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The Effect of Estradiol Valerate, Lng-IUD, and Micronized Progesterone Treatment On Health Quality of Patients with Heavy Menstrual Bleeding

Women who were admitted and treated for heavy menstrual bleeding were asked to participate in this comparative study. Women were eligible for entry if they had self-described heavy menstrual bleeding, had a regular cycle, had completed their family and were 40–50 years old at initial assessment.

After a thorough physical examination and ultrasonographic evaluation, all women underwent endometrial biopsy before the study by using a Pipelle endometrial suction curette to rule out any organic endometrial pathology. Blood samples were analysed to test for hemoglobin (Hb), hematocrit (Hct), ferritin, serum iron and iron-binding capacity and coagulation tests such as prothrombin time and activated partial thromboplastin time.

The study was approved by the Institutional Review Board and Local Ethics Committee. After they gave written informed consent, patients who fulfilled eligibility criteria were recruited to one of the following 3 groups:

Group 1: Women who were treated with estradiol valerate/dienogest regimen for heavy menstrual bleeding. 28 days of E2V/DNG was administered using a dynamic dosing regimen. (E2V 3 mg on days 1–2, E2V 2 mg/DNG 2 mg on days 3–7, E2V 2 mg/DNG 3 mg on days 8–24, E2V 1 mg on days 25–26 and placebo on days 27–28).

Group 2: Women who were treated with LNG-IUD for heavy menstrual bleeding. LNG-IUD is containing 52 mg levonorgestrel at initial placement and releases 20 microgram levonorgestrel per day. This is approved for 5 years of use by the US FDA for treatment of HMB.

Group 3: Women who were treated with oral Micronized Progesterone 200 mg for heavy menstrual bleeding. Cyclic, luteal-phase administration of progestin remained a widely used but little research treatment strategy for HMB for several decades.

None of the recruited patients were not prescribed oral iron preparations and patients who were symptomatic because of anemia (hb<10 mg/dl) were excluded.

Baseline characteristics of women are age (years), body mass index, parity, current smoker, days of bleeding, length of cycle (days), number of days of heavy bleeding, number of days of painful bleeding, unable to leave house on heaviest days, number of days housebound, number of nights disturbed, Pictorial Bleeding Assessment Chart (PBAC) score (A monthly score of 100 or more on this chart is significantly associated with heavy menstrual bleeding of more than 80 ml per cycle, as measured by the alkaline haematin method), endometrial thickness at time of treatment (mm), uterine size (length x width).

The Exclusion criteria are

1. ultrasound abnormalities (submucosal fibroids, intramural fibroids greater than 3 cm in diameter, large subserosal fibroids, endometrial polyps);
2. laboratory abnormalities (follicle stimulating hormone level higher than 40 iu/l, adverse endometrial histology)
3. hysteroscopic abnormalities (submucosal fibroids, endometrial polyps),
4. incidental adnexal abnormality on ultrasound,
5. severe intermenstrual bleeding, severe dysmenorrhoea, severe premenstrual pain, chronic pelvic pain,
6. medical contraindications to either study treatment,
7. previous endometrial ablation or resection,
8. uninvestigated postcoital bleeding
9. untreated abnormal cervical cytology.

10. pregnancy; lactation; occurrence of <3 menstrual cycles following childbirth, abortion or lactation;

11. current use of an intrauterine device; hypersensitivity to any of the study drug ingredients and known or suspected malignant or premalignant disease.

12. systemic diseases like hypertension, diabetes, thyroid diseases or coronary artery diseases; and history of previous medication for menorrhagia

13. using anticoagulant drugs

Women who were recruited the study will be assessed at 1,3 and 6 months with Hot Flush Rating Scale (HFRS), Menopause Rating Scale (MRS), menorrhagia multi-attribute scale (MM-AS), pictorial bleeding assessment chart and blood sample analysis.

The primary outcomes assessed

1. Hot flush rating scale: Measures included the HFRS, a self-report measure of frequency and problem rating of Hot Flushes/Night Sweats over the past week. Problem rating is calculated as the mean of the scores on three ten-point scales assessing the extent to which Hot Flushes/Night Sweats are problematic, distressing and causing interference in daily life. Scores for the problem rating range between 1 and 10, with higher scores indicating more problematic Hot Flushes/Night Sweats. The HFRS has been found to have reasonable test–retest reliability and good concurrent validity.

2. Menopause rating scale: The Menopause Rating Scale (MRS) is a questionnaire that assesses the presence and intensity of 11 menopausal symptoms. These are grouped into three subscales: the somatic subscale: assessing hot flushes/sweating, heart discomfort, sleeping problems, and muscle and joint discomfort (items 1–3 and 4 respectively); the psychological subscale: assessing depressive mood, irritability, anxiety, and physical and mental exhaustion (items 4–7 respectively); and the urogenital subscale: assessing sexual problems, bladder problems and vaginal dryness (items 8– 10, respectively). Each of the 11 items can be rated by the participant

from 0 (not present) to 4 (1 ¼ mild, 2 ¼ moderate, 3 ¼ severe and 4 ¼ very severe). The scores obtained for each individual item are summed to provide the corresponding total subscale score. The sum of subscales scores provide the total MRS score. Higher scores are indicative of more severe symptoms. Indeed values above 8 (somatic), 6 (psychological), 3 (urogenital) and 16 (total MRS) were defined as severe.

The secondary outcomes assesse

1. Quality of life as measured by menorrhagia multi-attribute scale: which is designed to measure the effect of menorrhagia on six domains of daily life (practical difficulties, social life, psychological health, physical health, work and daily routine, and family life and relationships). Summary scores, which range from 0 (severely affected) to 100 (not affected)

2. Menstruation, by pictorial bleeding assessment chart

3. Haemoglobin levels were also measured at pre-treatment,1, 3 and 6 months.

4. Adverse event (Breast pain, Headache, Acne, Alopecia, Migraine, Increase in body weight…)

Statistical analysis

Data analysis was performed by using SPSS (IBM SPSS Statistics for Windows, Version 20.0. Armonk, NY: IBM Corp.). A one-sample Kolmogorov–Smirnov test was performed to analyze the distribution of clinical variables. The frequency and percentage of the categorical variables and the mean, standard deviation of the continuous and ordinal variables were presented. The study groups were compared using One-way analysis of variance (ANOVA) test for parametric variables and the Kruskal Wallis H test for the non-parametric variables. Wilcoxon signed rank test was used for the comparison of the BAI and FSFI scores at the first visit and second visits. For all calculations, a p-value of <0.05 was considered statistically significant.