TÜRKİYE CUMHURİYETİ
ANKARA ÜNİVERSİTESİ
SAĞLIK BİLİMLERİ ENSTİTÜSÜ

COMPARISON OF SERUM NEUTROPHIL GELATINASE-ASSOCIATED LIPOCALIN (NGAL) AMOUNT IN INFERTILE WOMEN WITH ENDOMETRIOMA AND IN UNEXPLAINED INFERTILE WOMEN

Batuhan TURGAY

KADIN HASTALIKLARI VE DOĞUM ANABİLİM DALI

DOKTORA TEZİ

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Bu araştırma Ankara Üniversitesi Bilimsel Araştırma Projeleri Müdürlüğü'nün TDK-2024-3596 proje numarası ile desteklenmiştir.

ANKARA

2024

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To Ankara University

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The doctoral dissertation entitled "Comparison of Serum Neutrophil Gelatinase-Associated Lipocalin (Ngal) Amount In Infertile Women With Endometrioma and In Unexplained Infertile Women" was written by me in accordance with scientific ethics and values. The idea/hypothesis of the thesis belongs entirely to my thesis supervisors and me. The experimental study/research in the thesis was conducted by myself, and all sentences and comments belong to me.

I declare that the above-mentioned statements are true.

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ÖZET

Endometriozisli İnfertil Hastalarda ve Açıklanamayan İnfertilitesi Olan Hastalarda Serum Nötrofil Jelatinaz İlişkili Lipokalin (NGAL) Miktarının Karşılaştırılması

Bu çalışmada inflamatuar markerlardan olan ve bazı hastalıkların tanı ve takibinde kullanılan NGAL, MMP-9 ve MMP-9/NGAL oranının endometrioması olan infertil hastaların tanı ve takibinde kullanılıp kullanılamayacağı araştırılmıştır.

45 açıklanamayan infertilite ve 45 endometrioması olan infertil hasta çalışmaya dahil edilmiştir. Çalışmaya dahil edilen endometriomalı hastalar en az 3 cm boyutunda endometrioması olan hastalar içinden seçilmiş ve bu hastalara daha sonrasında laparoskopik olarak da tanı konulmuştur. Bu hastalardan venöz kan örneği alınmış, santrifüj edilmiş ve -80°C de saklanmıştır. Ameliyattan üç ay sonra bu hastalardan yeniden venöz kan alınmıştır. Kan örneklerinde NGAL, MMP-9 ve MMP-9/NGAL oranlarına bakılmıştır. Bu sonuçlar açıklanamayan infertilite grubu ve endometrioma grubu arasında; endometrioma grubunun kendi içerisinde preoperatif ve postoperatif sonuçları açısından karşılaştırılmıştır.

Endometrioma ve açıklanamayan infertilite grubu arasında ortalama yaş (32,5±3,4 ve 31,7±4,9) açısından fark bulunmamıştır, ancak AMH değerleri (1,8±0,6 ve 3,3±2,3 ng/ml) açısından iki grup arasında fark vardır (sırasıyla p=0,79; p=0,04). Endometrioma ve açıklanamayan infertilite gruplarında ortalama NGAL ve MMP-9 kan düzeyleri sırasıyla 22,0±4,0 ng/ml ve 25,4±4,9 ng/ml; 43,7±8,0 ng/ml ve 39,3±10,7 ng/ml olarak bulunmuş ve tüm sonuçlar istatistiksel olarak anlamlı çıkmıştır (p=0,001; p=0,012). Dört hasta takip için gelmediği için, bu hastaların sonuçları postoperatif sonuçlar değerlendirilirken analize dahil edilmemiştir. Endometrioma grubundaki hastaların ameliyat sonrası üçüncü ayda ortalama NGAL ve MMP-9 kan düzeyleri sırasıyla 24,9±4,9 ng/ml ve 27,0±4,9 ng/ml; 43,9±7,3 ng/ml ve 36,7±8,7 ng/ml olarak bulunmuştur (p=0,179; p=0,006). Endometrioma, açıklanamayan infertilite grubu ve postoperatif endometrioma hastalarının ortalama MMP-9/NGAL oranına bakıldığında 2,0±0,2, 1,5±0,2 ve 1,4±0,2 sonuçları bulundu. Endometrioma-açıklanamayan infertilite grubu arasınd ve endometrioma hastalarının preoperatif-postoperatif sonuçları arasında anlamlı bir fark bulundu (p=0,001;p=0,001). Endometrioma varlığında MMP-9/NGAL oranı ilişkisi ile ilgili ROC eğrisi analizi yapıldığında, bu değerin 1,75 üzerinde olmasının %86,1 sensivite ve %84 spesifite ile endometrioma varlığını gösterdiği tespit edildi (AUC=0,898).

Sonuç olarak, NGAL kan düzeyinin endometrioma grubunda anlamlı olarak daha düşük çıkması sürpriz bir sonuç olarak nitelendirilebilir. Bununla beraber MMP-9/NGAL oranı endometrioma tanısı konulmasında kullanılabilir.

Anahtar Sözcükler: Açıklanamayan infertilite, Endometrioma, MMP-9, NGAL

SUMMARY

Comparison of Serum Neutrophil Gelatinase-Associated Lipocalin (NGAL) Amount In Infertile Women With Endometrioma and In Unexplained Infertile Women

In this study, we aimed to investigate whether serum NGAL, MMP-9 and MMP-9/NGAL ratio that are inflammatory markers and used for diagnosis and follow-up in some diseases can be used as a diagnostic and follow-up marker in the diagnosis of endometrioma in infertile patients.

45 unexplained infertility patients and 45 infertile patients with endometrioma were included in the study. Patients with endometriomas of at least 3 cm in size were included in the study and all patients were also diagnosed with endometrioma laparoscopically. A venous blood sample were taken from the patients, centrifuged and stored at -80 degrees. 3 months after the surgery, venous blood sample were taken again. NGAL and MMP-9 levels from the venous blood sample and MMP-9/NGAL ratio of the unexplained infertility and endometrioma group and the preoperative and postoperative results of the endometrioma group were compared.

The mean age (32.5±3.4 vs 31.7±4.9) were not different but AMH values (1.8±0.6 vs 3.3±2.3 ng/ml) were different between endometrioma and unexplained infertility group, respectively (p=0.79;p=0.04). The mean blood level of NGAL and MMP-9 in endometrioma and unexplained group were 22.0±4.0 ng/ml and 25.4±4.9 ng/ml; 43.7±8.0 ng/ml and 39.3±10.7 ng/ml respectively and all results were statistically significant (p=0.001;p=0.012). 4 patients did not come for follow-up, so their results were not included in the analysis when evaluating the postoperative outcomes. The mean blood level of NGAL and MMP-9 in endometrioma and same patients on postoperative third months were 24.9±4.9 ng/ml and 27.0±4.9 ng/ml; 43.9±7.3 ng/ml and 36.7±8.7 ng/ml, respectively (p=0.179;p=0.006). The mean ratio of MMP-9/NGAL in endometrioma, unexplained group and postoperative patients were 2.0±0.2, 1.5±0.2 and 1.4±0.2. All these results between endometrioma-unexplained group and endometrioma-postoperative patients were statistically significant (p=0.001;p=0.001). When we made a ROC curve analysis for the presence of endometrioma, it was observed that the MMP-9/NGAL ratio value greater than 1.75 had 86.1% sensitivity and 84% specificity in indicating the presence of endometrioma (AUC=0.898).

Suprisingly, NGAL blood level was lesser in the endometrioma group. MMP-9/NGAL ratio can be useful in the diagnosis of endometrioma.

Keywords: Endometrioma, MMP-9, NGAL, Unexplained infertility

CONTENTS

ACKNOWLEDGEMENTS

I would like to extend my heartfelt thanks to everyone who supported me throughout my doctoral journey. I extend my deepest gratitude to all the faculty members in the Gynecology and Obstetrics and Urology departments who participated in the doctoral program for their valuable guidance and expertise.

I would like to especially thank the program coordinator and my thesis advisor, Prof. Dr. Batuhan Özmen, for being a constant source of motivation with his unwavering support and for all his help, and the department head, Prof. Dr. Ruşen Aytaç, for all he has taught me and for providing a collaborative and encouraging academic environment. I am especially grateful to Prof. Dr. Murat Sönmezer and Prof. Dr. Aslı Yarcı Gürsoy for their insightful perspectives and guidance throughout my thesis process.

I extend my heartfelt thanks to Assoc. Dr. Emre Şükür, who has guided me in both my doctoral studies and academic life. Additionally, I would like to thank my doctoral friends Dr. Arif İbiş and Dr. Eda Üreyen for their friendship and encouragement.

I would like to thank Dr. Harun Kılıçkıran for his assistance in data collection and the staff of the Immunology Laboratory at İbni Sina Hospital for their support in the analysis of blood samples.

Finally, I extend my deepest gratitude to my family and loved ones for their unconditional support and belief in me.

SYMBOLS AND ABBREVATIONS

NGAL	Neutrophil Gelatinase-Associated Lipocalin
MMP-9	Matrix Metalloproteinase-9
AMH	Anti Mullerian Hormone
CA-125	Carcinoembryonic Antigen 125
CRP	C Reactive Protein
AKI	Acute Kidney Injury
CKI	Chronic Kidney Injury
kDa	Kilodalton
ELISA	Enzyme-Linked Immunosorbent Assay
WHO	World Health Organization
IL-1β	Interleukin-1β
TNF-α	Tumor Necrosis Factor-Alpha
TVUSG	Transvaginal Ultrasound
AF	Antral Follicle
FSH	Follicle Stimulating Hormone
LH	Luteinizing Hormone
TSH	Thyroid Stimulating Hormone
IL-6	Interleukin-6
ECM	Extracellular Matrix
BBB	Blood Brain Barrier
NK cell	Natural Killer Cell
TIMP-1	Metallopeptidase Inhibitor 1
miR451	Micro RNA 451
IVF	In Vitro Fertilization
AUC	Area Under Curve

FIGURES

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1. INTRODUCTION

Infertility is typically described as a couple's inability to conceive after one year unprotected sexual intercourse (Dyer et al., 2016). Infertility is a multifaceted disorder that significantly impacts individuals' psychological, social, and economic circumstances ("WHO Fact Sheet on Infertility," 2021). The World Health Organization (WHO) estimates that roughly 10-15% of couples globally experience infertility concerns. Endometriosis profoundly affects women's reproductive health and is intricately linked to infertility. Research indicates that the existence of endometriomas substantially impacts women's reproductive rates. Endometriosis may result in ovulatory dysfunction, diminished ovarian reserve, and fallopian tube obstructions (Nisenblat, Prentice et al., 2016). These diseases may diminish the likelihood of conception and contribute to infertility.

