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Original Article

# Proliferative Effect of Erythropoietin on Endometrium of Postmenopausal Chronic Kidney Disease Patients

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## ABSTRACT

**Objective:** A glycoprotein hormone called erythropoietin (EPO) regulates hematopoiesis, but also affects many other tissues, such as the human endometrium. Patients with chronic kidney disease (CKD) are frequently treated for anemia using recombinant EPO. The aim of this preliminary study was to evaluate the impact of recombinant EPO on the postmenopausal endometrium of individuals with CKD.

**Methods:** This prospectively designed study, non-hysterectomized postmenopausal women who were scheduled for Epoetin alpha treatment for their renal conditions in a nephrology clinic of a tertiary centre were included to the study between February 2017 and January 2018. To assess endometrial thickness measurements by transvaginal ultrasonography before (day 0) and at the 3rd, 30th and 90th days after the first EPO injections.

**Results:** Endometrial thicknessess of the study participants who received EPO (50-150 IU/kg/week) were 2.98±1.07 mm at day 0, 5.01±1.51 mm at day 3, 4.41±2.01 mm at day 30, and 3.79±1.42 mm at day 90. Endometrial thicknessess were significantly higher at 3rd and 30th day visits, when compared to the basal measurements and declined gradually at the 90th day (Repeated measures analysis of variance, post-hoc Tuckey's test, $p<0.01$).

**Conclusion:** Short term recombinant EPO treatment has a reversible proliferative effect on postmenopausal endometrium. In this study, short term reversible proliferative effect of EPO was observed and in one patient a benign endometrial polyp developed. Larger prospective studies could answer the risk of neoplasia in patients on chronic EPO treatment. Our study may contribute to the early diagnosis of endometrial hyperplasia or neoplasia by raising awareness about patients receiving EPO treatment.

## INTRODUCTION

Erythropoietin (EPO) is a glycoprotein hormone that primarily regulates hematopoiesis by stimulating precursors of erythroid cell line in response to tissue hypoxia. On the other hand, EPO receptors have been found to exist in various tissues including nervous system, cardiovascular system, and reproductive organs.[1,2] It has been clearly shown that female reproductive organs can produce EPO, and signal transduction of EPO contributes to the cyclic changes in the female reproductive organs. EPO also has proliferative effect and contributes to the cyclic changes of the human endometrium.[2,3]

Anemia is a common problem among patients with chronic kidney disease (CKD), due to both insufficient EPO synthesis and destruction during hemodialysis.[4]

EPO has been widely used since 1989 in the treatment of CKD and anemia associated with end-stage renal disease.[5] Recombinant EPO injections are a common practice in nephrology clinics for those patients but possible effects of EPO on other tissues are usually neglected. In this preliminary study, the effect of recombinant EPO on the endometrium of postmenopausal CKD patients was assessed by transvaginal ultrasonography.

## MATERIALS AND METHODS

In the present study, 20 non-hysterectomized postmenopausal women who were scheduled for epoetin alfa treatment for their renal conditions in a nephrology department of a tertiary center were included in the study between February 2017 and January 2018. All patients gave informed consent. This prospectively designed study was approved by the Institutional Ethics Committee (Approval number: 2016/7) and registered with the National Clinical Trials Registry (NCT #03060603). None of the patients received hormone replacement therapy and patients with any type of malignancy were excluded from the study. After enrollment, 4 patients were excluded from the study due to intracavitary mass which might affect endometrial measurements (postmenopausal endometrial thickness over 5 mm, n=1; FIGO Class II and III intramural fibroid, n=2; and intracavitary fluid, n=1) at the initial examination. 2 patients were lost to the follow-up. Data from the remaining 14 patients were analyzed.

Recombinant human EPO (Eprex®, with the license of Janssen-Cilag AG Switzerland, produced in Vetter Pharma-Fertigung GmbH and Co. KG, Germany) of 50–150 IU/kg/week, until the correction of anemia was observed. Mean EPO dose was 62.290±8.410 IU (range: 48.000–80.000 IU).

The primary outcome measure was endometrial thickness measurements by transvaginal ultrasonography before (day 0) and at the 3rd, 30th, and 90th days after the first EPO injections. Demographic and clinical data were given as mean±standard deviation or standard error. Repeated measures analysis of variance (ANOVA) with Bonferroni correction and post hoc Tukey's tests and SPSS 20.0 software program were used for the statistical analyses.

