"TO COMPARE THE EFFICACY OF ORMELOXIFENE V/S CYCLICAL PROGESTERONE IN THE TREATMENT OF DYSFUNCTIONAL UTERINE BLEEDING IN PREMENOPAUSAL WOMEN – A ONE YEAR RANDOMIZED CONTROLLED TRIAL"

By

Dr. MEKHALA DWARAKANATH B.

DISSERTATION

SUBMITTED TO

KLE UNIVERSITY , BELGAUM

KARNATAKA

IN PARTIAL FULFILLMENT

OF THE REQUIREMENTS FOR THE DEGREE OF

MASTER OF SURGERY

IN

OBSTETRICS AND GYNAECOLOGY

Under the Guidance of

Dr. J. C. Shravage MD, DGO, FICOG
Professor

DEPARTMENT OF OBSTETRICS AND GYNAECOLOGY,

JAWAHARLAL NEHRU MEDICAL COLLEGE,

BELGAUM – 10, KARNATAKA

MAY - 2010

KLE UNIVERSITY BELGAUM, KARNATAKA

DECLARATION BY THE CANDIDATE

I hereby declare that this dissertation entitled **"TO COMPARE THE EFFICACY OF ORMELOXIFENE V/S CYCLICAL PROGESTERONE IN THE TREATMENT OF DYSFUNCTIONAL UTERINE BLEEDING IN PREMENOPAUSAL WOMEN – A ONE YEAR RANDOMIZED CONTROLLED TRIAL"** *is a bonafide and genuine research work carried out by me under the Guidance of* **Dr. J. C. Shravage** *Professor, Department of Obstetrics & Gynaecology, Jawaharlal Nehru Medical College, Nehru Nagar, Belgaum-590010.*

Date :

Place : Belgaum

Dr. Mekhala Dwarakanath B.

KLE UNIVERSITY, BELGAUM, KARNATAKA

CERTIFICATE BY THE GUIDE

This is to certify that the dissertation entitled **"TO COMPARE THE EFFICACY OF ORMELOXIFENE V/S CYCLICAL PROGESTERONE IN THE TREATMENT OF DYSFUNCTIONAL UTERINE BLEEDING IN PREMENOPAUSAL WOMEN – A ONE YEAR RANDOMIZED CONTROLLED TRIAL"** *is a bonafide research work done by* **Dr. Mekhala Dwarakanath B.** *in partial fulfillment of the requirement for* the award of the degree of **M.S. (Obstetrics and Gynaecology)**, *examination to be held in May 2010.*

Guide
Dr. J. C. Sharvage MD, DGO, FICOG.
Professor,
Department of Obstetrics & Gynaecology
J. N. Medical College, Belgaum

Date :
Place : Belgaum

KLE UNIVERSITY, BELGAUM, KARNATAKA

ENDORSEMENT BY THE HOD, PRINCIPAL/HEAD OF THE INSTITUTION

This is to certify that the dissertation entitled **"TO COMPARE THE EFFICACY OF ORMELOXIFENE V/S CYCLICAL PROGESTERONE IN THE TREATMENT OF DYSFUNCTIONAL UTERINE BLEEDING IN PREMENOPAUSAL WOMEN – A ONE YEAR RANDOMIZED CONTROLLED TRIAL"** *is a bonafide research work done by* **Dr. Mekhala Dwarakanath B.** *under the Guidance of* **Dr. J. C. Shravage** *Professor, Department of Obstetrics & Gynaecology, Jawaharlal Nehru Medical College, Nehru Nagar, Belgaum-590010.*

Seal & Signature of the
HOD

Seal & Signature of the
Principal

Dr. B. R. Desai **M.D.**
Professor & Head,
Department of Obstetrics & Gynaecology
J. N. Medical College,
Nehru Nagar, Belgaum-590010.

Date :
Place : BELGAUM

Dr. V. D. Patil **M.D. D.C.H**
Principal,
J. N. Medical College,
Nehru Nagar, Belgaum-590010.

Date :
Place : BELGAUM

KLE UNIVERSITY, BELGAUM, KARNATAKA

COPYRIGHT

Declaration by the Candidate

I hereby declare that the KLE University, Belgaum, Karnataka shall have the rights to preserve, use and disseminate this dissertation in print or electronic format for academic / research purpose.

Signature of Candidate

Date :
Place : Belgaum

Dr. Mekhala Dwarakanath B.

ACKNOWLEDGEMENTS

No dissertation can be completed without the help of many individuals. Hence thanks and gratitude are owed to them all for their help in various ways in completion of this work.

First and foremost, I would like to thank **Dr. J. C. Shravage** M.D., DGO, FICOG Professor, Department of Obstetrics and Gynaecology who being my guide helped me in every step of the study. It was because of her support, guidance and constant encouragement that I was able to carry out the dissertation efficiently. It was her sound advise, which helped me overcome the technical as well as practical difficulties which I encountered during the study. I am indebted to her for the pains taken by her for helping me to complete this study efficiently.

I wish to express my gratitude and sincere thanks to **Dr B.R Desai**, Professor and Head, Department of Obstetrics and Gynecology, J. N. Medical College, Belgaum for his valuable advice, constant encouragement throughout my post graduate career.

My gratitude and thanks to my beloved teachers Professor **Dr. B. R. Nilgar MD,** Professor **Dr. M. K. Swamy MD,** Professor, **Dr. M. B. Bellad MD,** Professor, **Dr.(Mrs)Kamal. P. Patil MD,** Professor, **Dr. Anita Dalal MD**, Associate Professor, **Dr. Yeshita Pujar MD**, Associate Prof, **Dr. Hema A. Dhumale MD,** Associate Professor, Dr**. M. C. Metgud, MD,** Associate Professor, **Dr. (Mrs.) Bhavana Sherigar MD,** Associate Professor**, Dr. (Mrs.) Geeta Durdi, MD,** Associate Professor**,, Dr. Sheetal J**, Assistant Prof, **Dr Pramila K.** Assistant Professor **Dr. Hema Patil,** Assistant Professor, **Dr. Uma T.,** Assistant Professor, Department of Obstetrics and Gynecology for their invaluable suggestions and support throughout the study.

I am also very grateful to **Dr. V. D. Patil,** Principal, J. N. Medical College, Belgaum, for his support and permission to undertake this study.

I would like to extend my heartfelt gratitude to **Dr. Saudagar** and all his staff of Kinaye PHC without whose co-operation it would not have been possible to conduct this study.

I am also thankful to Professor, **R. H. Dhareshwar** $_{\text{MSc,MPhil}}$ Statistician for statistical analysis.

I would like to acknowledge the tireless and timely work of **Mr. Mahesh** of **Malta Computers**, for his excellent data processing and completion of this manuscript.

I wish to offer my thanks to Department of Medical Education for their valuable information and support.

Most importantly I thank the backbone of this study "**Women**" for their co-operation and willing participation in the study

No amount of words can measure up to the deep sense of gratitude and thankfulness that I feel towards my in-laws, my uncles Sri V. R. Gourishankar and Sri B. S. Somanath and my other family members for their cherished blessings and support.

I am immensely thankful for my husband **Dr. Venkatesh Prasanna** for his continuous moral support extended with love and co-operation and son **Skanda** for never being a demanding child and giving me loads of energy with his angel like smile.

I offer my sincere thanks to all my friends Dr. Manu, Dr. Arveen, Dr. Soumya, Dr.Shrividya, Dr. Sameena, Dr. Chandara, Dr. Amit Galgali, Dr. Sudhakarbabu and other post graduate colleagues for their companionship and support.

I am extremely thankful to the staff of Paid Labour Room and Gynecology OPD for all the help and co-operation they have offered to me.

I owe everything in particular to my Father, Mother and Brother whose inspiration, encouragement, support and countless sacrifices are behind whatever I have achieved in my life.

Last but not the least, I express my ever lasting gratitude to His Holiness Sri Sri Bharathitheertha Maha Swamiji of Sri Shringeri Peetham and to the Almighty God for protecting me and showing me the right path through this gratifying task.

Dr. Mekhala D.

ABBREVIATIONS

b-FGF	: Basic Fibroblast Growth Factors
COCs	: Combined Oral Contraceptive Pills
D&C	: Dilatation and Curettage
DUB	: Dysfunctional Uterine Bleeding
eGLs	: Endometrial Granulated Lymphocytes
ER	: Oesterogen Receptor
ET	: Endometrial Thickness
FSH	: Follicle stimulating hormone
GnRH	: Gonadotropin-releasing hormone
HML	: Heavy Menstrual Loss
HRE	: Hormone Responsive Elements
LH	: Luteinizing hormone
LNG IUS	: Levonorgestrol Intra uterine system
MB	: Menstrual Bleeding
MBL	: Menstrual Bleeding Loss
MMPs	: Matrix Metalloproteinases secretion
MPA	: Medroxy Progesterone Acetate
NSAIDs	: Non-steroidal Anti-inflammatory Drugs
PBAC	: Pictorial Blood Assessment Chart
PR	: Progesterone Receptor
RCTs	: Randomized Controlled Trails
SERM	: Selective Estrogen Receptor Modulators
VEGF	: Vascular Endothelial Growth Factors

ABSTRACT

TITLE: TO COMPARE THE EFFICACY OF ORMELOXIFENE V/S CYCLICAL PROGESTERONE IN THE TREATMENT OF DYSFUNCTIONAL UTERINE BLEEDING IN PREMENOPAUSAL WOMEN – A ONE YEAR RANDOMIZED CONTROLLED TRIAL.

OBJECTIVE :.

Primary objective

To determine the efficacy of Ormeloxifene against Cyclical Progesterone in reducing blood loss in DUB as assessed by Pictorial Blood Assessment Chart (PBAC) score

Secondary objective

To compare endometrial thickness and haemoglobin percentage after treatment in the group receiving Ormeloxifene with the group receiving Cyclical Progesterone

Material and methodology

This double blinded randomized control trial was carried out on patients attending gynecology OPD of KLES Dr. Pabhakar Kore Hospital, Belgaum. 84 women with DUB aged between 35-50 years were enrolled. Exclusion criteria were presence of any pelvic pathology, systemic disorders, previous history of thrombosis, cervicitis, Hb% < 6.5 g% and endometrial thickness > 12 mm. Menorrhagia was defined as PBAC score of more than 100.

2 groups were identified as group A and group B for the convenience for administering drugs and all drugs were given in capsular form. The progesterone used in this study was Tab. Medroxy Progesterone Acetate.

Patients enrolled in Group A received Cap Ormeloxifene 60 mg 2 days a weeks with a minimum gap of 3 days and placebo form of Medroxy Progesterone Acetate in a capsular form for 21 days for 3 months starting from D-2 to D-5 of cycle.

Likewise patients enrolled in group B received Cap. Medroxy Progesterone Acetate 10 mg for 21 days and placebo from of Ormeloxifene in capsular form for 2 days a week with a minimum gap of 3 day for 3 months starting from D-2 to D-5 of cycle.

Double blinding was ensured by sending these labeled drug packets each containing medication for 3 months to the department of Clinical Pharmacy, KLE College of Pharmacy, Belgaum where they were numbered according to the randomization plan and returned after removing labels.

All patients used sanitary napkins of a similar kind. Monthly PBAC score were calculated.

At the end of the study mean PBAC score, Hb% and Endometrial thickness (by TVS) were compared in the 2 groups. Randomization plan was decoded after completion of the study.

Results

The mean pretreatment PBAC score in Group A and Group B were 262.26 and 238.71 respectively.

Effectively, 85.71% of patients were relieved of menorrhagia with 90% reduction in the passage of clots in subjects receiving ormeloxifene and 54.76% of patients were relieved of menorrhagia with 60% reduction in passage of clots in the group receiving cyclical

progesterone. There was a significant reduction in menstrual blood loss as assessed by PBAC score in group receiving ormeloxifene (mean PBAC – 73) compared to the group receiving cyclical progesterone acetate (mean PBAC- 108), p value 0.0205

There was a significant reduction in endometrial thickness in the group receiving Ormeloxifene (mean endometrial thickness = 4.94) compared to group receiving Medroxy progesterone acetate (mean endometrial thickness = 5.86), p value = 0.0942.

However there was no statistically significant difference in improvement of Hb% after treatment in the 2 groups.

11.90% of patients receiving Ormeloxifene 35.71% and of patients receiving Medroxy Progesterone Acetate did not respond to treatment.

4 patients, i.e. 9.5% receiving Ormeloxifene had amenorrhoea after 1st month of treatment. No other adverse outcomes were encountered.

Conclusion:

Ormeloxifene is a more efficacious and safe therapeutic option compared to Medroxy progesterone acetate (a commonly used progesterone) in the treatment of dysfunctional uterine bleeding.

Keywords:

Ormeloxifene ; Progesterone, Dysfunctional Uterine Bleeding

TABLE OF CONTENTS

LIST OF TABLES

LIST OF GRAPHS

LIST OF FIGURES

INTRODUCTION

Heavy menstrual bleeding or menorrhagia is a significant health problem in premenopausal women.[1] About 5% of women in the age group of 35-50 years of age seek medical help for heavy menstrual bleeding (HMB) which accounts for 12% of gynaecological referrals. [2,3]

Also, menstrual disorders are the second most common gynaecological condition resulting in hospital referrals.[4]

In today's world where women represent a major sector of paid work force in both the developing and developed countries, any regular source of debility like menorrhagia has important economic and personal consequences. Menorrhagia interferes with a woman's physical, social emotional and / or material quality of life.

Menorrhagia is objectively defined as monthly blood loss of more than 80 ml. Monthly blood loss in excess of 60 ml may result in iron deficiency anaemia.[5]

Any deviation in the normal cyclical menstruation resulting in heavy menstrual blood loss or menorrhagia is termed as Abnormal Uterine Bleeding (AUB).

AUB will be considered to arise from 1 of the 4 broad etiological causes.[5]

1. Pregnancy related etiologies such as abortion, ectopic, and trophoblastic disease.
2. Organic causes
    a. Systemic disease such as Von Willebrand disease, hypothyroidism, renal failure.
    b. Reproductive tract lesions such as myomas, polyps, adenomyosis

3. Iatrogenic causes such as exogenous hormones, non hormonal medications that may alter coagulation pathway and foreign bodies like copper intra uterine device.

4. Once all the above causes are excluded, the remaining causes of AUB can be attributed to what is generally referred to as Dysfunctional Uterine Bleeding (DUB). DUB affects 20-30% of woman and accounts for 12% of gynaecological referrals.[6] It could be anovulatory (90%) or ovulatory (10%)[2]

DUB is defined as `excessively heavy, prolonged or frequent bleeding of uterine origin that is not due to pregnancy or due to recognizable pelvic or systemic disease. This diagnosis is, therefore, one of exclusion and applies to 40-60% of cases of AUB.[2]

Ovulatory DUB occurs due to an abnormality in the paracrine control of endometrial spiral arteries which is indirectly influenced by ovarian steroid hormones causing increased Menstrual Blood Loss (MBL).

Anovulatory DUB occurs due to disturbances of the hypothalmo-pituitary ovarian axis with acyclic oestrogen production resulting in increased menstrual blood loss (MBL).

DUB can affect women from adolescence to perimenopausal years.

Patterns of DUB [7]

Patterns of presentation of Dysfunctional Uterine Bleeding

Menstrual	Ovulation	Phase change	Endometrial histology
Polymenorrhoea menorrhagia	Normal	Shortened follicular phase	Normal
Oligomenorrhea menorrhagia	Normal	Long FP	Normal
Premenstrual spotting menorrhogia	Abnormal corpus luteum	Short luteal phase	Deficient secretory endometrium
Prolonged cycles	Persistent corpus luteum	Long luteal phase	Well developed secretory endometrium
Polymenorrhoria metrorrhagia	Anovulation	Short cycle	Deficient proliferative endometrium
Oligomenorrhoea metrophathica hemorrhagica	Anovulation	Prolonged cycle	Proliferative / hyperplastic endometrium

Management options available for DUB

1. Medical Management :

There are variety of approaches to medical management of DUB ranging from hormonal treatment in the form of combined oral contraceptive pill (COCPs), Progestogens (Oral / intramuscular preparation / intra uterine implant system), Danazol and Gonadotropin – Releasing Hormone (GnRH) agonists to non hormonal drugs like

prostaglandin synthetase inhibitors, antifibrinolytics and Non-steroidal Antiinflammatory Drugs (NSAIDs).

Medical treatment needs to be individualized and is not suitable for all ages. It is noticed that the symptoms reappear once the therapy is stopped. It may not be very compliant as it is associated with many of side effects. Hormonal treatment, which is the most widely used (Progestogens or Oestrogen + Progestrone) is associated with side effects, which include fatigue, mood changes, weight gain, nausea, bloating, oedema, headache, depression, loss of libido, irregular bleeding and atherogenic changes in the lipid profile.[7] Cost effectiveness of the available options is questionable.

2. Surgical Treatment

Patients not responding to medical treatment are offered surgical line of treatment

Dilatation and curettage is opted as one the first line of surgical management, though evidence does not support its role in management of DUB. [8]

Minimally invasive surgery such as endometrial ablation or resection is attracting the attention of late in the treatment of DUB. Ablation may be performed with the laser by radiofrequency electrosurgical desiccation, resection or vaporization using a uterine resectoscope or by a number of non resectoscopic techniques including those employing thermal balloons bipolar radiofrequency, cryonics, heated free fluids or microwaves.[9] Ablation is achieved by using ball or barrel – shaped electrodes that coagulate the endometrial surface.[9] Complications associated with these procedures include fluid overload, electrolyte imbalance, uterine perforation, bleeding, and intestinal and urinary tract injury. The patient would have to forego her future fertility. The cost involved in

treatment, requirement of expertise in the field and also probable need of repeat procedure for recurrence of symptoms do not make it an ideal therapy for menorrhagia.[5]

Hysterectomy forms the definite mode of treatment. But it is an invasive procedure which is not suitable at all ages. It is the most expensive modality of treatment and is associated with post operative morbidity.

The social and economic cost of menorrhagia is considerable. 28% of female population consider their menstruation excessive and will plan their social activities around their menstrual cycle and nearly 10% of employed women will take off from work because of excessive menstrual blood loss (MBL).

Over the years, menorrhagia has become an increasingly frequent complaint for 2 main seasons. Firstly, the woman of today experiences more menstrual cycles than her ancestors did due to decrease in lactational amenorrhorea and advent of effective contraception. Secondly, women are increasingly unwilling to accept menstrual difficulties. There has been a rise in expectations owing to increasing intolerance of the inconvenience of menorrhagia. These factors have both led to an increased demand on the health services, and give scope for trial of new regimens in treatment of dysfunctional uterine bleeding.

Though surgical line of treatment, especially endometrial destruction (ablation and resection) and hysterectomy reduces menstrual blood loss at the end one year more than any form of medical treatment except Levenorgestrol Intra Uterine System (LNG – IUS). When deciding about surgical option for Heavy Menstrual Bleeding, more than one

outcome needs to be taken into account. Patient satisfaction, time lost from work, relief of the symptoms, total cost and side effects of surgery are all important factors.

Thus ideally a medical approach should be considered as first line of treatment. Approaches to medical management have been hindered by a lack of understanding of mechanisms causing DUB and by highly variable and non – evidence based prescribing habits. For instance, studies have shown that 50% of gynaecologists prefer to use luteal phase progestrogens in the treatment heavy menstrual bleeding as a 1st line of treatment though evidence states that it is an effective form of treatment only when given for 21 days starting early in the follicular phase.[10]

Various mechanisms of DUB have brought to the understanding that despite normal levels of circulating ovarian steroids, the action of oestrogen and progesterone at an endometrial level could be altered even in ovulatory DUB. Levels of endometrial oestrogen receptors (ER) and progesterone receptors (PR) are higher in the late secretory phase in women with ovulatory DUB compared with women with normal menstrual loss.[2] This is particularly marked for ER implying that an increased local oestrogen effect could be present in premenstrual endometrium leading to increased flow. As regards with anovulatory DUB it is a well known fact that excessive bleeding occurs from a hyperplastic endometrium exposed to a unopposed excessive oestrogen.[2]

Thus the ideal therapy for DUB should be a designer drug which can block the action of estrogen on the endometrium but not its beneficial actions on the other tissues. Selective Esterogen Receptor Modulators (SERMs) are one such class of a drugs which has both agonistic and antagonistic actions on estrogen receptors designed to act in

specific ways at each of the oestrogen receptor sites in different tissues.

Ormeloxifene is an optimally designed SERM with varied tissue response which behaves as an oestrogen antagonist in uterus and breast, being mildly oestrogenic on vagina, bone mineral density, CNS and serum lipids making it the perfect SERM for DUB. [11,12,13]

The current study was undertaken to test the hypothesis that ormeloxifene is superior to cyclical progesterone therapy in the treatment of premenopausal DUB. The progesterone employed in this study was Medroxy Progesterone Acetate.

OBJECTIVES

Primary objective

To determine the efficacy of Ormeloxifene against Cyclical Progesterone Therapy in reducing blood loss in DUB as assessed by PBAC score

Secondary objective

To compare endometrial thickness and hemoglobin percentage after treatment in the group receiving Ormeloxifene with the group receiving Cyclical Progesterone Therapy

REVIEW OF LITERATURE

The earliest reference to the problems of menorrhagia are in the ancient Hindu works dating around 1400 BC. Hippocrates also wrote on the subject and suggested cupping, applied to the breast, as a cure. Soranus of Ephesus (A.D. 98.138) suggested that ligatures be applied to the armpits and groins to reduce blood flow to the uterus. The first of the present day medical treatments was progesterone, first described by Albright in 1938.[14]

In the absence of gross and microscopic pelvic pathology menstrual disorders have been attributed to the hypothalamo pituitary ovarian endometrial axis dysfunction, hence the name dysfunctional uterine bleeding. This term was first coined by Graves.

DUB does not have a regular menstrual pattern. DUB is defined as `excessively heavy, prolonged or frequent bleeding of uterine origin that is not due to pregnancy or due to recognizable pelvic or systemic disease. This diagnosis is, therefore, one of exclusion and applies to 40-60% cases of AUB.[2] DUB could be anovulatory (90%) or ovulatory (10%). [5]

Dysfunctional uterine bleeding is one of the least understood common gynaecological conditions, even though it is responsible for a significant number of referrals to gynaecological clinics. This affects all ages of reproductive life from puberty to menopause, and rarely in post menopausal women.

Ovulatory DUB is predominantly associated with the decreased endometrial vasoconstriction and vascular haemostatic plug formation leading to defective control of

volume of blood which is lost during menstruation. Anovulatory DUB is very poorly understood but may be associated with disturbed angiogenesis, fragile vessels and defective haemostatic processes. [15]

The diagnosis of menorrhagia is also difficult and usually subjectively based on a patient's description of menstrual loss. Although the patient's impression is an important issue when managing menorrhagia, it is unfortunately an inaccurate assessment and there is lack of correlation with actual menstrual blood loss. Haemoglobin determination of menstrual blood, using the alkalie haematin method as described by Hallberg and Nilsson, is the most reliable technique and has been widely used in many studies. However, the method is expensive, time-consuming and inconvenient to the patients, and, as such, is not practical for everyday use in clinical practice.[16]

The pictorial blood assessment chart (PBAC) has been introduced as a simple, non-laboratory method for semi-quantitative measure of menstrual blood loss. Using a score of > 100 as equivalent to a menstrual loss of > 80 ml, the PBAC was shown to have a reasonable accuracy with a sensitivity of 86% and a specificity of 89% compared with the alkalie haematin method.[16,17] Janssen et al. re-validated the chart, but suggested a score of 185 as a cut-off point to maximize its predictive values. However, a score of 185 has a much lower sensitivity and negative predictive value compared to score of 100.[16,18] For all practical purposes a score of 185 is considered as menorrhagia significant enough to cause iron deficiency anemia. However PBAC score for menorrhagia is easy to use and has been the most accepted method of quantifying blood loss in various studies.