The implantation and proliferation of endometrial tissue beyond the uterine cavity are hallmarks of endometriosis, an hormone-dependent pelvic inflammatory disease (Hickey et al., 2014). Ten to fifteen percent of women who are of reproductive age are affected. Infertility and pelvic discomfort are the disease's most prevalent symptoms. In actuality, between 30 and 45 percent of infertile patients with pelvic discomfort have endometriosis (Burney & Giudice, 2012). Endometriosis can present with symptoms as dyspareunia and dysmenorrhea or be asymptomatic. Although endometriosis is a frequent and benign condition, dysmenorrhea, dyspareunia, chronic pain and also infertility can be related with the endometriosis and the inflammation that results from it (Vercellini et al., 2014).

1.1. Pathophysiology of Endometriosis

The pathophysiology of endometriosis is multifactorial and involves several interconnected theories:

The Retrograde Menstruation Theory: Introduced by Sampson in 1927, posits that menstrual flow is not exclusively expelled from the uterus but also reverses into the pelvic cavity, facilitating the implantation and proliferation of endometrial cells in ectopic sites (Montgomery & Giudice, 2017). Although retrograde menstruation is prevalent, affecting 76-90% of women, it does not explain all instances of endometriosis (Vercellini et al., 2024).

Stem Cell Theory: This theory posits that endometrial-like cells may arise from multipotent stem cells located in the bone marrow or the peritoneum, which can differentiate into ectopic endometrial tissue (Forte et al., 2014). This theory explains cases of endometriosis in individuals without a history of menstruation, such as premenarchal girls(Arosh et al., 2022).

Coelomic Metaplasia Theory: According to this theory, peritoneal cells undergo metaplasia, transforming into endometrial-like cells under hormonal and inflammatory stimuli(Agarwal et al., 2005). This theory is particularly relevant in explaining the development of endometriosis in areas not directly related to the reproductive system.

Müllerianosis Theory: This theory suggests that remnants of the Müllerian duct, which develops into female reproductive structures, can give rise to endometriotic tissue. It provides insight into congenital cases of endometriosis (Broi et al., 2019).

Inflammatory Mechanisms: Chronic inflammation is a keystone of endometriosis, characterized by the infiltration of immune cells which promote an inflammatory microenvironment (Parasar et al., 2017). Elevated levels of cytokines have been identified in the peritoneal fluid of affected women (Izumi et al., 2018).

1.2. Clinical Presentation

Endometriosis presents with a variety of findings that can profoundly affect a woman's life. The predominant symptoms encompass:

Chronic Pelvic Pain: This is the primary symptom of endometriosis, frequently aggravated during menstruation (dysmenorrhea)(Bulletti et al., 2010). Pain may also manifest during intercourse (dyspareunia) or during bowel motions and urine.

Infertility: An estimated 30-50% of women with endometriosis encounter infertility, rendering it a considerable issue for those desiring to conceive.

Menstrual Irregularities: Numerous women experience excessive or irregular menstrual flow (Dunselman et al., 2014).

Asymptomatic Cases: Certain individuals may possess endometriosis without exhibiting visible symptoms, underscoring the condition's variety (Moradi et al., 2014).

1.3. Diagnostic Methods

Laparoscopy is the definitive method for diagnosing endometriosis. This minimally invasive surgical technique enables direct observation of endometrial lesions and may involve biopsy for histological verification. It is especially effective for detecting deep infiltrating endometriosis and endometriomas (Bafort et al., 2020).

Imaging Modalities: Transvaginal Ultrasound (TVUS) is frequently employed to detect ovarian endometriomas and evaluate pelvic anatomy. Although transvaginal ultrasound (TVUS) is proficient at identifying bigger cysts, it may fail to detect smaller or superficial lesions (Vercellini et al., 2014).

Magnetic Resonance Imaging (MRI) offers comprehensive visualization of pelvic anatomy and is useful in detecting deep infiltrating endometriosis (Alonzo et al., 2024). It can clarify the scope of the disease and assist with surgical preparation.

Biomarker Evaluation: Investigations are under underway to discover non-invasive biomarkers for endometriosis. Increased concentrations of particular biomarkers, including CA-125 and some cytokines (e.g., IL-6, TNF-α), have been correlated with endometriosis; nevertheless, they are not yet dependable for regular diagnostic application (Nisenblat et al., 2016).

Histological Examination: The histological study of biopsied tissue is essential for the confirmation of endometriosis. The existence of endometrial glands and stroma beyond the uterus is diagnostic (Duleba, 1997).

1.4. Nature of Inflammation in Endometriosis

Inflammation is crucial in the pathophysiology of endometriosis, affecting the local microenvironment of lesions and systemic immune responses. Endometriosis is often characterized by a chronic inflammatory state. The presence of ectopic endometrial tissue

triggers an immune response that is typically abnormal and dysregulated. In contrast to the expected protective immune response, individuals with endometriosis frequently exhibit:

Altered Cytokine Profiles: Pro-inflammatory cytokines in the peritoneal fluid and the serum is increased in the patients with endometriosis (Bedaiwy et al., 2005). These cytokines contribute to the inflammatory milieu, promote angiogenesis, and stimulate the proliferation of endometrial cells.

Immune Cell Infiltration: Endometriotic lesions show an increased infiltration of immune cells, particularly macrophages, which are activated and exhibit an inflammatory phenotype. These macrophages produce additional cytokines and growth factors that support the survival and growth of ectopic endometrial tissue (Bacci et al., 2009).

Several mechanisms underpin the chronic inflammation observed in endometriosis:

Dysregulated Immune Response: Women with endometriosis often display an impaired immune response characterized by altered T-cell amount, decreased natural killer (NK) cell activity and macrophage function (H. Zhang et al., 2023). This dysfunction allows ectopic endometrial cells to evade immune detection and destruction, facilitating their survival and proliferation.

Inflammatory Mediators: Key inflammatory mediators, including prostaglandins and oxidative stress products, play a crucial role in promoting the inflammatory process. Prostaglandin E2 (PGE2) is notably elevated in endometriosis and is associated with increased pain perception and lesion viability (Laganà et al., 2019). Additionally, reactive oxygen species generated during inflammation can damage surrounding tissues, perpetuating the inflammatory cycle (Vitale et al., 2018).

Hormonal Influence: Estrogen has a well-established role in endometriosis pathology, not only stimulating endometrial cell proliferation but also enhancing the inflammatory response. Estrogen promotes the expression of inflammatory cytokines and can upregulate aromatase, leading to increased local estrogen production within lesions (Nothnick, 2011).

1.5. Matrix Metalloproteinase-9 and Neutrophil Gelatinase-Associated Lipocalin

Current studies have emphasized the significance of inflammation, oxidative stress, and immunological dysfunction in the pathophysiology of endometriosis. Biomarkers such NGAL and MMP-9 are frequently higher in individuals with endometriosis. NGAL is linked to inflammation, whereas MMP-9 promotes the destruction of the extracellular matrix, assisting in lesion invasion and adhesion (Macer & Taylor, 2012). Increased concentrations of these biomarkers have been suggested as possible diagnostic instruments; however, further study is required to confirm their effectiveness (Agarwal et al., 2012).

1.5.1. NGAL

NGAL is a secretory protein produced by active neutrophils, characterized by a single polypeptide and has become a significant biomarker for the early signal of renal injury. The principal function of NGAL is to regulate the biological activity of iron. The iron-containing NGAL binds to cell surface receptors, is internalized, and subsequently releases iron within the cell, resulting in increased cellular iron levels (Goetz et al., 2002). NGAL, a member of the lipocalin family, is predominantly synthesized in granulocytes and epithelial cells. It serves as a crucial biomarker in inflammatory responses, renal impairment, and other illnesses. Recent research have progressively examined the role of NGAL in numerous clinical situations, including renal illnesses, infections, malignancies, and endometriosis. NGAL was first identified in 1993 and has since been found in various cells and tissues, participating in numerous biological processes. NGAL plays a critical role, especially in the kidneys, in infection responses, and in inflammation.

1.5.1.1. Biochemical Functions of NGAL

- Kidney Injury and Protection: NGAL is recognized as an early indicator of kidney damage. Upon damage to renal cells, NGAL levels increase swiftly, facilitating its application in the early identification of acute kidney injury (AKI). The role of NGAL in the kidneys is associated with its anti-inflammatory and anti-apoptotic properties (Clerico et al., 2012).

- Inflammatory Response: NGAL stands out as an important protein that modulates the inflammatory response. During infection or inflammation, the production of

NGAL increases, supporting the immune response. NGAL is thought to play a role in the immune response against pathogens (Wasung et al., 2015).

- Metabolism and Immune System: NGAL also plays a significant role in iron metabolism. By preventing the release of iron, it has the ability to limit the growth of microorganisms. This property demonstrates NGAL's effectiveness in controlling pathogens during infections (Bojic et al., 2015).

- Tissue Repair: NGAL may function as a factor that aids in the repair of tissues after kidney injury. By supporting cell proliferation following damage and assisting in the elimination of apoptotic cells, NGAL contributes to the regeneration of kidney tissue (Ferreira et al., 2024).

1.5.1.2. Clinical Significance of NGAL

The clinical relevance of NGAL is closely related to its role in kidney diseases, infections, and inflammatory disorders. In recent years, studies have increasingly explored the use of NGAL as a prognostic marker in various clinical conditions.

- Acute Kidney Injury (AKI): NGAL is regarded as a crucial biomarker for the early detection of AKI. Numerous studies indicate that NGAL levels are significant in the progression of AKI. NGAL is detectable at elevated levels in blood and urine tests, correlating with disease severity (Marakala, 2022). The elevation of NGAL in urine may be observable even during the initial phases of renal impairment. Also, NGAL is correlated with the progression of chronic kidney disease. Increased NGAL levels are associated with the decline of renal function and serve as a prognostic indicator. Numerous studies indicate that NGAL serves a predictive function in the progression of renal disease stages (Schrezenmeier et al., 2017).

- Infections: NGAL levels also increase during bacterial infections. Particularly in cases of sepsis and lower respiratory tract infections, NGAL levels may reflect the severity of the patient's condition. Research has highlighted the role of NGAL in the diagnosis of sepsis, suggesting that NGAL levels may be useful in determining the prognosis of patients with sepsis (Kounatidis et al., 2024).

