TURKISH ENDOMETRIOSIS & ADENOMYOSIS SOCIETY 2009

11th year 2009-2020

ENDOMETRIOSIS BULLETIN

JULY 2020 / ISSUE XIII

WE WOULD LIKE TO EXPRESS OUR GRATITUDE TO ALL OUR HEALTH PROFESSIONALS AND COLLEAGUES WORKING ON THE FRONT LINES DUE TO COVID-19 PANDEMIC

1 in 10 Women are Affected by Endometriosis

www.endometriozis.org

PREFACE

We are pleased to present to you our 14th issue. Due to the cancellation of all events during the past 3 months because of the COVID-19 pandemic, most of the events were moved to online platforms worldwide. Many national and international webinars were organized online.

We started **weekly live sessions using the society's Instagram account** with the contribution of the board of directors, members and colleagues where we answered our followers' questions and broadcasted informative seminars on endometriosis. With the positive feedback we have received so far, we will continue our weekly live broadcasts with a different mentor and junior colleague.

We are very excited to announce our first international live webinar on **'Endometriosis 2020 Current Status-1'** which took place on the 7th of June. **Engin Oral** was the moderator. In addition to world renowned specialists of endometriosis **Catherina Exacoustos, Ceana Nezhat,** and **Michael Hibner**, **Taner Usta**, current president of our society, and **Ahmet Kale** participated in the webinar and shared their experiences.

European Endometriosis League, of which **Engin Oral**, our founding president, is the president, began its webinar series in March with valuable presentations by **Harald Krentel, Engin Oral** and **Sebastian Schaefer**. Until the end of the year, the webinar series will continue with monthly presentations. You can find the monthly webinar program in our bulletin.

Banu Kumbak Aygun, a valuable member of our board of directors, has decided to leave our society. We would like to thank her for all the support and effort she has given to our society since its foundation.

One of the members of our young group, **Hale Goksever Celik**, has been chosen as a member to the board of directors. We welcome her and wish her all the best.

We continue to work as a team and develop new online projects together with our patients and our followers. In our next issue we hope to share with you good news from Turkey and the world.

Best regards,

Board Members of Turkish Endometriosis & Adenomyosis Society

Turkish Endometriosis & Adenomyosis Society Board of Directors 2019-2022

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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 you would like to ask, you can contact us via e-mail at dr_pinaryalcin@hotmail.com or baharyl86@gmail.com.

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A SELECTED ARTICLES

A SELECTED ARTICLES

1 Laparoscopic Ablation or Excision With Helium Thermal Coagulator Versus Electrodiathermy for the Treatment of Mild-To-Moderate Endometriosis: Randomised Controlled Trial

Misra, G., Sim, J., El-Gizawy, Z., Watts, K., Jerreat, S., Coia, T., ... & O'Brien, S. BJOG: An International Journal of Obstetrics & Gynaecology.(2020).

Objective: To compare electrodiathermy with helium thermal coagulation in laparoscopic treatment of mild-to-moderate endometriosis.
Design: Parallel-group randomised controlled trial.
Setting: A UK endometriosis centre.
Population: Non-pregnant women aged 16-50 years with a clinical diagnosis of mild-to-moderate endometriosis.
Methods: If mild or moderate endometriosis was confirmed at laparoscopy, women were randomised to laparoscopic treatment with electrodiathermy or helium thermal coagulator.
Main outcome measures: Cyclical pain and dyspareunia (rated on a 100-mm visual analogue scale, VAS), quality of life at baseline and at 6, 12 and 36 weeks following surgery, operative blood loss and surgical complications.
Results: A total of 192 women were randomised. Of these, 155 (81%) completed the primary outcome point at 12 weeks. In an intention-to-treat analysis, VAS scores for cyclical pain were significantly lower in the electrodiathermy group compared with the helium group at 12 weeks (mean difference, 9.43 mm; 95% CI 0.46, 18.40 mm; P = 0.039) and across all time points (mean difference, 10.13 mm; 95% CI 3.48, 16.78 mm; P = 0.003). A significant difference in dyspareunia also favoured

electrodiathermy at 12 weeks (mean difference, 11.66 mm; 95% CI 1.39, 21.93 mm; P = 0.026). These effects were smaller than the proposed minimum important difference of 18.00 mm, however. Differences in some aspects of quality of life favoured electrodiathermy. There was no significant difference in operative blood loss (fold-change with helium as reference, 1.43; 95% CI 0.96, 2.15; P = 0.081).
Conclusions: Although electrodiathermy was statistically superior to helium ablation in reducing cyclical pain and dyspareunia, these effects may be too small to be clinically significant.
Tweetable abstract: Helium coagulation is not superior to electrodiathermy in laparoscopic treatment of mild-to-moderate endometriosis.
Keywords: Endometriosis; laparoscopic surgery; pelvic pain.

2 Use of Tumor Markers to Distinguish Endometriosis-Related Ovarian Neoplasms From Ovarian Endometrioma

Shinmura, H., Yoneyama, K., Harigane, E., Tsunoda, Y., Fukami, T., Matsushima, T., & Takeshita, T. International Journal of Gynecologic Cancer, ijgc-2020.)

Abstract

Objective: Only few studies have focused on tumor markers used in the preoperative diagnosis of endometriosis-related ovarian neoplasms, and previous studies have only assessed serum CA125 levels. This study investigated the significance of preoperative tumor markers and clinical characteristics in distinguishing endometriosis-related ovarian neoplasms from ovarian endometrioma.

Methods: A case-control study was conducted on 283 women who were diagnosed with confirmed pathology with endometriosis-related ovarian neoplasms (n=21) and ovarian endometrioma (n=262) at a single institution from April 2008 to April 2018. The serum CA125, CA19-9, carcinoembryogenic antigen (CEA), sialyl Lewis-x antigen (SLX), and lactate dehydrogenase (LDH) levels, age, tumor size, and the presence of mural nodule of the patients were analyzed.

