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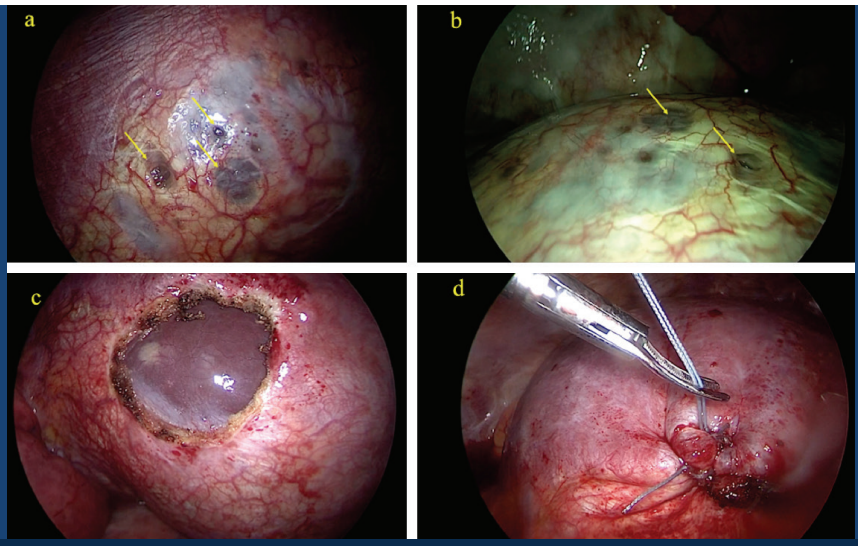

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Cover Picture: Thoracic and diaphragmatic endometriosis. Larraín et al. (Page 116)

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▶ **Kandidal vulvovajinit**,

Gardnerella vaginalis ve anaerob bakterilerin oluşturduğu
▶ **Bakteriyel vajinozis**,

Trichomonas vaginalis'in oluşturduğu
▶ **Trikomonal vajinit**,

▶ **Mikst vajinal enfeksiyonların**

ampirik tedavisinde tek form ile etkilidir.*

Tedavide rahatlık için*

* Trivag Kısa Ürün Bilgisi
ÜRÜN ADI: TRİVAG 300 mg/200 mg/100 mg ovül FORMÜLÜ: Her bir ovül 300 mg tinidazol, 200 mg tiokonazol, 100 mg lidokain içerir. TERAPÖTİK ENDİKASYONLAR: Candida albicans'ın oluşturduğu kandidal vulvovajinit; Gardnerella vaginalis ve anaerob bakterilerin oluşturduğu bakteriyel vajinoz ve Trichomonas vaginalis'in oluşturduğu trikomonal vajinit ile mikst vajinal enfeksiyonların tedavisinde kullanılır. KULLANIM ŞEKLİ VE DOZU: Gece yatmadan önce bir ovül, 3 gün süreyle uygulanır. TRİVAG sırtüstü yatar pozisyonda, paketin içindeki parmaklıkların yardımı ile vajen derinliğine uygulanmalıdır. İSTENMEYEN ETKİLER: Güçsüzlük, bitkinlik, halsizlik, baş ağrısı, baş dönmesi, ağızda metalik/acı tat, mide bulantısı, anoreksi, iştahsızlık, midede gaz toplanması, dispepsi, abdominal kramp, epigastrik rahatsızlık, kusma, konstipasyon, idrar renginde koyulaşma. GEBELİK VE LAKTASYON: Gebelik kategorisi C'dir. Tinidazol anne sütüne geçtiğinden emzirme döneminde tedavi sırasında bebek sütten kesilmelidir, tedavi bittikten 72 saat sonra emzirmeye devam edilmelidir. DİĞER TIBBİ ÜRÜNLERLE ETKİLEŞİMLER VE DİĞER ETKİLEŞİM ŞEKİLLERİ: Birlikte kullanıldığında tinidazolün emilmesine bağlı olarak etkileşim görülebilir; asenokumarol, anisindion, dikumarol, fenindion, fenprokumon, varfarin, kolestiramin, simetidin, siklosporin, disülfiram, fluorourasil, fosfenitoin, ketokonazol, lityum, fenobarbital, fenitoin, rifampin, takrolimus, CYP3A4 indükleyicileri/inhibitörleri. Tiokonazolün emilmesine bağlı olarak etkileşim görülebilir; oksikodon. Lidokainin emilmesine bağlı olarak etkileşim görülebilir; propranolol, simetidin, antiaritmik ürünler, fenitoin veya barbitüratlar. KONTRENDİKASYONLARI: Bileşimindeki etkin maddelere veya bunların türevlerine karşı aşırı duyarlılığı bulunanlarda, gebeliğin ilk üç ayında, emzirme döneminde, organik nörolojik bozukluğu bulunanlarda, kan diskrazisi tablosu veya geçmişi bulunan hastalarda. ÖZEL KULLANIM UYARILARI VE ÖNLEMLERİ: Vajinal yoldan kullanılmalıdır. Geçici lökopeni ve nötropeni gelişebilir. Tedavi süresince ve tedavi bittikten 3 gün sonrasına kadar alkol alınmamalıdır. Cinsel olgunluğa erişmemiş kız çocuklarında ve bakirelerde kullanılmamalıdır. Kardiyovasküler hastalıkları olanlarda dikkatli kullanılmalıdır. Kontraseptif diyafram ve prezervatifle temas etmemelidir. Lidokain özellikle yüksek dozda ve geniş deri yüzeylerine, bilhassa da oklüzyon altında uygulandığında kalp ritm bozuklukları, nefes alma zorluğu, koma ve hatta ölüme yol açabilmektedir. Spermisidler, vajinal duşlar veya vajinal yoldan uygulanan diğer ürünlerle birlikte kullanılmamalıdır. Trikomonal vajinit vakalarında eş tedavisi de gereklidir. TİCARİ TAKDİM ŞEKLİ VE FİYATI: Trivag ovül (Ruhsat tarihi ve no: 29.09.2017-2017/742) 16,53 TL. (Fiyat Tarihi: Mayıs 2018) Ruhsat Sahibi: Bilim İlaç San. ve Tic. A.Ş. Son Güncelleme: Mayıs 2018. Reçeteli satılır. Daha geniş bilgi için "BİLİM İLAÇ SAN. ve TİC A.Ş. 34440 Beyoğlu-İSTANBUL" adresine başvurunuz. Ürünlerimiz ile ilgili advers olayları PHARMACOVIGILANCE@bilimilac.com adresine e-posta göndererek veya 0 212 365 1717 iletişim numarasını arayarak ürün güvenliliği sorumlusuna bildirebilirsiniz.

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Editorial Office

Address: Abdi İpekçi Cad. 2/7 34367 Nişantaşı, İstanbul-Turkey
Phone: +90 212 241 45 45
Fax: +90 212 241 44 08
E-mail: tajev@tajev.org

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Kohler G; Egelkraut H. In Kohler G and Egelkraut H (edts).Munchener Funktionelle Entwicklungsdiagnostik im zweitem und drittem Lebensjahr. Handanweisung. Munchen: Uni Munchen, Institut fur Soziale Paediatrie und Jugendmedizin; 1984.

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Journal of the
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MOST CITED AND MOST VIEWED ARTICLES

Dear Readers,
I would like to present our most cited and most viewed articles on different platforms, like our website, Web of Science, Scopus and PubMed.

Website

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Impact of obesity on infertility in women by Zeynep Özcan Dağ, Berna Dilnaz

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Editorial

Dear Colleagues,

It is my great pleasure to meet with you again in the third issue of the Journal of the Turkish - German Gynecological Association *(J Turk Ger Gynecol Assoc)* in the publishing year of 2018.

The Turkish - German Gynecological Association *(J Turk Ger Gynecol Assoc)* is a leading academic journal devoted to reporting the latest, cutting-edge research progress and findings of basic research and clinical practice in the field of obstetrics and gynecology. We encourage gynecologists worldwide to submit manuscripts to the *J Turk Ger Gynecol Assoc* describing their original basic or clinical research findings that are of high academic value and which report new diagnostic techniques or summarize their treatment experiences. *J Turk Ger Gynecol Assoc* is a quarterly journal focused on the busy ob-gyn generalist. As usual, our goal is to help you keep abreast of the latest developments by providing you with topical review articles that cover the full breadth of issues in women's health care, written by experienced, thoughtful clinical leaders in their respective fields of obstetrics and gynecology. In addition, each quarterly journal will provide you with an update of the latest technologies on the market and offer you concise summaries of some of the more important articles published in our worldwide literature.

Dear Researchers,

We have a very interesting and astonishing issue. There are several well written manuscripts from all over the world. You will read a good paper from Chile about thoracic and diaphragmatic endometriosis. Another paper from Iranian colleagues pointed interesting inputs on menopause. An update for endometriosis from Indonesia could be seen in this particular issue. I hope you will see other many well organized and written manuscripts from our national colleagues. The long-term success of our journal can be achieved by publications with high scientific quality. To reach this purpose, we need support from all our members and our scientists.

I would like to wish a successful working period to all valued members in the Editorial Board. We are looking forward to receiving your valuable submissions and thank you in advance for your contributions.

On behalf of *J Turk Ger Gynecol Assoc*, we wish you a sunny autumn.

Sincerely,

Prof. Cihat Ünlü, M.D.
Editor in Chief of *J Turk Ger Gynecol Assoc*
President of TGGF

Thoracic and diaphragmatic endometriosis: Single-institution experience using novel, broadened diagnostic criteria

Demetrio Larraín[1,3], Francisco Suárez[2], Hernán Braun[3], Javier Chapochnick[4], Lidia Diaz[5], Iván Rojas[3]

[1]Department of Obstetrics and Gynecology, Endometriosis Unit, Clínica Santa María, Santiago, Chile
[2]Department of Thoracic Surgery, Clínica Santa María, Santiago, Chile
[3]Department of Obstetrics and Gynecology, Clínica Santa María, Santiago, Chile
[4]Department of Hepatobiliary Surgery, Clínica Santa María, Santiago, Chile
[5]Department of Pathology, Clínica Santa María, Santiago, Chile

Abstract

Objective: To describe our experience with the multidisciplinary management of both thoracic/diaphragmatic endometriosis (TED), applying a broadened definition of the "Thoracic endometriosis syndrome (TES)" to define cases.

Material and Methods: We present a retrospective series of consecutive patients affected by pathology-proven TED, treated at our institution, during a period of 7 years.

Results: Five women were included. Two patients were referred due to catamenial chest/shoulder pain, one due to recurrent catamenial pneumothorax, and one due to new-onset diaphragmatic hernia. One patient had no thoracic symptoms, but diaphragmatic endometriosis was found during gynecologic laparoscopy for pelvic endometriosis. Endometriosis was histologically confirmed in all cases. After follow-up, all patients remain asymptomatic.

Conclusion: Broadened TES criteria could increase the incidence of TED and determine better knowledge of this condition. Multidisciplinary, minimally invasive surgery is effective and safe, but should be reserved for tertiary referral centers. (J Turk Ger Gynecol Assoc 2018; 19: 116-21)

Keywords: Thoracic endometriosis syndrome, diaphragmatic endometriosis, thoracic endometriosis

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Introduction

Endometriosis is defined as the presence of endometrial glands and stroma outside the endometrial cavity; it can be categorized as pelvic and extrapelvic, based on anatomic distribution. It has been estimated that about 12% of women with endometriosis have extrapelvic disease, but the exact prevalence of diaphragmatic endometriosis is unknown (1). Endometriotic involvement of the diaphragm is often asymptomatic, but when symptoms occur they consist of chest pain, upper quadrant pain, and catamenial shoulder pain. These symptoms may or may not occur in relation to menstruation (2). Diaphragmatic endometriosis can also present with what is called thoracic endometriosis syndrome (TES), an entity that classically includes catamenial pneumothorax, catamenial hemothorax, catamenial hemoptysis or intrathoracic endometriotic nodules (3). However, a recent study has proposed including another three entities in the spectrum of TES, namely, endometriosis-related diaphragmatic hernia, catamenial chest pain, and endometriosis-related pleural effusion (4). We hypothesize that this "extended" definition of TES could increase the sensitivity of diagnosis of diaphragmatic endometriosis and lead to a better knowledge of this condition. The objective of the present study was to review our single-institution experience with the diagnosis and management of TES and diaphragmatic endometriosis using this recently-proposed criteria.

Address for Correspondence: *Demetrio Larraín*
e.mail: dlarraind@gmail.com ORCID ID: orcid.org/0000-0002-4161-0513

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Material and Methods

This is a retrospective observational study of all patients with a definitive diagnosis of diaphragmatic or thoracic endometriosis who were managed at our institution between January 2010 and October 2017. In our institution the diagnosis, of TES/diaphragmatic endometriosis can be first established in different ways: First, by thoracic surgeons, either at the time of video-assisted thoracoscopic surgery (VATS) or in patients presenting with TES but without previous diagnosis of endometriosis; these patients are referred to a gynecologic team for further treatment. Second, by the gynecologists, in patients with known history of pelvic endometriosis who present with TES, or as an incidental finding during gynecologic laparoscopy. These patients are either referred to the thoracic surgery team or evaluated by them intraoperatively. We included all patients who were evaluated for clinically-suspected diaphragmatic endometriosis or "extended" TES (i.e., including endometriosis-related diaphragmatic hernia, catamenial chest pain, and endometriosis-related pleural effusion) and those incidentally found to have diaphragmatic endometriosis during gynecologic laparoscopy for endometriosis. We consider this as a valid tool for diagnosis of diaphragmatic endometriosis because we routinely inspect the diaphragm for endometriosis at the time of laparoscopy. Visual diagnosis was confirmed with pathology whenever possible; however, in cases in which thoracic/diaphragmatic samples were not obtained, only cases with pathologic confirmation of endometriosis from other sites were included. Furthermore, we included all patients with a diagnosis of thoracic or diaphragmatic endometriosis in definitive pathology examinations obtained from both gynecologic and thoracic surgery databases. Available data about clinical symptoms, medical treatments, and surgical findings were tabulated and correlated with both clinical and pathologic features for each patient. Institutional Review Board approval was obtained from the Institutional Ethics Committee. Informed consent was obtained from all patients.

Results

We found five cases of thoracic/diaphragmatic endometriosis during the study period. Three patients were referred to our unit for evaluation from the thoracic surgery department, and the other two were primarily evaluated at our own gynecology department.

Case 1

A 36-year-old woman, gravida 1, para 1, with a history of laparoscopic fulguration of pelvic endometriosis 3 years previously was referred to our institution because of dysmenorrhea and monthly right-sided shoulder pain associated with menses. She was using oral contraceptive pills (OCP) without pain relief. Deep pelvic endometriosis with endometriotic involvement of the diaphragm was suspected and abdominopelvic and diaphragmatic magnetic resonance imaging (MRI) was performed. MRI showed deep pelvic endometriosis involving the bladder and the uterosacral ligaments, and multiple posterior subphrenic lesions suggestive of diaphragmatic endometriosis. We performed a multidisciplinary team laparoscopy (gynecologic and thoracic surgeons) and found deep pelvic endometriosis and extensive endometriosis involving the right posterior hemidiaphragm (only visible with the 30º optic and after liver mobilization). Laparoscopic partial cystectomy, uterosacral ligament resection and a full-thickness partial diaphragmatic resection were performed without complications; a chest drain was left in place for 2 days and she was discharged on postoperative day 5. Histopathology confirmed endometriosis in all specimens (Figure 1a-c). To date, she is using OCP and remains asymptomatic after 38 months' follow-up.

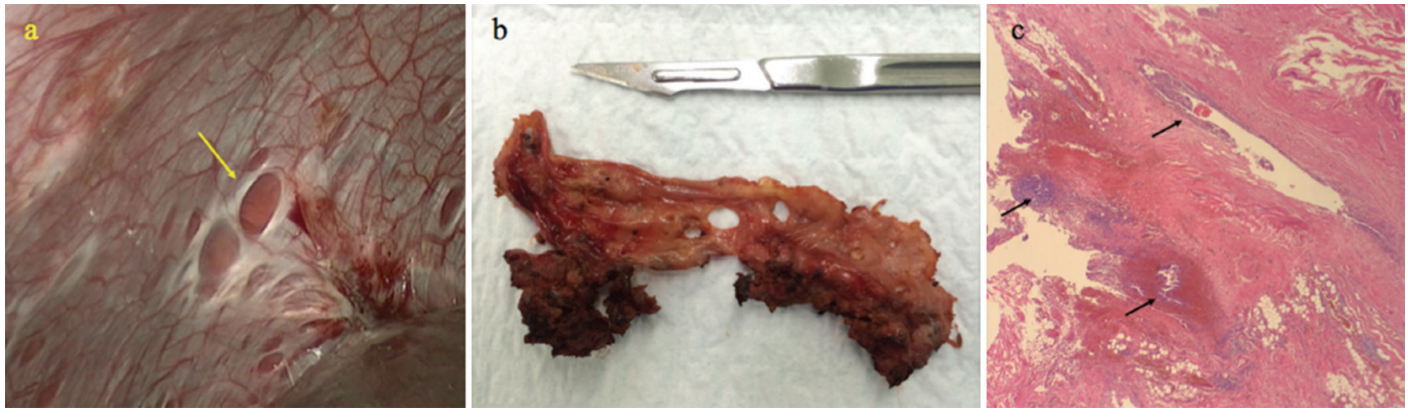

Figure 1. a) Laparoscopic aspect of diaphragmatic endometriosis. Note the "typical" fenestrations on the diaphragmatic surface (arrow). b) Macroscopic view of the surgical specimen in the same patient. c) Microscopic view of endometrial tissue (glands and stroma) in the resected diaphragm (arrows) (Hematoxylin & Eosin stain, ×10)

Case 2

A 42-year-old nulliparous woman with a history of infertility and recurrent catamenial pneumothorax (2 previous episodes, the last one 6 months earlier) was referred to our emergency department due to right-sided chest pain and mild dyspnea, which started within 48 hours of onset of menses. She had no previous history of endometriosis and never had dysmenorrhea or dyspareunia. The initial examination included chest X-ray, which revealed a right pneumothorax. A chest computed tomography (CT) scan confirmed the diagnosis and VATS was performed. During VATS, we found several diaphragmatic fenestrations that communicated with the abdominal cavity, through which the liver had herniated. The involved area was resected and the diaphragm was repaired using a nonabsorbable interrupted suture (Figure 2a-c). Pathologic report confirmed diaphragmatic endometriosis. The patient underwent in vitro fertilization (IVF) 4 months after surgery and became pregnant. She is now at 20-weeks of a normal pregnancy and remains asymptomatic.

