Karolinska Institutet

Institutionen för Kvinnors och Barns Hälsa

Pathophysiological factors and genetic association in endometriosis

AKADEMISK AVHANDLING
som för avläggande av medicine doktorsexamen vid Karolinska Institutet offentligen försvaras i Skandiasalen, Astrid Lindgrens Barnsjukhus

Fredagen den 18 februari 2011, kl 09.00

av

Johanna Sundqvist

Huvudhandledare:
Professor Kristina Gemzell-Danielsson
Karolinska Institutet
Institutionen för Kvinnors och Barns Hälsa

Bihandledare:
PhD. Luther Lalit Kumar
Karolinska Institutet
Institutionen för Kvinnors och Barns Hälsa
Enheten för obstetrik och gynekologi

M.D., PhD. Henrik Falconer
Karolinska Institutet
Institutionen för Kvinnors och Barns Hälsa
Enheten för obstetrik och gynekologi

PhD. Maria Seddighzadeh
Karolinska Institutet
Institutionen för Medicin
Enheten för reumatologi

Fakultetsopponent:
Professor Matts Olovsson
Uppsala Universitet
Institutionen för Kvinnors och Barns Hälsa
Enheten för obstetrik och gynekologi

Betygsnämnd:
Docent Daniel Altman
Karolinska Institutet
Institutionen för Medicinsk epidemiologi och biostatistik

Docent Catharina Lavebratt
Karolinska Institutet
Institutionen för Molekylär Medicin och Kirurgi
Enheten för neurogenetik

Professor Inger Sundström Porooma
Uppsala Universitet
Institutionen för Kvinnors och Barns Hälsa
Enheten för obstetrik och gynekologi

Stockholm 2011

ABSTRACT

Introduction: Endometriosis is a common benign gynecological disease where endometrial tissue forms lesions outside the uterine cavity. Endometriosis is estimated to affect about 10% of women of reproductive age, rising to 20-40% in patients with infertility, with a significant impact on physical, mental and social well-being of those affected. Today there is no cure for this disease and the most common medical treatments are not suitable for long term treatment due to side-effects. Although endometriosis is a well-known disease, the pathogenesis remains unclear. The most accepted theory about the pathogenesis is Sampson´s theory about retrograde menstruation. However, different properties, such as adhesion, invasion and proliferation of the shed menstrual cells seem to play an important role in the development of endometriosis. Also, altered immune surveillance, stem cells and genetic predisposition could be involved in the pathogenesis.

Aims: The overall aim of this thesis was to study the aetiology and pathophysiology of endometriosis, specifically the inflammatory profile in the follicular fluid of *in vitro* fertilization (IVF) patients and adhesion, attachment and invasion factors in endometriosis. Furthermore, the aim was to investigate the genetic background of endometriosis and a possible genetic linkage to rheumatoid arthritis (RA) and ovarian cancer.

Results: We found that women with endometriosis undergoing IVF have lower levels of anti-mullerian hormone (AMH) and a lower fertilization rate. These women also have an increased inflammatory profile in the follicular fluid. We observed genetic association of two RA-associated SNPs in CCL21 and HLA-DRB1 in women with moderate/severe disease. However, we could not observe any association of the ovarian cancer associated SNPs in the BNC2 gene. In addition, we found expression of ApoE, ITGB2, ITGB7, LAMC1, CD24 and JAM-1, in endometrium from healthy controls, endometrium from endometriosis patients and in endometriomas.

Conclusions: Our results support a strong inflammatory component in endometriosis, which may affect the ovarian reserve and lead to infertility problems. Furthermore, genetic associations in inflammatory related genes were found in women with moderate/severe disease. An aberrant expression of factors involved in adhesion, attachment and invasion may be important in the establishment of endometriotic lesions and may at least partly be regulated by inflammatory mediators.

ISBN 978-91-7457-224-7