Experimental
&
Clinical Article

Medroxyprogesterone Acetate Plus Metformin to Prevent Persistent Endometrial Hyperplasia

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OBJECTIVE: To determine the effect of metformin on treatment response in simple endometrial hyperplasia without atypia.

STUDY DESIGN: In this study, we identified 134 women with simple endometrial hyperplasia without atypia. Seventy two of these women were administered cylic oral medroxyprogesterone acetate 10 mg/day for 3 months, 62 of these women were also receiving metformin 1000 mg/day due to preexisting insulin resistance and and all subjects underwent control endometrial sampling after treatment. All subjects were evaluated in terms of age, gravidity, parity, body mass index (BMI), menstrual cycle, luteal phase endometrial thickness, uterine fibroids, ovarian cysts, serum CA 125 levels, systemic disorders, cigarette smoking. All parameters and metformin were assessed for the effects on treatment success.

RESULTS: Out of 72 women who were administered medroxyprogesterone acetate 10 mg/day for 3 months, 15 of them were diagnosed as endometrial hyperplasia in control endometrial sampling while only 5 women had persistent endometrial hyperplasia in group with receiving both medroxyprogesterone acetate 10 mg/day and metformin 1000 mg/day ($P<0.05$). Age, gravidity, serum CA125, BMI, pretreatment endometrial thickness were comparable between groups ($P>0.05$).

CONCLUSION: Medroxyprogesterone acetate and metformin may be used as an adjunctive therapy for persistent endometrial hyperplasias especially in women with high body mass index.

Key Words: Medroxyprogesterone acetate, Metformin, Endometrial hyperplasia

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Introduction

Endometrial hyperplasia is defined as a proliferation of endometrial glands that may progress to endometrial cancer. Endometrial hyperplasia is thought to be a result of unopposed chronic estrogen exposure. Endometrial hyperplasia is usually treated with progestin therapy.[1] Previous study indicated that the hyperinsulinemia may be one of the risk factors for endometrioid adenocarcinoma.[2] It has been shown that metformin reduces the metabolic syndrome, lowers insulin and testosterone levels in postmenopausal women, Metformin was accepted to be a potent inhibitor of endometrial cancer cell proliferation.[3]

We sought to determine metformin effects on treatment response in simple atypical endometrial hyperplasia.

Material and Method

Premenopausal women diagnosed with simple endometrial hyperplasia between 2010 and 2012 were identified from prospectively collected pathology and gynecologic database at Dr. Sami Ulus Maternity and Women's Health Teaching and Research Hospital. We identified 134 women with simple endometrial hyperplasia without atypia. Seventy two of these women were administered cylic oral medroxyprogesteron acetate 10 mg/day for 3 months, out of 134 women 62 of them were also receiving metformin 1000 mg/day due to preexisting insulin resistance and and all subjects underwent control endometrial sampling after treatment. All subjects were evaluated in terms of age, gravidity, parity, body mass index (BMI), menstrual cycle, luteal phase endometrial thickness, uterine fibroids, ovarian cysts, serum CA 125 levels, systemic disorders, cigarette smoking. All parameters and metformin were assessed for the effects on treatment success.

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Inclusion criteria were a diagnosis of simple endometrial hyperplasia in women with abnormal vaginal bleeding followed by progestin therapy for three months and posttreatment endometrial samplings. Final outcome was categorized as resolution, persistence, or progression based on the findings in the two final, consecutive endometrial samples. Post-treatment specimens were obtained within 3 weeks of discontinuing progestins. Patients were excluded if they were postmenopausal; if they had a history of other genital tract cancer, pelvic radiation, or hormonal therapy for breast cancer; or if either pretreatment or first follow-up specimen was unavailable for review. Pathologic review of the pretreatment and first follow-up endometrial specimens was performed independently by two gynecologic pathologists. When the two pathologists differed as to diagnosis, a third gynecologic pathologist was consulted; the majority diagnosis was used. Pathologists were blinded to final outcome. Subject data were collected until resolution. Resolution was defined as the absence of hyperplasia or carcinoma in a minimum of two sequential endometrial specimens. Persistence was defined as any continued simple hyperplasia during treatment. During TVS, the thickest part of the anteroposterior bilayer endometrial thickness was measured in the sagittal plane. Body mass index was calculated by body weight divided by height square. Serum levels of CA-125 were determined with use of the commercially available Tumor Markers CA 125 AxSYM® System (Abbott Laboratories; Abbott Park, Ill). The upper normal limit of CA-125 is 35 U/mL. All subjects were questioned about cigarette addiction, menstrual cycle, gravidity and parity. A blood loss of greater than 80 ml or lasting longer than 7 days constitutes menorrhagia