The diagnosis of DUB is a diagnosis of exclusion. Clinical history and examination are mandatory to exclude organic causes and to assess the amount of distress caused to the patients as well as to understand the expectation of the patients from treatment. DUB is a positive diagnosis by ultrasound based on the principles of clinical evaluation and sonographic exclusion of pelvic pathology. Persistent non cyclic finding of endometrial thickening of > 11 mm should trigger concern in premenopausal women and such cases should be offered a diagnostic curettage.[19]

A wide range of treatment options are available for DUB which can be broadly classified as medical and surgical lines of treatment.

Medical treatment can be advocated by means of hormonal or non hormonal therapies. Hormonal therapies range from use of Combined Oral Contraceptive pills (COCs), progestogens, (oral or intra muscular or in the form of LNG IUS), Danazol, while non hormonal therapies encompass the use of prostaglandin (PG) synthetase inhibitors, antifibrinolytics and ethamsylate.

Among the available medical therapies, progesterone has stood the test of time and is the most widely used medication in various forms and routes[20,21] till date.

Other drugs like COCs Danazol, GnRH agonists, Nonsteroidal Anti inflammatory Drugs (NSAIDs), Antifibrinolytic and Ethamsylate, though used produce variable results and lack consistency in reproducing same results in all scenarios. Side effects and cost effectiveness of treatment with these drugs limit their use in DUB.

Combined oral contraceptive pills (COCs) are one of the oldest regimens of treatment.

Reduction of MBL with COCs is by inducing endometrial atrophy. Studies state that COC can reduce blood loss, but there are not enough data to determine its value for the treatment of menorrhagia.[22] A randomized controlled trial of women taking 30 mg of ethinyl oestrodiol showed a 43% reduction in MBL compared to baseline.[23]

Use of COC is associated with mood changes, headaches, nausea, fluid retention and breast tenderness. Very rarely it can cause DVT, stroke. [4]

However, there is a paucity of randomized studies relating to the use of progestogens and of oestrogens and progestogens in combination in the treatment of irregular bleeding associated with anovulation.[27]

Danazol is an isoxazol derivative of 17-α ethinyl testosterone. It alters the pulsatile secretion of GnRh, it inhibits the LH and FSH surge and causes abnormal follicular maturation and thus reduces oestrogen production. It renders the endometrium functionally hypoestrogenic and hypoprogestrogenic. It reduces MBL by 80%. Danazol appears to be an effective treatment for heavy menstrual bleeding compared to other medical treatments. The use of Danazol may be limited by its side effects, its acceptability to women and the need for continuing treatment. The paucity of trials, and the small sample sizes of the included trials limit the recommendations for clinical care. Danazol should not be used routinely in the treatment of HMB. [4,8,23,25]

GnRH agonists down regulate pituitary receptors after an initial stimulatory effect and produce hypogonadotrophic hypogonadism. Patients receiving it will become amenorrhoeic within 2- 3 months of treatment. It can only be used as a short term measure because of associated bone demineralization associated with prolonged ovarian suppression. [4,6,8,23]

Prostaglandin synthetase inhibitors i.e. NSAIDs have been shown to be effective in reducing MBL between 20-40%.[4,6,8] It needs to be taken during days 1 -5 of menstrual cycle. NSAIDs reduce HMB when compared with placebo but are less effective than either tranexamic acid, Danazol or LNG IUS. [26]

Antifibrinolytic agents have a beneficial role in the management of menorrhagia as fibrinolytic activity increases during menstruation. Tranexamic acid significantly reduces endometrial tissue plasminogen activator activity and reduces menstrual blood loss in patients with menorrhagia in general, as well as in patients with inherited bleeding disorders. Antifibrinolytic therapy causes a greater reduction in objective measurements of heavy menstrual bleeding when compared to placebo or other medical therapies (Non-steroidal Anti-inflammatory Drugs, oral luteal phase progestogens and ethamsylate). This treatment is not associated with an increase in side effects compared to placebo, NSAIDs, oral luteal phase progestogens or ethamsylate. Flooding and leakage significantly improved after tranexamic acid therapy when compared with oral luteal progestogens but no other measures of quality of life were assessed. No study has used resource cost as an outcome.[4,6,8,27]

Ethamsylate is a non-hormonal agent that is thought to act by increasing capillary vascular wall resistance and platelet adhesiveness in the presence of trauma to the blood vessel lining. The results have been conflicting ranging from no effect to reduction of MBL by 46% from baseline. There is no conclusive evidence of effectiveness of ethamsylate for reducing HMB. [4,6,8,23]

Progestins halt endometrial growth and allow for an organized sloughing of the endometrium. They also increase PGF2α / PGE ratio by stimulating arachidonic acid formation in the endometrium, which may also contribute to decrease abnormal uterine bleeding. Progestins can be administered by 3 routes, oral, intramuscular or in the form of intrauterine implant system.

In the recent time Levonorgestrel intrauterine system is gaining (LNG-IUS) a lot of popularity particularly in the West. Various studies have reported its efficacy in reduction of MBL to the extent of 82-97%.[4,6,8,23,28,29,30] It is also associated with the side effects encountered routinely with progesterone, of which break through bleeding is a common feature. It is the most expensive of all types of medical treatments.

Intramuscular Progestogens have also been tried in the treatment of menorrhagia. A contraceptive depot preparation of medroxy-progesterone acetate will induce amenorrhoea in 50% of users by one year of use. The incidence of irregular or prolonged break through bleeding was found to be 15-20%.[4,6,10,23]

Oral progestogens

It is the oldest of all known treatments. They are the most widely used medical treatment for DUB and the form the main stay of treatment to date.

The drug dosage as well as duration for use will influence the effect on the endometrium and consequent pattern of bleeding.

The endometrial effects and clinical applications of different oral progesterone regimens

Days of menstrual cycle	Endometrial effect	Clinical application
16-25	Secretory transformation	Anovulatory DUB
5-25	Inhibits growth	Ovulatory DUB
Continuous	Endometrial suppression	Ovulatory & anovulatory DUB
Combined with estrogen	Endometrial suppression	Ovulatory & anovulatory DUB

Various studies have illustrated role of progesterone in treatment of DUB.

Evidence states that progesterone administered from D-15 or D-19 to D-26 of the cycle offer no advantage over other medical therapies such as Danazol. Tranexmic acid (TXA), NSAIDs and LNG – IUS in the treatment of ovulatory DUB. Progesterone therapy for 21 days of the cycle results in a significant reduction in MBL and can be used for both ovulatory as well as anovulatory cycles. [4,6,8,10,23]

A study conducted in University of Sydney, where in norethisterone (NET) / Medroxy Progesterone Acetate (MPA) was given from D12-25 in women with anovulatory cycles and D5-25 in women with ovulatory cycles 3 times daily reported an overall reduction in MBL by 51%.[31]

A study conducted in University of Wales quoted that progesterone is the most frequently prescribed drug and reports 50% reduction in women with anovulatory DUB and 33% reduction in women with ovulatory DUB. [8]

Another study conducted in Turkey where 60-120 mg MPA was given in the divided doses reported 25% of reduction in MBL at the end of 3 days. [33]

An RCT done in Turkey states that reduction in MBL in those using oral MPA and i.m. MPA were similar being about 50%, but reduction of MBL in the group using LNG IUS was significantly greater. [34]

An RCT conducted at AIIMS, New Delhi reported reduction of MBL by 57.7% with the use of MPA and recurrence of menorrhagia after 3 months was found to be 50%.[35]

RCTs show overall reduction of 15-50% in MBL with use of cyclical progesterone depending of type of DUB. [36]

Cochrane review states that progestogen therapy for 21 days of the cycle results in significant reduction in MBL. Oral progesterone reduces MBL by 50-52%.[10]

In comparison with various other medical treatments currently available, progesterone is considered as the gold standard drug in medical management of menorrhagia.

Side effects noted are weight gain, bloating, breast tenderness, headache, acne.[4]

Surgical treatment includes Dilatation and curettage, hysterectomy and the recently advocated minimal invasive surgeries. Dilatation and curettage has a proven role in diagnosis. One study to measure the blood loss before and after D&C found a reduction in MBL immediately after the procedure, but MBL returned to previous or

higher level by the end of second menstrual period. D&C is not found to be effective for therapy in women with HMB.[8]

Hysterectomy is the only definitive treatment for DUB.[37] It is a major operation and is associated with significant complications in a minority of cases. Side effects from hysterectomy are common. Wound and urinary tract infections are frequent and ranges from 7- 35%. A mortality rate of up to 1–2 per 1000 is quoted and morbidity of over 40% if all complications are considered.[9]

Cochrane review states that endometrial resection and ablation offers an alternative to hysterectomy as a surgical treatment for heavy menstrual bleeding. Both procedures are effective and satisfaction rates are high. The initial cost of endometrial destruction is significantly lower than hysterectomy but, since re-treatment is often necessary, the cost difference narrows over time.[38]

Major complications of endometrial resection and ablation are

- Perforation of the uterus,
- Intravasation of large volumes of fluid causing pulmonary or cerebral oedema, and requirement of repeat therapy to the extent of 11-40%.

In summary, there are a wide range of treatment options available for a patients presenting with DUB. The available medical treatments reduce MBL by 50-52% except for LNG IUS which causes a reduction in MBL by 80-87%. Evidence states that the 58% of patients receiving medical line of management (except for these who were on LNG IUS) had received surgical therapy by the end of 2 years. [37]

Though surgical therapy appears more promising, more than one outcome needs to be taken into account. Patient satisfaction, time lost from work, relief of other symptoms, total cost and side effects of the surgery are all important factors to be taken into consideration.

Therefore medical therapy is a principle tenet of treatment and surgical options is to be resorted to only when medical therapy fails. [39]

Studies in the recent past have given new insights into the local control of menstruation as well as mechanisms of DUB.

Newer insights in control of menstruation

Apoptosis plays a key role in the haemostatic maintenance of cell numbers. Evidence states that endometrial apoptosis is controlled by hormonally regulated mechanisms. It is observed that progesterone withdrawal stimulates endometrial apoptosis.[40]

Matrix metalloproteinases (MMPs) are a family of neutral pH enzymes, which degrade components of both interstitial and basement membrane extracellular matrix. These are held under inhibitory control by tissue inhibitors of MMPs (TIMPs). Progesterone withdrawal from endometrial cells induces matrix metalloproteinases secretion which is followed by breakdown of cellular membranes and dissolution of extra cellular matrix. TIMPs 1 and 2 are present throughout cycle, while MMPs 1,2,3,9 are detected perimenstually and menstrually. MMP's 1,3,9 are also stimulated by interleukin 9 and tumour necrosis factor α. Thus MMPs have a major role in the processes of endometrial regression and breakdown that are part of menstruation.[41]

Adhesion molecules play a role in the trafficking of white blood cells from the vasculature into the endometrial tissues. They include vascular cell adhesion molecule -1 and E-selectin which are under indirect control of steroid hormones and their receptors.[35]

Human endometrium contains a large population of leucocytes, which typically comprises about 70% endometrial granulated lymphocytes (eGLs), 20% macrophages and 10% lymphocytes. Some endometrial leucocytes that are positive for either leucocyte common antigen or CD3 have been reported as expressing estrogen receptors, indicating that hormonal control may regulate their function. One to two days prior to the onset of menstruation the endometrium is infiltrated by increased numbers of polymorphonuclear leucocytes and granulocytes.[40]

It is becoming increasingly clear that the endometrium expresses a large number of growth factors and cytokines, bearing on effect on the menstruation and that many of these factors are regulated during the menstrual cycle either directly or indirectly by estrogen and progesterone.

Steroid hormones are the systemic factors that drive the endometrium through characteristic sequential phases of menstrual cycle and necessarily act via their cognate receptors. The consequential initiation of gene transcription and cascade of downstream local events is responsible for the key functions of the endometrium. In the absence of sex steroid exposure endometrium is inactive. Sex steroid receptors for oestrogen (Estrogen Receptor α- Estrogen Receptor β), androgen (Andrgen Receptor- AR) and progesterone (Progesterone Receptor - A and Progesterone Receptor -B) are expressed in the epithelial, stromal and vascular cells. Their expression in different endometrial cells varies during different stages of the menstrual cycles.

The Estrogen Receptors [42,43,44]

The oestrogen receptor is a ligand activated transcription factor that mediate the effects of the steroid hormone 17-β oestrodiol in both males and females.

2 types of oesterogen receptors have been identified, ER-α and ER – β. The ER-β is 96% homologous in amino acid sequence with the ER-α in the DNA binding domain and 53% homologous in the hormone – binding domain. The oestrogen receptors are divided into 6 regions labeled A to F and 5 functional domains namely (Fig. 1)

N terminal region or regulatory domain (A/B region) containing Transactivation Factor (TAF -1) which is capable of stimulating transcription in the absence of hormone binding. (In ER-β, TAF-1 is either significantly modified or absent), DNA binding domain (C region) wherein hormone binding induces a conformational change that allows binding to the hormone responsive elements (HRE) in the target gene which in turn regulates the expression of nearby genes, Hinge region (D region) which is important for the movement of the receptor to the nucleus following syntheses in the cytoplasm, Ligand / hormone binding domain (E region) to which hormone binds, which additionally it contains the sites for co-factors binding by heat shock proteins and is responsible for dimerization, and harbours the transcription activation function called TAF-2 which is hormone dependent for activity and lastly the F domain which has a role in modulating the magnitude of gene transcription by oestrogen and antioesrogen. (Fig. 2).

Mechanism of action [43]

Steroid hormone are too hydrophobic and are transported on specific carrier proteins from their point of release to their target tissues. In target cells, these hormones pass through the plasma membrane by simple diffusion and bind to the specific hormone receptors in the nucleus. Steroid hormone receptors with no bound ligand often act to suppress the transcription of target genes. Once the hormone penetrates into the cell it induces dissociation of heat shock protein from the receptors. Hormone binding triggers changes in the confirmation of the receptor. It forms homodimers or heterodimers with other hormone of interacting with specific regulatory sequences in DNA called hormone response elements (HREs). The bound receptor – hormone complex interacts with other proteins which function either as co-activators or co-repressors and regulates transcription of the adjacent genes, increasing or decreasing the rate of mRNA formation. Altered levels of hormone regulated gene product produces the cellular response to the hormones. (Fig 3,4,5)

Differential expression of α and β receptors is likely in various tissues [42]

ER-α	ER-β
Endometrium	Brain
Breast	CVS
Parts of brain	Granulosa cells from ovarian follicle
	Mildly expressed in breast colon and endometrium

The Progesterone receptor [42]

The progesterone receptor is induced by estrogens at the transcriptional level and decreased by progestins at both the transcriptional and translational levels, has two major forms, A and B receptors. (Fig. 6)

The progesterone receptors function in the mechanism shared by this superfamily of receptors: an unbound complex with heat shock proteins, hormone binding, dimerization, DNA binding to a progesterone response element, and modulation of transcription by phosphorylation and various proteins.

Regulation of estrodial and progesterone action is brought about by the following [44]

1. Synergism
2. Co-factors
3. Phosphorylation of the receptor
4. Chromatin structure
5. Tissue specific regulation

Other than the non classical pathways of activation Ligand – independent pathway and Alternative pathway of ER action from a transaffected promoter have been described. (Fig. 7)

MECHANISMS OF DUB

Variations in hormones and their receptor levels, functional disorders of the endometrium and abnormalities of endometrial vasculature, endometrial vasoactive substances, tissue break down, and remodeling and endometrial repair lead to DUB.

Levels of endometrial oestrogen receptors (ER) and progesterone receptors (PR) are higher in the late secretory phase in women with DUB compared with women with normal menstrual loss in both ovulatory and anovulatry DUB. This is particularly marked for ER, implying that an increased local estrogen effect could be present in premenstrual endometrium.[45]

The endometrial patterns in the ovulotary DUB are related to the functional rather than the anatomical changes in the endometrial vasculature are mainly responsible for excessive menstrual bleeding.

The term 'functional disorders of the endometrium' encompasses endometrial abnormalities due to a paucity of oestrogen associated with a failure of normal ovarian follicular development, an excess of oestrogen due to a variety of causes, abnormalities of progesterone secretion following ovulation or an abnormality in the relative proportions of oestrogen and progesterone. There may be delayed secretion or paucity of progesterone secretion and abnormalities of corpus luteum involution associated both with early breakdown of the endometrium or a failure of involution of the corpus luteum associated with irregular. prolonged shedding of the endometrium.[46]

Hypo-estrogenic and hyper-estrogenic states are encounted in anovulatory DUB, while luteal phase insufficiency, irregular ripening and irregular shedding are seen in ovulatory DUB. However there could be superimposed patterns.

The endometrial vasoactive substances namely prostaglandins, endothelins and nitric oxide are under the paracrine control ER and PR. ER influences these factors in such away that they result in excessive bleeding.[2]

Lysosomes and matrix metalloproteinases bring down breakdown of endometrial tissue which is held under inhibitory control by progesterone. In DUB the mismatch in ER to PR ratio resulting in sequencing effect reduces progesterone levels leading to breakdown of endometrium with increased MBL.[2,44]

Macrophages can release platelet activating factors, PGE and potent vasodilators that could augment menstrual blood loss. They may also release free oxygen radicals that directly bring about destruction of endometrium. [2]

Endometrial granulated lymphocytes secretes perforins which can degrade endometrial cellular and vascular structures and promote bleeding. [2]

Interleukin-8 can activate leucocytes in the endometrium.

Production of IL-8 is inhibited by progesterone, and thus sex steroids may act indirectly to control leucocyte changes in the endometrium. [2]

Altered expression or action of adhesion molecules in the endometrium which is thought to be controlled by endocrine and paracrine factors promote influx and aggregation of leucocytes into the endometrium from the circulation. [2]

During repair and regeneration cytokines influence vasoconstriction, haemostatic plug formation and angiogenesis. Secretion of potent growth factors such as vascular endothelial growth factors (VEGF), basic fibroblast growth factor (b-FGF) and epidermal growth factor which are important for regeneration of endometrium are influenced by circulating ovarian steroid hormones. Estrogen stimulates these factors. When there is deficiency of these factors, there is incomplete repair leading to increased MBL. [2]

Endometrial hemostasis is influenced by fibrinolytic activity. Fibrinolysis will occur according to the balance of plasminogen activators, plasminogen inhibitors and plasminogen. Excessive MBL is associated with increased endometrial fibrinolysis. Estrogen stimulates and progesterone inhibits the release of tissue plasminogen activators, and progesterone also stimulates the release of fibrinolytic inhibitors. [47,48]

It seems likely that there is a common mechanism underlying these numerous changes in endometrial vasoactive factors, leucocytes and blood flow, such that these changes represent a cascade of events from a trigger. It is almost certainly a local endometrial mechanism may be expressed via estrogen and progesterone receptors. This abnormality appears not to affect endometrial histology nor glandular and stromal growth or morphology.

An important point to note is that though excessive oestrogen increases menstrual blood loss by mediating actions through ER, it has an important role epithelial regeneration following menstruation and priming of PR, in the absence of which progesterone cannot express its actions on the endometrium.

In the light of current understanding of endocrine physiology of reproduction and the emergence of the modern nonhormonal pharmacological agents the management of DUB has to be rationalized, simplified and rendered nonsurgical. The aim is not only to avoid surgical trauma but also to maintain the endocrine balance. The main endeavor of modern medicine in DUB, apart from avoiding surgical interferences, is to preserve endocrine and metabolic balance of the woman and to prevent degenerative diseases. In patients with anovulatory bleeding, the goal of

treatment is to minimize blood loss and prevent complications from chronic unopposed oestrogen.

With the knowledge of the recent understanding of the mechanism of DUB, it can be concluded that ER have a role to play in both ovulatory and anovulatory DUB. ER receptors are markedly raised in the premenstrual phase of both kinds of DUB ER indirectly control endometrial break down and remodeling. Though oestrogen has deleterious effects on endometrium with respect to DUB, low levels of oestrogen too leads to excessive MBL because of delay in repair and regeneration. Also despite its deleterious effects on endometrium and breast, it has positive effects on the lipid metabolism, CVS, bone mineral density and general well being of a woman.

Evidence states that progestins which form the gold standard therapy are ineffective in treatment of ovulatory DUB and are only successful in treatment of anovulatory DUB which is caused due to unopposed excessive oestrogen. Also, progesterone cannot act unless progesterone receptors are primed by oestrogen.

Thus an ideal therapy to encompass both varieties of DUB would be an agent which can decrease the expression of ER in endometrium thereby creating a hypo oestrogenic environment without disturbing its other positive effects.

A new category of agents called as SERMs have been identified to occupy a place in between estrogens and antioestrogens because they are designed to act in specific pathways at each of the receptor sites

SERMs are compounds whose oestrogenic activities are tissue – selective. The pharmacological goal of these drugs is to produce estrogenic actions in those tissues where these actions are beneficial (bone, brain, liver, heart) and to have either no activity or antagonistic activity in tissues such as breast or endometrium where estrogenic actions (cellular proliferation) might be deleterious. [49,50,51]

Currently approved SERMs in US are Tamoxifen, Raloxifene and ormeloxifene. Effects of known SERMs on various target tissues are as follows

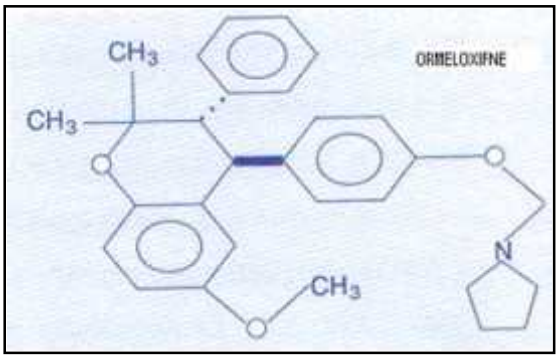
Tissue	**Ormeloxifene**	**Raloxifene**	**Tamoxifene**
Endometrium	AE	AE	E
Breast	AE	AE	AE
Vagina	E	AE	AE
Bone	E	E	AE
Liver / CVS	E	?E±	E
CNS	E	E?	AE

E : Estrogenic, AE : Anti Estrogenic

An ideal SERM is one that prevents bone loss, has no risk of uterine or breast cancer, positive effects on lipids and cardiovascular system (CVS), releases premenstrual syndrome (PMS) and maintain cognitive function of the brain. (Fig. 8)

Since ormeloxifene possess all the above said, is it an Ideal SERM and thus can be advocated in the treatment of DUB.

Chemistry of Ormeloxifene [52]



The chemical name of Ormeloxifene is trans-7-methoxy-2,2-dimethyl-3-phenyl-4(4-(2-pyrrolidinoethoxy) phenyl (-choman hydrochloride). It has been found to be a weak estrogen agonist and a potent antiestrogen. Such antiestrogen i.e. is activity likely to interfere with the post ovulatory events.

Mechanisms of action of SERMS

The SERMs bind the estrogen receptor (ER) and modulate ER-mediated gene transcription. Upon binding ER, alter receptor conformation, and facilitate binding of coregulatory proteins (co-activator or co-repressor proteins) that activate (agonism) or repress (antagonism) transcriptional activation of estrogen target genes. There are two estrogen receptors, ERα and ERβ, which acts as ligand dependant transcription factors that once bound to ligand, translocate into the nucleus, and in conjunction with co-activators or co-repressors, modulate gene expression. There also may be rapid, nongenomic signaling pathways that are activated by ER. (Fig 9)

Oremloxifene behaves as an antagonist with ERα receptors and agonist to ERβ receptors.[53] It behaves as an antiestrogen in the endometrium and breast and simultaneous exerts mild estrogen like activity on bone and cardiovascular system.

When taken orally, Ormeloxifene acts to produce the following effects. [46]

1.	Ovary	No effect on follicle maturation or ovulation
2	Hypothalamus pituitary ovarian axis	No alteration in levels of FSH / LH / Estradiol / progesterone. No inhibition of HPO axis.
3	Uterus	Mild uterotropic effect. Nuclear ad cytoplasm inhibition of estrogen receptors. No effect on progestogen receptors. Inhibits endometrial vascular permeability and mitotic activity.
4	Bone	Increases bone mineral density and calcification
5	Blood lipids	Reduces cholesterol and LDL lipids. No change in levels of HDL and triglycerides, possible anti-atherogenic effect.
6	Vagina	Estrogenic effect on vagina
7	Breast	Anti estrogenic activity on breast. Under evaluation as an adjuvant in the treatment of breast cancer.

