

# Comparison of levonorgestrel–releasing intrauterine system, medroxyprogesterone and norethisterone for treatment of endometrial hyperplasia without atypia: a randomized clinical trial

## Abstract

**Objective:** To assess the efficacy, acceptability and cost–effectiveness of the levonorgestrel–releasing intrauterine system (LNG–IUS) compared to oral Medroxyprogesterone (MPA) and Norethisterone (NETA) for treatment of endometrial hyperplasia (EH) without atypia in perimenopausal women.

**Methods:** This randomized clinical study included 150 perimenopausal women with endometrial hyperplasia (EH) without atypia who were randomly assigned into three groups; 50 patients received 15 mg Medroxyprogesterone acetate (MPA), 50 patients received 15 mg Norethisterone acetate (NETA) and 50 patients in whom levonorgestrel–releasing intrauterine system (LNG–IUS) was inserted. Endometrial sampling was repeated after 6 months of therapy. Primary outcome was regression of EH while secondary outcomes included side effects, patient acceptability and cost of treatment over six months.

**Results:** There was no significant difference between the three groups regarding regression of EH ( $p < 0.05$ ). The LNG–IUS has the highest cost and acceptability ( $p < 0.001$ ). There was a significant higher women suffering from nausea in NETA group ( $p < 0.05$ ), acne in MPA group ( $P < 0.05$ ) and vaginal discharge in LNG–IUS group ( $p < 0.05$ ).

**Conclusion:** In low–income and developing countries where the LNG–IUS is non affordable or unavailable, the use of norethisterone seems a viable cost–effective therapy in patients with endometrial hyperplasia without atypia.

**Keywords:** Endometrial hyperplasia, Levonorgestrel–releasing intrauterine system, Medroxyprogesterone, Norethisterone, Perimenopausal bleeding

Volume 5 Issue 4 - 2016

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## Introduction

Endometrial hyperplasia (EH) is characterized by non–physiological proliferation of endometrium that results in glands with irregular shapes and varying sizes. The World Health Organization (WHO) 1994 classification system is commonly used, in which the architectural disruption and cytological atypia are used to identify four types of EH, including simple or complex hyperplasia with or without atypia.<sup>1–3</sup> Surgical management of EH namely endometrial ablation and hysterectomy are highly effective, but are associated with perioperative and long–term complication risks.<sup>4,5</sup> Progestin treatment in various forms have been used for treatment of EH with proven efficacy including oral medroxyprogesterone, oral norethisterone, oral lynestrenol or micronized progesterone in vaginal cream.<sup>6–10</sup>

The levonorgestrel–releasing intrauterine device (LNG–IUS) releasing 20 µg levonorgestrel per 24 hours was developed for the beneficial effects of intrauterine and hormonal contraception and for the treatment of menorrhagia.<sup>10</sup> The aim of our study was to assess the efficacy, acceptability and cost–effectiveness of the levonorgestrel–releasing intrauterine system (LNG–IUS) compared to oral Medroxyprogesterone (MPA) and Norethisterone (NETA) for treatment of endometrial hyperplasia (EH) without atypia in perimenopausal women.

## Material and methods

This single–centre balanced randomized parallel group study

was performed at the Department of Obstetrics and Gynecology, Menoufia University Hospital, Menoufia, Egypt in the period between June 2012 and June 2016. The review board and the Ethics Committee of Menoufia Faculty of Medicine approved the study. The study protocol and its benefits and complications were explained to all participants, and all recruited patients completed and signed an informed consent form. Eligibility criteria included menstruating perimenopausal women above the age above 40 years presented with AUB with histologically confirmed endometrial hyperplasia without atypia, following clinical examination, transvaginal sonography and endometrial sampling by Pipelle. Women with associated lesions as uterine fibroid, cervical or vaginal pathology, bleeding tendency, hormonal contraception in the past three months, chronic medical diseases as diabetes mellitus, hypertension, chronic liver disease, any contraindication to progestin therapy and postmenopausal women were excluded from the study.