- Cardiovascular Diseases: Recent research has demonstrated a correlation between NGAL levels and cardiac disorders, including heart failure. Increased NGAL levels may affect the prognosis of cardiovascular events. NGAL's participation in these disorders highlights its importance as a determinant of renal function and cardiovascular health (Bolignano et al., 2010).

- Cancer: Certain studies indicate that NGAL may function as a prognostic biomarker in cancer patients. Elevated NGAL levels correlate with unfavorable prognosis in some cancer types (Tsakogiannis et al., 2020). Nevertheless, additional research is required to elucidate NGAL's function in cancer progression.

Various laboratory tests and methods are used to determine NGAL levels. Common methods include ELISA (Enzyme-Linked Immunosorbent Assay) and immunohistochemistry. These methods provide reliable results for measuring and evaluating NGAL levels. It is unclear whether serum NGAL levels change in the case of endometrioma, and while one of the two studies in the literature found no difference, the other indicated that the NGAL level was higher in the endometrioma group (Bostanci Durmus et al., 2019; Guney et al., 2023).

1.5.2. MMP-9

MMP-9 is a crucial enzyme that facilitates the degradation of extracellular matrix (ECM) constituents. It is crucial in various processes within the human body, including as tissue remodeling, wound healing, and inflammation (Stetler-Stevenson, 2001). The dysregulation of MMP-9 has been associated with various diseases, including cancer development, cardiovascular issues, and autoimmune diseases. Recent studies have emphasized its role in reproductive health, especially with diseases such as endometriosis and infertility (Shah & Catt, 2004).

MMP-9 has been thoroughly investigated in relation to numerous disorders, especially cancer. Increased concentrations of MMP-9 are frequently correlated with heightened tumor invasiveness and metastasis. It promotes tumor growth by destroying the extracellular matrix, enhancing angiogenesis, and facilitating cancer cell movement. MMP-9

expression is frequently associated with unfavorable prognosis in various cancer types, such as breast, lung, and colorectal malignancies (L. Zhang et al., 2021)

In cardiovascular diseases, MMP-9 is involved in pathologic processes. It contributes to the remodeling of the extracellular matrix within blood vessels, influencing plaque stability and vessel integrity (Wang & Khalil, 2018). MMP-9 is also implicated in inflammatory diseases where its expression is upregulated in inflamed tissues, contributing to tissue destruction and remodeling (Alamgeer et al., 2020).

1.5.2.1. Biochemical Functions of MMP-9

- Extracellular Matrix (ECM) Degradation: MMP-9 is involved in the breakdown of ECM components, particularly type IV and V collagens found in the basement membrane. This function is essential for physiological tissue remodeling and repair but also facilitates pathological processes like tumor invasion and metastasis (Visse & Nagase, 2003).

- Regulation of Cell Migration and Invasion: By degrading ECM proteins, MMP-9 creates a pathway for cell movement, essential in immune responses as leukocytes migrate toward infection or injury sites. In cancer, MMP-9 expression is upregulated, enhancing the invasive capabilities of tumor cells by breaking down physical barriers within tissues (Deryugina & Quigley, 2006).

- Angiogenesis and Vascular Remodeling: MMP-9 releases ECM-bound growth factors which promote angiogenesis. In both physiological and pathological states, angiogenesis is key for tissue growth and repair; however, in cancer, it supports tumor growth and metastasis by increasing blood supply to cancer cells (Bergers et al., 2000).

1.5.2.2. Clinical Implications of MMP-9

- Cancer Diagnosis and Prognosis: MMP-9 is an extensively researched biomarker in oncology, especially in breast, colon, and lung malignancies. MMP-9 has been investigated as a diagnostic marker and a prospective therapeutic aim in oncology (Chang & Werb, 2001).

- Cardiovascular Diseases: MMP-9 is associated with multiple cardiovascular disorders, including as atherosclerosis, and myocardial infarction. It exacerbates plaque instability by eroding the extracellular matrix in artery walls, resulting in atherosclerosis and heightening the risk of rupture and myocardial infarction. Increased MMP-9 levels are noted in individuals with heart failure, suggesting its potential as a marker for disease severity and progression (Blankenberg et al., 2003).

- Inflammatory Diseases and Autoimmune Conditions: MMP-9 exacerbates tissue damage in situations like rheumatoid arthritis and inflammatory bowel disease by degrading extracellular matrix components in inflamed regions. Elevated MMP-9 levels correlate with illness severity and progression, indicating its potential as an inflammatory marker and therapeutic target (Vincenti & Brinckerhoff, 2002).

- Neurological Conditions: MMP-9 contributes to the pathophysiology of neurological conditions such as multiple sclerosis and stroke. By degrading ECM proteins around the BBB, MMP-9 increases its permeability, allowing inflammatory cells and molecules to infiltrate the brain tissue and exacerbate injury (Rosenberg, 2009).

- Endometriosis: Recent articles have increasingly focused on the role of MMP-9 in reproductive health, particularly in the context of endometriosis and infertility. Endometriosis is associated with elevated levels of MMP-9 regardless of biological compartment studied (Huang et al., 2024). This upregulation is thought to facilitate the invasive characteristics of endometrial cells, contributing to the pathology of endometriosis.

Immunohistochemistry and ELISA are used the determination of level of MMP-9.

This study aims to assess the efficacy of NGAL, MMP-9, and the MMP-9/NGAL ratio in diagnosing endometrioma. The data derived from the concurrent application of NGAL and MMP-9 may facilitate a novel method for diagnosing endometrioma and enhance comprehension of the functions of these biomarkers in the disease mechanism. This work seeks to enhance the existing literature by identifying novel biomarkers for the diagnosis of endometrioma, a contributing factor to infertility.

2. MATERIALS AND METHODS

2.1. Study Design

This prospective, case-control study included 90 infertile women who were divided into two groups: 45 women with a diagnosis of endometrioma (study group) and 45 women with unexplained infertility (control group). The study was conducted at Ankara University School of Medicine, Department of Obstetrics and Gynecology, Reproductive Endocrinology Clinic and Ankara City Maternity Hospital and all participants provided written informed consent before enrollment. Detailed infertility investigations were conducted on the patients. Demographic features, hormone levels, ultrasound findings, and surgical reports of the patients who underwent surgery, as well as the findings from their postoperative follow-ups, were recorded. Ethical approval was taken from Ankara University School of Medicine Ethical Board (Number:İ11-656-22 Date:08.12.2022). The research was financed by Ankara University Scientific Research Projects (Number: TDK-2024-3596).

There is no any other article about this specific topic so the number of study population is determined according to the most similar article (Bostanci Durmus et al., 2019). There should be 35 patients in each group for a significant difference between the two groups with a 5% margin of error and 80% power according to G-power calculation. 45 patients in each group will be included because of the possibility of the decrease in the number of patients during follow up period.

Inclusion Criterias

- Age between 18-35 years.
- Diagnosis of infertility
- For the endometrioma group: presence of endometrioma confirmed by ultrasonography, with a cyst diameter of at least 3 cm, and a definitive laparoscopic confirmation.

- For the unexplained infertility group: infertility without identifiable causes after a full infertility examination, including tubal patency tests, ovulatory function assessment, and partner's semen analysis within normal limits.

Exclusion Criterias

- Having any cause of infertility.
- Presence of other pelvic inflammatory conditions, such as pelvic inflammatory disease or other ovarian cysts.
- History of previous endometrioma surgery.
- Presence of systemic inflammatory conditions or autoimmune diseases.
- Use of hormonal medications or immunosuppressive agents within 3 months prior to sample collection.
- Any contraindications to laparoscopic surgery (for the endometrioma group).

2.2. Sample Collection

Venous blood samples (5 mL) were collected from each participant in the early follicular phase to reduce hormonal variability. For the endometrioma group, blood samples were collected twice: once preoperatively and once three months postoperatively.

Blood samples were drawn into sterile vacutainer tubes without anticoagulants and immediately transported to the laboratory. The samples were allowed to coagulate at ambient temperature for 30 minutes, followed by centrifugation at 3000 rpm for 10 minutes to isolate the serum. Serum was aliquoted into Eppendorf tubes and stored at -80°C until analysis to preserve the stability of NGAL and MMP-9 levels.

2.3. Measurement of Biomarkers (NGAL and MMP-9)

Serum levels of NGAL and MMP-9 were assessed using enzyme-linked immunosorbent assay (ELISA) kits tailored for each biomarker. All ELISA techniques were

executed in accordance with the written protocol, and all assays were run in duplicate to assure precision (Shanghai Coon Koon Biotech Co., Ltd., Shanghai, China). The intra-assay and inter-assay coefficients for MMP-9 were less than 7% and less than 10%, respectively. The MMP-9/NGAL ratio was determined by dividing the MMP-9 concentration by the NGAL concentration for each sample, functioning as an auxiliary biomarker for comparative analysis.

2.4. Statistical Analysis

Comparative statistical studies were performed to assess differences in NGAL and MMP-9 levels, together with the MMP-9/NGAL ratio, between the unexplained infertility and endometrioma cohorts. The preoperative and postoperative parameters for the endometrioma group were evaluated to evaluate changes after surgical intervention. $p<0.05$ is accepted as statistical significant. A receiver operating characteristic (ROC) curve analysis was conducted to evaluate the diagnostic efficacy of the MMP-9/NGAL ratio in differentiating endometrioma. Sensitivity, specificity, and area under the curve (AUC) values were examined to determine the optimal threshold for endometrioma detection.

