A Comparison of Medroxyprogesterone Acetate and Norethisterone Side-Effects Used in Reproductive Age Women

REPRODÜKTİF ÇAĞ KADINLARINDA KULLANILAN MEDROKSİPROGESTERON ASETAT VE NORETİSTERON YAN ETKİLERİNİN KARŞILAŞTIRILMASI

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Summary

Objective: *To assess the tolerability to medroxyprogesterone acetate (MPA) and norethisterone (NET) prescribed as the first-choice progestogen for short-term use in reproductive-age women with abnormal uterine bleeding.*

Institution: *Baskent University, School of Medicine, Department of Obstetrics and Gynecology*

Materials and Methods: *Thirty reproductive-age women with abnormal uterine bleeding were randomly divided into two groups and MPA or NET was prescribed. Premenstrual-like symptoms were assessed using Moos Menstrual Distress Questionaire before and during the progestogen use. Twelve patients in the MPA group and seven patients in the NET group returned the questionaires.*

Results: *Progestogen sufferers were 66. 7% in the MPA group and 14.3% in the NET group. MPA caused significantly more severe premenstrual-like symptoms than NET (p=0,039). Symptoms of pain, lack of concentration, behavioural change, water retention, and negative effect were significantly more severe in the MPA group (p<0.05).*

Conclusion: *We suggest that NET be prefered to MPA as the first choice progestogen in the reproductive-age women to keep the progeslogenic side effects minimal and consequently to maximize compliance.*

Key Words: Progestogen intolerance. Medroxyprogesterone acetate, Norethisterone

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Özet

Amaç: *Anormal uterus kanaması olan reprodüktif çağdaki kadınlarda, kısa dönem kullanım için önerilen medroksiprogesteron asetat (MPA) ve noretisterona (NET) toleransın değerlendirilmesidir.*

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Materyal-Metod: *Anormal uterus kanaması nedeniyle progestogen verilmesi planlanan 30 kadın rastgele şekilde iki gruba ayrılarak bir gruba MPA diğerine NET uygulandı. Hastalarda oluşan premenstrüel belirtilere benzer semptomlar Moos Menstrual Distress Questionaire ile değerlendirildi. Anketleri, MPA grubunda 12, NET grubunda 7 kadın tamamladı.*

Bulgular: *Şiddetli progestogen yan etkileri MPA grubundaki kadınların %66.7'sinde, NET grubundakilerin %14.3'ünde saptandı. MPA'ın oluşturduğu semptomlar NET'a göre daha şiddetli idi (p=-0.039). Ağrı, konsantrasyon bozukluğu, davranış değişiklikleri, su tutulumu ve negatif etki belirtileri MPA grubunda belirgin olarak daha şiddetliydi (p<0.05).*

Sonuç: *Reprodüktif çağdaki kadında progestogen yan etkilerinin en az olmasını ve dolayısı ile önerilen ilaca devamın sağlanabilmesi için ilk seçenek olarak NET tercih edilmelidir.*

Anahtar Kelimeler: Progestogen intoleransı, Medroksiprogesteron asetat, Noretisteron

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Breast tenderness, bloatedness, edema, and abdominal cramping are frequent somatic symptoms that may be experienced during the luteal phase of the menstrual cycle (1). Psychological symptoms such as anxiety, irritability, and depression are also

common (1). These symptoms may occur as an "iatrogenic" premenstrual-tension-like syndrome in patients using progestogens (2).

Some patients (about 5%) are intolerant to any type of progestogen, however, most who experience premenstrual-tension-like problems with one type of progesterone benefit from a shift to another type (3). The commertially available progestogens are divided into two categories. The C-19-nortestostcronc derivatives such as norgestrel, norethindrone (norethisterone), or norethindrone acetate possess some androgenic activity and thus are commonly associated with acne and greasy skin and hair (4). The C-21 derivatives such as medroxyprogesterone acetate are less androgenic, however, appear to be more associated with depression and anxiety (4).

The aim of this study was to assess the tolerability to medroxyprogesterone acetate (MPA) and norethisterone (NET) prescribed as the first-choice progestogen for short-term use in reproductive-age women with abnormal uterine bleeding.

Materials and Methods

The study included 30 reproductive-age women who were recruited from the out-patient clinic at Baskent University Hospital. All had abnormal uterine bleeding, and were proven to have non-malignant disease by endometrial biopsy.