Results: Patients with endometriosis-related ovarian neoplasms were more likely to be older (48 (range, 26-81) vs 39

(range, 22-68) years, P<0.001), have higher levels of CA19-9 (42 vs 19 U/mL, P=0.013), CEA (1.3 vs 0.84 ng/mL, P=0.007), SLX (41 vs 33 U/mL, P=0.050), and LDH (189 vs 166 U/mL, P<0.001) and larger tumor size (79 vs 55 mm, P=0.001), and present with mural nodule (85.7 vs 4.5 %, P<0.001) than those with ovarian endometrioma. The CA125 levels did not significantly differ between the two groups. The area under the curve for each factor was as follows: CA19-9 level, 0.672 (95% CI 0.52 to 0.83; P=0.013); CEA level, 0.725 (95% CI 0.58 to 0.87; P=0.007); SLX level, 0.670 (95% CI 0.53 to 0.84; P=0.050); LDH level, 0.800 (95% CI 0.70 to 0.90; P<0.001); age, 0.775 (95% CI 0.65 to 0.90;

P<0.001); age, 0.775 (95% CI 0.65 to 0.90; P<0.001); and tumor size, 0.709 (95% CI 0.56 to 0.86; P=0.001). Age was a better marker than CA19-9, CEA, and SLX levels according to the receiver operating characteristic curve analysis. The optimal cut-off values for age and tumor size were 47 years and 80 mm, respectively.

Conclusions: The assessment of serum CA19-9, CEA, SLX, and LDH levels may be a useful tool in the preoperative evaluation to differentiate between endometriosis-related ovarian neoplasms and ovarian endometrioma.

Keywords: ovarian cysts; ovarian neoplasms.

3 Pregnancy Outcomes in Women With History of Surgery for Endometriosis

Farella, M., Chanavaz-Lacheray, I., Verspick, E., Merlot, B., Klapczynski, C., Hennetier, C. Roman, H. Fertility and Sterility. (2020).

Abstract

Objective: To assess the relationship between history of surgery for endometriosis and adverse obstetrical outcomes.

Design: Retrospective study using prospectively recorded data. Setting: Referral center.

Patient(s): Total of 569 women with history of surgery for endometriosis, postoperative conception, and pregnancy evolution over 22 weeks of gestation.

Interventions(s): Surgery for endometriosis.

Main outcome measure(s): Small for gestational age (SGA) status of the newborn, spontaneous preterm birth (PT, before 37 weeks' gestation), and placenta previa.

Results: Among 733 pregnancies included in the study, 566 deliveries were recorded (77.2%), of which 535 were singleton (72.9% of pregnancies) and 31 twins (4.2%). SGA was observed in 81 of 535 (15.1%) singleton pregnancies and in 9 of 31 (29%) twin pregnancies. PT occurred in 53 of 535 (9.9%) singleton pregnancies and in 19 of 31 (61.2%) twin pregnancies. The number of singleton and multiple pregnancies complicated by placenta previa were, respectively, 9 of 535 (1.7%) and 0 of 31. The independent factor found to relate to SGA was the absence of endometriomas; conception with the use of assisted reproductive technologies (ART) only tended toward statistical significance. Independent factors found to increase risk of PT were conception with the use of ART, body mass index >30 kg/m2, and surgery of deep endometriosis infiltrating the rectum and the bladder. Independent factors associated with placenta previa were

conception with the use of ART and history of stage III or IV endometriosis.. The independent factor found to relate to SGA was the absence of endometriomas; conception with the use of assisted reproductive technologies (ART) only tended toward statistical significance. Independent factors found to increase risk of PT were conception with the use of ART, body mass index >30 kg/m2, and surgery of deep endometriosis infiltrating the rectum and the bladder. Independent factors associated with placenta previa were conception with the use of ART and history of stage III or IV endometriosis.

Conclusion(s): The risk of SGA and PT is increased in women with a history of surgery for endometriosis, and a high rate of conception with the use of ART may jeopardize outcomes.

Keywords: Endometriosis; placenta previa; pregnancy; preterm birth; small for gestational age.

4 Bone Marrow in Pathophysiology of Endometriosis

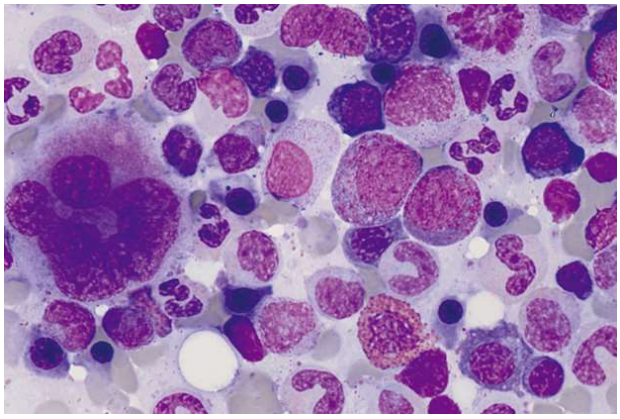
Taylor, H. S. Fertility and Sterility. (2020).on press

Summary

Endometriosis is dependent on active angiogenesis; hence new blood vessel formation is the hallmark of the lesions. The fact that bone marrow derived endothelial cells contribute widely to angiogenesis, leading to growth of endometriosis, endothelial progenitor cells are a target for treatment.

CXL12 is a chemoattractant which leads to migration and engraftment of bone marrow cells in normal endometrium as well as endometriosis. Because endometriosis produces high levels of CXCL12 (aka stromal derived factor1 (SDF-1)) it poses as a target for treatment. Protein kinase CK2 regulates CXCL12 expression, and by blocking this enzyme, formation of new blood vessels and growth of endometriosis may be blocked. In endometriosis, high level of estrogen in turn upregulates CXCL12 expression and CXCL12 attracts endothelial progenitor cells. Interruption at any level of this pathway; such as depletion of estradiol, blockade of CK2 activity (by potent and selective inhibitor CX-4945) or use of CXCL12 receptor antagonist (AMD3100) stand as a good opportunity for treatment.

Although the CK2 inhibitor CX-4945 has been developed for use against cancers, given the nonspecific action on almost all tissues, the risk of off target effects is high, and it is unlikely that inhibition of CK2 will be used as an endometriosis treatment. Antagonism



of CXCL12 action using AMD3100 is a promising and more realistic new option for endometriosis.

It is important to note that estrogen deprivation, not progestin, regulates CK2, CXCL12, and endothelial cell migration. Hence estrogen deprivation is still the gold standard treatment. If non-hormonal therapies are to be considered, it is important to note that CXCR4 antagonists are more specific and less toxic that CK2 inhibitors, although their effects on pregnancy are yet to be determined.

