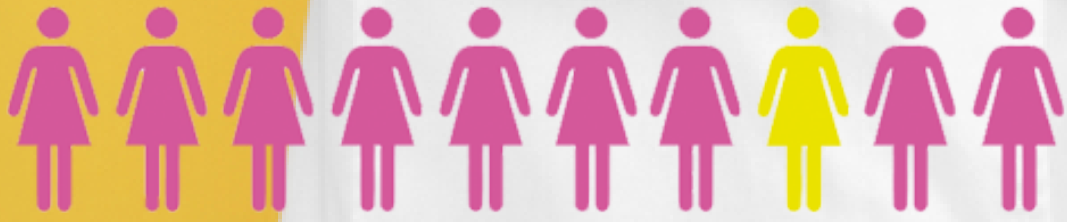
TURKISH ENDOMETRIOSIS & ADENOMYOSIS SOCIETY 2009

10th year 2009-2019

ENDOMETRIOSIS BULLETIN

July 2019 / Issue X



1 in 10 Women are Affected by Endometriosis

www.endometriozis.org

PREFACE

HELLO

We are with you again with our 10th issue. In this issue you will find newly published articles, you will get a chance to observe point of views of several physicians from different specialties and as in the previous issues you will find news from the world of endometriosis.

On **4th of July** we have organized a seminar on endometriosis at **Deniz Bank Headquarters** to the Deniz Bank employees. **Engin Oral, MD** and Salih Yilmaz, MD held the seminar, and the attendance was high. We are going to plan new seminars where we talk about reproductive health and endometriosis.

We are continuing with our '**Endo at School'** project. On 12th of April 2019 we came together with the high school students at **Robert College. Pinar Yalcin Bahat, MD, Bahar Yuksel Ozgor, MD** and F**itnat Topbas Selcuki, MD** talked about endometriosis and menstruation related pain to about 100 students from the 11th grade. We are going to continue with our school seminars during the following educational years.

On **15th of June 2019** at the B**askent Infertility Days, Engin Oral, MD, Umit Inceboz, MD, Banu Kumbak Aygun, MD, Ercan Bastu, MD, Hale Goksever Celik, MD, Yusuf Aytac Tohma, MD,** and **Hasan Onur Topcu, MD** from our society shared the most up-to-date information on **'Endometriosis and Endometriosis Related Infertility'** with the participants.

On **16th of June** at **Sanliurfa 10th Endoacademy meeting** took place with the collaboration of **Turkish Society of Gynecological Endoscopy (JED)**. With almost 60 participants we discussed endometriosis thoroughly from different perspectives of our experts. There was also live surgery integrated in the program. It was a pleasure to meet with our colleagues from this region.

We joined the group of societies recognized by World Endometriosis Society and thus, strengthened our international relations.

Engin Oral, MD held two talks on the management of endometriosis in patients at 16 and 45 years of age and assisted reproductive techniques in patients with advanced endometriosis at the **2nd Eastern Europe Endometriosis and Infertility Congress** in Romania.

In this issue same as the previous ones we have interviewed an international colleague who is a specialist in endometriosis. This time **Camran Nezhat, MD, FACOG, FACS** who is currently working in the **US** and who has been actively working to raise awareness for endometriosis worldwide over the years has kindly joined us for this interview. You can find a summary of the interview in this bulletin and on our website. You can also find the video link online.

In this issue you can read our **Endometriosis and Cancer guideline** which has been prepared with the most up-to-date data on this topic.

In this bulletin, in addition to the selected articles you can also read about articles written by Turkish authors on endometriosis in the past three months.

We hope to be with you in our next bulletin with more news and new developments in the field of endometriosis.

Best regards,

Board Members of Endometriosis&Adenomyosis Society

Founding President Prof. Engin Oral, MD.

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Endometriosis e-bulletin is prepared by Turkish Endometriosis & Adenomyosis Society. If there are any topics that you would like us to include in the bulletin or any questions that you would like to ask, you can contact us via e-mail to dr_pinaryalcin@hotmail.com or baharyl86@gmail.com.

TABLE OF CONTENTS

A SELECTED ARTICLES

1. **Prevalence of fibromyalgia among women with deep infiltrating endometriosis**
   Coloma, J. L., Martínez Zamora, M. A., Collado, A., Gràcia, M., Rius, M., Quintas, L., Carmona, F. International Journal of Gynecology & Obstetrics. 2019 Aug;146(2):157-163. doi: 10.1002/ijgo.12822. Epub 2019 May 9.
2. **Reduced pain thresholds and signs of sensitization in women with persistent pelvic pain and suspected endometriosis**
   Grundström, H., Gerdle, B., Alehagen, S., Berterö, C., Arendt Nielsen, L., &Kjølhede, P. Acta obstetricia et gynecologicaScandinavica, 98(3), 327-336. 2019
3. **Pain-related behavior and brain activation in cynomolgus macaques with naturally occurring endometriosis**
   Yano, M., Matsuda, A., Natsume, T., Ogawa, S. Y., Awaga, Y., Hayashi, I., Hama, A., Takamatsu, H. Human Reproduction. Volume 34, Issue 3Pages 469–478 (2019).
4. **Expression of Cannabinoid Receptors in Myometrium and its Correlation with Dysmenorrhea in Adenomyosis**
   Shen, X., Duan, H., Wang, S., Hong, W., Wang, Y. Y., & Lin, S. L. Reproductive Sci. 2019 Mar 4:1933719119833483. doi: 10.1177/1933719119833483. [Epub ahead of print]
5. **Surgical Oophorectomy for The Treatment of Medical Oophorectomy-Responsive Chronic Pelvic Pain: A Retrospective Case-Series on Quality of Life Outcomes**
   Bates, S., & Li, A. Journal of Obstetrics and Gynaecology Canada, 41(5), 709-710. (2019).
6. **Vaginal Bromocriptine Improves Pain, Menstrual Bleeding and Quality of Life in Women with Adenomyosis; A Pilot study**
   Andersson, J. K., Khan, Z., Weaver, A. L., Vaughan, L. E., Gemzell Danielsson, K., & Stewart, E. A Acta obstetricia et gynecologicaScandinavica. 2019 Apr 26. doi: 10.1111/aogs.13632. [Epub ahead of print]

B NEWS FROM OUR SOCIETY

C NEWS FROM THE WORLD OF ENDOMETRIOSIS

D INTERVIEW WITH AN 'ENDO SPECIALIST'

E ARTICLES ON ENDOMETRIOSIS FROM OUR COUNTRY FROM THE LAST THREE MONTHS

F RELATIONSHIP BETWEEN ENDOMETRIOSIS AND CANCER

G SOCIAL MEDIA

A SELECTED ARTICLES

1 PREVALENCE OF FIBROMYALGIA AMONG WOMEN WITH DEEP INFILTRATING ENDOMETRIOSIS

Coloma, J. L., Martínez Zamora, M. A., Collado, A., Gràcia, M., Rius, M., Quintas, L., Carmona, F. International Journal of Gynecology & Obstetrics. 2019 Aug;146(2):157-163. doi: 10.1002/ijgo.12822. Epub 2019 May 9.

Abstract

OBJECTIVE:

To estimate the prevalence of fibromyalgia among women with endometriosis and analyze the effect of fibromyalgia on health-related quality of life (HRQoL).

METHODS:

An observational case-control study conducted at a tertiary hospital in Barcelona between April 2015 and March 2017 among women with deep infiltrating endometriosis (DIE; n=80), women with superficial endometriosis or ovarian endometrioma (non-DIE; n=76), and control women without endometriosis (n=73). Fibromyalgia was assessed via the London Fibromyalgia Epidemiological Study Screening Questionnaire (LFESSQ). HRQoL was evaluated with the 36-Item Short Form (SF-36) questionnaire. The impact of fibromyalgia and other clinical characteristics was assessed by multivariate regression analysis.

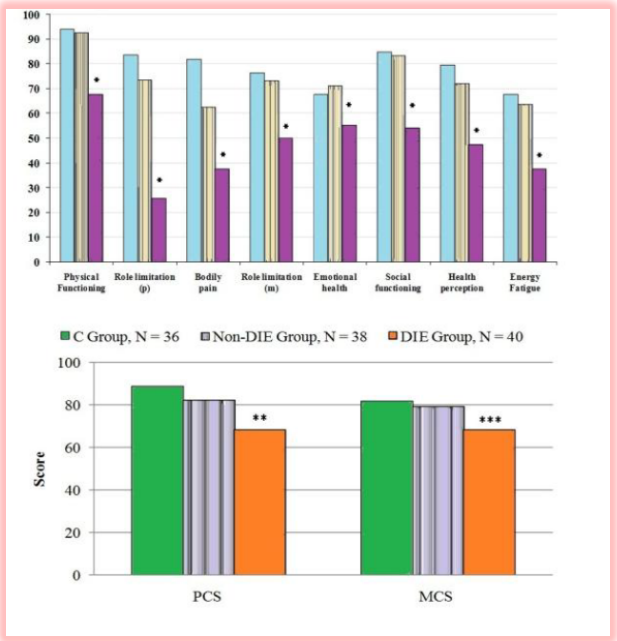
RESULTS:

More women fulfilled the criteria for fibromyalgia in the DIE group than in the non-DIE and control groups by LFESSQ-4 (31 [39%], 12 [16%], and 6 [8%], respectively; P=0.009) and LFESSQ-6 (22 [28%], 8 [11%], and 4 [5%], respectively; P=0.008). The DIE group reported significantly poorer HRQoL for all SF-36 dimensions. Women with DIE who fulfilled the criteria for fibromyalgia had lower physical component scores (-31.6; 95% confidence interval, -50.8 to -12.3; P=0.003).

CONCLUSION:

The estimated prevalence of fibromyalgia was higher among women with DIE. Women with DIE and positive fibromyalgia screening had lower HRQoL.

KEYWORDS: Deep infiltrating endometriosis; Endometriosis; Fibromyalgia; London Fibromyalgia Epidemiological Study Screening Questionnaire; Pain; Quality of life; SF-36 questionnaire



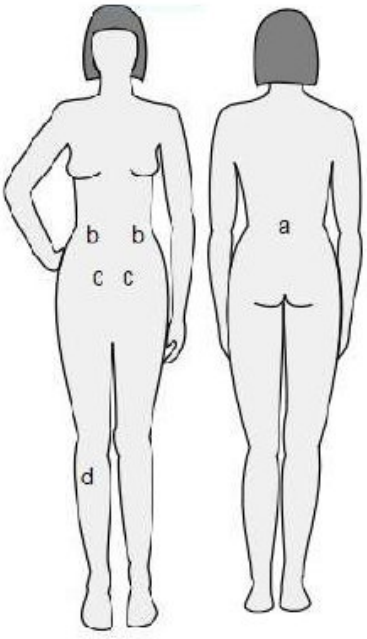
2 REDUCED PAIN THRESHOLDS AND SIGNS OF SENSITIZATION IN WOMEN WITH PERSISTENT PELVIC PAIN AND SUSPECTED ENDOMETRIOSIS

Grundström, H., Gerdle, B., Alehagen, S., Berterö, C., Arendt Nielsen, L., &Kjølhede, P. Acta obstetricia et gynecologicaScandinavica, 98(3), 327-336. 2019

Abstract

INTRODUCTION:

Endometriosis is a gynecological disorder that may cause considerable pelvic pain in women of fertile age. Determining pain mechanisms is necessary in order to optimize the treatment of the disease. The objective of the study was to evaluate pain thresholds in women with persistent pelvic pain with and without confirmed endometriosis, and healthy, unaffected controls, and analyze how pain thresholds in these cohorts related to duration of pelvic pain, quality of life, and symptoms of anxiety and depression.



MATERIAL AND METHODS:

Pain thresholds for heat, cold and pressure were assessed with quantitative sensory testing on six locations on a reference group of 55 healthy women and on 37 women with persistent pelvic pain who had been admitted for diagnostic laparoscopy on the suspicion of endometriosis. Validated instruments were applied to assess quality of life and symptoms of anxiety and depression. Data were analyzed by means of uni- and multivariate analysis of variance and Spearman's rank-order correlation.

RESULTS:

The women with persistent pelvic pain had significantly lower pain thresholds compared with the reference women. In the women with pain, no differences were observed in pain thresholds between women with (n = 13) and women without (n = 24) biopsy-proven endometriosis. The duration of pelvic pain correlated significantly positively with reduced pain thresholds, ie, the longer the duration, the more sensitization. In the persistent pelvic pain group, pain thresholds for heat correlated significantly with the Short Form Health Survey 36 dimension of bodily pain, and thresholds for cold correlated with Short Form Health Survey 36 bodily pain and with symptoms of depression.

CONCLUSIONS:

Our results showed widespread alterations in pain thresholds in women with persistent pelvic pain that are indicative of central sensitization and a time-dependent correlation. Women with pelvic pain and suspicion of endometriosis should probably be treated more thoroughly to prevent or at least minimize the concomitant development of central sensitization.