Case 3

A nulliparous, 26-year-old woman, with a known diagnosis of pelvic endometriosis and medical treatment with continuous OCP for 9 years was referred to our institution due to recurrent pelvic pain, severe dysmenorrhea, and dyspareunia. Moreover, she presented with chronic right shoulder pain, which was exacerbated during menstruation. She had a history of one previous laparoscopy for endometriosis in which both pelvic and diaphragmatic endometriosis were discovered, but the latter was not treated. The biopsy confirmed endometriosis in all pelvic samples. After the surgery she was treated with gonadotrophin-releasing hormone (GnRH) analogues for six months with transitory improvement, but she could not receive more OCP due to de discovery of a hepatic adenoma. Due to persistent and incapacitating catamenial right shoulder pain accompanied by severe dyspnea, a chest CT was performed with only nonspecific findings. She underwent an exploratory VATS and we found several endometriotic foci in the central tendon of the diaphragm and right hemidiaphragm, which were fulgurated and resected. The pathology report was consistent with fibrosis but not with endometriosis. However, it also reported a marked thermal effect on the tissue. Four months after surgery she conceived spontaneously and delivered a healthy newborn at 38 weeks of gestation. She is currently under treatment with an implantable contraceptive and reports great improvement after a 7-year follow-up.

Case 4

A 35-year-old nulliparous woman, was referred to our unit with a long history of infertility and chronic pelvic pain. She also

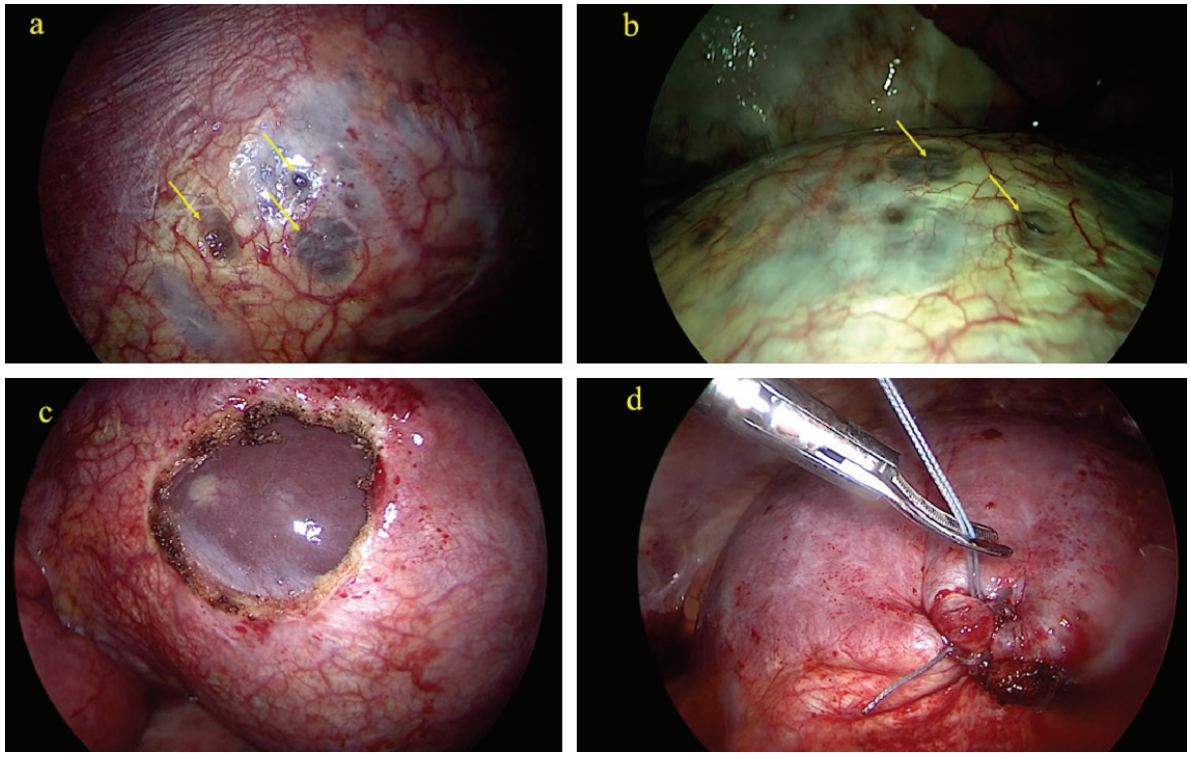

Figure 2. a, b) Thoracoscopic aspect of diaphragmatic endometriosis. Note the presence of fenestrations on the thoracic surface of the diaphragm (arrows). c) Diaphragmatic defect after surgical resection. The liver surface is visible through the defect. d) Diaphragmatic suture after endometriosis resection

had severe dysmenorrhea and dyspareunia, but reported no thoracic symptoms. She underwent gynecologic laparoscopy, and deep pelvic endometriosis in the uterosacral ligaments was resected; several endometriotic lesions in the right hemidiaphragm were left behind and not treated, due the lack of symptoms. The pathology report confirmed endometriosis in all pelvic specimens. Fourteen months after surgery, she underwent three cycles of intrauterine insemination and became pregnant. She underwent emergency cesarean section at 30 weeks of gestation due to placental abruption with good perinatal outcome. She remains asymptomatic after 55 months' follow-up.

Case 5

A 40-year-old nulliparous woman, with history of four previous surgeries for endometriosis, persistent dysmenorrhea, and infertility was evaluated in our emergency department due to epigastric and left flank pain, dyspepsia, and nausea. Abdominopelvic CT revealed a left diaphragmatic hernia, with the splenic flexure of the colon herniated into the chest and signs of severe pelvic endometriosis. Chest CT confirmed the diagnosis and the absence of pneumothorax. She had no history of diaphragmatic surgery, trauma or any pulmonary disease. Moreover, she had undergone chest CT one year earlier due to a deep venous thrombosis, which revealed no diaphragmatic defects. VATS was performed; the edges of the diaphragmatic hernia were resected and the diaphragm was repaired using a direct suture. A pathologic examination of the resected tissue confirmed endometriosis. She remains asymptomatic after 26 months' follow-up.

Discussion

TES refers to a broad spectrum of clinical manifestations related to the presence of ectopic endometriotic tissue in the diaphragm or in the thoracic cavity. Despite the many publications on this topic (3,5), only a few include endometriosis-related diaphragmatic hernia, catamenial chest pain, and endometriosis-related pleural effusion as part of TES (4). In the present study, we included these three entities in the TES definition and coined the term "extended TES" (Figure 3). Among our patients, if the "classic" definition was used, we could only include one case of diaphragmatic/thoracic endometriosis. However, when the broadened definition was used in addition to the laparoscopic findings among patients with endometriosis, we identified 5 patients, all of whom had pathologiy-confirmed endometriosis. Hence, rising the incidence in the same population. It has been considered that thoracic/diaphragmatic endometriosis is underdiagnosed and its incidence is often underestimated. It is often overlooked by gynecologists because of the lack of appreciation of the

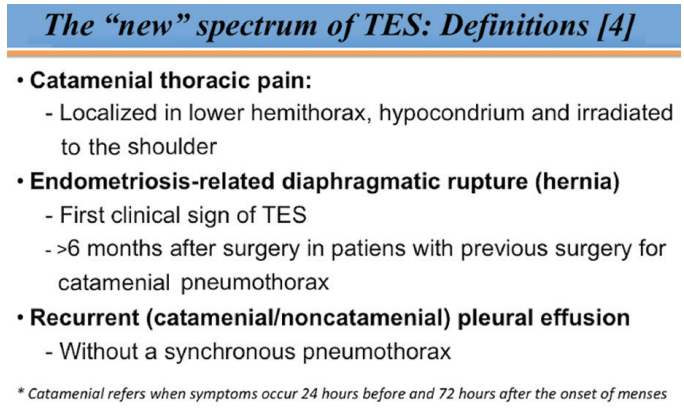

Figure 3. Recently proposed new entities of TES (4)
TES: Thoracic endometriosis syndrome

symptoms and the failure to properly examine the patient and evaluate the diaphragm during surgery. In our experience, we routinely inspect the diaphragm for endometriosis during surgery; however, diaphragmatic lesions can easily be missed because they are often located in the posterior diaphragm and hidden behind the liver (6). Furthermore, a significant number of patients with diaphragmatic endometriosis can go undiagnosed for long periods of time because of a traditional focus on the lower pelvic region and the variable appearance of endometriotic lesions (7). Moreover, diaphragmatic endometriosis is usually not systematically associated with pelvic endometriosis (5,8,9). For that reason, some cases are misdiagnosed as other conditions involving the gastrointestinal tract or of cardiothoracic origin. All these factors contribute to a significant delay in the diagnosis (10). In fact, the diagnosis of diaphragmatic endometriosis is often made later in life than that of pelvic disease (3), probably because a longer period of time is needed to affect the diaphragm and thorax. In our series as in others (5,7,10), the median age at diagnosis was more than 35 years. The diagnosis of diaphragmatic endometriosis requires a high level of clinical suspicion, and imaging studies such as chest CT and MRI can assist with diagnosis and surgical planning (11), but they are not mandatory (10).

The pathophysiology of diaphragmatic endometriosis is unknown, however the marked asymmetry in distribution of diaphragmatic and thoracic lesions (90% on the right side), supports the Sampson's retrograde menstruation theory (12). The most widely accepted mechanism is that endometrial cells in the peritoneal fluid may follow the clockwise peritoneal circulation, through the right paracolic gutter towards the right sub-diaphragmatic area; the phrenicocolic ligament on the left-hand side and the falciform ligament form barriers that prevent cells and fluid from reaching the left sub-diaphragmatic area (12). However, lesions have been found on both sides of the diaphragm (2). Endometrial cell implantation leads to the formation of endometriotic nodules on the abdominal side

of the diaphragm. The nodules undergo cyclical necrosis and cause diaphragmatic fragility, leading to the formation of the "typical" diaphragmatic fenestrations (Figure 1a). These perforations can coalesce into larger defects that can determine hernia formation. Moreover, it has been reported that diaphragmatic hernia can be the first clinical manifestation of TES (4,13). After endometrial tissue has entered the pleural space, it may colonize other part of the diaphragm or the pleural space. We speculate that the clinical manifestations (i.e., catamenial chest pain, endometriosis-related pleural effusion, endometriosis-related diaphragmatic hernia, catamenial pneumothorax, catamenial hemothorax, intrathoracic endometriotic nodules and catamenial hemoptysis) could be considered as a sequence of events, a consequence of endometrial tissue undergoing cyclical changes. Interestingly, despite diaphragmatic hernia being known as complication in patients with previous surgery for catamenial pneumothorax (10), hernia formation was reported as part of the evolution of diaphragmatic endometriosis when it was diagnosed more than six months after surgery for catamenial pneumothorax (4,14). In that sense, we think that this broadened definition of TES allows both gynecologic and thoracic surgeons a better understanding of the pathophysiology of TES.

Although the definitive diagnosis of endometriosis requires histologic confirmation, it is not always possible due to technical difficulties and the risk of diaphragmatic perforation (2,6), especially in asymptomatic patients. Moreover, the histologic diagnosis of endometriosis may be challenging on small pleural or lung biopsies and it is often overlooked due to the presence of fibrosis, inflammation, the effect of thermocoagulation, and the scant and patchy distribution of endometrial elements (15). This was the situation in Case 3, in which the surgical specimen had a marked thermal effect due to extensive fulguration. Notably, in our experience, in all cases in which diaphragmatic endometriosis was an incidental finding or it was not treated, the disease was confirmed histologically in other sites of the pelvis or abdomen.

In our practice, medical treatment is the first-line approach in patients who have no desire for pregnancy and includes the use of OCP or GnRH analogues. Surgery is reserved for symptomatic patients. We usually start with gynecologic laparoscopy, whereas VATS is reserved for symptomatic patients only who meet the "extended" TES criteria, when nonsurgical treatments have failed.

Surgical approach to diaphragmatic endometriosis has experienced several changes during the last 10 years, from the classic laparotomy/thoracotomy (6), to a less invasive laparoscopy/VATS (1,10,16). In our experience, the diaphragm is routinely inspected during all gynecologic laparoscopies. If better visualization of the diaphragm is required, the patient is positioned in steep reverse-Trendelenburg position and a 30º optic is used. When diaphragmatic lesions are not accessible from suprapubic trocars, additional 5-mm trocars are placed in the upper right or left abdominal quadrant, according to the implant location (16). In some patients (Case 1), liver mobilization is warranted in order to improve exposure (16). If pneumothorax occurred after excision of a full-thickness diaphragmatic nodule, the anesthesiologist is always notified; the resection is completed, and the thoracic surgeon repairs the diaphragmatic defect. However, if diaphragmatic resection is anticipated, a thoracic surgeon is always present in the operative room. VATS allows direct visualization of thoracic implants and nodules, and the ability to resect both parenchymal and diaphragmatic implants (4,10). When VATS is performed as the first procedure, the presence of pelvic endometriosis must be investigated. In our opinion, the best strategy is to perform a multidisciplinary procedure combining laparoscopy and VATS when necessary (1,10).

The necessity for postoperative medical therapy is defined by the gynecologist, and must be individually tailored taking to account patient age, severity of symptoms (pelvic or thoracic), and the desire for pregnancy (17).

Thoracic endometriosis was thought to be an unusual manifestation of extrapelvic endometriosis, but it seems to be increasing, likely because of an increased awareness of the condition among gynecologists and the use of a lower threshold of symptoms to make the diagnosis, such as the "extended" TES criteria. In addition, thoracic endometriosis is often treated as a respiratory disease, reducing opportunities for gynecologic evaluation. Based on our experience, we strongly suggest that patients with cyclic thoracic symptoms and pelvic pain should undergo an evaluation for both thoracic and pelvic endometriosis. For symptomatic patients, the multidisciplinary and minimally invasive surgical approach is safe and reproducible, but it should be reserved for tertiary referral centers where the collaboration between gynecologist and thoracic surgeons is really possible.

The diagnosis of diaphragmatic endometriosis is challenging and requires a high level of clinical suspicion. The use of more sensitive diagnostic criteria could increase the incidence of the disease by including new entities in the classic spectrum of TES. Multidisciplinary evaluation should be the standard in suspected cases. The use of minimally invasive surgical approach is effective and safe, but should be reserved to tertiary referral centers.

Ethics Committee Approval: *Institutional Review Board approval was obtained from the Institutional Ethics Committee for this study.*

Informed Consent: *Informed consent was obtained from all patients.*

Peer-review: *Externally peer-reviewed.*

Author Contributions: *Concept - D.L., F.S., J.C., H.B.; Design - D.L., F.S., J.C., H.B.; Supervision - I.R.; Materials - D.L., L.D., J.C., F.S.; Writer - D.L., I.R.*

Conflict of Interest: *No conflict of interest is declared by the authors.*

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A double-blind, placebo-controlled trial of Fennel *(Foeniculum vulgare)* on menopausal symptoms: A high placebo response

Masumeh Ghazanfarpour[1], Mona Najaf Najafi[2], Nosrat Baharian Sharghi[3], Mahsa Sadat Mousavi[4], Masoudeh Babakhanian[5], Hassan Rakhshandeh[6]

[1]Department of Midwifery, School of Nursing and Midwifery, Kerman University of Medical Sciences, Kerman, Iran
[2]Department of Community Medicine, Imam Reza Clinical Research Units, Mashhad University of Medicl Sciences School of Medicine, Mashhad, Iran
[3]Midwife, Omolbanin Hospital, Mashhad, Iran
[4]Department of Midwifery, Isfahan (Khorasgan) Branch, Islamic Azad University, Isfahan, Iran
[5]Social Determinant of Health Research Center, Semnan University of Medical Sciences, Semnan, Iran
[6]Pharmacological Research Center of Medicinal Plants, Mashhad University of Medical Sciences, Mashhad, Iran

Abstract

Objective: The present study aimed to evaluate the effects of oral fennel on menopausal symptoms.