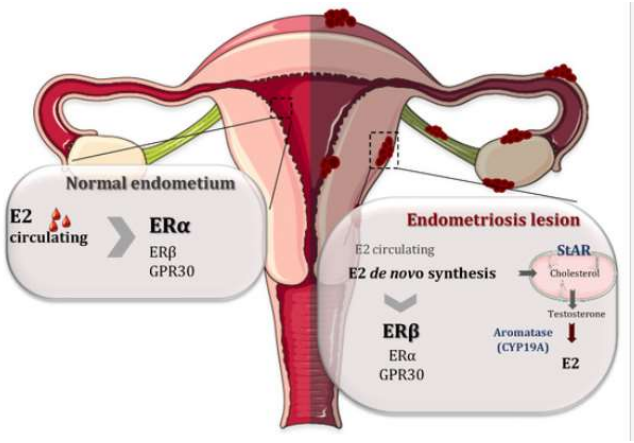
5 Estrogen Receptors and Endometriosis

Chantalat, E., Valera, M. C., Vaysse, C., Noirrit, E., Rusidze, M., Weyl, Arnal, J. F International Journal of Molecular Sciences, 21(8), 2815.(2020).

Abstract

Endometriosis is a frequent and chronic inflammatory disease with impacts on reproduction, health and quality of life. This disorder is highly estrogen-dependent and the purpose of hormonal treatments is to decrease the endogenous ovarian production of estrogens. High estrogen production is a consistently observed endocrine feature of endometriosis. mRNA and protein levels of estrogen receptors (ER) are different between a normal healthy endometrium and ectopic/eutopic endometrial lesions: endometriotic stromal cells express extraordinarily higher ERβ and significantly lower ERα levels compared with endometrial stromal cells.

Aberrant epigenetic regulation such as DNA methylation in endometriotic cells is associated with the pathogenesis and development of endometriosis. Although there is a large body of data regarding ERs in endometriosis, our understanding of the roles of ERα and ERβ in the pathogenesis of endometriosis remains incomplete. The goal of this review is to provide an overview of the links between endometriosis, ERs and the recent advances of treatment strategies based on ERs modulation.



We will also attempt to summarize the current understanding of the molecular and cellular mechanisms of action of ERs and how this could pave the way to new therapeutic strategies.

Keywords: endometriosis; estrogen receptors; modulation; treatment strategy.

6 Evidence in Support for the Progressive Nature of Ovarian Endometriomas

Ding, D., Wang, X., Chen, Y., Benagiano, G., Liu, X., & Guo, S. W The Journal of Clinical Endocrinology & Metabolism. (2020).on press

Abstract

Context

Whether endometriosis is a progressive disease is a highly contentious issue. While progression is reported to be unlikely in asymptomatic deep endometriosis, progression in symptomatic deep endometriosis has recently been reported, especially in menstruating women. However, pathophysiological reasons for these differences are unclear.

Objective

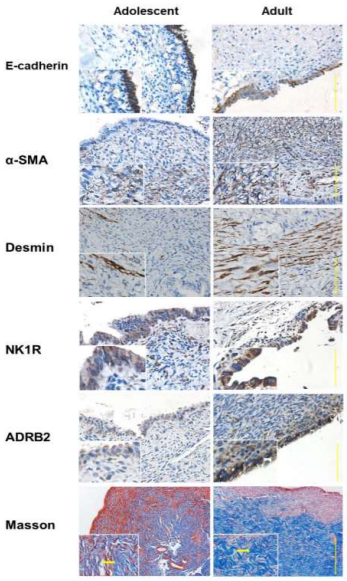
This study was designed to investigate whether ovarian endometrioma (OE) is progressive or not.

Setting, Design, Patients, Intervention and Main Outcome Measures

Thirty adolescent patients, aged 15 to 19 years, and 32 adult patients, aged 35 to 39 years, all laparoscopically and histologically diagnosed with OE, were recruited into this study after informed consent. Their demographic and clinical information were collected. Their OE tissue samples were collected and subjected to immunohistochemical analysis for E-cadherin, α-smooth muscle actin (α-SMA), desmin, and adrenergic receptor β2 (ADRB2), as well as quantification of lesional fibrosis by Masson trichrome staining.

Results

OE lesions from the adolescent and adult patients are markedly different, with the latter exhibiting more extensive and thorough progression and more extensive fibrosis, suggesting that lesions in adults progressed to a more advanced stage. Adult lesions and higher staining level of α-SMA and ADRB2 are positively



associated with the extent of lesional fibrosis, while the lesion size and the E-cadherin staining are negatively associated.

Conclusions

Our data provide a more definitive piece of evidence suggesting that OE is a progressive disease, since the adult lesions have had a longer time to progress. In addition, the pace of progression depends on lesional age as well as the severity of endometriosis-associated dysmenorrhea, if any.

Keywords: adrenergic receptor β2, endometriosis, epithelial-mesenchymal transition, fibroblast-to-myofibroblast transdifferentiation, fibrogenesis, progression

B NEWS FROM OUR SOCIETY

PAST ACTIVITIES

As we wait at home for the battle with COVID-19 to end, we started Instagram live broadcasts to get together with our followers. Experts in the field answered the questions of our patients.

COVID-19 and Endometriosis
Prof. Umit Inceboz, MD.
Pinar Yalcin Bahat, MD.

Endometriosis, Infertility and IVF during COVID-19 pandemic: What to do?
Prof. Ercan Bastu, MD.
Assoc. Prof. Hale Goksever Celik, MD.

Endometriosis Surgery: When? To Whom? How?
Prof. Ahmet Kale, MD.
Assoc. Prof. Cihan Kaya, MD.

Everything About Endometriosis!
Prof. Engin Oral, MD.
Assoc. Prof. Hasan Onur Topcu, MD.

Click here to watch the video.

Recurrent Endometriosis and Chronic Pelvic Pain
Assoc. Prof. Taner Usta, MD.
Isik Sozen, MD.

Everything You Want to Know About Endometriosis: Q&A
Prof. Kutay Biberoglu, MD.
Dilek Buldum, MD.

Click here to watch the video.

Everything You Want to Know About Endometriosis: Q&A - 2
Prof. Yucel Karaman, MD.
Salih Yilmaz, MD.

Click here to watch the video.

Everything You Want to Know About Endometriosis: Q&A - 3
Prof. Bulent Berker, MD
Uzm. Isil Ayhan, MD

Click here to watch the video.

Everything You Want to Know About Endometriosis: Q&A - 4
Prof. Turan Cetin, MD.
Gulfem Basol Igci, MD.

