treatment with Ormeloxifene after 6 months of usage, resulting in increase in

hemoglobin concentration (9.13 to 10.21), decrease in PBAC score (259.21 to 69.13), decrease in TVS-ET score (11.57 to 6.23), whereas the side effects like hypomenorrhea, amenorrhea, headache, etc. were almost negligible in most of the participants.

Annu M et al (2008) in their study found that Ormeloxifene significantly reduced endometrial thickness. [58] We also observed similar findings in our study.

Neha Agarwal.et.al. (2013) in their study found Ormeloxifene effective, quick-acting and, promising option for medical management of AUB-O. They also found the drug protective against endometrium carcinoma. [63] Our study supports these findings.

A study by Nandhini G. M., (2022) also corroborate our findings, showing that ormeloxifene improves haemoglobin, the pictorial blood loss assessment chart score, and endometrial thickness. [60]

Dhananjay BS et al (2012) found Ormeloxifene effective in increase in the hemoglobin concentration and decrease in the endometrial thickness in AUB-O patients. These findings are also similar with our results of present study. [61]

These results of Ormeloxifene therapy state toward the efficacy and potency of the drug in management of AUB-O.

So, Ormeloxifene can be an effective alternative in management of AUB-O in patients of middle age group where conventional treatment cannot be a choice.

TABLE 15: PBAC SCORE COMPARISON WITH OTHER STUDIES

PBAC SCORE	**PRETREATMENT**	**3 MONTHS**	**6 MONTHS**	**P VALUE**
Kanchan Nisha et.al (2019)	280	65	32	<0.001
Archana Kumari et.al (2018)	265	83	27	<0.001
Nandini G.M, et.al (2022)	206	100	81	<0.001
Nandini G.M, et.al (2022)	206	94	77	<0.001
Our study	259	113	69	<0.001

The substantial p value in Table.15 comparison of PBAC scores with various studies indicates that our analysis validates the studies mentioned before.

TABLE16: ENDOMETRIAL THICKNESS COMPARSION WITH OTHER STUDIES

ENDOMETRIAL THICKNESS(MM)	**PRETREATMENT**	**POSTTREATMENT**	**P value**
Kanchan Nisha et.al (2019)	10.14	7.35	<0.001
Archana Kumari et.al(2018)	11.81	7.63	<0.001
Nandini G.M, et.al (2022)	10.9	9.0	<0.001
Nandini G.M, et.al (2022)	11	8.9	<0.001
Our study	11.5	6.2	<0.001

Our analysis validates the aforementioned findings, which are supported by Table.16 comparison of Endometrial thickness with results from various studies that reveals a significant p value.

TABLE 17: HEMOGLOBIN LEVELS COMPARISON WITH OTHER STUDIES

HB LEVELS (gm/dl)	**PRETREATMENT**	**POSTTREATMENT**	**P value**
Kanchan Nisha et.al (2019)	8.6	11.8	<0.001
Archana Kumari et.al (2018)	9.15	10.36	<0.001
Nandini G.M, et.al (2022)	8.4	9.9	<0.001
Kanimozhi et.al (2017)	8.5	9.9	<0.001
Our study	9.1	10.2	<0.001

Our investigation confirms the studies mentioned above because Table.17 comparison of HB levels with various studies reveals a significant p value.

CONCLUSION

- Ormeloxifene, a drug having efficacy and potency to reduce the heavy menstrual bleeding significantly in patients with AUB-O, can be a drug of choice for the perimenopausal women specifically suffering from predisposed anaemia and other associated diseases.
- Ormeloxifene clearly has an advantage over other treatment alternatives like progesterones, combined oral contraceptive tablets, etc. in the pharmacological management due to its outstanding safety profile, simple dose schedule, and demonstrated efficacy in the treatment of AUB-O.
- This can reduce the burden of surgery in the patients suffering from AUB-O.
- Ormeloxifene can be used in patients who are suffering from AUB-O as it is having negligible side effects.