KEYWORDS:

chronic pain; endometriosis; health-related quality of life; pain thresholds; persistent pelvic pain; quantitative sensory testing; sensitization

3 PAIN-RELATED BEHAVIOR AND BRAIN ACTIVATION IN CYNOMOLGUS MACAQUES WITH NATURALLY OCCURRING ENDOMETRIOSIS

Yano, M., Matsuda, A., Natsume, T., Ogawa, S. Y., Awaga, Y., Hayashi, I., Hama, A., Takamatsu, H. Human Reproduction. Volume 34, Issue 3Pages 469–478 (2019).

Abstract

STUDY QUESTION:
Can pain be objectively assessed in macaques with naturally occurring endometriosis?

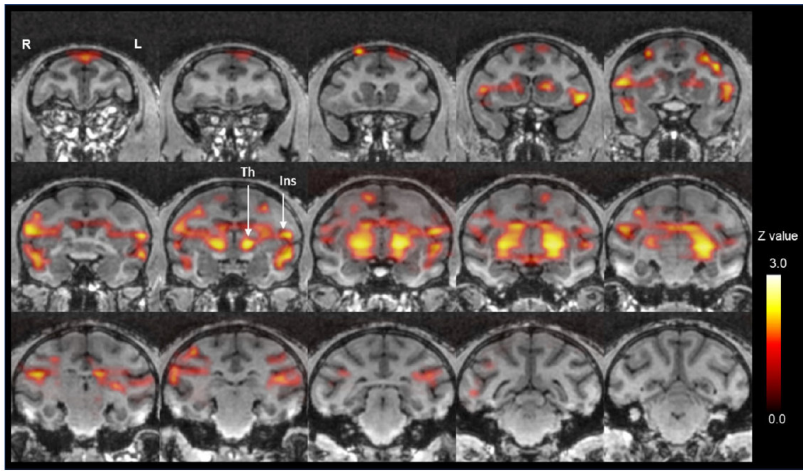
SUMMARY ANSWER:
Behavioral, pharmacological and in vivo brain imaging findings indicate that pain can be quantified in macaques with endometriosis.

WHAT IS KNOWN ALREADY:
Endometriosis is characterized by abdominopelvic hypersensitity. The mechanism by which endometriosis evokes pain is largely unknown, as currently available analgesics offer limited pain relief. Thus, there is a need for both greater understanding of the in vivo mechanism of endometriosis-associated pain and better methods of testing novel therapeutics.

STUDY DESIGN, SIZE, DURATION:
Pain-related behavior and brain activation were assessed in five cynomolgus macaques with endometriosis. Three healthy female macaques served as controls.

PARTICIPANTS/MATERIALS, SETTING, METHODS:
Abdominopelvic sensitivity to force was assessed with an algometer. Activation of brain areas using block design force stimulation and the effects of a single dose of the analgesic drug morphine and 2-month treatment with the progestin dienogest on brain activation were observed via functional magnetic resonance imaging.

MAIN RESULTS AND THE ROLE OF CHANCE:
Pain response thresholds in macaques with endometriosis were significantly less than that of healthy macaques (P = 0.0003). In addition, non-noxious force activated the insula and thalamus, which was reduced with morphine and 2-month dienogest treatment.



LIMITATIONS, REASONS FOR CAUTION:
The specific role of cysts, such as peritoneal cysts, in endometriosis pain was not explored. While non-noxious stimulation activated the insula and thalamus, macaques were sedated during fMRI scans. Current findings need further confirmation in a larger cohort.

WIDER IMPLICATIONS OF THE FINDINGS:
The current study demonstrated central sensitization and related pain behavior in macaques with naturally occurring endometriosis. Altered functioning of the central nervous system could be the focus of future mechanistic studies and for the development of novel therapeutics.

STUDY FUNDING/COMPETING INTEREST(S):
Supported by a grant from the Shizuoka Industrial Foundation. All authors are employees of Hamamatsu Pharma Research, Inc.

KEYWORDS:
analgesia; chronic pelvic pain; functional magnetic resonance imaging; hyperalgesia; non-human primate; progestin; translational model

4 ENDOMETRIOSIS: SEEKING OPTIMAL MANAGEMENT IN WOMEN APPROACHING MENOPAUSE.

Alio L1, Angioni S2, Arena S3, Bartiromo L4, Bergamini V5, Berlanda N6,7, Bonanni V8, Bonin C5, Buggio L7, Candiani M4, Centini G9, D'Alterio MN2, De Stefano F4, Di Cello A10, Exacoustos C11, Fedele L6,7, Frattaruolo MP7, Geraci E12, Lavarini E5, Lazzeri L9, Luisi S9, Maiorana A1, Makieva S13, Maneschi F14, Martire F11, Massarotti C15,16, Mattei A17, Muzii L8, Ottolina J4, Pagliardini L13, Perandini A5, Perelli F18, Pino I19, Porpora MG8, Remorgida V15,16, Scagnelli G19, Seracchioli R20, Solima E19, Somigliana E6,7, Sorrenti G11, Ticino A8, Venturella R10, Viganò P13, Vignali M19, Zullo F21, Zupi E11.

Table 1. WHO Medical Eligibility Criteria (MEC)[19] revised for women with endometriosis and modified according to age-related important cardiovascular risk factors.

	Age 18–40 years	*Age ≥40 years*
No cardiovascular risk factors	COC[a], R[a], POP[a], LNG-IUD[a]	POP[a], LNG-IUD[a], COC[b], R[b]
Body mass index ≥30	POP[a], LNG-IUD[a], COC[b], R[b]	POP[a], LNG-IUD[a], COC[b], R[b]
Smoking		
<15 cigarettes/day	R[a], POP[a], LNG-IUD[a], COC[b]	POP[a], LNG-IUD[a], R[b]
≥15 cigarettes/day	R[a], POP[a], LNG-IUD[a], COC[b]	POP[a], LNG-IUD[a]
Hypertension	POP[a], LNG-IUD[a]	POP[b], LNG-IUD[b]
>2 cardiovascular risk factors including vascular diseases	POP[b], LNG-IUD[b]	POP[b], LNG-IUD[b]

COC, combined oral contraceptives; LNG-IUD, levonorgestrel intrauterine device; POP, progestogen-only pill; R, vaginal ring.
[a]MEC category 1: method can be used in any circumstances.
[b]MEC category 2: method can be generally used.

4 EXPRESSION OF CANNABINOID RECEPTORS IN MYOMETRIUM AND ITS CORRELATION WITH DYSMENORRHEA IN ADENOMYOSIS

Shen, X., Duan, H., Wang, S., Hong, W., Wang, Y. Y., & Lin, S. L. Reproductive Sci. 2019 Mar 4:1933719119833483. doi: 10.1177/1933719119833483. [Epub ahead of print]

Abstract

The myometrium, especially the junctional zone (JZ), is now well documented to have a role in the pathogenesis of adenomyosis. Cannabinoid receptors have been shown to participate in the establishment of endometriosis and its pain perception. However, its relation to adenomyosis has not been identified yet. The aim of this study was to investigate the expression of cannabinoid receptor type I (CB1) and type II (CB2) in myometrium of uteri with and without adenomyosis and determine the correlation between their levels and clinical parameters of adenomyosis. We collected tissue samples of JZ and the outer myometrium from 45 premenopausal women with adenomyosis and 34 women without adenomyosis. CB1 and CB2 messenger RNA (mRNA) and protein expression levels were evaluated by the use of Western blotting and real-time quantitative polymerase chain reaction from all samples. Clinical information on the severity of dysmenorrhea and other data were collected. We found both CB1 and CB2 mRNA and protein levels in women with adenomyosis were significantly higher than those of controls, and CB1 expression levels in JZ were positively correlated with the severity of dysmenorrhea. These data suggest that cannabinoid receptor CB1 may be involved in the pathogenesis of dysmenorrhea in adenomyosis and may be a potential therapeutic target.

KEYWORDS: adenomyosis; cannabinoid receptor; dysmenorrhea; endometriosis; myometrium

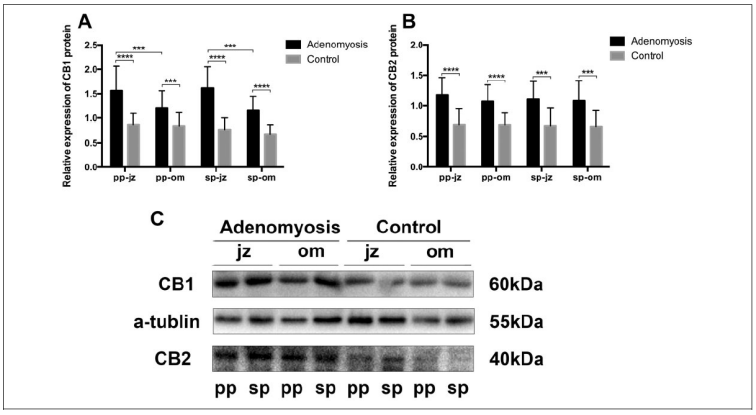


Figure 2. Relative expressions of cannabinoid receptor type I (CB1; A) and type II (CB2; B) protein in myometrium of uteri with or without adenomyosis. Representative Western blotting of CB1, CB2, and a-tublin (C).

5 SURGICAL OOPHORECTOMY FOR THE TREATMENT OF MEDICAL OOPHORECTOMY-RESPONSIVE CHRONIC PELVIC PAIN: A RETROSPECTIVE CASE-SERIES ON QUALITY OF LIFE OUTCOMES

Bates, S., & Li, A. Journal of Obstetrics and Gynaecology Canada, 41(5), 709-710. (2019).

Abstract

Objectives

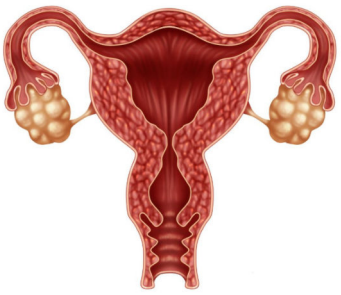
To determine the long-term post-operative impact of surgical oophorectomy on pain severity and quality of life (QOL) in women with chronic pelvic pain (CPP) responsive to medical oophorectomy pre-operatively.

Methods

Eligible patients were identified from the EMR of a community gynecologist. For inclusion, women with CPP must have had subjective pain improvement from leuprolide therapy of at least three months duration and subsequently undergone surgical oophorectomy for this pain. Participants were telephone-surveyed using a modified version of the validated Endometriosis Health Profile-30 QOL questionnaire. A five-point Likert scale was used to score both pain severity and QOL; 1) prior to leuprolide, 2) following leuprolide but prior to surgery and 3) following surgery.

Results

A total of 44 patients were identified from the period of June 2011 – April 2018 and surveyed. The mean age of patients was 42.8. The mean interval since surgery was 31.9 months. Mean pre-leuprolide pain severity score (max = 5) was 4.56 versus 1.29 post-surgery ($p<0.001$). Mean QOL scores pre-leuprolide versus post-surgery (greater scores correspond to poorer QOL) were general functioning 3.93 versus 1.16 ($p<0.001$), exercise/leisure 3.93 versus 1.21 ($p<0.001$), sleep 3.84 versus 1.16 ($p<0.001$), and sexual intercourse 4.14 versus 1.59 ($p<0.001$), respectively.



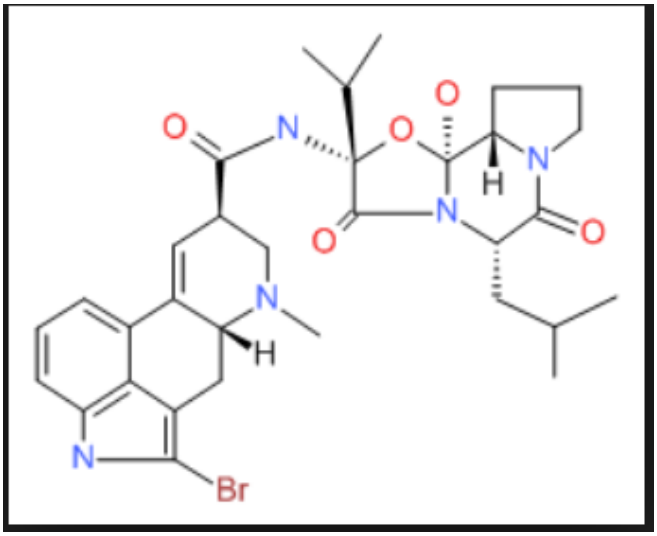
Conclusions

Treatment of medical oophorectomy-responsive CPP with surgical oophorectomy leads to a significant long-term reduction in pain severity and a marked improvement in all QOL domains assessed. Gynecologists can be assured that women with leuprolide-responsive CPP treated with surgical oophorectomy will have a sustained and significant improvement in symptoms after surgery.