Clinical uses

1. Confirmed DUB in any age group, after ruling out organic causes.
2. Puberty menorrhagia increased compliance and good response.
3. IUCD induces menorrhagia as prostaglandin synthesis is oestrogen dependent, anti estrogenic activity bleeding.
4. Peri menopausal ovulatory and anovulatory DUB.

Dosage

- Ormeloxifene can be started at a dose of 1 tablet twice a week
- This can be increased to a maximum dose of 2 tablets twice a week if needed to control DUB.
- Once the DUB has been controlled, Ormeloxifene can be continued at a dose of 1 tablet twice weekly for 12 weeks to prevent recurrence.

In this study, 60 mg of Ormeloxifene was given twice weekly with a minimum interval of 3 days starting from D2-D5 of the first cycle of treatment for a period of 3 months.

Contraindications of ormeloxifene

It has an excellent safety profile, very well tolerated and practically without any undesirable side effects. Few contraindications are

- History of liver dysfunction or clinical jaundice
- PCOD
- Cervical dysplasia, Chronic cervicitis
- History of hypersensitivity to the drug
- Nursing mothers
- Allergic conditions
- Renal disease and tuberculosis

Adverse effects : Delay in menstrual cycle, amenorrhoea, weight gain .

Studies have been done in the recent past to assess the efficacy of ormeloxifene in treatment of DUB.

An overview of phase III trials in India using the drug Ormeloxifene in DUB reported improvement in HMB by 87.78%.[52]

In a study conducted by Prasad S on 70 patients receiving 30 gm bi-weekly dosage of ormeloxifene for six months, 80% of subjects were relieved of menorrhagia.[54]

Another independent study conducted by Subramanian et al using Ormeloxifene in DUB showed similar results.[52]

A study conducted by Biswas SC using ormeloxifene in the treatment of DUB which enrolled 85 subjects showed that the success of treatment with ormeloxifene reduced MBL by 87.05%.[13]

In a study conducted Kriplani et al on 42 women, receiving tab ormeloxifene 60 mg bi-weekly for 3 months followed by once a week for one month showed that 97.7% were relieved of menorrhagia at 4 months.[55]

In the light of the current developments of newer treatment modalities like SERM for menorrhagia, this study was conducted to compare the efficacy of the ideal SERM ormeloxifene with the known Gold Standard of treatment, i.e. cyclical progesterones in the treatment of premenopausal DUB.

The progesterone selected for the study was Tab. Medroxy Progesterone Acetate.

METHODOLOGY

This study was designed to study the efficacy of Ormeloxifene against Medroxy Progesterone Acetate in Dysfunctional Uterine Bleeding.

Source of Data : Patients attending Gynecology OPD, of KLE Dr. Prabhakar Kore Hospital & Research Centre and Kinaye PHC, Belgaum for DUB.

Study type : Double blinded randomized controlled trial

Sample size : 42 in each group

Sample size calculation

Sample size was calculated using the formula

$N = 2(Z\alpha - Z\beta)^2 \, pf / (P_1 - P_2)^2$

Based on previously conducted studies, P_1 i.e., success rate of treatment with cyclical progesterone in DUB was 42%.

Based on theory of assumption hypothesis, success rate with treatment with the study drug ormeloxifene was assumed to be 75%. Thus, P2 was 75%

$P = (P_1 - P_2)/ 2$

$f = 100-p$

Taking level of significance as 5% and power of the test as 80%, the sample size was found to be 35 in each group.

Taking an error rate of 10% and drop out rate of 10%, effective sample size in each group was calculated to be 42 patients.

Women aged between 35-50 years with the diagnosis of DUB, with polymenorrhagia / menorrhagia were selected for the study. Exclusion criteria were presence of any pelvic pathology such as uterine fibroid or pelvic inflammatory disease (PID), polycystic ovaries, systemic disorders such as platelet disorders or coagulopathy, previous history of thrombosis, cervical hyperplasia, chronic cervicitis, Hb% less than 6.5g% and endometrial thickness > 12 mm.

Methodology of double blinding

Drugs used in the study, namely Ormeloxifene and Medroxy Progesterone Acetate were given in capsular form. Placebos for both the drugs were generated using starch powder of equal weight, which were also given in capsular form.

Capsules of 2 colours were selected, one being Yellow-Red in colour and the other being Orange-Pink in colour. Yellow-Red capsules were selected for Tab. Medroxy Progesterone Acetate 10 mg or its placebo. Likewise Orange-Pink capsules were used for selected for Tab Ormeloxifene 60 mg or its placebo.

The tablets of Medroxy Progesterone Acetate and Ormeloxifene were crushed into a powdered form, weighed and filled into the Yellow-Red and Orange-Pink capsules respectively. Placebos were generated by filling starch powder of equal weight as the 2 drugs intended to be tested in the 2 kinds of capsules. It was ensured that the amount of starch powder was equal the amount of actual drug with the help of the weighing scale.

As per the design of the study patients would be taking Tab Ormeloxifene and placebo form of Tab. Medroxy progesterone acetate or Tab Medroxy progesterone acetate and placebo form of Tab. Ormeloxifene. For convenience of the study two groups were identified, group A and group B.

Group A would receive Cap. Ormeloxifene 60 mg twice weekly with a minimum interval of 3 days and placebo form of Cap Medroxy progesterone acetate for a period of 21 days starting from $D_2 – D_5$ of the cycle for three consecutive months.

Group B would receive Cap Medroxy progesterone acetate 10 mg for a period of 21 days and placebo form of cap ormeloxifene twice weekly with a minimum interval of three days starting from $D_2 – D_5$ of the cycle for three consecutive months.

White plastic bottles with orange caps were selected for packing capsules of Medroxy Progesterone acetate and its placebo form. Smaller sized white plastic bottles with white caps were selected for packing capsules of Ormeloxifene and its placebo form.

- 126 white plastic bottles with orange caps were filled with 21 capsules of Medroxy Progesterone Acetate in each bottle
- 126 white plastic bottles with orange caps were filled with placebo form of Medroxy Progesterone Acetate containing 21 capsules in each bottle.
- 126 white plastic bottles with white caps were filled with 8 capsules of ormeloxifene in each bottle
- 126 white plastic bottles with white cap were filled with placebo of ormeloxifene, 8 capsules in each bottle.

All bottles were labeled with the name of drug, manufacture number and date of expiry.

84 similar looking plastic pouches were designed, 42 bearing the label group A and 42 bearing the label group B.

- Plastic pouches with the label group A contained 3 bottles of Cap. Ormeloxifene 60 mg and 3 bottles of placebo form of Tab Medroxy progesterone acetate in capsular form.

- Plastic pouches with the label group B contained 3 bottles of Cap Medroxy Progesterone acetate 10 mg and 3 bottles of placebo form of Tab Ormeloxifene in capsular form.

These plastic pouches with labels were given to Dr. Ganachari, HOD, Department of Clinical Pharmacy, KLE College of Pharmacy, where in the pouches were numbered according to the randomization plan generated there, and the labels were removed. Only numbered pouches were returned back to us which were given to the patients in sequential order. The placebos were certified to be clinically inert by the department of Clinical Pharmacy, KLE College of Pharmacy, Belgaum

Methodology

Informed written consent was obtained from all patients. All the patients were supplied with medication free of cost. However there was no financial incentive for participation of the study.

Patients enrolled in Group A received Cap. Ormeloxifene 60 mg in capsular form 2 days a weeks with a minimum gap of 3 days for 3 months and placebo form for 21 days for 3 months starting from D_2 to D_5 of cycle.

Patients enrolled in group B received Cap. Medroxy Progesterone Acetate in capsular form for 21 days starting from D2-5 of cycle for 3 months and placebo from of Tab Ormeloxifene in capsular form 2 days a week with a minimum gap of 3 day for 3 months.

2 pretreatment baseline cycles were compared to 3 consecutive treatment cycles They were advised to attend OPD on a monthly basis or earlier if needed.

All women having continuous per vaginal bleeding for more than 10 days and women presenting to OPD within the D_5 of cycle with passage of large clots were given Tab. Trapic for 2 days.

All patients were instructed to take medication as explained in consent form starting it within D-5 of each cycle for 3 months. Patients complaining of continuous PIV bleeding > 10 days were started with medication on the day of visit itself.

Patients enrolled in the study were made to undergo the following examination and investigations

- Per speculum examination
- Per vaginal examination
- Trans vaginal sonography
- Haemoglobin %
- VIA

During the period of treatment monthly PBAC scores forms were filled by health workers or OPD staff or PG students to maintain uniformity in filling the forms. All patients were instructed to use the sanitary napkins not containing the absorbent gel. In this study menorrhagia was defined as PBAC score of > 100.

At the end of 3 months of the study period mean PBAC score was calculated, Hb% was evaluated and TVS was repeated for Endometrial Thickness (ET) in the proliferative phase (Day 8 to Day 12 of the cycle) for each patient.

The main outcome measures were menstrual blood loss as assessed by PBAC score, blood Hb% levels and endometrial thickness in proliferative phase as studied by transvaginal sonography (TVS).

At the end of the study decoding of the randomization plan was done by the Department of Clinical Pharmacy and the sequence of patients belonging to group A and group B were obtained.

Variables considered for analysis were

1. PBAC score
2. Endometrial thickness
3. Hb%

Mean and SD were calculated for these parameters. The periodic mean PBAC scores in the two groups were compared using unpaired 't' test. The mean endometrial thickness and Hb% in the two groups were compared using unpaired 't' test.

The number of cases with PBAC score ≤ 100 were counted and the test of 2 sample proportions were applied to find the significant difference in the efficacy between the 2 drugs.

Using students paired 't' test, the significant reduction in PBAC score were compared to any period with respect to the immediately previous period in both the groups.

Yellow-red capsules used for Medroxy Progesterone Acetate and its placebos

Orange-Pink capsules used for Ormeloxifene and its placebos

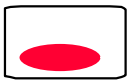
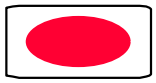
Drug packets bearing the labels Group A and Group B were given to the Department of Clinical Pharmacy

Drug packets allotted sequential numbers according to randomization plan generated at Department of Clinical

PICTORIAL BLOOD LOSS ASSESSMENT CHART

Name :

Day Start :

DAYS												
TOWEL	**1**	**2**	**3**	**4**	**5**	**6**	**7**	**8**	**9**	**10**	**11**	**12**
												
												
												
Clots / flooding												

Collecting monthly PBAC Scores

PHC, Kinaye

Yellow-red capsules used for Medroxy Progesterone Acetate and its placebos

Orange-Pink capsules used for Ormeloxifene and its placebos

Drug packets bearing the labels Group A and Group B were given to the Department of Clinical Pharmacy

Drug packets allotted sequential numbers according to randomization plan generated at Department of Clinical

Collecting monthly PBAC Scores

PHC, Kinaye

RESULTS

The present study was carried out in the Out Patient Department at KLES Dr.Prabhakar Kore Hospital and Medical Research Centre, and Kinaye PHC Belgaum from 1st September 2008 to 30th June 2009. Eight four women aged between 35-50 years of age who fulfilled the inclusion criteria were studied. It was a double blinded randomized control trial. Coding and decoding of randomization plan was done by department of Clinical Pharmacy, KLE College of Pharmacy, Belgaum. The demographic characteristics of age and parity were matched in the two groups.

Table No. 1 : Distribution of Age group

AGE	GROUP A	GROUP B
35-40	24	24
40-45	8	14
45-50	10	4
Total	**42**	**42**

In group A the mean age was found to be 39.64% (range 35-50 years) and in group B the mean age was found to be 39.61% (range 35-50 years). Which was comparable in the two groups.

Graph 1 : Distribution of Age group

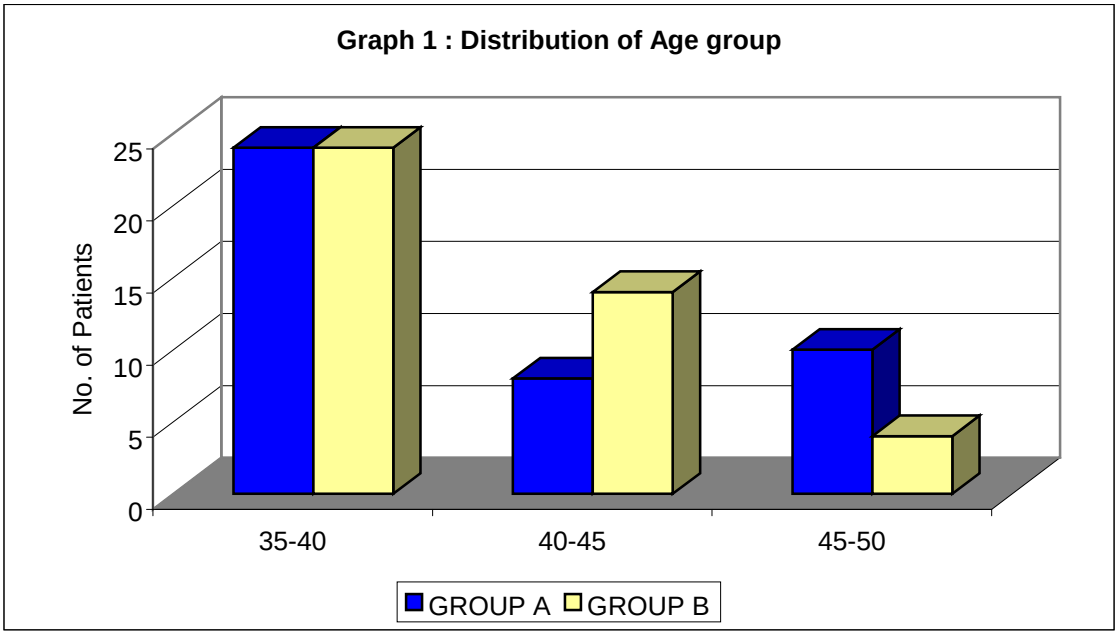
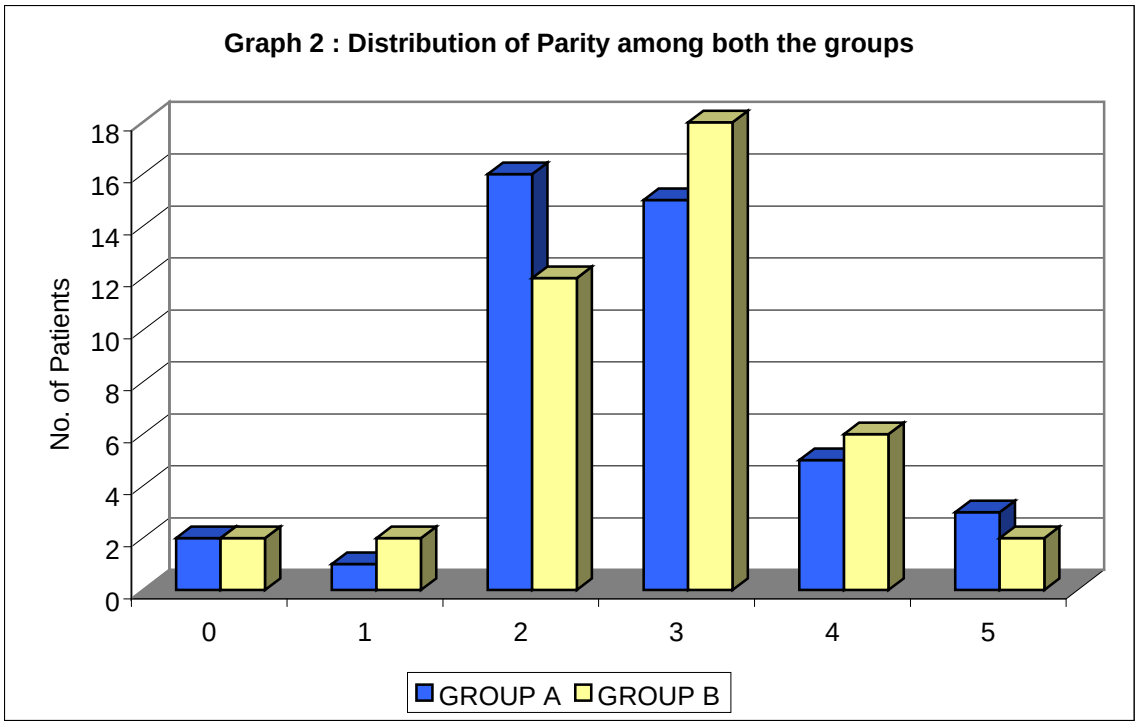


Table No. 2 : Distribution of Parity among both the groups

PARITY	GROUP A	GROUP B
0	2	2
1	1	2
2	16	12
3	15	18
4	5	6
5	3	2
TOTAL	**42**	**42**

The above table reveals that majority of the women were found to be multiparous. Most of them being para 2 or para 3. There was no statistically significant difference in parity between the two groups.



59.25% of patients in group A, and 54.76% in group B had received previous treatment for which they had failed to respond, or symptoms had recurred.

Table 3 : PBAC Score Before Treatment

PBAC	GROUP A	GROUP B
100-200	5	14
200-300	21	20
> 300	16	8
TOTAL	**42**	**42**

Mean PBAC score in Group A before treatment was 262.26% range (160-380) and the mean PBAC score in group B before treatment was 238.71% range (130-410). Majority of them had a score of above 200 in both the groups. They were comparable.

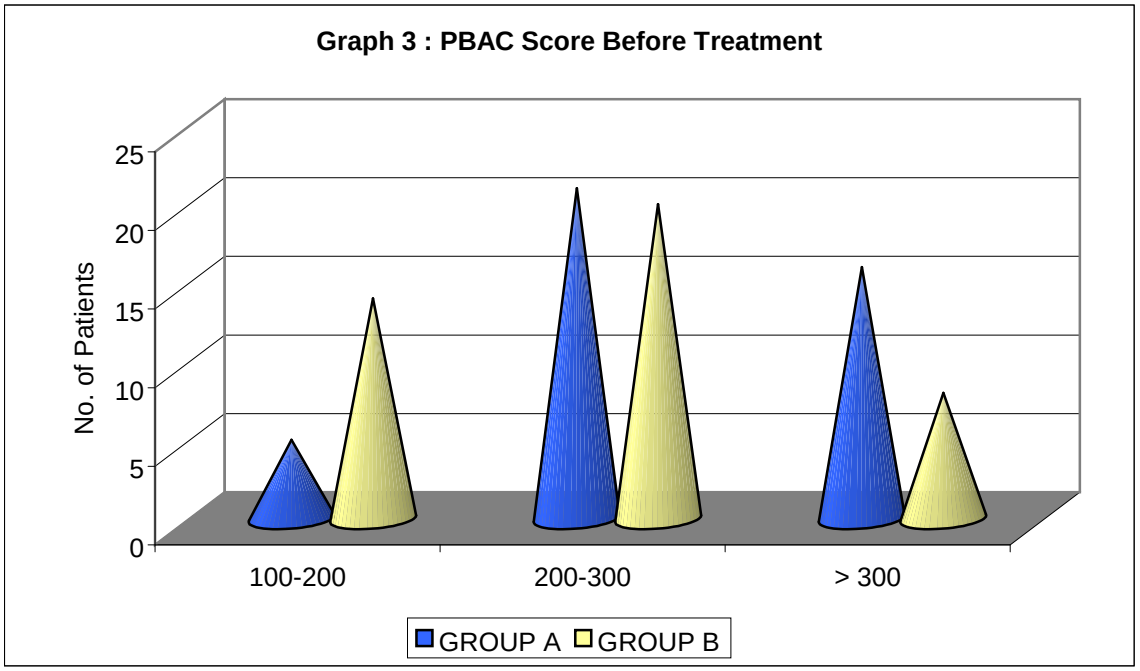
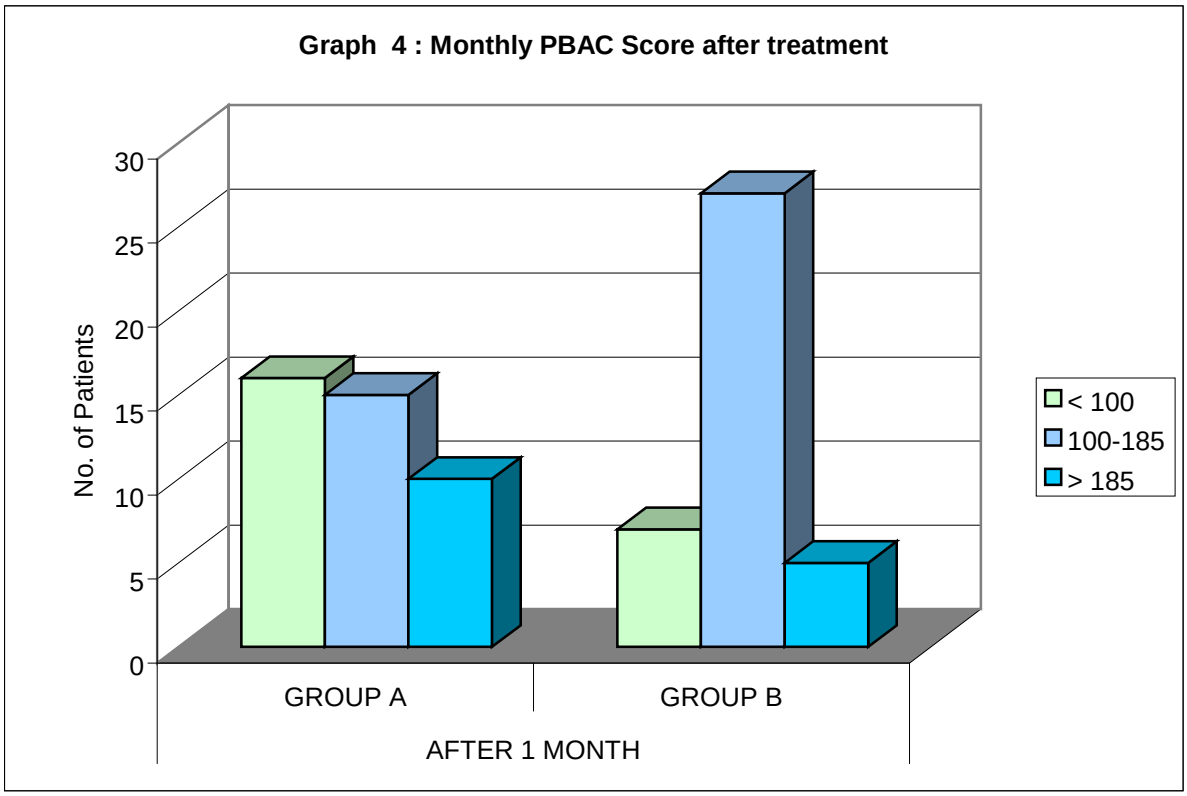
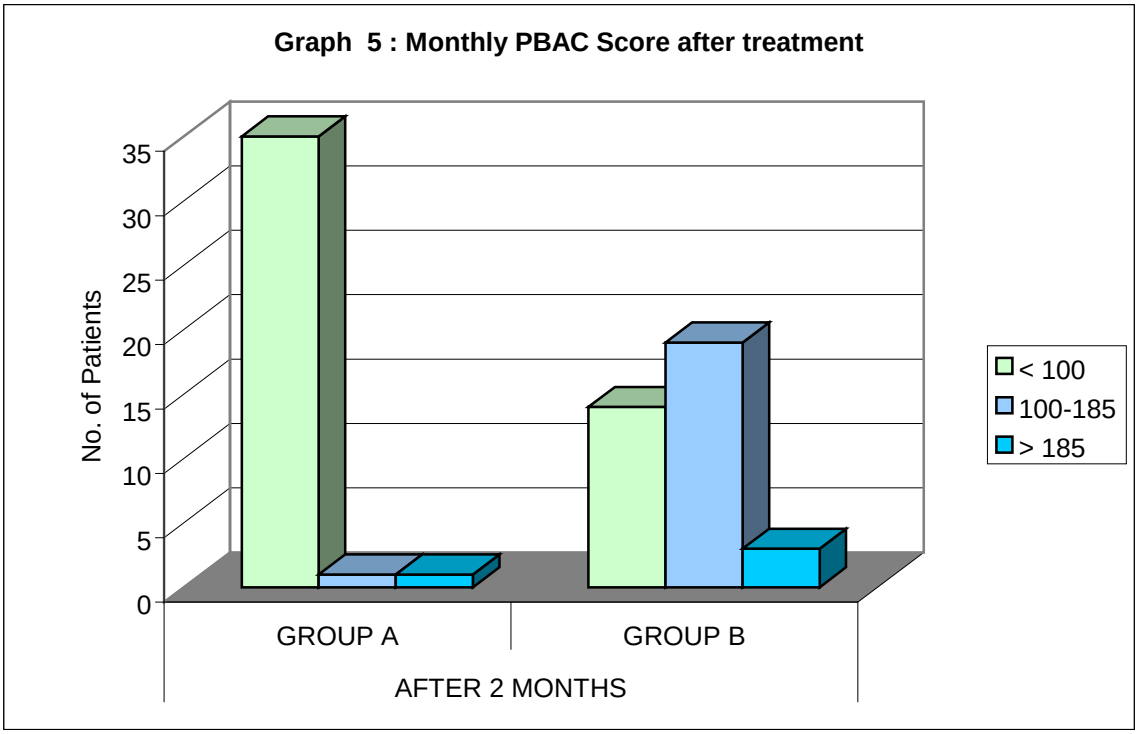