SUMMARY

- The study was conducted in Department of Obstetrics and Gynecology of Shri B M Patil medical college.
- It is a longitudinal study conducted on 52 patients aged 30-55 years, presenting with heavy menstrual bleeding were enrolled.
- All the participants were subjected for complete menstrual history, medical history, clinical examination, laboratory evaluation done and transvaginal ultrasound.
- Patients with Pelvic pathologies, liver dysfunctions or who are in use of IUCDs or oral contraceptives, were excluded from the study.
- Before starting therapy the patients were instructed on how to perform PBAC grading based on the quantity and size of clots that have passed,as well as the extent of sanitary napkin soiling.
- An 80ml menstrual blood loss is equivalent to a PBAC score of 100,which is used to diagnose heavy menstrual bleeding.
- All cases received Ormeloxifene 60mg twice weekly for the first 12 weeks, followed by once weekly for next 12 weeks.
- The participants were followed every three months and six months for subjective and objective improvement in menstrual blood loss by measuring PBAC score, endometrial thickness, hemoglobin concentration.

- The data obtained was entered in a MS excel sheet and Statistical analysis was performed by using Social Sciences software version 20.
- The study showed 50 out of 52 study participants had improvement after using Ormeloxifene for 6 months and the side effects was found negligible.
- There was improvement in hemoglobin concentration, PABC score, TVS-ET score in all the participants. It results in a notable increase in haemoglobin concentration and a notable decrease in endometrial thickness with very little adverse effects.
- Ormeloxifene, a drug having efficacy and potency to reduce the heavy menstrual bleeding significantly in patients with AUB-O, can be considered as alternative management for AUB-O.

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ANNEXURE-I

B.L.D.E. (DEEMED TO BE UNIVERSITY) IEC/no.09/202 Date-22/01/2021

(Declared vide notification No. F.9-37/2007-U.3 (A) Dated. 29-2-2008 of the MHRD, Government of India under Section 3 of the UGC Act, 1956)

The Constituent College

SHRI. B. M. PATIL MEDICAL COLLEGE, HOSPITAL AND RESEARCH CENTRE

INSTITUTIONAL ETHICAL CLEARANCE CERTIFICATE

The Institutional ethical committee of this college met on 11-01-2021 at 11-00 am to scrutinize the synopsis of Postgraduate students of this college from Ethical Clearance point of view. After scrutiny the following original/corrected and revised version synopsis of the Thesis has been accorded Ethical Clearance

Title: A study on ormeloxifene in management of abnormal uterine bleeding.

Name of PG student: Dr Karumuri Priyanka
Department of Obst/Gynaec

Name of Guide/Co-investigator: Dr Shailaja.R.Bidri, Professor of Obst/Gynaec

DR .S.V.PATIL
CHAIRMAN, IEC
Institutional Ethical Committee
B L D E (Deemed to be University)
Shri B.M. Patil Medical College,
VIJAYAPUR-586103 (Karnataka)

Following documents were placed before Ethical Committee for Scrutinization:

1. Copy of Synopsis / Research project
2. Copy of informed consent form
3. Any other relevant documents.

ANNEXURE-II

PROFORMA

A STUDY ON ORMELOXIFENE IN MANAGEMENT OF ABNORMAL UTERINE BLEEDING

NAME:
AGE:
IN PATIENT NUMBER (I.P No.):
DATE OF ADMISSION:
ADDRESS AND PHONE NUMBER:
SIGNS AND SYMPTOMS:
L.M. P(LAST MENSTRUAL PERIOD):
MENSTRUAL HISTORY:
MENARCHE:
MARITAL HISTORY:
PREVIOUS TREATMENT TAKEN:
RELATED DRUG HISTORY:
OBSTETRIC HISTORY:
PAST HISTORY:
PERSONAL HISTORY:
GENERAL PHYSICAL EXAMINATION:
PALLOR:
TEMPERATURE: PULSE:
BLOOD PRESSURE:
CARDIOVASCULAR SYSTEM:
RESPIRATORY SYSTEM:
PER ABDOMEN:
INVESTIGATIONS:
COMPLETE BLOOD COUNT
Hb-
Platelet count-
Total leucocyte count-
CT-
BT-
TRANSVAGINAL SCAN
Endometrial thickness-
TSH -
T_3-
T_4-
OUTCOME AT 12 WEEKS
No. Of Pads per day:
Endometrial Thickness:
Haemoglobin level:
OUTCOME AT 24 WEEKS
No. Of Pads per day:
Endometrial Thickness:
Haemoglobin level:

ANNEXURE-III

INFORMED CONSENT FOR PARTICIPATION IN DISSERTATION/RESEARCH

I, the undersigned,_____ , S/O D/O W/O _____, aged ___years, ordinarily resident of _____ do hereby state/declare that Dr _____ of _____ Hospital has examined me thoroughly on _____ at _____ (place) and it has been explained to me in my own language that I am suffering from _____ disease (condition) and this disease/condition mimic following diseases . Further Doctor informed me that he/she is conducting dissertation/research titled _____ under the guidance of Dr _____requesting my participation in the study.