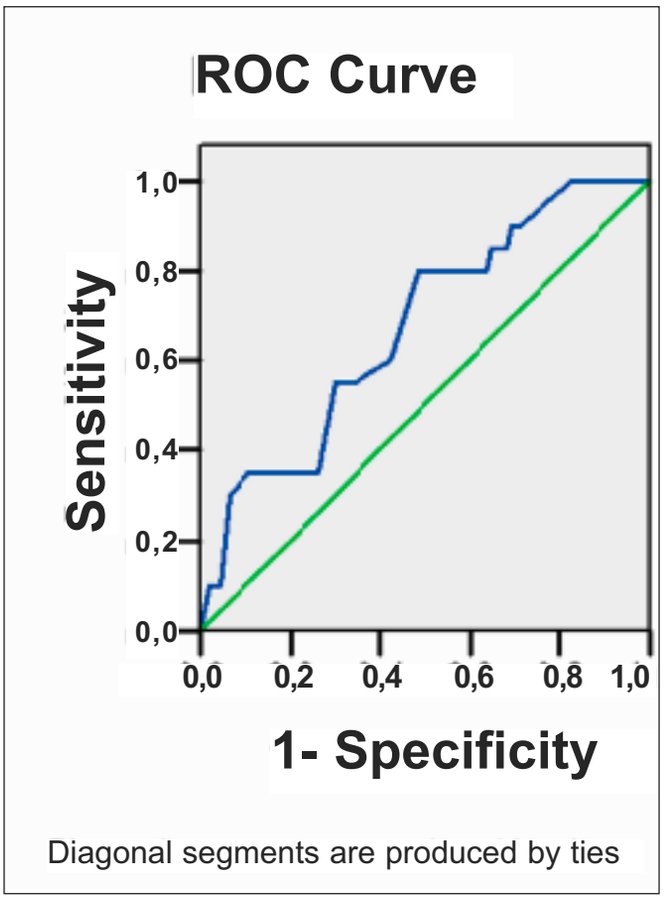
Statistical analysis

The statistical analyses were performed using the Statistic Package for Social Sciences (ver. 12.0; SPSS Inc., Chicago). Independent samples t test was used to compare continuous variables. Categorical variables are compared by Chi square test. ROC analysis was used to calculate cut off value. Linear regression analysis was used to calculate associations. Binary logistic regression analysis was used calculate odds ratio. P value < 0.05 was accepted as statistically significant.

Results

Mean age (range 22-48 years), gravidity (0-10), parity (0-6), BMI (19-39 kg/m^2), endometrial thickness (6-28 mm), CA 125 (5.1-104 U/ml) in the study group were 44.4±7.4 years, 3.2±1.8, 2.8±1.4, 27.9±5.1 kg/m^2, 14.1±5.9 mm, 16.4±17.9 U/ml respectively. Age (44.6 vs 44.1), gravidity (3.1 vs 3.2), parity (2.8 vs 2.8), serum CA125 (17 vs 15.6 U/ml), BMI (27.9 vs 27.8 kg/m^2), pretreatment endometrial thickness (14.2 vs 13.8 mm) were comparable between groups (P>0.05). Number of smokers, number of women with systemic disorders, ovarian cysts and uterine fibroids were similar between groups (P>0.05). Number of subjects with refractory hyperplasia was significantly lower in group under metformin treatment (5/62 vs 15/72, P<0.05). Endometrial thickness significantly predicted resistant cases (AUC:0.675, P=0.013, Fig. 1). Optimal cut off value was obtained at 20.5 mm with 65% sensitivity and 89% specificity. In regression analysis metformin use and endometrial thickness were associated with persistent hyperplasia (P<0.05). Endometrial thickness higher than 20.5 mm was a risk factor for refractory hyperplasia [odds ratio=4.6 (1.5-13.7, P=0.007). Metformin use was protective against treatment failure [odds ratio=0.333 (0.114-0.978, P=0.04).

