



10th year
2009-2019

ENDOMETRIOSIS BULLETIN

April 2019 / Issue IX



1 in 10 Women are Affected by Endometriosis

www.endometriosis.org

PREFACE

HELLO

We are with you again with our 9th issue. Here we would like to share with you a summary of the content of this issue and inform you from the world of endometriosis. In this issue you will find national and international updates, and also news from the world of endometriosis, read recently published articles and learn about the activities we organized for Endomarch.

On 10th of January at **Sabancı Center Headquarters of Akbank** we talked about endometriosis. **Banu Kumbak Aygun, Prof. MD.** held the seminar with a great attendance. This was one of the seminars organized for our awareness project where we talk with young adults about reproductive health and endometriosis.

Our **Endo at School** project had a very productive term. Slowly we aim to visit most of the high schools in Turkey. You can find the details of this project and find our poster in this bulletin and on our website. On the 6th of February **Pinar Yalcin Bahat, MD.** gave a talk to 150 students at **SEV College**, Istanbul. On the 2nd and 30th of March **Eda Ureyen Ozdemir, MD.** held a seminar at **MEV College Ankara** for 120 students and at **Tema College Ankara** respectively. One of our board members **Umit Inceboz, Prof. MD.** held a seminar at **Ozkanlar Primary School** in Izmir with the support of **Izmir Bornova High School**. Our next seminar will be at **Robert College** in Istanbul on the 12th of April.

We organized another Endo Academy meeting for our colleagues. On the **10th of February** we held the **9th Endo Academy** meeting in **Istanbul**. With approximately 200 participants we talked about endometrioma, adenomyosis and management of deep infiltrative endometriosis. You can find details about this meeting in our bulletin.

March is worldwide endometriosis awareness month. This year as the Turkish Endometriosis & Adenomyosis Society, we started working together with international organizations. We proudly announce that this year we joined '**Worldwide Endomarch Team**' as '**Worldwide Endomarch Team-Turkey**'. In addition, our founding president **Engin Oral, Prof. MD.** has been elected as an **ambassador of World Endometriosis Society (WES Ambassadors)**.

We started our **ENDOMARCH** activities on Monday the 11th of March at **Culinary Arts Academy Istanbul** where we learned how to prepare an endometriosis friendly menu. We had two **yoga** activities. First one was on the 17th of March in Istanbul with **yoga instructor Banu Cadirci**. The second one was in Izmir with **yoga instructor Betul Acar Duyar**. On 23rd of March in **Ankara** we hiked around **Eymir Lake** followed by a brunch where we talked about endometriosis with our fellow hikers. Under **Onur Topcu, Assoc. Prof. MD.**'s leadership we organized three awareness meetings in **Ankara**; at **Health Sciences University Zekai Tahir Teaching and Research Hospital**, at **Hacettepe Communications Club** and at **Ankara University Cebeci Campus**. On Friday the 27th of March at **Baskent University Communication Faculty Aytac Tohma, MD.** gave a talk on endometriosis followed by a campus tour with 5th year medical students to raise awareness. Finally, on Saturday the 30th of March at **Samsun** a group of volunteers under **Seher Sari, MD.**'s leadership cycled for endometriosis.

We are continuing with our interviews with our international colleagues whose hearts lie in the field of endometriosis. For this bulletin we interviewed **Mr. Shaheen Khazali, MSc, MRCOG** who has been lives in **UK** and has been working in the field of endometriosis for a long time. You can find a summary of the interview and the video-link in this bulletin and on our website.

In this bulletin under the section 'Endometriosis and Other Specialties' you can find **Selcen Bahadır, MD. MSc**'s piece with the title '**Sexual Life with Endometriosis**'

A group of volunteers and patients along with **Pinar Yalcin Bahat, MD.** and our secretary **Aylin Ileri** have produced a short movie to raise awareness for endometriosis with the title '**We need to talk**'. We cordially thank **Esra Ozban** and **Derem Ciray** for filming and producing this short movie which is drawing a lot of national and international interest and support.

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



Board Members of Endometriosis&Adenomyosis Society 2018



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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 bahary186@gmail.com.

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With the support and help of our patients we produced a short documentary named 'We need to talk about endometriosis'. This short movie which we are broadcasting through our YouTube Channel has attracted a lot of national and international attention.



A SELECTED ARTICLES

1 SENSORY NERVE-DERIVED NEUROPEPTIDES ACCELERATE THE DEVELOPMENT AND FIBROGENESIS OF ENDOMETRIOSIS.

Valerie A. Flores, Arne Vanhie, Tran Dang, and Hugh S. Taylor *The Journal of Clinical Endocrinology & Metabolism*, 103(12), 4561-4568, 2018

Abstract

STUDY QUESTION: Do sensory nerves play any role in the development of endometriosis?

SUMMARY ANSWER: Sensory nerves participate in all major steps (epithelial-mesenchymal transition (EMT), fibroblast-to-myofibroblast transdifferentiation (FMT) and smooth muscle metaplasia (SMM)) in the development and fibrogenesis of endometriotic lesions.

WHAT IS KNOWN ALREADY: Endometriotic lesions are known to be hyperinnervated due to neurogenesis resulting from neutrophins secreted by endometriotic lesions and possibly platelets. These neutrophins seem to preferentially favor production of sensory neurons at the expense of sympathetic neurons.

STUDY DESIGN, SIZE, DURATION: Three independent, yet complementary, prospective, randomized mouse experimentations were conducted. A total of 143 female Balb/C mice and 24 female immunodeficient nude Balb/C mice were used. The mice were sacrificed 2 or 4 weeks after the induction of endometriosis.

PARTICIPANTS/MATERIALS, SETTING, METHODS: In Experiment 1, 21 mice were randomly divided into three groups of equal size for sympathetic denervation, sensory denervation and controls. Denervation was carried out chemically. In Experiment 2, 24 nude mice were randomly divided into three equal-sized groups: the BEFORE and AFTER groups that respectively received surgical denervation 3 days before or after the induction of endometriosis by subcutaneous grafting of human endometriotic tissues, and the Control group that received a sham surgery without denervation 3 days before induction. For Experiments 1 and 2, all mice were sacrificed two weeks after induction of endometriosis. In Experiment 3, substance P (SP) and aprepitant, a potent and selective neurokinin 1 receptor (NK1R) antagonist, were used to activate and inhibit the NK1R signalling pathway, respectively. A total of 32 mice were randomly divided into four groups of equal sizes: control (CTL), SP, Before-Induction and After-Induction. One day before the induction of endometriosis, mice in CTL, SP and Before-Induction groups were infused with sterile saline, SP and aprepitant, respectively, via Alzet osmotic pumps. Two weeks after the induction, the After-induction group was infused with aprepitant in similar fashion. All mice were sacrificed four weeks after the induction of endometriosis. In all three experiments, the bodyweight and hotplate latency were evaluated before induction and sacrifice. In addition, all lesions were excised, weighed and processed for quantification and immunohistochemistry analysis of markers for EMT, FMT and SMM, and the extent of fibrosis was evaluated by Masson trichrome staining.

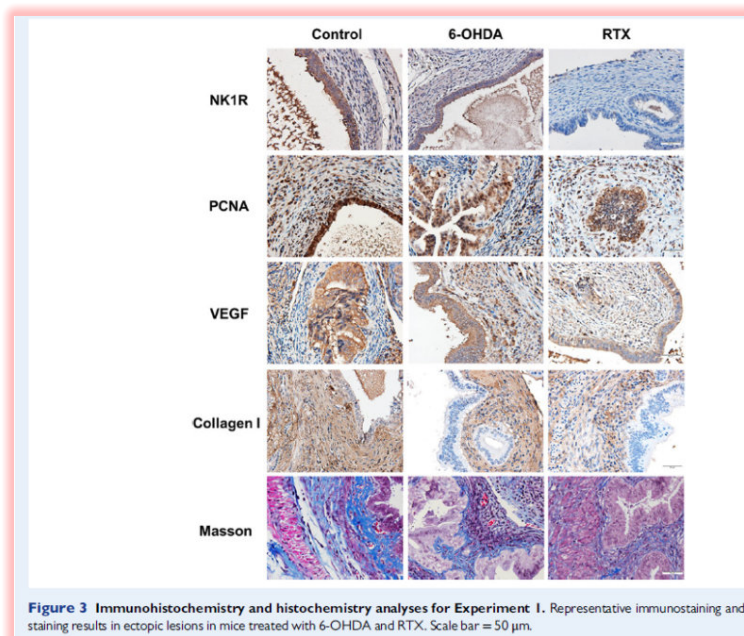


Figure 3 Immunohistochemistry and histochemistry analyses for Experiment 1. Representative immunostaining and staining results in ectopic lesions in mice treated with 6-OHDA and RTX. Scale bar = 50 μ m.

MAIN RESULTS AND THE ROLE OF CHANCE: In Experiment 1, chemical denervation of sympathetic and sensory nerves reduced the lesion weight by 43.2% (\pm 23.1%) and 68.7% (\pm 20.3%), respectively, as compared with controls. In particular, sensory denervation led to significantly greater reduction in lesion weight than sympathetic denervation. Sensory denervation also resulted in significantly improved hyperalgesia as compared with controls. In contrast, sympathetic denervation yielded only transient improvement in hyperalgesia. Both sympathetic and sensory denervation resulted in lower immunoreactivity against markers of proliferation and fibrosis, especially sensory denervation. In Experiment 2, surgical denervation before or after induction of endometriosis also decelerated the development of endometriosis, as manifested by significantly reduced lesion weight and extent of lesional fibrosis, along with improved hyperalgesia. In Experiment 3, NK1R activation by SP infusion accelerated lesional development, as evidenced by significantly increased lesional weight, more thorough progression of EMT, FMT, SMM, exaggerated lesional fibrosis and deteriorated hyperalgesia. In contrast, NK1R antagonism decelerated lesional development and improved hyperalgesia.