The women were randomly divided into two groups. Five mg bid of oral NET (Primolut-N, Schering, Istanbul, Turkey) were prescribed to the first group for ten days of each month for three months. The other group was on MPA (Farlutal, Deva, Istanbul, Turkey) for ten days of each month for the same period of time at a dose of 5 mg bid.

Physical, psychological and behavioural variables were assessed using Moos Menstrual Distress Questionaire (MMDQ) (3).The questionaire consisted of a total of 47 items grouped into eight complexes (Table 1). Each item was scored on a scale of 0 (none) to 3 (severe). The MMDQ was completed three days before the progestogen treatment was started to document the baseline for the patients' complaints and on the 8th day of the progestogen treatment to detect the progestogen related symptoms (4). The sum of scores of all 47 items or grouped items or items alone were then calculated producing two scores for each patient or each group, one score for the progesterone-used-period and the other for the baseline. Progesterone sufferers were selected if the summed MMDQ score for the progesterone-used-period was increased by at least 30% as compared with the baseline score (4). The data were then analysed using Fisher's exact chi square test.

Results

A total of 19 women completed the MMDQ, 12 in the MPA group and 7 in the NET group. The average age in the MPA and NET groups were 45.7±5.9 years (range 32-54 years) and 43.5±4.9 years (range 36-51 years), respectively, and there was no statistical difference between mean age of both groups. The mean gravidity and parity were 2.1+2.1 and 1.0±0.85 for the MPA group , and 3.0±1.6 and 2.0±1.1 for the NET group, which were statistically similar in both groups. In respect to educational level of the patients, nine (75%) were university graduates and three (25%) were secondary school graduates in the MPA group, and those figures were four (57%) and three (43%), respectively, in the NET group, and no difference was encountered between the educational levels of the two groups. In the MPA group, nine women (75%) were married and three (25%) were divorced, while corresponding figures for the NET group were six (86%) and one (14%), which were not significantly different from each other.

Progesterone sufferers were 66.7% (8 of 12) in the MPA group and 14.3% (1 of 7) in the NET group. Two patients (17%) were totally intolerant to MPA and did shift to NET after the first cycle, while none of the NET users experienced such severe symptoms. The patients on MPA suffered premenstrual-tension-like symptoms with a rate significantly higher than the patients on NET (p=0.039).

When the premenstrual-like-symptoms were grouped into complexes as described in Table 1, no difference was detected between the drags in causing symptoms of autonomic reactions, arousal, or control. On the other hand, patients on MPA experienced significantly more severe symptoms that were grouped in pain, concentration, behavioural change, water retention, and negative effect (Table 2).

Table 1. Moos Menstrual Distress Questionaire

(A) Pain
- Muscle stiffness
- Headaches
- Stomach pains
- Backache
- Tiredness
- Genera! aches and pains

(B) Concentration
- Difficulty sleeping
- Forgetfullness
- Confusion
- Difficulty concentrating
- Clumsiness
- Accidents
- Difficulty making decisions
- Distractable

(C) Behavioural change
- Lowered work performance
- Take naps, stay in bed
- Staying at home from work
- Avoid social activities
- Loss of efficiency

(D) Autonomic reactions
- Dizziness, faintness
- Cold sweats
- Feeling sick, vomitting
- Hot flushes
- Palpitation

(E) Water retention
- Gain in weight
- Skin disorders
- Painful or swollen breasts
- Feeling swollen or bloated

(F) Negative effect
- Crying spells
- Loneliness
- Anxiety
- Restlessness
- Irritability
- Mood swings
- Depression
- Tension

(G) Arousal
- Feeling affectionate
- Orderliness
- Excitement
- Feeling of well-being
- Burst of energy or activity
- Change in eating habits

(H) Control
- Feeling of suffocation
- Chest pain
- Ringing in the ears
- Numbness, tingling
- Blind spots, fuzzy vision

Considering the classical and well-known symptoms of premenstrual syndrom which are listed as the diagnostic criteria for Late Luteal Phase Dysphoric Disorder in the DSM-III-R (5), MPA users experienced all symptoms associated with premenstrual syndrome (Table 3). However, the only symptom significant for the NET users was the feeling of weight gain, none of the other items had scores that deviated by at least 30% from the baseline scores.