Material and Methods: This double-blind, randomized, placebo-controlled trial was conducted on 50 postmenopausal women in Mashhad (Iran). Patients were randomly divided into two groups of fennel (n=25) and placebo (n=25). Measurements were performed at baseline and after three months using the Menopause-Specific Quality of Life questionnaire.

Results: Both placebo and treatment groups revealed significant improvements in the hot flush score ($p<0.001$ for fennel and $p<0.01$ for placebo), night sweats ($p=0.007$ for fennel and $p<0.01$ for placebo), sweating ($p=0.002$ for fennel and $p<0.01$ for placebo), symptoms of anxiety ($p=0.05$ for fennel and $p=0.001$ for placebo), feeling depressed ($p<0.01$ for fennel and $p=0.006$ for placebo), and impatience with other people ($p<0.01$ for fennel and $p=0.003$ for placebo). There were no significant differences in any menopausal symptoms between the fennel and placebo groups, except for coughing and sneezing when urinating ($p=0.03$).

Conclusion: The failure to indicate a significant effect may have been caused by a high placebo response. It is suggested that future trials should include a placebo run-in phase or design a sequential, parallel study with larger sample sizes to mitigate the placebo effect. (J Turk Ger Gynecol Assoc 2018; 19: 122-7)

Keywords: *Foeniculum vulgare*, menopausal symptoms, menopause-specific quality of life, post menopause, quality of life

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Introduction

All women experience the menopause as a normal phenomenon. Most menopausal women (nearly 80%) experience vasomotor and vaginal symptoms, urinary incontinence, joint pain, headaches, tachycardia, depression, dizziness, irregular heart rate, mental disorders, sexual dysfunction, and sleeplessness during their postmenopausal period. A few of these symptoms may last for several years (1-3). These complications impose a significant economic burden on society (4,5) and disrupt the normal life of people (1). A number of studies have revealed that hormone replacement therapy (HRT) prevents depression (6), sleep disorder (7), osteoporosis (8), and hot flashes (9); however, HRT is known to be associated with increased thrombosis and breast cancer (10). Therefore, postmenopausal women prefer to use nonhormonal compounds such as phytoestrogens, which offer a safer option (11-13). Phytoestrogens, as polyphenolic and

Address for Correspondence: *Hassan Rakhshandeh*
e.mail: RakhshandehH@rnums.ac.ir ORCID ID: orcid.org/0000-0002-2118-1096

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nonsteroidal compounds in plants, can bind to human estrogen receptors; the effects of these compounds are less significant than those of endogenous steroidal estrogens. Based on *in vivo* and *in vitro* investigations, fennel, as a phytoestrogen, may treat several disorders including anxiety (14), depression, stress, sleep disorders (15), and vaginal atrophy (16), and various cognitive disorders such as Alzheimer's disease and dementia (17). Accordingly, this study was designed to evaluate the role of fennel on attenuating the disorders associated with menopause.

Material and Methods

Some menopausal symptoms, including quality of life and sleep, among postmenopausal women in Iran were studied following the oral consumption of fennel within the current randomized, double-blinded, placebo-controlled clinical trial. The Ethics Committee of Mashhad University of Medical Science approved the study protocol considering the principle of Declaration of Helsinki. This study continued for 17 months, from January 2015 to June 2016. All participants signed informed consent forms for their voluntary participation in the study, and they were allowed to leave the trial at any period. The inclusion criteria were healthy postmenopausal women with the age range of 45 to 65 years who had no vaginal bleeding in the previous year, a normal mammogram within the last year, and no history of taking systemic and tropical estrogen in the last six months. The subjects were selected from health centers in each area of Mashhad using the convenience sampling method. Therefore, Mashhad was divided into four geographic areas (north, south, west, and east) out of which 10 centers were randomly selected using cluster sampling. A list of menopausal women who were referred to the health centers was provided. All women on the list were contacted by telephone until 50 patients who met the eligibility criteria were selected. Participants were invited to the gynecology clinics of Game Hospital to complete a questionnaire.

Sample size

The aim of this study was to investigate the impact of fennel on the quality of life among Iranian postmenopausal women. To this end, we found a study that assessed *Glycyrrhiza glabra* to determine the beneficial impact of this medicinal plant on quality of life in Iranian menopausal women. We chose this article because both fennel and *Glycyrrhiza glabra* are considered as phytoestrogens and contain flavonoids. Thus, the sample size was determined based on the difference between *Glycyrrhizin glabra* and placebo reported in the study of Asgari et al. (18) on vasomotor (*Glycyrrhiza glabra* mean ± SD= 1.23±1.07 and placebo mean ± SD=2.8±1.82), psychological (*Glycyrrhiza glabra* mean ± SD=3.8±1.9 and placebo mean ± SD=8.52±3.11), physical (red clover mean ± SD=7.6±3.91 and placebo mean ± SD=10.8±5.03) and sexual (*Glycyrrhiza glabra* mean ± SD= 7.29±6.15 and placebo mean ± SD=1.36±1.21) symptoms. The sample size was estimated using NCSS PASS software. With an alpha error of 0.2 and power of 80%, a sample size of n=10 for vasomotor, n=20 for physical, and n=7 for sexual was estimated.

Measurements

The Menopause-Specific Quality of Life (MENQOL) questionnaire developed has three sections. Part I includes demographic information. Part II has researcher-made four items based on the literature to assess attitudes toward menopause (Are herbal medicines safer than chemical drugs? Are herbal medicines more effective than chemical drugs? Do you suggest using herbal therapy to address sexual issues for women? Do you think that herbal medicines can be harmful to your health?). Part III deals with 29 items within four subclasses, involving 3 vasomotor items, 7 psychosocial items, 16 physical items, and 3 sexual items. The scoring system of this questionnaire is based on a 6-point Likert scale ranging from 1 (no experience) to 5 (extremely bothersome), with higher scores indicating lower quality of life (19). The Persian version of this questionnaire has been validated by limited studies (20,21). The participants were asked to report the presence and severity of symptoms within the last month. If no (none), they continued to the subsequent item; if yes, they marked the severity of the symptom on a scale of 0-6. For participants who were illiterate, questions were read out by the interviewer and the responses were recorded.

Randomization and blinding

Patients' allocation sequencing was accomplished using a computerized random number generator. The study participants were randomly allocated to one of the two groups of fennel and placebo. To ensure that both patients and researchers were blinded to the treatment, capsules were identical in color (yellow), shape, and weight (100 mg capsules; as ensured by Barij Essence Company), and they all contained sunflower oil. Bottles contained high-density polyethylene and were labeled as "A" and "B." All drugs were administered by assistant researchers who were not involved in the study. The identity of the bottles was not disclosed until the end of study.

Intervention, compliance, and adverse event measures

Participants were instructed to consume capsules three times per day (morning, noon, and night) for a 3 month follow-up period. The soft 100 mg capsules contained 30% fennel (standardized to 21-27 mg anethole) supplemented with sunflower oil (http://www.barijessence.com). Compliance was

checked by asking patients to bring unused capsules to each follow-up visit. Adverse events were investigated retrospectively based on the patient's self-report.

Statistical analysis

The obtained data were analyzed using SPSS 19 (SPSS Inc., Chicago, IL) using the Kolmogorov-Smirnov test to check data normality, and the chi-square test (for categorical data) and independent t-test (for continual data) to find the differences between the study groups, and the paired t-test to compare the results before and after the intervention. The significance level for all tests was considered to be $p<0.05$.

Results

No adverse effects were reported in the study and there were no dropouts. The groups were comparable at baseline in terms of age, body weight, number of children, educational level, years of menopause, previous use of hormone therapy and vitamin supplement, use of herbal medicine, and cigarette smoking (Table 1). Both placebo and treatment groups revealed significant improvements in hot flush scores ($p<0.01$ for fennel and $p<0.001$ for placebo), night sweats ($p=0.007$ for fennel and $p<0.01$ for placebo), sweating ($p=0.002$ for fennel and $p<0.001$ for placebo), anxiety symptoms ($p=0.05$ for fennel and $p<0.01$ for placebo), feelings of depression ($p<0.01$ for fennel and $p=0.006$ for placebo), and impatience with other people ($p<0.01$ for fennel and $p=0.003$ for placebo). There was no significant difference between the two study groups. Sleep disorder scores were significantly reduced (2.3 points) on a 5-point scale (57%) in the fennel group, whereas this improvement was not significant in the placebo group (22%). The fennel group revealed a 43% decrease (improvement)

Table 1. The demographics and baseline characteristics of subjects in the two groups

Variables	Fennel group mean ± SD or number (%)	Placebo group mean ± SD or number (%)	p value
Body weight (kg)	68.4±16.25	70.92±12.40	0.541
Age (year)	56±4.2	55±4.7	0.414
Years since menopause	6.2±3.8	5.2±4.2	0.346
Number of children	5.2±2.3	5.1±1.7	0.946
History of hysterectomy*			0.695
Yes	2 (8%)	2 (8%)	
Marital status*			0.501
Married	20 (80)	23 (92)	
Divorced	2 (8%)	0	
Widow	3 (12%)	2 (80%)	
Cigarette smoking*	1	2	
Educational level of women*			0.836
Illiterate	2 (8%)	4 (16%)	
Primary school	11 (44%)	11 (44%)	
Middle school	2 (8%)	3 (12%)	
High school	7 (28%)	4 (16%)	
University	3 (12%)	3 (12%)	
Previous use of hormone therapy*			
Yes	2 (8%)	5 (20%)	0.417
No	23 (92%)	20 (80%)	
Use of herbal medicine*			
Yes	0	4 (16%)	0.11
No	25 (100%)	21 (84%)	
Use of vitamin supplement*			0.144
Yes	3 (12%)	4 (16%)	
No	22 (80%)	21 (84%)	
Attitude toward menopausal medicine	1.65±0.41	1.59±0.43	0.656

*Number (%); SD: Standard deviation

in the severity of memory loss score, whereas this score increased (worsened) slightly (17%) in the placebo group. Surprisingly, placebo was found to have greater effect on the relief of depression (38% for fennel and 49% for placebo) (Table 2).

Discussion

In this study, both fennel and placebo groups revealed a significant improvement in scores of hot flash, night sweats, sweating, anxiety, depression, and impatience with other people; however, the fennel group was not different from the placebo groups with respect to menopause symptoms. The high placebo response might have caused the negative results. A high placebo effect is often observed in psychiatric (22,23) and nonhormonal trials (24). Unexpectedly, the high placebo effect may be related to confounding factors such as patients' expectations of treatment efficacy, past or current drug use, severity and duration of illness prior to the treatment response, and natural fluctuating patterns of the disease (23).

As shown in Table 1, when comparing the two groups, there was no significant difference in age, years of menopause, history of taking hormonal medications and vitamin supplements, and history of taking herbal medicine. The baseline attitudes toward herbal medicines showed no significant difference between the two groups. Moreover, no significant effect was observed in the subgroup high placebo (more than 50% vs less than 50%) in the placebo group; however, the limited attitude statements made us to interpret these findings cautiously.

It is assumed that fennel may improve memory and intelligence. Joshi and Parle (17) reported that methanolic

Table 2. Comparison of menopausal symptoms between two groups

Menopause symptoms	Fennel group (n=25) mean ± SD	Placebo group (n=25) mean ± SD	p value	Post analysis power
Hot flashes	0.80±1.19	1.08±1.28	0.429	30%
Night sweats	0.72±1.2	1.16±1.43	0.247	41%
Sweating	0.76±1.23	0.88±1.45	0.754	22%
Dissatisfaction with personal life	4.4±1.47	4.20±1.97	0.699	23%
Anxiety and nervousness	1.79±1.64	2.50±1.97	0.157	25%
Loss of memory	1.52±1.66	2.32±1.81	0.111	33%
Less effective than before	1.64±1.57	2.5±2.19	0.126	62%
Feelings of depression	1.16±1.59	1.32±1.95	0.753	22%
Being impatient with other people	0.80±1.25	1.4±1.63	0.152	54%
Loneliness	0.76±1.53	1.24±1.73	0.306	39%
Feeling bloated	1.36±1.68	1.60±1.87	0.635	20%
Joint and muscle pain	2.36±2.15	2.64±2.36	0.664	23%
Feel like crying and worries	1.28±1.88	1.36±1.62	0.873	20%
Sleeplessness	1.32±1.95	2.04±2.16	0.223	46%
Headache and neck pains	1±1.522	1.95±2.13	0.07	66%
Reduced physical strength-	2.08±1.77	2.48±1.96	0.454	30%
Decrease in stamina	2±1.75	2.52±1.91	0.322	38%
Lack of energy	2.08±1.80	2.48±2.04	0.466	30%
Dry skin	2.25±1.73	1.56±1.80	0.175	51%
Weight gain	1.16±1.46	0.80±1.19	0.343	36%
Increased facial hair	0.36±0.86	0.60±1.18	0.473	31%
Changes in skin appearance and texture	1.24±1.42	1.36±1.46	0.840	20%
Feeling bloated	0.48±1.15	0.44±0.71	0.873	20%
Feeling lumbago	1.80±2.02	1.69±1.76	0.846	20%
Frequent urination	0.80±1.38	1.76±2.31	0.08	66%
Coughing and sneezing when urinating	0.76±1.23	1.80±2.08	0.038	77%
Reduced libido desire	3.44±2.36	3.12±2.40	0.637	24%
Vaginal dryness during intercourse	0.40±1	0.48±1.41	0.819	22%
Avoid intimate relationship	0.2±0.81	0.60±1.50	0.247	43%

SD: Standard deviation

extraction of fennel might have a memory-improving effect. This oral extraction at different concentrations of 50, 100, and 200 mg/kg was given to young mice for eight consecutive days. Fennel extract improved age-induced memory deficits. Moreover, fennel significantly increased step-down latency and acetyl cholinesterase inhibition. According to their conclusion, some cognitive disorders, including dementia and Alzheimer's disease might be treated by the fennel extraction.

The memory-enhancing activity of fennel was assessed in an animal model using the conditioned avoidance response. Thus, the study rats separately experienced the training schedule. The rats were placed in the chamber. The pre-shock was a buzzer and then the main shock was exerted via the grid floor. To prevent the foot shock, the training program was a jump of the rats to the pole, i.e. shock-free zone. When exposed to the buzzer, the rats showed two responses: escape (if the rats jumped on the pole) or avoidance (if the rats jumped prior to the onset of the shock). The rats were classified into four groups of five. Groups II, III, and IV received methanolic fennel extract at concentrations of 50, 100, and 200 mg/kg, and group I was the controls. The fennel group had greater avoidance responses compared with the controls, whereas the control group showed higher amnesia. In addition, the amnesia was induced by scopolamine butyl bromide. It took 3-5 days for the fennel group and over 6 days for the control group to recover from the scopolamine-induced amnesia (25).

A study reported the sedative effect of 200 mg/kg aqueous extracts of fennel seeds in male albino rates. It also revealed a significant increase in some neurotransmitter content in all brain regions (26). Mesfin et al. (25) studied the anxiolytic activity of *Foeniculum vulgare* essential oil on a murine model. The administration of fennel decreased anxiety and depression by 55% and 45% compared with baseline, respectively. The data from *in vitro* and *in vivo* studies suggest anti-anxiety and anti-depression effects of the fennel extract.

Shirazi et al. (15) demonstrated the impacts of fennel combined with officinalis (Melissa) on improving the Pittsburgh Sleep Quality Index among menopausal women with sleep disorders. A significant improvement was observed in the sleep disorders in the Melissa group compared with the citalopram and placebo groups. Consistent with the study of Shirazi et al. (15), this study mitigated sleep disorder by 57%. This improvement in sleep disorder could be related to the sedative effect of fennel.

In a trial by Yaralizadeh et al. (16), 60 postmenopausal women were randomly assigned to fennel 5% vaginal cream (5 g/day) and placebo vaginal cream for eight weeks. All symptoms such as itching ($p=0.017$), dryness ($p<0.001$), and pallor ($p<0.001$), with the exception of burning ($p=0.14$), improved significantly compared with placebo. In accordance with the study of Yaralizadeh et al. (16), our data suggested a 50% decline in vaginal dryness.

In an Iranian trial, 38 women were randomly assigned to 3 groups of 1% and 2% fennel cream, and placebo. Hair thickness plummeted in a dose-dependent manner from 7.8% with 1% cream to 18.3% with the 2% cream (27). Akha et al. (28) in Iran randomized 42 women with mild-to-moderate hirsutism into 3% fennel gel and placebo groups. After 24 weeks, the fennel group showed a significant decrease in hair thickness (from 97.9±31.5 to 75.6±26); there was no change in the placebo group.

Surprisingly, women in the placebo group of the present study reported a 56% decline compared with the fennel group (26%) in "body weight gain" symptoms, although the difference between the groups was nonsignificant. This is in contrast to other human and animal studies. Fennel, both as tea and aromatherapy, could suppress appetite in women with excess weight (29,30). Hur et al. (31) reported similar results in animal models. Their study indicated no significant reduction in body weight of rats. However, the fennel group had a lower rate of food efficacy when compared with the other groups. Nevertheless, the results should be interpreted cautiously because the fennel effect on body weight was assessed using subjective symptoms; however, the unpublished findings of a study on the effect of fennel on the lipid profile did not alter the body weight at the end of 3-months follows-up.

The main limitation of this study was the high placebo response observed in all symptoms. The results of a post analysis power calculation indicated that the present sample size was insufficient for all parameters of the MENQOL questionnaire.

