Endometrial Functionality On Infertile Patients Treated With Ovulation Inducing Agents

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Introduction

The medical treatment of infertile patients with hypothalamic-pituitary dysfunction is intended to restore folliculogenesis through the use of ovulation-inducing drugs such as clomiphene citrate (CC), and recombinant follicle stimulating hormone (rFSH), which are most of the common drugs used in the clinic. Although the ovulation rates are of 80% with these treatments, pregnancy rates are below 30%. These discrepancies are probably due to changes induced by the treatments in the cervical mucus and in the endometrial maturation.

The aim of this work was to characterize the expression patterns of endometrial receptivity markers in the endometrium of infertile patients with hypothalamic-pituitary dysfunction treated with CC or rFSH, and compare it with normal ovulatory patients.

Material and Methods

The patients were divided into 4 groups: 1) Control (n = 12) ovulatory patients; 2) anovulatory infertile patients (n = 11) treated daily with 100 mg of CC, from the 5th to the 9th day of the cycle; 3) anovulatory infertile patients (n = 5) treated with the rFSH step-up scheme and 4) anovulatory infertile patients without treatment (n = 10).

All patients underwent endometrial biopsy in mid-secretory phase. Histological analysis and dating of the endometrium was performed and Ki67, Bcl-2, Bax, ERα, PR, pluripotency markers (Sox-2, Oct-4, Nanog, c-kit, SCF and CD133) and endometrial receptivity markers (Glicodelin-A, E-cadherin, β-catenin, CD166 and VEFG) were detected by immunohistochemistry and immunofluorescence. Cell death was analyzed by TUNEL assay. Positive staining for each marker was assessed with the Image J Software and quantified by percentage of positive nuclei, optical density and HSCORE. Statistical analysis was performed using one way ANOVA followed by a Turkeys' multiple comparison test with Prism 5.0 Software.

