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ORIGINAL ARTICLE

A Comparison between Effectiveness of Norethisterone and Dydrogesterone for treatment of Irregular Menstrual Cycle due to Abnormal Uterine bleeding of Ovulatory and/or Endometrial Dysfunction in women presenting at Gynae Outdoor of a tertiary care hospital

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ABSTRACT

Background: Abnormal uterine bleeding is defined as irregularities in the menstrual cycle involving frequency, regularity, duration, and volume of flow outside of pregnancy. Up to 1/3rd of women experience abnormal uterine bleeding in their life, with irregularities most commonly occurs at menarche and perimenopause due to disruption of the hypothalamic-pituitary-ovarian axis.
Aim: To compare the effectiveness of Norethisterone and Dydrogesterone for the treatment of irregular menstrual cycles due to abnormal uterine bleeding of ovulatory or endometrial dysfunction and to check for patient satisfaction after the use of prescribed hormones by taking their feedback.
Methods: This observational, comparative, cohort-prospective study was conducted on 100 nonpregnant women between the ages of 15-45 years who presented with complaints of irregular menstruation in gynae outdoor of AMTH for 6 months from April 2021 to September 2021. After excluding pelvic pathology, known thyroid disease, coagulation disorder, or use of the contraceptive method, the participants were divided into Group A and Group B, each having 50 participants.
Results: The mean age±SD of the participants in Group A was 29±3.4 while Group B had mean age±SD was 29.5±3.6. In Group A, 38(76%) patients reported a regular menstrual cycle after 3 months of use while 12(24%) patients complained of persistent irregular menstrual cycle despite 3 months use of Norethisterone with compliance in Group B using Dydrogesterone, 22(44%) patients had regular menstrual cycles while 28(56%) patients had persistent irregular menstrual cycles after three months of use.
Conclusion: So we concluded from our study that Norethisterone had a better cycle control than Dydrogesterone.
Keywords: Abnormal uterine bleeding of ovulatory and/or endometrial dysfunction, Norethisterone, Dydrogesterone,

INTRODUCTION

Abnormal uterine bleeding (AUB) is defined as any aberration of the menstrual cycle in terms of menstrual volume, regulation, duration, and frequency in non-pregnant females[1]. The prevalence of AUB is 3-30% with higher rates reported at extremes of reproductive ages[2]. FIGO has classified AUB by using the acronym PALM-COEIN to categorize the etiology of AUB as Polyp, Adenomyosis, Leiomyoma, Malignancy (PALM) and Coagulopathy, Ovulatory disorders, Endometrial disorders, Iatrogenic, Not yet classified (COEIN). The PALM is assessed visually by ultrasound imaging and endometrial biopsy while COEIN is the non-structural cause of abnormal uterine bleeding[3].

Here we took abnormal uterine bleeding in premenopausal and perimenopause women, occurring due to ovulatory and endometrial dysfunction after excluding pelvic pathology, known thyroid disorder, coagulation disorder, or iatrogenic causes of bleeding like IUCD use. An ovulatory abnormal uterine bleeding results from delayed or absent ovulation that is either physiological (immature HPO axis) or due to PCO. This anovulation leads to progesterone deficiency and excessive estrogen production from ovarian follicles ultimately causing endometrial proliferation that is prone to unpredictable uterine bleeding varying in timing and amount[4,5]. In endometrial AUB, the primary endometrial dysfunction, which may be due to deficient local vasoconstrictor production or excessive plasminogen activator, prostaglandin, and prostacyclin production, leads to AUB-E. AUB-E may be caused by inflammation and infection of the endometrium[6]. For the treatment of irregular menstruation due to an ovulatory or endometrial dysfunction, cyclical progesterones like Norethisterone and Dydrogesterone should be prescribed to schedule orderly withdrawal bleeding by stopping excessive endometrial thickening[7]. Norethisterone is a synthetic progesterone that is derived from testosterone. It can bind to progesterone, estrogen, and androgen receptors. It is currently listed as the WHO Model List of Essential Medicines as a drug used for the treatment of abnormal uterine bleeding caused by hormonal imbalance in the absence of pelvic pathology. It is available as an oral formulation of 5mg. It is contraindicated in undiagnosed vaginal bleeding, known sensitivity to the drug, impaired liver function, CA breast, or history of depression. Its side effects include fluid retention, edema, weight gain, nausea, breast tenderness, depression, amenorrhea, breakthrough bleeding.[8] Dydrogesterone is orally active retroprogesterone, a stereoisomer of progesterone that differs slightly in molecular structure from natural progestins. It has highly selective binding to the progesterone receptor. It has good efficacy in treating irregular menstrual cycles. Dydrogesterone is a C21 derivative and it has less androgenic side effects[9,10]. The lifetime prevalence of AUB is 5-15% and almost 1/3rd of the gynecological outdoor consultations are done for the complaint of AUB in Pakistan[11]. The abnormal uterine bleeding resulting in irregular menstruation affects women's physical and psychological health and has economic consequences in terms of health care costs due to the consumption of prescribed costly hormones.[12] Health problems arising from menstrual irregularity can adversely affect employment prospects[13].