The failure to indicate a significant effect may be due to the high placebo response. It is suggested that future trials include a placebo run-in phase or design a sequential, parallel study or with a longer follow-up period with larger sample sizes to mitigate the placebo effect.

Ethics Committee Approval: *The Ethics Committee of Mashhad University of Medical Science approved the study protocol considering the principle of Declaration of Helsinki.*

Informed Consent: *All participants signed informed consent forms for their voluntary participation in the study, and they were allowed to leave the trial at any period.*

Peer-review: *Externally peer-reviewed.*

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Association between *fok1* polymorphism of vitamin D receptor gene with uterine leiomyoma in Turkish populations

Seda Güleç Yılmaz[1], Tuğçe Gül[1], Rukset Attar[2], Gazi Yıldırım[1], Turgay İşbir[3]

[1]Department of Molecular Medicine, Yeditepe University, Institute of Health Sciences, İstanbul, Turkey
[2]Departments of Obstetrics and Gynecology, Yeditepe University School of Medicine, İstanbul, Turkey
[3]Department of Medical Biology, Yeditepe University School of Medicine, İstanbul, Turkey

Abstract

Objective: The aim of this research was to determine the association between the *fok1* polymorphism and uterine leiomyomas.

Material and Methods: For genotyping the *fok1* polymorphism of the vitamin D receptor, real-time polymerase chain reaction was performed on blood samples of uterine leiomyoma (n=27) and control (n=33) groups. For statistical analyses, SPSS v.23 software (SPSS Inc., Chicago, IL, USA) was used.

Results: A statistically significant difference was observed for the frequency of the CC genotype between the uterine leiomyoma and control groups, and the frequencies of the T allele in the uterine leiomyoma groups were significantly higher than in the control group.

Conclusion: The presence of the *fok1* CC genotype may be a risk-reducing factor and the T allele may be a potential risk factor for developing uterine leiomyoma. (J Turk Ger Gynecol Assoc 2018; 19: 128-31)

Keywords: Vitamin D receptor, polymorphism, *fok1*, uterine leiomyoma

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Introduction

Uterine leiomyomas are the most common benign muscle tumors (1-4), with up to 60% prevalence in women of a fertile age (1). Leiomyomas can be present in multiples, round, and can vary in size from several millimeters to 20 cm or more (2). They are clonal tumors arising from the smooth muscle cells of the uterus and contain excessive extracellular components (3). In addition, their mitotic activity is usually low (2). It is known that the pathogenesis of uterine leiomyoma is multifactorial, although not exactly elucidated (4). In patients with uterine leiomyomas, dysmenorrhea, pelvic pain, menorrhagia, infertility, complications during pregnancy (1), heavy menstrual bleeding and bladder discomfort can be observed (5). Uterine leiomyomas decrease the quality of life because of these adverse effects.

Vitamin D is a hormone that regulates some biologic processes in normal tissues, such as cellular differentiation and proliferation. It also regulates proliferation, apoptosis, and cell adhesion in cancer tissues (6). The vitamin D precursor, 7-dehydrocholesterol, can be synthesized by the human liver. When 7-dehydrocholesterol is activated by ultraviolet light from sun, 1,25-dihydroxycholecalciferol is synthesized, which is the active form of vitamin D that shows its effects via the human vitamin D receptor (VDR) gene (7).

The VDR is known to be a member of the steroid hormone receptor superfamily of nuclear receptors (8), and it interacts with VDR response elements (VDRE) (6). The gene encoding the VDR is located on human chromosome 12q13-12q14 (8), and it has five promoter regions and 14 exons (eight of them protein coding and six of them non-protein coding) (9). When vitamin D binds to the VDR, it contacts with the retinoic acid receptor, as well. After the complex is formed, it binds to VDRE, and its transcription is regulated (10). At least 196 VDR single nucleotide polymorphisms have been identified (9). The *fok1*

Address for Correspondence: *Seda Güleç Yılmaz*
e.mail: seda0802@yahoo.com ORCID ID: orcid.org/0000-0002-8119-2862

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polymorphism was detected on the first ATG codon of the VDR gene (11).

Mun et al. (12) hypothesized an association between the *fok1* polymorphism of the VDR gene and female reproductive cancers in their meta-analysis. These studies consisted of 4107 ovarian and 16.453 breast cancer cases, which examined risks with fixed or random effects models under heterozygous, homozygous, dominant, and recessive models. It was shown that the *fok1* polymorphism was related to increased risk, whereas the BsmI polymorphism was associated with a decreased risk for gynecologic cancers (12). In addition to the meta-analysis, some significant associations between the *fok1* polymorphism and prostate, colorectal, skin, gastric, melanoma, and non-small cell lung cancers have been discovered (6). Vitamin D levels of females have been associated with uterine leiomyomas (13). Paffoni et al. (16) noticed that the vitamin D levels of patients with uterine leiomyomas were significantly lower than in control groups. Uterine leiomyoma is also associated with obesity. Sex steroids (e.g., estrogen) are responsible for regulating adipocyte metabolism (14). Thus, uterine leiomyomas can be considered as an estrogen-dependent tumors (1). Marshall et al. (15) and Paffoni et al. (16) studied the association between body mass index (BMI) and uterine leiomyomas.

The aim of this research was to determine the association between the *fok1* polymorphism and uterine leiomyomas. A part of the pathogenesis of uterine leiomyomas is thought to be related to the metabolism of vitamin D, which was illuminated through the determination of an association between the *fok1* polymorphism and uterine leiomyomas.

Material and Methods

For this study, samples were collected from the gynecology and obstetrics departments of Yeditepe and İstanbul University, to form control (n=33) and uterine leiomyoma groups (n=27). To compare and detect any association between the *fok1* polymorphism and the presence of a uterine leiomyoma, the first group of patients was formed according to the presence of uterine leiomyoma. The second group was made according to the BMI ranges in order to study the association between BMI, uterine leiomyoma, and the *fok1* polymorphism. The BMI ranges were determined according to the classification of the World Health Organization.

Peripheral blood samples were collected into EDTA-containing tubes with the consent of the volunteer participants in this research. DNA isolation was performed using an iPrep Purification Instrument (Invitrogen, Life Technologies, Carlsbad, California, USA) with 350 μL of peripheral blood and an Invitrogen iPrep PureLink gDNA blood isolation kit (Invitrogen, Life Technologies, Carlsbad, California, USA). After isolation, the DNA samples were measured spectrophotometrically by NanoDrop 2000 (Thermo Scientific, Waltham, Massachusetts, USA) for genotyping. An Applied Biosystems 7500 Fast Real-Time PCR instrument (Applied Biosystems, Foster City, CA, USA) was used for genotyping the VDR gene *fok1* polymorphism through the use of a TaqMan Genotyping Assay, TaqMan Genotyping Master Mix and 100 ng DNA of sample. With these materials, the reaction mixture was prepared as recommended by the manufacturer, and then 10 μL of the reaction mixture and 1 μL of the sample DNA were added to each well in the plate for genotyping. The polymerase chain reaction (PCR) reaction conditions consisted of a 10 minute at 95 °C hold stage followed by 40 cycles of 15 seconds at 92 °C for denaturation, and 60 seconds at 60 °C for extension. Allelic discriminations of the samples were detected by collecting and interpreting the fluorescent signals of the hybridization probes using the software associated with the Applied Biosystems 7500 Fast Real-Time PCR instrument.

For statistical analyses, SPSS v.23 software (SPSS Inc., Chicago, IL, USA) was used. Student's t-test was used to compare the means of the ages and the BMI ranges of the control and uterine leiomyoma groups. Chi-square and Fisher's exact tests were performed by detecting the significant differences between the genotypes of the groups. Risk estimations were examined through binary logistic regression analysis as an odds ratio (OR) with a 95% confidence interval (CI). When the p value of the statistical test was lower than 0.05, the test was considered to be statistically significant.

Results

The demographic characteristics of the uterine leiomyoma group (n=27) and the control group (n=33) are given in Table 1. The mean ages of the patients with uterine leiomyoma and the control group were 38.19±10.217 and 39.76±11.771 years, respectively. As a result of Student's t test, there was no statistical significance between the mean ages of the groups (p=0.587). Additionally, the mean BMI of the patients with uterine leiomyomas and the control group were 24.44 and 22.13 kg/m^2, respectively. The mean BMI of the uterine leiomyoma group

Table 1. Demographic information of the study groups

Parameter	Uterine leiomyoma (n=27)	Control (n=33)	p value
Age (years), mean ± SD	38.19±10.217	39.76±11.771	0.587
Body mass index (kg/m^2), mean	24.44	22.13	**0.034***
n: Number of individuals; SD: Standard deviation; *: p values less than 0.05 denoted statistical significance			

was significantly higher than the control group (p=0.034*).

The allelic and genotypic frequencies for *fok1* (rs2228570) were analyzed. As a result of this analysis, the frequencies of the CC, CT, and TT genotypes among the patients with uterine leiomyoma were 40.7%, 48.1%, and 11.1%, respectively. The frequencies of the CC, CT, and TT genotypes among the people in the control group were 66.7%, 30.3%, and 3.0%. When the statistical tests were performed, statistical significance was observed for the frequency of CC genotype occurrence between the uterine leiomyoma and control groups [$\chi 2$=4.033, p=0.045*, OR: 2.91, 95% CI: (0.120-0.987)], and no significance was found for the other genotypes. The frequency of the T allele in the uterine leiomyoma group was significantly higher than in the control group [$\chi 2$=4.033, p=0.045*, OR: 2.909, 95% CI: (1.013-8.355)] (Table 2).

When the BMI ranges of patients with uterine leiomyomas versus the control group were analyzed, it was observed that there was no statistical significance.

Discussion

Uterine leiomyoma is the most common benign tumor in women, and because of its adverse effects, uterine leiomyomas decrease quality of the life (1-4). In the United States of America, about $34.4 billion per year is spent for the treatment of uterine leiomyomas (17); however, in Turkey, this number could be lower because epidemiologically, uterine leiomyomas are more common in African-American women than in Caucasians (15,17,18).

Vitamin D has roles in proliferation, apoptosis, and cell adhesion in cancer tissues showing its effects through the VDR (6,7). Al-Hendy et al. (19) showed that vitamin D induces nuclear VDR. At least 196 VDR single nucleotide polymorphisms have been identified (9). The *fok1* polymorphism was detected on the first ATG code of the VDR gene (11). Mun et al. (12) hypothesized an association between the *fok1* polymorphism of the VDR gene and female reproductive cancers in their meta-analysis (12). VDR polymorphisms have not only been associated with uterine leiomyomas. Some studies found the *fok1* polymorphism associated with breast, ovarian, adenomatous polypopsis, colon (7), non-small cell lung, prostate, gastric, and melanoma cancers (6). Monitoring VDR gene polymorphisms and its molecular associations could give a route for the prognosis of uterine leiomyomas, and further, identify potential targets for the development of novel treatments as personlised medicine (12).

Bläuer et al. (20), compared the differences in effect of vitamin D on leiomyoma and myometrial tissues, and determined that vitamin D inhibited the proliferation of tissues *in vitro* (20). An article written by Sharan et al. (21), who used human uterine leiomyoma cells supported this result.

Shahbazi (22) wrote an original article about the *fok1* polymorphism and uterine leiomyoma. To the best of our knowledge, that report was the first and ours is the second on the association between the *fok1* polymorphism and uterine leiomyomas, and the results were similar in both studies, yet they conducted on different populations. Also, the present study was performed using RT-PCR with high-tech apparatus. From our analysis, the frequencies of CC, CT, and TT genotypes among patients with uterine leiomyoma were 40.7%, 48.1%, and 11.1%, respectively. The frequencies of CC, CT, and TT genotypes in the control group were 66.7%, 30.3%, and 3.0%. According to Shahbazi's research, the frequencies of CC, CT and TT genotypes among the patients with uterine leiomyoma were 35.5%, 42.5% and 22%, respectively, and the frequencies of these genotypes in the control group were 51%, 32%, and 17%. Shahbazi determined that the *fok1* polymorphism could impact the development of leiomyomas (22).

In conclusion, we found a statistically significant difference in the mean BMI of the uterine leiomyoma group versus the controls (p=0.034*). Carrying the CC genotype seemed to significantly decrease the risk of developing a uterine leiomyoma (p=0.045*), and carrying the T allele significantly increased

Table 2. VDR *fok1* (rs2228570) genotype and allele frequencies of the groups

	Uterine leiomyoma (n=27)	**Control (n=33)**	**p value**	**Odds ratio**	**95% Confidence interval**
Genotype *fok1* polymorphism	**n (%)**	**n (%)**			
CC	11 (40.7%)	22 (66.7%)	**0.045***	1/0.344=2.91	0.120-0.987
CT	13 (48.1%)	10 (30.3%)	0.157	2.136	0.741-6.157
TT	3 (11.1%)	1 (3.0%)	0.318	4.000	0.391-40.875
Allele	**Allelic count n (%)**	**Allelic count n (%)**			
C	35 (64.81%)	54 (81.82%)	0.318	1/0.250=4.00	0.032-2.109
T	19 (35.19%)	12 (18.18%)	**0.045***	2.909	1.013-8.355

n: Number of individuals, *: p values less than 0.05 denoted statistical significance

the risk of developing a uterine leiomyoma (p=0.045*) in the Turkish population. These results, however, are limited by the small sample size and require additional studies on a larger number of patients for verification.

Ethics Committee Approval: *Ethics committee approval of this study was assumed from the ethics committee of Yeditepe University.*

Informed Consent: *The written informed consent form was received from all individual participants included in the study.*

Peer-review: *Externally peer-reviewed.*

Author Contributions: *Concept - S.G.Y., R.A., T.İ.; Design - S.G.Y., T.İ.; Materials - S.G.Y., T.G., R.A., G.Y., T.İ.; Data Collection and/or Processing - S.G.Y., R.A., G.Y., T.İ.; Analysis and/or Interpretation - S.G.Y., R.A., T.İ.; Literature Review - S.G.Y., R.A., T.İ.; Writer - S.G.Y., T.İ.; Critical, Review - S.G.Y., R.A., T.İ.*

Conflict of Interest: *No conflict of interest is declared by the authors.*

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Dedifferentiated endometrioid adenocarcinoma; clinicopathologic and immunohistochemical features of five cases

Seyran Yiğit[1], Neşe Ekinci[1], Leyla Hayrullah[1], İrfan Öcal[1], İncim Bezircioğlu[2]

[1]Department of Pathology, İzmir Katip Çelebi University, Atatürk Training and Research Hospital, İzmir, Turkey

[2]Department of Obstetrics and Gynecology, İzmir Katip Çelebi University, Atatürk Training and Research Hospital, İzmir, Turkey

Abstract

Objective: Dedifferentiated endometrioid adenocarcinoma is a recently defined uterine tumor composed of low-grade endometrioid adenocarcinoma and undifferentiated carcinoma. Herein, we present clinicopathologic, morphologic, and immunohistochemical features of 5 cases of dedifferentiated endometrioid adenocarcinoma.

Material and Methods: All cases which were diagnosed as mixed endometrial adenocarcinoma (endometrioid+undifferentiated carcinoma) or dedifferentiated endometrioid adenocarcinoma between January 2008 and December 2014 were retrieved from the archives of our institution's pathology department.

Results: The median age of the patients was 58 years. Polypoid growth pattern was seen in 3 patients and 2 were diagnosed at advanced stage. All patients received either external radiotherapy, brachytherapy, chemotherapy or an appropriate combination according to the stage. Only one patient died of the disease. Microscopically, there was a sharp demarcation between the two tumor components. The undifferentiated carcinoma component was composed of diffuse sheets of monomorphic cells lacking any differentiation. Focal pleomorphism and rhabdoid features were also noted. The undifferentiated carcinoma component was variably positive for PAX-8, cytokeratin, EMA, estrogen receptor, and neuroendocrine markers.

Conclusion: Misdiagnosis of undifferentiated carcinoma in dedifferentiated endometrioid adenocarcinoma as grade 3 endometrioid adenocarcinoma is not uncommon. The recognition of morphologic and immunohistochemical features of this newly described entity is crucial because it alters treatment and prognosis. (J Turk Ger Gynecol Assoc 2018; 19: 132-6)

Keywords: Dedifferentiated endometrioid carcinoma, endometrioid adenocarcinoma, undifferentiated carcinoma

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Introduction

Uterine and ovarian dedifferentiated endometrioid adenocarcinoma (DEAC) was first described by Silva et al. in 2006 (1). Based on the definition of the authors, low-grade endometrioid adenocarcinoma (EmC) and undifferentiated carcinoma (UC) are two fundamental elements of this tumor. The low-grade component in these tumors is usually International Federation of Gynecology and Obstetrics (FIGO) grade 1 or 2 EmC. The UC component is characterized by proliferation of medium-sized, homogenous epithelial cells with no glandular differentiation, which grow in a patternless manner and form solid sheets (2). For accurate treatment and prognosis of this neoplasm, a correct pathologic diagnosis is essential (3). Herein, we report five cases of DEAC of the uterus.

