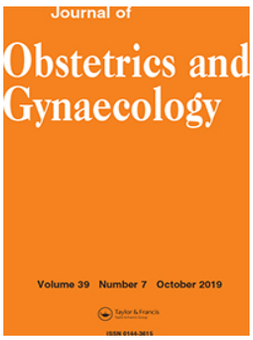

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ORIGINAL ARTICLE

The levels of matrix metalloproteinase-9 and neutrophil gelatinase-associated lipocalin in different stages of endometriosis

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ABSTRACT

This study was designed to explore matrix metalloproteinase-9 (MMP-9), neutrophil gelatinase-associated lipocalin (NGAL) levels and MMP-9/NGAL ratio in women with and without endometriosis diagnosed surgically and/or histopathologically. The correlation between biomarkers and the severity of the disease is analysed. The revised American Fertility Society classification system was used to determine the severity of endometriosis. Serum MMP-9 and Ca125, urine NGAL levels were measured in all participants. Serum MMP-9 levels were significantly higher in the study group ($n = 60$) compared to controls ($n = 31$) (15.0 pg/mL (6.0–143.0) vs. 12.0 (4.0–18.0), respectively; $p = .002$). MMP-9 levels were significantly higher in severe endometriosis compared to mild endometriosis subgroups ($p < .001$). No significant difference was found between NGAL levels in study and control groups ($p > .05$). The diagnostic value of MMP-9 and NGAL is not superior than CA-125 for endometriosis. Nevertheless, MMP-9 might be a potential predictive marker for advanced stage of the disease.

KEYWORDS

MMP-9; NGAL; endometriosis; stage

IMPACT STATEMENT

- **What is already known on this subject?** The gold standard diagnostic test for diagnosis of endometriosis is laparoscopy combined with histopathological confirmation of eutopic endometrial glands and/or stroma. Both invasiveness and possible accompanying complications limit the preference regarding the surgical approach. Among non-invasive markers none has been accepted as gold standard neither for diagnosis nor for determining the severity of the disease. MMPs are extracellular endopeptidases, which have a significant role in degradation and remodelling of extracellular matrix for cellular migration and invasion. Among these, MMP-9 has been shown to be higher in eutopic/ectopic endometrial tissue in women with endometriosis and has been suggested to have a role in pathogenesis of endometriosis by promoting invasion of the endometriotic lesions. NGAL is an acute phase protein, which is involved in a variety of physiological and pathophysiological processes. The molecule has also been revealed to correlate with endometriosis pathophysiology through the epithelial–mesenchymal transition process which is the basis for the onset of endometriosis. But also, NGAL which composes a complex with MMP-9 (MMP-9 and NGAL complex), has been shown to protect MMP-9 from autodegradation *in vitro* which might be a contributing factor for endometriosis pathophysiology.
- **What the results of this study add?** MMP-9 cut-off level for prediction of severe endometriosis is a novel finding obtained from this study with acceptable sensitivity and specificity. On the other hand, NGAL seems to have no significant value either for diagnosis of for determining severity of the disease. After all, MMP-9 might be an easy use acceptable biomarker for endometriosis but further studies on larger populations are needed.
- **What the implications are of these findings for clinical practice and/or further research?** MMP might be a potential non-invasive predictive marker for advanced stage disease.

Introduction

The prevalence of endometriosis range between 2 and 10% among reproductive age women (Dunselman et al. 2014). Despite, ongoing research on pathophysiology and treatment of endometriosis, pretty much unknown steps remain. Although, the diagnosis depends on imaging and surgery, numerous biomarkers are evaluated up today for diagnostic and follow-up purposes. A recent Cochrane review about blood biomarkers for non-invasive diagnosis of endometriosis revealed that, none of the biomarkers displayed enough accuracy to be used clinically outside a research setting

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(Nisenblat et al. 2016). Among the previous reports, matrix metalloproteinase-9 (MMP-9) and neutrophil gelatinase-associated lipocalin (NGAL) are two of these promising biomarkers, previously shown to be increased in endometriosis.