Table No. 4 : Monthly PBAC Score after treatment

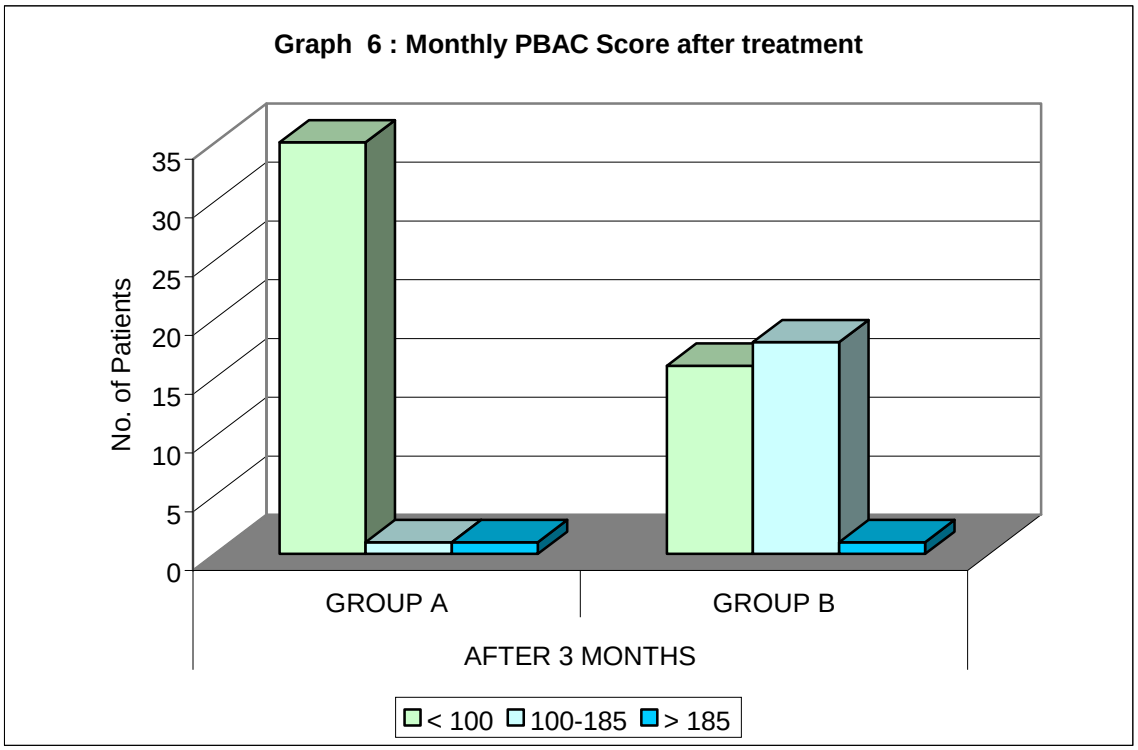
	AFTER 1 MONTH		AFTER 2 MONTHS		AFTER 3 MONTHS	
PBAC	**GROUP A**	**GROUP B**	**GROUP A**	**GROUP B**	**GROUP A**	**GROUP B**
< 100	16	7	35	14	35	16
100-185	15	27	1	19	1	18
> 185	10	5	1	3	1	1
TOTAL	**41**	**39**	**37**	**36**	**37**	**35**



At the end of 1 month of treatment, mean PBAC scores were 141.74 and 141.54 in groups A and B respectively, i.e. it had reduced by 46% and 40.7% in group A and B respectively. The efficacy of treatment were comparable in the 2 groups and there was no statistically significant difference in reduction between the 2 groups.



At the end of 2nd month PBAC score had reduced by 77.2% and 55.3% from the baseline in group A and group B respectively. There was a significant reduction in Group A (p value 0.016).



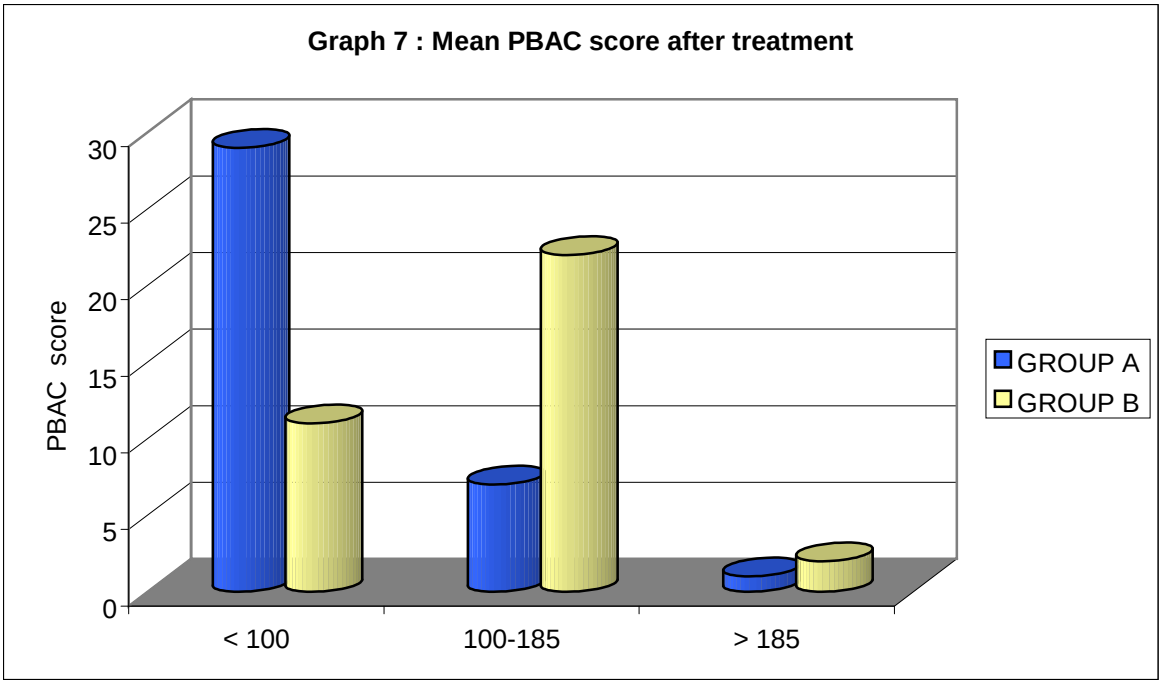
At the end of 3rd month PBAC score had reduced by 87.83% and 60% from the baseline in group A and B respectively. There was a significant reduction in Group A compared to Group B (p value 0.014).

Table No. 5 : Mean PBAC score after treatment

MEAN PBAC	GROUP A	GROUP B
< 100	29	11
100-185	7	22
> 185	1	2
TOTAL	**37**	**35**

The mean PBAC scores at the end of the study period were 73 and 108 in group A and B respectively, reporting an overall reduction in MBL by 85.71% and 54.76% in group A and B respectively. Thus there was significant reduction in menstrual blood loss in group receiving Ormeloxifene against the group receiving oral cyclical progesterone (p value = 0.0205)

Graph 7 : Mean PBAC score after treatment



An example of calculating the Pictorial Blood Loss Assessment Chart Score

NAME .....

	DATE								
	TOWEL	1	2	3	4	5	6	7	8
1		II	I	I	I	II	I		
5			~~IIII~~	III	II				
20			II	II					

Total Score = 265

Table No. 6 : Endometrial thickness before treatment

Endometrial thickness	GROUP A	GROUP B
0-5	6	5
5-10	21	28
10-15	15	9
TOTAL	42	42

The mean endometrial thickness in group A was found to be 7.81 and that of group B was found to be 6.8. The two values were comparable.

Table No. 7 : Endometrial thickness after treatment

Endometrial thickness	GROUP A	GROUP B
0-5	19	6
5-10	17	26
10-15	1	2
TOTAL	**37**	**34**

Mean endometrial thickness in group A was found to be 4.94% and that of group B was found to be 5.86. There was a significant reduction in endometrial thickness in group receiving Ormeloxifene compared to the group receiving Medroxy Progesterone Acetate (p value = 0.0942).

Graph 8 : Endometrial thickness before & after treatment

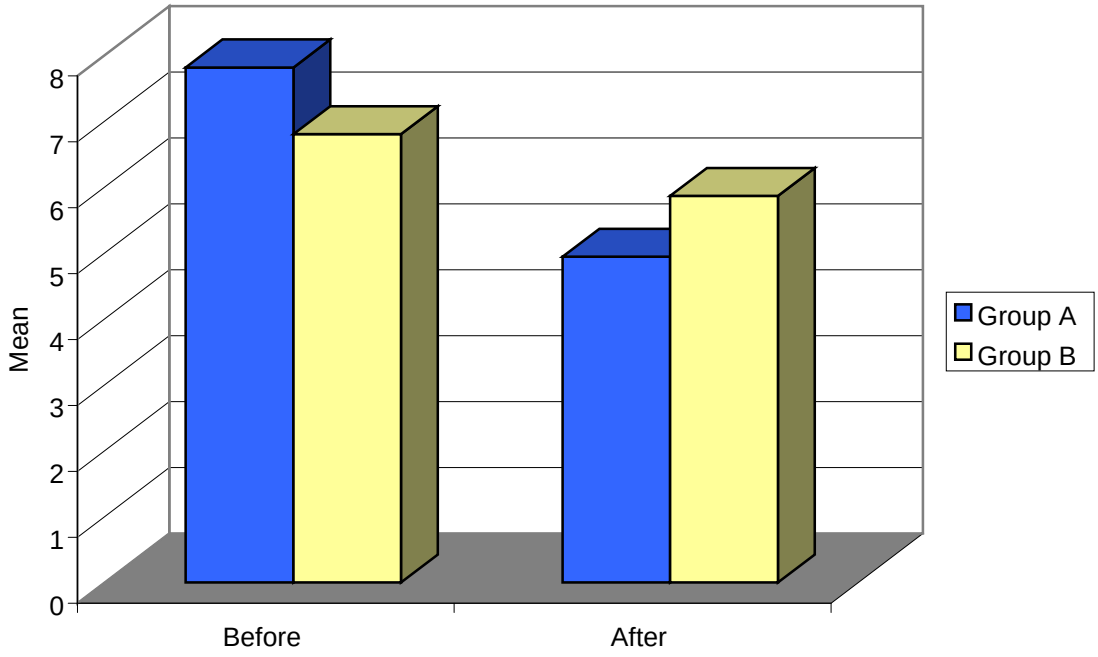


Table No. 8 : Hb before treatment

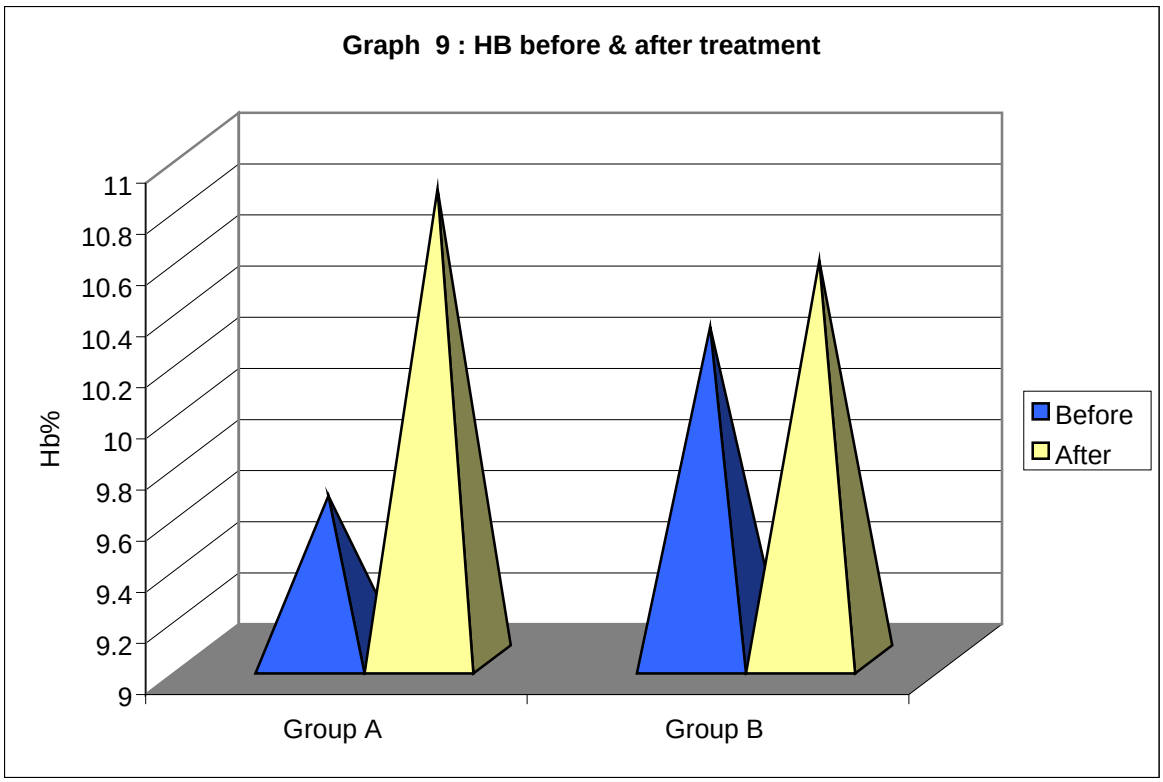
Hb	GROUP A	GROUP B
6.5-7.5	1	0
7.5-8.5	4	1
8.5-9.5	11	8
> 9.5	26	33
TOTAL	**42**	**42**

The above table reveals that mean Hb group A 9.64% and Group B 10.3%. Range in group A (7 to 10) and group B (8 to 11.5) before treatment. The two groups were comparable with respect to haemoglobin % before treatment.

Table No. 9 : Hb after treatment

Hb	GROUP A	GROUP B
6.5-7.5	0	0
7.5-8.5	0	0
8.5-9.5	3	4
> 9.5	34	30
TOTAL	**37**	**34**

Mean haemoglobin in group A after treatment it was 10.84 and that in group B was 10.56. There was no statistically significance in reduction between the two groups

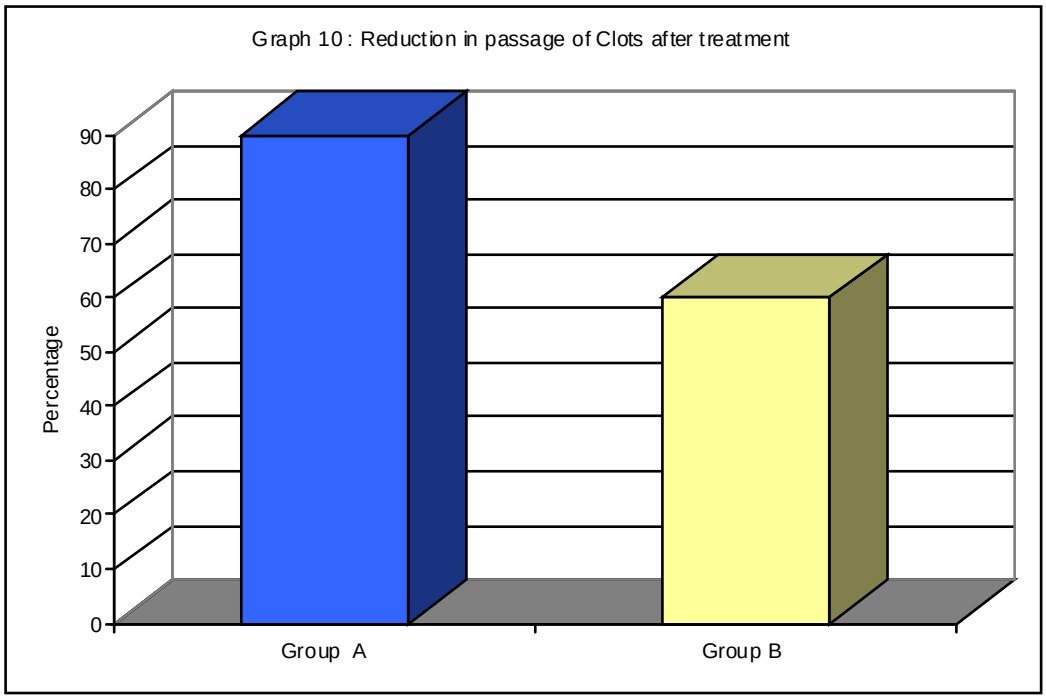


Mean haemoglobin in group A after treatment it was 10.84 and that in group B was 10.56. There was no statistically significance in reduction between the two groups

However in group A, mean increase of 1.28% in haemoglobin % was noted after treatment. There was no statistical significant increase in Hb% in subjects in group B after treatment

Reduction in passage of Clots after treatment

Reduction in passage of clot after treatment was 90% in Group receiving Ormeloxifene and 60% in the group receiving Medroxy progesterone acetate



The study showed that Ormeloxifene was 87.71% efficacious in reduction of menorrhagia with 90% reduction in the passage of clots after treatment, while Medroxy progesterone acetate was 54.76% efficacious in reduction of menorrhagia with 60% reduction in passage of clots after treatment.

11.9% of patients failed to respond to ormeloxifene and 35.71% of patients failed to respond to Medroxy progesterone acetate.

The predominant side effect noted with ormeloxifene was amenorrhoea, which occurred in 9.5% of patients. 5.96% of patients were lost for follow up.

DISCUSSION

Dysfunctional Uterine Bleeding is a common and disruptive condition affecting quality of life in women. Various medical therapies and surgeries have been advocated in the treatment of DUB. The primary modality of treatment is medical therapy and surgery is resorted to only when medical therapy fails.

The present study was a double blinded RCT to compare the efficacy of the ideal SERM ormeloxifene against the most popular cyclical progesterone therapy, using Medroxy Progesterone Acetate.

In the present study, 84 patients were recruited, 42 patients in Group A, i.e., group receiving Ormeloxifene and 42 patients in group B, i.e. group receiving progesterone. All patients were in the age group of 35-50 years, majority of them belonging to the age group of 35-40 years. Age of patients was found to be comparable in both groups.

Parity of patients were comparable in the 2 groups, 4 nulliparous women were enrolled in the study.

Blood loss during menstrual cycles was assessed by means of Pictorial Blood Assessment Chart (PBAC) score. In this study, PBAC scores before treatment were 262.26 (range 160-380) and 238.71 (range 130-410) in group A and group B respectively. 88.1% of patients in group A and 66.6% of patients in group B had PBAC scores of more than 200.

At the end of 1 month of treatment, mean PBAC scores were 141.74 and 141.54 in groups A and B respectively, i.e. it had reduced by 46% and 40.7% in group A and B respectively. The efficacy of treatment were comparable in the 2 groups and there was no

statistically significant difference in reduction between the 2 groups. However at the end of 1 month about 68% of patients were happy with the treatment.

At the end of 2nd month PBAC score had reduced by 77.2% and 55.3% from the baseline in group A and group B respectively. There was a significant reduction in Group A compared to Group B (p value 0.016).

At the end of 3rd month PBAC score had reduced by 87.83% and 60% from the baseline in group A and B respectively. There was a significant reduction in Group A compared to Group B (p value 0.014).

Ormeloxifene competes with estrodiol for binding with cytosol receptors. It not only blocks cytosol receptors but also causes their prolonged depletion and has long lasting post withdrawal effect. Thus efficacy of the drug improves with time which is depicted by increasing reduction in MBL with prolonged use.

The mean PBAC scores at the end of the study period were 73.7 and 108 in group A and B respectively, reporting an overall reduction in MBL by 85.71% and 54.76% in group A and B respectively. Thus 85.71% of patients in group A and 54.76% of patients in group B were relieved of menorrhagia at the end of the study. Ormeloxifene is more efficacious in treatment of DUB compared to cyclical progesterone.

Studies conducted in the year 2000 on 70 subjects using ormeloxifene in a dosage of 30 mg twice weekly for 6 months reported a reduction in menorrhagia by 80% - 87.78%.[52,54]

Another study in 2004 on 80 subjects using ormeloxifene in a dosage and 60 mg twice weekly for 3 months followed by 60 mg once weekly for another 3 months reported a reduction in menorrhagia by 85.7% at the end of 6 months.[13]

A similar study conducted on 42 women with menorrhagia administering Tab. Ormeloxifene 60 mg twice weekly for 3 months and then once a week for 1 month showed reduction in menorrhagia by 97.7% at 4 months. [55]

The results in our study with respect to efficacy of ormeloxifene in reducing MBL were comparable with majority of the other similar studies.

Evidence states that when oral progesterone is given cyclically from D_5 - D_{26}, 50-52% of reduction in MBL is seen. [10,32,34,35] In our study reports the efficiency of progesterone in reducing MBL to be 54.76% which is comparable with the previous studies.

In our study the endometrial thickness before treatment in group A (mean 7.8%) and group B (mean 6.8%) were comparable. However at the end of treatment endometrial thickness (ET) in group A (mean 4.94mm) was significantly less than ET in group B (5.86 mm), (p value =0.0942).

Reduction in ET is a definitive objective evidence showing reduction in MBL.

While both ormeloxifene and progesterone exhibit anti oestrogenic activity in the endometrium preventing endometrial proliferation, ormeloxifene is more efficacious as it directly blocks the estrogen receptors and thereby prevents mitogenic activity exhibited by oestrogen.

Similar study using ormeloxifene in DUB showed significant reduction in ET after 6 months of treatment.[13]

Studies using progesterone have not made any observation on ET during the study.

In our study, the Hb% levels in group A (mean 0.84%) and B (mean 10.86%) were

comparable (i.e. there was no statistically significant difference between the 2 groups).

However in Group A, a mean increase of 1.28% in Hb% was noted after treatment.

There was no statistically significant improvement in Hb% in group B after treatment.

In group A, 9.5% of patients had amenorrhoea and at the end of 3 months, MBL was reduced by 83.87%. This reduction in MBL explains the improvement in Hb% in group A.

A similar study using ormeloxifene in DUB reported a statistically significant improvement in Hb% by 1.3 g%.[13]

Another observation made was that, in group A, passage of clots had reduced by 90% at the end of treatment, whereas it had reduced by 60% in group B.

Subjects with PBAC scores > 100 and those who opted for surgical treatment together were taken as failure of treatment.

11.9% of patients failed to respond to treatment with ormeloxifene and 35.71% failed to respond to treatment with MPA. It was observed that 80% of subjects who failed to respond to ormeloxifene had ET ≤5 mm.