Based on the 80–90% regression rate of endometrial hyperplasia under progestin therapy from the literature. Accordingly, at  $\alpha = 0.05$  and a study power of 80% a total sample size of 135 participants (45 participants in each group) was required after adding a percentage of 10% for possible drop out cases during the study. A total of 162 perimenopausal women (98 with simple EH and 64 with complex EH) were enrolled and equally allocated into three groups via computer generated simple random tables according to the allocation ratio 1:1:1. Twelve patients were dropped out from the study (stopped treatment and lost follow up), accordingly 150 patients completed the study.

- i. **Group 1 (MPA group):** included 50 patients (32 with simple EH and 18 with complex EH) who received 15 mg of medroxyprogesterone acetate in the form of 5 mg tablet three times per day orally for 14 days per month (Provera 5mg tablets, Pfizer, USA) for 6 months.
- ii. **Group 2 (NETA group):** included 50 patients (31 with simple EH and 19 with complex EH) who received 15 mg of norethisterone acetate in the form of 5 mg tablet three times per day orally for 14 days per month (Cidolut nor 5 mg tablets, CID pharmaceuticals, Cairo, Egypt) for 6 months.
- iii. **Group 3 (LNG–IUS group):** included 50 patients (33 with simple EH and 17 with complex EH) to whom levonorgestrel–impregnated intrauterine system (LNG–IUS) (Mirena, Bayer HealthCare, Berlin, Germany) was inserted.

Patients were followed regularly in the outpatient clinic every 2–4 weeks starting from the time of hyperplasia diagnosis and underwent a second endometrial sampling after 6 months and followed-up for 24 months thereafter to detect relapses. Patients with recurrent bleeding and/or persistent endometrial hyperplasia after 6 months of therapy were managed by total abdominal hysterectomy according to our hospital policy.

### Outcome measures

Regression of endometrial hyperplasia after 6 months of progestin therapy was the primary outcome measure. Secondary outcome measures included the frequency of side effects during treatment, patient acceptability (in terms of compliance with follow-up, overall satisfaction and advisability of the method to other women) and cost of treatment over the six months of therapy.

### Statistical analysis

Statistical analysis was performed using Statistical Package for the Social Sciences Version 16 (IBM Corp., Armonk, NY, USA). Quantitative data are expressed as means and standard deviations. Chi-squared test and t-test were used to compare the two groups as appropriate.  $p \leq 0.05$  was considered to indicate significance and  $p \leq 0.001$  was considered to indicate strong significance.

### Results

Out of 192 eligible perimenopausal women attending the hospital with AUB, 162 patients fulfilled our inclusion criteria and equally allocated into three groups with 12 patients dropped from the study and 150 patients (50 in each group) completed the study. Figure 1: The flow diagram. Table 1 displays the patients' characteristics. There was no significant difference between the three groups regarding age, parity and body mass index ( $p > 0.05$ ). Table 2 reveals the outcome and cost of treatment, there was no significant difference between the three groups regarding regression of endometrial hyperplasia (88% in MPA group, 84% in NETA group and 94% in LNG–IUS group with  $p$ -value  $> 0.05$ ). There was a highly statistically significant difference between the three groups regarding the cost of treatment over 6 months with the highest cost in LNG–IUS group,  $p$ -value  $< 0.001$ .

Table 3 displays the adverse effects of progestin therapy, there was a significant higher women suffering from nausea in NETA group ( $p$ -value  $< 0.05$ ), acne in MPA group ( $p$ -value  $< 0.001$ ) and vaginal discharge in LNG–IUS group ( $p$ -value  $< 0.05$ ). Table 4 reveals the patient acceptability, there was a significant higher compliance with follow-up, overall satisfaction and advisability of the method to other women in LNG–IUS group ( $p$ -value  $< 0.05$ ).