LARGE SCALE DATA: N/A.

LIMITATIONS, REASONS FOR CAUTION: This study is limited by the use of histologic and immunohistochemistry analyses only and the lack of molecular data.

WIDER IMPLICATIONS OF THE FINDINGS: Since sensory nerves are known to be important in wound healing and fibrogenesis, our findings

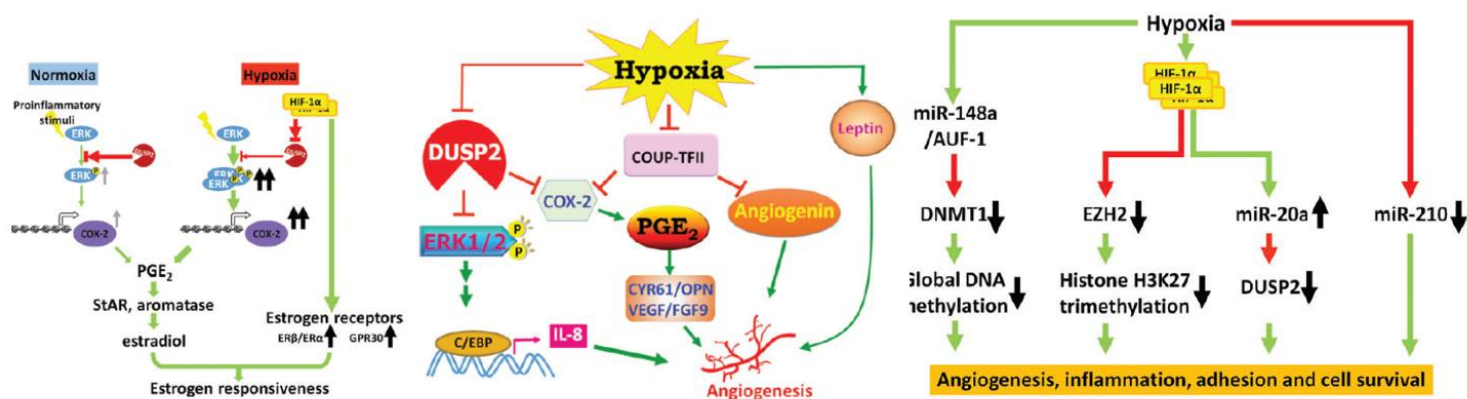
also give more credence to the notion that endometriotic lesions are wounds undergoing repeated tissue injury and repair. As such, sensory nerves or the NK1R signalling pathway in particular may be potential targets for intervention.

STUDY FUNDING/COMPETING INTEREST(S): This research was supported by Grants 81471434 (SWG), 81530040 (SWG), 81771553 (SWG), 81671436 (XSL) and 81871144 (XSL) from the National Natural Science Foundation of China and an Excellence in Centres of Clinical Medicine grant (2017ZZ01016) from the Science and Technology Commission of Shanghai Municipality. None of the authors have anything to disclose.

KEYWORDS: NK1R; denervation; endometriosis; fibrogenesis; mouse; sensory nerve; substance P

2 HYPOXIA: THE FORCE OF ENDOMETRIOSIS.

Wu MH1, Hsiao KY2, Tsai SJ3.



Abstract

AIM: Summarize recent findings of how hypoxia regulates numerous important processes to facilitate the implantation, proliferation and progression of ectopic endometriotic lesions.

METHODS: Most up-to-date evidences about how hypoxia contributes to the disease pathogenesis of endometriosis and potential therapeutic approaches were collected by conducting a comprehensive search of medical literature electronic databases. Quality of data was analyzed by experienced experts including gynecologist and basic scientists.

RESULTS: Uterus is a highly vascularized organ, which makes endometrial cells constantly expose to high concentration of oxygen. When endometrial tissues shed off from the eutopic uterus and retrograde to the peritoneal cavity, they face severe hypoxic stress. Even with successful implantation to ovaries or peritoneum, the hypoxic stress remains as a critical issue because endometrial cells are used to live in the well-oxygenated environment. Under the hypoxia condition, cells undergo epigenetic modulation and evolve several survival processes including steroidogenesis, angiogenesis, inflammation and metabolic switch. The complex gene regulatory network driven by hypoxia ensures endometriotic cells can survive under the hostile peritoneal microenvironment.

CONCLUSION: Hypoxia plays critical roles in promoting pathological processes to facilitate the development of endometriosis. Targeting hypoxia-mediated gene network represents an alternative approach for the treatment of endometriosis.

KEYWORDS: angiogenesis; epigenetics; gene regulatory network; hypoxia; steroidogenesis

3 CLINICAL DIAGNOSIS OF ENDOMETRIOSIS: A CALL TO ACTION.

Agarwal SK1, Chapron C2, Giudice LC3, Laufer MR4, Leyland N5, Missmer SA6, Singh SS7, Taylor HS8.

Abstract

Endometriosis can have a profound impact on women's lives, including associated pain, infertility, decreased quality of life, and interference with daily life, relationships, and livelihood. The first step in alleviating these adverse sequelae is to diagnose the underlying condition. For many women, the journey to endometriosis diagnosis is long and fraught with barriers and misdiagnoses. Inherent challenges include a gold standard based on an invasive surgical procedure (laparoscopy) and diverse symptomatology, contributing to the well-established delay of 4-11 years from first symptom onset to surgical diagnosis. We believe that remedying the diagnostic delay requires increased patient education and timely referral to a women's healthcare provider and a shift in physician approach to the disorder. Endometriosis should be approached as a chronic, systemic, inflammatory, and

heterogeneous disease that presents with symptoms of pelvic pain and/or infertility, rather than focusing primarily on surgical findings and pelvic lesions. Using this approach, symptoms, signs, and clinical findings of endometriosis are anticipated to become the main drivers of clinical diagnosis and earlier intervention. Combining these factors into a practical algorithm is expected to simplify endometriosis diagnosis and make the process accessible to more clinicians and patients, culminating in earlier effective management. The time has come to bridge disparities and to minimize delays in endometriosis diagnosis and treatment for the benefit of women worldwide.

KEYWORDS: chronic pelvic pain; cyclic progressive pain syndrome; diagnosis; endometriosis; infertility; pelvic pain

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.

^aMEC category 1: method can be used in any circumstances.

^bMEC category 2: method can be generally used.

Abstract

The incidence of endometriosis in middle-aged women is not minimal compared to that in the reproductive age group. The treatment of affected women after childbearing age to the natural transition toward menopause has received considerably poor attention. Disease management is problematic for these women due to increased contraindications regarding hormonal treatment and the possibility for malignant transformation, considering the increased cancer risk in patients with a long-standing history of the disease. This state-of-the-art review aims for the first time to assess the benefits of the available therapies to help guide treatment decisions for the care of endometriosis in women approaching menopause. Progestins are proven effective in reducing pain and should be preferred in these women. According to the international guidelines that lack precise recommendations, hysterectomy with bilateral salpingo-oophorectomy should be the

definitive therapy in women who have completed their reproductive arc, if medical therapy has failed. Strict surveillance or surgery with removal of affected gonads should be considered in cases of long-standing or recurrent endometriomas, especially in the presence of modifications of ultrasonographic cyst patterns. Although rare, malignant transformation of various tissues in endometriosis patients has been described, and management is herein discussed.

KEYWORDS: Perimenopause; endometriosis; endometriosis malignant transformation; endometriosis treatment; management; middle-aged women

5 DOES PRESENCE OF ADENOMYOSIS AFFECT REPRODUCTIVE OUTCOME IN IVF CYCLES? A RETROSPECTIVE ANALYSIS OF 973 PATIENTS.

Sharma S1, Bathwal S2, Agarwal N2, Chattopadhyay R2, Saha I2, Chakravarty B2.

Abstract

RESEARCH QUESTION: Reports on the effect of adenomyosis on assisted reproductive technology (ART) outcomes are conflicting. Does presence of adenomyosis affect reproductive outcome in IVF cycles in women pretreated with gonadotrophin releasing hormone (GnRH) agonist?

DESIGN: In this retrospective cohort study, 973 women were divided into four groups: only endometriosis (n=355); endometriosis and adenomyosis (n=88); adenomyosis alone (n=64); and tubal factor infertility as controls (n=466). The pregnancy outcome parameters (clinical pregnancy, miscarriage rate, live birth rate) were compared between these groups.

RESULTS: The clinical pregnancy rate was 36.62% in women with endometriosis alone, 22.72% in women with endometriosis and adenomyosis, 23.44% in women who only had adenomyosis and 34.55% in controls. Miscarriage rates were as follows: 14.62%, 35%, 40% and 13.04%, respectively. Live birth rates were 27.47% in controls; 26.48% in women with only endometriosis; 11.36% in women with endometriosis and adenomyosis; and 12.5% in women with only adenomyosis. Live birth was observed to be less in adenomyosis groups compared with controls and women with only endometriosis. No significant difference was observed in clinical pregnancy, miscarriage or live birth rate between controls and women with only endometriosis. Live birth rate was significantly different between controls and women with adenomyosis only (P=0.01) and women with endometriosis and adenomyosis (P=0.002).