## RESULTS

Demographic data of the patients were as follows: Mean age of the patients was 59.7±13.6 years (range: 34–76) and median parity was 3 (Interquartile range: 2.25). Mean body mass index was found as 25.9±4.81 kg/m2. The last menstrual period was 16.8±13.7 years ago (range 1–48).

Endometrial measurements are given in Table 1 . Mean endometrial thickness was different between measurements at days 0, 3, 30, and 90 significantly (p<0.01, ANOVA with repeated measures, post-hoc Tukey's test).

**Table 1.** Measurements of endometrial thickness with transvaginal ultrasonography in postmenopausal chronic renal failure on epoetin treatment. A) measurements 0, 3, 30 and 90 s after the first EPO injection (Repeated measures analysis of variance, p<0.01); B) Post-hoc analysis of the measurements.

| A) | | Endometrial Thickness | | | |
|---|---|---|---|---|---|
| | n | Min. | Max. | Mean | SD |
| Day 0 | 14 | 0.80 | 4.80 | 2.98 | 1.07 |
| Day 3 | 14 | 3.30 | 7.90 | 5.01 | 1.51 |
| Day 30 | 14 | 2.20 | 8.80 | 4.41 | 2.01 |
| Day 90 | 14 | 2.00 | 7.60 | 3.79 | 1.42 |
| **B)** | | **Mean Diff.** | **p** | **95% CI** | |
| Day 0 | Day 3 | -2.029* | 0.000 | -2.855 | -1.202 |
| | Day 30 | -1.436* | 0.017 | -2.655 | -0.217 |
| | Day 90 | -0.807* | 0.092 | -1.707 | 0.092 |
| Day 3 | Day 3 | 2.029* | 0.000 | 1.202 | 2.855 |
| | Day 30 | 0.593 | 0.700 | -0.503 | 1.689 |
| | Day 90 | 1.221* | 0.012 | 0.242 | 2.201 |
| Day 30 | Day 3 | 1.436* | 0.017 | 0.217 | 2.655 |
| | Day 30 | -0.593 | 0.700 | -1.689 | 0.503 |
| | Day 90 | 0.629 | 0.623 | -0.488 | 1.745 |
| Day 90 | Day 3 | 0.807 | 0.092 | -0.092 | 1.707 |
| | Day 30 | -1.221* | 0.012 | -2.201 | -0.242 |
| | Day 90 | -0.629 | 0.623 | -1.745 | 0.488 |

*: p<0.05

All of the 14 patient's basal endometrial measurements were <5 mm. At their 3rd and/or 30th days of EPO treatment, the endometrium of five patients was measured >5 mm all of which returned below 5 mm at their 90th day visit. A benign endometrial polyp was seen at the 30th day visit of one patient which was then extirpated by hysteroscopy. Her endometrial thickness measurements were 4.8, 7.6, 8.8, and 4.4 mm at her 0, 3rd, 30th, and 90th-day visits, respectively. Measurement of only one of the 14 patients was over 5 mm at 90th day.

## DISCUSSION

It has been demonstrated that EPO has physiological roles unrelated to erythropoiesis. Animal studies showed that mouse uterus expresses EPO and its receptor and produces EPO protein in an estrogen-dependent manner. In human endometrium, both EPO and EPO-R were detected in all samples of isolated epithelial cells analyzed throughout the menstrual cycle and have been suggested to play a physiological role in the endometrial proliferation.[3]

In the present study, 14 postmenopausal CKD patients who were prescribed EPO for anemia were investigated. None of these patients had abnormal finding on their basal transvaginal ultrasonographic examinations. On EPO treatment, at their 3rd and 30th day visits, endometrial thicknesses were found as significantly higher than the basal measurements and declined gradually at the 90th day (Table 1). Ovarian hormone changes, such as estrogen and progesterone during the menopausal period, cause amenorrhea and vasomotora symptoms.[6] In our study, postmenopausal women were included instead of not being a confounding factor since the menstrual cycle would have an effect on the thickness of the endometrium.