Ormeloxifene though in theory is supposed to improve MBL even in hypo oestrogenic states by virtue of exerting a mild estrogenic effect by means of agonistic action of ER – β receptors, such an effect has not be seen in our study. These cases would have probably responded to treatment with combined oestrogen and progesterone therapy.

One of the major side effects of use of ormeloxifene was amenorrhoea (9.5% of subjects) and increased cycle length. This is due to hypo oestrogenic effects, causing delay in

ovulation thereby lengthening the follicular phase. In various studies conducted, in majority of the subjects, menstrual cyclicity returned to normalcy after 3 months. The limitation of our study was lack of follow up after 3 months of study as a result of which it is not possible to comment on whether the menstrual cyclicity returned to normal or not.

Ormeloxifene has been evaluated for management of menorrhagia in various studies since the year 2000. It has been marketed extensively for DUB management in the recent times. However, it has not gained popularity amongst the existing drugs used for menorrhagia. Some of the reasons for this could be lack of large scale studies done to prove the efficacy of the drug in menorrhagia, lack of RCTs with large subjects comparing the drug to other medical therapies and lack of effective marketing strategies. Ormeloxifene is associated with a number of advantages. It can be started at anytime during the cycle. It is an effective endometrial hemostat controlling bleeding within 48 hours. It is economical compared to any drug. While preventing DUB it is a concurrent contraceptive / interceptive. It also offers perimenopausal bone and cardiovascular protection which is not found in any other drug treating DUB.

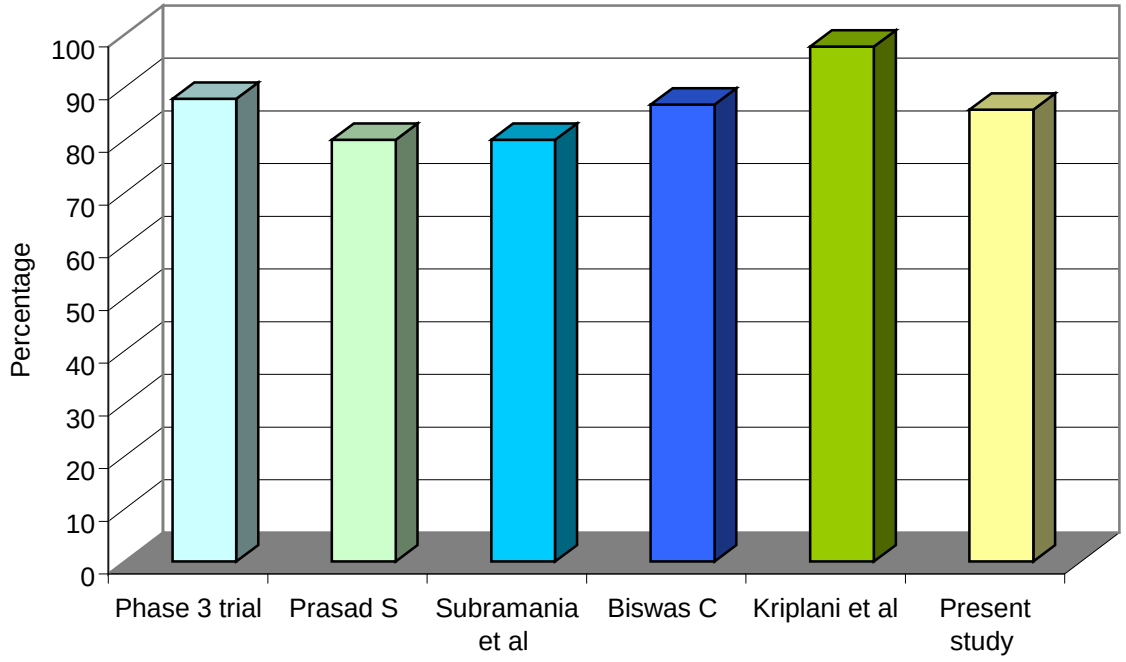
Ormeloxifene possesses an excellent therapeutic safety index and is devoid of any pharmacologic effects which may be reflected as side effect during clinical use. The drug is readily absorbed from the gut and with dose of 60 mg it reaches peak serum concentration of 125 ngm / ml, 4 hours, though its maximal action is seen after 2 days of taking the drug.[52]

The most popular form of medical treatment for menorrhagia has been administration of cyclical progesterone from 1938 to date. Disadvantages of progesterone limit their use. They will be effective only on a oestrogen primed endometrium such as proliferative or

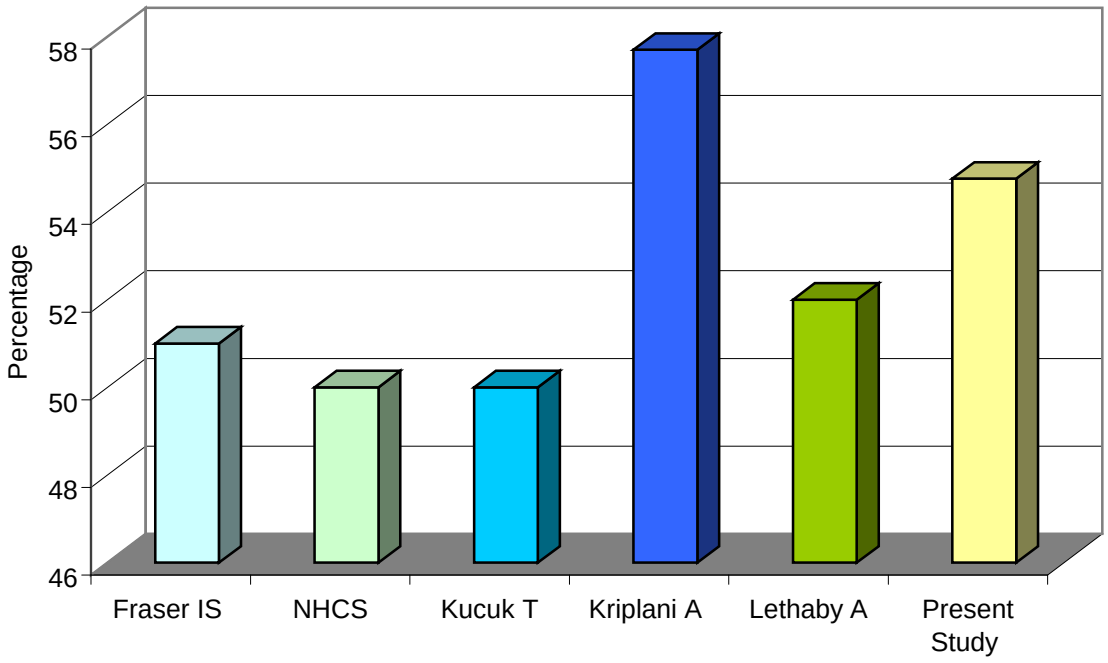
hyperplastic endometrium. They are not suited for control of threshold bleeding where oestrogen levels are low and bleedings associated with secretory endometrium. In nearly 50% or more of the anovulatory DUBs within 24 hours of the bleeding episode the estrogens levels decline fast resulting in steep fall of progesterone receptors in the endometrium. Evidence states that it is not very effective in treatment of ovulatory DUB.[10,32] Also these are associated with a number of undesirable side effects.[56]

Problems encountered with hormonal treatment can be averted by using ormeloxifene a non steroidal compound which is more cost effective and can be started at any time irrespective of the phase of the menstrual cycle and the type of DUB in all age groups from menarche to menopause.

Graph 11 : Comparison of various studies of Group A



Graph 12 : Comparison of various studies of Group B



CONCLUSION

DUB should be viewed as a part of the general endocrine disturbance affecting the entire system of the woman and not as a mere local pathology of the uterus or reproductive organ. The approach to management is to ensure general well being and improved quality of life in addition to control of bleeding. Hysterectomy controls the abnormal bleeding by removal of end organs and not by a scientific correction of the basic systemic disorder. Hysterectomy is usually combined with removal of ovaries resulting in surgical menopause and its after effects resulting in deterioration of quality of life.

Medical management and avoidance of surgery is always recommended because a short period of drug therapy successfully bridges the temporary phase of menstrual alterations wherein young subjects settles down with normal cycles and elderly subjects attain menopause.

The preference should always be for non steroidal agents, since steroidal agents will only aggravate the existing endocrine dysfunction.

Among the available non steroidal drugs for DUB, Ormeloxifene is easier to administer, more cost effective and has lesser side effects. It can be given in all age groups and in all types of DUB. The drug can be started at any point of time in the cycle and even during the bleeding episode. Thus it can be used as one of the first line drugs in the treatment of DUB.

The menstrual delays (increased length of menstrual cycle to a range of 35-50 days) and scanty flow experienced in the first 3 months of usage (due to poor decidual endometrial

changes) and occasional transient amenorrhoea (due to hypoestrogenic effect on endometrium) are the only limitations. In various studies conducted in majority of subjects after 3 cycles of treatment, the menstrual cyclicity is usually returned to normal. The altered menstrual patterns are not associated with endometrial proliferation or hyperplasia.

One of the major limitations of this study was that the 9.5% of subjects who became amenorrhoeic after onset of treatment were not followed up after 3 months to know whether the menstrual cyclicity returned to normal or not.

However randomized control trials with larger subjects over a longer period of time comparing the drug with other medical therapies are needed to establish the definitive efficacy of the drug.

SUMMARY

This study was a double blinded randomized controlled trial conducted in KLES Dr.Prabhakar Kore Hospital and MRC, Belgaum between September 2008 to June 2009 which intended to compare the efficacy of Ormeloxifene, a selective estrogen receptor modulator against Medroxy progesterone acetate, a popularly employed progesterone in the treatment of premenopasual dysfunctional uterine bleeding.

Eighty four women fulfilling the criteria (with respect to inclusion and exclusion criteria) for the study were enrolled. For the purpose of study, 2 groups were identified i.e., group A and group B. All medications were given in capsular form. Subjects enrolled in group A received Cap Ormeloxifene 60 mg twice weekly with a minimum gap of 3 days and placebo form of Cap. Medroxy Progesterone Acetate for 21 days a month, starting from D_2 – D_5 of the menstrual cycle for 3 consecutive months. Subjects enrolled in group B received Cap. Medroxy Progesterone Acetate 10 mg for 21 days and placebo form of capsule Ormeloxifene twice weekly with a minimum interval of 3 days starting from D_2 – D_5 of the menstrual cycle for 3 consecutive months.

Double blinding of the study was done with the help of department of clinical pharmacy. Patients were followed-up on monthly basis.

At the end of the study, average PBAC score of 2 pretreatment cycles were compared with the mean PBAC score at the end of 3 months of treatment within the respective groups, and mean PBAC score, Endometrial thickness and Hb% were compared between the 2 groups.

The mean PBAC in the group receiving Ormeloxifene was significantly lesser than the mean PBAC score in the group receiving Medroxy progesterone acetate being 73 versus 108 (p value 0.0205).

Ormeloxifene was 85.71% efficacious and Medroxy Progesterone was 54.75% efficacious in reducing menorrhagia with their respective groups.

Endometrial thickness was significantly lesser in ormeloxifene group (mean – 4.94) than in the Medroxy Progesterone group (mean 5.86) p value was 0.0942.

There was no statistically significant difference in the 2 groups with regard to improvement in Hb%.

11.9% of patients failed to respond to ormeloxifene and 35.71% of patients failed to respond to Medroxy progesterone acetate.

The predominant side effect noted with Ormeloxifene was amenorrhoea, which occurred in 9.5% of patients. However one of the major limitations of this study is that these cases were not further followed up to see whether the normal cyclical menstruation was returned or not, and if resumed, the time required for return of normal cyclical menstruation.

5.96% of patients were lost for follow up.

No other major side effects were encountered in either of the groups.

The main strength of the study is that there was no bais either on part of the investigator or on part of the subjects.

Hence it can be concluded that ormeloxifene is highly efficacious in the treatment of premenopausal dysfunctional uterine bleeding. It is easy to administer, cost effective and possess a high safety index and is associated with minimal side effects.

However studies recruiting larger number of subjects with longer follow up period are required to emphasize its efficacy and demonstrate its effects on the length of menstrual cycle.

BIBLIOGRAPHY

1. Lethaby A, Hickey M, Garry R Endometrial destruction techniques for heavy menstrual bleeding. Cochrane Database of systematic reviews 2005 Issue 4. Art. No. CD001501. DOI : 10.1002/14651858.CD001501.pub2

2. Frager IS, Jansen RPS, Lobo RA, Whitehead MI. Estrogens and Progestogens in clinical practice. Chapter No 35 "Dysfunctional Uterine Bleeding", Churchill Living Stone Publication 1998 : 419-437.

3. Lethaby A, Hickey M, Garry R Endometrial destruction techniques for heavy menstrual bleeding. Cochrane Database of systematic reviews 2005 Issue 4. Art. No. CD001501. DOI : 10.1002/14651858.CD001501.pub2

4. National Institute for Health and Clinical Excellence. Heavy Menstrual Bleeding. 2007 ; www.nice.org.uk/cg044.

5. Hatasaka H. The evaluation of Abnormal Uterine Bleeding. Clinical Obstetrics and Gynecology 2005 ; 48(2) : 382-397.

6. Studd J. Progress in obstetrics and Gynaecology, Chapter 16 "Current minimal access techniques for dysfunctional uterine bleeding" Churchill Living Stone Volume 15 ; 2003 ; 259-272.

7. Davey DA. Dysfunctional uterine bleeding. In : Whitefield CR, Ed. Dewhurst's textbook of OBSTETRICS and gynaecology for postgraduates, 5th edn. London : Blackwell Scientific, 1995 ; p 509.

8. National Health Committee. Guidelines for the management of heavy menstrual bleeding. May 1998, updated in 2001.

9. Berek JS. Berek and Novak's Gynecology. Chapter 21 "Gynecologic Endoscopy", Lippincott Williams and Wilkins 14th Edition 2007 ; 749-805.

10. Lethaby A, Irvine GA, Cameron IT. Cyclical progestogens for heavy menstrual bleeding. Cochrane Database of systematic reviews 2008 Issue 1. Art. No. CD001016. DOI : 10.1002/14651858.cd001016.pub2.

11. Jatwa R, Kar A. Positive influence of Centchroman on cardiovascular system and tissue lipid peroxidation in rats. Contraception. 2007 ; 76(5) : 408-12.

12. Thomas L. Asad M, Hrishikeshavan HJ, CHandrakala GK. Effect of centchroman on cellular and humoral immunity. Indian J Physiol Pharmacol 2007 ; 51(4) : 387-94.

13. Biswas SC, Saha SK, Bag TS, Ghosh Roy SC, Roy AC, Kabiraj SP. Ormeloxifene A selective estrogen receptor modulatory, for treatment of dysfunctional menorrhagia. J Obstet Gynecol Ind 2004 ; 54(1) : 56-59.

14. Studd J. Progress in obstetrics and Gynaecology, Chapter 17 "Abnormal uterine bleeding : diagnosis and medical management" Churchill Living Stone Volume 12 ; 2003 ; 309-327.

15. Livingstone M, Eraser IS. Mechanisms of abnormal uterine bleeding. Hum Reprod update 2002 ; 8(1) : 60-7.

16. Bonnar J and Dunlop W. Recent advances in Obstetrics and Gynaecology, Chapter 9 "Menorrhagia and bleeding disorders" The Royal Society of Medicine Press Limited. 2003 ; 109-124.

17. Higham JM, O'brien PMS, Shaw RW. Assessment of menstrual blood loss using a pictorial chart. British Journal of Obstetrics and Gynaecology 1990 ; 97 : 734-739.

18. Jasseen AH, Scholten PC and Heintz PM. A simple visual assessment technique to discriminate between menorrhagia and normal menstrual blood loss. Obstetrics and Gynecology 1995 ; 85(6) : 977-982.

19. Speroff L, Fritz M. Clinical gynecologic endocrinology and infertility. Chapter 15 "Dysfunctional Uterine Bleeding" 7th edition. Lipincott Williams and Wilkins. 2005 ; 547-573.

20. Shaw RW. Assessment of medical treatments for menorrhagia. Br J Obstet Gynaecol. 1994 Jul;101 Suppl 11:15-8.

21. Irvine GA, Cameron IT. Medical management of dysfunctional uterine bleeding Baillieres Best Pract Res Clin Obstet Gynaecol. 1999 Jun;13(2):189-202.

22. Iyer V, Farquhar C, Jepson RG. Oral contraceptive pills for heavy menstrual bleeding. Cochrane Database of systematic reviews 1997 Issue 2. Art. No. CD000154. DOI : 10.1002/14651858.CD00154.

23. Vilos GA, Lefebvre G, Graves GR. SOGC Clinical Practice Guidelines. Guidelines for the management of abnormal uterine bleeding. JOGC 2001 ; 106 : 1-6.

24. Hickey M, Higham JM, Fraser I. Progestogens versus oestrogens and progestogens for irregular uterine bleeding associated with anovulation. Cochrane Database of systematic reviews 2007 Issue 4. Art. No. CD001895. DOI : 10.1002/14651858.CD001895.pub2.

25. Beaumonth HH, Augood C, Duckitt K, Lethaby A. Danazol for heavy menstrual bleeding. Cochrane Database of systematic reviews 2007 Issue 3. Art. No. CD001017. DOI : 10.1002/14651858.CD001017.pub2

26. Lethaby A, Augood C, Duckitt K, Farquhar C. Nonsteroidal anti-inflammatory drugs for heavy menstrual bleeding. Cochrane Database of systematic reviews 2007 Issue 4. Art. No. CD00400. DOI : 10.1002/14651858.CD00400.pub2.

27. Lethaby A, Farquhar C, Cooke I. Antifibrinolytics for heavy menstrual bleeding. Cochrane Database of systematic reviews 2000 Issue 4. Art. No. CD000249. DOI : 10.1002/14651858.CD000249.

28. Sara B. Fazio and Amy N. Ship. Abnormal Uterine Bleeding. Southern Medical Association 2007 ; 100(4) : 376-381

29. Kaunitz AM, Meredith S, Inki P, Kubba A and Ramos LS. Levonorgestrel releasing intrauterine system and endometrial ablation in heavy menstrual bleeding. A systematic review and meta-analysis. Obstetrics and Gynecology 2009 ; 113 (5) :1104-1116.

30. Lethaby A, Cooke I, Rees MC. Progesterone or progestogen releasing intrauterine systems for heavy menstrual bleeding. Cochrane Database of systematic reviews 2005 Issue 4. Art. No. CD002126. DOI : 10.1002/14651858.CD002126.pub2.

31. Fraser IS. Treatment of ovulatory and anovulatory dysfunctional uterine bleeding with oral progestogens. Aust N Z J Obstet Gynaecol. 1990 Nov;30(4):353-6.

32. Fraser IS, McCarron G. Randomized trail of 2 hormonal and 2 prostaglanin – inhibiting agents in women with a complaint of menorrhagia. Aust N Z J Obstet Gynaecol. 1991;31:66-70.

33. Aksu F, Madazli R, Budak E, Cepni I, Benian A. High-dose medroxyprogesterone acetate for the treatment of dysfunctional uterine bleeding in 24 adolescents. Aust N Z J Obstet Gynaecol. 1997 May;37(2):228-31.

34. Küçük T, Ertan K. Continuous oral or intramuscular Medroxy progesterone acetate versus the levonorgestrel releasing intrauterine system in the treatment of perimenopausal menorrhagia: a randomized, prospective, controlled clinical trial in female smokers. Clin Exp Obstet Gynecol. 2008;35(1):57-60.

35. Kriplani A, Kulshrestha V, Agarwal N, Diwakar S. Role of tranexamic acid in management of dysfunctional uterine bleeding in comparison with medroxyprogesterone acetate. J Obstet Gynaecol. 2006 Oct;26(7):673-8.

36. Sivanesaratnam V, Chatterje A., Kumar P. Essentials of Gynaecology. Chapter 8 "Abnormal menstrual bleeding" 1st edition Jaypee Publications, India.2005 : 63-72

37. Marjoribanks J, Lethaby A, Farquhar C. Surgery versus medical therapy for heavy menstrual bleeding. Cochrane Database of systematic reviews 2006 Issue 2. Art. No. CD003855. DOI : 10.1002/14651858.CD003855.pub2.

38. Lethaby A, Sheppered S, Farquhar C, Cooke I. Endometrial resection and ablation versus hysterectomy for heavy menstrual bleeding. Cochrane Database of systematic reviews 1999 Issue 2. Art. No. CD000329. DOI : 10.1002/14651858.CD000329.

39. Morana B, Zarbo R, Puglisi F, Zarbo G. Dysfunctional uterine bleeding : medical therapies. Minerva Ginecol. 2003 ; 55(3) : 241-51.

40. Fraser IS, Jansen RPS, Lobo RA, Whitehead MI. Estrogens and Progestogens in clinical practice. Chapter No 14 "Menstruation", Churchill Living Stone Publication 1998 ; 163-173.

41. Zhang X, Qi C, Lin J. Enhanced expressions of matrix metalloproteinase (MMP)-2 and -9 and vascular endothelial growth factors (VEGF) and increased microvascular density in the endometrial hyperplasia of women with anovulatory dysfunctional uterine bleeding. Fertil Steril. 2009 Feb 26. [Epub ahead of print]

42. Speroff L, Fritz M. Clinical gynecologic endocrinology and infertility. Chapter 2 "Hormone Biosynthesis, Metabolism, and Mechanism of Action" 7th edition. Lipiincott Williams and Wilkins. 2005 ; 25-96.

43. Cox MM, Nelson DL. Lehninger Principles of Biochemistry. Chapter 12 "Biosignaling" 5th edition.2008 ; 419-423

44. Fraser IS, Jansen RPS, Lobo RA, Whitehead MI. Estrogens and Progestogens in clinical practice. Chapter No 11 "Actions of Oestrogen and Progesterone at cellular level", Churchill Living Stone Publication 1998 ; 119-132.

45. N. Gleeson, M. Jordan, B. Sheppard and J. Bonnar Cyclical variation in endometrial oestrogen and progesterone receptors in women with normal menstruation and dysfunctional uterine bleeding European Journal of Obstetrics & Gynecology and Reproductive Biology, Volume 48, Issue 3, March 1993, Pages 207-214.

46. Haines and Taylor. Obstetrical and Gynaecological Pathology. Chapter 11 "Normal endometrium and non-proliferative conditions of the endometrium" 5th Edition volume 1 Churchill Livingstone, 391-443.

47. Gleeson N., Devitt M, Sheppard BL and Bonnar J. Endometrial fibrinolytic enzymes in women with normal menstruation and dysfunctional uterine bleeding. British Journal of Obstetrics ad Gynaecology 1993 ; 100 : 768-771.

48. Gleeson NC. Cyclic changes in endometrial tissue plasminogen activator and plasminogen activator inhibitor type 1 in women with normal menstruation and essential menorrhagia. Am J Obstet Gynecol 1994 ; 171 : 178-83.

49. ACOG Practice Bulletin. Selective estrogen receptor modulators. Clinical management guidelines for Obstetrician – Gynecologists 2002 ; 39(4) : 835-844.

50. Wendy Shelly, Michael W Draper, Venkatesh Krishnan, Mayme Wong, Robert B Jaffe. Selective estrogen receptor modulators: an update on recent clinical findings. Obstetrical & gynecological survey. 2008 Mar;63(3): 163-81.

51. Leslie KK, Walter SA, Torkko K, Stephens JK, Thompson C, Singh M. Effect of tamoxifen on endometrial histology, hormone receptors, and cervical cytology : a prospective study with follow-up. Appl Immunohistochem Mol Morphol. 2007 Sep;15(3):284-93

52. Singh MM. Centchroman, a selective estrogen receptor modulator, as a contraceptive and for the management of hormone – related clinical disorders. Med. Res. Rev 2001 ; 21(4) : 302-347.