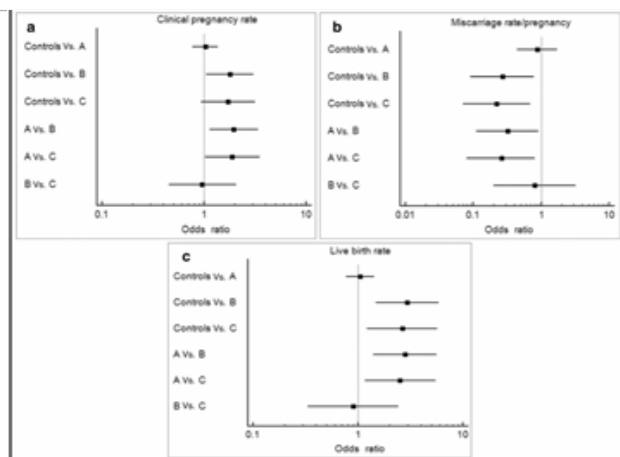


FIGURE 2 Forest plots comprising different group analysis and depicting significance of (A) clinical pregnancy rate; (B) miscarriage rate per pregnancy; and (C) live birth rate between the four groups: controls (tubal); group A (endometriosis); group B (endometriosis + adenomyosis); and group C (only adenomyosis).

CONCLUSION: Presence of adenomyosis seems to have adverse effects on IVF outcomes in clinical pregnancy rate, live birth rate and miscarriage rate. Screening for adenomyosis might be considered before ART so that the couple has better awareness of the prognosis.

KEYWORDS: Adenomyosis; Endometriosis; In-vitro fertilization; Live birth; Miscarriage

6 ACOG COMMITTEE OPINION NO. 760 SUMMARY: DYSMENORRHEA AND ENDOMETRIOSIS IN THE ADOLESCENT.

Andersen CL, Boisen MM, Sikora MJ, Ma T, Tseng G, Suryawanshi S, Vlad A, Elishaev E, Edwards Geri D, Hewitt, MD and Karen R. Gerancher, MD.

Abstract

Dysmenorrhea, or menstrual pain, is the most common menstrual symptom among adolescent girls and young women. Most adolescents experiencing dysmenorrhea have primary dysmenorrhea, defined as painful menstruation in the absence of pelvic pathology. When the patient's history suggests primary dysmenorrhea, empiric treatment should be initiated. When a patient does not experience clinical improvement for her dysmenorrhea within 3-6 months of therapy initiation, her obstetrician-gynecologist should investigate for possible secondary causes and for treatment adherence. Secondary dysmenorrhea refers to painful menses due to pelvic pathology or a recognized medical condition. Endometriosis is the leading cause of secondary dysmenorrhea in adolescents. Endometriosis should be considered in patients with persistent, clinically significant dysmenorrhea despite treatment with hormonal agents and nonsteroidal antiinflammatory drugs, particularly if no other etiology for chronic pelvic pain or secondary dysmenorrhea has been identified based on history, physical examination, and pelvic ultrasonography.

The appearance of endometriosis may be different in an adolescent than in an adult woman. In adolescents, endometriotic lesions are typically clear or red and can be difficult to identify for gynecologists unfamiliar with endometriosis in adolescents. Endometriosis in adolescents is considered a chronic disease with potential for progression if left untreated. The goals of therapy include symptom relief, suppression of disease progression, and protection of future fertility. Therapy must be individualized, and obstetrician-gynecologists should consider patient choice, the need for contraception, contraindications to hormone use, and potential adverse effects and counsel the adolescent and her family on treatment options.

B NEWS FROM OUR SOCIETY

PLANNED ACTIVITIES

EndoAcademy Meeting IX 10.02.2019 Istanbul



Summary

On Sunday February the 10th 2019 9th Endo Academy meeting took place in Istanbul with 200 participants. We broadcasted this meeting live on our society's Facebook page. Our guest of honor was **George Pistofidis MB. BS. FRCOG** from Greece.

The program started at 9 am with the first session on endometrioma under **Bulent Baysal, Prof. MD.**'s coordination. First talk was given by **Cem Demirel Prof. MD.** on the subject 'who should we operate on?'. Due to health issues our second speaker **Hakan Yarali, Prof. MD.** joined us online and talked about 'when and whom should we offer IVF?' in detail. Our 3rd speaker **Taner Usta, Assoc. Prof. MD.** explained endometriosis surgery which was followed by **Engin Oral, Prof. MD.**, who talked about the management of endometriosis on two very different patient profiles; endometriosis patient of 16 years of age and endometriosis patients of 42 years of age.

During the management of endometrioma the choice for surgery was discussed thoroughly. Factors such as the structural features of the cysts, presence of the signs of malignancy (intramural hypervascularity or nodules), a high score of ROMA serum test, a fast increase in the size of the cyst, symptomatic patients and resistance to medical treatment were considered as possible criteria for surgery. It was also stated that for patients with infertility problems surgery should never be the first choice of treatment while most of the time AMH levels fall postoperatively.

It was pointed out that several recent studies revealed that excision of endometriomas with a diameter of 1-2 cm could also stop the progression of endometriosis. However, data on this subject was still limited.

In that session it was also discussed that IVF was an effective choice for patients with low AMH levels and who had failed to conceive spontaneously. Negative effects of endometrioma on the quality of oocytes and on endometrial receptivity were pointed out. However, due to the fact that there were no randomized controlled studies on this topic, these hypotheses were not supported with significant data.

It was also mentioned that endometriosis surgery should not only be considered as endometrioma excision. Small peritoneal endometriosis loci which were negligible to the eye or deep infiltrative nodules could be the main problem. It was pointed out that similar to malignancy surgeries indocyanine green might be used to detect peritoneal endometriosis loci. Furthermore, it was also pointed out that during endometrioma excision energy modalities should be used carefully to protect ovarian reserve. They should be used to coagulate in order to avoid hematomas but there should be a fine balance so that excessive tissue damage could be avoided. Sutures and coagulant powders could also be used instead of energy modalities when suitable.

Etiology of endometriosis was discussed as well. Since recently it is hypothesized that endometriosis is triggered early in intrauterine life, starts at menarche, and 5 to 6 years following menarche the symptoms set in. It is the most common cause of dysmenorrhea in patients at the age of 16 – 18. There haven't been enough studies to conclude on the incidence among adolescents. However, it is thought that 20% of adolescents with dysmenorrhea has endometriosis. ACOG Guideline on endometriosis and dysmenorrhea in adolescents which was

published in December 2018 was mentioned as well. In this bulletin it was stated that adolescents especially starting with 16 years of age should receive medical treatment either with only progestin-only pills (POP) or with combined oral contraceptives (COC). These medications could be given until fertility wish of the patient. During the premenopausal period the main concern was malignancy risk. However, this risk percentage rose from 1,4 to 2 in the presence of malignancy criteria, so a standard endometrioma treatment would be appropriate also during this period.

The second session was about deep endometriosis and adenomyosis which was chaired by **Cem Celik, Assoc. Prof. MD. Ayse Seyhan Assoc. Prof. MD.** talked about clinical diagnosis of adenomyosis. Our guest speaker **George Pistofidis MB. BS. FRCOG** gave a talk on medical and surgical management of adenomyosis. This was followed by **Levent Senturk, Prof. MD.** who talked about management of menorrhagia caused by adenomyosis. **George Pistofidis MB. BS. FRCOG** shared with us his experience in and important steps of deep endometriosis surgery. The last talk was given by **Faruk Buyru, Prof. MD.** who talked about the usage of inositol in PCOS patients.

In this session it was stated that adenomyosis could be diagnosed with the help of a thorough anamnesis and ultrasonography. Among ultrasonography findings asymmetric endometrial wall thickness, hypervascularization, asymmetric endometrial lining and discontinuity and question mark sign are the ones that would hint to the presence of adenomyosis. Under hysteroscopy adenomyosis could present itself with cystic tumors or nodules which infiltrate towards endometrium. It was explained that in the treatment of adenomyosis and “menorrhagia” caused by adenomyosis, first line of treatment options were POPs or progestin releasing intrauterine devices. When this first line of treatment was unsuccessful then the GnRH analogues could be administered keeping in mind the side effect of bone loss. However, GnRH analogues and aromatase inhibitors still were not widely accepted treatment modalities. In addition to these medical treatment options or when there is no improvement with the above-mentioned treatment, patients who completed their family planning could be offered hysterectomy as a cure. On the other hand, patients who wish to have children may be candidates for resection. These operations can be done either by laparoscopy or laparotomy, expertise is needed and endometrial integrity should either be protected or damage should be kept to a minimum. Closure should be done with the flap technique (double or triple). During the management of postoperative pregnancies risk for uterine rupture should always be kept in mind, and patients should be thoroughly informed about the risks. Patients should receive a hysteroscopy at 3 months after surgery for a cavity control and a possible pregnancy may be allowed afterwards.

Following adenomyosis, “deep endometriosis” was discussed. It was stated that still bimanual vaginal examination and transvaginal ultrasonography (TVSUG) were the two important methods in diagnosis of deep endometriosis. Experienced physicians could identify small endometriotic nodules and could achieve views with clarity comparable to MRIs with TVUSG. The importance of a thorough informed consent of patients and patient-based decisions of colonoscopy, cystoscopy and MRI preoperatively were also discussed. During the last talk pro-ovulatory effects of inositol on PCOS patients were mentioned and mechanism with which inositol prevents gestational diabetes and related articles were discussed.