Click here to watch the video.

Everything You Want to Know About Endometriosis: Q&A - 5
Prof. Hulusi Zeyneloglu, MD.
Tolga Karacan, MD.

Click here to watch the video.

Informing Endometriosis Patients During The COVID-19 Pandemic

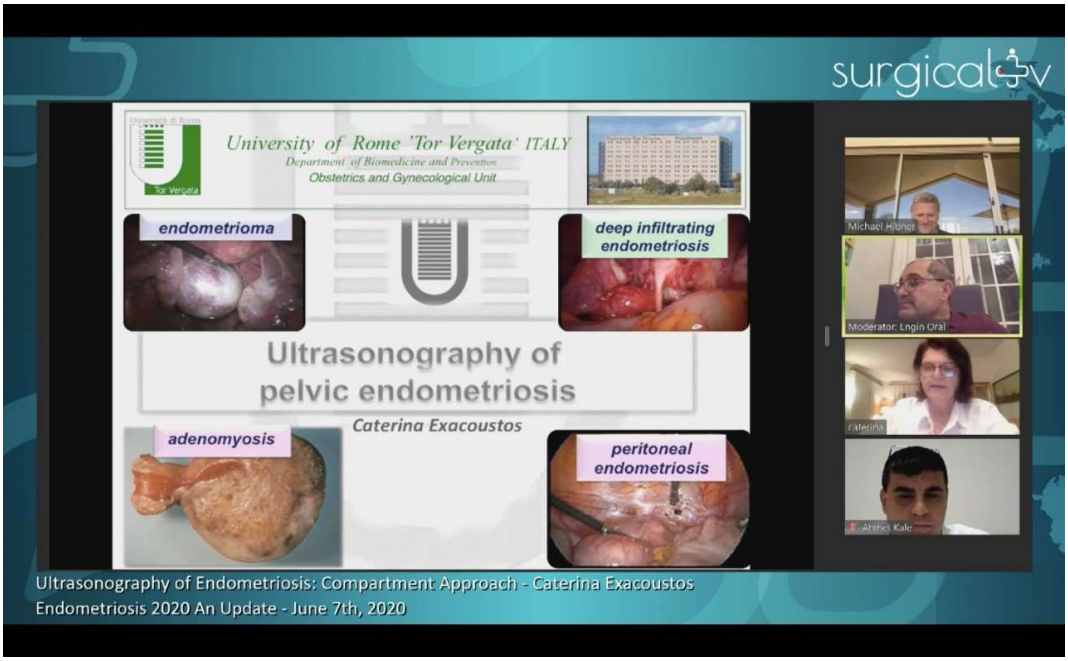
We tried to support our endometriosis patients by informing them about **'COVID-19 and Endometriosis'** on our social media accounts. We answered frequently asked questions like when to go to the hospital, dietary habits, risk factors for COVID-19, potential interference of COVID-19 with endometriosis, how to cope with endometriosis related pain and potential effects of medications used for COVID-19 on endometriosis symptoms.

A Joint Live Broadcast with Adim Adim (Step by Step - Turkish Charity Run Platform) - Baking Gluten-Free Bread!

Owner of **"Beambakes"**, our dear ***Berfe Tumen***, who has been supporting our society with dietary suggestions for endometriosis patients, shared her recipe for gluten-free bread, which was broadcasted live on Adim Adim's Instagram account. We express our gratitude to Berfe Tumen for her collaboration and support.

Endometriosis 2020: Current Status Webinar

Endometriosis 2020: Current Status Webinar



On Sunday the 7th of June on Cerrahi TV, our society broadcasted live our first international webinar called '**Endometriosis 2020 Current Status-1**'. Moderated by Engin Oral, we had the chance to listen to Catherina Exacoustos, Ceana Nezhat and Michael Hibner, who have vast experience on endometriosis and renowned all over the world. In addition, our president, Taner Usta and Ahmet Kale shared their experiences in the field of endometriosis.

NEWS FROM THE WORLD OF ENDOMETRIOSIS

UNIVERSITY OF OXFORD

EndometriosisCaRe OXFORD Care & Research

NUFFIELD DEPARTMENT OF WOMEN'S & REPRODUCTIVE HEALTH
Medical Sciences Division

Medical and self-care advice for women with endometriosis during the COVID-19 pandemic

'' Medical and Self-Care Advice for Women with Endometriosis During The COVID-19 Pandemic'' published by Oxford University, Oxford Endometriosis Care and Nuffield Women and Reproductive Health Department. You can find the full text under the following link:

https://www.wrh.ox.ac.uk/research/endometriosis-care-covid19

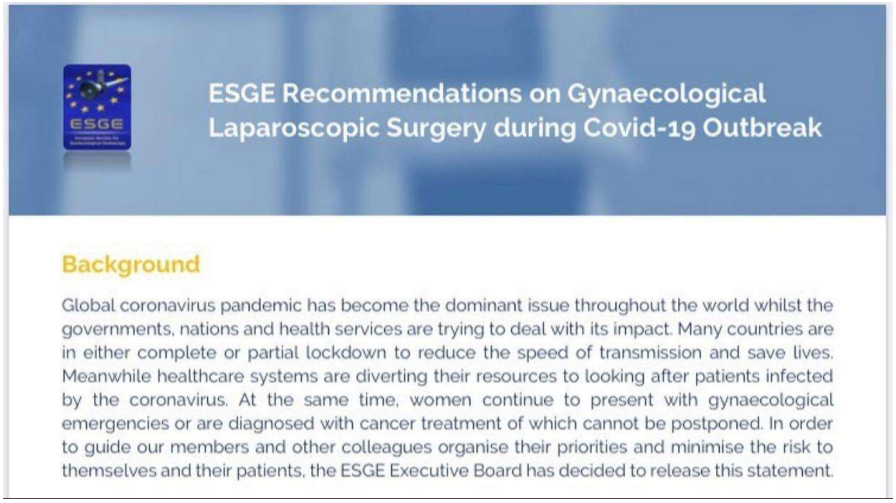
EEL WEBINAR

Under the leadership of **Engin Oral** - president of the European Endometriosis League (EEL), an EEL Webinar program was prepared. Following the first one which was held in March, the second webinar titled **'What's new in the diagnosis and treatment of adenomyosis in 2020'** took place in April. The General Secretary of EEL, **Harald Krentel** presented the second webinar. The third one named **'What is the current management in advanced endometriosis and infertility'** was carried out by **Engin Oral** in May. In June **Sebastian Schaefer** presented the webinar titled as **'How is ultrasonography linked to surgery in advanced endometriosis'.** In this webinar program, which is planned to continue monthly, international physicians experienced in endometriosis will share their knowledge on different topics. For more information, you can visit: https://www.endometriosis-league.eu/home or follow the European Endometriosis League or Euro Endo League accounts on social media.

