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Endometrial polyps prevent embryo implantation *via* creatine and lactate pathways

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Abstract. – OBJECTIVE: This study was planned to investigate the concentration of basic endometrial metabolites such as endometrial choline (Cho), creatine (Cr) and lactate in subfertile women diagnosed with endometrial polyps.

PATIENTS AND METHODS: Twenty patients with endometrial polyps detected in routine infertility evaluation and 20 fertile control patients with at least two children were included in the study. The endometrium of the patients in both groups was subjected to spectroscopy at mid-luteal phase and Cho, Cr, and lactate signals were recorded as a ppm.

RESULTS: Compared to the fertile group, a decrease in Cr signal and an increase in lactate signal were detected in patients with endometrial polyp. Cho densities of both groups were found to be similar. The Cho peak of patients with endometrial polyp was 3.01 ± 1.22 ppm, while the Cho peak of the control patients was 2.90 ± 1.13 ppm. The Cr peak of patients with endometrial polyp was 1.36 ± 0.33 ppm, while the Cr peak of the control patients was 1.99 ± 0.02 ppm. The lactate peak of patients with endometrial polyp was 0.87± 0.10 ppm, while the lactate peak of the control patients was 0.54 ± 0.32 ppm.

CONCLUSIONS: Decreased Cr and increased lactate signals may be evidence of impaired receptivity in subfertile patients with endometrial polyps.

Key Words:
Endometrial polyp, Spectroscopy, Cho, Cr, Lactate.

Introduction

Endometrial polyps are benign lesions that occur in the presence of high estrogen and rarely show malignant transformation. They can be stalked, sessile, single or multiple. Its incidence increases with advancing age and increase in BMI. Its incidence in infertile cases approaches 40%. Polypectomy is considered to improve polyp-induced subfertility. It is accepted that polyps cause subfertility by disrupting sperm-oocyte interaction with mechanical effect. However, in a small polyp, it can lead to subfertility by impairing endometrial receptivity. However, evaluating receptivity by performing a biopsy is not preferred because it is invasive. With MR spectroscopy, it is possible to determine what kind of changes occur in the endometrium at the base of the polyp without performing a biopsy[1-4].

Spectroscopy provides information about the cell's living conditions non-invasively by detecting metabolite levels in living tissues. In a healthy tissue, choline signals indicate cell integrity, while creatine signals indicate the integrity of energy pathways. Lactate signals indicate that the physiological conditions of the cell are disturbed. The endometrium is one of the first tissues to be evaluated spectroscopically[5-7]. To date, endometrial metabolites have not been evaluated in cases of polyps. This study was planned to determine non-invasively the non-mechanical effects of endometrial polyps on the endometrium metabolites content. To the best of our knowledge, this is the first study on this subject. The main endometrial metabolites, choline, creatine, and lactate levels were measured in mid-luteal phase and compared to metabolite values of fertile women.

Patients and Methods

This case-controlled study was conducted on women who applied to Istanbul IVF-Center with complaints of infertility between January 1, 2019 to January 1, 2020. A total of 40 patients, including 20 patients diagnosed with endometrial polyp in the two-step evaluation and 20 fertile patients with at least two children, were included in the study. In women with suspected endometriaal polyp in TVS performed during infertility evaluation, the diagnosis was confirmed by performing

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saline infusion sonography (SIS). Women without endometrial polyp in SIS were excluded from the study. Women who did not accept SIS were not included in the study. Patients in the endometrial polyp and control groups underwent MR spectroscopy in the mid-luteal phase of the cycle. Spectroscopy was performed successfully in both groups and Cho, Cr and lactate peaks, which are the main metabolite signals, were detected. The metabolite intensities of endometrial cells were analysed with Magnetic Resonance User Interface software. The endometrial signal of each peak was measured in units and denominated parts per million. In order to avoid false results due to signals from adjacent tissues voxel was placed in the center of the endometrium. Endometrial metabolites were quantitatively analyzed from spectroscopic images and results were recorded as ppm. Among the metabolite peaks, Cho 3.2 ppm, Cr 3-3.1 ppm, lactate 1.4 ppm, and compound peak containing lactate and lipid were localized at 0.8-1.4 ppm. All procedures performed in this study were in accordance with the Ethical Standards of the Institutional and/or National Research Committee and informed consent was obtained from participants at the time of enrollment.

Statistical Analysis

SPSS 21.0 (IBM Corporation, Armonk, NY, USA) was used for the statistical analysis of data in both groups of participants. The quantitative data were expressed as mean ± standard deviation (SD). The normality distribution of data was analysed with Shapiro-Wilk test and found to be normal. The continuous variables were analyzed by Mann Whitney U test. A p-value <0.05 was considered significant.

Results

Spectroscopy analysis of patients in both groups provided Cho, Cr, and lactate peaks (Table I). Compared to the fertile group, a decrease in Cr signal and an increase in lactate signal were detected in patients with endometrial polyps. Cho peak densities of both groups were found to be similar. The Cho peak of women with endometrial polyp was 3.01 ± 1.22 ppm, while the Cho peak of the patients in the control group was 2.90 ± 1.13 ppm. There was no significant difference between the women with endometrial polyp and the control participants in terms of Cho peak (p<0.44). The Cr peak of the women with endometrial polyp was 1.36 ± 0.33 ppm, while the Cr peak of the women in control group was 1.99 ± 0.02 ppm. The Cr peak of the women with endometrial polyp was found to be significantly lower than the control group (p<0.02). The lactate peak of the women with endometrial polyp was 0.87± 0.10 ppm, while the lactate peak of the patients in the control group was 0.54 ± 0.32 ppm. The lactate peak of the women with endometrial polyp was found to be significantly higher than the women in the control group (p<0.01). Since other endometrial metabolite peaks were not detected in the spectroscopy images, they were not included in the statistical evaluation.