During the last session of the meeting operation videos filmed by our experienced operators were shared and interesting cases were discussed. This session was moderated by **George Pistofidis MB. BS. FRCOG.** First case was presented by **Yucel Karaman, Prof. MD.** He performed an adenomyomectomy with double flap technique on a patient with 3 failed IVF attempt despite good quality, normal embryos confirmed by PGT. The patient was still under postoperative recovery period and a control hysteroscopy was planned. This case was followed by an operation video shared by **Ahmet Kale, Prof. MD.** where a hysterectomy due to adenomyosis was initially planned. However, because of extensive intraabdominal adhesions entrance to the pararectal and paravesical spaces were necessary. These techniques along with ureter and rectal retraction techniques were explained. **Ercan Bastu, Assoc. Prof. MD.** explained a case of deep endometriosis surgery performed on a patient with persistent chronic pelvic pain. He described the vaginal nodule excision and adhesiolysis followed by a partial resection and opening an ileostomy with the use of a stapler. The last case video was presented by **Bulent Urman, Prof. MD.** He explained a case of a patient with bilateral endometriomas which turned out to be a possible borderline tumor according to the frozen pathology result where a per-operative thermal rectal damage has also been observed. The damage was primarily repaired, but a rectovaginal fistula persisted postoperatively. The operation and postoperative management of the fistula were explained in detail.

We hope that the subjects covered and the experiences shared during this meeting was useful and informative to our colleagues. We hope to see you at our next meeting.



ENDO AT SCHOOL SEV AMERICAN COLLEGE – MEV COLLEGE PRIVATE ANKARA SCHOOLS – IZMIR OZKANLAR ELEMENTARY SCHOOL



As a part of our endo at school project, we are continuing our seminars at high schools all around the country. Pinar Yalcin Bahat, MD. in Istanbul at SEV American College, Eda Ureyen, MD. in Ankara at MEV College Private Ankara Schools and Prof. Umit Inceboz, Prof. MD. in Izmir at Ozkanlar School held seminars to a total of 250 students and their families.

If you are interested in our Endo at School project and want to reach us please fill out and email us our application form which you can reach using the following link: <https://www.endometriosisdernegi.org/en/news-eng/endo-at-school>



ENDOMARCH

MARCH 11, 2019 ISTANBUL CULINARY ARTS ACADEMY (MSA)

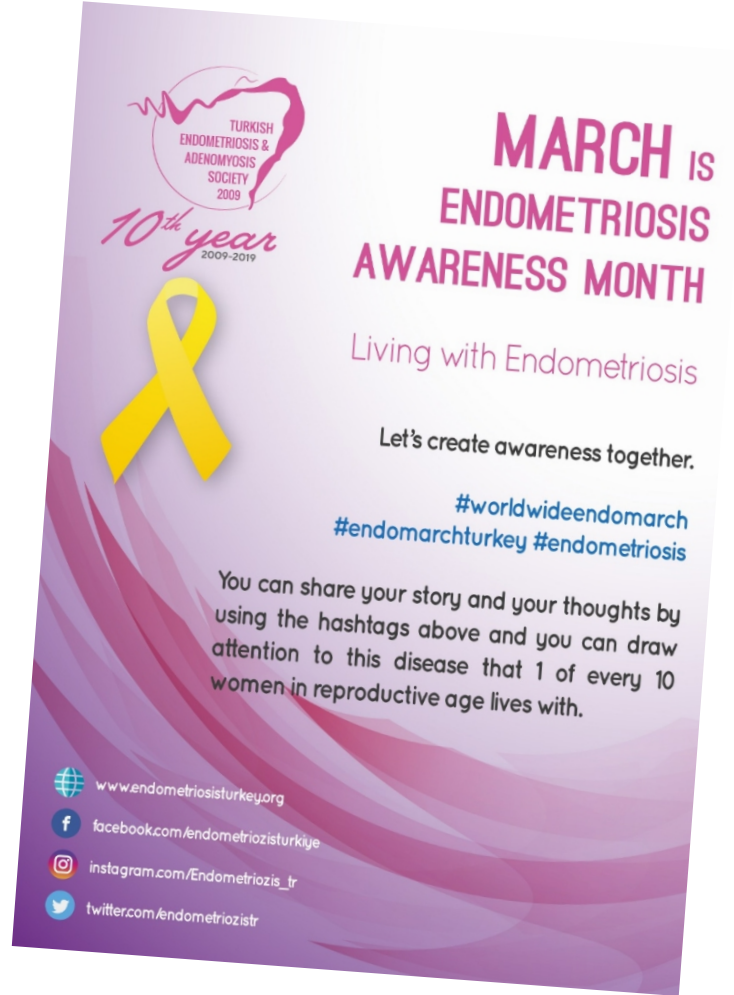
On Monday evening the 11th of March as a part of March Endometriosis Awareness Month Activities we organized our **Endo Kitchen** event at MSA in Istanbul. **Pinar Yalcin Bahat, MD.** explained the importance of nutrition for endometriosis patients. She described what an anti-inflammatory and pain-relieving diet is and which ingredients belong in that diet. With these recommended ingredients we prepared a delicious menu. We would like to thank **Istanbul Culinary Arts Academy** for their professional support.

We also would like to thank **Yucel Karaman, Prof. MD., Engin Oral, Prof. MD.** and **Taner Usta, Assoc. Prof. MD** for joining us in the kitchen.

You can find the details of "endometriosis friendly diet" on our website.

Menu:

- Broccoli Soup with Ginger
- Mediterranean Salad
- Sautéed lentils with turmeric
- Oven cooked seabass with mint gremolata and cauliflower puree
- Chai pudding





MARCH 17, 2019 YOGA IN ISTANBUL




Yoga Terapisti
BANU ÇADIRCI ile
Yoga ve meditasyon sonrası hep birlikte brunch yapıp
Endometriosis'i konuşacağımız söyleşiye
davet ediyoruz.

Yer: Maçka Parkı
Tarih: 17.03.2019
Saat: 08:30

İletişim: info@endometriosis.org

About Banu Cadirci

Participated the following certification programs:

- 500 hours of Viniyoga™ yoga instructor program with Gary Kraftsow, 2015
- 500 hours of Viniyoga™ basics with Gary Kraftsow, 2013
- 72 hours online yoga anatomy with Leslie Kaminhoff, 2012
- 200 hours of specialization in yoga with Zeynep Aksoy, 2006

She organizes yoga therapy courses for stress, anxiety, pelvic health, a better life with fibromyalgia, chakras, and illumination for heart.

On Sunday the 17th of March we organized a yoga lesson with **yoga instructor Banu Cadirci** at Cihangir Sports Club. Banu Cadirci showed yoga moves to ease pelvic pain and relax pelvic muscles. She pointed out the importance of combining our movements with our breathing. She also showed movements which can easily be done at home. We would like to thank **Taner Usta, Assoc. Prof. MD** and **Fitnat Topbas Selcuki, MD** for organizing this event and we also would like to thank Banu Cadirci for her support.



MARCH 23, 2019 EYMIR LAKE HIKE IN ANKARA

To raise awareness for endometriosis on Saturday the 23rd with the support of **Eda Ureyen, MD, Aytac Tohma, MD** and **Nilufer Akgun, MD** we organized a hike around Eymir Lake in Ankara.



MARCH 20, 2019 ANKARA ZEKAI TAHIR BURAK TEACHING AND RESEARCH HOSPITAL IN ANKARA

We organized an "awareness meeting" with the support of **Onur Topcu, Assoc. Prof. MD.** at **Zekai Tahir Burak Teaching and Research Hospital** in Ankara. During the meeting patients shared their experiences and physicians talked about the disease. We would like to thank **Yaprak Ustun, Prof. MD.** for her support.



Hastalarımızla birlikte **Endometriozisi** konuşacağımız **EndoMart** etkinliğimize sizleri bekliyoruz.



Yer: SBÜ, Ankara Dr. Zekai Tahir Burak Kadın Sağlığı Eğitim Araştırma Hastanesi, Konferans Salonu
Tarih: 20 Mart 2019
Saat: 12:30-13:30



MARCH 24, 2019 YOGA IN IZMIR

On **Sunday the 24th of March** we did yoga with yoga instructor **Betul Acar Duyar** at **Izmir Culture Park**. She gave instruction on how to ease menstruation related pain. One of our board members **Umit Inceboz, Prof. MD.** and our secretary **Aylin Ileri** joined us in this event. One of our members **Cagdas Sahin, MD.** answered questions at brunch following the yoga lesson.

About Betul Acar Duyar

A. Betul Acar Duyar born in 1967 in Istanbul, is the cofounder of Anka Yoga studio in Kusadasi. She has been a yoga instructor at Anka Yoga studio since the beginning. She is giving lessons and teaching instructor candidates about hatha yoga, yoga for pregnant and yoga for health. Her education started with 350 hours of basic yoga with Monica Munzinger followed by an internship of 350 hours of health yoga. Finally, she did a 200 hours course on yoga for pregnant women at Cihangir Yoga.



MARCH 25-27, 2019 ANKARA UNIVERSITY CEBECI CAMPUS AND HACETTEPE UNIVERSITY BUSINESS CLUB ANKARA

On Monday the 25th of March at Ankara University Cebeci Campus and at Hacettepe University Business School Campus we set up our stands to raise awareness. We thank **Onur Topcu, Assoc. Prof. MD.** and the university students for their support.