ESHRE 2020

36th Annual ESHRE Meeting will be held virtually due to the COVID-19 pandemic. The first ever online meeting of ESHRE (European Society of Human Reproduction and Embryology) will be on 5-8 July, 2020.

ESGE



ESGE (European Society for Gynaecological Endoscopy) published recommendations on gynecological laparoscopic surgery during the COVID-19 pandemic.

D INTERVIEW WITH AN 'ENDO SPECIALIST'

Prof. Kutay Biberoglu, MD.
Interview: Assoc. Prof. Yusuf Aytac Tohma, MD

A Short Curriculum Vitae

Professor Dr. Kutay BIBEROGLU graduated from Hacettepe University Faculty of Medicine and in 1977. He received his gynecology and obstetrics specialization from Hacettepe University Faculty of Medicine.
In 1977-1981, he studied reproductive endocrinology and infertility at Wayne State University Medical School William Beaumont Hospital, Michigan, USA and reproductive biology at University of Texas Medical School, Texas, USA. In 1987, he was appointed as a professor faculty member at Gazi University, Ankara, Turkey. He worked as the chief of the department between 1987-1991 and as associate dean of education between 1989-1990.

In 1997-2001, he worked as Founder Directorate of Family Planning, Infertility and Reproductive Health Center at Gazi University. He served as a member of the Turkish Ministry of Health, Family Planning, Mother-Child Health General Directorate, Pharmaceutical Commission, IVF Scientific Commission, and Obstetrics and Gynecology Advisory Board. In addition, he served as the Chairman of the Board of the Turkish Gynecology Association in Ankara, and has several other board memberships such as Reproductive Medicine Association, Private IVF Centers Association and Geriatrics Association. He received "William Beaumont Hospital" - Royal Oak, Michigan, USA Best Scientific Researcher Award (1980) and "Ephraim McDowell" Chicago, Illinois, USA Best Scientific Study Award (1979). In November 2016, he was deemed worthy of "Lifetime Achievement Award" by Reproductive Endocrinology (TSRM) Association. He has over 300 articles, congress papers, and more than 50 works in English that were published in several international medical journals.

Hello,
We are with Prof. Kutay Biberoglu. Thank you, Prof. Biberoglu, for kindly accepting our request and agreed to be interviewed online during this pandemic period.

Turkish Endometriosis and Adenomyosis Society (TEAS): Hello Prof. Biberoglu, can you briefly introduce yourself to us?

Kutay Biberoglu (KB): Hello. First of all, I would like to thank the Board of Directors of the Turkish Endometriosis and Adenomyosis Society, of which I am one of its founders, for giving me this opportunity. I was born and raised in Ankara. After graduating from TED Ankara College, I got both my medical degree from and did my specialty training in OB/GYN at Hacettepe University. Following my specialization, I finished 2 years of Reproductive Endocrinology and Infertility subspecialty training and worked for 2 years as a consultant/lecturer in USA. Then I returned back to Hacettepe and worked as an assistant professor and later as an associate professor. I was appointed to Gazi University Faculty of Medicine as a professor, because back then it was not possible to continue working as a professor at the same university. I served as vice dean, as chief of the department of OB/GYN, as the founding director of the IVF center, and as a lecturer until retirement. I also provided patient service in my private practice, which I still keep on doing.

TEAS: Actually, we were going to talk about endometriosis but can you tell us your observations, experience and comments about the pandemic process?

KB: Since I have worked in reproductive endocrinology and infertility for decades, endometriosis is one of the diseases I am most engaged with. During my medical practice, both in the US and in Turkey, in the 80's and 90's, the surgical approach was essential

in diagnosis and treatment. My contribution to the medical literature in this area was Biberoglu Behrman Scoring system, briefly known as the B & B score, published in 1981 when I was working with Doctor Jan Behrman in the US. In this study we classified pelvic pain in endometriosis. Staging was done according to the symptoms and examination findings. Our staging system was conditioned to use for all researchers of endometriosis for 20 years. It has been used in many studies for 40 years. Formerly, we could not diagnose endometriosis without laparoscopy, and each diagnosis was followed by surgical treatment. The diagnosis of unexplained infertility could only be made after laparoscopy. There was a period without laparoscopy IVF treatment could not be initiated. In Hacettepe, I remember performing a total of 16 laparoscopic surgeries in 2 separate ORs in one day. Then the medical world decided that to name the cause of infertility was not as important as increasing pregnancy rates. With this understanding, surgical diagnosis and treatment have become selectively applied under limited conditions, rather than being a routine approach.
We now know that endometriosis is commonly a disease of women in reproductive age that does not have a cure and has a high risk of recurrence. The patient has to learn to live with endometriosis. Patients with pelvic pain benefit from a suppression of estrogen through long-term medical treatments. We can say that now a more pragmatic approach dominates medicine.
During the pandemic, we continued to follow up and treat our patients with remote communication methods. We postponed surgeries except for emergencies. IVF treatments have been stopped for 2-3 months. Recently, we have started with new IVF cycles in a controlled manner.

TEAS: You are a very experienced person in endometriosis, can you briefly tell us about the history of endometriosis?

KB: Endometriosis has a long history. The symptoms were first described by Vincent Knapp in Germany in 1690, histopathological diagnosis was reported for the first time by Carl Rokitansky in 1860, and then in 1882 Cullen claimed for the first time that endometriosis originated from mesonephric remnants. In 1903 Mayer spoke of inflammatory epithelial invasion. And finally, in 1927, Sampson showed that peritoneal endometriosis developed from spilled menstrual blood, which is still the commonly accepted. In summary, we must admit that this disease, whose symptoms have been known for 320 years, and histopathology for 160 years, still maintains a mystery. We still do not know why in some women it causes complaints, while in others it remains silent, and with which mechanism it causes infertility.

TEAS: What do you think about the physician and patient awareness of endometriosis in our country, what can be done?