3. RESULTS

3.1. Demographic Features

Table 3.1. Demographic features of patients

	Endometrioma (N:45)	Unexplained (N:45)	p
Age (years) (Mean±SD)	32.53±3.42	31.72±4.98	0.79
BMI (kg/m^2) (Mean±SD)	24.72±1.79	23.82±1.54	0.32
Smoking(N)	3	2	0.43
Systemic disease(N)	5	6	0.72
Previous surgery(N)	10	8	0.65
Gravida (Mean±SD)	1.21±0.52	1.13±0.41	0.51
Parity(Mean±SD)	0.92±0.33	0.88±0.42	0.67
Abortus (Mean±SD)	0.22±0.21	0.45±0.32	0.55
Infertility duration (years) (Mean±SD)	2.82±1.11	2.55±1.22	0.33
Primary infertility (N)	21	24	0.12

The average age in the endometrioma group is 31.53 (±3.42) years, while in the unexplained infertility group, it is 30.28 (±2.98) years (p=0.79). The mean BMI is 24.72 (±1.79) for the endometrioma group and 23.82 (±1.54) for the unexplained group (p=0.32). The endometrioma group has 5 individuals with systemic disease, compared to 6 in the unexplained group (p=0.72). 3 patients had a hypothyroidism without antibodies, 1 patient had a ashtma and 1 patient had a type 2 diabetes mellitus in the endometrioma group; 3 patients had a hypothyroidism without antibodies, 2 patients had a type 2 diabetes mellitus and 1 patient had a epilepsy. The number of individuals with previous surgeries is 10 in the endometrioma group and 8 in the unexplained group (p=0.65). In the endometrioma group, eight patients had cesarean sections and two had appendectomies; in the unexplained group, five patients had cesarean sections, two had appendectomies, and one had a cholecystectomy. The average infertility duration is 2.82 (±1.11) years for the endometrioma group and 2.55 (±1.22) years for the unexplained group (p=0.33). Endometrioma group were underwent surgery cause of pain (N:24), big adnexal mass (N:15) and difficulties on the oocyte pick-up (N:6). Twelve patients with endometriomas and complaints of primary infertility underwent embryo cryopreservation before the operation.

Table 3.2. Hormonal and blood parameters of patients

	Endometrioma (N:45)	Unexplained (N:45)	p
AMH (ng/ml)	1.89±0.63	3.32±2.31	0.04
FSH (IU/L)	7.67±2.21	6.93±2.12	0.56
LH (mlU/ml)	4.21±2.32	5.01±2.89	0.41
E2 (pg/ml)	43.12±10,92	39.58±9.99	0.68
TSH (mU/ml)	2.98±1.21	3.12±1.05	0.77
Hemoglobin (g/dl)	11.94±1.39	12.88±1.32	0.91
White blood cell (mcL)	7.03±2.33	7.42±1.65	0.15
Neutrophil (mcL)	5.44±6.85	4.66±1.36	0.06
Lymphocyte (mcL)	2.02±0.70	2.08±0.56	0.25
CRP(mg/L)	4.02±0.52	3.52±0.58	0.18
CA-125 (U/ml)	79.08±48.95	No data	

(Mean±SD)

The mean AMH level are 1.89 (±0.63) and 3.32 (±2.31) in the endometrioma group and in the unexplained infertility group, respectively (p=0.04), indicating a statistically significant difference. The mean CA-125 level is 79.08 (±48.95) in the endometrioma group (no data available for the unexplained group). There is no statistically significance in other parameters between these groups.

Table 3.3. Ultrasonographic features of patients

	Endometrioma (N:45)	Unexplained (N:45)	p
Antral follicle count (Mean±SD)	10.52±2.32	13.33±2.11	0.04
Bilateral endometrioma (N)	6	No	
Endometrioma size (cm)	5.95±2.39	No	

The mean antral follicle count is 10.52 (±2.32) in the endometrioma group and 13.33 (±2.11) in the unexplained infertility group (p=0.04), indicating a statistically significant difference. There are 6 cases of bilateral endometrioma in the endometrioma group, while no cases are reported in the unexplained infertility group.

3.2. NGAL and MMP-9 Levels of Patients

Table 3.4. Biomarker levels of endometrioma and unexplained group

	Endometrioma	Unexplained	p
NGAL(ng/ml)	22.01±4.04	25.46±4.91	0.001
MMP-9 (ng/ml)	43.74±8.00	39.38±10.75	0.012
MMP-9/NGAL	2.01±0.24	1.51±0.28	0.001

(Mean±SD)

The mean NGAL level is 22.01 (±4.04) ng/ml in the endometrioma group and 25.46 (±4.91) ng/ml in the unexplained infertility group (p=0.001), indicating a statistically significant difference. The mean MMP-9 level is 43.74 (±8.00) ng/ml in the endometrioma group and 39.38 (±10.75) ng/ml in the unexplained infertility group (p=0.012). The mean MMP-9/NGAL ratio is 2.01 (±0.24) in the endometrioma group and 1.51 (±0.28) in the unexplained infertility group (p=0.001), showing statistical significance. All parameters are significantly different between the two groups.

Table 3.5. NGAL and MMP-9 levels of endometrioma group in preoperative and postoperative

	Preoperative	Postoperative	p
NGAL(ng/ml)	24.9±4.9	27.0±4.98	0.179
MMP-9 (ng/ml)	43.9±7.3	36.7±8.7	0.006
MMP-9/NGAL	2.02±0.23	1.45±0.26	0.001
CA-125(U/ml)	77.06±46.35	68.89±49.27	0.146
AMH (ng/ml)	1.78±0.55	1.55±0.31	0.127

(Mean±SD)

4 patients did not come for follow-up, so their results were not included in the analysis when evaluating the postoperative outcomes. The mean NGAL level is 24.9 (±4.9) ng/ml preoperatively and 27.0 (±4.98) ng/ml postoperatively, with no statistically significant difference (p=0.179). The mean MMP-9 level decreases from 43.9 (±7.3) ng/ml preoperatively to 36.7 (±8.7) ng/ml postoperatively, a statistically significant change (p=0.006). The MMP-9/NGAL ratio significantly decreases from 2.02 (±0.23) preoperatively to 1.45 (±0.26) postoperatively (p=0.001).

3.3. The Correlation of NGAL, MMP-9 and MMP-9/NGAL Levels

The relationship among NGAL, MMP-9, and the MMP-9/NGAL ratio is examined. NGAL exhibits a positive connection with MMP-9 (R:0.304) and a negative correlation with the MMP-9/NGAL ratio (R:-0.394) (p=0.01).

Table 3.6. The correlation between NGAL, MMP-9, and the MMP-9/NGAL ratio

	NGAL	MMP-9	MMP-9/NGAL
NGAL	1	0.304**	-0.394**
MMP-9	0.304**	1	0.285**
MMP-9/NGAL	-0.394**	0.285**	1

**p:0.01

There is no correlation between the NGAL, MMP-9 and MMP-9/NGAL ratio and the size, and unilaterality/bilaterality of endometrioma.

Table 3.7. The correlation between the presence of endometrioma and NGAL, MMP-9, the MMP-9/NGAL ratio

	NGAL	MMP-9	MMP-9/NGAL
Presence of endometrioma	-0.361*	0.228*	0.691**

**p:0.01 *p:0.05

The MMP-9/NGAL ratio had a stronger positive correlation with the presence of endometrioma (R = 0.691, p:0.01)

3.4. The Predictive Value of NGAL, MMP-9 and MMP-9/NGAL Levels in The Presence of Endometrioma

A regression analysis is being conducted to investigate whether the presence of endometrioma is related to NGAL, MMP-9, and MMP-9/NGAL levels. The coefficient for the MMP-9/NGAL ratio is 5.176, with a standard error of 1.322 and a high odds ratio of 176.93, which is statistically significant (p=0.001).In summary, the ratio shows a strong and statistically significant association with the outcome, while NGAL and MMP-9 alone are not statistically significant predictors in this model.

Table 3.8. The regression analysis of the biomarker in the presence of endometrioma

	B	S.E.	Exp(B)	p
Constant	-13.022	3.454	-	0.001
NGAL	-0.153	0.078	0.858	0.065
MMP-9	0.053	0.036	1.054	0.145
MMP-9/NGAL	5.176	1.322	176.93	0.001

ROC analysis is conducted to determine the level of the MMP-9/NGAL ratio in predicting the presence of endometrioma.

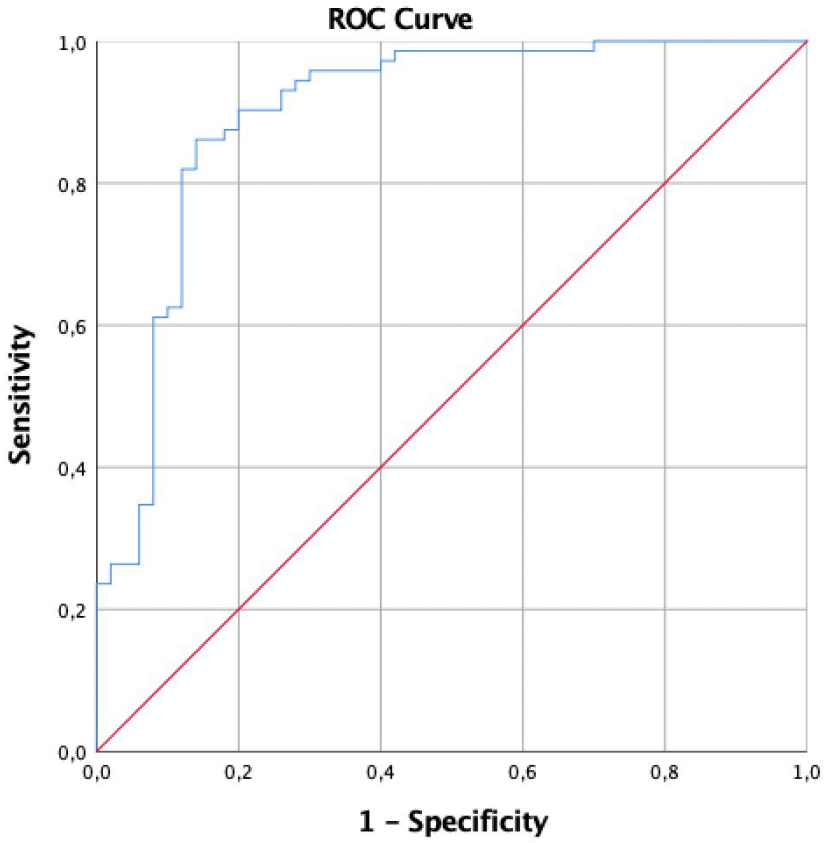

Figure 3.1. ROC analysis of MMP-9/NGAL ratio in the presence of endometrioma

Table 3.9. The cut-off value of MMP-9/NGAL ratio for the presence of endometrioma

Cut-off	AUC(95%)	Sensitivity(%)	Specificity(%)	p	Lower bound	Upper bound
1.75	0.898	86.1	84	0.001	0.837	0.960

This table summarizes the diagnostic performance of a cut-off value of 1.75 for MMP-9/NGAL ratio. The sensitivity of this cut-off values is 86.1% and the specificity is 84%.

The ROC analysis is conducted for NGAL and MMP-9 and the AUC is 0.267 and 0.678, respectively.