On Wednesday the 27th of March Ankara University Cebeci Campus hosted a day for endometriosis. On this beautiful day we gathered around the art house and marched around campus accompanied by a band. Our march was followed an informational meeting. We thank all the students who participated in this event and we also thank **Yaprak Ustun, Prof. MD., Onur Topcu, Assoc. Prof. MD.** and **Deniz Sezgin, Assoc. Prof.** for their support.

HACETTEPE ÜNİVERSİTESİ
SAĞLIK, KÜLTÜR VE SPOR
DİREKTÖRLÜĞÜ

endometriosis.org

Her On Kadından Birini Endometriosis

ENDO MARCH

ENDOMART

"Endometriosis Hakkında Bilinmesi Gerekenler
VE
Kadın Hastalıkları Konularında Merak Ettikleriniz"

"Endometriosis Hastalığı Farkındalık Ayı Mart!"

Prof. Dr. Yaprak Üstün

Doç. Dr. Onur Topçu

(Sağlık Bilimleri Üniversitesi Ankara Dr. Zekai Tahir Burak Kadın Sağlığı Eğitim ve Araştırma Hastanesi)

25.03.2019 - 15.00 | Mehmet Akif Ersoy
Öğretim Elemanları Salonu





EndoMart
Endometriosis Hastalığı Farkındalık Ayı

27 Mart Çarşamba
Ankara Üniversitesi Cebeci Kampüsü

Program

11:00 - 12:00
ATK Sanat Evi önünde toplanma ve bilgilendirme

12:00 - 13:00
Bando ile kampüs girişinden etkinlik alanına öğrencilerle beraber yürüyüş

13:00 - 13:30
İletişim Fakültesi MTÖ Sinema Salonu
EndoMart Endometriosis Farkındalık Toplantısı

13:00 - 13:15
Doç Dr. Deniz Sezgin
Ankara Üni. İletişim Fakültesi

13:15 - 13:30
Doç Dr. Onur Topçu
Dr. Zekai Tahir Burak Kadın Sağ. Eğt. Araş. Hastanesi Endometriosis Klinik Sorumlusu

13:15 - 13:30
Prof Dr. Mehmet Gülüm
Ankara İl Sağlık Müdürlüğü (Tensipleri Halinde)

13:15 - 13:30
Endometriosis hakkında bilinmesi gerekenler



MARCH 28, 2019 BASKENT UNIVERSITY SCHOOL OF COMMUNICATION

On Thursday the 28th of March at 11:00 we were at **Baskent University's Campus for School of Communication** with the support of **Aytac Tohma, MD.** to talk about and answer questions on endometriosis. After the seminar we walked around the campus with fifth year medical students and visited several classes to raise awareness. We thank all the participants for their support.



A poster for an endometriosis awareness event. The top part features a woman in a pink dress holding a sign that says "10 kişiden 1'iyim". The text on the poster reads "REGL SANCISI OLDUĞUNU MU DÜŞÜNÜYORSUN" and "ENDOMETRİOZİS HAKKINDA BİLİNMESİ GEREKENLER". The event is organized by Başkent Üniversitesi Hastanesi Kadın Hastalıkları ve Doğum AD. on 28 Mart 2019 at 11:00 in the Abdullah Demirtaş Toplantı Salonu.



MARCH 30, 2019 IN SAMSUN

On **Saturday the 30th of March** at Samsun a group of volunteers led by one of our members **Seher Sari, MD.** cycled to raise awareness for endometriosis. Despite of cold weather many joined us for this event. We thank everyone for their interest and support.



MART
ENDOMETRİOZİS
FARKINDALIK AYIDIR

ENDOMETRİOZİS
(ÇİKOLATA KİSTİ HASTALIĞI)
için
pedal çeviriyoruz

Tarih: 24 Mart Pazar
Saat: 16:00
Yer: Çobanlı iskelesi
SAMSUN

www.endometriosis.org
facebook.com/endometriozisturkiye
instagram.com/Endometriozis_tr
twitter.com/endometriozistr



© NEWS FROM THE WORLD OF ENDOMETRIOSIS

WES AMBASSADOR (PROF. ENGIN ORAL, MD.)

We hereby proudly announce that our founding president and the active president of European Endometriosis League (EEL) Prof. Engin Oral, MD has been elected as an Ambassador of World Endometriosis Society.



About · News · Endometriosis · World Congress · Membership · Research · Resources

— Ambassadors



ORAL Engin

- Professor of Obstetrics and Gynaecology, Istanbul, Turkey
- President, European Endometriosis League

Professor Engin Oral MD is a reproductive endocrinologist and a gynaecologic surgeon. He has been working in the field of obstetrics and gynaecology since 1993. His main areas of expertise are: in-vitro fertilization, infertility,

EEL



5TH European Congress on Endometriosis which will take place in Prague this year. Details will be published online soon.
<https://www.eec2019.com/>

SEUD 2019



You can find the details of this congress which will take place in Montreal Canada by using the following link:
<http://seud.org/scientific-program-2019/>

ESHRE CAMPUS 2019

You can find the details of Eshre Campus Workshop on Deep Endometriosis which will take place in Munster under the following link:
<https://www.eshre.eu/Education/Calendar-Campus-events/Deep-endometriosis/Programme>



Deep endometriosis – from pathophysiology to clinic

ASIAN CONFERENCE ON ENDOMETRIOSIS

The details of the 8th Asian Conference on Endometriosis can be reached using the following link:
<https://www.ace2019thailand.com/>



WES 2020



For further information on World Congress on Endometriosis
<http://endometriosis.ca/world-congress/wce2020/#2>

D INTERVIEW WITH AN 'ENDO SPECIALIST'

Interview with Mr. ShaheenKhazali, MSc, MRCOG



A short curriculum vitae

Mr. Khazali has a worldwide reputation in his expertise in laparoscopic and hysteroscopic surgery especially in the field of endometriosis. He is the director of CEMIG (Centre for Endometriosis and Minimally Invasive Gynecology) at Ashford and St Peter's Hospitals NHS Foundation Trust in Surrey, one of the busiest endometriosis centers in the UK, accredited by the British Society for Gynecological Endoscopy (BSGE). He frequently travels to Iran and teaches about endometriosis surgery. He started his specialty training at John Radcliff Hospital, Oxford, having spent his basic training in London and Cambridge. He holds a Master's Degree in Advanced Gynecological Endoscopy from the University of Surrey where he still is a faculty member.

Hello Mr. Khazali. I, BaharYuksel am a member of Turkish Endometriosis & Adenomyosis Society. First of all, I would like to thank you for kindly accepting to do this interview.

Could you please tell us about yourself and your experience in the field of endometriosis?

I am a specialist in obstetrics and gynecology. However, currently I only care for endometriosis patients in UK at Surrey. I also visit Tehran often where I teach about endometriosis surgery.

Why did you choose to specialize in endometriosis?

This is a very interesting question. I think I was very fascinated by the endometriosis cases I saw during residency. I had a chance to meet and watch advanced endometriosis surgeons in Cambridge and thus I was infected. During the first year of my residency I was already thinking about becoming an endoscopic surgeon. As the years passed I decided to learn endoscopic surgery in the field of endometriosis. Afterwards it has become a selfish act. I was doing what I loved the most. You have to find what makes you happy at work and you should work on that. Some surgeons prefer a routine. They prefer the same course of events day after day. This makes them feel safe. However, I think I like to challenge my capabilities. Of course, this comes with a toll. You have to deal with complications and long operations.

So, what is the most challenging part? Is it diagnosis, management, dealing with patients' psychology or is it the surgery itself?

Surgery is probably the third most challenging part when dealing with endometriosis. The hardest part is to make a decision. There are a lot of things which we do not understand about this disease, so it is hard to put the pieces together and decide what to do next while explaining everything to the patient. Each patient is like a puzzle. Each one has a different need and so it is hard to solve the problem. The other challenge is the management of chronic pelvic pain when you cannot visualize endometrioma or endometriosis loci preoperatively. Surgery does not necessarily relieve pain. Thus, management of these patients are the second most challenging part of endometriosis. And of course, the third most challenging part is the surgery itself and the postoperative back pain the surgeon suffers from.

How do you manage endometriosis in adolescents in your daily clinical life?

The management is not that different. The approach to pelvic pain in adolescents is very similar; first you listen to the patient. You ask how this pain affects their daily life. The only difference is that the effect of pain could be more dramatic in adolescents, because the pain affects their school attendance, their university choice, choice of a career and thus their course of life. Also, you do not want to operate on a 16-year-old patient with bilateral endo and reduce her ovarian reserve. As to summarize the answer to your question the principle and logic of management in adolescents is very similar to adults.

For my final question, what do you think about the ENZIAN classification? Do you use it in your daily practice? What were your inputs in this classification?

There is a conflict of interest on this topic. Because I am developing a similar classification myself. It is like classification for cancer. During my research in this field I have realized that we are underestimating endometriosis. What I am trying to say is that when we are making these classifications we assume that the stage of the disease correlates with pain, but it is not always the case with endometriosis. I believe that a good classification should describe the disease like a painting. ENZIAN lets us picture the disease in detail, so I think that it is a good classification modality. It is easily applicable once you get used to it. However, it needs improvement so that it can be used worldwide and thus physicians around the world can speak the same language.

Thank you so much for everything ...