Unopposed estrogen and excessive proliferation of endometrium is the most common cause of endometrial hyperplasia and endometrioid endometrial carcinoma but transvaginal ultrasonography as the first-line screening tool for endometrial cancer in postmenopausal women without bleeding remains to be controversial.[7,8]

In this study, short-term reversible proliferative effect of EPO was observed and in one patient, a benign endometrial polyp developed. We think that our study encourages a multidisciplinary approach in postmenopausal womans with chronic renal disease as a comorbidity. On the other hand, long-term effects chronic EPO treatment remains to be investigated. Larger prospective studies could answer the risk of neoplasia in patients on chronic EPO treatment. The effect of EPO on endometrium in reproductive period is also unknown and this might open a new perspective for understanding endometrial proliferation (i.e., in infertility).

## Conclusion

Short-term recombinant EPO treatment has a reversible proliferative effect on postmenopausal endometrium. Long-term effects of EPO in these patients and in those with reproductive period remain to be investigated.

### Ethics Committee Approval

This study approved by the Fatih Sultan Mehmet Training and Research Hospital Clinical Research Ethics Committee (Date: 28.01.2016, Decision No: FSM KEAH-KAEK 2016/7).

### Informed Consent

Retrospective study.

### Peer-review

**Externally peer-reviewed.**

### Authorship Contributions

Concept: P.B.İ., M.Y., A.İ.; Design: M.Y., E.A., N.T., M.A.S.; Supervision: M.Y., N.T., P.B.İ.; Fundings: M.Y.; Materials: P.B.İ., E.A., A.İ., Ma.Y.; Data: Ma.Y., A.İ., P.B.İ., M.A.S.; Analysis: P.B.İ., M.Y., A.İ., M.A.S., N.T.; Literature search: E.A., A.İ., M.Y.; Writing: P.B.İ., M.Y., Ma.Y.; Critical revision: E.A., A.İ., M.A.S., N.T., M.Y.

### Conflict of Interest

None declared.

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## Eritropoetin'in Postmenopozal Kronik Böbrek Yetmezliği Hastalarının Endometriyumu Üzerine Proliferatif Etkisi

**Amaç:** Eritropoietin (EPO), hematopoezi düzenlemenin yanı sıra insan endometriyumu da dahil olmak üzere çeşitli dokularda rol oynayan glikoprotein bir hormondur. Rekombinant EPO, kronik böbrek yetmezliği olan hastalarda anemi tedavisi için yaygın olarak kullanılmaktadır. Rekombinant EPO'nun kronik böbrek yetmezliği olan postmenapozal kadınların endometriumu üzerindeki etkisi, bu çalışmanın amacı olarak belirlendi.

**Gereç ve Yöntem:** Prospektif olarak tasarlanmış bu çalışmaya Şubat 2017- Ocak 2018 tarihleri arasında üçüncü basamak bir merkezin nefroloji kliniğinde renal sorunları nedeniyle eritropoetin tedavisi planlanan, histerektomi yapılmamış postmenopozal kadınlar dahil edildi. İlk EPO enjeksiyonlarından önce (0. gün) ve sonraki 3., 30. ve 90. günlerde transvajinal ultrasonografi ile endometrial kalınlık ölçümleri yapıldı.

**Bulgular:** 62.290±8.410 IU EPO alan 14 hastanın transvajinal endometriyal kalınlık ölçümleri 0. gün: 2.98±1.07, 3. gün: 5.01±1.51, 30. gün: 4.41±2.01 ve 90. gün: 3.79±1.42 idi. 3. ve 30. gün ziyaretlerinde endometriyal kalınlıkların bazal ölçümlere göre anlamlı olarak yüksek olduğu ve 90. günde kademeli olarak azaldığı görüldü (Tekrarlanan ölçümler varyans analizi, post-hoc Tuckey's test, $p<0.01$).

**Sonuç:** Sonuç olarak, kısa süreli rekombinant EPO tedavisi menopoz sonrası endometrium üzerinde geri dönüşümlü bir proliferatif etkiye sahiptir. Bu çalışmada, EPO'nun kısa vadede geri dönüşümlü proliferatif etkisi gözlenmiş ve bir hastada benign endometrial polip gelişmiştir. Daha büyük prospektif çalışmalar, kronik EPO tedavisi alan hastalarda neoplazi riskine cevap verebilir. Çalışmamız EPO tedavisi alan hastalar hakkında farkındalık yaratarak endometrial hiperplazi veya neoplazinin erken tanısına katkı sağlayabilir.

**Anahtar Sözcükler:** Endometrium; EPO; eritropoetin.