Material and Methods

All cases, which were diagnosed as mixed endometrial adenocarcinoma (EmC+UC) or DEAC between January 2008 and December 2014, were retrieved from the archives of the Pathology Department of our institution. Clinicopathologic data regarding patient age, symptoms, operative procedure, tumor stage (FIGO), lymphovascular invasion, postoperative additional therapies, and survival (months) were assessed. Immunohistochemical (IHC) studies including PAX-8, cytokeratin

Address for Correspondence: *Seyran Yiğit*
e.mail: seyranyigit@hotmail.com ORCID ID: orcid.org/0000-0002-3530-988X

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(CK) AE1-AE3 (epithelial lineage marker, also referred to as 'keratin' or 'pankeratin'), epithelial membrane antigen (EMA) (glandular and ductal epithelial marker, highly expressed by most adenocarcinomas), vimentin (mesenchymal tissue marker), chromogranin A (common neuroendocrine marker), synaptophysin (common neuroendocrine marker), CD56 (common neuroendocrine marker), estrogen receptor (ER) [used to distinguish endocervical (ER-) from endometrial (ER+) adenocarcinoma], and progesterone receptor (PR) (positive in uterine endometrial carcinoma, rules out serous endometrial carcinoma) for routine diagnostic purposes were performed in all cases. Leucocyte common antigen (LCA) (also referred to as CD45, inflammatory and hematopoietic tumor marker), desmin (mesenchymal marker) and CD 99 (small-blue-round-cell tumor marker) were additionally applied to case number 2.

Local ethics committee approval was not sought for this study because it represents a retrospective database review.

Results

Table 1 illustrates the clinicopathologic features of the cases. The ages of the patients ranged from 54 to 61 years (mean, 58 years). All patients had endometrial biopsies performed because of postmenopausal bleeding. Three patients were diagnosed with grade 1 or 2 endometrioid endometrial adenocarcinoma, others with UC and non-keratinizing squamous cell carcinoma. Total abdominal hysterectomy with bilateral salpingo-oophorectomy (TAH+BSO) and pelvic lymphadenectomy (PL) were performed in all patients.

Macroscopic findings: The tumor growth pattern in three cases (cases 1, 3 and 4) was polypoid while the remaining two exhibited infiltrative growth. In cases 2 and 5, cervical involvement and ovarian metastases were also observed.

Microscopic findings: Tumors in all cases showed sharp demarcation between areas of low-grade EmC and UC (Figure 1, case 4). The undifferentiated component was characterized by solid growth of monomorphic discohesive cells (Figure 2, case

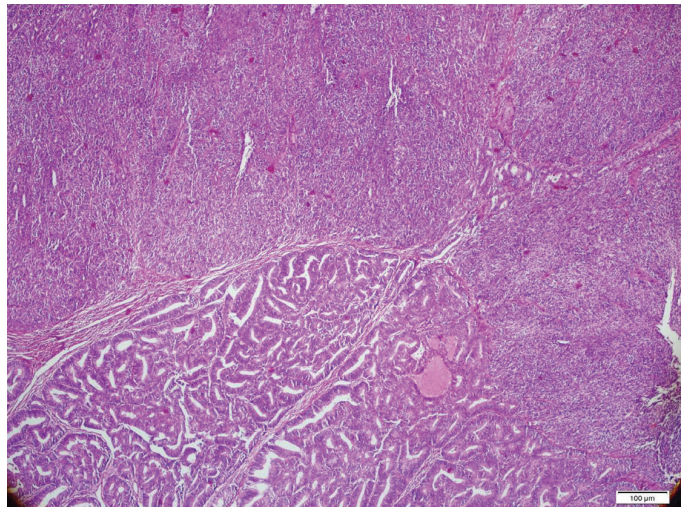

Figure 1. Abrupt transition of low-grade EmC and UC (case #4, Hematoxylin & Eosin, x4)
EmC: Endometrioid adenocarcinoma; UC: Undifferentiated carcinoma

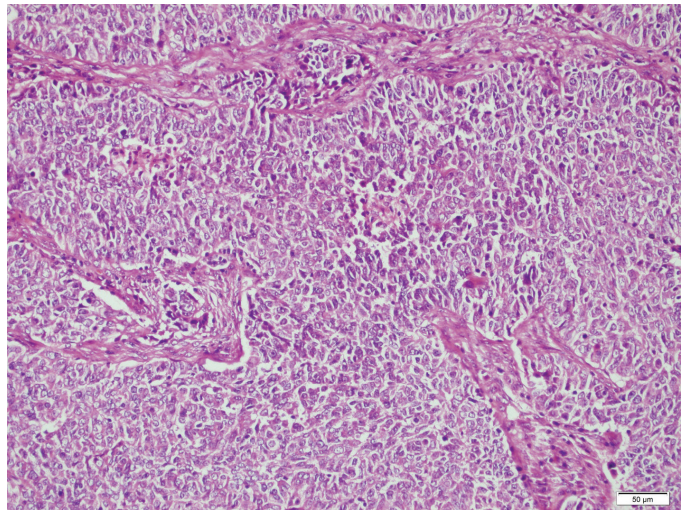

Figure 2. Solid sheets of monotonous cells exhibiting a patternless growth (case #3, Hematoxylin & Eosin, x10)

Table 1. Clinicopathologic features of the cases

Case #	Age	Pre-op curettage	Type of surgery	Lymph node status	Cervical involvement	Extra-uterine involvement	FIGO stage	Post-surgery treatment	Survival (months)
1	61	Non-keratinizing SCC	TAH+BSO+PLN	0/28	No	No	IA	BRT	100
2*	58	UC	TAH+BSO+PLN	6/21	Yes	Yes	IVB	CT	1.3
3	60	Grade 1 EmC	TAH+BSO+PLN	0/88	No	No	IA	CT+BRT	39
4	56	Grade 2 EmC	TAH+BSO+PLN	0/17	No	No	IA	CT+External RT+BRT	42
5	54	Grade 1 EmC	TAH+BSO+PLN	10/57	Yes	Yes	IIIC2	CT+External RT+BRT	50

SCC: Squamous cell carcinoma; UC: Undifferentiated carcinoma; EmC: Endometrioid adenocarcinoma; TAH+BSO: Total abdominal hysterectomy with bilateral salpingo-oophorectomy; PLN: Pelvic lymphadenectomy, BRT: Brachytherapy, CT: Chemotherapy, RT: Radiotherapy, FIGO: Federation of Gynecology and Obstetrics; *Dead of disease

3). Scattered rhabdoid cells and focal marked pleomorphism (cases 2 and 5, respectively) also stood out (Figure 3-4, cases 2 and 5). Four cases exhibited areas of focal or extensive necrosis. All morphologic features are summarized in Table 2.

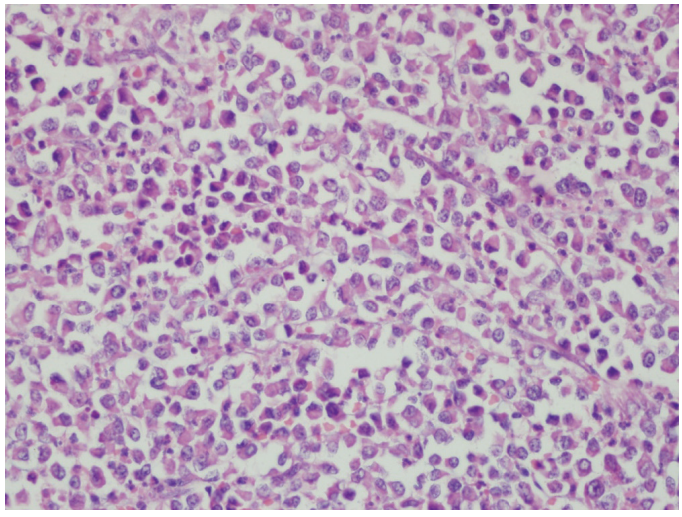

Figure 3. Higher magnification of UC cells showing rhabdoid features (case #2, Hematoxylin & Eosin, x40)
UC: Undifferentiated carcinoma

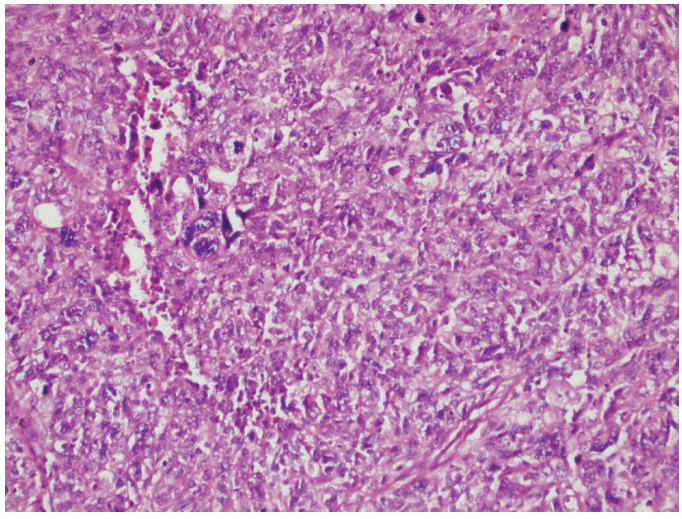

Figure 4. Marked focal pleomorphism in the UC (case #5, Hematoxylin & Eosin, x20)
UC: Undifferentiated carcinoma

Vascular invasion was only present in case number 2. Lymph node metastases were detected in two patients.

IHC features: PAX-8, CK, EMA, ER and PR were strongly and diffusely expressed in the low-grade EmC component (Figure 5, 6, cases 3 and 4), whereas the UC component was diffusely positive for vimentin, focally positive for CK, EMA, and neuroendocrine markers such as synaptophysin, chromogranin A, and CD 56. PAX-8 was negative in UC components of three cases, whereas it was focal positive in two cases (Figure 7, case 1).

Two patients presented with advanced stage disease (FIGO stages III-IV) at the time of diagnosis. Four patients received both radiotherapy (RT) and chemotherapy (CT). All patients but one were still alive as of August 2017.

Discussion

Uterine EmC is a common neoplasm that is frequently seen in pure form. UC represents 1.6-9% of all endometrial carcinomas (2-4). Silva et al. (1) described morphologic features of DEAC in 2006 and it was included in the 2014 version of the book, 'World Health Organization Classification

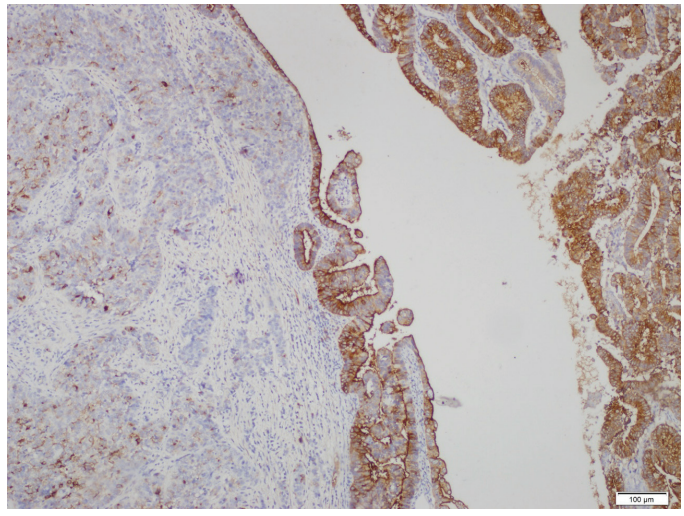

Figure 5. EMA; strong positivity in low-grade EmC component versus patchy, weak staining in the UC component (case #3, x4)
EMA: Epithelial membrane antigen; EmC: Endometrioid adenocarcinoma; UC: Undifferentiated carcinoma

Table 2. Morphologic features of the tumor components

Case no	Undifferentiated component			Endometrioid component	
	Cell type	Necrosis	%	Grade	%
1	Monotonous-medium size	Extensive	80	1	20
2	Monotonous-small size-rhabdoid	Extensive	90	1	10
3	Monotonous–medium size	Focal	80	1	20
4	Pleomorphic-medium size	Focal	80	2	20
5	Monotonous-medium size	Absent	50	1	50

of the Tumors of Female Reproductive Organs' (5). Although DEAC is generally presented as case reports, a series of such tumors was recently reported in the literature (6-12). DEAC primarily occurs during the 6th and 7th decades; consistent with previous studies, the mean age at diagnosis in our study was 58 years (11-15). Similar to existing studies, all patients in our study underwent TAH+BSO and PL (1,6-15). Advanced FIGO stage of DEAC in the literature is reported to be between 52-92%, whereas in our study, it was found as 40% (1,11-14). Similar to the cases reported in the literature, all of our patients also received post-operative RT and/or CT (1,8,9,11-15).

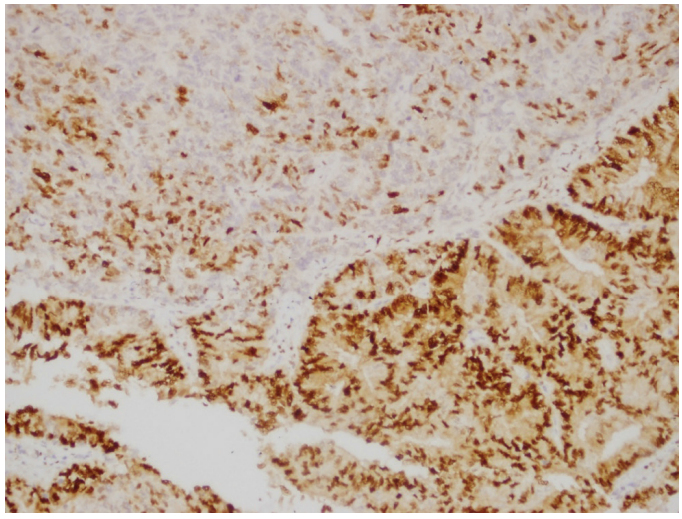

Figure 6. PR; strong nuclear positivity in low-grade EmC component versus sparse nuclear staining in the UC component (case #4, x10)
PR: Progesterone receptor; EmC: Endometrioid adenocarcinoma; UC: Undifferentiated carcinoma

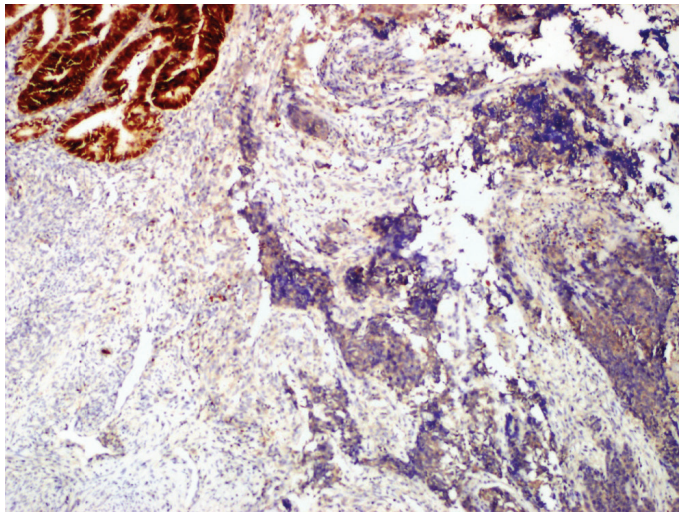

Figure 7. PAX-8 positivity in low-grade EmC and negativity in the UC component (case #1, x20)
EmC: Endometrioid adenocarcinoma; UC: Undifferentiated carcinoma

Although only a single case was reported to exhibit polypoid growth pattern in studies that described macroscopic features, the main growth pattern in the current study was also found to be polypoid (7-10).

Similar to previous reports, EmC and UC components of the tumors mentioned herein were sharply demarcated from each other and EmC component was either grade 1 or 2 (1,7,9,10,13). The UC component of the current study was characterized by solid sheets of proliferated medium-sized monotonous epithelial cells with no specific pattern, identical to previous reports (2-4).

In consonance with the literature, rhabdoid cells, focal pleomorphism, and neuroendocrine differentiation of the DEAC were also noted in some of our cases (1,9,13). Previous studies underscored the use of IHC studies in the diagnosis of DEAC. Even though UC components of DEACs are variably positive for keratins, EMA, and ER, they are mostly negative for PAX-8. In some studies, loss of DNA mismatch repair (MMR) proteins was observed relatively commonly in UC components (1,14). In Stewart and Crook's study, concordant MMR protein expression in low and undifferentiated components of DEAC was noteworthy (15).

Furthermore, vimentin and focal neuroendocrine marker expressions may be observed in the undifferentiated component. The IHC results of our study are also concordant with the literature except for PAX-8, which was focal positive in 2 of 5 cases (1,9,13).

Inadvertently, the undifferentiated component in DEAC is often misdiagnosed as grade 3 EmC, serous carcinoma (SC), malignant mixed Mullerian tumor (MMMT), undifferentiated endometrial sarcoma, poorly differentiated neuroendocrine carcinoma or malignant lymphoma (1,9,10,13).

However, in grade 3 EmC, the tumor cells are morphologically similar to carcinoma cells in glandular areas; solid sheets or nests, and conspicuous glandular structures might also coexist (13). Recent studies showed inactivation of SWI/SNF complex subunits such as INI1 (SMARCB1), BRG1 (SMARCA4) and ARID1A (BAF250a) whose alterations might help distinguish poorly (grade 3) differentiated endometrial carcinoma from DEAC (15,16).