Interview with Mr. ShaheenKhazali, MSc, MRCOG



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

Comparison of the effect of isotretinoin and alitretonin 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.
Gynecol Endocrinol. (pp)2019.(on press)

OBJECTIVE

To compare the effects of alitretonin and isotretinoin 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 isotretinoin 10 mg/kg per day for 10 d, group 3: rats receiving po isotretinoin 20 mg/kg per day for 10 d and group 4: rats receiving po alitretonin 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 isotretinoin on endometriosis. However, alitretonin (potent retinoid) does not have potent regressive effect on endometriotic implants as in isotretinoin.

KEYWORDS:

Alitretonin; VEGF; endometriosis; isotretinoin; retinoid

Association between endometriosis, headache, and migraine

Burcin Karamustafaoglu Balci, Zehra Kabakci, Damla Y Guzey, Bartu Avci, Murathan Guler, Erkut Attar
Journal of Endometriosis and Pelvic Pain Disorders, 2019,2284

Introduction:

Available data suggest that there is an association between endometriosis and a group of disorders including autonomic nervous system irregularities. A deeper understanding of relationship between endometriosis and autonomic nervous system is needed as it may lead to novel discoveries on the causes or consequences of endometriosis. In this study, we analyzed the prevalence of migraine in patients with endometriosis.

Methods:

In this cross-sectional study, medical records of women were reviewed through January 2013 to December 2017. Women with laparoscopically proven endometriosis (n = 185) were compared with those without endometriosis (n = 168). The 3-item screening questions (ID Migraine™) test was used to screen migraine. Data were analyzed using SPSS v25 (IBM Corporation). The χ^2 test was used for analyzing the nominal parameters and group comparisons. Pearson χ^2 was used to study the association between endometriosis and migraine.

Results:

The mean age was 31.86 ± 4.49 years of the endometriosis group and 28.95 ± 5.11 years of the controls ($p = 0.408$). The two pre-screening questions of ID Migraine test were answered positively by 86 patients of the endometriosis group (75.4%) and by 53 patients of the control group (54.6%) ($p = 0.001$). Of these patients, 51 (44.7% of endometriosis group) and 26 (26.8% of control group) were diagnosed as having migraine using 3-item Migraine questionnaire ($p = 0.007$).

Conclusion:

This study showed that the prevalence of migraine was significantly higher in patients with endometriosis. Because there is a strong correlation, patients with endometriosis should be screened for headache and migraine to increase the benefits of care.

HOXA-10 gene expression in ectopic and eutopic endometrium tissues: Does it differ between fertile and infertile women with endometriosis?

Özcan, C., Özdamar, Ö., Gökbayrak, M. E., Doğer, E., Çakıroğlu, Y., & Çine, N.
European Journal of Obstetrics & Gynecology and Reproductive Biology, 2019, 233, 43-48

Objective To compare HOXA-10 gene expression in eutopic endometrium samples, between fertile and infertile endometriosis patients and the fertile control cases, and in endometrium and endometrioma specimens, between severe and moderate endometriosis cases.

Study Design Prospective clinical study included women without infertility and endometriosis (Group 1); women without infertility but with endometrioma (Group 2); and infertile women with endometrioma (Group 3). In addition, the Group 2 and 3 cohort were assessed based on the findings obtained during laparoscopy, based on the (rAFS) scoring, as women with a rAFS score of 16–40 were evaluated in Group A, whereas those with rAFS score above 40 were considered in Group B. HOXA-10 gene expression was evaluated in both secretory endometrium tissue and endometrioma specimens.

Results Eutopic endometrium samples from group 2 (reference gene = 0,680 vs. target gene = 0,362) and group 3 (reference gene = 0,641 vs. target gene = 0,183) patients revealed a 1,871-fold and 3,509-fold decrease in HOXA-10 gene expression, respectively, as compared to group 1. Endometrial HOXA-10 gene expression was 1,778-fold down-regulated in group 3 women (reference gene = 1,510 vs. target gene = 0,850), when compared to group 2. Both eutopic endometrium and endometrioma tissue samples from severe endometriosis patients revealed 1,259-fold (reference gene = 1,523 vs. target gene = 1,210) and 1,338-fold (reference gene = 1,274 vs. target gene = 0,952), down-regulation in HOXA-10 gene expressions, respectively, as compared to moderate cases.

Conclusion Endometrial HOXA-10 gene expression in women with endometriosis is significantly down-regulated than in those without endometriosis. Endometriosis patients with infertility have significantly lower levels of endometrial HOXA-10 gene expression than endometriosis without infertility; thus decreased expression of this gene may, directly or indirectly, be related with the endometriosis-associated infertility. Severe endometriosis cases express, in their both endometrium and endometrioma tissues, significantly lower levels of HOXA-10 gene than moderate endometriosis cases.

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, 2019, 1-8.

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.

The prognostic significance of stage I ovarian clear cell and endometrioid carcinomas arising from endometriotic cysts: is it a myth?

Ayhan, A., Akilli, H., & Haberal, N
Archives of gynecology and obstetrics, 299(1), 2019, 217-222

Abstract

PURPOSE: The aim of this study was to determine the clinicopathologic features and the prognostic significance of Stage I ovarian clear cell and endometrioid carcinomas arising from endometriotic cysts.

MATERIALS AND METHODS: Patients with either Stage I ovarian clear cell or endometrioid carcinoma were divided into three groups. *Group 1: Patients with cancers arising from endometriotic cysts *Group 2: Patients with ovarian and pelvic endometriosis *Group 3: Patients without endometriosis Patient characteristics (overall survival and disease-free survival) were compared between groups.

RESULTS: Of the 78 patients who participated in this study, 39 were in group 1, 13 were in group 2, and 26 were in group 3. The mean age in groups 1, 2, and 3 were 46 years, 54 years, and 48 years, respectively ($p = 0.39$). Tumoral characteristics, including capsule rupture, positive cytology, grade, and the presence of synchronous endometrial cancer were similar in both groups. The 5-year overall survival rate in groups 1, 2, and 3 were 100, 90, and 93%, respectively ($p = 0.4$). Moreover, the recurrence rates did not differ significantly between groups. Furthermore, subgroup analysis of clear cell carcinoma and endometrioid adenocarcinoma separately showed no effect of endometriosis on disease-free survival (DFS) or overall survival (OS).

CONCLUSION: Clear cell or endometrioid ovarian carcinoma arising from ovarian and/or pelvic endometriosis shares the same clinicopathologic characteristics with their counterparts that do not arise from endometriosis and patients have similar overall and disease-free survival.

KEYWORDS: Endometriotic cyst; Gynecologic oncology; Prognosis; Stage I EOC

Metabolomics analysis of follicular fluid in women with ovarian endometriosis undergoing in vitro fertilization

Karaer, A., Tuncay, G., Mumcu, A., & Dogan, B
Systems biology in reproductive medicine, 2018, 1-9.

Abstract The purpose of this study was to investigate whether a change in the follicular fluid metabolomics profile due to endometrioma is identifiable. Twelve women with ovarian endometriosis (aged <40 years, with a body mass index [BMI] of <30 kg/m²) and 12 age- and BMI-matched controls (women with infertility purely due to a male factor) underwent ovarian stimulation for intracytoplasmic sperm injection (ICSI). Follicular fluid samples were collected from both of groups at the time of oocyte retrieval for ICSI. Next, nuclear magnetic resonance (NMR) spectroscopy was performed for the collected follicular fluids.

The metabolic compositions of the follicular fluids were then compared using univariate and multivariate statistical analyses of NMR data. Univariate and multivariate statistical analyses of NMR data showed that the metabolomic profiles of the follicular fluids obtained from the women with ovarian endometriosis were distinctly different from those obtained from the control group. In comparison with the controls, the follicular fluids of the women with ovarian endometriosis had statistically significant elevated levels of lactate, β -glucose, pyruvate, and valine. We conclude that the levels of lactate, β -glucose, pyruvate, and valine in the follicular fluid of the women with endometrioma were

higher than those of the controls. Abbreviations: ASRM: American Society for Reproductive Medicine; BMI: body mass index; CPMG: Carr-Purcell-Meiboom-Gill; E2: estradiol; ESHRE: European Society of Human Reproduction and Embryology; ERETIC: electronic to access in vivo concentration; FF: follicular fluid; FSH: follicle-stimulating hormone; hCG: human chorionic gonadotropin; HEPES: 2-hydroxyethyl-1-piperazineethanesulfonic acid; ICSI: intracytoplasmic sperm injection; IVF: in vitro fertilization; NMR: nuclear magnetic resonance spectroscopy; PCA: principal component analysis; PCOS: polycystic ovary syndrome; PLS-DA: partial least squares discriminant analysis; ppm: parts per million; PULCON: pulse length-based concentration determination; TSP: 3-(trimethylsilyl)-1-propanesulfonic acid sodium salt; VIP: variable importance in projection.

KEYWORDS: fertilization; Endometrioma; infertility; metabolomics; nuclear magnetic resonance

The prognostic significance of stage I ovarian clear cell and endometrioid carcinomas arising from endometriotic cysts: is it a myth? The Endobiota Study: Comparison of Vaginal, Cervical and Gut Microbiota Between Women with Stage 3/4 Endometriosis and Healthy Controls.

Ata, B., Yildiz, S., Turkgeldi, E., Brocal, V. P., Dinleyici, E. C., Moya, A., & Urman, B
Scientific Reports, 9(1), 2019, 2204.

Dysbiosis in the genital tract or gut microbiome can be associated with endometriosis. We sampled vaginal, cervical and gut microbiota from 14 women with histology proven stage 3/4 endometriosis and 14 healthy controls. The V3 and V4 regions of the 16S rRNA gene were amplified following the 16S Metagenomic Sequencing Library Preparation. Despite overall similar vaginal, cervical and intestinal microbiota composition between stage 3/4 endometriosis group and controls, we observed differences at genus level.