Doctor has also informed me that during conduct of this procedure adverse result may be encountered. Among the above complications most of them are treatable but are not anticipated hence there is chance of aggravation of my condition and in rare circumstances it may prove fatal in spite of anticipated diagnosis and best treatment made available. Further Doctor has informed me that my participation in this study will help in evaluation of the results of the study which is useful reference to treatment of other similar cases in near future, and also I may be benefited in getting relieved of suffering or cure of the disease I am suffering.

The Doctor has also informed me that information given by me, observations made/ photographs/ video graphs taken upon me by the investigator will be kept secret and not assessed by the person other than me or my legal hirer except for academic purposes.

The Doctor did inform me that though my participation is purely voluntary, based on information given by me, I can ask any clarification during the course of treatment / study related to diagnosis, procedure of treatment, result of treatment or prognosis. At the same time I have been informed that I can withdraw from my participation in this study at any time if I want or the investigator can terminate me from the study at any time from the study but not the procedure of treatment and follow-up unless I request to be discharged.

After understanding the nature of dissertation or research, diagnosis made, mode of treatment, I the undersigned Shri/Smt _____ under my full conscious state of mind agree to participate in the said research/dissertation.

Signature of Patient:

Signature of Doctor:

Witness: 1.

2.

Date:

Place:

ANNEXURE-IV

MASTER CHART

Sl No.	NAME	AGE (Years)	Parity	Number of days of flow	Cycle length (Days)	Duration of SYMPTOMS	PREVIOUS TREATMENT TAKEN	PALLOR	PULSE (beats/min)	BP (mmHg)	Platelet Count (lakh cells/cu. mm)	TC (cells/cu. mm)	TSH (mg/dl)	PABC Score 0 month	PABC Score 3 month	PABC Score 6 month	HB 0 month (gm/dl)	HB 3 month (gm/dl)	HB 6 month (gm/dl)	TVS-ET 0 month	TVS-ET 3 month	TVS-ET 6 month	Duration of Treatment (months)	Improvement	Side Effect Amenorrhoea	Side Effect Hypomenorrhoea	side effect headache
1	MALLAMA	40	2	12	20	24	NO	PRESENT	86	110/70	1.8	9.84	2.15	360	130	80	9.5	10.8	11.6	12	10	8	6	yes	no	no	no
2	SHEELA	39	2	14	20	2	NO	ABSENT	78	110/70	2.3	11.08	1.2	280	110	70	11	11.5	12	14	12	9.8	6	yes	no	no	no
3	KASTURIBAI	34	4	7	25	18	NO	ABSENT	78	120/70	1.5	6.74	2.01	185	105	95	10.7	12	12.5	13	10	8	6	yes	no	no	no
