

Pathogenesis of endometriosis: Cellular and molecular approach to understand the disease development and progression.

Pr Dr Janko Gogusev,

Cochin Institute, Inserm 1016/Department of Development, Reproduction and Cancer/,
Medical Faculty-Université Paris Descartes, Paris, France

Endometriosis is chronic, benign, estrogen-dependent inflammatory disease affecting approximately 10% of women in reproductive age and 35-50% of women with pelvic pain and infertility. Its etiology and pathogenesis are controversial but it is believed to involve multiple genetic, environmental, immunological, angiogenic, and endocrine factors. The anatomical features of the ectopic organoid structures identified in fetal female reproductive tract suggest that endometriotic disease in adult women may as well originate from misplaced endometrial glands and /or embryonic remnants.

Numerous studies support the view that cellular and molecular features of endometriotic lesions differ from those of eutopic endometrium. A substantial body of evidence also suggests that the eutopic endometrium from patients with endometriosis differs from that of women without endometriosis.

With aim to investigate novel tissue parameters controlling disease progression, the cellular, cytochemical, molecular cytogenetic and phenotypic features of endometriotic tissues and cultured cells were investigated. In severe forms in stage III and IV according to the revised AFS classification, chromosome instability was evidenced by using cytogenetics (RHG-banding), situ hybridization (FISH) and comparative genomic hybridization (CGH). By means of the CGH molecular strategy, recurrent copy number alterations were found in 15 of 18 (83%) cases with advanced stage endometriotic lesions indicating clonal genomic changes. The most common altered chromosomal regions showing loss of DNA sequences were located on 1p32-36 (50%), 5p (33%), 6q (27%), 7p14-22ter (22%), 16qter (22%) and 22q12.3 qter (50%). Deletions of

chromosome 1 were particularly common in all types and stage of lesions, including the peritoneal implants, endometriomas and tissue lesions from deep infiltrating endometriosis (DIE). Deletions of 5q and 6q chromosomes were detected in approximately one third of the endometriotic cases studied. We confirmed by allelotyping, the significant percentage of LOH with molecular markers located at 5q and 6q chromosomal segments. In this context, it has been reported that a putative tumor suppressor gene/s are located on the 6q arm which are involved in development of ovarian carcinoma. The potential tumor suppressor gene for this region is the superoxide dismutase gene 2 (SOD2) located on 6q25. High frequencies of LOH encompassing the SOD2 gene were shown in ovarian carcinoma. Gain DNA sequences were less common and were localized on chromosomes 6q and 17q in three cases.

Concerning the correlation between the endometriotic tissue molecular phenotype and the clinical parameters, we identified and validated an applicable immunohistochemistry panel including Ki-67, c-MYC, estrogen receptor (ER- α) and progesterone receptor isoforms A/B (PR-A/B) in patients affected by Deep-Infiltrating Endometriosis. The study was realized on tissue microarrays from selected endometriotic lesions from a cohort of 113 patients. The phenotypic profile of the panel molecules was evaluated in glands and stroma in parallel with micro vessels and stroma density measurements. Principal component analysis was performed on 8 immunohistochemical variables, 2 histological variables, and 8 subgroups of clinical parameters. The immuno-histochemical profiling showed consistent Ki-67 immunoreactivity in 17.9% of the samples and c-MYC in 83.1% , while the intense ER- α immunostaining was detected in 84% of the samples and PR-A/B isoforms in 24.1% of them. The combination of clinical parameters and tissue phenotype allowed an innovative stratification of endometriosis-affected patients. Currently, we are developing further research projects to evaluate the correlation between a panel of four genomic markers including SOX2, Nanog, Oct3/4 and Superoxide dismutase /SOD2 genes and the clinical parameters in a larger cohort of patients affected with aggressive forms of endometriosis (rAFS IV). Such novel

phenotypic/genomic and clinical correlations studies could be helpful for a better clinical/pathological stratification of the disease aiming at a personalized gynecological patient care.

Title: Endometriosis in the reproductive age.

Authors: Ass.Prof. Rajko Fureš, prim. MD, PhD 1,2, Prof. Miroslav Kopjar, MD, PhD 1,2,3, Prim. Damir Hodžić, MD, PhD4

1Department of gynecology and obstetrics. General Hospital Zabok, Croatia.

2Faculty of Medicine Osijek. University of Josip Juraj Strossmayer – Osijek, Croatia.

3Libertas International University, Zagreb, Croatia.

4Department of Gynecology and Obstetrics. University Hospital "Merkur", Zagreb, Croatia.

SUMMARY: In more than half of patients with deep pelvic endometriosis who infiltrated

Rectovaginal septum find and rectal lesions. In this anamnesis infertility is found in over half of patients with deep pelvic endometriosis. The method of choice for treatment of deep pelvic endometriosis is

operating, due to the reversible effects of drug therapy. When this is the laparoscopic approach today has become the gold standard in the treatment of endometriosis in the reproductive period. And the treatment of endometriosis laparoscopic bowel treatment is the primary choice, considering all the advantages over conventional surgical approach. When it is necessary multidisciplinary approach and meticulous training with superior operating technique, which confers long-term and continuous improvement. The advantage of the laparoscopic approach compared to the traditional surgical approach is faster postoperative recovery and insurance later incomparably better quality of life. In view of their results, we analyze the experience of thirty years of practicing endoscopic surgery, by reference to the issue of endometriosis in women of reproductive age, underwent surgery in the Department of

Gynecology and Obstetrics, General Hospital Zabok hospital and Croatian veterans. Of particular importance is the fact that endometriosis is a growing problem due to the younger age groups in which they develop, as well as considering that in all younger age groups occur and cases of more advanced disease. Also in everyday work and we meet with the increasing incidence of women due to certain socio- economic and professional conditions delaying conception and this is one of the current momentum with which we encounter daily. In this context it is particularly important moment and preserving ovarian reserve as very significant reproductive parameters. During the said period of thirty years, we could experience a number of challenges laparoscopic treatment of endometriosis, which in the reproductive period of women, given recent demographic indicators, gaining increasing importance.