The complete absence of Atopobium in the vaginal and cervical microbiota of the stage 3/4 endometriosis group was noteworthy. In the cervical microbiota, Gardnerella, Streptococcus, Escherichia, Shigella, and Ureoplasma, all of which contain potentially pathogenic species, were increased in stage 3/4 endometriosis. More women in the stage 3/4 endometriosis group had Shigella/Escherichia dominant stool microbiome. Further studies can clarify whether the association is causal, and whether dysbiosis leads to endometriosis or endometriosis leads to dysbiosis.

Does the anti-Müllerian hormone truly reflect ovarian response in women with endometrioma?

Inal, Z. O., Engin Ustun, Y., Yilmaz, N., Aktulay, A., Bardakci, Y., & Gulerman, C.
Journal of Obstetrics and Gynaecology, 2019,1-6.

Abstract

In this study, our aim was to determine which factor is more correlated with the number of oocytes retrieved in patients with endometrioma compared with controls undergoing in vitro fertilisation-intracytoplasmic sperm injection (IVF-ICSI) cycles: antral follicle count (AFC) or anti-Müllerian hormone (AMH). A total of 60 women with endometrioma and a control population of 60 women without endometrioma in the same period were randomly selected underwent the injection IVF-ICSI treatment.

No significant differences were found between the groups in terms of age (28.78 ± 3.49 vs. 29.52 ± 2.47 , $p = .187$), body mass index (23.62 ± 2.05 vs. 23.91 ± 2.11 , $p = .449$), duration of infertility [(3 (2-4) vs. 3 (2-3), $p = .139$)], AMH level (1.52 ± 0.51 vs. 1.32 ± 0.92 , $p = .133$), duration of stimulation [(9 (9-10) vs. 10 (9-10), $p = .135$)], total gonadotropin dose [(2750 (2262.5-3337.5) vs. 2770 (2680-3562.5), $p = .125$)], endometrial thickness [(10 (10-11) vs. 10 (9-11), $p = .463$)], fertilisation rates (67.20 ± 18.04 vs. 62.28 ± 17.13 , $p = .123$), grade I embryo (43.3% vs. 30%, $p = .185$), clinical pregnancy rates (40% vs. 26.7%, $p = .123$), and the perinatal outcomes between the groups. The AFC was higher in the controls than in those with endometrioma (9.20 ± 1.80 vs. 6.32 ± 2.04 , $p < .001$).

The number of oocytes retrieved was also higher in the controls than in those with endometrioma [(7 (6-8) vs. 4 (4-5.75), $p < .001$)]. We found that women with endometrioma had a significantly lower number of oocytes retrieved than the controls despite the same AMH levels in both groups. AFC is a better marker of ovarian response than AMH in women with endometrioma undergoing IVF-ICSI. Impact statement What is already known on this subject? Utilising the ovarian reserve is important in the success of ovarian stimulation and in evaluating the success of assisted reproductive technologies.

The anti-Müllerian hormone (AMH) level and the antral follicle count (AFC) are widely used in the prediction of ovarian functional reserve and response. However, no perfect marker exists in the evaluation of ovarian reserve and ovarian response. What do the results of this study add? Our study demonstrated that women with endometrioma have a significantly lower number of oocytes retrieved than the controls, despite the same AMH levels in both groups; which strongly suggests that AFC is a better reflection of ovarian response than AMH in women with endometrioma undergoing an in vitro fertilisation-intracytoplasmic sperm injection (IVF-ICSI). What are the implications of these findings for clinical practice and/or further research? This important issue has been reviewed and discussed for years, however, the conclusions are still controversial. Additional research is needed to understand which ovarian reserve test could better predict ovarian response outcome?

Abdominal wall endometriosis: A monocentric continuous series and review of the literature

Goksever Celik, H., Karacan, T., Kaya, C., Uhri, M., Savkli, A. O., Yalcin Bahat, P. Oral, E. (2019). Journal of Endometriosis and Pelvic Pain Disorders, 2019, 3.

Abstract

Introduction: Endometriosis is characterized by the presence of endometrial cells anywhere outside the uterine cavity. Endometriosis has been encountered on surgical scars especially resulting from a cesarean section recently. Our aim was to investigate the patients with abdominal wall endometriosis in our clinics where all the patients having this disease are managed via surgical resection. We also compared them with the patients presented in the literature.

Methods: A study was conducted on the patients with histopathological diagnosis of abdominal wall endometriosis as a case series. All the subjects were analyzed through a comprehensive medical assessment including documentation of the detailed history and physical and gynecological examination based on the patients' medical records.

Results: A total of 53 patients diagnosed with abdominal wall endometriosis were included in this study. The mean age and the mean body mass index of the patients were 32.6 ± 6.5 years and 25.2 ± 3.5 kg/m², respectively. A total of 49 patients had at least one operation history, mainly cesarean section. The most common sites for abdominal wall endometriosis were skin and the region containing the rectus abdominis muscle and rectus sheath, 56.6% and 18.9% respectively. The main symptom was the pain getting worse during menstruation and the presence of a mass in all patients. The main diagnostic tools in all patients were detailed history and physical examination, ultrasonography, and then histopathological confirmation after surgical excision.

Conclusion:

Abdominal wall endometriosis is a common diagnosis mainly due to increased cesarean section rate. Clinical suspicion has the most important place in correct diagnosis and management of abdominal wall endometriosis.

F ENDOMETRIOSIS AND OTHER SPECIALTIES



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A short curriculum vitae

TED American College 1998, Baskent University 2004, Ankara Zekai Tahir Burak 2010.

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Endometriosis and Sexuality

Sexuality is a basic and irreplaceable part of being human. It affects physical and psychological health and also quality of life. In women it has a positive impact on psychology, feeling feminine and also improves the satisfaction in a relationship. Sexuality is a phenomenon which is influenced by psychosocial (personality, experience, belief, habits) and physical factors. Our focus, endometriosis, is most commonly seen in young, sexually active women and affects one out of ten, so one can conclude that it is an important factor in sexual dysfunction. Thus, when an endometriosis patient is examined not only symptoms such as pelvic pain but also sexual behavior should be taken into consideration and should be taken into account in management planning. Many aspects of a patient's life with advanced endometriosis is affected. Along with restoring the physical health of a patient psychological support should also be offered in order to maintain psychological health.

Sexual dysfunction of women can be examined under desire, arousal problems, orgasm dysfunctions and dyspareunia. Sexual dysfunction of women is also a common problem in society. Psychiatric and psychological problems, chronic diseases, endocrinological problems, medication, gynecological disorders like previous vaginal operations, endometriosis, myoma uteri and pelvic inflammatory disease could be the underlying causes of sexual dysfunction.

In 2013 American Psychiatric Association published DSM-V (Diagnostic and Statistical Manual of Mental Disorders – V) where they included a new section on 'Genito-pelvic Pain/Penetration Disorder'. They included vaginismus, dyspareunia and vulvodynia under this section. They aimed to consider sexual pain disorders under a broader and inclusive perspective.

According to the new diagnosis criteria of penetration disorder along with pelvic muscle contractions, dyspareunia, anxiety or fear of penetration are also considered as assessment factors. For diagnosis of Genito-pelvic Pain/Penetration Disorder at least one of the following conditions should exist for at least 6 months or at least one of the following conditions should be repetitive. These conditions are as follows; penetration failure, vulvovaginal or pelvic pain during penetration (dyspareunia), anxiety or fear of dyspareunia or penetration and pelvic muscle tension during penetration.

Endometriosis is the most common cause of deep dyspareunia. Deep dyspareunia as the name hints is described as the pain which is caused by deep vaginal penetration. It suggests the existence of a chronic gynecological or organic problem rather than a psychological one. On the other hand, superficial dyspareunia is the pain felt during penetration of vaginal introitus or vulva. Psychological or organic factors can both be the underlying reasons. According to several studies 28% of the cases dyspareunia is the primary symptom with which endometriosis patients seek a physician's opinion. 61% of endometriosis patients suffer from dyspareunia and 54% avoid sexual intercourse because of this reason. Dyspareunia may cause a negative approach and lead to less frequency of sexual intercourse. Patients may avoid having sex and this may lead to anxiety. Due to these reasons problems in the relationship may arise. Patients may lose self-confidence and their quality of life may be negatively affected.

In comparison to the general population dyspareunia rate is 9 times higher in women with endometriosis. 60-70% of patients with endometriosis who had previous surgery for endometriosis, and 50-90% of patients with endometriosis receiving medical therapy have dyspareunia. Although dysmenorrhea is the most common symptom in endometriosis it is mostly menstruation-related. However, dyspareunia is experienced at each sexual intercourse and thus, it is a great disappointment to the patient. The experience of pain at each intercourse leads to a defect in sexual cycle, because pain does not allow sexual satisfaction. Anticipation of pain decreases the libido which in return decreases the lubrication of the vagina which leads to a hypertonus of the pelvic muscles and mechanic trauma of vestibular mucosa and urethral meatus, and increases the resistance against penetration. Tripoli et al. have shown that all these factors lead to sexual aversion and vaginismus.