Rationale: To find out the most effective, cheap hormone to be prescribed to regulate the menstrual cycle thus treating abnormal uterine bleeding (O, E) and minimizing its debilitating effects on the life of our female population.

The objective of the study was to compare the effectiveness of Norethisterone and Dydrogesterone for the treatment of irregular menstrual cycle due to abnormal uterine bleeding of ovulatory and/or endometrial dysfunction and check for patient satisfaction after the use of prescribed hormones by taking their feedback.

Operational definition:

Regular menstrual cycle: The cycle was labeled as regular if the length of the menstrual cycle was between 21-35 days with the regular pattern.

Irregular menstrual cycle: The cycle was labeled as irregular if the length of the menstrual cycle was less than 21 or more than 35 days with an irregular pattern.

Effectiveness: The two hormones prescribed were labeled to be effective if the menstrual cycle become regular after 3 months of use of the respective hormone.

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MATERIALS AND METHODS

Approval was taken from the Ethical Review Board of Rashid Latif Medical Complex. This prospective observational, comparative study was carried out for a period of 6 months from April 21 to Sept 21 on 100 women by doing convenient sampling, after permission from IRB and taking their written informed consent and maintaining their confidentiality who presented in Gynae outdoor of Arif Memorial Teaching Hospital.

The inclusion criteria for the study population was

- All women between the ages of 15-45 years have an irregular menstrual cycle for at least 3 months.
- The study population has irregular menstruation without any recognizable pelvic pathology, coagulopathy, known thyroid disorder, or use of any contraceptive method.

The exclusion criteria were all women who did not tolerate the side effect of the drug during the study period and patients having contraindications to the use of progesterone e.g. those having active liver disease.

The patients who agreed to participate in the study were diagnosed as having abnormal uterine bleeding due to an ovulatory cycles and/or endometrial dysfunction after excluding underlying pelvic pathology by taking a detailed history, examination, and certain investigation. In history, menstrual cycle pattern (regular/irregular), amount of bleeding, any dysmenorrhea, dyspareunia, any bleeding disorder, or symptoms of thyroid disease were inquired. History was also taken about intake of any non-hormonal or hormonal prior treatment, use of any contraceptive methods, or anticoagulant drugs (Warfarin or heparin). General physical examination to check for pallor, enlarged thyroid, petechae, was done. Abdominal examination was done to palpate for liver, spleen, and any abdominopelvic mass. Speculum and pelvic examination were carried out to exclude any pelvic pathology like infection, polyp, IUCD thread, fibroid, ovarian cyst respectively. Investigations included a complete blood count to assess the severity of anemia, coagulation profile, and TFT to rule out coagulation disorder and subclinical thyroid disorder respectively. Pelvic/Transvaginal ultrasound was advised to patients to exclude a pelvic pathology including fibroid, ovarian cyst, endometrial polyp, IUCD. Endometrial thickness was also noticed to rule out the suspicion of any endometrial hyperplasia/ malignancy. The patients were explained about the nature of the hormone, the need for compliance to take the hormones, and the side effects of both hormonal preparations. The 100 females enrolled were divided into 2 groups. No patient in either group was prescribed with NSAID or anti fibrinolytic to control the irregular bleeding during the use of the two prescribed hormones.