In SC glandular component with papillary features, slit-like lumens, background endometrial atrophy and architectural-cytological discordance can also support the diagnosis. MMMT is a biphasic tumor composed of high-grade carcinoma, usually serous carcinoma, and a sarcomatous component that is typically reminiscent of a pleomorphic sarcoma (9,13). Undifferentiated endometrial sarcomas are composed of more pleomorphic cells and focally spindled cells (14). Neuroendocrine carcinoma and malignant lymphoma can be differentiated on the basis of their specific IHC features in

the absence of well-differentiated endometrioid carcinoma (13,14). Extensive sampling, high awareness of the morphologic characteristics of this tumor and IHC studies are essential for accurate diagnosis.

Follow up studies revealed that DEAC is a much more aggressive tumor than grade 3 EmC (1,13). Due to the small number of patients and the short follow-up period, the non-aggressive tumor behavior present in our study prevents us from reaching a similar conclusion. POLE mutations are associated with a favorable prognosis; however, we were unable to perform molecular analysis in our study (17).

In conclusion, DEAC is a rare, but most frequently misdiagnosed aggressive tumor. Due to variable therapeutic approaches and prognostic implications, identifying and correctly diagnosing DEAC in the endometrium is crucial.

Ethics Committee Approval: *Ethics committee approval was not sought for this study since it represents a retrospective database review.*

Informed Consent: *Informed consent was not obtained for this study since it represents a retrospective database review.*

Peer-review: *Externally peer-reviewed.*

Author Contributions: *Concept - S.Y., L.H.; Design - S.Y., L.H.; Supervision - S.Y., N.E., L.H.; Materials - S.Y., N.E., İ.Ö., İ.B.; Writer - S.Y., N.E., L.H.*

Conflict of Interest: *No conflict of interest is declared by the authors.*

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The effect of a pre-procedure information video on anxiety levels in patients undergoing hysterosalpingography: A prospective case-control study

Selçuk Erkılınç[1], Nazlı Aksoy Kala[2], Meryem Kuru Pekcan[2], Ali İrfan Güzel[3], Mehmet Çınar[3], Nafiye Yılmaz[3]

[1]Clinic of Gynecologic Oncology, University of Health Sciences, Tepecik Training and Research Hospital, İzmir, Turkey

[2]Clinic of Gynecology and Obstetrics, University of Health Sciences, Ankara Numune Training and Research Hospital, Ankara, Tukey

[3]Clinic of Gynecology and Obstetrics, University of Health Sciences, Zekai Tahir Burak Women's Health Training and Research Hospital, Ankara, Turkey

Abstract

Objective: To evaluate the effect of a pre-procedural information video on anxiety levels in patients undergoing hysterosalpingography (HSG).

Material and Methods: Among a total of 131 primary or secondary infertile patients, 66 were shown an information video and 67 control patients received standard care between August 2014 and January 2016. The video included information on the procedure, personnel, and the room for the procedure; the video was shown on the morning of the procedure. Patients were randomized using the complete randomization technique through which patients were included in the study and control groups week by week, randomly. The Beck Anxiety Inventory scale was conducted to the patients one hour before the procedure.

Results: There were no differences in demographic data. The history of previous gynecologic operations was higher in the control group. The Beck Anxiety score was significantly lower in the study group compared with the control group (6 vs 10).

Conclusion: Our findings suggest that as an easy intervention to implement, a pre-procedural video education may be a beneficial tool for the management of HSG-related anxiety. (J Turk Ger Gynecol Assoc 2018; 19: 137-41)

Keywords: Hysterosalpingography, anxiety, beck anxiety inventory

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Introduction

Infertility is one of the most prevalent diseases that affects young adults, defined as one year of attempted conception without success (1). Hysterosalpingography (HSG) is an ancillary diagnostic method for evaluating the uterine cavity and tubes (2). Infertility and congenital Mullerian anomalies are the main indications for HSG. Although there are alternative techniques such as hydrosonography, HSG is now widely used in the evaluation of infertility (2). HSG is recommended for the evaluation of the fallopian tubes as the gold standard (3).

Although HSG is one of the most beneficial ancillary tests in the evaluation of infertility, the pain reported by patients is a critical disadvantage of the method. Up to 72% of patients reported pain during the procedure (4). The causes of the pain were reported to be peritoneal irritation caused by contrast media, uterine dilatation, and downward traction of the uterine cervix (5). The perception of pain, however, is barely affected by anatomic and physical factors. Cicinelli (6) reported social and psychological status such as depression and anxiety was a factor in the perception of pain during gynecologic invasive procedures. Women undergoing HSG evaluations have also been reported to have considerable stress and anxiety in correlation with invasiveness of the procedure (7). Furthermore, infertility in itself is an independent stressor and a source of

Address for Correspondence: *Selçuk Erkılınç*
e.mail: selcukerkilinc@hotmail.com ORCID ID: orcid.org/0000-0002-6512-9070

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anxiety and depression and levels of anxiety correlate with the duration of infertility (8). Video education was found to reduce pre-procedural anxiety levels in patients undergoing cardiac catheterization (9). The video included information on the cardiac catheterization procedure. The authors commented that a pre-procedural information video could be used for reducing peri-procedural anxiety.

In light of information in the literature, our hypothesis was that a pre-procedural video would have a positive effect on anxiety levels in patients undergoing HSG. Therefore, in the current study, we aimed to evaluate the effect of an educational video on anxiety levels of patients undergoing HSG for infertility.

Material and Methods

Design

This study was conducted at the Department of Infertility and Reproductive Medicine between August 2014 and January 2016 after approval was received from the institutional review board. Patients were asked to participate in the study voluntarily. All patients consented to participate in the study and signed informed consent forms. The principles written in Declaration of Helsinki were followed. The patients had primary or secondary infertility. Infertility was regarded as attempting to have children for one year without conception. Patients undergoing HSG for the investigation of uterine malformations regardless of infertility treatment were excluded. Patients with a psychiatric disease, treatment with anxiolytic medication, and hearing problems in the video group were also excluded.

Measures

The Beck Anxiety Inventory (BAI) (10) was the objective measure for anxiety levels. This inventory is a self-report questionnaire containing 21 questions related with how much each symptom bothered the patients. The patients answered the questions on the inventory scale, which were graded between *not at all* (0) and *severe* (3). The total score ranged from 0 to 63. Similar cut-off scores with a previous study on gastrointestinal endoscopy was used for the classification of anxiety (11). The classification of anxiety scores was as follows; 0-7, minimal; 8-15, mild; 16-25, moderate; and 26-63, severe anxiety. The data collected were: age, type of infertility, gravidity, parity, history of gynecologic operation, family type, income, and educational status. The BAI (10) was applied to all patients one hour before the HSG procedure.

Procedure

The patients were scheduled for HSG after their first appointment at the infertility outpatient clinic. After obtaining informed consent, the information video was shown on a computer to the patients who were selected for the study group. On the morning of the procedure, the video was shown to all patients together who were scheduled on the same day. The surgeon was present in the room for possible questions from the patients. Patients who were selected for the control group received standard care; they received verbal information about the type, risks and benefits of the procedure by the surgeon.

Video content

A video was recorded using a hand-held camera by one of the authors. The presenter was a female medical doctor who dressed in a white coat. The HSG procedure and risk factors, the waiting room, staff, room for the procedure, table and instruments for the procedure, and when and how to take the results were introduced to the patients.

Patient selection

During the 6 months of the study, patients were included in the study or control groups week by week. A total of 227 patients underwent HSG during the study period and all patients were invited to participate in the study; 55 refused. The number of patients enrolled in the study was 172. Patients with psychiatric disorders, anxiolytic medication use, illiteracy, and hearing-impairment were excluded. One hundred thirty-three patients were eligible for the study. Patients scheduled for first week were proposed to participate in the video group and the those in the second week were included in the control group. At the fourth month of the study, the control group contained 66 patients, in the following two months, all patients were offered participation in the study group.

Statistical analysis

The Kolmogorov-Smirnov or Shapiro-Wilk tests were used to test the normality of continuous data. The comparison of the continuous data was performed using the independent-sample t-test or Mann-Whitney U test where suitable. The chi-square test was performed for analyzing categorical data. P values <0.05 were considered as significant. Statistical analysis was performed using the SPSS statistics for Windows version 21.0. software package (Armonk, NY: IBM Corp.). Power analysis was performed using the G*power software package (Faul and Erdfelder 1998 Universitat Kiel, Germany).

Results

The mean age of the study and control groups were 26.1 years and 26.8 years, respectively; there was no difference between the groups. The study and control groups showed similar results in terms of family type; living in nuclear families was the most prevalent type in both groups. The rate of patients who graduated from university in the study and control groups was 16% and 18%, respectively; similar educational status was

observed in both groups. Another socioeconomic indicator, family income, was similar in the stratified income groups. Therefore, all demographic and social data investigated between the study and control groups were similar. There were no differences in terms of primary or secondary infertility. History of gynecologic surgery including myomectomy, ovarian cystectomy, diagnostic laparoscopy was present in 6% of the study group and 22% of the control group; the number of previous gynecologic procedures was significantly higher in the control group ($p<0.05$). Patients in the study group had significantly lower BAI scores than those in the control group (6 vs 20, respectively). The comparison of the study and control group is shown on Table 1. A Post hoc power analysis was performed. The sample sizes in the study and control groups were used for statistical power analysis. The post-hoc statistical power analysis revealed an adequate power 0.88 at large size effect.

Table 1. Comparison of the data between study and control groups

	Study group (n=67)	Control group (n=66)	p value
Age	26.1±5.9	26.8±5.8	
Type of family			
Nuclear family	58 (86.6)	60 (90.9)	0.429
Extended family	9 (13.4)	6 (9.1)	
Educational status			
Primary/high school	56 (83.6)	54 (80.2)	0.788
University	11 (16.4)	12 (18.2)	
Income			
0-750 USD	41 (61.2)	48 (72.7)	0.078
750-1500 USD	24 (35.8)	13 (19.7)	
>1500 USD	2 (3)	5 (7.6)	
Previous gynecologic operation			
No	63 (94)	51 (77.3)	0.006
Yes	4 (6)	15 (22.7)	
Type of infertility			
Primary	41 (61.2)	38 (57.6)	0.671
Secondary	26 (38.8)	28 (42.4)	
Cause of infertility			
Unexplained	49 (73.1)	44 (66.7)	0.718
Female factor	14 (20.9)	17 (25.8)	
Male factor	4 (6)	5 (7.6)	
Infertility treatment			
No	41 (61.2)	45 (68.2)	0.399
Ovulation induction	26 (38.8)	21 (31.8)	
Beck score (median)	6	10	
Quartile 25%	2	9	<0.001
50%	6	10.5	
75%	12	13.25	

The severity of anxiety scores was stratified as minimal, moderate, and severe, and compared between the study and control groups. The minimal anxiety score was significantly higher in study group than in the controls (56.7% vs 20.8%). Inversely, mild anxiety was higher in the control group compared with study group (71.4 vs 29.9). No significant difference was found regarding severe anxiety. The comparison of the groups in terms of the severity of anxiety is presented in Table 2 and Figure 1.

Discussion

This prospective case control study was designed to assess the effectiveness of an information video on reducing anxiety levels in patients undergoing HSG. The main finding of the study was that lower anxiety scores were observed in patients who watched the information video about the procedure.

HSG was reported to be related with fear and anxiety in patients (12). Various tools for reducing procedure-related anxiety such as music and medication have been identified (13,14). Group education was another intervention for reducing HSG-related anxiety. La Fianza et al. (12) investigated the importance of group education on reducing anxiety levels in women who underwent HSG, and in their preliminary report, they found a positive effect of group education on anxiety levels. Similarly, in the current study, the patients watched the educational video as a group. The patients in our study may have further benefited

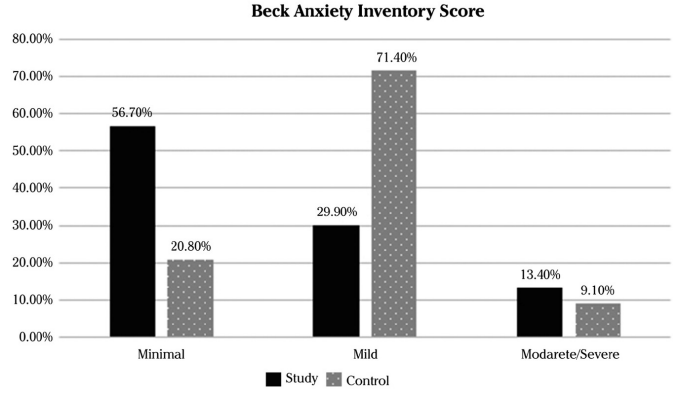

Figure 1. Comparison of Beck Anxiety Inventory

Table 2. Beck Anxiety Inventory in study and control groups

Beck score	Study	Control	p value
Minimal (n, %)	38 (56.7)	10 (20.8)	<0.001
Mild (n, %)	20 (29.9)	50 (71.4)	<0.001
Moderate/severe (n, %)	9 (13.4)	6 (9.1)	0.429

from group education in addition to the positive effects of video education.

Patient education with a video before a procedure was investigated in previous studies (15,16). Goodman et al. (15) found that video education had a positive effect on parents whose children had influenza vaccination. The use of an information video was investigated by Ruffinengo et al. (16) who highly recommended it as an instrument to reduce anxiety levels in the cardiology department. Similarly, our findings suggest that lower anxiety levels resulted after using a pre-procedural informative video. It is valuable that it supplies lower levels of anxiety without using medication. There is evidence that anxiolytics are useful in reducing anxiety levels in patients undergoing HSG. Women prescribed valeric acid as an anxiolytic were reported to have reduced anxiety levels (13). However, the use of these drugs is limited because of adverse effects. Another method for reducing anxiety is listening to music during the procedure. Women who listened to music during HSG were reported to have lesser anxiety levels (14). Both these studies used different anxiety score scales so it is not possible to make a comment as to which was best; prospective studies for the comparison of anxiolytics, music and information videos may reveal valuable information regarding which method is the most effective.

What should an educational video include for reducing anxiety? Chair et al. (17) investigated the effect of an information video in patients undergoing cardiac catheterization. The video included information on cardiac catheterization, the room, and staff for the procedure. Similar to our study, they found low levels of anxiety in the study population compared with the controls. Freeman-Wang et al. (18) used an information video to reduce anxiety in patents attending a colposcopy clinic. Their video included images from the reception area, nursing and medical staff in order to familiarize the patients with the department (18). Uncertainty and unfamiliarity were found to cause anxiety in patients who underwent invasive procedures (19).

In this study, the video content had certain information about HSG. The low levels of anxiety observed in the current study may be related with study group patients' familiarity with the procedure and place where they underwent the procedure. Patient education may be performed through various routes. Patient education was reported to reduce the level anxiety regardless of the route of intervention (17). Video education was found to have more favorable psychological effects than standard education with brochures (19). In the current study, standard care was communication with the patient about the types, risks and benefits of the procedure, and our findings were compatible with the literature.

Although severe anxiety did not differ between the groups, mild anxiety was less common in the study group. Intervention with an information video might not be sufficient for effecting severe anxiety, however. Further strategies may be needed for managing sever anxiety in patients undergoing HSG. Nevertheless, the information video may a sufficient for managing mild level of anxiety.

The strong points of this study are the use of standardized tools (BAI) and adequate statistical power with large effect size.

The study was limited by the lack of true randomization. A future study recruiting randomized patients to the groups can be conducted. The higher numbers of previous gynecologic operations in the study group was a confounding factor and might have interfered with the higher levels of anxiety in the study group.

In conclusion, our findings suggest that implementing a pre-procedural education video is an easy intervention that may be used as a beneficial tool for reducing HSG-related anxiety

Ethics Committee Approval: *This study was conducted at the Department of Infertility and Reproductive Medicine between August 2014 and January 2016 after approval was received from the institutional review board.*

Informed Consent: *All patients consented to participate in the study and signed informed consent forms.*

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Detection of major anomalies during the first and early second trimester: Single-center results of six years

Erol Arslan, Selim Büyükkurt, Mete Sucu, Mehmet Özsürmeli, Selahattin Mısırlıoğlu, S. Cansun Demir, İ. Cüneyt Evrüke

Department of Obstetrics and Gynecology, Unit of Perinatology, Çukurova University School of Medicine, Adana, Turkey

Abstract

Objective: Fetal structural malformations affect approximately 2-3% of all pregnancies. Only focusing on trisomy screening in first trimester and deferring the anatomic screening to second trimester may result with late detection of major anomalies that can be diagnosed earlier with careful examination.

Material and Methods: This was a descriptive study of retrospective data that were obtained from all terminated single pregnancies due to ultrasonographic findings of major anomalies from 2011 to 2016 in our department. The study was based on a chart review and only abnormalities that were diagnosed before the 16th week were included.

Results: Two hundred forty-four first trimester pregnancy terminations were performed. In total, 273 anomalies were detected in the 244 patients. Cranial NTD comprised 32% of all anomalies (n=89). Fifteen percent of anomalies (n=41) needed detailed anatomic scanning for early diagnosis.