Key Words: Endometriosis, Chronic Pelvic Pain, GnRH Analogues, Surgical Ooophorectomy

6 VAGINAL BROMOCRIPTINE IMPROVES PAIN, MENSTRUAL BLEEDING AND QUALITY OF LIFE IN WOMEN WITH ADENOMYOSIS; A PILOT STUDY

Andersson, J. K., Khan, Z., Weaver, A. L., Vaughan, L. E., Gemzell Danielsson, K., & Stewart, E. A Acta obstetricia et gynecologicaScandinavica. 2019 Apr 26. doi: 10.1111/aogs.13632. [Epub ahead of print]



Abstract

INTRODUCTION:

Adenomyosis is a benign uterine disease where endometrial glands and stroma are found within the myometrium surrounded by an area of hypertrophic myometrium. Symptomatology includes heavy menstrual bleeding and pelvic pain. The pathogenesis of adenomyosis is not known; however, animal models have shown increased uterine concentration of prolactin as a risk factor. Prolactin acts as a smooth muscle cell mitogen. If prolactin is central to adenomyosis pathogenesis, reducing uterine prolactin could be a possible medical treatment option. In this pilot study, we aim to evaluate the effect of bromocriptine, a prolactin inhibitor, on menstrual bleeding and pain in women with adenomyosis.

MATERIAL AND METHODS:

23 women with diffuse adenomyosis were enrolled from a university hospital in Sweden and a tertiary care center in the USA. Nineteen patients completed 6 months of treatment with vaginal bromocriptine at a dose of 5 mg daily. Participants completed validated measures at baseline, 3 and 6 months of treatment, and at 9 months (3 months after cessation of bromocriptine). Validated measures utilized included Pictorial Blood Loss Assessment Chart (PBLAC), Aberdeen Menorrhagia Clinical Outcomes Questionnaire (AMCOQ), Visual Analog Scale for pain (VAS), McGill Pain Questionnaire (MPQ), Endometriosis Health Profile (EHP-30), Female Sexual Function Index (FSFI) and the Fibroid Symptom Quality of Life (UFS-QOL) symptom severity and health-related quality of life (HRQL) subscores. Scores were compared between baseline and 9 months using the Wilcoxon signed rank test.

RESULTS:

Mean age of participants was 44.8 years. About 77.8% reported PBLAC scores >250 and 68.4% reported moderate to severe pain at baseline. Compared with baseline, women had lower 9-month scores (median [interquartile range] for all) on PBLAC (baseline 349 [292-645] vs 9-month 233 [149-515], P = 0.003), VAS (5.0 [4-8.3] vs 2.5 [0-4.5], P < 0.001), EHP Core Pain (15.9 [9.1-50.0] vs 3.4 [2.3-34.1], P = 0.029), EHP Core Self-image (41.7 [16.7-58.3] vs 25 [0-5], P = 0.048) and Symptom Severity Score (60 [44-72] vs 44 [25-56], P < 0.001) and higher HRQL scores (57 [37-63] vs 72 [51-85], P < 0.001) following bromocriptine treatment. Other EHP core parameters and FSFI were not significantly different.

CONCLUSIONS:

Significant improvement in menstrual bleeding, pain and quality of life after vaginal bromocriptine treatment suggests a novel therapeutic agent for adenomyosis

KEYWORDS: adenomyosis; bromocriptine; menstrual bleeding; pain; prolactin

B NEWS FROM OUR SOCIETY

PAST ACTIVITIES

ENDO AT SCHOOL – Istanbul – Izmir

ROBERT COLLEGE, Istanbul

As a part of our 'Endo at School' project we were at Robert College on Friday the 12th of April, 2019. We talked about 'endometriosis' with 180 students from the 11th grade. We thank school administration and teachers of their support and the students for their interest.

ISTEK SCHOOLS, Izmir

On Wednesday the 17th of April we were at Istek Schools in Izmir. Umit Inceboz, MD gave a seminar about reproductive health and endometriosis to 50 students from the 9th grade. We thank biology teacher Mulkiyet Simsek, school administration and the students for their interest and support.

To apply for our Endo at School project please fill out the form using the following link:
https://www.endometriozisdernegi.org/dernekten-haber/endo-okulda-projesi

BASKENT INFERTILITY DAYS, Ankara

On 15th of June 2019 at the Baskent Infertility Days Engin Oral, MD, Umit Inceboz, MD, Banu Kumbak Aygun, MD, Ercan Bastu, MD, Hale Goksever Celik, MD, Yusuf Aytac Tohma, MD, and Hasan Onur Topcu, MD from our society shared the most up-to-date information on 'Endometriosis and Endometriosis Related Infertility' with the participants.

ENDOACADEMY MEETING, Sanliurfa

On 16th of June at **Harran University in Sanliurfa 10th Endoacademy meeting** took place with the collaboration of Turkish Society of Gynecological Endoscopy (JED). In addition to seminars and discussion there was also a session of live surgery. We thank all the participants for their interest and feedback and we are very much thankful to Prof Erdal Sak, MD and his OB/GYN-team from Harran University for their kind hospitality.

ENDOMETRİOZİS & ADENOMYOZİS DERNEĞİ VE JİNEKOLOJİK ENDOSKOPİ DERNEĞİ İşbirliği ile

X. ENDOAKADEMİ DOĞU VE GÜNEYDOĞU ANADOLU 2019

16 Haziran 2019 - Pazar, Şanlıurfa
Harran Üniversitesi Fen Edebiyat Fakültesi Konferans Salonu
ENDO AKADEMİ BAŞKANLARI: M. Erdal Sak, Taner Usta

Destekleyenler

"Toplantı, Harran Üniversitesi Fen Edebiyat Fakültesi Konferans Salonu'nda düzenlenecektir"

AWARENESS MEETING AT DENIZBAK HEADQUARTERS

As a part of our "awareness meetings" we were at **Denizbank Headquarters** on Thursday the 4th of July. **Engin Oral, MD.** as the guest speaker talked about endometriosis, reproductive health and pelvic pain with a young and dynamic group of listeners. We thank all Denizbank employees for their warm hospitality.

https://www.youtube.com/watch?v=ffj-oFGybYk

2ND EASTERN EUROPEAN ENDOMETRIOSIS AND INFERTILITY CONGRESS

Engin Oral, MD held two talks on management of Endometriosis in patients at 16 and 45 years of age and assisted reproductive techniques in patients with advanced endometriosis at the **2nd Eastern Europe Endometriosis and Infertility Congress** in Romania.

ADIM ADIM (STEP BY STEP) PROJECT

We are happy to announce that we joined Adım Adım (Step by Step, a Turkish charity run fundraising initiative), which unites volunteers who run or swim for charity projects and NGOs. We are very excited to be part of this family. From now on when we run to raise awareness we are going to be able to earn support for our projects. With your support we are going to affect more lives.

ENDOACADEMY XI

11th Endoacademy meeting will take place on **20th October 2019** at **Istanbul Lutfi Kirdar Kartal Training and Research Hospital's Conference Hall.** Program will be announced soon.

ENDOSCHOOL 2019

2nd Endometriosis School of Turkey will take place on December 16-17, 2019 in Istanbul with international participants who are experts in their fields. A detailed program will be available soon.

ENDOMETRIOSIS SCHOOL of TURKEY - 2

December 16 - 17, 2019, Medtronic Innovation Center, Istanbul - Turkey
Course Directors: *Engin Oral, Ertan Sarıdoğan*
Course Coordinators: *Taner Usta, Ercan Baştu*

TURKISH ENDOMETRIOSIS & ADENOMYOSIS SOCIETY 2009 — 10th year 2009-2019

Day I (December 16, Monday)

08:00 - 08:30	**Registration**
08:20 - 08:30	**Opening: The aim and objectives of the International Endometriosis School** **Preschool Evaluation of The Participants (Keypad)**
	Session I
08:30 - 09:00	Diagnosis, classication and staging of peritoneal disease, endometrioma and deep infiltrating endometriosis
09:00 - 09:30	Imaging in endometriosis and adenomyosis
09:30 - 10:00	Endometriosis and infertility: reproductive outcomes
10:00 - 10:30	Current approach to management of adenomyosis
10:30 - 10:50	Discussion
10:50 - 11:10	**Coffee Break**
	Session II
11:10 - 11:40	Medical treatment options for patients with endometriosis
11:40 - 12:10	Pain management in endometriosis
12:10 - 12:40	Management of endometriosis at the extremes of reproductive years
12:40 - 12:50	Discussion
12:50 - 15:30	**Live Transmission Session** *(This session consist of 2 part; First: Ultrasonografic Live case demonstrations, Second; Live surgery transmission)* **Live Ultrasonografic Demonstration of Endometriosis Cases** **Live Surgery**
	Session III
15:30 - 16:00	Surgical techniques for endometriomas
16:00 - 16:30	Deep endometriosis: the road map
16:30 - 17:00	How can we prevent complications during endometriosis surgery: tips and tricks
17:00 - 17:30	Management of recurrent endometriosis after surgical treatment
17:30 - 17:50	Discussion

Day II (December 17, Tuesday)

	Session IV *Guidelines, Bowel Endometriosis and Complications*
08:30 - 08:50	Useful anatomy for pelvic laparoscopic surgery
08:50 - 09:20	Bowel endometriosis: indication and surgical techniques
09:20 - 09:50	Current guidelines on endometriosis
09:50 - 10:00	Discussion
	Hands On Training
10:00 - 10:30	Pig model for laparoscopy - Evaluation
10:30 - 12:30	**Training on live animal tissue** *Practice of different energy types in live animal model* *Bladder injury and repair* *Dissection of the ureters and major pelvic vessels*
12:30 - 13:10	**Lunch**
13:10 - 16:00	**Training on live animal tissue** *Ureteric injury and reanastomosis* *Bowel injury and repair* *Hysterectomy*
16:00 - 16:20	**Coffee Break**
16:20 - 17:20	**Wrap-up** End of the course - Delivery of Certificates of Attendance
17:20 - 17:30	Postschool evaluation of the course by the participants (Keypad)

Invited International Faculty

Ertan Sarıdogan
Joerg Keckstein
Alessandra Di Giovanni
Ernesto Bosch
Sawsan As-Sanie
Natasha Curran
Mario Malzoni
Horace Roman
Catrina Exacoustos
Mario Castellanos
Vito Chiantera
Marcelo Ceccaroni
Gernot Hudelist
Natasha Curran
Andrew Baranowski

NEWS FROM THE WORLD OF ENDOMETRIOSIS

EEL

5th European Endometriosis Congress will take place in Prague. Details will be announced soon.
https://www.eec2019.com/

ESHRE CAMPUS 2019

You can find detailed information on Eshre Campus' next meeting which will take place in Münster Germany where Deep Endometriosis will be discussed under the following link.
https://www.eshre.eu/Education/Calendar-Campus-events/Deep-endometriosis/Programme

Deep endometriosis – from pathophysiology to clinic

ASIAN ENDOMETRIOSIS CONGRESS

8th Asian Endometriosis Congress will take place in August in Thailand. Our founding president **Engin Oral, MD.** will be representing our society with his talk.
https://www.ace2019thailand.com/

WES 2020

Abstract submission has already started for World Endometriosis Congress. you can find detailed information under the following link:
http://endometriosis.ca/world-congress/wce2020/#2

AGES FOCUS MEETING 2019

The details of this meeting organized by joint efforts of World Endometriosis Society and Australasian Gynaecological Endoscopy & Surgery Society can be find under the following link.
https://ages.com.au/wp-content/uploads/2019/03/AGES-FM-2019-4pp-Program.pdf

INTERVIEW WITH AN 'ENDO SPECIALIST'

Interview with Camran Nezhat, MD, FACOG, FACS

A short curriculum vitae

Camran Nezhat is also known as the father of modern surgery. He invented Video Laparoscopy and Video Assisted Endoscopy Surgery. He pioneered the use and adaptation of DaVinci Surgical System in gynecology. He is the immediate past president and a member of the Board of Trustees of the Society of Laparoendoscopic Surgeons, is the Director of the Center for Special Minimally Invasive Surgery and is the Clinical Professor of Surgery and OB/GYN at Stanford University School of Medicine. He has published more than 500 articles, book chapters, abstracts, letters to the editor, and video presentations. He is coauthor of 2 textbooks and has won numerous awards and honors from prestigious societies like ACOG, ACS, ASRM, and the Excel Award from the Society of Laparoendoscopic Surgeons. More recent awards include the ACOG 2004, ASRM 2004, and ACOG 2005. He is on the editorial board of the Journal of Fertility and Sterility and is an associate editor for the Journal of Society of Laparoendoscopic Surgeons.

May 20, 2019

nterview with Camran Nezhat: About endometriosis and Endomarch

Hello Dr. Nezhat, I am Salih Yilmaz. Before starting with the interview, I would like to thank you on behalf of our society for agreeing to do this interview. Today we are going to talk about endometriosis and adenomyosis.

1. As someone who has been dealing with endometriosis for so many years could you tell us what endometriosis is from your perspective?