KB: As a result of years of studies, both patients and physicians recognize this disease, and in parallel with this, the incidence and prevalence of endometriosis is gradually increasing. With ultrasound, we can now diagnose both ovarian and deep endometriosis with high sensitivity and specificity. Surgical approaches are less common and performed more carefully to protect the ovarian reserve. The knowledge that the disease requires a long-term follow-up and treatment has become widespread. These are positive developments.

TEAS: Endometriosis is a disease that cannot be cured, so patients should learn to live with endometriosis. What are your suggestions?

KB: There are still some problems. Theoretically, all physicians know that endometrioma surgery reduces ovarian reserve, there is a 50% recurrence risk in 3-5 years, so young women sometimes need to have surgery 6-7 times. However, when we look at the routine application, we still observe that there are many surgeries performed even patients don't have any symptoms. Although it is known that endometriomas increase in size gradually and very slowly and rarely cause emergencies, unnecessary attempts are still made rather than applying expectant management. Even young women without pelvic pain are prescribed unnecessary medications to shrink their cysts. Although endometriomas are known to return to their original size within 1 month after discontinuation of medical treatment, many unnecessary treatments are performed. While it is possible and more effective to treat only with progestins, for years combined oral contraceptive have been prescribed for pain.
One of the issues we have forgotten is the fact that many of the patients with endometriosis conceive and deliver many times without any problems. To assume that it will surely lead to infertility causes unnecessary anxiety and treatment. IVF is applied frequently without giving a chance to spontaneous pregnancy. The right approach is to perform a complete infertility assessment in these patients as if endometriosis was not present and to treat the causes of infertility. If no other causes are present or pregnancy is not achieved despite treatment then endometriosis management should be planned accordingly.

TEAS: Finally, do you have a message for the patients?

KB: Endometriosis is not cancer and yet it is very common. It is a chronic disease. It does not necessarily cause pain or lead to infertility. At the same time, many other organs such as bladder, bowel, muscle or soft tissue can be involved and the main cause of pain may be one of them, not endometriosis. Psychological problems can also be the trigger of pain. The focus is not the treatment of the disease, but the treatment of the symptoms. In other words, it is essential to "manage pain if there is pain and infertility if there is infertility". Not to rush, to be patient, to find the right management with calm and without panic is the right approach for both physicians and patients. It is very important for the patients to be well informed, to seek second and third professional counseling during their decision process regarding their treatment.

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

1. Evaluation of the Ocular Surface by Impression Cytology in Patients With Endometriosis

Meydan Turan , Gulay Turan , Akin Usta Graefes Arch Clin Exp Ophthalmol. 2020 Apr;258(4):931-937

Abstract

Objective: The aim of this study was to investigate the effect of endometriosis on the ocular surface.

Methods: A total of 50 patients were included in the study and divided into two groups. Group 1 consisted of 25 patients with endometriosis. Group 2 had 25 control patients. All patients underwent complete ophthalmic examination, and the right eyes were included in the study. To evaluate the ocular surface, both groups were tested with the following: the Schirmer I test, tear breakup time (TBUT), the conjunctival impression cytology (CIC), and the Ocular Surface Disease Index (OSDI). The results were subsequently compared.

Results: The average Schirmer I test results were 8.40 ± 2.74 mm in group 1 and were significantly lower in patients with endometriosis ($P < 0.001$). The average TBUT test results were 9.04 ± 3.61 s in group 1 and were significantly lower in patients with endometriosis ($P < 0.001$). The average OSDI results were 24.04 ± 9.29 in group 1 and were significantly higher in patients with endometriosis ($P < 0.001$). The average CIC results were 1.76 ± 0.88 in group 1 and were significantly higher in patients with endometriosis ($P < 0.001$).

Conclusions: Ocular surface changes, including squamous metaplasia, may be observed in the conjunctiva of patients with endometriosis.

Keywords: Conjunctival impression cytology; Dry eye; Endometriosis; Schirmer I test; Tear breakup time.

2. Evaluation of Complement System Proteins C3a, C5a and C6 in Patients of Endometriosis.

Elif Karadadaş , İsmet Hortu , Handan Ak , Ahmet Mete Ergenoğlu , Nedim Karadadaş , Hikmet Hakan Aydın Clin Biochem. 2020 Apr 20,120(20)30153-3.

Abstract

Background: Endometriosis is a disease that shows auto-immune and chronic characteristics, suggesting a role for proteins mediating immune interactions in its pathophysiology. The aim was to evaluate C3a and C5a for their role in inflammatory responses and C6 as the down-stream interactor following our previous findings on C5 mRNA expression changes in endometriosis.

Methods: Sera from 71 endometriosis patients and 77 women without endometriosis were taken. While the samples were taken only once from the controls, the patient samples were taken before, in 1st and in 7th days after laparoscopy. Levels of complement proteins C3a, C5a and C6 were measured with ELISA assays. MPV (Mean Platelet Volume), CRP (C-Reactive Protein) and NLR (Neutrophil-to-Leukocyte Ratio) were also analyzed from the retrospective data.

Results: C6 levels of early-stage patients at postoperative 1st day were significantly higher than controls. Patients with high MPV measurements had significantly higher C3a ($p<0.0001$) and C6 ($p<0.05$) levels than controls at all times of measurement.

Conclusions: C6, an integral component of the membrane attack complex (MAC), could play a role at early disease-stage. The changes in levels of complement proteins and their relation to high MPV levels suggests a broader area of interplay for immune interactors in endometriosis. Although a bigger and longitudinal study design is needed to obtain more accurate results to evaluate these proteins as potential biomarkers, an important role of complement system within the pathophysiology of endometriosis is apparent.

Keywords: Complement C3a; Complement C6; Endometriosis; Mean Platelet Volume.

3. The Relationship Between C-reactive Protein (CRP), Carbohydrate Antigen (CA) 125 and Haematological Parameters to Endometriotic Nodule Localisation in Pelvis

Emsal Pinar Topdagi Yilmaz , Yunus Emre Topdagi , Ragıp Atakan Al , Yakup Kumtepe J Chin Med Assoc. 2020 Mar 24

Abstract

Background: Endometriosis is a pelvic inflammatory process, and hormonal, environmental and genetic factors play a role in its etiopathogenesis; especially, deep pelvic endometriosis exhibits an extensive anatomical distribution. In the present study, we evaluated the contribution of routinely measured haematological parameters to the diagnosis as the number of endometriotic nodule localisation increases, when evaluated with C-reactive protein (CRP) and carbohydrate antigen (CA) 125.