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Results

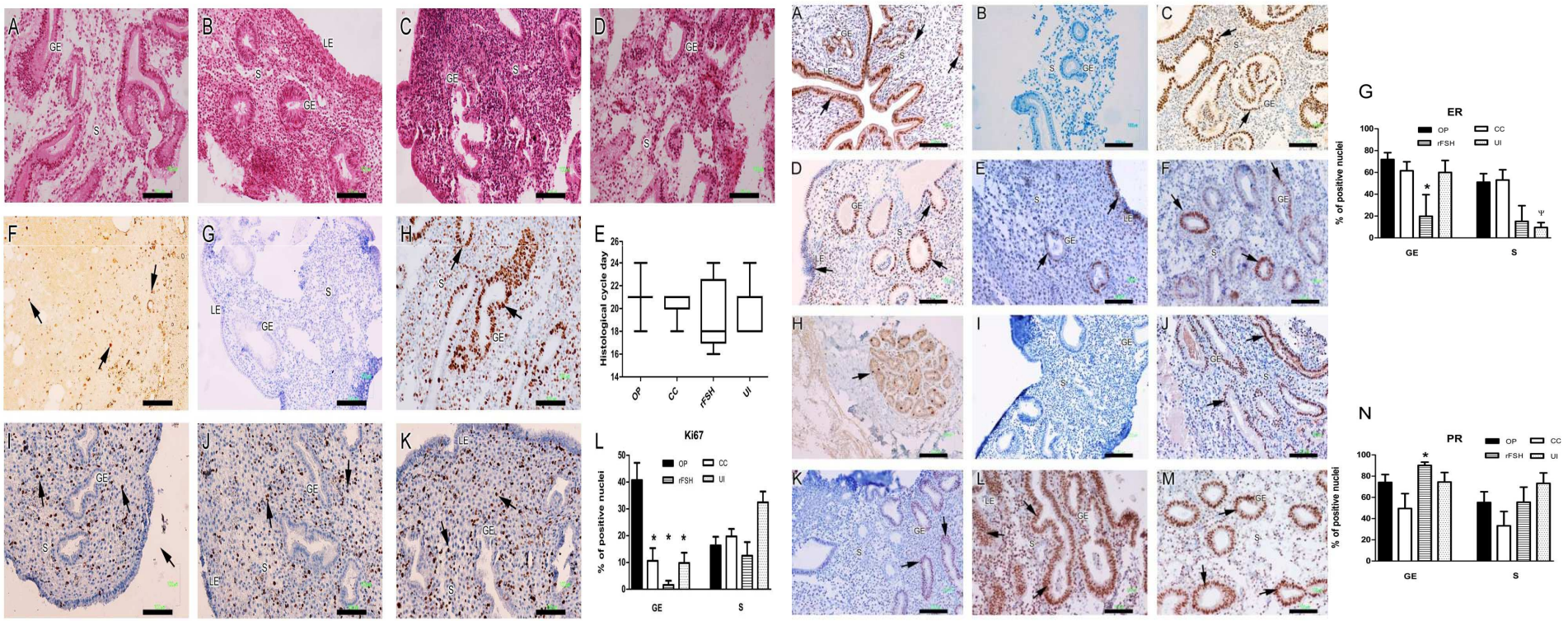

Figure 1. HE staining and immunohistochemistry of ovulatory (A, C, I, J) CC-treated (B, I, D, K), rFSH-treated (C, J, E, L,) and untreated (D, K, F, M) women mid secretory endometrium. Representative images of each group with positive (F, A, H) and negative controls (G, B, I). The graphs represents the media ±SD. P<0.05 was considered statistically significant.

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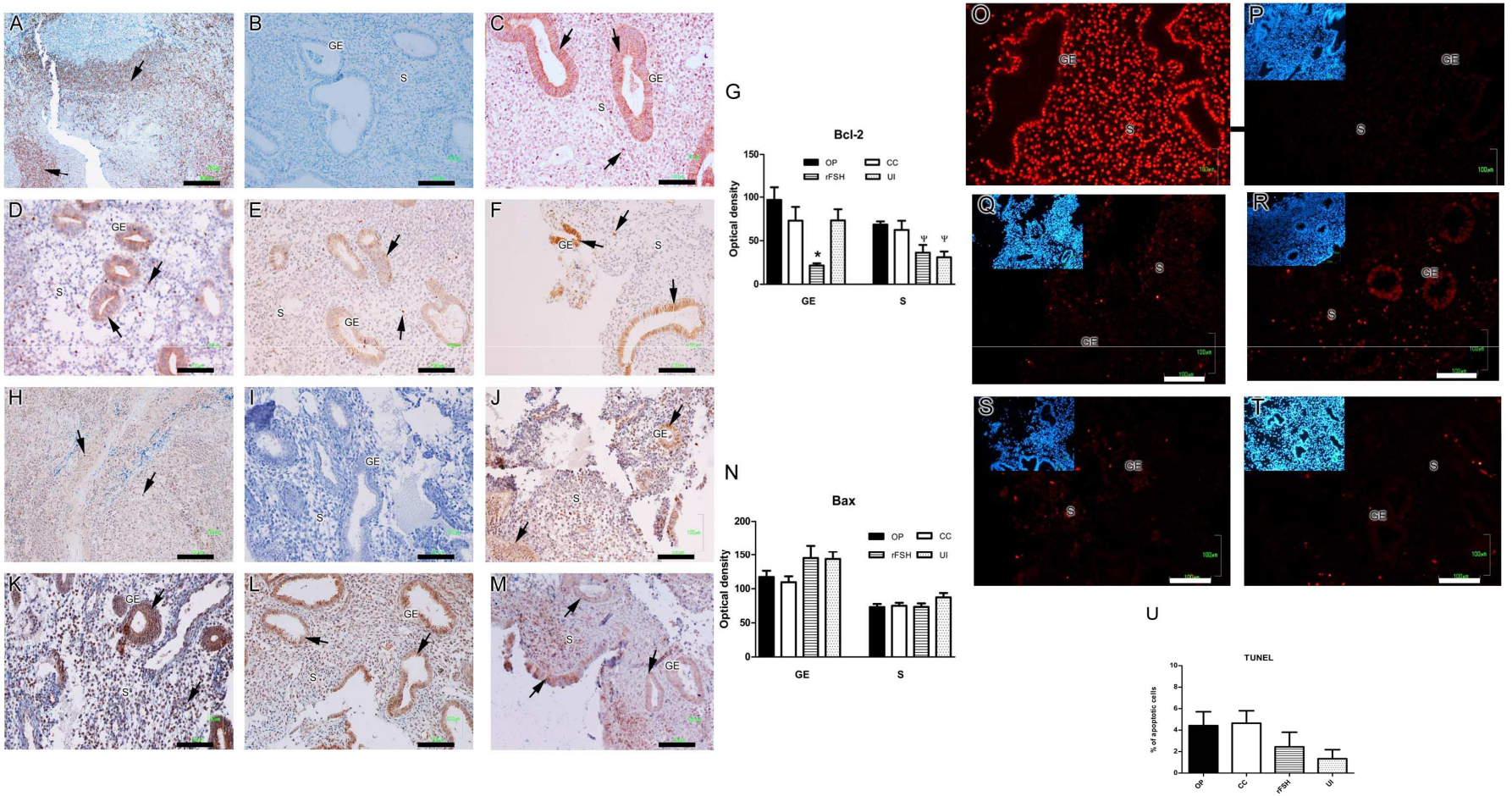