Group A: Containing 50 women with an irregular menstrual cycle. They have been prescribed with tablet Norethisterone 5mg three times a day on any day of irregular periods for 10 days. Usually, the bleeding stopped in the next 72 hours. After completing the 10 days course, a withdrawal bleed occurred and then the females in group A were prescribed with tablet Norethisterone 5mg three times a day from day 5 -25 taking 1st day of withdrawal bleed as 1st day of the menstrual cycle. After completion of 21 days course, on stopping the intake of a hormone, they had a withdrawal bleed and they were advised to restart to take the tablet from day 5-25 for the next 3 cycles. They were called for follow-up on the 1st day of withdrawal bleed to make a notice of the menstrual cycle pattern. Those patients having persistent irregular menstruation were called for follow-up on any day during the use of that particular drug.

Group B: 50 women in group B were prescribed tablet Dydrogesterone 10mg 2 times a day for 7 days. The bleeding stopped in the next 48-72 hours. After completing 7 days course, a withdrawal bleed occurred on the 1st day which was taken as the 1st day of the next menstrual cycle. So here the women of group B were prescribed with tablet Dydrogesterone 10mg twice a day from day 5-25th of the cycle. They were advised to take the same regimen every 5-25 days for the next 3 cycles. They were also called for follow-up on a monthly basis on1st the day of withdrawal bleed to ask about the menstrual cycle pattern. Those patients having persistent irregular menstruation were called for follow-up on any day during the use of that particular drug. At the completion of 3 months, the patient's satisfaction rate after the use of prescribed hormones was noted by asking them to fill a feedback proforma. Data were analyzed using SPSS version 25. Age was presented as mean and standard deviation. P-value was calculated to assess the level of significance. The patient satisfaction rate was calculated as a percentage.

RESULTS

Group A had mean age±SD= 29±3.4 while Group B had mean age±SD= 29.5±3.6. After application of t-test; T=1.83, p-value< 0.05 so in terms of mean age, there was no substantial difference between the two groups as shown in table 1.

Table 1: Feature of the study population

Groups	n	Age (mean±SD)
A	50	29±3.4
B	50	29.5±3.6

To compare the effectiveness of two hormones, a note was made of menstrual cycle regulation in both groups. In Group A, the participants were prescribed with Norethisterone, 38(76%) patients reported a regular menstrual cycle after 3 months of use while 12(24%) patients complained of persistent irregular menstrual cycle despite 3 months use of Norethisterone with compliance. In Group B using Dydrogesterone, 22(44%) patients had regular menstrual cycle while 28(56%) patients had persistent irregular menstrual cycle after three treatment given to the patients in two groups, there was a very significant difference between the two groups, and Norethisterone was months of use with compliance. So we applied a chi-square test that was (X^2)= 16.9 and calculated p-value to compare the effectiveness of the two hormones for the treatment of abnormal uterine bleeding and found out significant p-value >0.05. So we concluded on the basis of these results that according to the type of found to have a better cycle control than Dydrogesterone.

Figure 1: Percentage of patients with the regular menstrual cycle in Group A (Norethisterone) and Group B (Dydrogesterone)

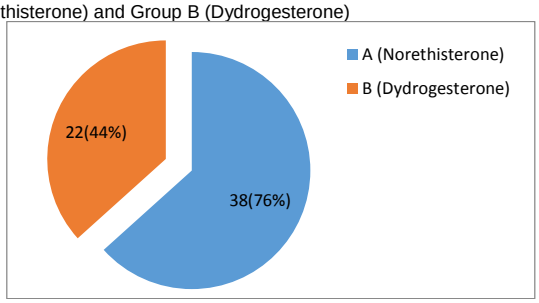

Figure 2: Percentage of patients with the irregular menstrual cycle in Group A (Norethisterone) and Group B (Dydrogesterone)