Conclusion: In this study, we presented the number and percentage of our early diagnosed anomalies by years, as well showed our diagnostic performance for specific anomalies such as atrioventricular septal defect during a 5-year period. The study provides valuable information for future studies in Turkey and shows the need for an anatomic scan protocol while performing aneuploidy screening during early gestation. (J Turk Ger Gynecol Assoc 2018; 19: 142-5)

Keywords: First trimester, anomaly, ultrasound, termination

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Introduction

Major congenital anomalies affect 2-3% of all pregnancies (1). Although second trimester ultrasound screening between the 18-23th gestational weeks has routinely been used for anomaly screening (2), it is widely accepted that most anomalies can be detected earlier. In this aspect, major abnormalities have been separated into three groups due to the probability of their detection rate by 11-14th weeks' ultrasound (3). The first group includes anomalies that can be easily detected in the first trimester such as anencephaly, the second group comprises anomalies that reveal ultrasonography signs later in gestation and have no possibility of early detection such as hypoplasia of cerebellum. The third group anomalies can be detected in first trimester with meticulous examination using high-tech devices. This group of anomalies includes spina bifida occulta, skeletal dysplasia, and some kinds of cardiac defects, which sometimes need to be examined using transvaginal ultrasound (3).

First trimester ultrasound has mostly been used for confirmation of fetal viability, establishment of gestational age, measurement of nuchal translucency (NT), and for first trimester screening (4). Improvements in sonographic technology and ultrasonography scanners with high-resolution imaging, as well increased experience of sonographers regarding fetal imaging, have enabled the concept of early screening of fetal structural malformations in the late first trimester (5,6). Furthermore, early fetal echocardiogram has been defined for echocardiography implemented before the 16th gestational week for investigating congenital heart defects, especially in patients with high risk (7).

Screening in the first and early second trimester and early detection of major anomalies will lead to early decisions of

Address for Correspondence: *Erol Arslan*
e.mail: dr_erolarslan@hotmail.com ORCID ID: orcid.org/0000-0002-9111-0744

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pregnancy termination. Moreover, doing it before the 16th gestational week brings the advantage of early termination before women feel movements of the fetus. This is important for women, especially in cultures in which beliefs strongly affect social life rules. Furthermore, early termination of pregnancy has physical and physiological advantages for women and their families compared with late termination.

In this study, we aimed to investigate the major anomalies that resulted with termination of pregnancy before the 16th gestational week by years, and so to find their distribution during a six-year period. Moreover, we tried to ascertain whether early anatomic screening during the first and early second trimester might result in determining anomalies such as atrioventricular septal defect (AVSD) and spina bifida, which were ranked in the third group of anomalies by Syngelaki et al. (3), as discussed previously.

Material and Methods

This was a retrospective study of all terminated single pregnancies due to ultrasonographic findings of major congenital anomalies from 2011 to 2016 that were diagnosed in our department. This was a descriptive study and based on chart review and only anomalies that were diagnosed at or before 16^{+0} gestational weeks were included. Only major anomalies that required termination of pregnancy were included and diagnoses were confirmed by fetal autopsy. Ultrasonographic findings such as thickened NT, nasal bone hypoplasia, tricuspid regurgitation, and reversed a-wave on ductus venosus Doppler were excluded. Women who did not accept termination or who underwent termination outside of our center were excluded. The patients' ages and gestational weeks are presented as mean and standard deviation. This study was approved by the local ethics committee of our university.

Results

The women's mean age was 28.8±6.1 years and the mean gestational age at termination was $13^{+5/7}\pm1^{+3/7}$ weeks. A total of 244 pregnancies were terminated at $\leq16^{+0}$ weeks from 2011 to 2016. Two hundred seventy-three anomalies were detected among the 244 patients during the study period. Although 218 patients had isolated anomalies, 26 of 244 patients had at least two different anomalies. The detected anomalies and their distribution by years are shown in Table 1. Cranial neural tube defects (NTD) such as anencephaly and encephalocele accounted for 32.6% of all detected anomalies (n=89). These were followed by cystic hygroma (23%, n=63). Two hundred thirty-two anomalies could easily be diagnosed during early gestation; however, 41 of 273 (15%) anomalies (14 skeletal dysplasia, 9 spina bifida occulta, 7 multicystic renal dysplasia, 6 AVSD, 2 hypoplastic left heart, 1 ductus venosus agenesia, 1 sacroccocygeal teratoma, 1 micrognathia) belonged to third group of anomalies (Table 1).

Table 1. The number of patients and diagnosed anomalies and their distributions from 2011-2016

	2011	2012	2013	2014	2015	2016	Total
Number of terminated pregnancies	29	30	50	39	42	54	244
Number of detected anomalies	31	34	55	41	51	61	273
Cranial NTD	8	10	27	14	14	16	89
Spina bifida occulta★	-	1	4	1	2	1	9
Sacrococcygeal teratoma★	-	1	-	-	-	-	1
Holoprosencephaly	-	-	3	4	1	1	9
Ventriculomegaly	-	3	-	2	1	3	9
AVSD★	-	-	-	1	5	-	6
Hypoplastic left heart★	-	-	-	-	2	-	2
Agenesis of DV★	-	-	-	-	1	-	1
Cystic hygroma	7	10	7	8	10	21	63
Hydropsfetalis	5	5	3	3	2	1	19
Micrognathia★	-	-	1	-	-	-	1
Multicystic dysplastic kidney★	1	1	2	-	1	2	7
Renal agenesis	-	-	-	-	2	1	3
Megacystis	3	-	3	1	1	5	13
Abdominal wall defects	5	1	4	5	8	4	27
Skeletal dysplasia★	2	2	1	2	1	6	14

NTD: Neural tube defect; AVSD: Atrioventricular septal defect; DV: Ductus venosus; ★: These anomalies were ranked in the third group anomalies that were potentially detectable as described by Syngelaki et al. (3).

Discussion

In the present study, it was observed that the number of diagnosed anomalies increased by years except in 2014, which had a lower number of abnormalities compared with 2013. The higher numbers of abnormalities were related with high numbers of cranial NTD detected in 2013, which were 2-3 times higher than in other years. Excluding this peak in 2013, there was a linear increase from 2011 to 2016. This might be simply explained by an arbitrary increase in the number of anomalies; nevertheless, more detailed anatomy screening could be the cause of this increase from 2011 to 2016.

Cranial NTD comprised 31% of major structural anomalies that were terminated from 2011 to 2016 and it was the most common abnormality during the study period, followed by cystic hygroma, which is consistent with the literature (8). Forty-one of the 273 (15%) anomalies that were diagnosed before the 16th gestational week were classified in third group of anomalies as described by Syngelaki et al. (3). These sorts of anomalies needed a detailed examination, as well transvaginal ultrasound evaluation in some cases for early detection. Although 15% was not a small rate among the total anomalies considering the extremely high percentage of cranial NTD and cystic hygroma, we still believe that more anomalies could be detected by using an anatomic screening protocol during the first trimester screening, in addition to using transvaginal ultrasound at least in suspected cases.

In our study, we determined the 16th gestational week as cutoff beside the 14th gestational week for various reasons. First, our primary aim was not to recognize all abnormalities during the first trimester aneuploidy screening, but to diagnose major anomalies that would undergo termination of pregnancy as early as possible, preferably before the mother could feel fetal movements, which might make the decision for termination easier. Second, examining the fetal heart and other body parts in the first trimester was not appropriate for most of the patients, when it was considered that examination by transvaginal ultrasound was not a favorable method for pregnant women in our country. Moreover, studies in the literature used both the 14th and 16th gestational weeks as cutoff points for early anomaly screening (7,9). Four of 6 AVSD cases and all hypoplastic left heart syndrome cases (n=2) were diagnosed before the 14th gestational week, which might encourage us to perform more early scanning of cardiac defects, at least for gross pathologies that can give signs in earlier gestational weeks. Moreover, there were 9 cases of spina bifida and 14 cases of lethal skeletal dysplasia in total that were diagnosed before the 16th gestational week. As discussed previously, these anomalies were grouped in the literature as anomalies that could be diagnosed by meticulous screening, and our results were encouraging regarding early diagnosis of these anomalies.

Several studies in the literature, those searching for the effectiveness of early anomaly screening, were designed prospectively and compared the first trimester screening with 18-24th week screening (10,11). In addition, some other studies retrospectively looked over the early anomaly screening, as in our study (8). Those studies determined that early anomaly screening could diagnose nearly 50% of major abnormalities in unselected patients, and 61% of all kinds of abnormalities in high-risk patients (8). In our study, we could not categorize patients according to their risk factors because we did not have enough information. Likewise, our data could not reveal a percentage of anomalies that were diagnosed during the first trimester in a selected population because of its retrospective design and the fact that it only included terminated pregnancies in our center. It should be born in mind that some patients did not accept termination or underwent termination in other centers. Different than those studies, we investigated specific anomaly rates among total anomalies.

To the best of our knowledge, this is the first study to investigated early diagnosis of fetal anomalies in Turkey. Despite its retrospective characteristic and indirect measurement of early anomaly screening effectiveness, it provides valuable information for future studies in our country. Furthermore, this study shows the need for an anatomic scan protocol while performing aneuploidy screening during early gestation in our country.

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Clinical predictors of successful vaginal myomectomy for prolapsed pedunculated uterine leiomyoma

Serdar Aydın[1], Hale Göksever Çelik[2], Mustafa Maraşlı[1], Rabia Zehra Bakar[3]

[1]Department of Obstetrics and Gynecology, Bezmialem Vakıf University School of Medicine, İstanbul, Turkey

[2]Department of Obstetrics and Gynecology, Saglik Bilimleri University, İstanbul Kanuni Sultan Süleyman Training and Research Hospital, İstanbul, Turkey

[3]Department of Obstetrics and Gynecology, Erbaa State Hospital, Tokat, Turkey

Abstract

Objective: Uterine leiomyomas are the most common pelvic tumor in women. The calculated prevalence of prolapsed pedunculated leiomyoma was 2.5% in patients who underwent surgery. Although vaginal removal is safe and effective, hysterectomy demand is questionable. We aimed to analyze the association between patient characteristics, clinical features of prolapsed pedunculated submucosal leiomyoma, and the probability of successful vaginal myomectomy.

Material and Methods: This study was conducted in 35 women who presented with prolapsed pedunculated uterine leiomyoma. Patients were grouped according to the treatment procedure, either vaginal myomectomy or hysterectomy.

Results: Hysterectomy was performed in 14 patients and vaginal myomectomy was performed in 21 women. The mean ages and menopausal status were similar. Parity was higher in the hysterectomy group (p=0.02). The preoperative hematocrit value of patients undergoing vaginal myomectomy was significantly lower (p=0.04). There was no significant difference between the groups regarding the largest leiomyoma diameter. However, the median calculated leiomyoma volume was lower in the vaginal myomectomy group (p=0.04). None of the variables were independently associated with successful vaginal myomectomy on multivariable logistic regression analysis.

Conclusion: The feasibility and choice of vaginal myomectomy is associated with low parity, absence of coexisting leiomyoma, high volume of leiomyoma estimated via ultrasound measurement, and severe anemia. (J Turk Ger Gynecol Assoc 2018; 19: 146-50)

Keywords: Leiomyoma, prolapsed pedunculated submucosal leiomyoma, vaginal myomectomy, hysterectomy

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Introduction

Uterine leiomyomas are the most common pelvic tumor in women arising from the smooth muscle of the myometrium (1). Leiomyomas are classified according to their location within the myometrium. Prolapsed pedunculated submucous myoma is classified as type 0 submucous leiomyoma (2). In general, the prevalence of uterine leiomyoma is approximately 25% of reproductive-aged women and submucosal leiomyoma account for approximately 15-20% of these (3). The real prevalence of prolapsed pedunculated submucosal myoma is unknown but the calculated prevalence was 2.5% in patients who underwent surgery for leiomyoma (4). They typically present with vaginal bleeding, pelvic pain that is generally cramping in nature during the expulsion of the myoma from the cervix, and dysmenorrhea and bloody discharge. Surgery is recommended for symptomatic patients. Although vaginal removal is safe and effective for uterine prolapsed pedunculated leiomyoma, hysterectomy demand is questionable (4-6).

Few series in the English literature about the management of uterine prolapsed pedunculated submucous myomas have been reported (4-9). However, this report mainly addresses the early results, complications, and feasibility of vaginal removal. There is an evidence gap regarding how patient characteristics and leiomyoma features influence the choice of operative procedures. Better understanding of factors that influence the

Address for Correspondence: *Hale Göksever Çelik*
e.mail: hgoksever@yahoo.com ORCID ID: orcid.org/0000-0002-5162-3262

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probability of undergoing hysterectomy would help deliver patient-centric uterine leiomyoma care. The aim of this study was to analyze the association of patient characteristics and the probability of hysterectomy and the results of the two procedures in patients with prolapsed pedunculated submucosal myoma.

Material and Methods

This retrospective cross-sectional study was based on the analysis of medical records of 35 women who presented with prolapsed pedunculated uterine leiomyoma. We reviewed the hospital records of all patients admitted to departments of gynecology of two centers with a clinical diagnosis of prolapsed pedunculated submucous myoma between November 2011 and March 2016. The local ethics committee approved the study.

Demographic, clinical and pathologic data, including age, gravidity, parity, history of uterine surgery and cesarean section, smoking status, menopausal status, medical history, complications, and preoperative and postoperative hematocrit were all retrieved from the medical records. A history of medical conditions, including hypertension, diabetes mellitus, hypercholesterolemia and thyroid disease were recorded if hospital records confirmed the diagnosis. Patients with amenorrhea for more than one year since the last menstrual period were considered to be menopausal.

Only myomas with a pedicle base originating at or above the level of the internal cervical os were included. There was a total of 35 patients during the study period. Patients were grouped according to the performed procedure; either vaginal myomectomy or hysterectomy. Vaginal myomectomy was performed with general anesthesia under sterile conditions. The myoma was grasped using tenaculum forceps under direct vision and twisted around its pedicle. Too much downward traction on the myoma was avoided so as not to cause inversion of the uterus. In some cases, when feasible, the pedicle was clamped and ligated as high as possible. Myomectomy was successfully accomplished without dilatation of the cervix. Total abdominal hysterectomy with or without concomitant bilateral salpingo-oophorectomy were performed using a standard clamp technique as performed in benign gynecologic indications. All patients in whom hysterectomy was performed were decided at the beginning of the patients' examinations. If laparoscopic hysterectomies were performed, vaginal removal of the leiomyoma was performed first to place the uterine manipulator.

Statistical analysis

Data are expressed as mean ± standard deviation or number and percentage, median and range, as appropriate. Statistical analysis was performed after normality testing (histogram analysis and/or Kolmogorov–Smirnov) using IBM SPSS version 22. Student's t-test was used for comparisons of normally distributed variables, and the Mann-Whitney U test was used for categorical variables. Chi-square and Fisher's exact tests were used to compare the proportion of categorical variables. Multivariable logistic regression models were developed to predict the probability of successful vaginal removal of a prolapsed pedunculated leiomyoma using variables identified during univariate analysis. Odds ratios with 95% confidence intervals were also calculated. The Statistical Package for Social Sciences (SPSS) for Windows version 22.0 (SPSS Inc., Chicago, IL, USA) was used for the analysis and two-sided p value of <0.05 was considered as significant.

Results

Vaginal myomectomy was successful in 21 women. Hysterectomy for prolapsed pedunculated submucosal leiomyoma was performed in 14 patients. The mean age of the study population was 46.1±8 years (range, 29-62 years). Parity was 2.7±1.7 (range, 0-7). Two women were nulliparous (5.7%) and one was nulligravida (2.8%). Only 4 women were in the postmenopausal period (11.4%). The patient characteristics, laboratory and imaging features of patients undergoing vaginal myomectomy or hysterectomy for prolapsed pedunculated vaginal leiomyoma are presented in Table 1. The mean ages were 44.8±9.2 and 47.9±5.4 years in the vaginal myomectomy and hysterectomy groups, respectively. The mean parity of the hysterectomy group was statistically higher than the uterus-sparing group (3.6±1.6 vs 2.1±1.6, p=0.02). All of the hysterectomy group patients were parous and 2 (9.5%) women in the vaginal myomectomy group were nulliparous (p=0.2). One woman (7.1%) in the hysterectomy group and 3 women (14.3%) in the vaginal myomectomy group were postmenopausal (p=0.5). Also, comorbidity profiles of the patients in both groups were similar.

On admission, hematocrit value of the patients undergoing vaginal myomectomy (29.9±5.2) was significantly lower than those undergoing hysterectomy (33.4±3.8, p=0.04). Blood transfusion prior to surgery because of preoperative severe anemia was performed to 11 patients (52.6%) in the vaginal myomectomy group and 5 patients (35.7%) in the hysterectomy group (p=0.3).

All patients who underwent vaginal myomectomy had no more than one prolapsed pedunculated leiomyoma. The total leiomyoma number in the hysterectomy group ranged from 1 to 5 with median number of 1 (p=0.03). Median of the largest diameter of prolapsed pedunculated submucosal leiomyoma was 5 cm (range 2-10 cm) in the vaginal myomectomy group and 5.5 cm (range, 3-13 cm) in the hysterectomy group (p=0.2).

The median leiomyoma volume was 60 cm^3 (range, 24-660 cm^3) in the vaginal myomectomy group and 112 cm^3 (range, 40-910 cm^3) in the hysterectomy group (p=0.04).

Multivariable logistic regression models were developed to predict hysterectomy using variables parity, preoperative hematocrit value, leiomyoma number, and estimated leiomyoma volume, which were identified during the univariate analysis (Table 2). None of the variables were independently associated with successful vaginal myomectomy or those undergoing hysterectomy.