Figure 2. Immunohistochemistry and TUNEL of ovulatory (C, J, Q) CC-treated (D, K, R), rFSH-treated (E, L, S) and untreated (F, M, T) women mid secretory endometrium. Representative images of each group with positive (A, H, O) and negative controls (B, I, P). The graphs represents the media ±SD. P<0.05 was considered statistically significant.

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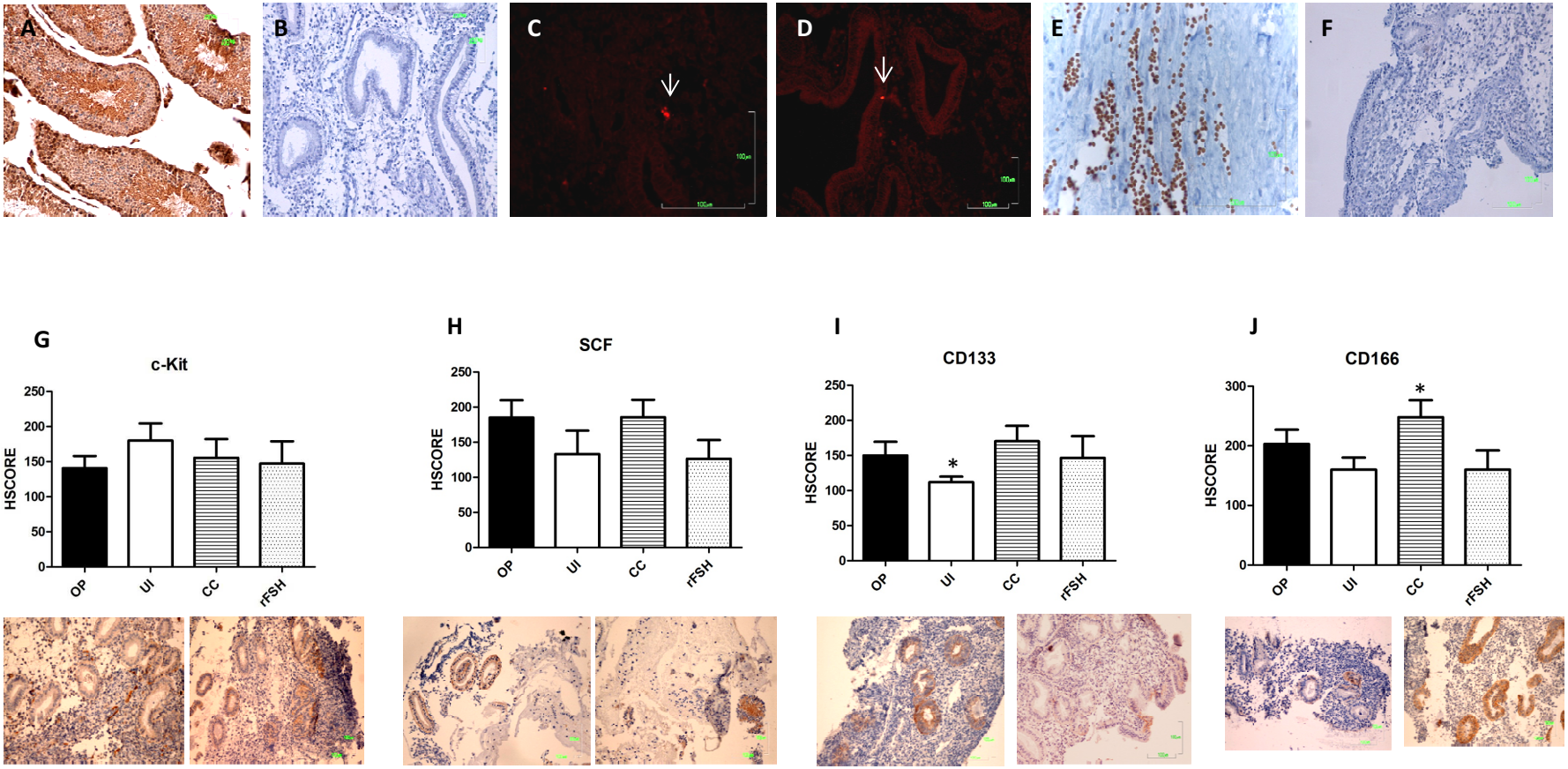