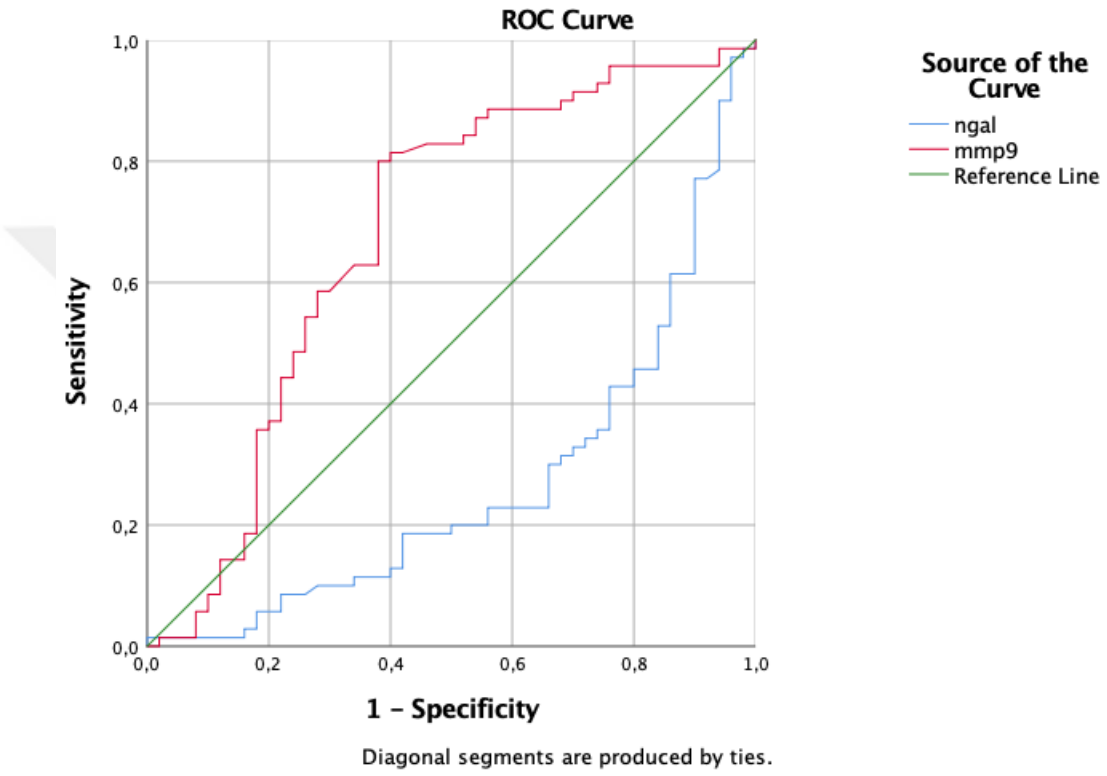

Figure 3.2. ROC analysis of NGAL and MMP-9 level in the presence of endometrioma

4. DISCUSSION

This study investigates the serum levels of NGAL and MMP-9 in women with endometrioma and unexplained infertility, adding to the growing body of research identifying these markers as key contributors in endometriosis. Our findings reveal significantly elevated MMP-9 levels and reduced NGAL levels in patients with endometrioma compared to those with unexplained infertility, reinforcing the hypothesis that these biomarkers may play essential roles in the pathophysiology and potential diagnosis of endometriosis. According to our initial hypothesis, we expected the MMP-9 level to be high in the endometrioma group, and the results we obtained were consistent with this. However, surprisingly, a decrease in NGAL levels was observed in the endometrioma group compared to the unexplained infertility group. According to our initial hypothesis, this result was different. However, it was determined that an MMP-9/NGAL ratio above 1.75 indicates the presence of endometrioma with 86.1% sensitivity and 84% specificity.

NGAL is a lipocalin protein secreted by neutrophils in response to infection and inflammation, and it is recognized to elevate in instances of tissue injury (Anastasiu et al., 2020). NGAL levels have been demonstrated to be applicable for diagnosis and prognosis in many disorders characterized by significant inflammation (Zappitelli et al., 2007). It is important to highlight that NGAL levels were shown to be low in the endometrioma cohort in our investigation. The literature indicates that NGAL levels are elevated in inflammatory process like endometriosis; yet, its reduced levels in endometrioma imply that the microenvironment of endometriotic tissue may possess distinct properties. This microenvironment may possess a distinctive structure that inhibits NGAL production or diminishes circulating NGAL levels. In a study conducted in Turkey in 2019 on this topic, urinary NGAL results of 60 endometriosis patients and 30 control patients were examined, and no difference was found between the groups. In the same study, when grouping according to whether endometriosis was mild or severe, no significant difference was found (Bostanci Durmus et al., 2019). In another study conducted in 2023, 36 patients with endometriomas and 36 control patients were included, and it was reported that the amount of NGAL was significantly higher in patients with endometriomas (Guney et al., 2023). To our knowledge, there are no other studies in the literature regarding endometrioma and NGAL levels, and in these three studies reported along with ours, it has been shown that NGAL levels do not change, decrease, or increase with the presence of endometrioma. So it can not

be exactly determined the relationship between NGAL level and the presence of endometrioma.

MMP-9 is involved in the remodeling of the extracellular matrix through proteolytic activity. It plays a key role in physiological and pathopysiological uterine processes (Liu et al., 2016). Elevated MMP-9 levels in endometriotic lesions may facilitate ectopic endometrial tissue growth, thereby promoting disease progression and symptom severity. In our study, serum MMP-9 level is significantly higher in the endometrioma group compared with the unexplained group. According to the review conducted in 2024, it is reported that there are four candidate biomarkers should be considered in the presence of endometriosis. These biomarkers are TNF-α, MMP-9, TIMP‑1 and miR451 that are supported by at least two distinct research teams and are located in at least three or more biological compartments (Brulport et al., 2024). This review indicates that MMP-9 levels were consistently elevated in endometriosis across all investigations and irrespective of the biological compartment examined. Another meta-analysis included 15 papers with 996 endometriosis and 582 without endometriosis patients reported that the concentration of MMP-9 in the patients with endometriosis was markedly elevated in comparison to the control group (Huang et al., 2024). In this review, they made also a subgroup analysis because articles included in this meta-analysis had various studies' populations for example uterine fibroids, uterine polyps and other disesaes. Even if the patients had a another gynecological pathologies, MMP-9 levels were still higher in the endometriosis group compared to the control group. Also the article reported that severity of the disease had a positive correlation with the MMP-9 levels.

A study excluded from the aforementioned meta-analysis demonstrated a significant increase in blood MMP-9 levels in the endometriosis group (Bostanci Durmus et al., 2019). The diagnostic efficacy of this biomarker seems appropriate, albeit it remains unverified. Our findings regarding the elevated MMP-9 levels in endometrioma align with existing research (Bostanci Durmus et al., 2019). Establishing a cut-off value for this issue is necessary; however, the usage of various kits producing results in different units complicates the matter. A 2013 study indicated that an increase in MMP-9 was related to inadequate oocyte and embryo development in women with endometriosis undergoing IVF. The equilibrium of MMP-9/TIMP-1 in these women was markedly disturbed, and the injection of progesterone appeared to dramatically rectify this imbalance, hence enhancing the IVF success rate indirectly (Singh et al., 2013).

The primary finding of this investigation is the diagnostic efficacy of the MMP-9/NGAL ratio, which demonstrated an AUC of 0.898, with sensitivity and specificity values of 86.1% and 84%, respectively. The increased diagnostic accuracy suggests that it may serve as a crucial non-invasive biomarker for endometrioma. To our knowledge, the examination of the this ratio within the endometriosis cohort was performed in a singular study. This study revealed a significant elevation in the MMP-9/NGAL ratio in the endometriosis cohort compared to the control group, and also in the stage III/IV endometriosis group relative to the stage I/II group (Bostanci Durmus et al., 2019). Prior research has shown that conventional markers such as CA-125 had limited effectiveness, as they often lack the specificity necessary to differentiate endometriosis from other gynecological conditions (Nisenblat et al., 2016). The results of the current study validate the diagnostic significance of the MMP-9/NGAL ratio, suggesting that it may exceed CA-125 and other markers by offering a more direct evaluation of extracellular matrix remodeling and inflammatory processes associated with endometriosis.

In line with recent reviews, biomarkers that directly reflect ECM degradation and inflammation may provide better diagnostic insights compared to general inflammatory markers alone. NGAL and MMP-9 are not only reflective of the inflammatory milieu in endometriotic lesions but also relate to disease severity and invasiveness. Studies suggest that in advanced stages of endometriosis, these biomarkers levels tend to increase in serum and peritoneal fluid, correlating with the extent of endometrial invasion and inflammatory activity.

The biomarkers used for the follow up in the chronic diseases are very important for the clinical practice. CA-125 is used usually for the diagnosis and the follow-up period in the endometriosis but Cochrane meta-analysis revealed that CA-125 and the other biomarkers can not meet the criteria as a diagnostic tool (Nisenblat et al., 2016). Additionally, there is a paper reported that especially VEGF is more sensitive follow-up biomarker than CA-125 (Mohamed et al., 2013). Our study shows that MMP-9 level and MMP-9/NGAL ratio decreased significantly in the postoperative period but NGAL and CA-125 level were not changed significantly. So MMP-9 and the ratio can be used for the follow up period of the endometrioma especially if its level were checked preoperatively.

The study's strengths are its exclusive focus on patients with infertility issues and the exclusion of those with other diseases that could cause inflammation. This study offers

significant insights, however it has limits. The sample size, while adequate for statistical analysis, constrains the generalizability of the results. Furthermore, our research concentrated exclusively on women with endometrioma or unexplained infertility, omitting other stages of endometriosis that can have unique biomarker profiles. Subsequent research should focus on including bigger and more diverse patient cohorts to assess the MMP-9/NGAL ratio throughout various phases of endometriosis. Additionally, further studies are needed to evaluate the temporal variations of NGAL and MMP-9 levels in relation to different therapeutic interventions, potentially enhancing their effectiveness in tracking illness development and recurrence.

5. CONCLUSION

This work emphasizes the crucial involvement of NGAL and MMP-9 in the etiology of endometriosis and underlines the potential of the MMP-9/NGAL ratio as a diagnostic biomarker for endometrioma. Considering the constraints of existing diagnostic instruments, it presents a viable non-invasive option that could enhance early diagnosis and patient outcomes. Ongoing research is elucidating the molecular processes of NGAL and MMP-9 interactions in endometriosis, potentially facilitating their integration into individualized treatment regimens and disease monitoring, thereby enhancing endometriosis management. MMP-9 and especially MMP-9/NGAL ratio can be used as a diagnostic and follow up biomarkers in the endometriosis. For the use of these markers in the diagnosis of endometriosis, further studies are needed.