MMPs are extracellular endopeptidases, which have a significant role in degradation and remodelling of extracellular matrix for cellular migration and invasion (Becker et al. 2010). MMP-2 and MMP-9 constitute gelatinase subgroup of MMPs, secreted from macrophages and neutrophil leukocytes (Long et al. 2012). Especially MMP-9, have been shown to be elevated in eutopic/ectopic endometrial tissue in women with endometriosis and both have been suggested to have a role in pathogenesis of endometriosis by promoting invasion of the endometriotic lesions (Bruner et al. 1997; Sharpe-Timms et al. 1998; Chung et al. 2001; Sillem et al. 2001; Chung et al. 2002; Ria et al. 2002; Szamatowicz et al. 2002; Huang et al. 2004; Collette et al. 2006).

NGAL is an acute phase protein, which is involved in a variety of physiological and pathophysiological processes, such as metabolic homeostasis, apoptosis, infection, immune response or inflammation (Abella et al. 2015). The molecule has also been revealed to correlate with endometriosis pathophysiology through the epithelial–mesenchymal transition process which is the basis for the onset of endometriosis (Liao et al. 2013). Besides, NGAL which composes a complex with MMP-9 (MMP-9 and NGAL complex), has been shown to protect MMP-9 from autodegradation *in vitro* (Becker et al. 2010) which might be a contributing factor for endometriosis pathophysiology.

The current study is designed to explore MMP-9 and NGAL levels and MMP-9/NGAL ratio in women with and without endometriosis diagnosed by surgical evaluation. In addition, the correlation between these biomarkers and the severity of the disease is analysed as well.

Materials and methods

Study population

This is a cross-sectional study conducted in University Hospital setting between November 2016 and June 2017. The study has been approved by the University Ethical Committee (Number: 15112016-6) and written informed consent was taken from all participants. The study population consisted of patients with endometriosis undergoing laparoscopy without any medical treatment in the last six months before surgery. Controls were women undergoing laparoscopy for other benign gynaecological indications (infertility, ruptured ovarian cyst, tubal cannulation, fimbrioplasty, hydrosalpinx, leiomyoma, ovarian drilling) during the same period. Exclusion criteria were lean (BMI $<19\,kg/m^2$) and obese (BMI $>30\,kg/m^2$) women and women who have irregular periods, acute urinary tract infection, women with chronic diseases (hypoxic ischaemic vascular diseases, abnormal renal functions, cardiovascular diseases) and nephrotoxic medication use. Cases with intraoperative bleeding necessitating blood transfusion and conversion to laparotomy were also excluded.

All patients received general anaesthesia. Pneumoperitoneum was established by insufflation of carbon dioxide gas through automatic insufflators. A maximum 15 mm Hg intra-abdominal pressure was maintained throughout the operation. For the surgery, the patient was placed in the Trendelenburg position at a 30° angle.

The revised American Fertility Society (rAFS) classification system was used to determine the severity of endometriosis by point scoring followed by staging. The scores were assigned by the gynaecologist who performed the surgery (ASRM 1997).

Serum and urine samples

Before any surgical intervention, a venous blood sample for MMP-9 and urine sample for NGAL by urethral catheterisation were taken in the theatre room. The serum and urine samples were taken into flat tubes and were stored at –80 °C until assayed. Serum MMP-9 levels were analysed by a commercially available enzyme-linked immunosorbent assay (ELISA) kit for MMP-9 (Chemwell 2900 Aurenesness, Cloud-Clone Corp., Palm City, FL). Intra-assay and inter-assay coefficients for MMP-9 were <10% and <12%, respectively. Urinary NGAL levels were measured by chemiluminesant microparticle immunoassay (CMIA) by Abbott Architect *i* 1000 autoanalyzer (Abbott Park, IL). Intra-assay and inter-assay coefficients for NGAL were 3.3% and 1.7%, respectively. Preoperative CA-125 levels were measured in all participants. CA-125 levels were measured CMIA by Abbott Architect *i* 2000 (Abbott Park, IL) autoanalyzer. Intra-assay and inter-assay coefficient variations for NGAL were 3.2% and 3.9%, respectively.