Endometriosis is frequently seen among women in reproductive age. Approximately 1 out of every 8 – 10 women has it. It is defined as the presence of 'endometrium' the tissue which makes the inner lining of uterus outside of uterus on other organs. It can affect all organs of the abdomen. It is usually located at reproductive organs, colon or intestines, bladder and rarely ureters (the ducts which connect the kidneys with the bladder), diaphragm and skin. It causes pain most of the time. Pain related with menstruation or during sexual intercourse, back pain, if the colon is affected then pain during defecation, pain during urination if bladder is involved and shoulder pain when diaphragm is affected can be observed. In addition, it can cause infertility. It can reveal itself with infertility problems without causing any other symptoms, because only 40% of patients with endometriosis experience pain. The underlying reason of infertility in women without any pain, with normal tubal anatomy and with normal sperm test results of partners is most of the time endometriosis.

2. As you stated endometriosis is a very complex disease. What made you become interested in this disease?

As you know I have two brothers and we are all gynecologists. My siblings are also interested in gynecological oncology and IVF. Our interested in endometriosis started years ago when a couple of our family members and a couple of friends were diagnosed with endometriosis. We did a lot of research on endometriosis and we introduced Video Laparoscopy as a surgical technique in endometriosis surgery. We invented a lot of

new techniques and these techniques are currently applied all over the world. Furthermore, due to the fact that this disease is not well known we introduced month of March as the world endometriosis awareness month to increase awareness on this disease.

3. My next question was going to be about endometriosis. How did you come up with Endomarch?
This is an excellent question. Me, my brothers and a cousin of ours who is also a gynecologist when we used to come together to talk about newest updates in medicine and endometriosis we realized the things which we failed to recognize over the years. On this topic we published an article called 'Endometriosis: Ancient Disease, Ancient Treatments'. Women suffered a lot from this disease over the years. In the past people did work on endometriosis, but then they lost interest. This way awareness for this disease increased and decreased over the years. We wanted to change this. We wanted to increase awareness and empower women to ask for help. Thus, we invented Endomarch. During the last 5 years we came a long way worldwide. Not only the health providers but everyone started to learn about endometriosis. Endometriosis is as common as diabetes and hypertension. Because of Endomarch awareness of endometriosis increased worldwide and even in some countries endometriosis became integrated in the high school education system.

4. We have a strong team in Turkey and we are organizing a lot of events to raise awareness. Did you achieve your goals with Endomarch? What did you succeed with this idea?
Endomarch is definitely a success. Turkey has also progressed a lot in endometriosis awareness. In Turkey and in Cyprus a lot of gynecologists have started doing a good job with endometriosis.

5. Do you think there is still room for improvement in Endomarch?
First of all, I am really happy that you are also supporting us. Yes, it definitely needs improvement. Endomarch became an annual organization which aims to inform women, adolescent girls and their families on endometriosis and to raise awareness and it grows every year. More patients get involved each year and more awareness activities are organized. I hope that we can find a noninvasive diagnostic method, we can improve our surgical management and we can stop the progress of the disease. Hopefully in the future we will find a method of prevention so that patients will never need surgery. Surgery means complication and endometriosis surgery is a very aggressive method.

6. An experienced surgeon like yourself is saying this?
For years I have been operating with my brother in this field. We have operated on colon, intestines, bladder and diaphragm. Surgery should be avoided if possible or it should be the last option. If surgery is needed than it should be done by talented surgeons in this field and the aim should always be maximum organ protection. One shouldn't be too aggressive. According to our experiences endometriosis is like a tree. If we can the tip of the tree the tree dies. By shaving off endometriotic lesions one can avoid resection of colon, resection of the bladder and unnecessary nerve incisions. Following an operation hormonal therapy can be used to treat the lesions which were left behind. One should never forget that endometriosis is a benign disease, it is not like cancer.

7. As you know we still don't know the underlying mechanism of endometriosis. There are a lot of hypothesis, but a definitive cause has not yet been found. Do you believe that someday we will understand the cause of endometriosis? And what should we do to find a cause?
Endometriosis does not have only one cause, but many. Endometriosis is not just one disease, it has many forms. With these characteristics it is very similar to cancer. Some cancers are very aggressive whereas others are milder. I strongly believe that in the future we will find the cause of endometriosis. My recommendation is that in endometriosis surgery we should be more conservative (aiming organ protection). Over the years we operated a lot and we wrote many articles on endometriosis of the colon, bladder and other rare sites. From all our experiences we have concluded that surgery should be the last option. If we think that surgery is the only option then we should aim for a conservative surgical technique.

8. As you have mentioned you contributed a lot to the field of endometriosis. When you look at the past do you see anything which you would say that you did wrong or did incompletely?
Yes, we definitely need to learn from the past. If we don't learn from our mistakes we can repeat them. When we were writing 'Endometriosis: Ancient Disease, Ancient Treatments' we realized that almost 100 years ago some surgeons were very aggressive and then they chose to be less and less aggressive finally opting for conservative surgery. If I were to read this article before, I would never have done some of the surgeries, because back then I operated a lot. I did a lot of bladder resection, colon resection. If I had avoided these there wouldn't be complications. I would have been more conservative and would have shaved off the lesion. Then would have given hormonal therapy. Now we manage our patients this was and they are very satisfied. Unfortunately, some of our colleagues are still too aggressive, although it is not needed. Patients endure complications during these surgical procedures. The new management techniques should be adapted by all of our colleagues. We do not recommend aggressive surgery anymore.

9. You introduced many techniques to endometriosis surgery. What would you recommend young gynecologist who are interested in endometriosis in terms of endometriosis management and how could they improve their surgical techniques?
This is a very important question. You should think of surgery as the last option and you should operate less. If you think that surgery is needed you should leave it up to experts. As a surgeon who has been operating since 1970 and who still does I came to the conclusion that surgery should be applied less and should be done according to patient's symptoms. If patient has no complaints then you shouldn't do a bladder or colon resection. If you are operating because of infertility you should evaluate only the ovaries and the fallopian tubes you shouldn't touch the colon or the intestines. My recommendation is that if a patient has pain then you should first try medical treatment. If you think of surgery than you should do the shaving method.

10. How do you manage endometriosis in your country? As far as we know in your country there are endometriosis centers. How do patients enter these centers?
Since we have been working in this field for so many years and we have a center patients and other physician have heard about us and they send their patients to us. It usually is the word of mouth.

11. What do you think of Turkey?
I really like Turkey. Turkey is the country in the world which I visit the most. I come here every year and I feel like at home. I know many colleagues here.

ARTICLES ON ENDOMETRIOSIS FROM OUR COUNTRY FROM THE LAST THREE MONTHS

1. A Rare Cause of Abdominal Pain: Scar Endometriosis.
Karapolat, B., & Kucuk, H. Emergency medicine international, p1-5. 5p.2019.

INTRODUCTION:
Scar endometriosis (SE) is a rare pathology that develops in the scar tissue formed on the anterior abdominal wall usually after a cesarean section. There have been instances of women presenting to emergency or general surgery clinics with abdominal pain due to SE.
MATERIALS AND METHODS:
This study retrospectively reviews 19 patients who were operated on in our clinic between January 2010 and January 2017 with a prediagnosis of SE and were reported to have SE based on their pathology results.
RESULTS:
The mean age of the patients was 30.8 years (range: 20-49 years). The body mass indexes of 12 (63.2%) patients were ≥ 25. All patients had a history of cesarean section and 9 (47.4%) patients had undergone cesarean section once. With the exception of one patient who had her SE localized in her inguinal region, all patients had a mass localized on their anterior abdominal wall neighboring the incision and complained about cyclic pain starting in their premenstrual periods. The complaints began 2 years after their cesarean section in 10 (52.6%) patients. Mostly abdominal ultrasonography was used for diagnostic purposes. The lesions were totally excised and the SE diagnosis was made through a histopathological examination in all patients. No postoperative complications or recurrences were seen in any of the patients.
CONCLUSION:
Suspicion of SE is essential in women of reproductive age who have a history of cesarean section and complaints of an anterior abdominal wall mass and a pain at the scar site that is associated with their menstrual cycle. An accurate and early diagnosis can be established in such patients through a careful history and a good physical examination and possible morbidities can be prevented with an appropriate surgical intervention.

2.Laparoscopic low anterior resection for extragenital endometriosis (hybrid surgery: endoscopic guidance and laparoscopic surgery) - a video vignette.
Turan ACAR , &, Mehmet HACIYANLI Colorectal disease,p74 ,2019,video presentation

Dear Editor;
Endometriosis is defined as the presence of endometrial glands and stroma outside the uterine cavity [1]. It was first defined by Recklinghausen in 1896, and described in more detail by Sampson in 1921. It most frequently occurs in the adjacent pelvic organs, and its location outside the pelvis is referred to as extragenital or extrapelvic disease. Extragenital endometriosis can affect all organs, but mainly the bowel and the urinary tract [2]. The most common site affected within the gastrointestinal tract is the rectosigmoid junction, followed by the ileum and the appendix [3]. Intestinal endometriosis is usually asymptomatic. However; gastrointestinal bleeding, nausea, vomiting, crampy abdominal pain, diarrhoea, constipation, and intussusception may also occur. Symptoms alone are not helpful in the diagnosis. The complaint in our case was rectal bleeding. Intestinal endometriosis can lead to narrowing of the lumen and subsequent obstruction by creating, in time, intestinal inflammation and fibrosis. Therefore, intestinal obstruction and perforation may occur. The majority of patients with intestinal endometriosis are diagnosed by laparoscopy or laparotomy [4]. In this case, we report one patient with endometriosis of the rectosigmoid colon lumen who underwent a laparoscopic low anterior resection (Video). A 32-year-old female presented to our hospital with a six month history of rectal bleeding. G1P1A0 (Gravida, Parity and Abortus), who gave birth by cesarean section, and was having regular menstrual cycles. Physical examination was normal and there were no palpable masses on rectal examination. A colonoscopy showed a submucosal mass with a diameter of 6-7 cm in the rectosigmoid colon (about 12. cm) which suggested malignancy, a gastrointestinal stromal tumor or endometriosis. Two biopsies were reported as nondiagnostic. A laparoscopic low anterior resection was performed as the mass was not suitable for endoscopic submucosal dissection. An intraoperative colonoscopy was performed in order to confirm the location of the lesion. Pathology reported extragenital endometriosis. She had an uneventful post-operative recovery and was discharged on the fourth day. Accepted Article This article is protected by copyright. All rights reserved. Management of complex endometriosis with rectal involvement can be more difficult than cancer surgery. In such patients, resection and anastomosis of the affected bowel segment is accepted as the best treatment option, and this can be performed safely laparoscopically.

3. Cyprus Women's Health Research (COHERE) initiative: determining the relative burden of women's health conditions and related co-morbidities in an Eastern Mediterranean population.

Hocaoglu, M. B., Gurkas, S., Karaderi, T., Taneri, B., Erguler, K., Barin, B., ... & Boynukalin, K. BMC women's health, 19(1), 50. 2019

Background

Cyprus is the third largest Mediterranean island with approximately 300,000 Turkish Cypriot and 700,000 Greek Cypriot residents. Due to the, to date, unresolved political circumstances, Northern Cyprus, has been relatively isolated from the rest of Europe for more than 45 years [1]. Although Cyprus has been a member of the European Union (EU) since May 1, 2004, the acquis communautaire is suspended in the northern part of the island [2], and unfortunately official collaborations between the north and south administrations and institutions have been absent. Consequently, population-level health data from Northern Cyprus have not been included in health statistics reported for Cyprus [3]. Moreover, there is an absence of population-level data on common benign women's health conditions such as endometriosis, uterine fibroids, polycystic ovary syndrome (PCOS) and related co-morbidities generally from the Eastern Mediterranean region. It is well established that women's cohorts such as the Nurses' Health Study from the USA [4] and the Million Women Study from the UK [5] have been crucial in investigating how various reproductive and lifestyle factors affect women's health. Hence, establishment of a resource to investigate women's health conditions and causal environmental and genetic factors that can be specific to populations is necessary for the Eastern Mediterranean populations.

The Cyprus Women's Health Research (COHERE) Initiative aims to establish a women's health cohort in Cyprus, with current emphasis on the north for the above-mentioned reasons of data paucity to collect vital health, morbidity, and resource use data, and investigate factors affecting women's health and care seeking. COHERE Initiative is a population-based, cross-sectional study, based on a household/workplace sampling method utilising an extended version of the Endometriosis Phenome and Biobanking Harmonisation Project (EPHect) questionnaire [6–11] that consists of validated instruments used in previous studies, targeting 10% of all women aged 18–55 (N = 8000) living in Northern Cyprus. Study participants completing the questionnaire also have the opportunity to provide a saliva sample for genotyping to understand the underlying genetic architecture of this population. Moreover, participants are invited to a clinical follow-up visit at a women's health clinic that includes a transvaginal or transabdominal pelvic ultrasound scan (USS) that provides clinical data on diagnosis of uterine fibroids, polycystic ovaries, and some endometriosis cases.

