International Journal of Reproduction, Contraception, Obstetrics and Gynecology
Laila TR et al. Int J Reprod Contracept Obstet Gynecol. 2024 Jun;13(6):1360-1364
www.ijrcog.org
pISSN 2320-1770 | eISSN 2320-1789

DOI: https://dx.doi.org/10.18203/2320-1770.ijrcog20241281

Original Research Article

Low dose estrogen progestin pill is better than cyclical progestin as medical management of abnormal uterine bleeding due to ovulatory dysfunction in premenopausal women

Tarafdar Runa Laila[1], Khairun Nahar[1], Sheikh Salahuddin Ahmed[2], Bidisha Chakma[1], Walida Afrin[1], Samira Moyeen[1], Hasina Khatun[1], Shakeela Ishrat[3]*

[1]Department of Obstetrics and Gynecology, Bangabandhu Sheikh Mujib Medical University, Dhaka, Bangladesh
[2]Department of Medicine, New Castle University Medicine Malaysia, Johor, Malaysia
[3]Department of Reproductive Endocrinology and Infertility, Bangabandhu Sheikh Mujib Medical University, Dhaka, Bangladesh

Received: 23 March 2024
Accepted: 30 April 2024

***Correspondence:**
Dr. Shakeela Ishrat,
E-mail: shakeelaishrat@bsmmu.edu.bd

ABSTRACT

Background: In abnormal uterine bleeding due to ovulation dysfunction, unopposed estrogen causes persistent proliferative or hyperplastic endometrium and periods of amenorrhea followed by excessive bleeding. This is managed medically by cyclical use of some hormonal agents. The aim of the study was to compare the effectiveness and acceptability of cyclical progestin alone and low dose estrogen progestin pill as medical management of AUB-O in premenopausal women.
Methods: The study composed of 57 premenopausal women with anovular type of bleeding. The study participants were randomly allocated to take either norethisterone 10 mg daily from 16th to 25th day of menstrual cycle or low dose estrogen progesterone pill, one pill daily from 1st day of menstrual cycle up to 24th day. These patients were followed up after three and six months to assess subjectively the persistence of abnormal uterine bleeding, patient's satisfaction, need for hysterectomy and any side effects.
Results: The symptomatic improvement was more apparent with estrogen progestin pill than cyclical norethisterone. More patients chose hysterectomy in the norethisterone group because they were not satisfied with medical management.
Conclusions: Symptomatic improvement is more with low dose estrogen progestin pill than cyclical norethisterone in women with AUB-O. More women decline hysterectomy as they accept estrogen progestin pill.

Keywords: Abnormal uterine bleeding, Anovulatory type, Low dose estrogen-progestin pill, Norethisterone

INTRODUCTION

Any uterine bleeding outside the normal volume, duration, regularity, or frequency is considered abnormal uterine bleeding (AUB). AUB is one of the most common debilitating problems that have a significant impact on health status and quality of women's lives. The prevalence of AUB is 3-30, with higher prevalence clustering at the extremes of reproductive life-perimenarche and premenopause.[1] In 2011, the FIGO classification system (PALM-COEIN) was published to standardize terminology, diagnosis and investigations in women presenting with AUB. The classification system includes nine categories, organized under the acronym ''PALM-COEIN''. PALM group includes four structural etiologies of AUB that can be diagnosed with ultrasound and/or

histopathology (polyp, adenomyosis, leiomyoma, malignancy). COEIN group includes non-structural entities i.e., coagulopathy, ovulatory dysfunction, endometrial, iatrogenic, and not yet classified. AUB accounts for more than 70 of all gynecological consultations in the peri-menopausal age group.[2] Ovulatory disorders are relatively common in premenopausal women. Abnormal uterine bleeding due to ovulatory dysfunction (AUB-O) is a diagnosis of exclusion. *S*tructural causes of bleeding are best assessed with ultrasound preferably Transvaginal Sonography (TVS) which may also guide the need for endometrial sampling to evaluate for hyperplasia or malignancy. Saline infusion sonography is superior to TVS in detecting intrauterine benign lesions.[3] When regular ovulation does not occur, unopposed estrogen exposure may result in a persistent proliferative or hyperplastic endometrium due to ovulatory dysfunction.[4] It is characterized by periods of amenorrhea followed by excessive bleeding. The management of AUB-O in premenopausal age is mainly medical and the aim is to regulate the cycle and reduce the heavy flow. Progestins and estrogens-progestin in combination are already widely used in the management of irregular or heavy bleeding due to disturbed ovulation, but the regime, dose and type of progestins used vary widely with little consensus about the optimum treatment approach. The unwanted effects of progestin vary according to the type and dose of progestin, whether the preparations are given cyclically (for up to three weeks in a month) or continuously and vary between individuals. Common non menstrual unwanted effects of progestin include headaches, weight gain and breast tenderness. Irregular bleeding and spotting are common side effects of progestin of all types and regimes, particularly continuous low-dose preparations.[5] When medical treatment fails hysterectomy is done. In many instances patient does not undergo adequate medical treatment as there is little consensus about the optimum treatment approach regarding the regime and type of drug. Commonly cyclical oral progestin is used. Now a days very low dose estrogen progestin pill having anti-mineral corticoid activity are available in our country. These can be prescribed safely to premenopausal women who have no contraindications. There is a paucity of randomized studies relating to the use of progestin and estrogen-progestin combination in the treatment of irregular menstrual bleeding associated with anovulation.[6] So, this study has been designed to determine and compare the effectiveness and acceptability of cyclical progestin and low dose estrogen progesterone pill in the management of AUB-O in premenopausal women.