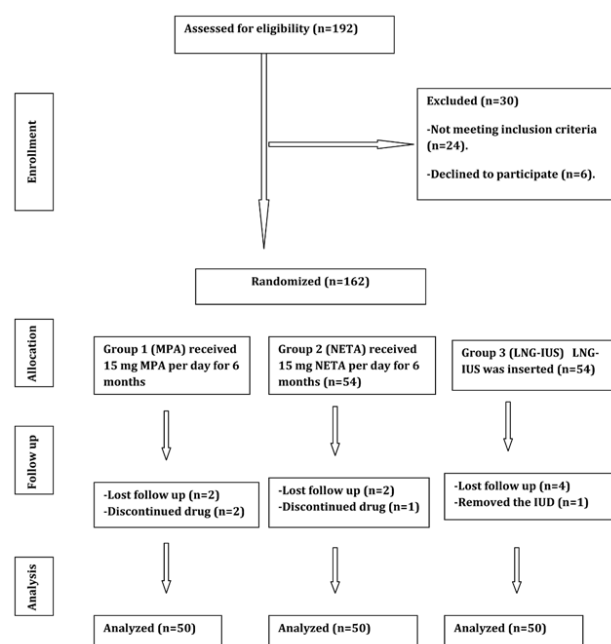


Figure 1 Flow Diagram.

### Discussion

In our study, there was no significant difference between the three groups regarding regression of endometrial hyperplasia (EH) without atypia (88% in MPA group, 84% in NETA group and 94% in LNG–IUS group. These results are in agreement with previous studies.<sup>7–10</sup> In this study, No patients experienced recurrence of genital bleeding during the subsequent 20 months following the second endometrial sampling. Patients with persistent endometrial hyperplasia underwent total abdominal hysterectomy (6 patients in MPA group, 5 patients in NETA group and 6 patients in LNG–IUS group).

Regression of endometrial hyperplasia has been observed in 60–90% of subjects receiving cyclic MPA for 3–6 months.<sup>7,11</sup> Horn et al.<sup>8</sup> conducted a study in which women with complex EH without atypia were treated with norethindrone acetate (5 mg/day) and MPA (10–20 mg/day) for 3–5 months, and a second biopsy was obtained; regression was evident in 61.5%.<sup>8</sup> Regression of endometrial hyperplasia was achieved in 94.8% of patients treated with the LNG–IUS compared with 84.0% of patients treated with oral progestogens in a recent study with long term follow-up.<sup>10</sup>

In a previous randomized trial, Eighty-two women with simple EH without atypia were included. Patients were randomized to one of three options for 3 months: medroxyprogesterone acetate (MPA, 10 mg/day), lynestrenol (LYN, 15 mg/day) and norethisterone (NET, 15 mg/day) for 10 days per cycle. No significant difference between progestins regarding the regression rate of EH which was 36.7% in MPA group, 37% in LYN group and 56% in NET group after 3 month treatment.<sup>9</sup> The lower rate of regression of EH in this study compared to our results may be attributed to lower dose and shorter duration of progestin therapy which were administered for only 10 days per month and for only 3 months. Bese et al.<sup>12</sup> evaluated the effect of 3 months of cyclic progesterone (NET, 15 mg/day) treatment on proliferation and apoptosis in simple EH without atypia and reported that progesterone treatment reduced both proliferative and apoptotic activities in endometrial tissue of these patients.<sup>12</sup>

**Table 1** Patients' Characteristics

	Group 1 (MPA, n=50)	Group 2 (NETA, n=50)	Group 3 (LNG–IUS, n=50)	Student t–test	p–value
Age	44.56±4.07	45.53±3.89	44.63±4.19	0.005	> 0.05
Parity	2.5±0.77	2.4±0.62	2.06±0.73	3.01*	> 0.05
Body mass index	21±3.04	22.1±2.05	21±4.1	0.28	> 0.05

\*Wallis Kruskal test.