4	GANGABAI	45	4	12	28	1	NO	ABSENT	84	130/80	1.8	11.24	1.08	480	110	60	10	10.5	10.7	10	9	7	6	yes	no	no	no
5	MAHADEVI	35	3	8	28	3	NO	PRESENT	92	120/74	2.82	6.17	2.4	320	90	75	9.6	10.3	11	12	9	8	6	yes	no	no	no
6	PARVIN BANU	35	2	20	60	1	NO	PRESENT	102	130/80	1.86	6.84	1.6	250	100	60	8.9	9.5	10	9	8	6	6	yes	no	no	no
7	KASTURI RATHOD	30	2	5	20	5	YES	ABSENT	88	110/70	1.7	8.24	1.54	280	110	75	11.4	12	12.3	9	8.4	7	6	yes	no	no	no
8	KAVERI BADIGER	45	3	15	25	2	NO	PRESENT	94	130/80	1.2	6.48	1.1	340	150	90	9.4	9.6	10	10	9.8	9	6	yes	no	no	no
9	AMBIKA	50	3	10	28	12	YES	ABSENT	82	120/70	2.44	7.63	3.4	270	120	70	10.2	10.4	11	10	8	5	6	yes	no	no	no
10	YALLAWA	40	3	6	20	6	NO	PRESENT	104	110/70	2.86	5.47	2.4	210	100	65	8.6	9.9	11	12	9	7	6	yes	no	no	no
11	SHASHIKALA	40	3	15	20	2	NO	ABSENT	84	100/70	1.7	8.43	2.7	180	110	80	10.8	11	11.4	13	10	6	6	yes	no	no	no
12	PADMAVATI	37	5	5	15	1	NO	ABSENT	76	124/70	3.17	8.8	1.6	230	140	95	12.4	12.5	12.7	9.8	8	6	6	yes	no	no	no
13	VAISHALI	37	3	10	20	20	NO	PRESENT	86	110/70	1.8	6.48	1.5	210	120	90	9.7	10	10.5	9	7	5	6	yes	no	no	yes
14	CHANAMMA	46	6	8	25	3	NO	PRESENT	104	90/70	2.76	7.84	1.7	250	135	75	7.8	9.9	10.4	14	9	7	6	yes	no	no	no
15	BHAGIRATI	47	2	15	20	2	NO	PRESENT	100	100/70	1.6	6.48	1.2	280	115	60	9.4	9.8	10.5	16	10	8	6	yes	no	no	no
16	SHABANA	30	2	6	15	3	NO	ABSENT	68	100/70	2.11	5.66	1.3	310	110	50	10.6	10.8	11	8.5	6	5	6	yes	no	no	no
17	SAVITRI	32	2	10	25	3	YES	present	98	110/80	1.8	6.48	1.5	380	140	80	8.4	9	10	14	10	6	6	yes	no	no	yes
18	SUJATA	45	4	7	20	3	NO	ABSENT	78	130/80	1.6	7.89	1.4	260	125	55	9.6	10	10.5	10.5	8	6.5	6	yes	no	no	no
19	SUNAANDA	30	2	12	25	12	NO	PRESENT	88	100/60	1.9	6.48	1.2	350	145	85	8	9	10.2	10	8	7	6	yes	no	no	no
20	RAJASRI	48	2	4	20	2	NO	PRESENT	96	100/70	2.4	9.8	1.6	400	330	0	7	8.5	0	17	12	0	4	no	no	no	yes
21	DANAMMA	30	3	15	30	1	NO	PRESENT	88	100/70	2	8.46	2.1	275	155	60	9.4	10	11	12	8	6	6	yes	no	no	no
22	SARASWATI	40	3	12	28	8	NO	PRESENT	106	90/70	1.8	9.64	1.4	265	135	75	7	8.8	11.4	14	9	7	6	yes	no	no	no
23	BOURAMMA	46	4	9	45	6	NO	PRESENT	90	100/80	1.4	9.64	1.7	380	125	80	9.6	10	10.5	10	8	6	6	yes	no	no	no
24	VIDYASHREE	30	2	10	28	3	NO	PRESENT	82	100/60	1.8	8.26	1.4	300	115	95	9.4	9.8	10.2	13	9	5	6	yes	no	no	no
25	JAYASHRI	32	4	15	30	4	NO	ABSENT	78	110/70	2.2	7.82	1.6	310	100	60	9.9	10.2	10.5	15	10	8	6	yes	no	no	no
26	VIJAYLAXMI	33	2	6	20	4	NO	PRESENT	70	90/70	1.7	6.46	1.4	250	95	60	8.2	9	9.6	9	7	5	6	yes	no	no	yes
27	SWETA	38	3	8	30	3	NO	ABSENT	82	160/70	1.84	5.46	1.8	190	80	50	9.5	10	10.2	11	9.6	7.8	6	yes	no	no	no
28	SAVITRI	45	2	8	28	5	NO	PRESENT	94	100/60	1.4	6.42	1.5	270	125	80	7.2	9	10	16	8	6	6	yes	no	no	yes