METHODS

This prospective observational comparative study was conducted in the department of Obstetrics & Gynecology of Bangabandhu Sheikh Mujib Medical University (BSMMU) during the period of 1st July 2022 to 30th June 2023 after obtaining Institutional Review Board approval. A total 57 study subjects were enrolled upon fulfilling inclusion and exclusion criteria from the outpatient department of Obstetrics and Gynecology BSMMU. Initial screening included a questionnaire to aid with the determination of eligibility and other baseline data. Inclusion criteria were: premenopausal women within the age range of 40-53 years having anovulatory pattern of abnormal uterine bleeding. Exclusion criteria were: uterine pathology (fibroid uterus, adenomyosis, uterine polyp, cervical or endometrial carcinoma), chronic liver disease, migraine, epilepsy, uncontrolled hypertension, uncontrolled diabetes mellitus, coagulation disorder, history of thromboembolism and breast malignancy. Routine physical and gynecologic examinations were done including the pelvic ultrasound for selection of the cases. Eligible women were invited to participate in the study. The exact nature and purpose of the study was explained to them and those who signed the approved informed consent document were consecutively enrolled. Enrollees were randomly assigned to either norethisterone group or to OCP group. Women assigned to norethisterone group received 5 mg norethisterone twice daily from 16th to 25th day of menstrual cycle. Those assigned to OCP group were given one pill (Ethinylestradiol 0.02 mg and Drospirenone 3 mg) daily from 1st day of menstrual cycle up to 24 days as per instruction of the attached leaflet. To find out the effectiveness of this treatment regime patients were followed up after 3 month and 6 months by face-to-face visits or telephone interviews. The outcome variables included the persistence of abnormal uterine bleeding assessed subjectively using patient's observations in Likert scale, patient's satisfaction with treatment as measured with Likert scale, any need for hysterectomy from the woman's perspective and appearance of any side effect of the drugs. SPSS version 26 was used for analysis**.** Socio-demographic, clinical and laboratory characteristics were summarized as frequency for categorical variables, mean±SD for continuous variables.

RESULTS

A total of 57 participants were recruited for the study, 32 in norethisterone group and 25 in the OCP group. Three patients dropped out from the norethisterone group before first follow up at 3 months. Seven out of 29 patients in the norethisterone group were lost to follow up after 6 months. The base line sociodemographic and clinical characteristics of the study participants are described in (Table 1 and 2, Figure 1-3) describes the severity of symptoms at baseline, after 3 months and after 6 months in the two groups.

Unbearable symptoms were present in both groups at baseline, but not after 3 months. Instead, there were patients with no symptoms appearing after 3 months and their proportion substantially increased after 6 months, comparatively more in the OCP group. Table 3 shows that unsatisfied patients were 1.49 times more (after 3 months) and 2.56 times more (after 6 months) in the norethisterone group compared to OCP group.

Table 1: Sociodemographic characteristics of study participants.

Characteristics	Norethisterone (n=32), Frequency (%)	Low dose oral contraceptive (n=25), Frequency (%)	P value
Age (years) mean±SD	42.94±3.068	42.56±3.015	0.644
Residence (%)			
Rural	43.8	28.0	0.221
Urban	56.3	72.0	
Occupation (%)			
Housewife	84.4	96.0	0.156
Service	15.6	4.0	
Monthly income in Taka*			
Lower class (≤7,378)	2 (6.3)	1 (4.0)	
Lower middle class (7,379-<28,810)	19 (59.4)	19 (76.0)	0.537
Upper middle class (28,811-89,280)	10 (31.3)	5 (20.0)	
Upper class (>89,281)	1 (3.1)	0 (0.0)	

*World Bank Data Team on July 2020

Table 2: Baseline clinical characteristics of study participants.