This study will provide the first systematically collected population health data for Northern Cyprus - an emerging region in Europe for which public health issues have been unexplored to date. The study will aid the understanding of regional women's health and illness patterns, and the personal, social and economic burden of symptomatology and disease. Disease rates, clinical profiles, and healthcare statistics of women in this population will be utilised to assess the relative burden of disease, and results will form the basis for targeted hypothesis-driven follow-up studies. Moreover, the Cypriot adaption of the 'Mediterranean lifestyle' allows for investigation of the influence of both environmental as well as genetic factors specific to Eastern Mediterranean populations. With this study, the genetic architecture of the population will be unravelled to better inform future gene association studies, investigating genetic risk variants for disease/traits from this population. Moreover, given the genetic susceptibilities, it will lay the foundation to promote changes in potential environmental modifiers for common complex women's health conditions in the region. Furthermore, the health statistics that will be generated from the study will inform the health authorities about prevalence and distribution of certain women's health issues that can be used in development of data-driven health strategies in the region.

Study aims

This study aims to (1) estimate prevalence rates of gynaecological conditions and associated symptomatology, auto-immune, inflammatory, metabolic and pain co-morbidity profiles; (2) investigate how various reproductive and lifestyle factors affect women's health including diet, exercise, employment patterns, oral contraceptive use, childbirth and breastfeeding, family history of illness, in relation to a wide range of reproductive and endocrine conditions, (3) investigate the geospatial distribution of identified conditions in Northern Cyprus and also comparison of disease rates with other 19 centres collecting data using EPHECT based data collection tool, (4) understand the genetic architecture of this population by genotyping DNA extracted from saliva samples collected from a minimum of 1000 participating women, (5) quantify women's access to health care and estimate the economic burden of diseases such as endometriosis in Northern Cyprus, (6) gain insights into women's perceptions of research and interest in participation in subsequent follow-up studies.

Ethics

The study was approved by the Oxford Tropical Research Ethics Committee (OxTREC) of the University of Oxford (OxTREC reference: 37–17). The study also received local ethics approval from the Eastern Mediterranean University Ethics Committee (ETK00-2017-0240).

Eligibility

Women aged 18 to 55 years, who are either citizens of Northern Cyprus or have been residing in Northern Cyprus for the last 5 years, and who are able to give informed consent are eligible to participate in the study. Women younger than 18 or aged over 55, non-citizen women who have been residing in Northern Cyprus for less than 5 years, women who cannot understand the information on the participant information sheet or informed consent form due to being very unwell or illiterate will be excluded from the study.

Recruitment procedures

Participants are recruited through two different routes (Fig. 1): (i) Face-to-face recruitment where household/workplace visits are conducted by the research assistants to inform the women about the study and invite them to participate in the study. If women are interested in taking part, they provide informed consent and then complete the questionnaire. Additionally, they have the option of providing a saliva sample and/or undergoing an appointment at the women's health clinic for a pelvic USS. (ii) Online recruitment, which is promoted through dedicated social media (https://web.facebook.com/KISAAInisiyatifi) page and study page (http://www.cohereinitiative.com). Participants can anonymously complete the study questionnaire online. At the beginning of the questionnaire, they read the participant information sheet and complete an online consent. At the end of the online questionnaire, if they would like the opportunity to take part in the clinical follow-up or provide saliva samples, they are instructed to call the research assistants, using their assigned study participant codes from the online questionnaire. The research assistants arrange an appointment to meet the participant face-to-face to complete a written consent followed by saliva sample collection and/or scheduling of the women's health clinic appointment.

Study design

COHERE Initiative is a population-based cross-sectional study composed of two main steps (Fig. (Fig.1):1): (i) Baseline assessment includes informing participant, getting consent, collecting of questionnaire-based health and lifestyle data, taking anthropometric measurements, collecting saliva sample for DNA extraction and genotyping, (ii) Clinical follow-up includes a pelvic USS by an experienced gynaecologist.

Baseline assessment

All women are informed about the study and the consenting women are given a unique participant ID to be used throughout the study. Participants are asked to complete the baseline EPHect-based health questionnaire [10] with validated instruments used in previous studies either on paper or on tablet computer (Additional file 1). The questionnaire takes around 20–30 min. After the completion of the baseline health EPHect-based questionnaire, basic anthropometric measurements are taken from consenting women. A saliva sample is collected for DNA extraction from a subset of the consenting women. As the last item on the baseline assessment, women are provided with the food frequency questionnaire (FFQ) [12–14], which they can complete in their own time. There are two options to complete the FFQ: (1) Online, using their unique participant ID, they can login to complete FFQ with the given questionnaire web-link, (2) Paper-based, on which the research assistants put a sticker with the unique participant ID and hand the questionnaire to the participant to complete in their own time and drop their FFQ to the near-by questionnaire collection boxes. Clinical appointments for the consenting participants are given by the research assistant at the end of the baseline assessment at most within 2 weeks of their baseline assessment.

Clinical follow-up

At the clinical follow-up, participants undergo a pelvic USS performed by an experienced gynaecologist. Ideally, this is a transvaginal procedure but can be transabdominal if preferred by the participant. As well as being linked to the unique participant ID, scan reports are also provided to the participant in the form of a medical report.

Data collection tools

Expanded EPHect-based health questionnaire

Each consenting woman is asked to complete the EPHect-based health questionnaire. EPHect consists of a set of tools to standardise globally the collection of clinical/lifestyle data and samples across studies to allow for more effective large-scale international collaborative research studies on endometriosis. We have utilized the EPHect health questionnaire as the basis of this study questionnaire and expanded it to capture data on other benign women's health conditions such as uterine fibroids, polycystic ovary syndrome, various chronic pain conditions such as bladder pain and migraine, endocrine conditions such as thyroid conditions. The questionnaire was translated into Turkish, and then back-translated into English. Differences between the original English version and translated English version were compared by an expert panel. The Turkish version was revised where there were differences. The Turkish version was piloted in 100 Turkish Cypriot women of different age segments (Ages: 18–30; 30–40; 40–55) and education levels (Highest education attained: primary school diploma; high school diploma; university degree). Comments from the participants for any unclear questions were also incorporated to the final version. For the Turkish validated and published versions of the questionnaire, scales were identified and incorporated into the questionnaire including the SF36 v2 [15] and Pain Catastrophizing Scale [16].

Measurements

Research assistants take blood pressure, weight, height, waist and hip circumference measurements. Each measurement is taken twice; where there is a significant difference between the two measurements, a third measurement is also taken.

Saliva collection kits

Saliva samples are collected for DNA extraction for genotyping [17–19]. A total of 2 ml of saliva sample is collected by the participant actively spitting into an ORAGENE-saliva collection tube. The standard operation protocol that comes with the saliva collection kit is followed

by each participant and overseen by the research assistant. This is a risk-free, non-invasive method for high-quality DNA extraction from saliva samples.

Food frequency questionnaire
The last item on the baseline assessment is to provide women with the Food-Frequency Questionnaire (FFQ), which they can complete in their own time. The semi-quantitative food frequency questionnaire that has been validated for use in Turkish adults [12] is utilised for this cohort of women, and has also been used in a global study previously [13, 14].

Pelvic ultrasound scan (USS)
Either a transvaginal or transabdominal pelvic USS is conducted on consenting women at the clinical follow-up to examine their reproductive organs. The pelvic USS results provide clinical data on diagnosis of uterine fibroids, polycystic ovaries and some of the endometriosis cases. Both transvaginal and transabdominal USS are safe, risk-free tests routinely conducted in gynaecology clinics. Pelvic USS uses high-frequency sound waves (no radiation) to create images of the female reproductive organs and the pelvic cavity. Some participants may find transvaginal scans uncomfortable since it involves the transducer being inserted into the vagina and this would be inappropriate for women who are virgo intacta. Therefore, as an alternative, we are offering a transabdominal USS where the transducer moves only over the abdomen to image the pelvis.

Data management
All study data will be entered on a custom-made cloud-based survey platform maintained by our study technology funder DMD consulting with servers employing secure cloud computing environment located in Frankfurt, Germany. The cloud-based data are securely transferred to high-compliance University of Oxford servers on a monthly basis. Direct access will be granted to authorised representatives from the University of Oxford and any host institution for monitoring and/or audit of the study to ensure compliance with regulations.
The participants will be identified by a unique participant ID number in the database and nowhere in the electronic database, patient identifiable data are to be stored. Paper records (including consent forms) will be held in locked cabinets in the Chief Investigator's office at Eastern Mediterranean University during data collection. After data collection is finished, these will be transferred to University of Oxford premises and stored in a locked cabinet at the University of Oxford until 31st January, 2028 (end date of the study) and archived for another 10 years after the completion of the study.

Discussion
This study is the first population-based study that will collect data in a standardized way allowing for investigation of women health conditions, related co-morbidities and symptomatology from an Eastern Mediterranean population. The unique setting of the target Turkish Cypriot population will also provide critical insights into the successes and disparities of health-care among women living in an internationally under-represented community that may be applicable across the globe.
The standardised data collection tools utilised in the study will allow for comparison of disease rates, clinical profiles, and healthcare statistics of women in this population with at least 19 other EPHect centres globally (https://endometriosisfoundation.org/ephect/) to better understand the relative burden of disease.
Moreover, the results of this study will form the basis for targeted, hypothesis-driven follow-up studies. They will facilitate addressing of the environmental factors, such as diet as well as the genetic factors causal for women's health conditions that may be specific to Eastern Mediterranean populations. The genetic architecture of women in Northern Cyprus will be revealed to better inform future genetic association studies.

This study is envisaged to promote evidence-based reproductive medicine in the region, not only benefitting the local population but also providing a basis for an Eastern Mediterranean women's health resource.

4. Examination of cervical swabs of patients with endometriosis using Fourier transform infrared spectroscopy.
Bozdag, G., Igci, N., Calis, P., Ayhan, B., Demiralp, D. O., Mumusoglu, S., & Yarali, H. Archives of gynecology and obstetrics, 1-8.2019

Abstract
PURPOSE:
There is no established non-invasive method to diagnose patients with endometriosis. As a nondestructive type of radiation, infrared light might be used for discrimination by causing vibration of the covalent bonds of the molecules when absorbed by the tissues. The aim of the study was to test whether cervical swab can be used to diagnose women with endometriosis using Fourier transform infrared spectroscopy (FTIR).

METHODS:
In this prospective case-control study, women between 18-45 years old and undergoing laparoscopy due to various reasons were recruited (n = 20). According to the findings during laparoscopy, patients were stratified as stage I-II or stage III-IV endometriosis groups. Women lacking any visible lesions of endometriosis were recruited as controls. A cervical swab was taken from all patients just before the surgical procedure and pulled into a tube containing saline solution. FTIR spectra were obtained and the fingerprint region (1750-850 cm-1) was used for analyses.

RESULTS:
Finally, three samples in stage I-II, five samples in stage III-IV and five samples in the control group were analyzed. Hierarchical cluster analysis and principal component analysis were performed as the chemometric method. A total of ten observable peaks were detected in the absorbance spectra of samples. The peaks at 1450 and 1405 cm-1 originating from lipids and proteins significantly increased in the stage III-IV endometriosis group when compared with controls. In addition, nucleic acid/carbohydrate ratio was significantly lower in the stage I-II group indicating that the alteration of the carbohydrate level might be important.

CONCLUSIONS:
Examination of cervical swab with FTIR spectroscopy might be a proper candidate for a non-invasive diagnostic approach of endometriosis.

5. The impact of endometriosis on early embryo morphokinetics: a case-control study
Boynukalin, F. K., Serdarogullari, M., Gultomruk, M., Coban, O., Findikli, N., & Bahceci, M. Systems biology in reproductive medicine, 1-8.2019

Abstract
The aim of this study was to evaluate the possible effects of endometriosis on early embryo development, by comparing the morphokinetic development of embryos obtained from women with clinically confirmed endometriosis with the ones obtained from tubal factor infertility cases. A total of 82 cycles/patients including 53 cycles with endometriosis and 29 cycles with tubal factor infertility were evaluated. A total of 439 embryos were scored for embryo morphokinetics. Age, body mass index, fertilization rates were similar within the groups. However, the number of previous ART trials was found to be higher ($p < 0.05$) in the study group. Also, the number of retrieved oocytes and M2 oocytes were found to be significantly lower in patients with endometriosis ($p < 0.01$). The duration of the first cell cycle (ECC1) and S2 (the time between t3 and t4) displayed significant distortions compared with embryos in the control group. All other analyzed early morphokinetic parameters (t2, t3, t4, t5, t6, t7, t8) and duration of events (VP, cc2a, ECC2, ECC3, S3) showed similar values between study and control groups, respectively. In the light of these findings, it is apparent that endometriosis predominantly affects the duration of the early morphokinetic events and cell cycles.