Statistical analysis

The statistical analysis was performed using SPSS version 20.0 for Mac OS (IBM Corp., Released 2011, IBM SPSS Statistics for Windows, Version 20.0, IBM Corp., Armonk, NY). Data were shown as mean ± standard deviation (SD) or median (minimum–maximum) where applicable. The Mann–Whitney *U* test, chi-squared test and Fisher's exact test were used to analyse the data. Correlation between numerical variables and presence of endometriosis/severe endometriosis were tested with Spearman's correlation coefficient. Variables which were found to have a p value <.05 were included in the multivariate linear regression analysis. AUC and 95% confidence interval for presence of endometriosis/severe endometriosis were evaluated by receiver operating characteristics (ROC) analysis. The performance of variables to predict presence of endometriosis/severe endometriosis was evaluated by adjusted OR and 95% CI. The best cut-off point for MMP-9 and diagnostic performance such as sensitivity, specificity, and positive and negative predictive values were calculated. A p value <.05 was considered statistically significant.

Results

The demographic characteristics of the study population (age, body mass index, gravidity and parity) are given in Table 1. Ninety one women were eligible for the study. The intraoperative diagnosis at laparoscopy ($n = 91$) is given at

Table 1. Sixty cases diagnosed as having endometriosis were taken as the study group, the remaining 31 women constituted the control group. In the study group, 30 cases were staged as I–II and 30 cases were staged as III–IV according to rASRM classification for endometriosis (ASRM 1997).

The CA-125 levels were statistically significantly higher in the study group compared to control group (30.4 U/mL (3–503.0) vs. 10.0 U/mL (2.1–151.0), respectively; <.001). Serum MMP-9 levels were significantly higher in the study group compared to controls (15.0 pg/mL (6.0–143.0) vs. 12.0 (4.0–18.0), respectively; $p = .002$) (Table 2). Moreover, significantly higher levels of MMP-9 were detected in severe endometriosis (stages III and IV) compared to mild endometriosis (stages I and II) subgroups ($p < .001$, Table 2). No significant difference was found between NGAL levels in study and control groups ($p > .05$) (Table 2). In addition, NGAL did not change between severe and mild endometriosis subgroups ($p > .05$). MMP-9/NGAL ratio was significantly higher in the study group compared to controls ($p < .05$) and also was statistically significantly higher in the severe endometriosis subgroup compared to mild ($p < .05$).

According to Spearman's rank correlation analysis, neither NGAL levels nor MMP-9 levels were correlated with presence of endometriosis in the study group ($r = -0.073$, $p = .545$). Similarly, NGAL and MMP-9 levels were not statistically significantly correlated with presence of severe (stages III and IV) endometriosis ($r = 0.272$, $p = .153$).

Multivariate regression analysis revealed that, among all variables (age, BMI, CA-125, NGAL, MMP-9 and MMP-9/NGAL ratio) only CA-125 levels significantly predicted presence of endometriosis (OR: 1.032; 95% CI: (1.001–1.064); $p = .044$). Among the same variables, CA-125 and MMP-9 levels were predictive for severe endometriosis (OR: 1.040; 95% CI: (1.010–1.060); $p = .002$ and OR: 1.690; 95% CI: (1.170–2.430); $p = .005$). The predictive accuracy of MMP-9 for severe endometriosis was found by ROC analysis (AUC = 0.878, (95% CI: 0.792–0.964), $p < .001$) (Figure 1). The best cut off point for MMP-9 and diagnostic performance such as sensitivity, specificity, and positive and negative predictive values were also calculated. An MMP-9 threshold of 14.13 pg/mL had a sensitivity of 80%, specificity of 73.3%, positive predictive value of 74.2% and negative predictive value of 78.6% with an accuracy of 76.27% for severe endometriosis.

Table 1. The characteristics of the study and control groups.