Figure 1:



Discussion

Our data showed that combined use of metformin and medroxyprogesterone acetate provided significantly increased rate of response to treatment. And our study revealed that endometrial thickness before treatment can significantly predict refractory cases.

Based on the systematic review of the contemporary literature, 66% of endometrial hyperplasia cases respond to hormonal therapy. Disease persistence was found in 14% of

cases.[4] In our study population we have observed higher rates of persistent cases, this was thought to be due to the high BMI of the population.

The goal of treatment is to prevent progression to cancer although the risk is approximately 1%.[5] Although the risk for cancer development is not so high, due to the effective treatment and psychological impact of this condition on women lead gynecologists to treat this kind of disorders.

Data suggested that higher BMI is associated with endometrial hyperplasia as compared to women with lower BMIs and abnormal bleeding.[6] Our study population consisted of women with high body mass index, generally persistent cases are expected in these group of patients.

Metformin reduces the metabolic syndrome, lowers insulin and testosterone levels in postmenopausal women, and it is a potent inhibitor of endometrial cancer cell proliferation.[3]

Metformin may potentiate the effects of paclitaxel in endometrial cancer cells. Study concluded that combination of them may be a promising targeted therapy for endometrial cancer.[7]

This antiproliferative effect of metformin was also shown in breast cancer treatment and study concluded that "metformin appears to be significantly more effective against trastuzumab-resistant as compared to sensitive breast cancer cells." [8]

Metformin was found to have antiproliferative effect on the endometrium via inhibiting the mTOR mediated S6K1 activation.[9]

Aforementioned studies showed that metformin has antiproliferative effect especially against tissues consist of estrogen responsive cells.

According to our data medroxyprogesterone acetate and metformin may be used as an adjunctive therapy for persistent endometrial hyperplasias especially in women with high body mass index.

Persiste Endometriyal Hiperplazi Önlenmesinde Medroksiprogesteron Asetat ve Metformin

AMAÇ: Biz bu çalışmada basit atipisiz endometriyal hiperplazi tedavisinde metforminin etkisinin araştırılmasını amaçladık.

GEREÇ VE YÖNTEM: Bu çalışmada, 134 basit atipisiz endometrial hiperplazisi olan hasta belirlendi. Bu hastalardan 72 tanesi basit atipisiz endometrial hiperplazi tedavisi için medroksiprogesteron asetat 10 mg/gün alırken kalan 62 tanesi 10 mg/gün medroksiprogesteron asetata ek olarak 1000 mg/gün metformin tablet alıyordu. Tüm hastalardan 3 aylık tedaviden sonra kontrol endometriyal örnekleme yapılmıştı. Tüm hastalar yaş, gravide, parite, vücut kitle indeksi, menstruel siklus, luteal faz endometrial kalınlık, uterin fibroid, ovaryen kist, serum CA 125 düzeyi, sistemik hastalıklar ve sigara açısından değerlendirildi. Tüm bu parametrelerin ve metforminin tedavi başarısındaki etkisi değerlendirildi.

BULGULAR: Üç ay medroksiprogesteron asetat 10 mg/ gün alan 72 hastanın kontrol örneklemesinde 15 hastada endometrial hiperplazi saptanırken, medroksiprogesteron asetat 10 mg/gün ve metformin 1000 mg/gün alan grupta sadece 5 hastanın kontrol endometrial örneklemesinde endometrial hiperplazi saptandı (P<0,05). Yaş, gravide, serum CA 125 seviyesi, BMI, tedavi öncesi endometrial kalınlık açısından iki grup arasında fark saptanmadı (P>0,05).

SONUÇ: Persistan endometriyal hiperplazi tedavisinde özellikle vücut kitle indeksi yüksek hastalarda medroksiprogesteron asetat ve metformin birlikte kullanılabilir.

Anahtar Kelimeler: Medroksiprogesteron asetat, Metformin, Endometriyal hiperplazi

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