Methods: The present study included patients with histopathologically confirmed diagnosis of endometriosis who underwent surgery at our hospital between January 2007 and December 2018. Their medical records were examined retrospectively.

Results: In total, 205 patients were included in the study; 129 patients (62.9%) with ovarian endometrioma and 76 patients (37.1%) with deep infiltrative endometriosis were assigned to Group 1 and Group 2, respectively, and the two groups were compared. Endometriotic nodules were observed in several localisations in 71 patients (34.6%) of the 205 patients with endometriosis. Pelvic nodules were grouped as per their four different localisations: uterosacral, recto-vaginal, bladder and ureteral. Because the anatomical localisation of endometriotic nodules increased in the pelvis, the variability in the levels of CA 125 and CRP as well as haematological parameters was examined. There were significant differences in haemoglobin ($p < 0.036$), CA 125 ($p < 0.000$) and CRP ($p < 0.007$) levels between patients with nodules in ≤2 localisations and those with nodules in ≥3 localisations.

Conclusion: Our study included a total of 205 patients. There was a significant difference in the CRP, CA 125 and haemoglobin levels between Group 1 and Group 2, but it was concluded that coexistence of the endometriotic nodule had no effect on the other haematological parameters. For this purpose, prospective studies with a larger number of patients are needed.

4. The Regression of Endometriosis With Glycosylated Flavonoids Isolated From Melilotus Officinalis (L.) Pall. In an Endometriosis Rat Model

Mert Ilhan , Zulfiqar Ali , Ikhlas A Khan , Hakkı Taştan , Esra Küpeli Akkol Taiwan J Obstet Gynecol. 2020 Mar;59(2):211-219.

Abstract

Objective: Melilotus officinalis (L.) Pall. is commonly used for treating bronchitis, painful menstruation, hemorrhoids, kidney stones, ulcers of the eyes, earache, and hardening and swelling of uterus. The European Medicines Agency reported the use of M. officinalis orally against stomach ache, gastric ulcer, and disorders of the liver and uterus in folk medicine. The present study aimed to appraise the activity of M. (L.) Pall. aerial parts in endometriosis rat model.

Materials and methods: The endometriosis rat model was used to evaluate the potential activity of M. officinalis aerial parts based on its folkloric usage. The aerial parts of M. officinalis were extracted with n-hexane, ethyl acetate (EtOAc), and methanol (MeOH), respectively. The adhesion scores, endometrial foci areas, and cytokine levels were measured in all treated groups. After the biological activity studies, phytochemical studies were performed on the active extract and the fractions obtained from the active extract.

Results: The MeOH extract significantly decreased the endometrial foci areas and cytokine levels in rats with endometriosis. Fractionation was performed on the MeOH extract to achieve bioactive molecules. Following the fractionation, the fractions obtained from the MeOH extract were tested. Fraction C showed the highest activity in the rat endometriosis model. Phytochemical investigation of the active fraction (Fraction C) resulted in isolation and elucidation of some quercetin and kaempferol glucoside derivatives.

Conclusion: Fraction C obtained from the MeOH extract of M. officinalis showed the highest activity, yielding four glycosylated flavonoids.

Keywords: Endometriosis; Fabaceae; Glycosylated flavonoids; Melilotus officinalis; Rat.

5. Protective Effect of Cabergoline on Mitochondrial Oxidative Stress-Induced Apoptosis Is Mediated by Modulations of TRPM2 in Neutrophils of Patients With Endometriosis

Elif İlknur Ekici, Mehmet Güney, Mustafa Nazıroğlu J Bioenerg Biomembr. 2020 Mar 29

Abstract

Calcium ion (Ca^{2+}) signaling in endometriosis (ENDO) is associated with increased neutrophil activation and oxidative stress. A Ca^{2+} signaling modulator and antioxidant actions of cabergoline (CBG) in some cells were recently reported. TRPM2 cation channel is activated by reactive oxygen species (ROS). Antioxidant action of CGB via inhibition of ROS may modulate the channel. We aimed to investigate the effect of CBG on TRPM2 inhibition in serum and neutrophils of patients with ENDO. The serum and neutrophil samples were grouped into healthy samples (no treatment), ENDO and ENDO + CBG treated groups (n = 10 in each). In some experiments, the neutrophils were also incubated with TRPM2 (ACA) and PARP-1 (PJ34) blockers. The values of intracellular ROS, Ca^{2+} concentration, mitochondrial membrane depolarization, lipid peroxidation, apoptosis, and caspase - 3, caspase - 9, PARP-1 and TRPM2 expressions were high in the neutrophils of patients with ENDO, although antioxidant levels (reduced glutathione, glutathione peroxidase, vitamin A, and vitamin E) were low in the neutrophils and serum from these patients. However, markers for apoptosis, oxidative stress, and mitochondrial dysfunction were reduced with CBG, ACA and PJ34 treatments, although the antioxidant levels were increased in the serum and neutrophils following treatment with CBG. Taken together, our current results suggest that CBG are useful antagonists against apoptosis and mitochondrial oxidative stress via inhibition of TRPM2 in neutrophils of patients with ENDO.

Keywords: Apoptosis; Cabergoline; Endometriosis; Oxidative stress; TRPM2 channel.

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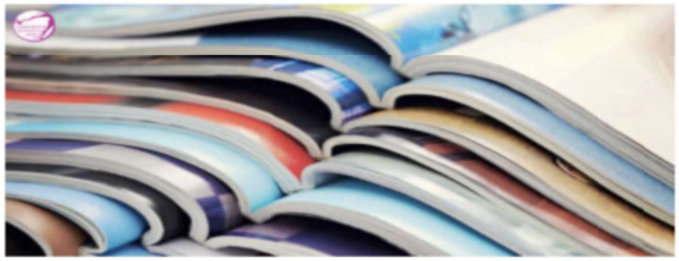