29	JYOTHI	30	2	4	20	12	YES	PRESENT	74	100/60	1.8	7.65	1.8	290	115	70	7.8	8.6	9.4	14	9	7	6	yes	no	no	no
30	POOJA	32	3	4	25	4	NO	PRESENT	98	100/70	1.6	3.84	2.1	200	105	65	7.4	9.3	10	12	9	7	6	yes	no	no	no
31	LAXMI	37	2	7	25	2	NO	ABSENT	88	100/70	1.84	8.76	2.4	240	125	90	9.6	10	10.4	9.8	7	6	6	yes	no	no	no
32	BHAGYA	30	2	24	30	4	NO	PRESENT	102	100/60	2.4	9.8	3.4	290	90	65	8.2	9.4	10	14	9	6.7	6	yes	no	no	no
33	SEJAL	34	3	12	30	3	NO	ABSENT	84	100/70	3.1	8.64	2.6	170	95	60	9.9	10.5	10.9	9	7	5	6	yes	no	no	no
34	SHILARANI	30	2	8	20	3	NO	ABSENT	78	100/70	1.9	8.48	2.4	300	95	75	8.4	10	10.5	11	9	8.4	6	yes	no	no	yes
35	RAJASHREE	34	2	15	28	2	NO	PRESENT	88	100/60	1.8	7.82	2.1	250	110	70	9.6	10	10.4	13	10	7	6	yes	no	no	no
36	VARSHA	36	3	15	30	1	NO	PRESENT	84	100/70	2.8	9.64	2.6	275	105	80	9.4	10.8	11	12	9	7.8	6	yes	no	no	yes
37	KEERTI PATIL	32	2	6	20	4	NO	PRESENT	88	100/70	2.4	9.68	2.4	156	104	66	8.1	9.4	10	10	8.6	6	6	yes	no	no	yes
38	POOJA PATIL	34	3	6	20	3	NO	PRESENT	80	110/70	3.4	8.42	2.1	174	110	86	9.6	10.1	10.8	13	10	7.4	6	yes	no	no	no
39	KAMALA	35	2	20	30	1	NO	PRESENT	86	100/70	1.6	8.64	1.6	204	102	68	8.8	9.4	10	9	7.4	5	6	yes	no	no	no
40	SANGEETA	42	4	15	28	4	NO	PRESENT	74	110/70	1.8	9.48	2.1	402	0	0	7.2	0	0	15	0	0	2	no	no	no	yes
41	ROOPA	30	3	15	30	2	NO	PRESENT	88	100/70	1.8	7.46	1.2	152	88	60	9.4	10.2	10.6	9	8.5	6	6	yes	no	yes	no
42	DEEPA	32	2	10	28	3	NO	PRESENT	76	110/70	1.8	7.46	1.8	215	123	56	9.2	10	10.7	8	7.4	5	6	yes	no	yes	no
43	SHASHIKALA	30	3	6	28	2	NO	ABSENT	74	120/70	2.1	9.66	2.5	176	112	84	10	10.5	10.7	8	7.1	5	6	yes	no	no	no
44	MAHADEVI	40	5	7	30	3	NO	PRESENT	96	100/60	1.6	8.46	3.1	394	116	70	8	10	10.4	16	10	6	6	yes	no	no	no
45	RAJESWARI	36	1	6	20	12	NO	PRESENT	94	100/70	3.1	11.4	1.6	174	92	55	8.4	9	9.7	8	6	5	6	yes	no	no	no
46	SHOBHA	37	4	7	28	2	NO	PRESENT	84	120/70	1.6	8.46	1.9	238	124	68	9.8	10.4	10.7	11	7	5	6	yes	no	no	no
47	KAMALABAI	46	3	5	26	12	NO	PRESENT	88	110/70	2.4	8.46	1.6	210	90	74	7.2	8.9	10	14	7.8	6	6	yes	no	no	no
48	JYOTHI	35	2	6	28	1	NO	PRESENT	104	116/70	2.7	3.84	2.06	218	85	83	8.6	9.4	10	10	8.7	6.4	6	yes	no	no	no
49	HUSENBI	45	3	8	20	3	NO	ABSENT	78	120/80	2.4	8.64	1.5	170	132	90	9.9	10.2	10.7	9	7.4	6.2	6	yes	no	no	no
50	SWEETY	37	3	4	15	3	NO	PRESENT	82	110/70	2.3	10.6	2.6	154	84	76	9.2	10.1	10.6	10	8.2	5	6	yes	no	no	no
51	SHAKUNTALA	45	2	6	25	3	NO	PRESENT	94	110/70	2.7	7.64	3.1	190	92	60	8.2	9.8	10.2	11	7.4	6	6	yes	no	no	no
52	RENUKA	36	4	8	28	2	NO	ABSENT	78	120/80	3.1	7.84	2.7	172	88	54	9.8	10	10.6	13	8	7	6	yes	no	no	no

ANNEXURE-V

Similarity Check Certificate

20BMOBG006-PRIYANKA-Abnormal uterine bleeding

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