Characteristics	Norethisterone (n=32)	Low dose oral contraceptive (n=25)	P value
Duration of symptoms, Frequency (%) (months)			
<6	8 (25.0)	6 (24.0)	
6-12	13 (40.6)	10 (40.0)	0.991
>12	11 (34.4)	9 (36.0)	
Duration of menstrual period (%) (days)			
<10	14 (43.8)	16 (64.0)	
10-20	17 (53.1)	8 (32.0)	0.279
>20	1 (3.1)	1 (4.0)	
BMI (kg/m^2) mean±SD	23.14±5.85	22.83±3.218	0.810
Haemoglobin (gm/dl) mean±SD	9.53±1.82	10.05±1.509	0.252
Serum Ferritin (ng/ml) median (interquartile range)*	11.42 (7.85-17.90)	14.93 (7.85-17.90)	0.923

*Non homogeneous distribution

Table 3: Unsatisfied patients in both groups after 3 and 6 months and patients who opted for hysterectomy after 3 months.

Parameters	Norethisterone		Oral contraceptive pills		Relative risk (RR)	95 CI of RR	P value
Unsatisfied after 3 months	19/29	65.5	11/25	44.0	1.48	0.89-2.49	0.113
Unsatisfied after 6 months	9/22	40.9	4/25	16.0	2.55	0.91-7.15	0.057
Opted for hysterectomy	6/29	20.7	3/25	12.0	1.72	0.48-6.19	0.393

Table 4: Adverse effects of the drugs.

Adverse effect	Norethisterone (n=29), Frequency (%)	Low dose oral contraceptive (n=25), Frequency (%)
Headache	10 (34.48)	6 (24)
Weight gain	6 (20.68)	10 (40)
Breast tenderness	12 (41.37)	10 (40)
Nausea	8 (27.58)	8 (32)
Mood change	12 (41.37)	8 (32)
Intermenstrual bleeding	4 (13.79)	10 (40)

Patients who opted for hysterectomy were 1.72 times more in the norethisterone group compared to the OCP group. The (Table 4) shows the adverse effects of the drugs. The norethisterone group mostly had headache, breast tenderness and mood change. The OCP group had weight gain, breast tenderness and intermenstrual bleeding.

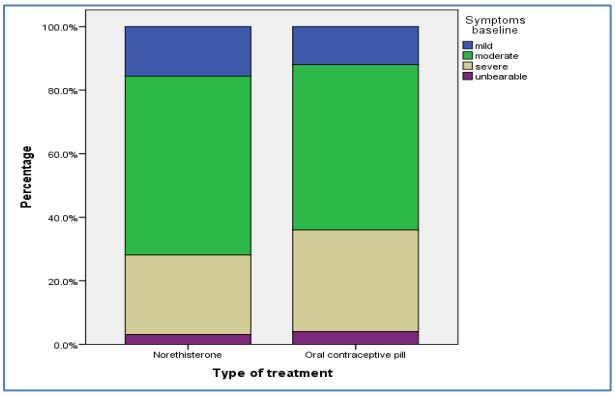

Figure 1: Distribution of symptom severity in patients given norethisterone (n=32) and oral contraceptive pills (n=25).

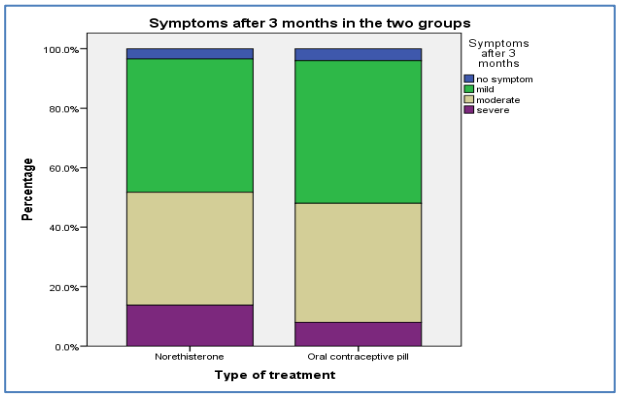

Figure 2: Distribution of symptom severity in patients given norethisterone (n=29) and oral contraceptive pills (n=25).