REFERENCES

Agarwal, A., Gupta, S. & Sharma, R.K. (2005). Role of oxidative stress in female reproduction. *Reproductive Biology and Endocrinology*, 3(1), 28. https://doi.org/10.1186/1477-7827-3-28

Alamgeer Hasan, U.H., Uttra, A.M., Qasim, S., Ikram, J., Saleem, M. & Niazi, Z.R. (2020). Phytochemicals targeting matrix metalloproteinases regulating tissue degradation in inflammation and rheumatoid arthritis. *Phytomedicine: International Journal of Phytotherapy and Phytopharmacology*, 66, 153134. https://doi.org/10.1016/j.phymed.2019.153134

Alonzo, L., Cannella, R., Gullo, G., Piombo, G., Cicero, G., Lopez, A., Billone, V., Andrisani, A., Cucinella, G., Lo Casto, A. & Lo Re, G. (2024). Magnetic Resonance Imaging of Endometriosis: The Role of Advanced Techniques. *Journal of Clinical Medicine*, 13(19), 5783. https://doi.org/10.3390/jcm13195783

Anastasiu, C.V., Moga, M.A., Elena Neculau, A., Bălan, A., Scârneciu, I., Dragomir, R.M., Dull, A.-M. & Chicea, L.-M. (2020). Biomarkers for the Noninvasive Diagnosis of Endometriosis: State of the Art and Future Perspectives. *International Journal of Molecular Sciences*, 21(5), 1750. https://doi.org/10.3390/ijms21051750

Arosh, J.A., Sivakumar, K.K., Lee, J. & Banu, S.K. (2022). Effects of selective inhibition of prostaglandin E2 receptors EP2 and EP4 on the miRNA profile in endometriosis. *Molecular and Cellular Endocrinology*, 558, 111728. https://doi.org/10.1016/j.mce.2022.111728

Bacci, M., Capobianco, A., Monno, A., Cottone, L., Di Puppo, F., Camisa, B., Mariani, M., Brignole, C., Ponzoni, M., Ferrari, S., Panina-Bordignon, P., Manfredi, A.A. & Rovere-Querini, P. (2009). Macrophages Are Alternatively Activated in Patients with Endometriosis and Required for Growth and Vascularization of Lesions in a Mouse Model of Disease. *The American Journal of Pathology*, 175(2), 547–556. https://doi.org/10.2353/ajpath.2009.081011

Bafort, C., Beebeejaun, Y., Tomassetti, C., Bosteels, J. & Duffy, J.M. (2020). Laparoscopic surgery for endometriosis. *The Cochrane Database of Systematic Reviews*, 10(10), CD011031. https://doi.org/10.1002/14651858.CD011031.pub3

Bedaiwy, M.A., Falcone, T., Goldberg, J.M., Attaran, M., Sharma, R., Miller, K., Nelson, D.R. & Agarwal, A. (2005). Relationship between cytokines and the embryotoxicity of hydrosalpingeal fluid. *Journal of Assisted Reproduction and Genetics*, 22(4), 161–165. https://doi.org/10.1007/s10815-005-4913-7

Bergers, G., Brekken, R., McMahon, G., Vu, T. H., Itoh, T., Tamaki, K., Tanzawa, K., Thorpe, P., Itohara, S., Werb, Z. & Hanahan, D. (2000). Matrix metalloproteinase-9 triggers the angiogenic switch during carcinogenesis. *Nature Cell Biology*, 2(10), 737–744. https://doi.org/10.1038/35036374

Blankenberg, S., Rupprecht, H.J., Poirier, O., Bickel, C., Smieja, M., Hafner, G., Meyer, J., Cambien, F., Tiret, L. & AtheroGene Investigators. (2003). Plasma concentrations and genetic variation of matrix metalloproteinase 9 and prognosis of patients with cardiovascular disease. *Circulation*, 107(12), 1579–1585. https://doi.org/10.1161/01.CIR.0000058700.41738.12

Bojic, S., Kotur-Stevuljevic, J., Kalezic, N., Stevanovic, P., Jelic-Ivanovic, Z., Bilanovic, D., Memon, L., Damnjanovic, M., Kalaba, Z. & Simic-Ogrizovic, S. (2015). Diagnostic Value of Matrix Metalloproteinase-9 and Tissue Inhibitor of Matrix Metalloproteinase-1 in Sepsis-Associated Acute Kidney Injury. *The Tohoku Journal of Experimental Medicine*, 237(2), 103–109. https://doi.org/10.1620/tjem.237.103

Bolignano, D., Coppolino, G., Lacquaniti, A. & Buemi, M. (2010). From kidney to cardiovascular diseases: NGAL as a biomarker beyond the confines of nephrology. *European Journal of Clinical Investigation*, 40(3), 273–276. https://doi.org/10.1111/j.1365-2362.2010.02258.x

Bostanci Durmus, A., Dincer Cengiz, S., Yilmaz, H., Candar, T., Gursoy, A. Y. & Sinem Caglar, G. (2019). The levels of matrix metalloproteinase-9 and neutrophil gelatinase-associated lipocalin in different stages of endometriosis. *J Obstet Gynaecol*, 39(7), 991–995. https://doi.org/10.1080/01443615.2019.1584889

Broi, M.G. Da, Ferriani, R.A. & Navarro, P.A. (2019). Ethiopathogenic mechanisms of endometriosis-related infertility. *JBRA Assisted Reproduction*. https://doi.org/10.5935/1518-0557.20190029

Brulport, A., Bourdon, M., Vaiman, D., Drouet, C., Pocate-Cheriet, K., Bouzid, K., Marcellin, L., Santulli, P., Abo, C., Jeljeli, M., Chouzenoux, S., Chapron, C., Batteux, F., Berthelot, C. & Doridot, L. (2024). An integrated multi-tissue approach for endometriosis candidate biomarkers: a systematic review. *Reproductive Biology and Endocrinology*, 22(1), 21. https://doi.org/10.1186/s12958-023-01181-8

Bulletti, C., Coccia, M.E., Battistoni, S. & Borini, A. (2010). Endometriosis and infertility. *Journal of Assisted Reproduction and Genetics*, 27(8), 441–447. https://doi.org/10.1007/s10815-010-9436-1

Burney, R.O. and Giudice, L.C. (2012). Pathogenesis and pathophysiology of endometriosis. *Fertility and Sterility*, 98(3), 511–519.

Chang, C. and Werb, Z. (2001). The many faces of metalloproteases: cell growth, invasion, angiogenesis and metastasis. *Trends in Cell Biology*, 11(11), S37-43. https://doi.org/10.1016/s0962-8924(01)02122-5

Clerico, A., Galli, C., Fortunato, A. & Ronco, C. (2012). Neutrophil gelatinase-associated lipocalin (NGAL) as biomarker of acute kidney injury: a review of the laboratory characteristics and clinical evidences. *Clinical Chemistry and Laboratory Medicine (CCLM)*, 50(9). https://doi.org/10.1515/cclm-2011-0814

Deryugina, E.I. and Quigley, J.P. (2006). Matrix metalloproteinases and tumor metastasis. *Cancer Metastasis Reviews*, 25(1), 9–34. https://doi.org/10.1007/s10555-006-7886-9

Duleba, A.J. (1997). Diagnosis of endometriosis. *Obstetrics and Gynecology Clinics of North America*, 24(2), 331–346. https://doi.org/10.1016/s0889-8545(05)70307-7

Dunselman, G.A.J., Vermeulen, N., Becker, C., Calhaz-Jorge, C., D'Hooghe, T., De Bie, B., Heikinheimo, O., Horne, A. W., Kiesel, L., Nap, A., Prentice, A., Saridogan, E., Soriano, D., Nelen, W. & European Society of Human Reproduction and Embryology. (2014). ESHRE guideline: management of women with endometriosis. *Human Reproduction (Oxford, England)*, 29(3), 400–412. https://doi.org/10.1093/humrep/det457

Ferreira, G.S., Frota, M.L., Gonzaga, M.J.D., Vattimo, M. de F. F. & Lima, C. (2024). The Role of Biomarkers in Diagnosis of Sepsis and Acute Kidney Injury. *Biomedicines*, 12(5), 931. https://doi.org/10.3390/biomedicines12050931

Forte, A., Cipollaro, M. & Galderisi, U. (2014). Genetic, epigenetic and stem cell alterations in endometriosis: new insights and potential therapeutic perspectives. *Clinical Science*, 126(2), 123–138.

Goetz, D.H., Holmes, M.A., Borregaard, N., Bluhm, M.E., Raymond, K.N. & Strong, R.K. (2002). The Neutrophil Lipocalin NGAL Is a Bacteriostatic Agent that Interferes with Siderophore-Mediated Iron Acquisition. *Molecular Cell*, 10(5), 1033–1043. https://doi.org/10.1016/S1097-2765(02)00708-6

Guney, G., Taskin, M.I., Laganà, A.S., Tolu, E., Aslan, F., Hismiogullari, A.A. & Kaya, C. (2023). Neutrophil gelatinase-associated lipocalin serum level: A potential noninvasive biomarker of endometriosis? *Medicine*, 102(41), e35539. https://doi.org/10.1097/MD.0000000000035539

Hickey, M., Ballard, K. & Farquhar, C. (2014). Endometriosis. *BMJ*, 348, g1752. https://doi.org/10.1136/bmj.g1752

Huang, Q., Song, Y., Lei, X., Huang, H. & Nong, W. (2024). MMP-9 as a clinical marker for endometriosis: a meta-analysis and bioinformatics analysis. *Frontiers in Endocrinology*, 15. https://doi.org/10.3389/fendo.2024.1475531

Izumi, G., Koga, K., Takamura, M., Makabe, T., Satake, E., Takeuchi, A., Taguchi, A., Urata, Y., Fujii, T. & Osuga, Y. (2018). Involvement of immune cells in the pathogenesis of endometriosis. *The Journal of Obstetrics and Gynaecology Research*, 44(2), 191–198. https://doi.org/10.1111/jog.13559