For patients with endometriosis dyspareunia is not "the only" problem. 2/3 of the patients suffer from sexual dysfunction as stated above. Dyspareunia has negative effects on the sexual cycle which leads to a decrease in sexual desire, lubrication, problems of orgasm and sexual satisfaction. It is thought that as a result of the pain the patient feels at each intercourse there is an increase in the anticipation of pain which leads to a decrease in sexual desire and repetition of such an experience produces a negative self-schema which results in a dysfunctional sexual life. Although patients start sexual intercourse, they might ask for a change in position or disrupt the intercourse because of pain. However, due to a feeling of guilt or fertility desire, they might endure the intercourse despite of pain.

Pressure of endometriotic nodules on uterosacral ligaments, on Douglas, infiltration of subperitoneal or visceral nerves, inelastic traction of parametrium and immobilization of pelvic structures are the causes of dyspareunia. In addition, there is an association between deep infiltrative endometriosis and neuropathic pain like hyperalgesia. Neuropathic pain can either be caused by destruction of the nerve endings or can be caused by anti-inflammatory mediators such as histamine, TNF α , NGF, prostaglandins, serotonin, interleukine-1 leucocytes, macrophages and mast cells which are synthesized and released from endometrial lesions. These substances cause local neurogenesis and increase sensitivity which leads to hyperalgesia. Despite the size and pressure caused by the nodules this neurogenesis can augment pain. Deep infiltrative endometriosis is seen in 20% of the cases and 2/3 of these patients experience deep dyspareunia. Dyspareunia has been reported in 90% of cases with infiltration of uterosacral ligaments, 42% of cases with bladder invasion, 40% of cases with adnexal adhesions, 27% of cases with colon infiltration and 25% of endometrioma cases. Presence of vaginal nodules and uterosacral ligament infiltration cause neuronal invasion and nodular pressure which lead to pain. Thus, in this group of patients a severe form of sexual dysfunction is observed. When group of patients with rectovaginal endometriosis are compared to the control group

three times increase in sexual dissatisfaction and two times decrease in intercourse frequency and orgasm has been reported. According to multivariable analysis stage 3-4 (according to ASRM) endometriosis patients are associated with a higher rate of sexual dysfunction.

Along with pain and decreased intercourse frequency, endometriosis patients experience less sexual desire and orgasm. Hypoactive sexual desire is seen 45% of endometriosis patients. Presence of pain is a strong inhibitory factor on sexual desire. It has been statistically proven that a reduced frequency of sexual intercourse decreases sexual satisfaction and increases sex related stress. Especially a desire to reproduce causes emotional problems as a woman ages. Fertility strategies disrupts the spontaneity of sexual cycle and thus decreases sexual desire. Due to the anticipation of pain patients start avoiding sexual intercourse all together. When a patient develops negative thoughts on self-reflection, a feeling of guilt and inadequacy in the relationship, these negative thoughts can damage the relationship. Furthermore, in endometriosis patients there is a tendency to develop psychological disorders. Chronic pelvic pain has especially been associated with depression and anxiety. When infertility problems are added the toll on the psychological status can be severe. It is not correct to tie sexual dysfunction only to organic damage, psychological and social status should also be evaluated.

Dyspareunia seen almost in 66% of the cases is one of the most important components of treatment. While gynecologists are the first in line physicians from whom a patient seeks help, it is our responsibility to assess sexual cycle and pain related sexual dysfunction. Questionnaires or scales to assess sexual health should be used, thought, emotions, symptoms and questions related to sexual health should be discussed and patients should be questioned in a way which allows a patient to speak freely. When designing a treatment plan sexual dysfunction should not be neglected and if needed a specialist should be consulted. A therapist specialized in psychosexual psychology should evaluate the patient's psychologic, sociologic and cultural take on a relationship and this specialist should be a part of the treatment team. Patient's quality of life should be increased by working on issues such as self-confidence, self-image, quality of, and expectations from a relationship.

The main goal in the treatment of endometriosis is to ease pelvic pain, increase the quality of life and to provide psychological support. The decision of treatment modality especially in restoring sexual function should be taken with the patient, because especially the treatment of deep infiltrative endometriosis surgically has a lot of risks. Furthermore, although a quick recovery can be achieved with surgery, dyspareunia can return in time. It has been observed that restoration of pelvic anatomy and excision of endometriosis nodules with radical surgery lead to a decrease in dyspareunia and an increase in sexual frequency, desire and orgasm at 12th month postoperatively. However more research is needed to evaluate if this positive impact on the symptoms are long-term.

An answer to hormonal treatment is seen later than surgery, but the treatment effects last throughout the course of the treatment. When choosing the medical treatment option, it should be kept in mind that one third of the patients discontinue their medication and there is also an incompliance to treatment in the group of patients with reproductive desires. Furthermore, although these medications have a positive effect on dyspareunia they decrease a patient's libido. Especially GnRH analogues in comparison to other hormone replacement therapies show their effects on dyspareunia and pelvic pain faster, but due to their hypoestrogenic effects their long-term usage is not advisable. In a study conducted by Vercelli et al. on patients with deep dyspareunia the effects of surgery and low dose norethisterone has been compared. Both treatment modalities have revealed similar effects on sexual function, psychologic well-being and quality of life 1 year postoperatively. Same group in a different study have reported a higher rate of sexual pain disorders at 1 year postoperatively. According to Ferrero et al. best results have been obtained with a combination of surgery followed by medical treatment. More studies are needed to evaluate surgery and adjuvant pharmacological treatment. Female sexuality is a multifactorial, complex and psychological mechanism. Pain associated with endometriosis is affected by not only organic factors but more. Patient's personality, coping capacity, closeness in the relationship, support level of the partner, harmony in the marriage and medical treatment, these factors all have an impact on pain perception. As a summary dyspareunia is not only a pain symptom. It should be evaluated thoroughly keeping in mind the relationship status, psychologic well-being, sexual function and general health of the patient.

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Article Full texts uploaded by **Hale Goksever Celik, Assoc. Prof. MD**.

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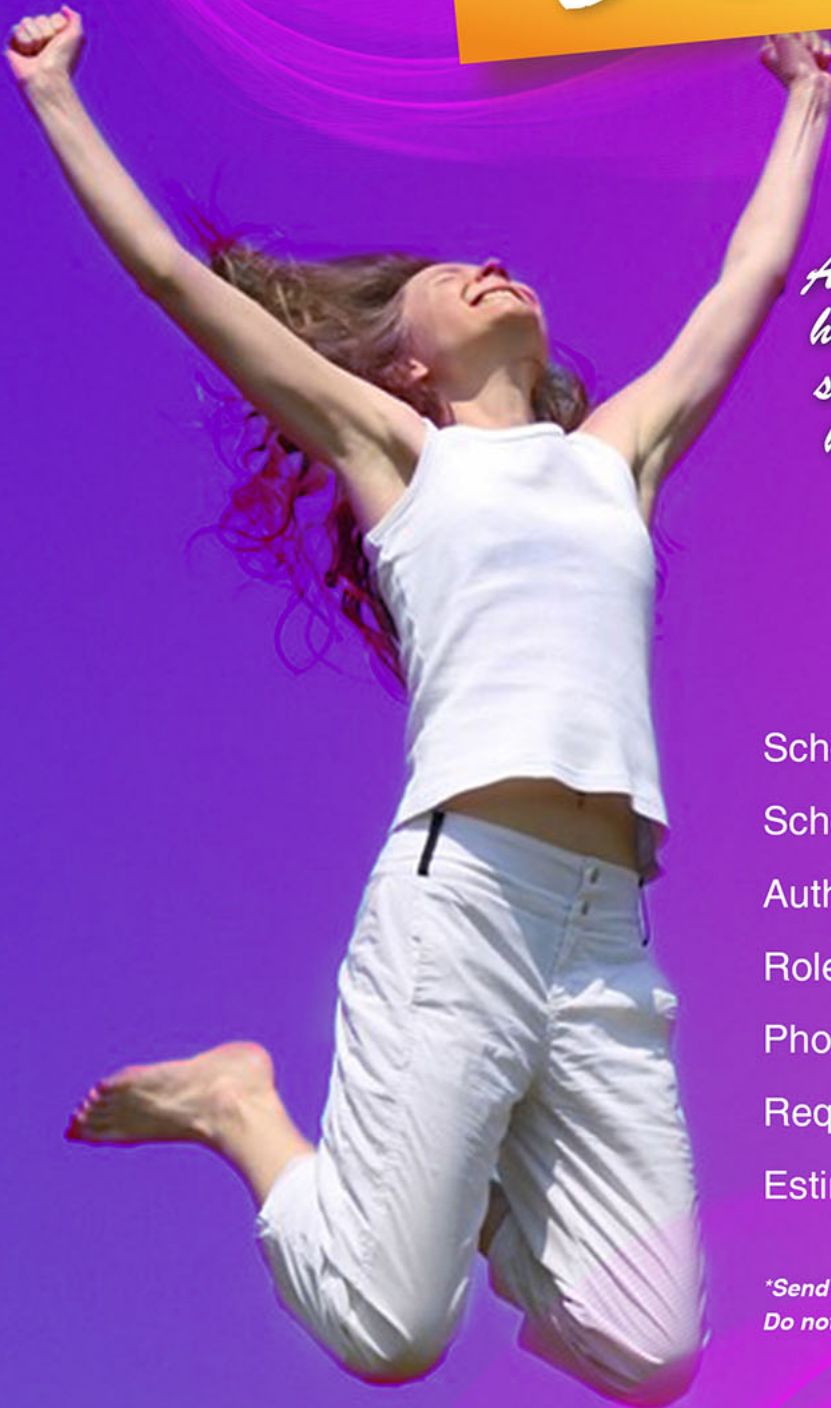
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