Figure 3. Immunohistochemistry and Immunofluorescence of Oct-4 (A,B), Sox-2(C,D), Nanog (E,F). Representative images of with positive (A, E) controls. (B, I, P).C-Kit (Panel G), SCF (Panel H), CD133 (Panel I), CD166 (Panel J). The graphs represents the media ±SD. $P<0.05$ was considered statistically significant.

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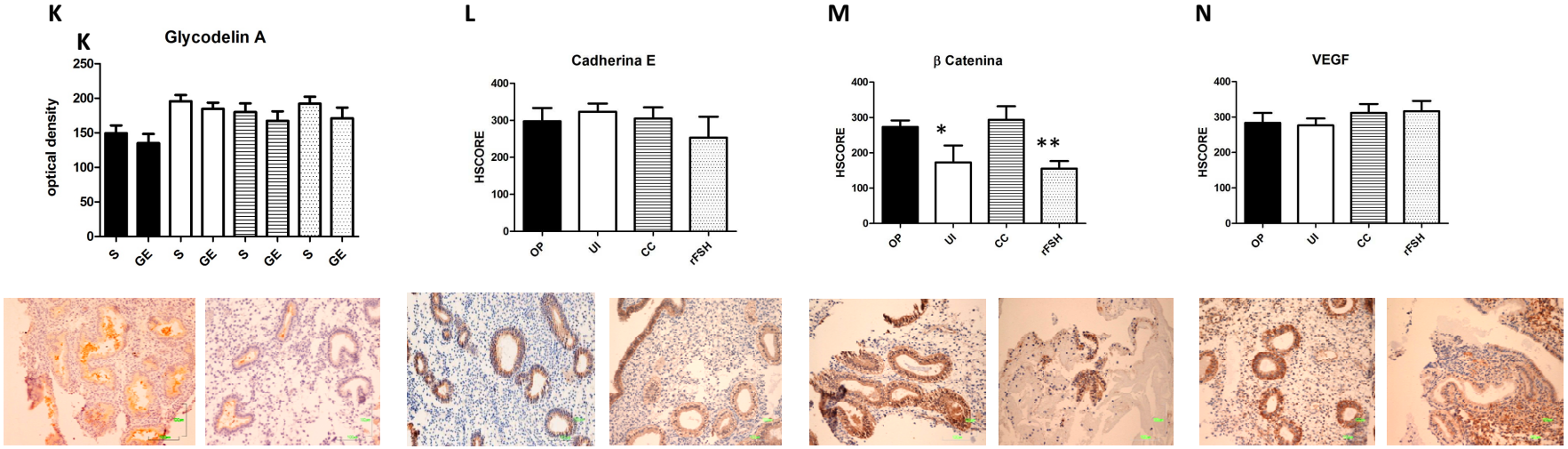

Figure 4. Immunohistochemistry of Glicodelin A (K), E Cadherin (L), β Catenin(M) and VEGF (N) with representative images. The graphs represents the media ±SD. P<0.05 was considered statistically significant.

Conclusions

These data demonstrate that treatment with ovulation-inducing agentes such as CC and rFSH produces significant differences in the expression of mid secretory endometrial functionality markers.

Acknowledgments

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