KEYWORDS: Endometriosis; ICSI; embryo morphokinetic

6. Comparison of the effect of isotretionin and alitretionin on endometriotic implants and serum vascular endothelial growth factor level: an experimental study.
Kulaksiz, D., Kart, C., Guven, S., Akbulut, K., Cobanoglu, U., & Deger, O. Gynecological Endocrinology, 1-4.2019

Abstract
OBJECTIVE:
To compare the effects of alitretionin and isotretionin on endometrial peritoneal implants and serum vascular endothelial growth factor (VEGF) levels.

STUDY DESIGN:
Forty-eight female Sprague Dawley rats were used. Initially surgical rat endometriosis model was done. The endometrial implant volume was measured and rats were randomly divided into four groups. Group 1: Control group (rats did not get any drug but having endometriotic implants), group 2: rats receiving po isotretionin 10 mg/kg per day for 10 d, group 3: rats receiving po isotretionin 20 mg/kg per day for 10 d and group 4: rats receiving po alitretionin 80 mg/kg per day for 10 d. After 1-week medication, rats were sacrificed and size, histopathology of endometriotic implant and levels of VEGF were evaluated.

RESULTS:
Volumes of peritoneal endometrial implants were significantly decreased in Group 2 and Group 3 compared with initial values. However, there were no significant changes in histopathological scores and serum VEGF levels in all groups.

CONCLUSIONS:
This study finding may suggest the possible medical treatment modality of isotretionin on endometriosis. However, alitretionin (potent retinoid) does not have potent regressive effect on endometriotic implants as in isotretionin.

KEYWORDS: Alitretionin; VEGF; endometriosis; isotretionin; retinoid

7. The levels of matrix metalloproteinase-9 and neutrophil gelatinase-associated lipocalin in different stages of endometriosis.
Bostanci Durmus A, &, Sinem Caglar G J Obstet Gynaecol. 10:1-5.2019

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. 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.

keywords: MMP-9; NGAL; endometriosis; stage

8. Laparoscopic Diagnosis and Treatment of Obturator Nerve Entrapment Because of a Deep Infiltrating Endometriotic Nodule: A Case Report.
Kalkan, Ü. & Daniilidis, A Journal of minimally invasive gynecology, 26(4), 766-769.2019

Deep infiltrating endometriosis (DIE) is a particular form of endometriosis causing a variety of severe pelvic pain in women. The involvement of peripheral nerves by DIE implants is very rare. The most common involved site is the sacral plexus. There are few reported cases of involvement of the obturator nerve by DIE. To our knowledge, only 6 cases of symptomatic obturator nerve involvement by DIE have been described (according to PubMed database search in July 2018), and 3 of them were treated laparoscopically. We report a rare case of a deep infiltrating endometriotic nodule entrapping the right obturator nerve. Unlike the previously reported cases, patient history, clinical and laboratory data, and missed findings in previous imaging studies made our case difficult to diagnose. We successfully diagnosed the case and treated the patient with laparoscopic surgery. A video showing the surgery is also included. The recent follow-up in July 2018 (18 months after the operation was performed in January 2017) showed no signs or symptoms of recurrence or any other new complaints. The 18-month follow-up for this case is the longest follow-up data reported in the literature.

F RELATIONSHIP BETWEEN ENDOMETRIOSIS AND CANCER

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Contents

1. Definition and Epidemiology of Endometriosis

2. Mechanisms in Ovarian Cancers Associated with Endometriosis

2.1. Molecular, Immune and Genetic Mechanisms

3. Risk Factors in Ovarian Cancers Associated with Endometriosis

4. Types of Ovarian Cancer Associated with Endometriosis

5. Biomarkers in Endometriosis and Ovarian Cancers Associated with Endometriosis

6. Prognosis in Ovarian Cancers Associated with Endometriosis

7. Endometriosis and Non-Gynecological Cancers

7.1. Endometriosis and Breast Cancer

7.2. Endometriosis and Thyroid Cancer

7.3. Endometriosis, Melanoma and Other Skin Malignancies

7.4. Endometriosis and Non-Hodgkin's Lymphoma and Other Non-Gynecological Cancer Types

8. Association Between Adenomyosis and Endometrial Cancer

9. References

1. Definition and Epidemiology of Endometriosis

Endometriosis is a chronic disease characterized by the presence of the endometrial layer outside the uterine cavity.[1] It is an important public health issue that can cause symptoms such as chronic pelvic pain, dyspareunia, dysuria, dyschezia and infertility; depending on the localization.[2] The estimated prevalence of endometriosis is 7-15% in reproductive age and can go up to 50% in patients who have fertility problems.[2] Although the onset of the disease is generally in the early stages of reproductive ages (before 30 years of age), it has the highest incidence in women aged between 35-44 years, due to delays in diagnosis (mean 4-7 years).[2]

Endometriosis is a serious public health problem that can cause chronic pelvic pain, dyspareunia, dysuria, dyschezia, and infertility.

Various theories have been proposed in the etiology of endometriosis. The most convincing one is that the implantation of endometrial cells on the ovary, peritoneum or other pelvic organs caused by the reflux of the endometrial tissue during menstruation from the fallopian tubes..[2, 3]

Early menarche[4-6], short menstrual cycle[7], alcohol use[8] and caffeine consumption[9], which can cause increased amount of estradiol and estrone in the circulation that stimulates ectopic and eutopic endometrial tissue, were associated with increased risk; while parity[10], and oral contraceptive use [11, 12] were associated with decreased risk for endometriosis that is seen during the reproductive period.

There are conflicting results in the literature regarding the relationship between the use of combined oral contraceptives (COCs) and the risk of endometriosis. [13,14] However, the general view of the relationship in between is that, especially for the treatment of pain, endometriotic foci suppressed by the use of COCs may reappear after discontinuation of medication.

Although the relationship between smoking and endometriosis is not yet clear, it is thought that smoking can reduce the growth of endometriotic foci by reducing estrogens in the circulation.[15] However, in a recent meta-analysis published by Bravive et al, there was no relationship found between history of smoking or amount of daily cigarette consumption and endometriosis. [16]

Furthermore, it is thought that lifestyle and eating habits may play an important role in the development of endometriosis, due to its effects on tumor necrosis factor alpha (TNFα), interleukin 6

and other inflammatory cytokines. Particularly in a recent study; dioxins, polychlorobiphenyls and some pesticides, which are organic pollutants, have been reported to be found on an increased rate in the omental and parietal fatty tissues of endometriosis patients.[17] The relationship between physical activity and endometriosis is not yet clear, thus long-chain omega 3 fatty acid consumption has been found to be associated with a reduced risk of endometriosis.[18]

Although it is accepted as a benign disease, endometriosis and especially ovarian endometriomas have been considered to have malignant potential in recent years. As a result of large-scale studies, the incidence of ovarian carcinomas on the basis of endometriosis was reported to be around 2%.[19]

Kumar et al. showed that approximately 19% of epithelial ovarian cancers were associated with endometriosis.[20] Melin et al. also reported an increased risk of endometriosis-related ovarian carcinoma in young women with endometriosis. [21]

The incidence of ovarian carcinoma related to endometriosis is around 2%.

It has been shown that endometriosis-related carcinomas are more likely to be unilateral while carcinomas that are not associated with endometriosis are more likely to be bilateral and co-occurrence with ascites.[21] This situation can be explained by the fact that endometriosis-related carcinomas originate from the cyst itself and that non-endometriosis-related carcinomas form de novo within the cyst.

2. Mechanisms in Ovarian Cancers Associated with Endometriosis

2.1. Molecular, Immune and Genetic Mechanisms

Endometriosis is acknowledged as a benign disease, it has shown a similar to malignant tumors characteristics; such as uncontrolled growth, neo-angiogenesis, local invasion and distant spread trait etc[22].There are many studies on endometriosis-related cancers and their molecular and immune mechanisms.

Cancer cells typically show genomic instability[23]. Most of neoplasms are monoclonal, and many studies have shown monoclonality in endometriosis as well [24,25]. Recently, several molecular pathways have been proposed to explain the transformation from endometriosis to a typical endometriosis and malignancy. Furthermore, many studies present that genetic and epigenetic changes play a role in the pathogenesis of ovarian cancer which associated with endometriosis. According to some studies, 50% of endometriosis lesions ovarian tumor pathogenesis (KRAS, PTEN, B-catenin /

Wnt) contains genes in chromosomal regions somatic genetic changes specifically in endometrioid histological subtype[26-28]. Otherwise, missing of BAF250 protein, increase in HNF-1β and loss of estrogen receptors have been reported to be prevalent in a typical endometriosis. [29]

Ovarian tumors are associated with endometriosis more similar to type 1 epithelial ovarian cancers, but also, they are related with histopathologic types of endometrioid, clear cell, mucinous, and low-grade serous carcinoma. [30]

Somatic genetic alterations in chromosomal regions containing 50 % of endometriosis lesions genes in ovarian tumor pathogenesis (K-RAS, PTEN, B-catenin / Wnt) are resulted particularly in the endometriosis histological sub type. BAF250a protein damage, increase in HNF-1β and diminishing of estrogen receptors are common in a typical endometriosis.

i) Heterozygosity Loss:

It is associated with the tumor suppressor genes revealed in endometriosis inactivation. Phosphatase and Tensin Homolog (PTEN) gene inactivation due to loss of heterozygosity might be initiated the transformation of endometriosis-related ovarian cancer at early stage [31].

ii) PTEN and K-ras: PTEN gene inactivation may play a part in the early malign transformation of endometriosis. [23]

PTEN gene inactivation is observed in clear cell and endometrioid ovarian carcinomas, whereas K-ras mutation is particularly enroll malignant transformation of clear cell carcinoma.

PTEN mutation was shown in 8% of clear cell ovarian carcinomas and in 20% of endometrioid ovarian carcinomas[32]. Dinulesco et al. described that in a rat model where endometrial morphology was observed by stimulated PTEN deletion and K-Ras expression in the ovarian surface epithelium, that suggest a relationship between endometriosis and malignant transformation with these genetic changes[33].

It has also been revealed that K-Ras mutation is not observed in normal endometriosis and atypical endometriosis but noticed in malignant transformation of clear cell carcinoma. [27, 34]

iii) Tumor suppressor p53: Tumor protein 53 (p53) a tumor suppressor gene product, which acts as a transcription factor that regulates cell cycle, function missing, or mutation is a critical problem on development of ovarian cancer. [35] p53 chromosome loss has also been demonstrated severe /late stage of endometriosis. [36]

Type II epithelial ovarian tumors are composed of high-grade serous carcinomas may be related with P53 tumor suppressor gene mutations. While p53 mutation was recognized in 30% of endometriosis-related clear cell ovarian cancers, this mutation is not detected in endometriosis related endometrioid type ovarian cancer and endometriosis [37].

p53 chromosome failure has been determined in severe /late stage endometriosis.
High grade serous carcinomas seen in Type II epithelial could be accompanied by P53 tumour suppressor mutations.

iv) AT-rich interactive domain-containing protein 1A (ARID 1A): ARID 1A is a tumor suppressor gene which encodes BAF250a protein involved in restructuring of chromatins with eukaryotic genome.

This complex is named as one of the accessory subunits of the SWI–SNF remodelling complex that is responsible for cell proliferation, differentiation, tumour suppression and DNA repair process.[23]

ARID1A gene mutation and loss of expression of the BAF250a protein have been found a useful marker for malignant transformation of atypical endometriosis [38, 39]. However, there is still no conclusive evidence about atypical endometriosis histopathologic correlation based on precursor lesion or inflammation.

In case of mutation in ARID1A gene, repair or replication mistakes of damaged DNA may develop and carcinogenesis could accelerate as well. Wiegand et al. reported that, ARID1A expression is lost in 86% of all atypical endometriosis and non-atypical endometriosis. Furthermore, ARID 1A mutation has been shown in both clear cell and endometriosis related endometrioid type ovarian cancer. [40]

BAF250a encoded by ARID1A expression loss might be a potentially useful marker to identify the initiation of malignant transformation of atypical endometriosis.

v) Other Genetic Mechanisms: β-catenin and Wnt/β-catenin pathway mutations are recognized in endometrioid adenocarcinoma.[40-41] There are often functional mutations appeared particularly in PIK3CA (phosphatidylinositol-4,5-bisphosphate 3-kinase, catalytic subunit alpha) and PTEN genes.

However, high-grade endometrioid carcinomas include TP53 mutations, whereas CTNNB1, PIK3CA and PTEN mutations are absent [42]. Early activation of the PI3K / ACT pathway is found in endometriosis and endometriosis- associated ovarian carcinomas. 40% of clear cell carcinomas have been reported with PIK3CA somatic mutation while 70% ARID1A deficiency has been reported in those [43].

It has also been described that PIK3CA is mutated in the early stages of atypical endometriosis.[44] Besides, it has been reported that RUNX3 promoter methylation is at a higher frequency in patients with endometriosis than that is in control patients and higher levels are in endometriosis-related ovarian carcinoma rather than that is in benign ovarian endometriosis. RUNX3 methylation develops early period in the pathogenesis of endometriosis-related ovarian carcinoma [44].