53. S Awasthi, C S Blesson, A Dwivedi. Expression of oestrogen receptors alpha and beta during the period of uterine receptivity in rat: effect of ormeloxifene, a selective oestrogen receptor modulator. Acta physiologica (Oxford, England). 2007 Jan;189(1): 47-56

54. Prasad S. Centchroman : A novel drug for DUB. J. Obstet Gynecol India. 2000 ; 50 : 77-79.

55. Kriplani A, Kulshrestha V, Agarwal N. Efficacy and safety of ormeloxifene in management of menorrhagia. A pilot study. The Journal of Obstetrics and Gynaecology Research 2009 ; 35(4) : 746-752.

56. Chaudhuri SK, Das A, De KC, Ghosh M. Some hitherto unreported findings on the extragenital effects of progesterone in human females – a clinical study. Indian J Physiology Pharmacol. 1994 ; 38(3) : 174-80.

ANNEXURE – I

TO WHOMSOEVER IT MAY CONCERN

This is to state that the randomization plan (Seed No. 2334) for the study "**TO COMPARE THE EFFICACY OF ORMELOXIFENE V/S CYCLICAL PROGESTERONE IN THE TREATMENT OF DYSFUNCTIONAL UTERINE BLEEDING IN PREMENOPAUSAL WOMEN – A ONE YEAR RANDOMIZED CONTROLLED TRIAL",** conducted under the guidance of **Dr. J. C. Shravage** was generated in the Department of Clinical Pharmacy, KLE College of Pharmacy, Belgaum under the guidance of **Dr. Ganachari**. The randomization plan was decoded after completion of the study.

The placebos used in the study were found to be Pharmacologically inert.

Dr. Ganachari
Prof. and Head,
Department of Clinical Pharmacy,
KLE College of Pharmacy, Belgaum

Date :
Place : Belgaum

ANNEXURE - II

INFORMED CONSENT FORM

ID.NO :- | | | | |

TITLE **:** **"**TO COMPARE THE EFFICACY OF ORMELOXIFENE V/S CYCLICAL PROGESTRONE IN THE TREATMENT OF DYSFUNCTIONAL UTERINE BLEEDING IN PREMENOPAUSAL WOMEN – A ONE YEAR RANDOMIZED CONTROLLED TRIAL **".**

Abnormal excessive uterine bleeding is an important cause of ill health in women and since 80% cases have no anatomical pathology. Medical therapy with avoidance of possible unnecessary surgery is an attractive alternative. Altered endometrial morphology and increased receptors levels in abnormal excessive bleeding patients suggest that unopposed estrogen effect could have an important role in the pathogenesis.. The purpose of this study is to assess the efficacy of ormeloxifene a selective estrogen receptor modulator having anti oestrogenic action on endometrial that has been newly advocated in treatment of heavy menstrual bleeding V/s cyclical progesterone which is conventionally given.

You are invited to participate in a research study being conducted under the guidance of Dr. J. C. Shravage, Professor, Department of Obstetrics & Gynecology, J. N. Medical College, Belgaum.

Your participation in the study is voluntary. You would be enrolled into one of the 2 groups, as per the randomization chart by the department of clinical pharmacy after being

screened for eligibility for which your will have to undergo a routine pelvic examination, transvaginal sonography and Hemoglobin percentage estimation.

To which ever group you would be enrolled into, you will be given 2 kind of capsules contained in plastic bottles of 2 kinds. You are advised to take red – yellow capsules contained in plastic bottles with orange caps daily for 21 days after your first visit and subsequently from D-2 of cycle daily for 21 days for the following 2 months; simultaneously you will also be advised to take the orange - pink capsules contained in smaller plastic bottles with white caps twice a week with a minimum gap of two days (for e.g. on Wednesdays and Sundays or Tuesdays and Fridays) for a period of 3 months.

One of the two drugs is a pharmacologically active drug which is either Ormeloxifene or Medroxyprogestrone acetate and the other is a placebo, a pharmacologically inert drug which is certified to be inert and will not have any adverse effect on you.

During this period you should be willing fill in the PBAC every month. This study may or may not benefit you, but may be beneficial to the other patients. Standard care will be provided even if you refuse to participate in this study. You are free to stop participation in this study at any time and for any reason. However the drugs used in this study have a good safety profile and are not known to have any major adverse effects. Though studies on ormeloxifene are limited, they have shown beneficial results.

Every effort will be made to protect the confidentiality of the information you provide. You will be given an ID number and the same will be used for study purpose preventing your identification; confidentiality of the data will be maintained. Results of this study may be published for scientific purposes, but you will not be identified. You will not

receive any financial incentives for participating in this study. However the medication will be provided free of cost to you irrespective of which ever group you may belong to.

In case of emergency, you may please call Dr. Mekhala, P.G., Department of Obstetrics and Gynecology, Tel. No. 9980155717 / 9964749069 or Dr. J. C. Shravage, Professor, Department of Obstetrics and Gynecology, J.N.M.C. Belgaum. Mobile No. 9448305362.

If you have any questions about this study, you may please call, visit or write to Dr. Mekhala, Post Graduate (Obstetrics and Gynecology), Tel. No. 9980155717 or Dr. J. C. Shravage, Professor, Department of Obstetrics and Gynaecology, J.N.M.C, Belgaum-590010, Tel. No. 9448305362. If you have any questions regarding your rights as study participant, you may contact Dr. V. D. Patil, Principal & Chairman of Ethical Committee, J. N. Medical College, Belgaum, Tel. No. 0831- 2471530

Statement of Consent: I volunteer and consent to participate in this study. I have read the consent document or it has been read and interpreted to me in my vernacular language. I accept to participate in this study .All the information regarding this study has been provided to me and I have understood the same. I have been given an opportunity to ask questions and obtain appropriate answers.

Signature or left thumb print of the participant or legally authorized representative.

Participant's Name: _____

Signature or left thumb print :_____

Address : _____

Telephone No. : _____

Witness's Name: _____

Signature or left thumb print :_____

Investigator's Name: _____

Signature:_____

Date :

ANNEXURE – III

PROFORMA

"TO COMPARE THE EFFICACY OF ORMELOXIFENE V/S CYCLICAL PROGESTRONE IN THE TREATMENT OF DYSFUNCTIONAL UTERINE BLEEDING IN PREMENOPAUSAL WOMEN – A ONE YEAR RANDOMIZED CONTROLLED TRIAL **".**

Name : **Date :**

Age :

Address :

Contact No :

Occupation :

Socio – economic status:

SCREENING

1. Pulse Rate

   Blood Pressure

2. Per speculum examination

I.	Cervix	: a) Healthy b) Unhealthy	a | b
II.	Vagina	: a)Healthy b)Unhealthy	a | b
III.	Discharge	: a)Present b) Absent	a | b
IV.	VIA	: a)Positive b)Negative	a | b

Per vaginal examination :

1. Uterus

I. Size : a) Normal
b) Bulky
c) Enlarged

a	b	c

II. Mobility : a) Mobile
b) Fixed

a	b

III. Contour : a)Normal
b)Irregular

a	b

2. Fornices : a) Free
b) Fullness

a	b

3. Tenderness : a)Present
b) Absent

a	b

4. Adnexal Mass : a)Present
b)Absent

a	b

4. Hemoglobin Percentage
Hemoglobin Percentage < 6.5
Hemoglobin Percentage > 6.5

a	b

5. Have you received any medical treatment for similar complaints (menorrhagia) in the past

Yes / No

If yes, when

Details of the treatment received

6. Do you have any chronic illness

Yes / No

Eligibility for study

a) Eligible
b) Not Eligible

a	b

c) PARTICIPATION RECORD

1. Nature of previous menstrual cycles

   ---------- days / ---------- days

   Regular / Irregular

   No of pads used in a day

   Passage of clots

   Dysmenorhoea

   Intermenstrual bleeding

2. Nature of present menstrual cycles

   ---------- days / ---------- days

   Regular / Irregular

   No of pads used in a day

   Passage of clots

   Dysmenorhoea

   Intermenstrual bleeding

   PBAC score

3. LMP

4. Obstetric history

INVESTIGATION

1. Hb%

2. Transvaginal sonography with Endometrial thickness

GENERAL EXAMINATION

PR -

BP -

PALLOR -

CVS -

RS -

P/A -

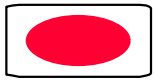
P/S -

P/V -

SCORE

Name :

Day Start :

DAYS												
TOWEL	**1**	**2**	**3**	**4**	**5**	**6**	**7**	**8**	**9**	**10**	**11**	**12**
												
												
												
Clots / flooding												

Pictorial Blood Assessment Chart and Scoring System for Assessment of Menstrual Blood Loss

How to use the PBAC scoring system:

- During the course of your period record your use of tampons and sanitary towels by placing a tally mark under the day next to the box that represents how stained your sanitary materials are each time you change them.
- Record clots by indicating whether they are the size of a 1p or 50p coin in the clots/ flooding row under the relevant day. E.g. under day 1 you may say 50p x 1 and 1p x 3.
- Record any incidences of flooding by placing a tally mark in the clots/ flooding row under the relevant day.

Scores:

- A lightly stained towel (pic 1) will score 1 point, a moderately stained towel (pic 2) 5 points, a towel which is saturated with blood (pic 3) will score 20 points.
- A lightly stained tampon (pic 4) will score 1 point, a moderately stained tampon (pic 5) 5 points and a tampon that is fully saturated will score 10 points
- A clot the size of 1p scores 1 point, a 50p sized clot scores 5 points and flooding also scores 5 points

Results

Once you have finished your period total up your scores. A score of 100 or greater may indicate that you have heavy periods and you should seek advice from your doctor.

FOLLOW UP

PBAC will be given to all participants, to be filled duly by patients every month

Every month PBAC score will be assessed

At the end of 3 months, following investigations will be done

Hb%

TVS for endometrial thickness

	Before treatment	**After treatment**
PBAC score		1. First month -
		2. Second month -
		3. Third month -
		Mean PBAC score -
TVS for ET		
Hb%		

A Randomization Plan

from

http://www.randomization.com

1.	A
2.	B
3.	A
4.	B
5.	A
6.	A
7.	A
8.	B
9.	B
10.	A
11.	A
12.	B 26/9/08.
13.	B ~~26/9~~
14.	B
15.	A
16.	B
17.	B
18.	B
19.	A
20.	A
21.	B
22.	A
23.	B
24.	B
25.	B
26.	A

McKhala, 2008.

1 of 3

27. A
28. B
29. B
30. B
31. B
32. A
33. B
34. A
35. A
36. A
37. A
38. A
39. B
40. B
41. A
42. B
43. B
44. B
45. A
46. A
47. B
48. A
49. A
50. A
51. A
52. B
53. B
54. A
55. A
56. B
57. B
58. B

59.	B
60.	B
61.	A
62.	A
63.	A
64.	B
65.	B
66.	A
67.	A
68.	A
69.	B
70.	A
71.	A
72.	B
73.	B
74.	B
75.	B
76.	A
77.	A
78.	B
79.	A
80.	B
81.	A
82.	B
83.	A
84.	A

84 subjects randomized into 1 block

To reproduce this plan, use the seed 2334

Randomization plan created on Thursday, September 25, 2008 1:32:02 PM

Mekhala, 2008.

3 of 3

KEYS TO MASTER CHART

Sl. No. : Serial Number

Yrs : Years

Parity

0 : Nulliparous

1 : Primipara

2 : Para 2

3 : Para 3

4 : Para 4

5 : Para 5

Per speculum examination

Cervix

1 : Healthy

2 : Unhealthy

Vagina

1 : Healthy

2 : Unhealthy

Discharge

1 : Present

2 : Absent

VIA

1 : Positive

2 : Negative

Per vaginal examination

Size

1 : Normal

2 : Bulky

3 : Enlarged

Mobility

1 : Mobile

2 : Fixed

Coutour

1 : Normal

2 : Irregular

Fornices

1 : Free

2 : Fullness

Tenderness

1 : Present

2 : Absent

Adnexal mass

1 : Present

2 : Absent

H/o previous treatment

Yes : 1

No : 2

Medical : 1

Surgical : 2

H/o chronic illness

Yes : 1

No. : 2

Passage of clots

1 : Present

2 : Absent

MASTER CHART : GROUP A

Sl. No.	Randomization No.	Group Code	Name	Age (in yrs)	Per speculum examination				Per vaginal examination						H/o previous treatment		H/o chronic illness	PBAC score before treatment	Endometrial thickness prior to treatment (In mm)	Passage of Clots Before Treatment	HB before treatment	PBAC score			Mean	Endometrial thickness after treatment (In mm)	HB after treatment	Passage of Clots After Treatment	FAILURE OF TREATMENT
					Cervix	Vagina	Discharge	VIA	Uterus			Fornices	Tenderness	Adnexal Mass	Yes / No	Med/Surg	Yes / No					After 1st month	After 2nd month	After 3rd month					
									Size	Mobility	Contour																		
1	1	A	Manjula Kalal	48	1	1	2	2	1	1	1	1	2	2	1	1	2	300	7.3	1	10.0	0	0	0	0	7	12	2	
2	3	A	Arifa Shaiek	46	1	1	2	2	2	1	1	1	2	2	1	1	2	380	9.7	1	10.6	0	0	0	0	6	11.5	2	
3	5	A	Gouabee Georikhan	48	1	1	2	2	2	1	1	1	2	2	1	1	2	215	6.9		10.0	0	0	0	0	4	12		
4	6	A	Tara Weerodai	44	1	1	2	2	1	1	1	1	2	2	1	1	2	300	8.0	1	10.0	60	60	65	61.67	5	11	2	
5	7	A	Sumithra Uppar	35	1	1	2	2	2	1	1	1	2	2	1	1	2	280	5.0	2	8.3	105	70	60	78.33	4	10	2	
6	10	A	Rekha Gundoji	47	1	1	2	2	2	1	1	1	2	2	1	1	2	295	10.0	2	9.6	125	65	60	83.33	6	10.6	2	
7	11	A	Dishad Kotwal	36	1	1	2	2	1	1	1	1	2	2	1	1	2	160	11.3	1	11.0	65	65	50	60	6	11.5	2	
8	15	A	Sunanda Kadgavi	48	1	1	1	2	2	1	1	1	2	2	1	1	2	300	8.0	1	10.4	140	60	45	81.67	4	12	2	
9	19	A	Gangawwa Channikoppa	36	1	1	2	2	1	1	1	1	2	2	2		2	305	9.0	1	9.2	115	75	75	88.33	4	10.5	2	
10	20	A	Rabiya L Anniger	45	1	1	2	2	1	1	1	2	2	2	2		2	300	11.0	1	8.6	110	60	0	56.67	8	10	2	
11	22	A	Malu Chapgannavar	40	1	1	2	2	2	1	1	1	2	2	2		2	265	2	1	8.2	85	75	70	76.67	4	10	2	
12	26	A	Jareena Mulla	35	1	1	2	2	2	1	1	1	2	2	1	1	2	270	6	1	10.5	100	80	60	80	5	12	2	
13	27	A	Geetha Aptekar	35	1	1	2	2	1	1	1	1	2	2	2		2	260	8	1	10.2	90	85	70	81.67	5	11.5	2	
14	32	A	Lakshmi Y Lohar	36	1	1	2	2	1	1	1	1	2	2	1	2	2	220	10	2	10.0	130	50	0	60	6	12	2	
15	34	A	Sunita Yallurkar	39	1	1	2	2	1	1	1	1	2	2	1	1	2	240	5	1	9.2	200	60	60	106.7	4	10.5	1	
16	35	A	Anuna G Badiger	36	1	1	2	2	2	1	1	1	2	2	1	1	2	205	10	2	8.5	125	75	60	86.67	6	9.6	2	
17	36	A	Vijaylakshmi Patil	35	1	1	2	2	1	1	1	1	2	2	1	1	2	220	11	1	8.5	95	70	60	75	4	9.5	2	
18	37	A	Parwathi Patil	40	1	1	2	2	1	1	1	1	2	2	2		2	340	4		9.0	320	Underwent D & C						F
19	38	A	Tejaswini Mannolkar	35	1	1	2	2	1	1	1	1	2	2	1	1	2	280	13	1	10.5	100	60	0	53.33	7	11.2	2	
20	41	A	Sureka Patil	38	1	1	2	2	2	1	1	1	2	2	1	1	2	250	6	1	10.0	180	100	120	133.3	6	9.2	1	F
21	45	A	Shantha Goguri	42	1	1	2	2	2	1	1	1	2	2	1	1	1	310	5.0	1	9.0	80	80	60	73.33	3	10	2	
22	46	A	Rubina Nidgundi	39	1	1	2	2	1	1	1	1	2	2	2		2	300	11.0		12.1	0	0	0	0	2	13.6		
23	48	A	Shantabai Bellad	45	1	1	2	2	2	1	1	1	2	2	1	1	2	200	11.0	2	10.0	95	30	20	48.33	4	11	2	
24	49	A	Meenaxi Neepani	36	1	1	2	2	2	1	1	1	2	2	2		2	240	6.0	1	10.0	90	40	35	55	4	11	2	
25	50	A	Rekha Uttam Gundoji	35	1	1	2	2	2	1	1	1	2	2	1	1	2	150	6.0	2	10.0	70	0	0	23.33	10	12	2	
26	51	A	Mangal P Pawar	38	1	1	2	2	2	1	1	1	2	2	2		2	190	3.0	1	10.0	80	0	0	26.67	4	11	2	
27	54	A	Naido D Patil	35	1	1	2	2	1	1	1	1	2	2	1	2	2	185	9.0	1	10.0	145	80	90	105	6	10.5	2	
28	55	A	Lakkawwa R Sanjimani	35	1	1	2	2	1	1	1	1	2	2	2		2	200	6.0	1	9.0	200	70	60	110	5	10.2	2	
29	61	A	Kamalabai Narolkar	42	1	1	2	2	2	1	1	1	2	2	2		2	320	9.0		8.2	360	Underwent D & C						F
30	62	A	Laxmi Ramu Dabale	36	1	1	2	2	2	1	1	1	2	2	2		2	200	7.0		10.0	340	Underwent D & C						F
31	63	A	Dilshad Jatti	45	1	1	2	2	2	1	1	1	2	2	2		1	360	10.0	1	11.8	90	95	20	68.33	4	13	2	
32	66	A	Vrushali V Shahpurkar	42	1	1	2	2	2	1	1	1	2	2	1	1	2	215	8.0	1	9	215	60	40	105	4	10	2	
33	67	A	Laxmi Nagevkar	36	1	1	2	2	2	1	1	1	2	2	2		2	230	2.0	1	10	170	80	40	96.67	5	11	2	
34	68	A	Roopali B Parle	35	1	1	2	2	2	1	1	1	2	2	1	2	2	340	6.0	1	9.2	340	60	40	146.7	4	10.5	1	
35	70	A	Shobha Tulogavergol	35	1	1	2	2	2	1	1	1	2	2	2		2	180	10.0	1	10	60	60	40	53.33	4	11	2	
36	71	A	Archana Dodmani	38	1	1	2	2	2	1	1	1	2	2	1	1	2	330	12.0	1	10	160	0	0	53.33	8	10	2	
37	76	A	Kasturi H S	35	1	1	2	2	2	1	1	1	2	2	2		2	320	4.8	1	7	220	80	0	100	3	8.5	2	
38	77	A	Kaviya Aralimani	37	1	1	2	2	2	1	1	1	2	2	1	1	2	340	10.0	1	10	Lost for followup							
39	79	A	Anitha M Lokhande	48	1	1	2	2	2	1	1	1	2	2	2		2	240	11.0	1	10	170	60	0	76.67	3	11.2	2	
40	81	A	Prabhavathi H	47	1	1	2	2	1	1	1	1	2	2	1	1	2	280	10.0	1	10	180	60	40	93.33	4	11	2	
41	83	A	Vasantha Mundewadi	40	1	1	2	2	2	1	1	1	2	2	1	1	2	300	4.0		8.2	380							F
42	84	A	Aarthi Hosamani	42	1	1	2	2	2	1	1	1	2	2	2		2	200	6.0	1	9	220	240	225	228.3	5	9	1	o