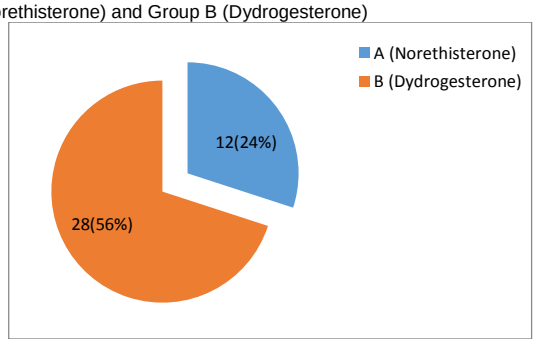

Table 2: Determination of the effectiveness of Norethisterone vs Dydrogesterone

Groups	Menstrual cycle Regularized	Irregular menstrual cycle	Total
A (Norethisterone)	38 (76 %)	12 (24 %)	50
B (Dydrogesterone)	22 (44 %)	28 (56 %)	50

The patient satisfaction rate was calculated as patient satisfaction rate= satisfied responses/total number of responses x 100. For Group A using Norethisterone, the patient satisfaction rate was calculated to be 76% which was considerably higher than Group B using Dydrogesterone i.e., 44%.

DISCUSSION

Abnormal uterine bleeding that occurs in the absence of recognizable pelvic pathology, medical disorders, pregnancy, coagulopathy, and contraceptive use reflects a disruption in a normal cyclical pattern of ovulation leading to abnormal hormonal stimulation to the endometrial lining resulting in an unpredictable menstrual cycle.[14]This irregular cycle leads to psychological stress[15].

Norethisterone, a derivative of testosterone has progesterone effects that are 10 times greater than simple progesterone. Androgen in the Norethisterone can change endometrium into the secretory phase and inhibits estrogen receptors thus increasing the metabolic clearance rate of estrogen. Norethisterone decreases the amount of withdrawal bleed, promotes angiogenesis, and regulates the menstrual cycle. It improves the quality of life, has low prices, and better compliance with good cycle control[16].

Dydrogesterone's effectiveness for menstrual cycle regulation has been reported to be equal to other orally administered progestins like Norethisterone, on eliciting secretory phase activity.[17] But these above-mentioned studies were done on the international level and no local studies have been found to compare the effectiveness of the two hormones for menstrual cycle regulation.

We conducted our study where a comparison of effectiveness was made by prescribing two hormones to the two groups of women with an irregular cycle. In our study, we found that there was no significant difference in the age groups having irregular menstrual cycles when we compared the two groups. This finding of our study is in comparison with a study of Yaaqoub N et al[18].

38(76%) patients in Group A had a regular menstrual cycle after 3 months of Norethisterone use in a cyclical manner while 12(24%) patients reported no improvement in a cycle pattern. In Group B, about 22(44%) patients had regular menstruation after 3 months of use of Dydrogesterone use but 28(56%) patients reported irregular cycles at the end of 3 months. After calculating the p-value, we found a significant p-value >0.05 and concluded that Norethisterone is a better option for treatment of irregular cycles in patients suffering from AUB-O, and/or AUB-E as it has improved menstrual cycle control, cheaper in price, and patient's satisfaction was more when compared with Dydrogesterone. This finding our study is in comparison with that of Yaaqoub N et al[18].

e strength of our study was that no such study to compare the effectiveness of the two hormones for the treatment of abnormal uterine bleeding has been conducted at the national and local levels. So this study can be a guide for future researchers.

The weakness of the study was that the sample size was small and results were collected only from one hospital. To make the conclusion and recommendations more effective, a multicenter trial of the two hormones at the national level should be carried out in the future.

CONCLUSION AND RECOMMENDATION

Although both Norethisterone and Dydrogesterone are used for the treatment of abnormal uterine bleeding, we found Norethisterone superior to Dydrogesterone in treating menstrual irregularity. Also, the patient satisfaction rate was noticed to be high with the use of Norethisterone than Dydrogesterone in our study. But still, we recommend more studies to be conducted on our population with different ethnicity, environment, local factors, and genetics at the national level to emphasize our research findings.

Conflict of interest: Nil

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