Variable	Study group ($n = 60$)	Control group ($n = 31$)	p
Age Mean±SD	34.12 ± 4.71	34.52 ± 5.45	.923
BMI Median (min–max)	26.7 (19.5–34.4)	26.4 (19.1–33.6)	.756
Gravidity Median (min–max)	1 (0–6)	1 (0–4)	.404
Parity Median (min–max)	0 (0–6)	1 (0–3)	.444
Diagnosis at laparoscopy n (%)			
Endometrioma	31 (51.7)	0	
Ovarian cyst[a]	12 (20.0)[b]	13 (41.9)	
Tubal pathology	6 (10.0)[b]	1 (3.2)	
Leiomyoma	7 (11.7)[b]	6 (19.4)	
Others	4 (6.7)[b]	11 (35.5)	

[a]Other than endometrioma.
[b]Accompanying endometriosis.

Discussion

The gold standard diagnostic test for diagnosis of endometriosis is laparoscopy combined with histopathological confirmation of eutopic endometrial glands and/or stroma (Dunselman et al. 2014). A systematic review by Wykes et al. (2004) reported a sensitivity of 94% and a specificity of 79% for the laparoscopy in the diagnosis of endometriosis. Both invasiveness and possible accompanying complications limit the preference regarding the surgical approach. Many researchers work on mostly biochemical markers as less invasive methods for diagnosis. However, to date, neither a single biomarker nor a combination of few have reached the desired level of accuracy for a diagnostic test for endometriosis (Nisenblat et al. 2016). Unfortunately, the results of this study also shows that MMP-9, NGAL or MMP-9/NGAL ratio is not superior than CA-125 to be used for diagnosis. Nevertheless, MMP-9 might be a potential predictive marker for advanced stage disease.

Although the latest ESHRE guideline on endometriosis does not recommend use of any biomarkers, including CA-125, in plasma or serum to diagnose endometriosis (Dunselman et al. 2014), CA-125 is still the most clinically used biomarker both for diagnosis and follow up of the disease. For the diagnosis of endometriosis, CA-125 cut-off level ≥30 units/ml has a specificity of 93% (95% CI 89–95%) and sensitivity of 52% (95% CI 38–66%) (Hirsch et al. 2016). On the other hand, CA-125 is significantly more sensitive for the diagnosis of severe endometriosis compared with milder forms of the disease (63%, 95% CI 47–77% vs. 24%, 95% CI 19–32%, $p = .001$) (Hirsch et al. 2016). In this study, CA-125 levels were statistically significantly higher in endometriosis group compared to controls. In addition, CA-125 was

Table 2. Ca 125, NGAL and MMP-9 values in study and control groups.

Variable	Study ($n = 60$)	Control ($n = 31$)	p	Endometriosis Stages I and II	Endometriosis Stages III and IV	p
Ca 125 (U/mL) (min–max)	30.4 (3–503.0)	10.0 (2.1–151.0)	<.001*	13.0 (3–181)	90 (14.9–503)	<.001*
NGAL (ng/dL) (min–max)	2.1 (0.1–15.5)	2.2 (0.1–14.1)	.542	3.6 (0.1–13.1)	1.2 (0.1–15.5)	.542
MMP-9 (pg/mL) (min–max)	15.0 (6.0–143.0)	12.0 (4.0–18.0)	.002*	12.0 (6–18)	23.0 (10–143)	<.001*
MMP-9/NGAL ratio (min–max)	15.30 (0.6–403.3)	4.80 (0.8–130.0)	.013*	4.80 (0.8–130.0)	27.8 (1.2–403.3)	.003*

NGAL: neutrophil gelatinase-associated lipocalin; MMP-9: matrix metalloproteinase-9.
*$p < .05$.