MASTER CHART FOR GROUP B

Sl. No.	Randomization No.	Group Code	Name	Age (in yrs)	Per speculum examination				Per vaginal examination						H/o previous treatment		H/o chronic illness	PBAC score before treatment	Endometrial thickness prior to treatment (In mm)	Passage of Clots Before Treatment	HB before treatment	PBAC score			Mean	Endometrial thickness after treatment (In mm)	HB after treatment	Passage of Clots After Treatment	FAILURE OF TREATMENT
					Cervix	Vagina	Discharge	VIA	Uterus			Fornices	Tenderness	Adnexal Mass	Yes / No	Med/Surg	Yes / No					After 1st month	After 2nd month	After 3rd month					
									Size	Mobility	Contour																		
1	2	B	Ashwini Birje	35	1	1	2	2	1	1	1	1	2	2	1	1	2	370	10.9		8.0	165	255	160	193.3	10	9		F
2	4	B	Pushpa R Patil	39	1	1	2	2	2	1	1	1	2	2	2		2	240	4.5	1	9.6	95	55	40	63.33	6	10	2	
3	8	B	Rekha V Jadhav	43	1	1	2	2	2	1	1	1	2	2	2		1	320	5.6	1	10.1	100	130	180	136.7	6	10	1	F
4	9	B	Kavitha M Patil	38	1	1	2	2	2	1	1	1	2	2	2		2	130	5.0	1	11.0	45	45	35	41.67	3	12	2	
5	12	B	Shanta Parashuram	40	1	1	1	2	2	1	1	2	2	2	1	1	2	385	7.0	1	9.0	215	225	140	193.3	7	9	1	F
6	13	B	Binitha Singh	39	1	1	2	2	1	1	1	1	2	2	1	2	2	220	10.0	1	11.0	125	145	125	131.7	6	11.5	1	F
7	14	B	Dr. Deepali Patil	38	1	1	2	2	2	1	1	1	2	2	2		2	480	10.0	1	11.4	125	0	0	41.67				
8	16	B	Parwatewwa Pujar	48	1	1	2	2	1	1	1	1	2	2	1	1	2	240	6.0		11.5	170	125	80	125	6	12	1	
9	17	B	Savita Muchandikar	38	1	1	2	2	1	1	1	1	2	2	2		2	310	6.0	1	11.0	150	150	175	158.3	7	11		F
10	18	B	Kashawwa Kannurkar	44	1	1	2	2	2	1	1	1	2	2	1	1	2	190	4.0	2	11.0	140	100	100	113.3	5	11.5	1	
11	21	B	Parvathi Kanoji	38	1	1	2	2	2	1	1	1	2	2	1	1	2	170	6.0	1	9.4	140	145	130	138.3	6	10	1	F
12	23	B	Sunitha Jade	36	1	1	2	2	1	1	1	1	2	2	2		2	190	5	1	9.6	130	10	80	73.33	5	10	2	
13	24	B	Kalpana Apre	36	1	1	2	2	1	1	1	1	2	2	2		2	260	5		10.1	320	Lost for followup						F
14	25	B	Vanitha M Patil	38	1	1	2	2	2	1	1	1	2	2	1	1	2	215	8	1	10.0	130	100	100	110	6	11	2	
15	28	B	Renuka Naik	36	1	1	2	2	2	1	1	1	2	2	2		2	150	8		9.0	90	85	85	86.67	7	10		
16	29	B	Prema B Hawaldar	35	1	1	2	2	1	1	1	1	2	2	1	1	2	180	5	1	9.2	120	100	100	106.7	5	9.2	2	
17	30	B	Sunitha Pawashe	35	1	1	2	2	2	1	1	1	2	2	2		2	220	7		9.8	140	100	85	108.3	7.2	10		
18	31	B	Jayashree J Bastwade	41	1	1	2	2	2	1	1	1	2	2	1	1	2	235	4		10.0	205	300	Underwent D & C					F
19	33	B	Jayashree Nandgedkar	35	1	1	1	2	2	1	1	1	2	2	2		2	175	5	1	10.1	115	100	100	105	8	10.5	2	
20	39	B	Sujatha Desurkar	41	1	1	2	2	1	1	1	1	2	2	2		2	190	11	1	10.6	110	90	100	100	10	10.5	2	
21	40	B	Aarthi N Desai	44	1	1	2	2	2	1	1	1	2	2	2		2	200	8		9.6	Lost for followup							
22	42	B	Shivannawwa Kolkar	48	1	1	2	2	2	1	1	1	2	2	1	2	2	340	9		9.0	80	0	0	26.67	3	10		
23	43	B	Vanitha Patil	35	1	1	2	2	2	1	1	1	2	2	2		2	170	5.0		9.5	105							
24	44	B	Manisha M Raad	37	1	1	2	2	2	1	1	1	2	2	1	1	2	125	2.0	1	10.0	80	75	90	81.67	6	11	2	
25	47	B	Prema B Hiremath	47	1	1	2	2	2	1	1	1	2	2	2		2	275	7.0	1	10.5	140	140	105	128.3	6	10.5	2	F
26	52	B	Geetha Satish Jamse	35	1	1	2	2	2	1	1	1	2	2	2		2	240	6.0		10.0	70	90	79	79.67	6	10.5		
27	53	B	Sumangala Chikmath	35	1	1	2	2	2	1	1	1	2	2	1	1	2	160	11.0		11.0	Lost for followup							
28	56	B	Anuradha A Desurkar	39	1	1	2	2	1	1	1	1	2	2	2		2	186	11.0	1	10.2	160	80	80	106.7	7	11	2	
29	57	B	Sulochanna Kamble	43	1	1	2	2	2	1	1	1	2	2	1	1	2	220	3.0	1	9.6	100	110	220	143.3	5	9	1	F
30	58	B	Lakshmi Pundalik	43	1	1	2	2	2	1	1	1	2	2	1	1	2	240	6.0	1	10.0	160	100	120	126.7	6	10	2	F
31	59	B	Smitha Patil	44	1	1	2	2	2	1	1	1	2	2	1	1	2	200	10.0		12.5	195	60	20	91.67	4	13		
32	60	B	Laxmi D Modannavar	44	1	1	2	2	2	1	1	1	2	2	1	1	2	410	6.0	1	11.0	170	140	120	143.3	6	11.5	2	F
33	64	B	Mahabooba Roan	40	1	1	2	2	2	1	1	1	2	2	2		2	200	8.0	1	10.5	90	46	20	52	3	12	2	
34	65	B	Shantha Atmaling S	38	1	1	2	2	1	1	1	1	2	2	1	1	2	240	7.0	1	10	140	160	80	126.7	4	11	2	
35	69	B	Lata Narayan Hundre	35	1	1	2	2	2	1	1	1	2	2	1	1	2	230	11.0	1	9	140	120	140	133.3	7	10	2	F
36	72	B	Mahadevi Kalburgi	36	1	1	2	2	1	1	1	1	2	2	2		2	280	8.0		10	Lost for followup							
37	73	B	Leelavathi Akkimani	42	1	1	2	2	1	1	1	1	2	2	1	1	2	180	8.0	1	10	160	100	100	120	6	11	2	
38	74	B	Sujatha Hiremath	38	1	1	2	2	1	1	1	1	2	2	1	1	2	200	5.0	1	9.5	150	80	100	110	7	10.2	2	
39	75	B	Manjula Hunsikatti	40	1	1	2	2	2	1	1	1	2	2	2		2	280	6.0		9	380	Underwent D & C						F
40	78	B	Malik Nargund	38	1	1	2	2	2	1	1	1	2	2	1	1	2	410	5.0	1	9	110	100	100	103.3	5	10.2	2	
41	80	B	Mahadevi S. P.	48	1	1	2	2	2	1	1	1	2	2	1	1	2	170	10.0	1	10	140	80	60	93.33	3	10	2	
42	82	B	Rani S. Murkibhavi	42	1	1	2	2	1	1	1	1	2	2	1	1	2	200	8.0	1	10	120	100	80	100	5	11	2	
42	MEAN			39.62														238.71	6.98		10.03	141.54	106.7	95.11	108	5.86	10.562		14
	S.D.			3.963														80.50	2.38		0.8487	61.357	61.72	48.49	37.8	1.68	0.93		
																						0	2	2					
																						2.13E-08 S	2.30E-10 S	5.99E-11 S		1.07E-02 S	9.21E-08 S		
				0.9800 NS														0.1279 NS	0.1472 NS		0.0529 NS	0.9927 NS	0.0003 S	7.46E-06 S	0.0006 S	0.0224 S	0.2510 NS		0.019 S

S.No		Name	Age (in yrs)	Per speculum examination				Per vaginal examination						H/o previous treatment		H/o chronic illness	PBAC score before treatment	Endometrial thickness prior to treatment (In mm)	HB before treatment	PBAC score			Mean	Endometrial thickness after treatment (In mm)
								Uterus			Fornices	Tenderness	Adnexal Mass							After 1st month	After 2nd month	After 3rd month		
	CODE			Cervix	Vagina	Discharge	VIA	Size	Mobility	Contour				Yes / No	Med/ Surg	Yes / No								
22	A		40	1	1	2	2	2	1	1	1	2	2	2	-	2	265	2	8.2	85	75	70	76.7	4
23	B		36	1	1	2	2	1	1	1	1	2	2	2	-	2	190	5	9.6	130	10	80	73.3	5
24	B		36	1	1	2	2	1	1	1	1	2	2	2	-	2	260	5	10.1	320	Lost for followup			
25	B		38	1	1	2	2	2	1	1	1	2	2	2	-	2	215	8	10.0	130	100	100	110	6
26	A		35	1	1	2	2	2	1	1	1	2	2	2	-	2	270	6	10.5	100	80	60	80	5
27	A		35	1	1	2	2	1	1	1	1	2	2	2	-	2	260	8	10.2	90	85	70	81.7	5
28	B		36	1	1	2	2	2	1	1	1	2	2	2	-	2	150	8	9.0	90	85	85	86.7	7
29	B		35	1	1	2	2	1	1	1	1	2	2	2	-	2	180	5	9.2	120	100	100	107	5
30	B		35	1	1	2	2	2	1	1	1	2	2	2	-	2	220	7	9.8	140	100	85	108	7.2
31	B		41	1	1	2	2	2	1	1	1	2	2	2	-	2	235	4	10.0	205	300	Underwent D & C		
32	A		36	1	1	2	2	1	1	1	1	2	2	2	-	2	220	10	10.0	130	50	0	60	6
33	B		35	1	1	1	2	2	1	1	1	2	2	2	-	2	175	5	10.1	115	100	100	105	8
34	A		39	1	1	2	2	1	1	1	1	2	2	2	-	2	240	5	9.2	200	60	60	107	4
35	A		36	1	1	2	2	2	1	1	1	2	2	2	-	2	205	10	8.5	125	75	60	86.7	6
36	A		35	1	1	2	2	1	1	1	1	2	2	2	-	2	220	11	8.5	95	70	60	75	4
37	A		40	1	1	2	2	1	1	1	1	2	2	2	-	2	340	4	9.0	320	Underwent D & C			
38	A		35	1	1	2	2	1	1	1	1	2	2	2	-	2	280	13	10.5	100	60	0	53.3	7
39	B		41	1	1	2	2	1	1	1	1	2	2	2	-	2	190	11	10.6	110	90	100	100	10
40	B		44	1	1	2	2	2	1	1	1	2	2	2	-	2	200	8	9.6	Lost for followup				
41	A		38	1	1	2	2	2	1	1	1	2	2	1	1	2	250	6	10.0	180	100	120	133	6
42	B		48	1	1	2	2	2	1	1	1	2	2	2	-	2	340	9	9.0	80	0	0	26.7	3

HB after treatment
10
10
11
12
11.5
10
9.2
10
C
12
10.5
10.5
9.6
9.5
11.2
10.5
9.2
10

S.No		Name	Age (in yrs)	Per speculum examination				Per vaginal examination						H/o previous treatment		H/o chronic illness	PBAC score before treatment	Endometrial thickness prior to treatment (In mm)	HB before treatment	PBAC score			Mean	Endometrial thickness after treatment (In mm)
								Uterus			Fornices	Tenderness	Adnexal Mass							After 1st month	After 2nd month	After 3rd month		
	CODE			Cervix	Vagina	Discharge	VIA	Size	Mobility	Contour				Yes / No	Med/Surg	Yes / No								
43	B		35	1	1	2	2	2	1	1	1	2	2	2	-	2	170	5.0	9.5	105				
44	B		37	1	1	2	2	2	1	1	1	2	2	1	1	2	125	2.0	10.0	80	75	90	81.7	6
45	A		42	1	1	2	2	2	1	1	1	2	2	1	1	1	310	5.0	9.0	80	80	60	73.3	3
46	A		39	1	1	2	2	1	1	1	1	2	2	2	-	2	300	11.0	12.1	0	0	0	0	2
47	B		47	1	1	2	2	2	1	1	1	2	2	2	-	2	275	7.0	10.5	140	140	105	128	6
48	A		45	1	1	2	2	2	1	1	1	2	2	2	-	2	200	11.0	10.0	95	30	20	48.3	4
49	A		36	1	1	2	2	2	1	1	1	2	2	2	-	2	240	6.0	10.0	90	40	35	55	4
50	A		35	1	1	2	2	2	1	1	1	2	2	2	-	2	150	6.0	10.0	70	0	0	23.3	10
51	A		38	1	1	2	2	2	1	1	1	2	2	1	1	2	190	3.0	10.0	80	0	0	26.7	4
52	B		35	1	1	2	2	2	1	1	1	2	2	2	-	2	240	6.0	10.0	70	90	79	79.7	6
53	B		35	1	1	2	2	2	1	1	1	2	2	1	1	2	160	11.0	11.0	Lost for followup				
54	A		35	1	1	2	2	1	1	1	1	2	2	1	1	2	185	9.0	10.0	145	80	90	105	6
55	A		35	1	1	2	2	1	1	1	1	2	2	2	-	2	20	6.0	9.0	200	70	60	110	5
56	B		39	1	1	2	2	1	1	1	1	2	2	2	-	2	186	11.0	10.2	160	80	80	107	7
57	B		43	1	1	2	2	2	1	1	1	2	2	2	-	2	220	3.0	9.6	100	110	220	143	5
58	B		43	1	1	2	2	2	1	1	1	2	2	1	1	2	240	6.0	10.0	160	100	120	127	6
59	B		44	1	1	2	2	2	1	1	1	2	2	1	1	2	200	10.0	12.5	195	60	20	91.7	4
60	B		44	1	1	2	2	2	1	1	1	2	2	1	2	2	410	6.0	11.0	170	140	120	143	6
61	A		42	1	1	2	2	2	1	1	1	2	2	2	-	2	320	9.0	8.2	360	Underwent D & C			
62	A		36	1	1	2	2	2	1	1	1	2	2	2	-	2	200	7.0	10.0	340	Underwent D & C			
63	A		45	1	1	2	2	2	1	1	1	2	2	2	-	1	360	10.0	11.8	90	95	20	68.3	4

HB after treatment
11
10
13.6
10.5
11
11
12
11
10.5
10.5
10.2
11
9
10
13
11.5
13

S.No		Name	Age (in yrs)	Per speculum examination				Per vaginal examination						H/o previous treatment		H/o chronic illness	PBAC score before treatment	Endometrial thickness prior to treatment (In mm)	HB before treatment	PBAC score			Mean	Endometrial thickness after treatment (In mm)
								Uterus			Fornices	Tenderness	Adnexal Mass							After 1st month	After 2nd month	After 3rd month		
	CODE			Cervix	Vagina	Discharge	VIA	Size	Mobility	Contour				Yes / No	Med/ Surg	Yes / No								
64	B		40	1	1	2	2	2	1	1	1	2	2	2	-	2	200	8.0	10.5	90	46	20	52	3
65	B		38	1	1	2	2	1	1	1	1	2	2	2	-	2	240	7.0	10	140	160	80	127	4
66	A		42	1	1	2	2	2	1	1	1	2	2	2	-	2	215	8.0	9	215	60	40	105	4
67	A		36	1	1	2	2	2	1	1	1	2	2	2	-	2	230	2.0	10	170	80	40	96.7	5
68	A		35	1	1	2	2	2	1	1	1	2	2	2	-	2	340	6.0	9.2	340	60	40	147	4
69	B		35	1	1	2	2	2	1	1	1	2	2	1	1	2	230	11.0	9	140	120	140	133	7
70	A		35	1	1	2	2	2	1	1	1	2	2	2	-	2	180	10.0	10	60	60	40	53.3	4
71	A		38	1	1	2	2	2	1	1	1	2	2	2	-	2	330	12.0	10	160	0	0	53.3	8
72	B		36	1	1	2	2	1	1	1	1	2	2	2	-	2	280	8.0	10	Lost for followup				
73	B		42	1	1	2	2	1	1	1	1	2	2	1	1	2	180	8.0	10	160	100	100	120	6
74	B		38	1	1	2	2	1	1	1	1	2	2	1	1	2	200	5.0	9.5	150	80	100	110	7
75	B		40	1	1	2	2	2	1	1	1	2	2	2	-	2	280	6.0	9	380	Underwent D & C			
76	A		35	1	1	2	2	2	1	1	1	2	2	2	-	2	320	4.8	7	220	80	0	100	3
77	A		37	1	1	2	2	2	1	1	1	2	2	2	-	2	340	10.0	10	Lost for followup				
78	B		38	1	1	2	2	2	1	1	1	2	2	2	-	2	410	5.0	9	110	100	100	103	5
79	A		48	1	1	2	2	2	1	1	1	2	2	2	-	2	240	11.0	10	170	60	0	76.7	3
80	B		48	1	1	2	2	2	1	1	1	2	2	2	-	2	170	10.0	10	140	80	60	93.3	3
81	A		47	1	1	2	2	1	1	1	1	2	2	1	1	2	280	10.0	10	180	60	40	93.3	4
82	B		42	1	1	2	2	1	1	1	1	2	2	2	-	2	200	8.0	10	120	100	80	100	5
83	A		40	1	1	2	2	2	1	1	1	2	2	1	1	2	300	4.0	8.2	380				
84	A		42	1	1	2	2	2	1	1	1	2	2	2	-	2	200	6.0	9	220	240	225	228	5

HB after treatment
12
11
10
11
10.5
10
11
10
11
10.2
8.5
10.2
11.2
10
11
11
9

	F	
	F	
	F	
	F	
	F	
	F	
	F	
	F	
	F	
	F	
	F	
	F	
1	F	
1	F	
1		
1		
1		
1		
1		
1		
1		
1		
1		
1		
1		
1		
1		
1		
1		
1		1
1		1
2		1
2		1
2		1
2		1
2		1
2		1
2		1
2		1
2		1
2		1