Discussion

This is the first clinical study investigating the relationship between endometrial polyp and endometrial metabolites. This study is also of clinical importance since it demonstrates the non-mechanical effects of endometrial polyp on endometrial metabolites for the first time by using spectroscopy. Endometrial polyps are the most common benign pathologies of the uterus and are considered to cause subfertility. Subfertility effects of polyps occur in two different ways (i) mechanical effect and (ii) non-mechanical effect. Broad-based polyps located close to the tubal ostia or internal cervical os may impair sperm transport and lead to infertility. However, endometrial polyp located far from the tubal ostia can cause subfertility. The subfertility-producing effects of small and non-obstructing endometrial polyps occur non-mechanically. Endometrial polyps are thought to hinder implantation by impairing endometrial receptivity or physiological inflamma-

Table I. Choline, creatine and lactate levels of women with endometrial polyp and control participants.

	Endometrial polyp (n=20)	Fertile control (n=20)	p-value
Choline	3.01 ± 1.22 ppm	2.90 ± 1.13 ppm	0.44
Creatine	1.36 ± 0.33 ppm	1.99 ± 0.02 ppm	0.02
Lactate	0.87± 0.10 ppm	0.54 ± 0.32 ppm	0.01

tion. Consistent with this, the rising endometrial NF-kB p65 expression in patients with endometrial polyp is important evidence that endometrial polyp stimulates pathological endometrial inflammation[8]. Since NF-kB p65 is a cellular indicator of inflammation and its expression decreased to the level of healthy controls after polypectomy, it is important evidence that endometrial polyps cause pathological inflammation in the endometrium. Concordantly, it has been reported that the synthesis and release of molecules involved in receptivity and inflammation, such as TNF-alpha, osteopontin, IGFBP-1 and glycodelin, which are measured in the endometrial flushing of patients with polyps, are impaired and polypectomy reverses their secretion[9,10]. Disturbances in the synthesis and release of glycodelin in the presence of polyps may cause subfertility by disrupting sperm-oocyte interaction and decidualization. The decrease in serum or endometrial glycodelin levels in patients with habitual abortion or recurrent implantation failure is important evidence of the role of this molecule in implantation. In the light of these data, Cr and lactate, whose synthesis and release are impaired in the presence of endometrial polyps, may contribute to polyp-mediated subfertility by causing both sperm-oocyte interaction and decidualization defects.

Cho is a metabolite that is an indicator of cell membrane integrity. Its level increases in hyperplastic lesions, precancerous conditions and cases with increased mitosis[11,12]. Since Cho levels in women with endometrial polyp are similar to controls, we can suggest that there is no proliferative pathology in the endometrium due to polyp. Cr is a metabolite that indicates that the energy pathways of the cell are healthy[11]. In general, this metabolite is considered stable. The decrease in Cr levels in women with endometrial polyp compared to control group suggests that there may be a defect in energy production in endometrial cells[13]. Since there is a high energy requirement for decidua formation, the presence of decreased Cr suggests that endometrial polyp impairs energy production and leads to subfertility[14]. The increased lactate peak in women with endometrial polyp is another important evidence of disruption of energy pathways. In healthy tissues, the lactate peak is detected within physiological limits. The presence of increased lactate peak indicates activation of the anaerobic glycolysis. We do not know with which mechanism endometrial polyps disrupt glycolysis, but increased lactate and decreased Cr are the clear evidence of impaired energy production in the endometrium containing polyp[12,15].

The fact that the number of infertile women was 40 is an important limitation of our study that increases the risk of type II error. Another limitation is that we did not evaluate receptivity analysis of endometrium. Finally, we would like to state that the number of our participants is not sufficient to reach a definite conclusion. Despite all these limitations, our study is important as it is the first clinical study investigating the effects of polyps on receptivity.

Conclusions

It is known that subfertility producing effects of endometrial polyps occur with mechanical effect. However, subfertility in the presence of very small endometrial polyps suggests that polyps have a non-mechanical effect. However, the non-mechanical effects of endometrial polyps have not been demonstrated non-invasively until today. In addition to their mechanical effects, polyps may cause subfertility by causing changes in endometrial receptivity. Changes in the endometrial metabolite level in the presence of endometrial polyps may be responsible for impaired receptivity. However, larger clinical scale trials are needed to be able to use clearer statements about the subfertility-producing effects of endometrial polyps.

Authors' Contributions

R.O., and N.T. conceived, designed, performed the study and analyzed the data; R.O. wrote the paper.

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Animal and Human Rights Statement

All procedures performed in this study were in accordance with the Ethical Standards of the Institutional and/or National Research Committee and with the 1964 Helsinki declaration and its later amendments or comparable Ethical standards.

Conflicts of Interest

The authors declare no conflicts of interest.

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