**Table 2** Outcome and cost of treatment

	Group 1 (MPA, n=50) n(%)	Group 2 (NETA, n=50) n(%)	Group 3 (LNG–IUS, n=50) n(%)	Chi square	p–value
Regression of EH					
–Simple EH	44 (88%)	42(84%)	47(94%)	0.28	> 0.05
–Complex EH	30 14	29 13	32 15		
Cost of treatment in £E (US\$)	700±16.8£E (100±2.4 US\$)	70±7.7£E (10±1.1 US\$)	700±326.9£E (100±46.7 US\$)	18.6*	<0.001

\*t–test, EH: Endometrial Hyperplasia, £E: Egyptian Pounds, US\$: United States dollars.

**Table 3** Adverse effects of progestin therapy

	Group 1 (MPA, n=50)	Group 2 (NETA, n=50)	Group 3 (LNG–IUS, n=50)	Chi square	p–value
Headache	40	23	28	2.24	> 0.05
Nausea	27	43	22	7.84	<0.05
Weight gain	24	22	23	0.08	> 0.05
Acne	38	18	12	16.35	<0.001
Menstrual changes	32	29	27	0.43	> 0.05
Mood changes	21	19	18	0.24	> 0.05
Vaginal discharge	23	21	40	7.78	<0.05

**Table 4** Patient acceptability

	Group 1 (MPA, n=50)	Group 2 (NETA, n=50)	Group 3 (LNG–IUS, n=50)	Chi square	P–value
Overall compliance with Follow–up:					
–Moderate/High/Extreme	25	27	44	6.81	<0.05
–None or slight	25	23	6		
Overall satisfaction with treatment:					
–Very or somewhat satisfied	28	30	47	6.22	<0.05
–Neutral or somewhat not satisfied	22	20	3		
Would recommend the method to other women:					
–Highly or somewhat agree	24	26	42	6.34	<0.05
–Neutral or somewhat disagree	26	24	8		

A recent multicenter randomized trial involving 170 women with low– or medium–risk EH. Eligible women were randomly assigned to one of three treatment arms: levonorgestrel–impregnated intrauterine device (LNG–IUS); oral medroxyprogesterone acetate (MPA) 10 mg administered for 10 days per cycle, or continuous oral MPA 10 mg daily, for 6 months. Regression of EH was obtained for all the women in the LNG–IUS group (100%), 96% of women in the continuous oral group and only 69% of women in the cyclic oral group.<sup>13</sup>

In this study, low–dose progestin therapy for 6 months was chosen as the minimum duration of therapy varies between 8 weeks to 6 months to be followed by a second biopsy<sup>14</sup> and low dosage seemed more effective when continued for 6 months compared with withdrawal after 3 months.<sup>11,13,15</sup> In our study, there was a significantly higher women suffering from nausea in NETA group, acne in MPA group and vaginal discharge in LNG–IUS group. Most of these adverse events were reported to be mild–to–moderate in intensity and

did not require specific intervention or led to discontinuation of therapy.

To the authors' knowledge, this is the first study to assess the cost–effectiveness of progestin therapy because health insurance does not cover the entire population in Egypt as well as in many other low–income countries. NETA was the most cost–effective drug. Although patient acceptability was higher in the LNG–IUS group, it was not cost–effective. A recent systematic review and meta–analysis comparing the LNG–IUS and medical therapy concluded that the LNG–IUS was associated with a lower rate of discontinuation, fewer treatment failures and better quality of life over conventional medical treatment for menorrhagia.<sup>16</sup>

Inability to include women younger than 40 years or postmenopausal women as well as non–using of hysteroscopic guided biopsy, were the main limitations of this study.

## Conclusion

In conclusion, in low-income and developing countries where the LNG-IUS is unaffordable or unavailable, the use of norethisterone seems a viable cost-effective therapy in patients with endometrial hyperplasia without atypia.

## Acknowledgments

None.

## Conflicts of interest

None.

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