Kounatidis, D., Vallianou, N.G., Psallida, S., Panagopoulos, F., Margellou, E., Tsilingiris, D., Karampela, I., Stratigou, T. & Dalamaga, M. (2024). Sepsis-Associated Acute Kidney Injury: Where Are We Now? *Medicina*, 60(3), 434. https://doi.org/10.3390/medicina60030434

Laganà, A.S., Garzon, S., Götte, M., Viganò, P., Franchi, M., Ghezzi, F. & Martin, D.C. (2019). The Pathogenesis of Endometriosis: Molecular and Cell Biology Insights. *International Journal of Molecular Sciences*, 20(22), 5615. https://doi.org/10.3390/ijms20225615

Liu, H., Wang, J., Wang, H., Tang, N., Li, Y., Zhang, Y. & Hao, T. (2016). The plasma and peritoneal fluid concentrations of matrix metalloproteinase-9 are elevated in patients with endometriosis. *Annals of Clinical Biochemistry*, 53(Pt 5), 599–605. https://doi.org/10.1177/0004563215626458

Macer, M.L. and Taylor, H.S. (2012). Endometriosis and infertility: a review of the pathogenesis and treatment of endometriosis-associated infertility. *Obstetrics and Gynecology Clinics of North America*, 39(4), 535–549. https://doi.org/10.1016/j.ogc.2012.10.002

Marakala, V. (2022). Neutrophil gelatinase-associated lipocalin (NGAL) in kidney injury – A systematic review. *Clinica Chimica Acta*, 536, 135–141. https://doi.org/10.1016/j.cca.2022.08.029

Mohamed, M.L., El Behery, M.M. & Mansour, S.A.E.-A. (2013). Comparative study between VEGF-A and CA-125 in diagnosis and follow-up of advanced endometriosis after conservative laparoscopic surgery. *Archives of Gynecology and Obstetrics*, 287(1), 77–82. https://doi.org/10.1007/s00404-012-2539-4

Montgomery, G.W. and Giudice, L.C. (2017). New lessons about endometriosis-somatic mutations and disease heterogeneity. *New England Journal of Medicine*, 376(19), 1881–1882.

Moradi, M., Parker, M., Sneddon, A., Lopez, V. & Ellwood, D. (2014). Impact of endometriosis on women's lives: a qualitative study. *BMC Women's Health*, 14, 123. https://doi.org/10.1186/1472-6874-14-123

Nisenblat, V., Bossuyt, P.M.M., Shaikh, R., Farquhar, C., Jordan, V., Scheffers, C.S., Mol, B.W.J., Johnson, N. & Hull, M.L. (2016). Blood biomarkers for the non-invasive diagnosis of endometriosis. *The Cochrane Database of Systematic Reviews*, 2016(5), CD012179. https://doi.org/10.1002/14651858.CD012179

Nothnick, W.B. (2011). The emerging use of aromatase inhibitors for endometriosis treatment. *Reproductive Biology and Endocrinology*, 9(1), 87. https://doi.org/10.1186/1477-7827-9-87

Parasar, P., Ozcan, P. & Terry, K.L. (2017). Endometriosis: Epidemiology, Diagnosis and Clinical Management. *Current Obstetrics and Gynecology Reports*, 6(1), 34–41. https://doi.org/10.1007/s13669-017-0187-1

Rosenberg, G.A. (2009). Matrix metalloproteinases and their multiple roles in neurodegenerative diseases. *The Lancet Neurology*, 8(2), 205–216. https://doi.org/10.1016/S1474-4422(09)70016-X

Schrezenmeier, E.V., Barasch, J., Budde, K., Westhoff, T. & Schmidt-Ott, K.M. (2017). Biomarkers in acute kidney injury – pathophysiological basis and clinical performance. *Acta Physiologica*, 219(3), 556–574. https://doi.org/10.1111/apha.12764

Shah, B.H. and Catt, K.J. (2004). Matrix metalloproteinases in reproductive endocrinology. *Trends in Endocrinology and Metabolism: TEM*, 15(2), 47–49. https://doi.org/10.1016/j.tem.2004.01.004

Stetler-Stevenson, W.G. (2001). The role of matrix metalloproteinases in tumor invasion, metastasis, and angiogenesis. *Surgical Oncology Clinics of North America*, 10(2), 383–392, x.

Tsakogiannis, D., Kalogera, E., Zagouri, F., Zografos, E., Balalis, D. & Bletsa, G. (2020). Determination of FABP4, RBP4 and the MMP-9/NGAL complex in the serum of women with breast cancer. *Oncology Letters*, 21(2), 85. https://doi.org/10.3892/ol.2020.12346

Vercellini, P., Vigano, P., Somigliana, E. & Fedele, L. (2014). Endometriosis: pathogenesis and treatment. *Nat Rev Endocrinol*, 10(5), 261–275. https://doi.org/10.1038/nrendo.2013.255

Vincenti, M.P. and Brinckerhoff, C.E. (2002). Transcriptional regulation of collagenase (MMP-1, MMP-13) genes in arthritis: integration of complex signaling pathways for the recruitment of gene-specific transcription factors. *Arthritis Research*, 4(3), 157–164. https://doi.org/10.1186/ar401

Visse, R. and Nagase, H. (2003). Matrix Metalloproteinases and Tissue Inhibitors of Metalloproteinases. *Circulation Research*, 92(8), 827–839. https://doi.org/10.1161/01.RES.0000070112.80711.3D

Vitale, S.G., Capriglione, S., Peterlunger, I., La Rosa, V.L., Vitagliano, A., Noventa, M., Valenti, G., Sapia, F., Angioli, R., Lopez, S., Sarpietro, G., Rossetti, D. & Zito, G. (2018). The Role of Oxidative Stress and Membrane Transport Systems during Endometriosis: A Fresh Look at a Busy Corner. *Oxidative Medicine and Cellular Longevity*, 2018(1). https://doi.org/10.1155/2018/7924021

Wang, X. and Khalil, R.A. (2018). Matrix Metalloproteinases, Vascular Remodeling, and Vascular Disease. *Advances in Pharmacology (San Diego, Calif.)*, 81, 241–330. https://doi.org/10.1016/bs.apha.2017.08.002

Wasung, M.E., Chawla, L.S. & Madero, M. (2015). Biomarkers of renal function, which and when? *Clinica Chimica Acta*, 438, 350–357. https://doi.org/10.1016/j.cca.2014.08.039

Zappitelli, M., Washburn, K.K., Arikan, A.A., Loftis, L., Ma, Q., Devarajan, P., Parikh, C.R. & Goldstein, S. L. (2007). Urine neutrophil gelatinase-associated lipocalin is an early marker of acute kidney injury in critically ill children: a prospective cohort study. *Critical Care*, 11(4), R84. https://doi.org/10.1186/cc6089

Zhang, H., Sheng, S., Pan, Z., Zhao, L., Yang, C., Li, C. & Wang, F. (2023). Immune and endocrine regulation in endometriosis: what we know. *Journal of Endometriosis and Uterine Disorders*, 4, 100049. https://doi.org/10.1016/j.jeud.2023.100049

Zhang, L., Zhang, D., Yang, L., Gu, Y., Zuo, Q., Wang, H., Xu, J. & Liu, D. (2021). Roles of cell fusion between mesenchymal stromal/stem cells and malignant cells in tumor growth and metastasis. *The FEBS Journal*, 288(5), 1447–1456. https://doi.org/10.1111/febs.15483

APPENDICES

Ethical Approval

İNSAN ARAŞTIRMALARI ETİK KURULU KARAR FORMU

ETİK KURULUN ADI	ANKARA ÜNİVERSİTESİ TIP FAKÜLTESİ İNSAN ARAŞTIRMALARI ETİK KURULU
AÇIK ADRES	Ankara Üniversitesi Tıp Fakültesi Morfoloji Binası 06100 Sıhhiye/ANKARA
TELEFON	0312 595 82 27
FAKS	0312 310 63 70
E-POSTA	tipinsanetik@ankara.edu.tr

BAŞVURU BİLGİLERİ	ARAŞTIRMANIN AÇIK ADI	Endometrioması olan infertil kadınlarda serum nötrofil jelatinaz ilişkili lipokalin (NGAL) miktarının açıklanamayan infertil hasta grubu ile karşılaştırılması - Başvuru No: 2022000614-1(2022/614)	
	KOORDİNATÖR/SORUMLU ARAŞTIRMACI ÜNVANI/ADI/SOYADI	Prof.Dr.Batuhan ÖZMEN	
	PROJE YÜRÜTÜCÜSÜ UNVANI/ADI/SOYADI (TÜBİTAK vb. gibi kaynaklardan destek alanlar için)		
	KOORDİNATÖR/SORUMLU ARAŞTIRMACININ UZMANLIK ALANI	Kadın Hastalıkları ve Doğum	
	KOORDİNATÖR/SORUMLU ARAŞTIRMACININ BULUNDUĞU MERKEZ	Ankara Üniversitesi Tıp Fakültesi Kadın Hastalıkları ve Doğum Anabilim Dalı	
	ARAŞTIRMAYA KATILAN MERKEZLER	TEK MERKEZ ☒	ÇOK MERKEZLİ ☐

KARAR BİLGİLERİ	**Karar No:İ11-656-22**	**Tarih: 08 Aralık 2022**
	Yukarıda bilgileri verilen başvuru dosyası ile ilgili belgeler araştırmanın/çalışmanın gerekçe, amaç, yaklaşım ve yöntemleri dikkate alınarak incelenmiş ve uygun bulunmuş olup araştırmanın/çalışmanın başvuru dosyasında belirtilen merkezde gerçekleştirilmesinde etik ve bilimsel sakınca bulunmadığına toplantıya katılan etik kurul üye tam sayısının salt çoğunluğu ile karar verilmiştir.	