Early activation of the PI3K / ACT pathway was associated with EOC.

eEF1A2, PTCH2, PPP1R1AB and XRCC5 genes were found to be more common at ovarian clear cell carcinoma related endometriosis cases compared to non-cancer related endometriosis cases. SPINTI, Keratin 8, FoxM1B, FOLR1, CRABP1 and Claudin-7 genes in endometriosis-related ovarian carcinoma and ovarian cancers were more common than endometriosis or benign ovarian lesions, while the StAR gene is seen less. In addition, hMLH1 methylation rates have been reported at a higher rate in ovarian carcinoma associated with endometriosis than the benign ovarian endometriosis.

Proapoptotic activation factors BAX, BIM and γH2AX was found to be higher in endometriosis than endometriosis related cancer. This can be considered as a barrier to prevent preinvasive endometriotic lesions from carcinogenesis.

vi) Estrogens:

It has been associated with the development of many cancers especially breast, ovary and endometrium cancers. Increased estrogen levels stimulate proliferation in endometrial cells. This may be involved in malignant transformation of endometriotic cysts. The aromatase enzyme, which converts androgens to estrogen, is not present in normal endometrial tissue, although high concentrations are shown in endometriotic foci. In addition, 17-beta hydroxysteroid dehydrogenase

type 2 enzyme which is found in the normal endometrium and inactivates estradiol by converting it to estrone is not found in endometriotic foci, whereas 17-beta hydroxysteroid dehydrogenase type 1 enzyme which converts the estrone to estradiol, which is a more potent estrogen than estron, is found in endometriotic foci. In addition, estradiol increases Prostaglandin E2 by stimulating the cyclooxygenase 2 enzyme. In the study by O'Donnel et al. carcinogenic effects of estrogens in ovarian cancer are reported to be via estrogen receptor (ER) alpha.[53] It has been shown that levels of both ER alpha and ER beta are increased in active foci compared to inactive endometriotic foci.

The enzyme 17-beta hydroxysteroid dehydrogenase type 1, which converts from estrogen to estradiol, is found in endometriotic foci.

Hepatic nuclear factor beta, VEGF (vascular endothelial growth factor), PDGF (platelet derived growth factor) levels have also been shown to increase in clear cell ovarian cancer and endometriosis-related endometrioid ovarian cancer.[55]

In conclusion, although there are many studies on the possibility of endometriotic tissue harboring mutations in critical genes in the stages up to the development of carcinogenesis, the actual frequency and importance of these genetic mutations are not fully known. ARID1A, K-RAS, PTEN, B-catenin / Wnt and microsatellite instability are believed to play an important role in endometriosis-related ovarian cancer progression. Although ARID1A mutations are thought to be the basis of endometriosis-related carcinogenesis, its clinical significance is still unknown.

3. Risk Factors in Ovarian Cancers Associated with Endometriosis

Although endometriosis is considered to be a benign disease, it is associated with some features of malignant tumors such as tissue invasion, abnormal growth pattern, increased angiogenesis and decreased apoptosis.[56]

Besides, atypical cells detected in many malignant tissues have been reported to be the primary precursor cellular changes for endometriosis-related epithelial ovarian cancer (EOC).57 The incidence of atypical endometriosis (AE) cells in endometriosis-related EOC varies between 20-80%. This great variability of incidence is due to the lack of consensus in the pathological diagnosis of AE. [57]

Various risk factors have been accused in EOC developing based on endometriosis.[58-60] These factors include increased estrogenic activity, resistance to the anti-proliferative effects of progesterone, increased levels of iron as a consequence of tissue oxidative mechanisms resulting with somatic mutations. It is also thought that selective DNA damage may occur due to increased angiogenesis and iron levels as a result of increased tissue oxidative stress.[61]

Although endometriosis is defined as a benign disease, it could present similar features to malignant tumors. In particular, atypical cells are thought to play a role in endometriosis-associated EOC.

In particular, an estrogen-rich and progesterone-poor microenvironment has been reported to increase the risk of endometrioid type carcinoma 35 while iron-dependent oxidative stress is associated with clear cell type of ovarian cancer. [61]

In addition to the aforementioned molecular mechanisms, it is also claimed that some of the clinical parameters are also associated with increased risk of EOC. The risk of endometriosis-associated EOC is thought to increase with advanced age. [62] In particular, when women under 30 years of age have been accepted as a reference, it is reported that women with endometriosis over 50 years of age have a 4.97-fold increase in the risk of EOC.[63] Also, studies reporting that endometrioma size has also an effect on the development of EOCs. [63]Furthermore, if the endometrioma diameter is 9 cm or above, an increased risk of EOC has been reported. [63]

Advanced age and size (> 9cm) might increase risk in endometriosis-associated EOC, while endometriosis surgery reduces this risk. The effect of exogenous estrogen is contradictory.

Some studies investigating the relationship between endometriosis-associated EOC risk and hormone use have reported that exogenous or endogenous estrogen use may increase the risk of EOC. [64] Also, obesity or unopposed estrogen use after hysterectomy is thought to be associated with the increased risk of EOC. [65] In contrast, oral contraceptives used in the treatment of endometriosis symptoms is known to reduce the risk of EOC. In particular, combined oral contraceptives use for over 10 years, might reduce the risk of EOC in women with endometriosis. [66, 67] Although, the relationship between the use of gestagens or GnRH agonists usage and EOC it is not clear due to the insufficient

number of patients, in the studies with the use of Danazol has been proposed to increase the risk of EOK. [68]

There are several opinions related to the course of endometriosis-associated EOC risk after endometriosis surgery. In a study, it is reported that performing a unilateral oophorectomy or removal of all visible endometriotic foci where ovaries are not affected is associated with reduced risk of EOC.[69]

In another study, even if the other ovary was left in place when the other affected one is extirpated, the risk is reported to be reduced. This is specifically explained by the reduction of AE cell load and inflammatory process. [70, 71] However, there is no evidence about adding hysterectomy in the presence of endometrioma reduces the risk of EOC. This could be interpreted that the risk of EOC is already increased when endometrioma is detected and that adding a hysterectomy will not reduce this risk. [69]

In conclusion, advanced age, increased mass size, and estrogenic activity, increased oxidative radicals are accused in the development of EOC associated with endometriosis. It is also reported that these risks can be minimized by surgical removal of endometriotic foci.

4. Types of Ovarian Cancer Associated with Endometriosis

Epidemiological studies have demonstrated that endometriosis is associated with specific subtypes of ovarian carcinoma, particularly with clear cell and endometrioid carcinoma.[72-74] It is now widely accepted in the literature that endometriosis is a direct precursor to the two specific ovarian carcinomas above.

In a pooled analysis of case-control studies, the relationship between ovarian cancers and self-reported endometriosis was investigated in 13 case control series. According to the results of the analysis, the self-reported endometriosis group had significantly higher incidence of clear cell ovarian carcinoma, low-grade serous carcinoma, and endometrioid-invasive ovarian carcinoma compared to the control group.[75] There was no association found between endometriosis and mucinous ovarian carcinoma, high-grade serous carcinoma, or borderline tumors.[18]

Clear cell ovarian carcinoma, low grade serous carcinoma and endometrioid invasive ovarian carcinoma are more common in endometriosis patients.

Scarfone et al. focused on endometrioid subtype of ovarian carcinoma in their study. They reported that endometrioid carcinoma that is associated with endometriosis and endometrioid carcinoma that is not associated with endometriosis have different clinical features. In addition, the researchers in this study included patients with both endometriosis-related endometrioid carcinoma and endometriosis-related clear cell carcinoma and consequently suggested that, unlike the cases that are not associated with endometriosis, different histologic subtypes should be considered as two different clinical entities, with the exception of higher prevalence in young women.[76]

Endometriosis-associated endometrioid carcinomas are usually diagnosed at an earlier stage and are related with a high rate of concurrent endometrial tumors. In endometriosis-associated clear cell tumors, patients usually have a clinical presentation with a pelvic mass without ascites, and a better survival rates than cancers without an association with endometriosis. The reason may be the more frequent follow-up of patients who have endometriosis, but due to the small sample size, it was not possible to generalize the results. In another study, 41.4% of endometrioid carcinomas and 3.8% of clear cell carcinomas were diagnosed with synchronous endometrial cancer. This may be due to the high amount of estrogen in the disease, causing malignant proliferation of endometriotic cysts or mutations in the ARID1A gene and loss of BAF250a expression. In addition, primary, asynchronous tumors are more common in endometriosis-related cancers.[77]

BAF250a protein expression loss is seen in almost 42% of clear cell carcinomas. In a study, it was reported that clear cell carcinoma originates from HNF-1β-positive epithelial cells and endometrioid carcinoma originates from HNF-1β-negative cells.[78]

In conclusion, endometriosis is associated with an increased risk of epithelial ovarian cancer, particularly endometrioid and clear cell subtypes.

High estrogen concentration, ARID1A gene mutation and increased oxidative stress due to iron are associated with EOC in endometriosis.

5. Biomarkers in Endometriosis and Ovarian Cancers Associated with Endometriosis

The diagnosis of endometriosis may be delayed due to the variability of the signs and symptoms of the disease. Currently, there are no reliable biomarkers that can be used in the diagnosis of the disease. Although it is accepted as a benign disease, it is not possible to distinguish it from possible malignancies resulting referral of patients to oncology centers might cause increased anxiety and

possible unnecessary radical surgeries could lead to loss of fertility. [79] Currently, the only reliable method for the diagnosis of endometriosis is the inspection of the abdominal cavity by laparoscopy and histological examination of biopsies obtained from suspicious lesions. However, non-invasive methods such as imaging modalities, genetic tests, serum or tissue biomarkers are being investigated in the diagnosis due to the risks and cost of surgery that brings to the patient. [80]

Currently, there is no reliable biomarker in the diagnosis of endometriosis. Laparoscopy is still the most reliable method in the diagnosis of endometriosis.

In a review investigating the results of 122 biomarkers of more than 15,000 patients, biomarkers from the family of hormones and cytokines such as activin A, folistatin, urocortin 1, IL-6, IL-33 and TNF-alpha were studies and only data of 4 markers were analyzed after exclusion criteria due to differences in analyzing methods and small sample sizes. The sensitivity for anti-endomysial antibodies was 0.81 and specificity was 0.75, the sensitivity of interleukin-6 was 0.63 and its specificity was 0.69, and the sensitivity for CA-19-9 was 0.36 and the specificity was 0.86. The sensitivity and specificity for CA-125 were found to be 0.40 and 0.9, respectively. However, no marker was found to be reliable in diagnosing endometriosis. [81, 82]

The most studied antigen in the current literature is Ca-125. However, due to it may also increase in ovarian cancer, inflammation, gynecologic and gastrointestinal system diseases, there is no evidence of using Ca125 alone in the diagnosis of endometriosis. [79, 83] In a meta-analysis comprised of more than 1500 patients, the sensitivity and specificity of Ca125 were reported as 52.4% and 92.7%, respectively in the diagnosis of endometriosis. The results >30 IU may be considered sufficient to support the diagnosis in symptomatic patients, whereas its utilization as a screening test is not recommended. [84]

The most commonly studied tissue biomarker is a family member of ubiquitin hydrolase proteins called Protein gene product 9.5 (PGP 9.5). Although it was thought to be a good biomarker, (98-100% sensitivity and 85-100% specificity), recent studies have shown that PGP 9.5 is not sufficient for the diagnosis of endometriosis. [85, 86]

In parallel with advances in the field of genetics in recent years, miRNAs which are non-coding RNA ones with 18-22 nucleotides in length were investigated and it is claimed that they could be

involved in angiogenesis, inflammation, abnormal cell differentiation and invasion causing endometriosis and infertility. [87] It is also found that various miRNA types could increase or decrease in patients with endometriosis.[88] However, there is not enough reliable data to be used in the diagnosis of the disease because they may be affected by cardiovascular diseases, cancer or stress. [89] Also, specifically, thanks to new technologies that enable multiple molecules to be screened at the same time in the diagnosis of complex diseases, recent studies are focused on omics (genomics, transcriptomics, proteomics, metabolomics, etc.) biomarkers. [90] Moreover, in whole genome-wide association studies (GWAS) are investigated the changes in the genome that could be associated with a particular disease, and it was thought that detection of single nucleotide polymorphisms (SNP) could be effective in the diagnosis of chronic complex diseases. [91] In a meta-analysis evaluating GWAS studies of European, American and Japanese patients with stage 3-4 endometriosis, 6 genome region (7p15.2, WNT4, VEZT, CDKN2B-AS1, ID4, and GREB1) SNP changes were detected. However, as the studies on the subject may vary with the societies and disease stage, there is not enough reliable data have been found yet. Besides, in a review of markers obtained from menstrual fluids and endometrial tissues; markers such as CYP19, TIMP-1, and VEGF were found to be significant, but there was insufficient evidence to use them for screening purposes. [92]

In recent years, there are studies on increased levels of HE4 (human epididymis protein, a member of the Whey acidic protein family) 4) in the differential diagnosis of malignant and benign adnexal masses and also in EOC. [93, 94] The sensitivity of HE4 to differentiate ovarian endometriosis from other EOCs in premenopausal patients was found to be 82.1% and specificity was 100%. [93]

Although HE4 levels were independent of the menstrual cycle as opposed to Ca 125, it was claimed that age (> 55 years) [95.96], postmenopausal status, presence of advanced ovarian cancer, impaired renal function and smoking could affect the level of HE4. [97] As an important advantage of HE4, it has been shown to increase 5-8 months before Ca125, especially in detecting recurrences in postoperative EOC follow-up periods. [98]

Recently, in addition to serum markers, various researches are performed especially on tissue markers. [99] In a study, endometriosis-related EOC showed a 40% loss of ARID1A gene expression which is defined as a proto-oncogene. [99, 100] Loss of ARID1A expression was also detected in typical and atypical endometriosis tissues. [101]

Ca 125 which is the most studied biomarker in the diagnosis, it is reliability is still limited. HE4 may be effective in differentiating malignancy especially in premenopausal patients.