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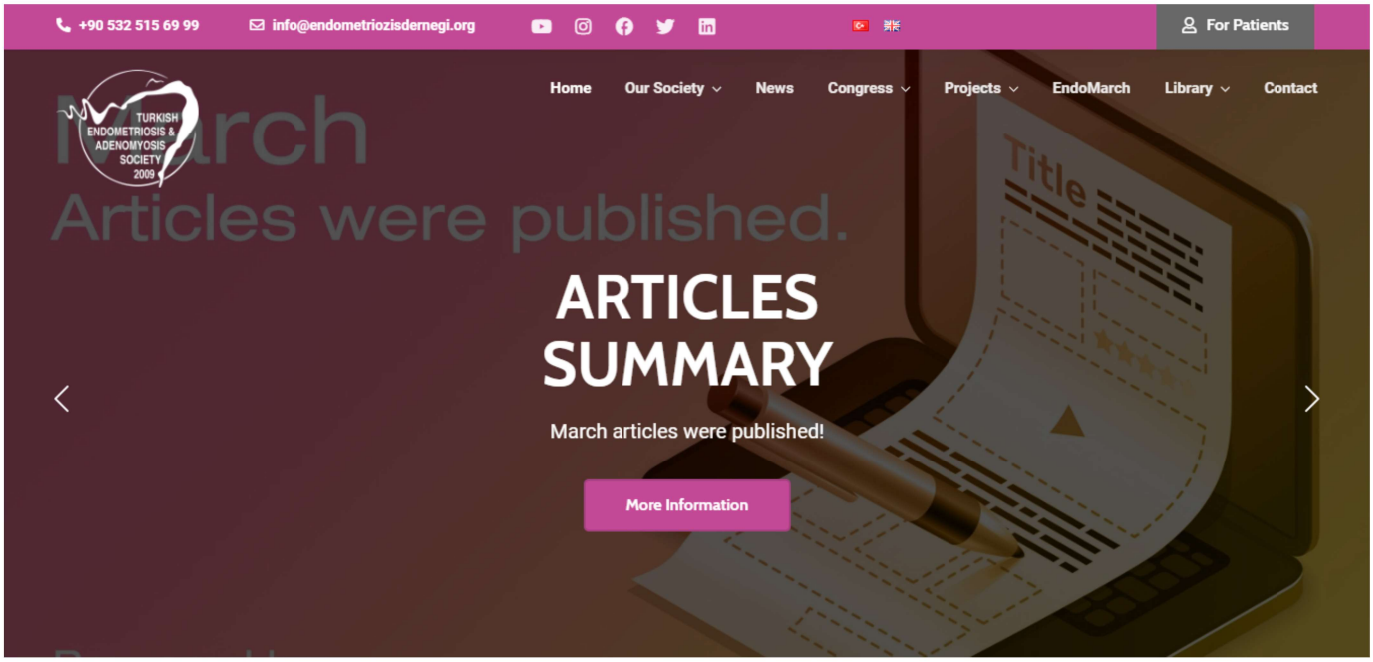

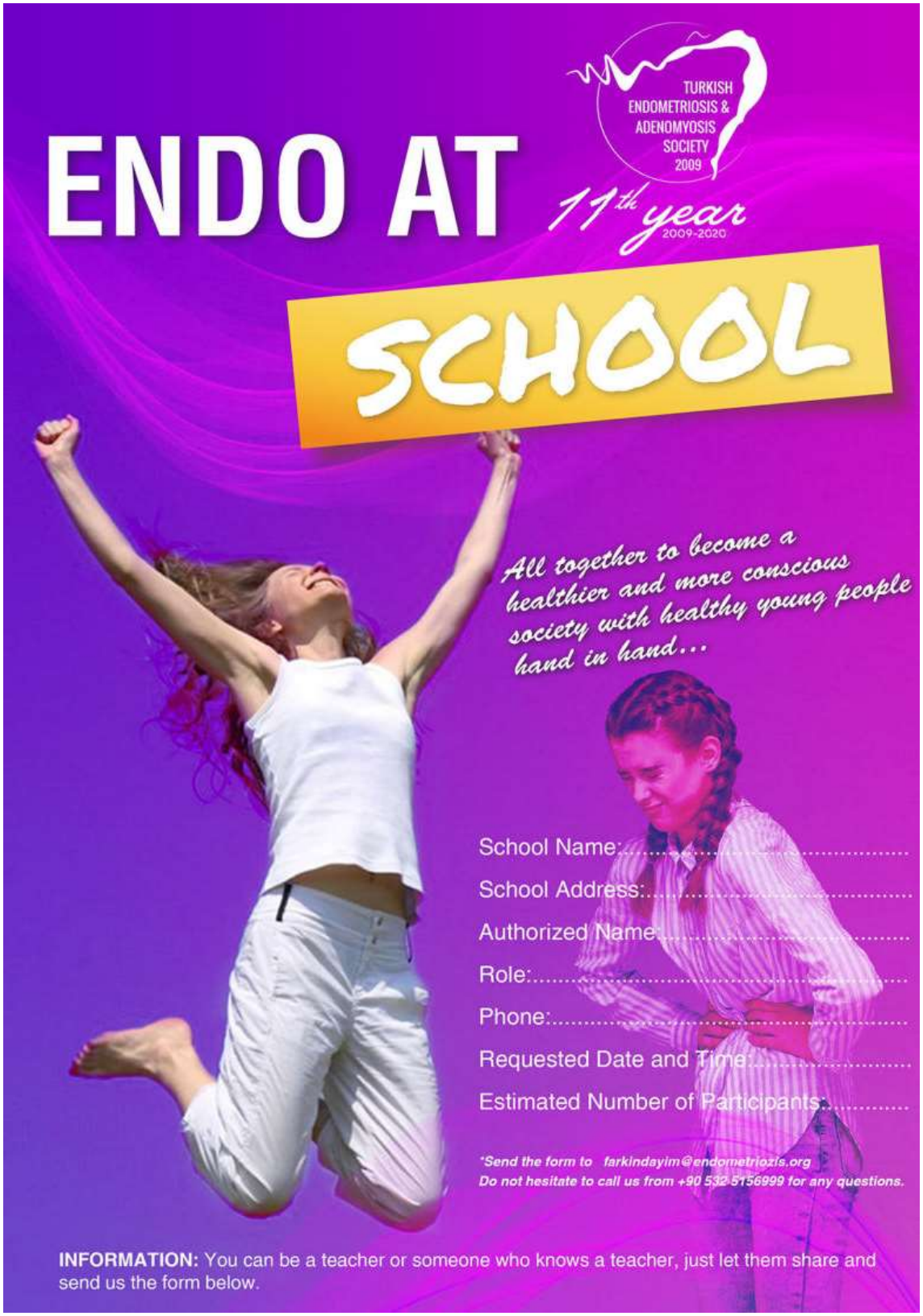

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