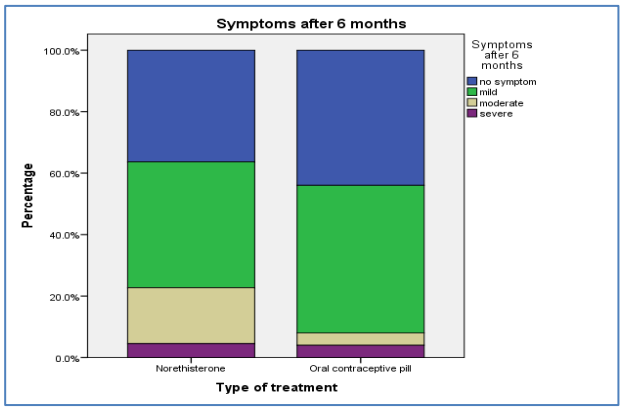

Figure 3: Distribution of symptom severity in patients given norethisterone (n=22) and oral contraceptive pills (n=25).

DISCUSSION

The objective of this study was to assess and compare the effectiveness and acceptability of norethisterone and estrogen progestin pill in premenopausal women with AUB-O. The results showed that symptomatic improvement was more apparent with estrogen progestin pill than with cyclical progestin norethisterone and more patients opted for hysterectomy when given cyclical norethisterone because they were not satisfied with medical management. Literature review reveals many studies on the effectiveness of cyclical progestin or estrogen progestin pill on anovulatory bleeding in women including PCOS, but studies on premenopausal women with anovulatory bleeding are few. To the best of our knowledge there has been no such comparative study as ours of the effect of cyclical progestin and estrogen progestin pill on anovulatory bleeding of pre-menopausal women.

Progesterone derivatives or progestins have been used for years in treatment of abnormal uterine bleeding due to ovulatory dysfunction. Fraser et al, 1990 published the study of 6 patients of AUB-O given 5 mg of norethisterone acetate or 10 mg of medroxy progesterone acetate (MPA) from days 12 to 25 of the cycle; there was 39 and 51 decrease in menstrual blood loss after first and second month respectively.[7] Dunphy et al, 1998 reported a 25 and 41 reduction in bleeding after 1 and 2 months when 11 women with AUB-O received luteal phase progesterone MPA from day 16 to 25 of the cycle.[8] Bender RA, 2022 reported that improved menstrual cycle, decreased abnormal uterine bleeding, and decreased prolonged MPA requirement were achieved with MPA given on the 16th and 25th days, rather than on the 11th and 25th days of the cycle.[9] Combined oral hormonal contraceptives has been used traditionally as treatment of abnormal uterine bleeding where ovulation dysfunction is the cause, but the data comparing this treatment to that with cyclical progesterone is scarce.[10] Few studies reported the effectiveness of COC containing estradiol valerate and dydrogesterone in reducing heavy menstrual blood loss, and improving hemoglobin concentration in blood and quality of life, while compared to placebo.[10]The American College of Obstetricians and Gynecologist recommends OCP to regulate cycle and to reduce menstrual blood loss in adolescents aged 13-18 years as well as in women 18 to 39 year old.[11] Cyclical progesterone or low dose OCP may be prescribed in women from 40 to menopause for the same purpose. Conditions of ovulation dysfunction include PCOS, thyroid disorders, hyperprolactinemia and premature ovarian failure. Ovulation dysfunction physiologically occurs in premenopausal women due to reduced number and quality of oocytes and in adolescents due to immaturity of hypo-thalamo -pituitary axis. Absence of ovulation and corpus luteum formation results in lack of progesterone and unopposed estrogen secretion. There is continual endometrial proliferation without any shedding induced by progesterone withdrawal. The endometrium is fragile and vascular without any stromal support.[11] The affected women clinically present with unpredictable menstrual bleeding and heavy menstrual

bleeding. Women of reproductive age are considered to have AUB-O when they have unpredictable bleeding, sometimes interspersed with periods of amenorrhea.[1] The likelihood of unscheduled and potentially heavy bleeding can be decreased by regulating cycles with hormonal medication in women with prolonged and heavy menstruation.[12] To the best of our knowledge ACOG is the first society to recommend specific treatment of AUB-O. Low dose oral contraceptive pills, when prescribed to premenopausal women suffering from AUB-O, results in better symptom control and better satisfaction than cyclical progesterone. Oral combined hormonal contraceptives have some additional benefits in this group of women. There is a benefit of contraception against the risk of unwanted pregnancy. Oral contraceptive pills ameliorate the vasomotor symptoms like menstrual migraine (headaches related to fall in estrogen) that affects more than 60 premenopausal women.[13-15] The hormonal contraceptives prevent bone demineralization and enhances bone mass density both of which provides protection against osteoporosis in postmenopausal women.[16] The incidence of endometrial ovarian and colorectal cancer peaks at premenopausal age and combined hormonal contraceptives reduces the risk of these cancers.[17]

CONCLUSION

Symptomatic improvement is more with combined estrogen progestin pill than with cyclical norethisterone in patients with AUB-O without any serious side effects. More women decline hysterectomy as they accept estrogen progestin pill.

