2. Summary

Endometriosis represents one of the most frequent gynecological diseases of women in reproductive age nowadays. Histopathologically, endometriosis is defined as the presence of functional endometrial tissue outside the uterine cavity, which is retrogradely shed through the Fallopian tubes into the peritoneal cavity during menstruation. It is a chronic disease, which is often diagnosed relatively late because of its unspecific symptoms. A typical symptom of endometriosis is chronic, cyclic pelvic pain. Furthermore, patients often suffer from infertility.

Because a sufficient blood perfusion is necessary for an adequate nutrient and oxygen supply, angiogenesis is a major prerequisite for the long-term survival of the ectopic endometrial tissue. Thus, anti-angiogenic therapy, as already used in the therapy of cancer, may represent a promising therapeutic strategy also in the treatment of patients with endometriosis.

For this reason, the aim of the present study was to analyze the anti-angiogenic effects of the dietary supplements epigallocatechin-3-gallate (EGCG), glycine and genistein on the vascularization of endometriotic lesions in the dorsal skinfold chamber model of Syrian golden hamsters. To clarify the specifity of potential anti-angiogenic effects of the dietary supplements on endometrial tissue, it was further analyzed for the first time, how these supplements affect angiogenesis and vascularization of transplanted ovarian follicles.

Endometrial fragments and ovarian follicles of Syrian golden hamsters were isolated and transplanted into dorsal skinfold chambers. Using this model, it was possible to repetitively analyze in vivo angiogenesis and vascularization in developping endometriotic lesions and ovarian follicles over a time period of 14 days by means of intravital fluorescence microscopy.

In the first part of this study the anti-angiogenic effect of the polyphenol EGCG was investigated. EGCG suppressed angiogenesis in endometriotic lesions and reduced the blood perfusion of the ectopic endometrial tissue. Histological analysis revealed the regression of EGCG-treated endometriotic lesions. Furthermore, EGCG suppressed the expression of vascular endothelial growth factor (VEGF) in ectopic endometrium in vivo and inhibited the estrogen (E2)-stimulated activation, proliferation and VEGF-expression of endometrial cells in vitro. The analysis of ovarian follicles showed no differences between the groups, indicating that EGCG may selectively inhibit angiogenesis of ectopic endometrium. Thus, this component of green tea represents a promising therapeutic agent in the treatment of endometriosis.

In the second part of the study the effect of the non-essential amino acid glycine on angiogenesis of endometriotic lesions and ovarian follicles was analyzed. Dietary glycine did not affect angiogenesis of endometrial and ovarian grafts. Accordingly, glycine-treated hamsters presented with a normal reproductive function. Interestingly, glycine inhibited apoptosis in endometrial and ovarian tissue by down-regulation of nuclear factor-κB (NF-κB). This may be beneficial for the establishment of novel fertility preservation techniques, where ovarian tissue is cryopreserved and transplanted in patients, whose gonadal function is threatened by several diseases or by treatments such as radiotherapy and chemotherapy.

The third part of the study showed that the isoflavone genistein inhibits angiogenesis neither in endometriotic lesions nor in ovarian follicles. Thus, genistein may be used as a selective inhibitor of pathological angiogenesis of certain tumor types without affecting blood vessel development in the female reproductive organs.

In summary, it was possible to analyze for the first time simultaneously in vivo angiogenesis of endometriotic lesions and ovarian follicles. The results of the study indicate that dietary supplements represent promising candidates for the anti-angiogenic treatment of endometriosis and other angiogenic diseases. Because of its effects on ectopic endometrium, EGCG may be used in the treatment of endomet-

riosis, preventing the establishment of new endometriotic lesions. Glycine and genistein may be used as selective inhibitors of pathological angiogenesis during tumor growth without inducing serious side effects in the female reproductive tract.