Table 2. The rate of affected patiets by medroxyprogesterone acetate or norethisterone on eight symptom complexes

Symptom Complex	MPA	NET	p
Pain	7/12	0/7	0.016
Concentration	8/12	1/7	0.039
Behavioural change	9/12	1 ,'7	0.017
Autonomic reactions	5/12	1/7	0.238
Water retention	11/12	2/7	0.009
Negative effect	8/12	1/7	0.038
Arousal	5/12	2/7	0.474
Control	4/12	1/7	0.366

Discussion

The effect common to all progestogens is that of inducing a secretory phase in the estrogen-primed endometrium. However, depending on their derivation, progestogens may have androgenic and/or estrogenic or antiandrogenic and/or antiestrogenic effects. Progestogens may also have mineralocorticoid and glucocorticoid type effets. There is no general agreement among physicians about the first choice progesterone to prescribe in the premenopausal patient so that the patient would suffer minimum or no side effects due to these medications.

The nor-testosterone derived C19 progestogens lead to unfavorable lipid changes. In postmenopausal women treated with 5 mg of norethisterone per day, it has been demonstrated that a significant drop in high-density lipoprotein concentra-

Table 3. Classical premenstrual-tension-like symptoms described by patients who were on medroxyprogesterone acetate or norethisterone

Symptom	MPA	NET
Weight gain	+	+
Swellings/Bloatedness	+	-
Painful or tender breasts	+	-
Fatigue	+	-
Skin disorders	+	-
Restlessness	+	-
Irritability	+	-
Tension	+	-
Mood swings	+	-
Headaches	+	-
Anxiety	+	-
Depression	+	-
Change in eating habits	+	-
Crying spells	+	-

"+" indicates scores that exceeded baseline scores by at least 30%
"-" indicates scores that did not exceed baseline scores by at least 30%

tion (HDL2 and HDL3) occurs (6-8). Furthermore, the C19 progestogens can oppose the increases in HDL induced by estrogens, but do not suppress the levels below baseline if the estrogen dose is adequate (9, 10). In contrast, the C21 progestogens appear to have no significant effects on lipoprotein metabolism when used in moderate and low dosages (11). However, recent data from Postmenopausal Estrogen Progestin Intervention and Nurses Health Study have shown that the addition of progestogen does not attenuate the improved lipid pattern and consequently the cardiovascular benefits of estrogens (12,13). No studies exist to detenmne the changes in the lipid levels of premenopausal patients who are on progestogens alone. However, no long term adverse effects of progestogens on serum lipids should develop in reproductive-age patients, since HDL levels are not suppressed to levels below baseline if the estrogen levels are adequate (9,10).

Androgenic effects such as acne, greasy skin and darkening of facial hair tend to occur mainly with the 19-nortestosterone derivatives, which have strong binding affinity for the androgen receptor. Meanwhile, MPA has mild androgenic effects, as their binding of the androgen receptor is a little higher than that of progesterone (14). However, none of the patients in our series have complained of androgenic effects either in the NET group or the MPA group.

Progesterone receptors are found in the caudate, cerebellum, cortex, habenula, hippocampus, hypothalamus, olfactory lobe, lamina terminalis, area postrema (15). Limbic system functions, which suserve emotion and behaviour, can therefore be influenced by circulating reproductive steroids such as progesterone and progestogens. There are reports relating negative mood changes during hormonal replacement therapy to the addition of progestogens in sequential therapy, the symptoms occur soon after progestogens are commenced and last for a couple of days after progestogens are ceased (2,16,17). However, it has been reported that not all progestogens cause adverse effects with similar severity, 19-nortestosterone progestogens, for example, have been found to cause only mild adverse effects (18). In our series, patients on NET experienced no significant mood changes, while patients on MPA suffered these symptoms.

Most of the physical symptoms associated with progestogen intolerance, such as edema, weight gain, bloating and migraine, may be due to the mineraiocorticoid-like effect of progestogens. The progestogens produce these effects by competing for the mineralocorticoid receptor. This effect can lead to retention of sodium and fluid gain during the progestogenic phase (14). MPA caused severe symptoms due to fluid retention in our series. These symptoms were so severe in two patients (17%) that they urged to shift to NET at the end of the first cycle of MPA use. Meanwhile, NET caused mild symptoms due to fluid retention.

As demonstrated in Table 3, NET caused significantly less symptoms than MPA in regard to premenstrual-like-symptoms. Therefore, NET may be prefered to MPA as the first choice progestogen for the reproductive-age patient to deal with less progestogenic side effects, consequently to improve compliance with the progestogen regimen prescribed.

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