Funding: Bangabandhu Sheikh Mujib Medical University
Conflict of interest: None declared
Ethical approval: The study was approved by the Institutional Ethics Committee

REFERENCES

1. Munro MG, Critchley HO, Broder MS, Fraser IS. FIGO classification system (PALM-COEIN) for causes of abnormal uterine bleeding in nongravid women of reproductive age. Int J Gynaecol Obstet. 2011;113(1):3-13.
2. Mahajan N, Aggarwal M, Bagga A. Health issues of menopausal women in North India. J Midlife Health. 2012;3:84-7.
3. Vitale SG, Watrowski R, Barra F, D'Alterio MN, Carugno J, Sathyapalan T, et al. Abnormal Uterine Bleeding in Perimenopausal Women: The Role of Hysteroscopy and its Impact on Quality of Life and Sexuality. Diagnostics (Basel). 2022;12(5):1176.
4. Lacey JVJ, Chia VM. Endometrial hyperplasia and the risk of progression to carcinoma. Maturitas. 2009;63(1):39-44.
5. Hickey M, Salamonsen LA. Endometrial structural and inflammatory changes with exogenous progestogens. Trend Endocrinol Metab. 2008;19(5):167-74.
6. Hickey M, Jenny M, Higham J M, Fraser I. Progestogens with or without oestrogen for irregular uterine bleeding associated with anovulation. Cochrane Datab Syst Rev. 2012;9:CD001895.
7. Fraser IS. Treatment of ovulatory and anovulatory dysfunctional uterine bleeding with oral progestogens. Aust N Z J Obstet Gynaecol 1990;30(4):353-6.
8. Dunphy BC, Goerzen J, Greene CA, Ronde SDL, Seidel J, Ingelson B. A double-blind randomized study comparing danazol and medroxyprogesterone acetate in the management of menorrhagia. J Obstet Gynaecol. 1998;18(6):553-5.
9. Bender RA. Medroxyprogesterone Acetate for abnormal uterine bleeding due to ovulatory dysfunction: The effect of 2 different-duration regimens. Med Sci Monit. 2022;28:e936727.
10. Lethaby A, Wise MR, Waterings MAZ, Rodriguez MB, Brown J. Combined hormonal contraceptives for heavy menstrual bleeding. Cochrane Database of Systematic Reviews 2019, 2019(2):34-7.
11. Rodriguez MB. Management of abnormal uterine bleeding associated with ovulatory dysfunction. Am Coll Obstet Gynecol. 2013;122(1):176-85.
12. Singh S, Best C, Dunn S, Leyland N, Wolfman WL. Abnormal uterine bleeding in pre-menopausal women. J Obstet Gynaecol Can. 2013;35(5):473-9.
13. Di Bella ZIK, De Mello Bianchi AMH, De Araujo FF, Sartori MGF, Girão MJBC. Contraception and family planning at the extreme of reproductive life - climacteric. Rev Assoc Medica Bras. 2016;62(5):454-7.
14. Marret H, Fauconnier A, Chabbert-Buffet N, Cravello L, Golfier F, Gondry J, et al. Clinical practice guidelines on menorrhagia: management of abnormal uterine bleeding before menopause. Eur J Obstet Gynecol Reprod Biol. 2010;152(2):133-7.
15. MacGregor EA. Menstrual and perimenopausal migraine: a narrative review. Maturitas. 2020;142:24-30.
16. Gambacciani M, Monteleone P, Ciaponi M, Sacco A, Genazzani AR. Effects of oral contraceptives on bone mineral density. Treat Endocrinol. 2004;3(3):191-6.
17. Cibula D, Gompel A, Mueck AO, Vecchia CL, Hannaford PC, Skouby SO, et al. Hormonal contraception and risk of cancer. Hum Reprod. 2010;16(6):631-50.

Cite this article as: Laila TR, Nahar K, Ahmed SS, Chakma B, Afrin W, Moyeen S, et al. Low dose estrogen progestin pill is better than cyclical progestin as medical management of abnormal uterine bleeding due to ovulatory dysfunction in premenopausal women. Int J Reprod Contracept Obstet Gynecol 2024;13:1360-4.