2
2
2
2

1
1
1
1
1
1
1
1
1
1
2
2
2

1
1
1
1
1
1
1
1
1
1
2
2
2
2
2
2
2
2
2
2
2
2
2
2
2
2
2
2
2
2
2
2
2
2
2
2
2
2

1
1
1
1
1
1
1
1
1
1
1
1
1
1
1
1
1
1
1
1
1
1
1
2
2
2
2
2
2
2
2
2
2
2
2
2
2
2

1
1
1
1
1
1
1
1
1
1
1
1
1
1
1
1
1
1

2
2
2
2

2
2
2
2

1
1
1
2
2

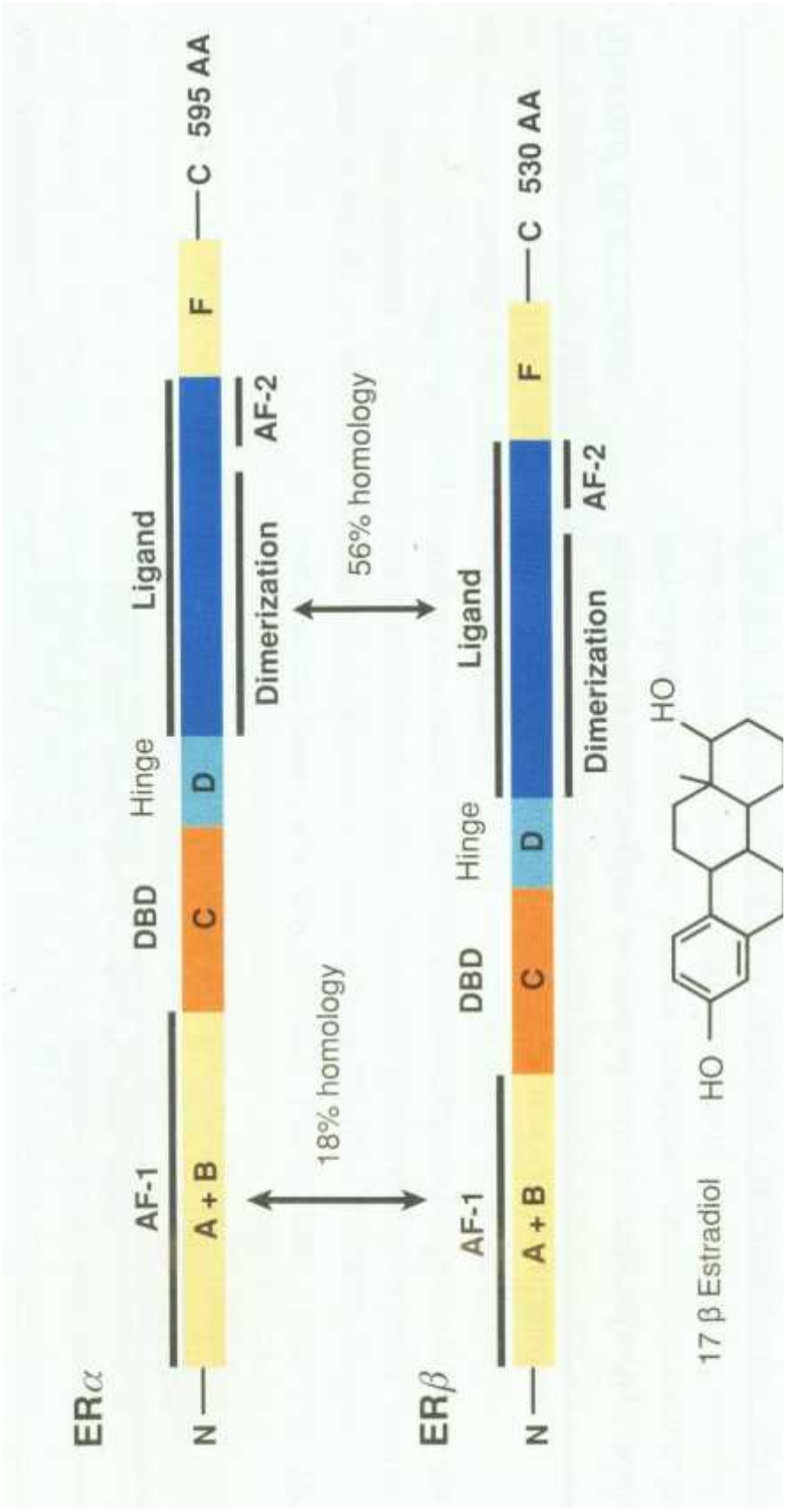


Fig.1 : Estrogen Receptors

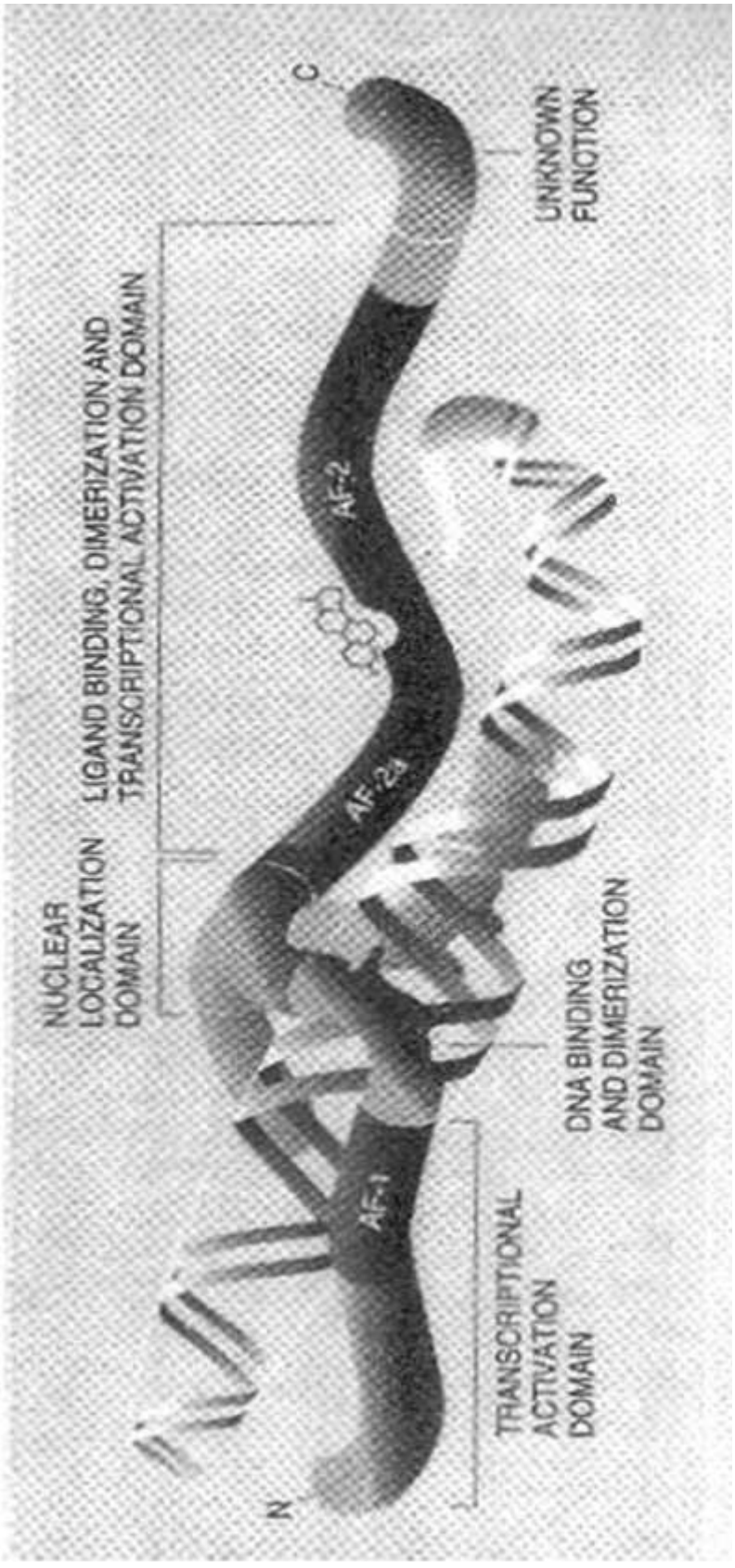


Fig. 2 : Estrogen Receptor

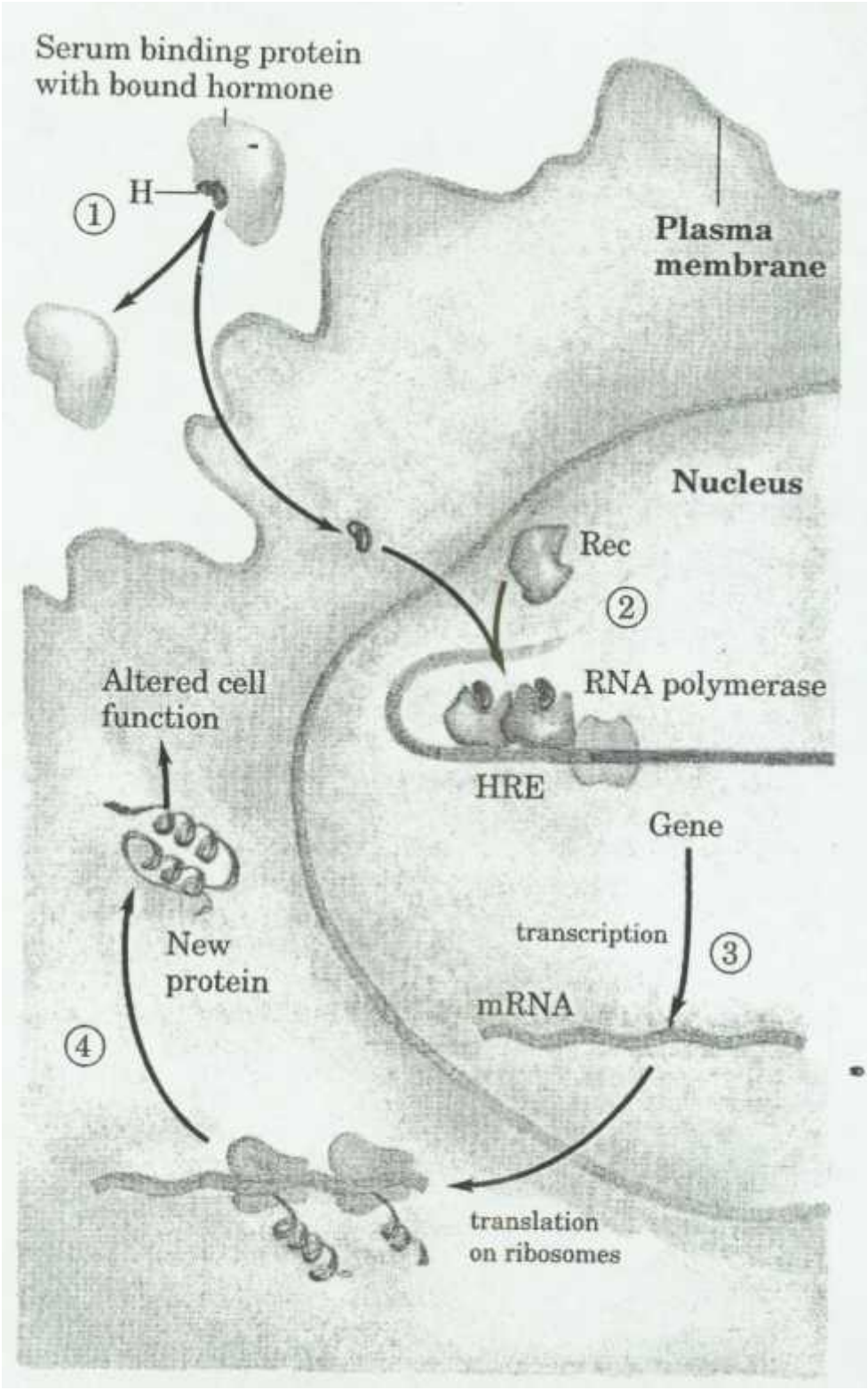
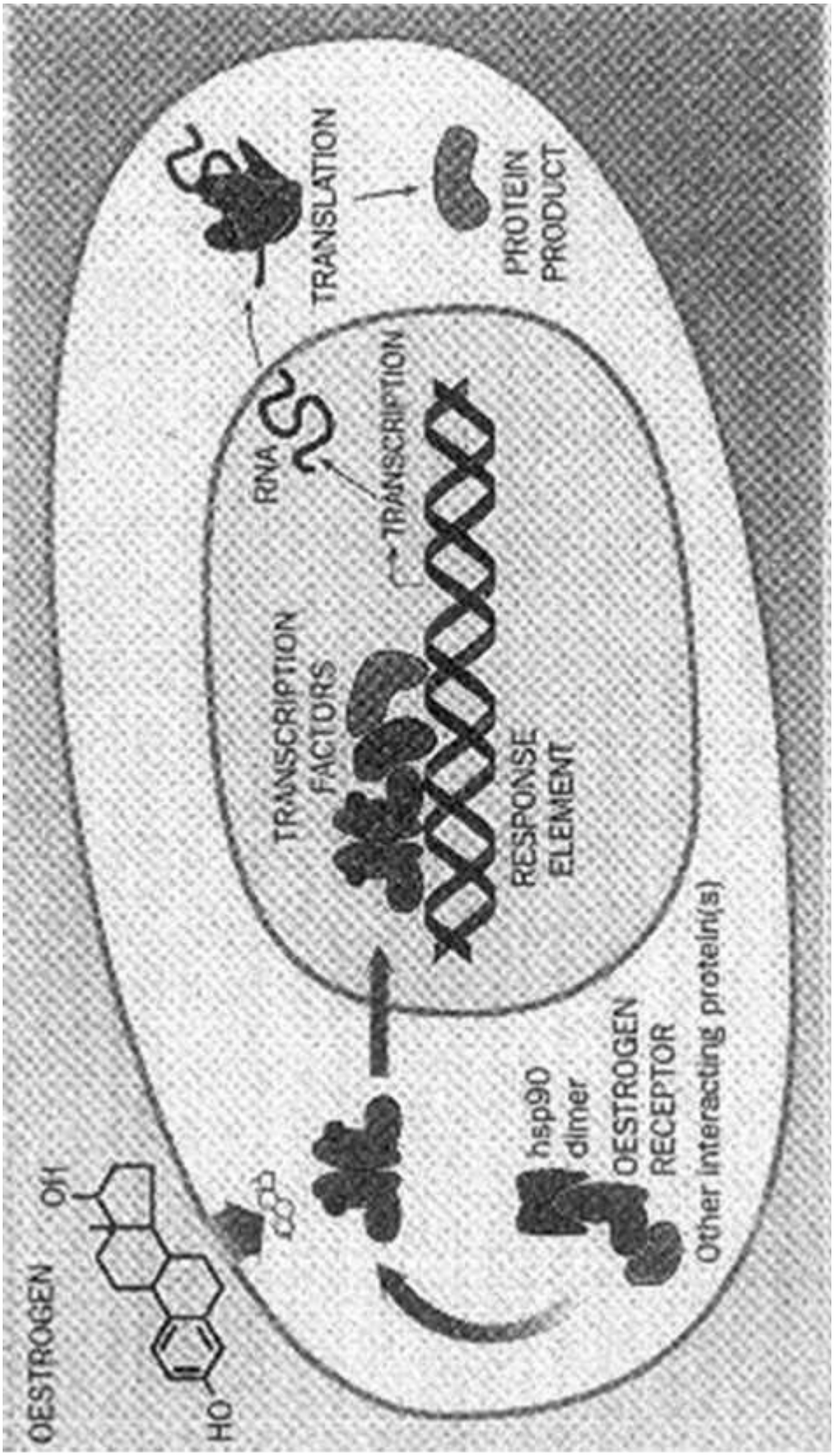


Fig. 3 : Mechanism of Action



hsp90 – heat shock protein90

Fig. 4 : Molecular Action of Estrogen

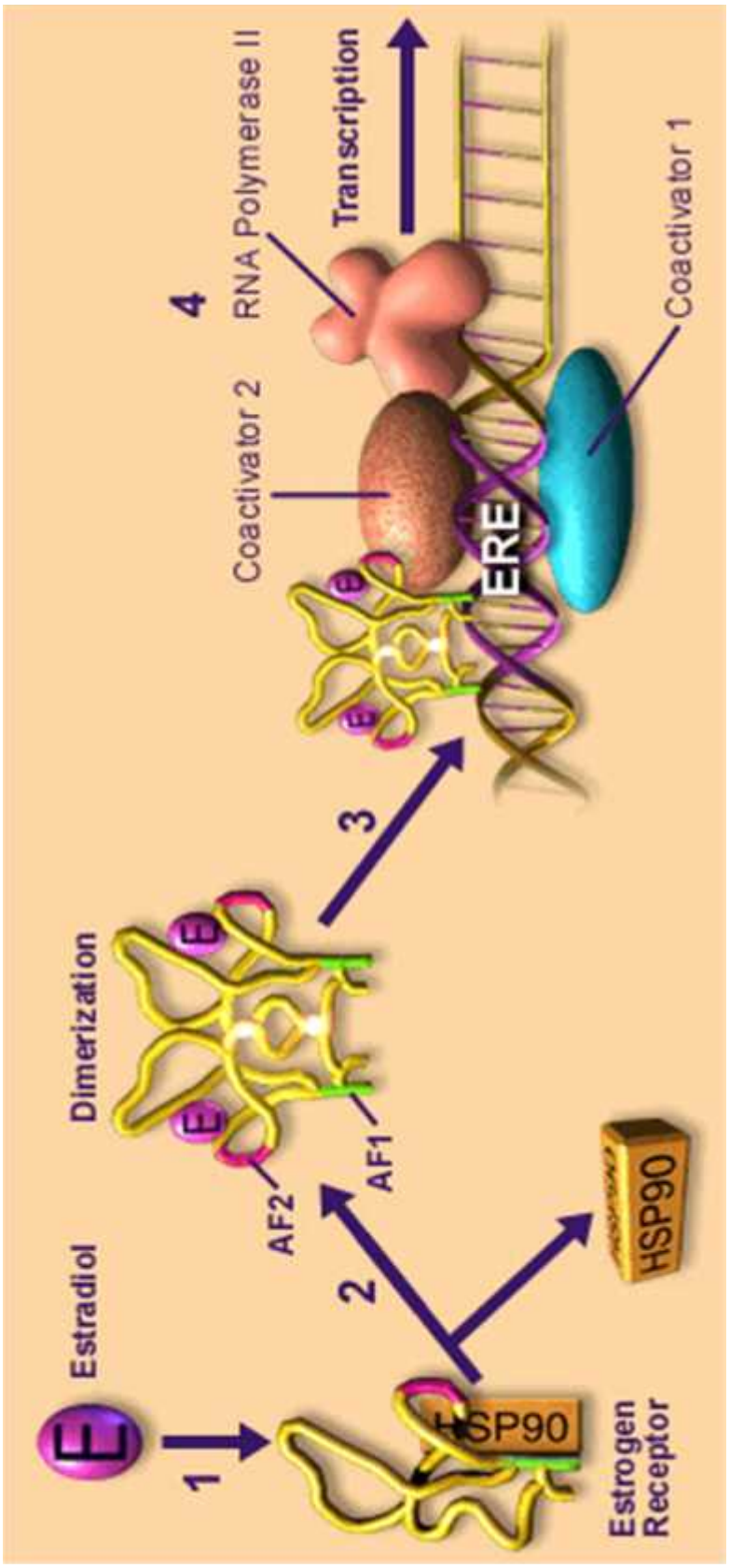


Fig. 5 : MECHANISM OF ACTION AT THE CELLULAR LEVEL

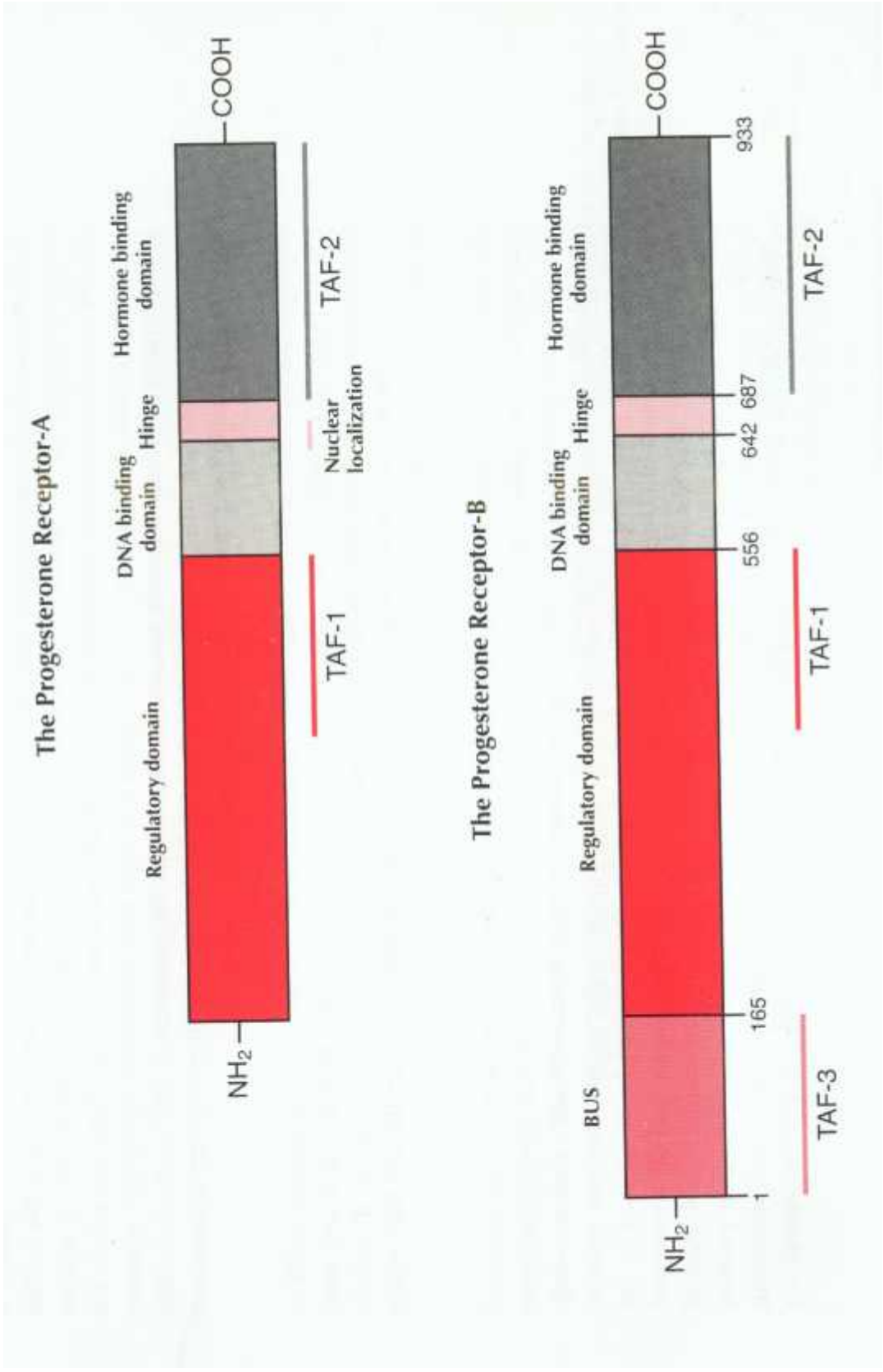


Fig. 6 : Progesterone Receptor

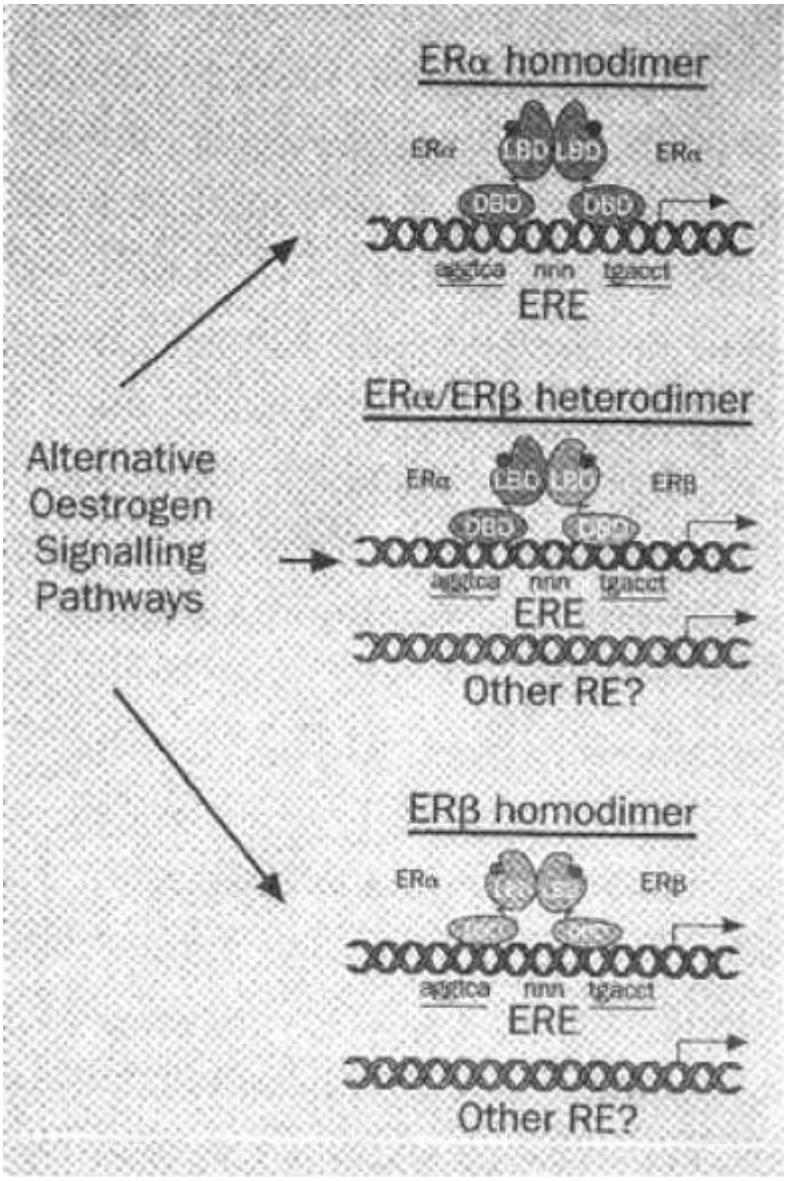


Fig. 7 : Alternative Oestrogen Signalling Pathways

Alternating estrogen signaling pathways

- **~ homodimer**
- **homodimer**
- **~ & heterodimer**
- **Non-genomic effects**

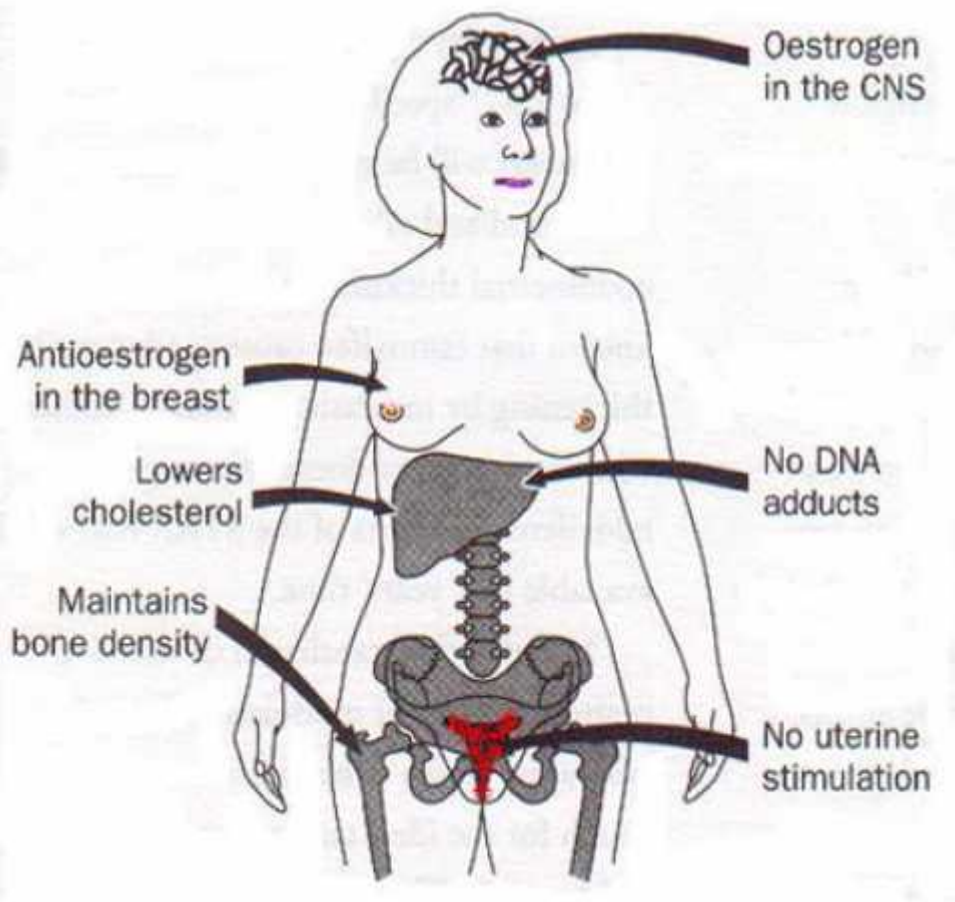


Fig. 8 : The Ideal Selective Ostrogen Receptor Modulator

The ideal SERM is one that prevents bone loss, has no risk of uterine or breast cancer, a +ve effect on lipids & cardiovascular system, relieves PMS and maintains cognitive function of the brain

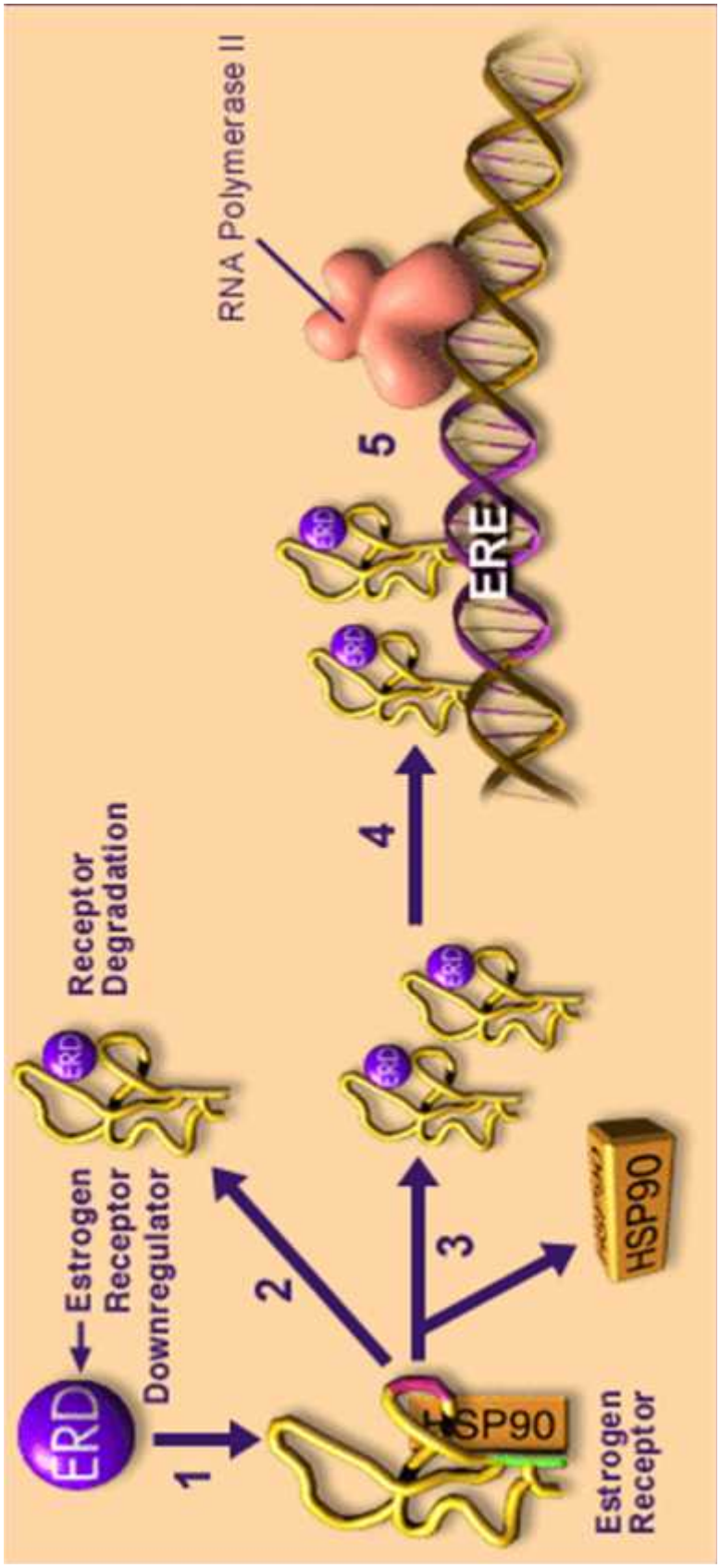


Fig. 9 : Mechanism of Action of Ormeloxifene