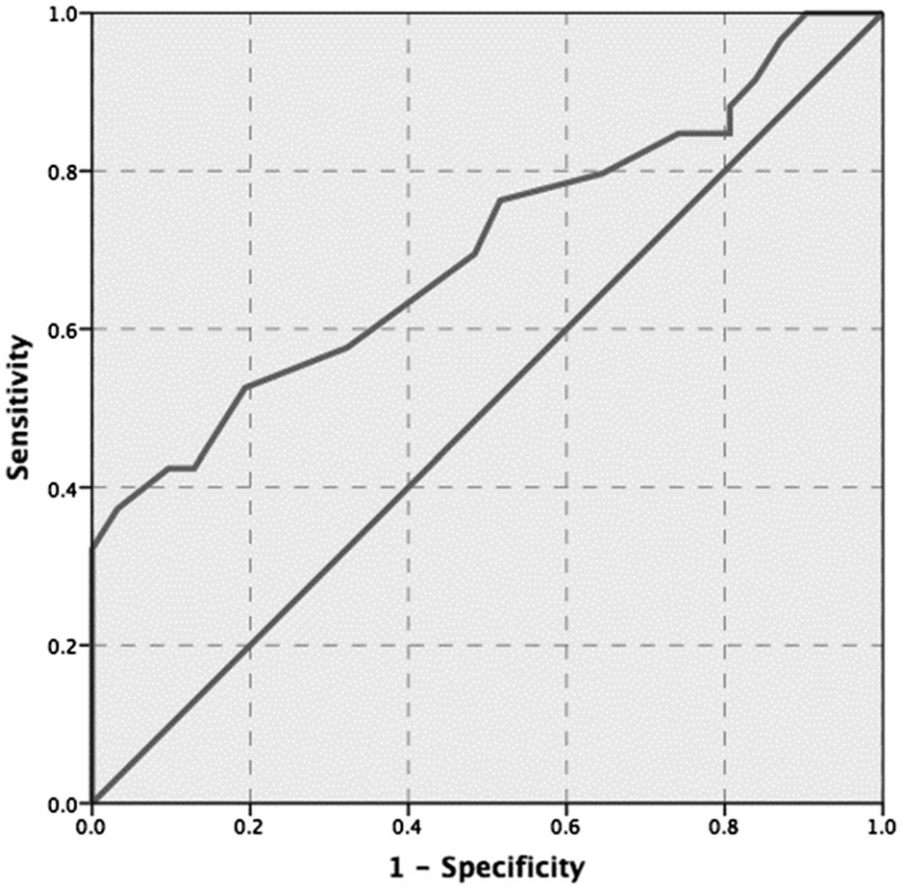

Figure 1. ROC analysis for MMP-9 to predict severe endometriosis.

predictive for endometriosis and severe forms of the disease confirming the previous data.

MMP-9 levels are elevated in serum samples of women with endometriosis (Becker et al. 2010) confirming the data obtained from our study. MMP-9 degrades collagen and elastin, induces neovascularisation, accelerates expansion of vascular endothelial cells and increases blood flow (De Sanctis et al. 2011; Mei et al. 2012). Moreover, MMP-9 has been shown to be higher in peritoneal washings of women with endometriosis in ectopic compared to eutopic endometrium (Liu et al. 2015). In endometriosis, the main mechanism of action of MMP-9 is to promote the invasion process of endometriotic tissues (Becker et al. 2010). The higher levels of MMP-9 in severe endometriosis compared to mild endometriosis in our study support the previous information. MMP-9 is also a NGAL associated endopeptidase (Cymbaluk-Płoska et al. 2017) since NGAL prevents its degradation promoting its effects (Becker et al. 2010; Cymbaluk-Płoska et al. 2017). This is why, the ratio of MMP-9/NGAL might be a promising biomarker for endometriosis. The current study supports this hypothesis, with statistically significantly higher MMP-9/NGAL ratio in endometriosis and a remarkably high ratio in severe forms of the disease. The high ratio has been mostly dependent on MMP-9 levels since NGAL levels were not significantly different both in the study group and severe endometriosis subgroup.

The small sample size is a limitation of this study and with the data available from this study it is hard to draw strong conclusions. However, MMP-9 cut-off level for prediction of severe endometriosis is a novel finding obtained from this study with acceptable sensitivity and specificity. In conclusion, MMP-9 might be an easy use acceptable biomarker for endometriosis but further studies on larger populations are needed.

Disclosure statement

No potential conflict of interest was reported by the authors.

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