In conclusion, the biomarkers studied in the diagnosis of endometriosis and endometriosis-associated EOC were not reliable due to small numbers of case series, different study designs, heterogeneous laboratory methods, and high bias rates.

6. Prognosis in Ovarian Cancers Associated with Endometriosis

According to FIGO ovarian cancer staging system, early stage and low grade means an increase in 5-year survival [102]. Endometriosis related ovarian cancer has been diagnosed at an early age, with a lower stage and grade, therefore it is thought to have a better prognosis [103].

The study of Komiyama et al suggested that when ovarian cancer stage was discarded from being variable, endometriosis related ovarian cancers have a better prognosis. However, in the other studies no significantly difference has been shown between endometriosis related or non-endometriosis related ovarian cancer in terms of 5-year survival [77,103,104].

The chance of early diagnosis of endometriosis-related ovarian cancer may provide better prognosis than ovarian cancers unrelated to endometriosis [42]. Since endometriosis represents tissue with well differentiation, it is not associated with aggressive oriented cancer prognosis. %13 of endometriosis related ovarian cancers are endometrioid carcinoma and the high sensitivity of this histological type to chemotheraphy provides advantage in prognosis [42].

Paik et al. studied the endometriosis related and unrelated ovarian cancers in terms of progression and survival and compared stage, age, lymph node metastasis, Ca125 level and postoperative residue in these groups. Both progression and survival showed significantly better prognosis in endometriosis related ovarian cancers. However, there was no significant difference in terms of survival in multivariate analysis [105].

In conclusion, the association between ovarian cancer and endometriosis is not accepted as a poor prognostic factor.

Endometriosis related ovarian cancers can be diagnosed at an early stage. Association with endometriosis may have better prognosis in ovarian cancer.

7. Endometriosis and Non-Gynecological Cancers

The relationship between endometriosis and non-gynecological cancers has been shown in very few studies in the literature contrary to a large number of strong studies showing the relationship between endometriosis and ovarian carcinoma.[21, 106, 107] The most common of these are breast cancer, thyroid cancer, melanoma/non-melanoma, and non-Hodgkin's lymphoma.

7.1. Endometriosis and Breast Cancer

The relationship between breast cancer and endometriosis is still controversial due to studies reporting positive relationship,[108-110] negative relationship,[69, 111, 112] and no relationship.[21, 74, 113-115] The relationship between endometriosis and breast cancer, which was revealed in a meta-analysis by Gandini et al. in 2018, was investigated in 6000 breast cancer female patients with endometriosis. A total of 32 studies were included in the meta-analysis: 17 were cohort design, 13 were case-control studies and two were cross-sectional studies. In studies included in the meta-analysis, the endometriosis was diagnosed surgically, clinically by an expert during an outpatient examination, through scanning the hospital database and based on patients' statements in patients evaluated for infertility. According to this meta-analysis, there was no relationship between endometriosis and breast cancer. [116] In a retrospective cohort study carried out in Finland, which included a total of 49933 patients with surgically confirmed endometriosis, the risk of breast cancer was reported to be the same as in the normal population and this rate did not differ between endometriosis sub-types. Similarly, rates were found to be similar for ductal and lobular breast cancer. In this study, there was a higher risk of breast cancer particularly in the age groups of 20–29 and 30–39. According to the analysis, increased incidence of breast cancer in young ages was attributed to the fact that young endometriosis patients were extremely symptomatic and they, therefore, received frequent treatment. These treatments may cause additional risk factors for breast cancer. [114]

Data from different studies are not consistent with each other. Brinton et al. reported in their study that the risk of breast cancer was higher in patients with pelvic endometriosis compared to patients with endometriosis. [117]

Similarly, Williams et al. [108] emphasized the increased risk of in-situ breast cancer although they indicated no increase in total breast cancer rates. Mogensen et al. [118] reported an increased risk in patients with endometriosis who were older than 50 years of age. In a study by Chuang et al. investigating the data of 4884 patients with breast cancer, the risk of breast cancer was emphasized to increase significantly in patients with endometriosis and there was a need for further studies with greater population. [110]

However, in contrast to these studies, Farland et al. 119 found no increased risk of breast cancer in premenopausal or postmenopausal patients in their prospective study. Interestingly, Gemmill et al. emphasized low incidence rates for breast cancer in patients with endometriosis.

In that study, the authors suggested that the high breast cancer risk due to hormonal therapy used in patients with endometriosis might be reduced by high rates of oophorectomy. [111]

According to Savalanien et al. [114], patients with endometriosis and young patients with breast cancer may share similar risk factors. Genetic factors included in these risk factors and breast cancer genes 1 and 2 (BRCA1-2) may explain young patients with breast cancer among patients with endometriosis.[120]

No direct relationship has been found between endometriosis and breast cancer in the researchers conducted so far. Both diseases share common risk factors such as infertility, nulliparity and early menarche.

It has been further reported in the current literature that low body mass index and oral contraceptives used in patients with symptomatic endometriosis may be responsible for breast cancer in young patients. [114] Studies have reported that the increase in the rate of in situ cancer in the age range of 40-59 may be due to the more frequent application of imaging techniques for endometriosis patients over the age of 40 compared to the normal population. [108]

Estrogen hormone is held responsible for the development of breast cancer and both diseases occur when this hormone reaches higher levels.

7.2. Endometriosis and Thyroid Cancer

A total of five studies on thyroid cancer was investigated and the data obtained from four of these studies were interpreted as there was a moderate positive relationship between endometriosis and thyroid cancer,[69, 107, 117, 121] however, Melin et al. found no relationship between endometriosis and thyroid cancer in their study carried out in 2010. [69]

The complex relationship of estrogen-progesterone hormones should be considered in the development of breast cancer in the presence of endometriosis. Regular breast examinations are still applicable to all women regardless of the presence of endometriosis.

In a study by Brinton et al. where the types of cancer seen in infertile patients were investigated, the relative risk of thyroid cancer was found to be 4.65 when endometriosis was considered as the primary cause of infertility, however, the relative risk was reported as 2.89 when endometriosis was considered as the secondary cause of infertility. [117]

The increased thyroid cancer risk in patients with endometriosis can be explained by unstable estrogen metabolism and autoimmunity.[121] Estrogen can increase the invasiveness, migration and proliferation of thyroid cancer. It has been further suspected that progesterone may play a key role in the development and growth of thyroid cancer. [121]

However, the relationship between exogenous hormonal therapy and thyroid cancer has not been demonstrated yet. [122] Furthermore, thyroid peroxidase antibodies were found to be higher in patients with endometriosis compared to healthy individuals. [121,122]

Estrogen can increase proliferation, adhesion and invasion of thyroid cells under in vitro conditions.

7.3. Endometriosis, Melanoma and Other Skin Malignancies

Six of 10 studies investigating the relationship between endometriosis and melanoma were reported that there was a positive relationship between them, [21,69, 107, 111, 123], however, three studies reported no relationship [21, 117, 122] and one study reported a negative relationship.[124] In a cohort study carried out in 2014, there was a moderate risk between various colored pigmented skin lesions, nevus density, melanoma family history, and endometriosis, and it was emphasized that there was uncertainty about the underlying mechanism. [125]

A prospective study carried out in France in 2007 showed that there was a significantly increased risk of melanoma in 5959 patients with endometriosis. [126] Similarly, in an 18-year prospective study in 2017, endometriosis has been reported to have an increased correlation with all skin cancers and it has been shown that there was a higher risk of melanoma development rather than squamous cell cancer when the sub-types were taken into consideration. [123]

In a meta-analysis by Gandini et al., the relative risk between melanoma and endometriosis was found to be 1.30 in 10 independent studies examining more than 500 melanoma patients with endometriosis. Significant results were reported in only one of the four studies in basal cell carcinoma which is one of the non-melanoma skin cancer types. [116]

The relationship between endometriosis and melanoma has not yet been clarified due to the diversity of skin lesions and the apparent phenotype characteristics (e.g. white race or ginger hair) of endometriosis patients.

7.4. Endometriosis and Non-Hodgkin's Lymphoma and Other Non-Gynecological Cancer Types

In three of the five studies, a positive correlation was reported between Non-Hodgkin's lymphoma and endometriosis [21, 117, 123, 124], however, one reported a negative relationship 69 and one reported no relationship [111]. Melin et al. reported that endometriosis was a good prognostic factor for non-Hodgkin's lymphoma. [69] It has been suggested that patients with endometriosis are less exposed to human papillomavirus (HPV) due to its relationship with endometriosis and thus, the development risk of pharyngeal and oral carcinomas is reduced by 40%. Pancreatic cancer was observed to decrease in patients with endometriosis. [114-122]

8. Association Between Adenomyosis and Endometrial Cancer

Adenomyosis which is a benign gynecological disease which is characterized by the presence of endometrial gland and stroma in the myometrium and accompanied by hyperplasia and hypertrophy in the surrounding myometrium. Although malignancy occurs in approximately 1% of endometriosis cases, malignant transformation is rarer in adenomyosis. [127]Goumenou et al. demonstrated loss of cellular heterozygosity in adenomyosis for the first time.[128]

There are some clinical symptoms of endometrial adenocarcinoma in the background of adenomyosis including abnormal uterine bleeding, menorrhagia, anemia and weight loss. [129] Malignant transformation of adenomyosis usually occurs in postmenopausal women, however, it is very rare in premenopausal patients. [130] Although it has been suggested that adenomyosis associated with uterine leiomyoma and/or endometrial polyp as a precursor to malignancy, there is not enough evidence. [131,132]

Although adenomyosis has malignant features such as rapid growth, angiogenesis and invasion, progression to malignancy is rare. [129]

Genetic changes, inactivation of specific tumor suppressor genes and mutations may be effective factors. In the study of Goumenou et al., it was stated that loss of heterozygosity may be influential in the initial stages of adenomyosis. [128]

In addition, the DNA mismatch repair genes including hMSH2 and hMLH1, p16INK4 (CDKN2A, cyclin-dependent kinase inhibitor 2A) and GALT (galactose 1 phosphate uridyltransferase) genes have also been implicated in the development of adenomyosis. [128] Loss of heterozygosity in chromosome regions such as 2p22.3-p16.1 and 3p24.2-p22 which codes DNA

mismatch repair genes (hMSH2, hMLH1), may be associated with cancer predisposition in adenomyosis. [128]

Malignant transformation of adenomyosis usually occurs in postmenopausal women. However, the risk factors that cause malignant transformation are not yet clear. [133]

Furthermore, in ectopic endometrial tissue in the adenomyotic focus, bcl-2 expression decreased in contrast to normal endometrial tissue. In addition, progesterone receptor in adenomyosis shows epigenetic variation due to methylation in the promoter region. Progesterone receptor B isoform is hypermethylated in adenomyosis and its expression is decreased simultaneously. [134] Currently, malignant transformation of adenomyosis is thought to be due to endometrial epithelial transmission. It is also thought that malignant transformation may begin with the transformation of the endometrial epithelium into monolayer tumor cells. However, the specific molecular mechanisms of adenomyosis and the risk factors for malignant transformation are still unclear. [127]

Malignant transformation of adenomyosis usually occurs in postmenopausal women. However, the risk factors causing malignant transformation are not clear yet.

In summary, ovarian cancers associated with endometriosis are rare. Various molecular, immune, genetic and environmental factors have been blamed in the etiology. Risk factors include advanced age, mass size, increased estrogenic activity, increased oxidative radicals have been blamed and endometriosis surgery has been reported to minimize these risks. Epidemiological studies have often reported that endometriosis may be associated with clear cell and endometrioid type ovarian carcinoma. Although there is no clear biomarker to date, HE4 and ARID1A seems to be promising. It is thought to have a better prognosis than other EOCs because of early diagnosis. In addition, there is not a close association between endometriosis and non-gynecologic cancers.

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