İNSAN ARAŞTIRMALARI ETİK KURULU

ÇALIŞMA ESASI	İyi Klinik Uygulamaları Kılavuzu
BAŞKANIN UNVANI / ADI / SOYADI:	Prof.Dr.Hakan ERGÜN

Unvanı/Adı/Soyadı	Uzmanlık Alanı	Kurumu	Araştırma ile ilişki		İmza
Prof.Dr.Hakan ERGÜN	Tıbbi Farmakoloji	A.Ü. Tıp Fakültesi	E☐	H☒	
Prof.Dr.Berna ARDA	Tıp Tarihi ve Etik	A.Ü. Tıp Fakültesi	E☐	H☒	
Prof.Dr.Hatice ILGIN RUHİ	Tıbbi Genetik	A.Ü. Tıp Fakültesi	E☐	H☒	
Prof.Dr.Sevim AYDIN	Histoloji ve Embriyoloji	A.Ü. Tıp Fakültesi	E☐	H☒	
Prof.Dr.Berna SAVAŞ	Tıbbi Patoloji	A.Ü. Tıp Fakültesi	E☐	H☒	
Prof.Dr.Yüksel ÖRÜN	Tıbbi Onkoloji	A.Ü.Tıp Fakültesi	E☐	H☒	
Prof.Dr.Cihangir AKYOL	Genel Cerrahi	A.Ü. Tıp Fakültesi	E☐	H☒	
Doç.Dr.Başak Ceyda MEÇO	Anesteziyoloji ve Reanimasyon	A.Ü. Tıp Fakültesi	E☐	H☒	
Doç.Dr.Halil ÖZDEMİR	Çocuk Sağlığı ve Hastalıkları	A.Ü. Tıp Fakültesi	E☐	H☒	
Doç.Dr.İsmet OKULU	Çocuk Sağlığı ve Hastalıkları	A.Ü. Tıp Fakültesi	E☐	H☒	
Doç.Dr.Beyza DOĞANAY ERDOĞAN	Biyoistatistik	A.Ü. Tıp Fakültesi	E☐	H☒	
Doç.Dr.Zahide Çilen BÜYÜKATALAY YALDIZ	Kulak, Burun ve Boğaz Hastalıkları	A.Ü. Tıp Fakültesi	E☐	H☒	
Doç.Dr.Rezzak YILMAZ	Nöroloji	A.Ü. Tıp Fakültesi	E☐	H☒	
Doç.Dr.Serkan AKBULUT	Cerrahi Onkoloji	A.Ü. Tıp Fakültesi	E☐	H☒	

Approval of Hospital

T.C.
ANKARA ÜNİVERSİTESİ REKTÖRLÜĞÜ
Hastaneler Başhekimliği
Klinik Araştırmalar Birimi

Sayı : E-32557014-604.01.02-655903 20.09.2022

Konu : Dr. Batuhan TURGAY'ın tez çalışması hk.

KADIN HASTALIKLARI VE DOĞUM ANABİLİM DALI BAŞKANLIĞINA

İlgi : 14.09.2022 tarihli ve E-12405952-622.03-649443 sayılı yazınız.

İlgide kayıtlı yazınızda belirtilen Anabilim Dalınız öğretim üyelerinden Prof. Dr. Batuhan ÖZMEN'in sorumluluğunda infertilite doktora programı öğrencilerinden Dr. Batuhan TURGAY tarafından yürütülecek olan "Endometrioması Olan İnfertil Kadınlarda Serum Nötrofil Jelatinaz İlişkili Lipokalin (ngal) Miktarının Açıklanamayan İnfertil Hasta Grubu ile Karşılaştırılması" başlıklı tez çalışması kapsamında Anabilim Dalınızda kayıtlı/kayıt edilecek hastalara ait verilerin kullanılması, Etik Kurul onayı alındıktan sonra, "Kişisel Sağlık verilerinin İşlenmesi ve Mahremiyetinin Sağlanması" hakkındaki yönetmelikte (24.11.2017 tarih, 30250 sayılı resmi gazete) belirtilen esaslara uyulmak kaydıyla uygundur.

Ancak yapılacak olan çalışma kapsamında rutin uygulama dışında ilave hizmet alımı (test, değerlendirme, işlem vb.) olması durumunda bütçelendirilmesi gerekmektedir. Bütçelendirme yapılabilmesi için alınacak hizmetlere ait ICD/SUT kodlarının ve çalışmanızın destekleyicisinin (öğretim üyesi, BAP, Tübitak, Meslek Derneği vb) tarafımıza iletilmesi gerekmektedir.

Gereğini bilgilerinize saygılarımla rica ederim.

Prof. Dr. Akın KAYA
Hastaneler Başhekimi

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Bilgi için:Ayfer TEZCAN
Hemşire

Informed Constent

Versiyon No: 01

Tarih: 28.11.2022

BİLGİLENDİRİLMİŞ GÖNÜLLÜ OLUR FORMU

Çalışma adı: Endometrioması olan infertil kadınlarda serum nötrofil jelatinaz ilişkili lipokalin (NGAL) miktarının açıklanamayan infertil hasta grubu ile karşılaştırılması

Çalışmanın kolay anlaşılır adı (halk diliyle): Çikolata kisti olan kısır kadınlarda serumdaki bir enfeksiyon belirtecinin (serum nötrofil jelatinaz ilişkili lipokalin) miktarının herhangi bir kısırlık nedeni bulunamayan kadınlarla karşılaştırılması

Sorumlu hekim: Prof. Dr. Batuhan Özmen

Tedavinin yürütüleceği yer:

Ankara Üniversitesi Üreme Sağlığı Teşhis Tedavi Eğitim Araştırma ve Uygulama Merkezi ve Ankara Üniversitesi Tıp Fakültesi Kadın Hastalıkları ve Doğum Anabilim Dalı

Sayın gönüllü,

Bu form sizin dahil olmanız istenen çalışma ilgili olarak sizi bilgilendirmek amacı ile düzenlenmiştir. ‘Endometrioması olan infertil kadınlarda serum nötrofil jelatinaz ilişkili lipokalin (NGAL) miktarının açıklanamayan infertil hasta grubu ile karşılaştırılması ‘ başlıklı bu çalışmaya, kısırlık tedavisi için hastaneye başvuran çikolata kisti olup bu nedenle operasyon geçiren ve kısırlık nedeni araştırmasında herhangi bir bulgu bulunamayan hastalar dahil edilecektir. 18-35 yaş arasındaki 45 çikolata kisti hastası ve 45 kısırlık nedeni bulunamayan hastanın dahil edilmesi planlanmaktadır ve çalışma Ocak 2023- Haziran 2023 tarihleri arasında yapılacaktır.

İnfertilite kliniğine başvuran hastalar halihazırda rutin muayeneye tutulmaktadır ve hastalarda kısırlık nedeni araştırılmaya çalışılmaktadır. Bu çalışmaya bu rutin tarama sonrasında herhangi bir kısırlık nedeni bulunamayan ve kısırlık nedeni olarak sadece çikolata kisti tespit edilen ve bu nedenle ameliyat olan hastalar dahil edilecektir. Çikolata kisti kısırlık nedenlerinden birisi olarak kabul edilmektedir ve kesin tanısı sadece ameliyatla örnek alınarak konulabilmektedir. Bunun dışında ultrasonografi gibi görüntüleme araçları ile bu

hastalık varlığından şüphelenilebilir fakat kesin tanı ve gerekirse tedavi için ameliyat şarttır. Ameliyatın ise kısırlık şikayeti olan hastalarda yumurtalık dokusuna zarar verilebilme olasılığı nedeniyle riskleri bulunmaktadır. Bu çalışma ile ameliyat gerekmeden kanda bakılan bir madde ile bu hastalığın tanısının konulabilmesi amaçlanılmaktadır.

Bu çalışmaya katılmayı tercih etmeniz durumunda size planlanacak tedavilerde rutin uygulamaya göre bir değişiklik olmayacaktır. Size halihazırda rutin kısırlık muayenesi yapılmıştır ve çikolata kistiniz var ise size halihazırda ameliyat kararı alınmıştır. Bu çalışma ile ilgili olarak yaş, kilo, boy, kısırlık ile ilgili olan kan ve görüntüleme sonuçlarınız kayıt altına alınacaktır ve sizden kısırlık araştırması için alınan kan örneklerinden arta kalan bir tüp kan alınıp bir buzdolabı yardımıyla saklanacaktır. Ameliyat olan hastalar ameliyat olduktan 2 ay sonra rutin kontrole geldiğinde rutin alınan kanlardan arta kalan bir tüp yine alınıp saklanacaktır. Takiben bu saklanan kanlar enfeksiyon belirteçleri olan serum nötrofil jelatinaz ilişkili lipokalin ve Matriks metallopeptidaz 9 miktarlarının belirlenmesi amacıyla labaratuarda bir kit yardımıyla çalışılacaktır.

Bu tedavi ile ilgili kişisel bilgileriniz araştırma sorumlusu ve araştırmacılar dışında hiç kimse ile paylaşılmayacaktır. Size ait laboratuvar sonuçları ve ultrasonografi bulguları hastane içerisinde bir araştırmacının kontrolünde olan sadece bir bilgisayarına kaydedilecek ve çoğaltılmayacaktır. Bu bilgisayar kayıtlarında hiçbir hastanın ismi yer almayacak olup her hasta bir numara ile temsil edilecektir. Bu şekilde kişisel verilerinizin gizliliğinin sağlanması planlanmaktadır. Çalışılan kanlar ise çalışma sonrası uygun bir şekilde imha edilecektir.

Bu çalışmaya gönüllü katılacağınızı belirtmektesiniz, çalışmaya katılmayı reddetme hakkına sahipsiniz ve çalışmaya devam etmek istemediğiniz herhangi bir zamanda mazeret belirtmeksizin çalışmadan çıkma hakkına sahipsiniz. Bu çalışmaya katılmamanız durumunda rutin takiplerinizde herhangi bir aksama yaşamayacaksınız. Tedavi ile ilgili bilgi alma isteğiniz olduğunda Prof. Dr. Batuhan Özmen'i cep tel[redacted] arayabilirsiniz.

ONAM FORMU

Ben……

yukarıda adı geçen ‘Endometrioması olan infertil kadınlarda serum nötrofil jelatinaz ilişkili lipokalin (NGAL) miktarının açıklanamayan infertil hasta grubu ile karşılaştırılması’ ile ilgili bilgiler bana sözlü olarak da anlatıldı. Sorularım aklımda şüphe bırakılmadan tatmin edici bir şekilde yanıtlandı. Bu tedaviyi hasta olarak kendi arzum ve isteğim dahilinde gönüllü olarak kabul ediyorum.

Hastanın Adı Soyadı Tarih İmza

Doktor Adı Soyadı Tarih İmza

Patient Follow-up

Hasta Takip Formu

Ad soyad

Yaş

Boy-kilo:

FSH

LH

E2

TSH

AMH

İnfertilite süresi

Ultrasonografi bulguları

Antral folikül

Hb

Beyaz küre

Nötrofil

Lenfosit

Açıklanamayan infertilite Endometrioma

NGAL

MMP-9

MMP-9/NGAL

Postoperatif

NGAL

MMP-9

MMP-9/NGAL