The mean duration of hospitalization in women who underwent hysterectomy was 6.7±3 days, whereas the duration was 3.5±3 days in the vaginal myomectomy group (p=0.005). The mean postoperative hospital stay durations were 1.7±1.4 days in vaginal myomectomy group and 3.1±1.6 days in hysterectomy group. However, the overall hospitalization (4 days, p=0.7) and the postoperative hospitalization (2±0.8, p=0.7) for the small subgroup of laparoscopic myomectomy were similar to vaginal myomectomy. Postoperative hematocrit values were similar. We did not encounter any major complications except a case of febrile morbidity seen after vaginal removal because of abrupt bleeding controlled with pedicle ligation.

Discussion

The preference of vaginal removal or hysterectomy in patients with prolapsed pedunculated submucosal leiomyoma depends on many factors. There is an association between patient characteristics and the choice of management. Younger age and parity, lower preoperative hematocrit levels, smaller leiomyoma diameter and volume were observed in the vaginal myomectomy group, which resulted in shorter hospitalization time and postoperative hospitalization duration.

Table 1. Demographic, baseline characteristics and clinical features of patients in vaginal myomectomy and hysterectomy

	Vaginal myomectomy (n=21)	Hysterectomy (n=14)	p
Age, years (mean ± SD)	44.8±9.2	47.9±5.4	0.2
Gravidity (mean ± SD)	4.4±2.7	4.6±1.7	0.1
Parity (mean ± SD)	2.1±1.6	3.6±1.6	**0.02**
Nulliparity [n (%)]	2 (9.5)	0	0.2
Menopause status [n (%)]	3 (14.3)	1 (7.1)	0.5
Comorbidty [n (%)]	5 (23.8)	7 (50)	0.1
Previous uterine surgery [n (%)]	5 (23.8)	4 (28.6)	0.7
Previous myomectomy [n (%)]	2 (9.5)	1 (7.1)	0.5
Blood transfusion [n (%)]	11 (52.4)	5 (40)	0.8
Preoperative hematocrit (mean ± SD)	29.9±5.2	33.4±3.8	0.04
Postoperative hematocrit (mean ± SD)	30.4±3	31.8±3.7	0.3
Units of erytrocyte suspension transfusion (mean ± SD)	1.2±1.9	1.6±1.7	**0.4**
Number of leiomyoma [median (range)]	1	1 (1-5)	**0.03**
Concomitant intramural leiomyoma [n (%)]	0	6 (42.9)	**0.001**
Leiomyoma diameter, cm [median (range)]	5 (2-10)	5.5 (3-10)	0.2
Leiomyoma volume, cm^3 [median (range)]	60 (24-660)	112 (40-910)	**0.04**
Hospitalization time, days (mean ± SD)	3.5±3	6.7±3	**0.005**
Postoperative hospitalization duration, days (mean ± SD)	1.7±1.4	3.1±1.6	**0.04**
SD: Standard deviation			

Table 2. Multivariable logistic regression analysis of factors for the prediction of undergoing hysterectomy

Parameters	Adjusted odds ratio	CI	Significance
Parity	1.63	0.86-3.08	0.1
Leiomyoma volume	1.01	0.99-1.01	0.09
Concomitant leiomyoma	0	0	0.9
Preoperative hematocrit	1.02	0.80-1.31	0.8
CI: Confidence interval			

The least invasive management option for women with symptomatic prolapsed pedunculated submucosal leiomyoma, in other words myoma in status nascendi, was evaluated in a few retrospective studies. These studies claimed that vaginal removal of prolapsed pedunculated leiomyoma was a safe and simple procedure with shorter hospitalization and minimal morbidity (4-6). The most probable potential complications of vaginal removal of prolapsed pedunculated leiomyoma are excessive hemorrhage from the pedicle, infection, and uterine inversion due to excessive traction. However, they did not report any complications in these series. Also, in our series, we encountered no major complications except a case of febrile morbidity controlled with antipyretic treatment and a minimal surgical procedure, as mentioned before.

Vaginal removal of prolapsed pedunculated leiomyoma appears to be feasible in most cases (5,6). Until now, there has been no analysis of factors to predict successful vaginal removal. Although without evidence, the widely accepted features of prolapsed pedunculated leiomyoma that cannot be removed through vaginal myomectomy are leiomyoma with broad-based pedicle, non-visualized pedicle, leiomyoma larger than 4 cm, and cervical leiomyoma rather than submucosal. In a retrospective series of 46 women with prolapsed pedunculated leiomyoma, only two cases failed due to the difficulty of reaching the pedicle of the leiomyoma (6). Caglar et al. (10) reviewed 70 patients retrospectively. They concluded that leiomyoma diameter over 5 cm could not be successfully managed vaginally. They could not perform logistic regression or other statistical analysis to detect predictors, and they did not explain the rationale of choosing the diameter of 5 cm. In another retrospective series, vaginal myomectomy, abdominal myomectomy or hysterectomy were compared in the management of prolapsed pedunculated leiomyoma, but the rate of conversion from a vaginal removal to abdominal procedure was not reported (5). Even very large leiomyomas, up to 10 cm, were successfully removed vaginally and completed without any complications. In our vaginal myomectomy group, 62% of women had a leiomyoma diameter larger than 5 cm. Ultrasound estimated leiomyoma volume may help to predict vaginal myomectomy on univariate analysis, but on logistic regression it loses its importance as an independent determinant.

Surgery has been the mainstay of leiomyoma treatment. Leiomyoma, irrespective of location, was reported as the most common indication for hysterectomy according to the literature (11-13). Hysterectomy has the advantages of the elimination of symptoms and no risk of recurrence. Also, significant and sustained improvements are seen for symptoms, psychological function and quality of life after hysterectomy (14). Uncertainty remains regarding how different patient characteristics are associated with uterine-sparing procedures and hysterectomy (15). The choice of procedures depends on the age of the woman, reproductive potential, accompanied diseases, and anemia. The preference for hysterectomy has decreased with infertility, higher income and education, and decreasing age (16). Furthermore, concomitant menstrual disorders, uterovaginal prolapse, and previous myomectomy history increase the need for hysterectomy (17-19). We found that low parity, preoperative anemia, and absence of coexisting leiomyomas were associated with preferences for uterine-sparing surgery. Hysterectomy is usually required in women with multiple leiomyomas. Dicker et al. (5) presented a series of 142 patients managed with different methods, either vaginally or abdominally over 10 years. A total of 46 women had a vaginal myomectomy, 12 had abdominal hysterectomy, usually following vaginal removal of the prolapsed pedunculated leiomyoma, and 18 underwent vaginal hysterectomy. Riley (8) presented 41 patients, 13 were treated by abdominal hysterectomy. The authors reported that hysterectomy was related to slightly higher postoperative morbidity, but comparable to that of hysterectomy for other indications. As expected, the duration of hospitalization after vaginal myomectomy is shorter than with an abdominal operation (5,10). In our series, hospital stay was longer with abdominal hysterectomy, but was comparable with vaginal removal in the small series of laparoscopic hysterectomy.

In a broad sense, the disadvantage of myomectomy is the risk of recurrence or formation of new leiomyomas. The risk of a second operation after myomectomy ranges from 11% to 26% (20,21). The detection of new leiomyomas through imaging is about 50% of women within 5 years after abdominal myomectomy (22). Although the risk of leiomyoma recurrence may be attributed to a prolapsed pedunculated leiomyoma, myoma-related symptoms appear to occur infrequently. A retrospective series of 46 women reported that 20% of cases continued to be symptomatic, 9% cases required a repeat vaginal myomectomy, and 6% had a hysterectomy at 5.5 year follow-up (4). Hysterectomy in these cases may have been performed due to indications other than the original prolapsed leiomyoma. In another series of 46 women, hysterectomy was required in an additional 14% of patients in whom vaginal removal of prolapsed pedunculated leiomyoma was successful.

The present study has several limitations; first, the retrospective design of the study and lack of follow-up of the patients, and secondly, the relatively small sample size of the study population. The strengths of our study include new data regarding the prediction of success or choice of vaginal removal for prolapsed pedunculated leiomyomas that presented with prolapse from the cervical canal with more preoperative factors than previous studies, in the setting of laparoscopic hysterectomy.

In conclusion, both vaginal removal and hysterectomy are safe procedures for prolapsed pedunculated leiomyoma. The feasibility and choice of vaginal removal or hysterectomy depend on many factors. Lower parity, absence of coexisting leiomyoma, lower volume of presenting leiomyoma estimated via ultrasound measurement, and more severe anemia, which may be a sign that less stable hemodynamics were associated with preference of vaginal removal. However, neither of these factors predicted the operation choice or obligation independently.

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Does the presence of endometriosis cause a challenge for transvaginal oocyte retrieval? A comparison between patients with and without endometriosis

Işıl Kasapoğlu, Pınar Türk, Aylin Dayan, Gürkan Uncu

Department of Obstetrics and Gynecology, Uludağ University School of Medicine, Bursa, Turkey

Abstract

Objective: The aim of the study was to compare patients with and without endometriosis regarding performance rates, difficulties, and complications associated with transvaginal oocyte retrieval (TVOR) procedures.

Material and Methods: A prospective cohort study was conducted at the In Vitro Fertilization Unit of the Division of Reproductive Endocrinology and Infertility Department of a university hospital. Fifty-eight patients with endometriosis and 61 patients without endometriosis underwent TVOR procedures consecutively. Primary outcome measures were; number of needle entries per patient and performance rating defined as the total number of oocytes retrieved per vaginal needle entry. The requirement for manual compression of the abdominal wall (assistance) to reach the ovaries, procedure-related pain, and procedural complications were also evaluated.

Results: The median number of needle entries through the vaginal wall per patient was comparable between the two groups (p=0.45). Performance rates were higher in the control group (p=0.001). Performance rates and total number of the needle entries through the vaginal wall were not significantly correlated with ovarian endometrioma (OMA) diameter (r=0.28; p=0.68; r=0.275, p=0.068, respectively) in the endometriosis group. Body mass index (BMI) scores were found to be correlated with the number of the needle entries and higher BMI scores were associated with higher numbers of vaginal wall punctures (p<0.001). The requirement for manual compression of the abdominal wall was significantly higher in the control group (57.4% vs 27.6%, p=0.001). A similar proportion of women needed analgesic medications after the TVOR procedure in both groups (10.3% vs 16.4%, p=0.33). Hospital readmissions for any symptoms were also comparable between the two groups (p=0.22). Three women were treated for pelvic infection, all of whom were in the endometriosis group.

Conclusion: Endometriosis seems to cause a challenge for TVOR that may have reflection on individual surgeon's performance rates for the procedure, independently from the diameter of a pre-existing OMA or ovarian adhesions. Obesity is another factor that may present a challenge for the procedure. (J Turk Ger Gynecol Assoc 2018; 19: 151-7)

Keywords: Endometriosis, oocyte pickup, obesity, complication, in vitro fertilization

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Introduction

In vitro fertilization (IVF) has become the treatment of choice for many cases of infertility. Such common use of IVF has promoted ongoing development of methods to be used in each individual stage of IVF (1).

Oocyte pickup (OPU) is one of the most important stages and since the first description of follicular aspiration under transvaginal ultrasound guidance in the early 1980s, it has gained superiority because of its simplicity and because it is a successful method (2,3).

Although transvaginal oocyte retrieval (TVOR) has been accepted as a safe, straightforward, gold standard procedure, it may be associated with complications (4) and it is recommended to collect as many oocytes as possible with a minimal number of punctures (5). Procedural complications include vessel punctures, hemorrhage, injury of adjacent organs, ovarian torsion, pelvic infection, and vaginal vault bleeding (6,7). Although there are limited data on TVOR complications in the literature, serious complications are currently reported to be less than 1.5% (8). Intraabdominal hemorrhage or bleeding from vaginal puncture sites are the

Address for Correspondence: *Işıl Kasapoğlu*
e.mail: kasapogluisil@hotmail.com ORCID ID: orcid.org/0000-0002-1953-2475

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most common complications (9). There is limited knowledge about complications, probably as a result of underreporting.

A significant proportion of patients with endometriosis may require assisted reproductive technologies. Previous studies and meta-analyses on endometriosis have only included reproductive outcomes and have also highlighted inadequacy of data on complications that might occur in the course of IVF treatment, especially during the OPU procedure (10). It may be reasonable to suppose that TVOR can be more complex and challenging to perform in patients with endometriosis because of ovarian endometriomas or pelvic adhesions associated with endometriosis. Nevertheless, currently available data are limited to estimate complication rates and challenges associated with oocyte retrieval procedure in patients with endometriosis; further clinical studies are required in this field. Furthermore, the impact of the presence of endometriosis has not been specifically examined in the literature, especially in terms of success rates and challenges and complications associated with oocyte retrieval procedures.

In this study, we aimed to compare complications, performance rates and challenges associated with TVOR procedures between patients and without endometriosis.

Material and Methods

This was a prospective cohort study conducted in 119 consecutive patients who underwent IVF treatment for a time period of three months (2017) at the IVF Unit of the Division of Reproductive Endocrinology and Infertility Department of a university hospital. Fifty-eight women with endometriosis and 61 without endometriosis who were body mass index (BMI)-matched, and who underwent a TVOR procedure before intracytoplasmic sperm injection (ICSI) during the same period were included in the study. Each TVOR procedure was performed by the same experienced physician. The diagnosis of endometriosis was confirmed by the demonstration of ovarian endometriomas (OMAs) either through laparoscopic surgery or using ultrasound scans.

The control group consisted of women who underwent IVF/ICSI due to male factor indications, diminished ovarian reserve, tubal factors, polycystic ovary syndrome, hypogonadotropic hypogonadism, fertility preservation, and unexplained infertility. The study protocol was approved by the institutional Review Board and each participant provided written informed consent. Although different ovarian stimulation protocols were used according to IVF indications, all patients received human chorionic gonadotropin (hCG) when the leading follicle(s) reached a diameter of 17 to18 mm and a TVOR procedure was performed 34-36 hours after hCG administration.

All TVOR procedures were conducted under general anesthesia with propofol and fentanyl administered to every patient. Following induction anesthesia, patients were placed in the dorsal lithotomy position; the vagina was cleaned with saline solution. Ultrasound scans were performed with a SIUI CTS-310B ultrasound machine equipped with a 3.5 to 7.5-MHz probe. A single-lumen 17-gauge aspiration needle (K-OSN-1735-A-90-US, Cook) was used in all TVOR procedures.

After the OPU procedure, patients were observed for a minimum of 2 hours. If any suspicious intraabdominal hemorrhage occurred during the TVOR procedure, patients were observed for an extra day. All patients were recommended to use 3 doses of 500 mg tablets of oral azithromycin after the TVOR procedure.

Immediately after each TVOR procedure, the surgeon filed a report consisting of objective and quantitative parameters about the details of the procedure. Ovarian adhesions were assessed using transvaginal ultrasound and adherent ovaries were described as remained unchanged after simultaneous pressure of the transvaginal ultrasound and abdominal palpation, ovaries which become directly adherent to the peritoneum of the pouch of Douglas. Procedure reports were prepared and replicated as hardcopies before starting the study. The report included a number of questions such as total number of punctures, whether abdominal manual fixation of the ovaries was necessary (abdominal compression to push the ovaries towards the pelvis by an assistant), number of mature follicles (>14 mm) counted with transvaginal ultrasound before the retrieval procedure, number of oocytes collected during the procedure, number of mature oocytes (MII) collected, whether the ovaries were adherent (ovaries at unexpected location on ultrasound, especially behind the uterus), necessity of needle passage through the uterus, necessity of increased aspiration pressure, ovarian or vaginal bleeding, method used to control bleeding (suturing/local pressure) and severe early postoperative pain (need for additional analgesia). Presence of OMA, their location (central/peripheral), and diameters of OMAs, appearance of endometrioma content inside the pipe, and necessity of needle passage through an OMA were all recorded. For all patients, postoperative clinical or laboratory evidence of an early pelvic infection were noted.

The primary outcome measures that were compared between the two groups included the number of needle entries per patient, performance rating for OPU procedures defined as the total number of oocytes retrieved per needle entry, the requirement for assistance by manual compression of the abdomen to help reach the ovaries, OPU-related pain, and procedural complications (bleeding, infection, injuries of adjacent organs).

Statistical analysis

The Shapiro-Wilk test was used for assessing whether the variables followed normal distribution. The variables

are reported as mean (±standard deviation) or median (minimum-maximum) values. According to the normality test result, intergroup comparisons were performed using the independent samples t-test or the Mann-Whitney U test. The Kruskal-Wallis test was used for comparisons involving more than two groups. Pearson's chi-square and Fisher's exact tests were used to compare categorical variables. Relationships between continuous variables were examined using correlation analysis. Pearson's and Spearman's correlation coefficients were computed to interpret normality test results. The SPSS (IBM Corp. Released 2012. IBM SPSS Statistics for Windows, Version 21.0. Armonk, NY: IBM Corp.) software was used to perform statistical analyses and a p value of <0.05 was set as the level of statistical significance.

Results

After excluding duplicated cycles of a patient, a total of 119 OPU cycles were included in the final analysis. The study group included 58 patients with endometriosis and the control group included 61 patients without endometriosis.

The analysis of patient characteristics reveal no statistically significant differences between two groups in BMI, age, and nulliparity (p=0.17, p=0.36, and p=0.25, respectively). Significant differences were found between the two groups in serum anti-Müllerian hormone (AMH) levels, previous ovarian surgery, total gonadotropin dose administered, and ovarian adhesions; these variables are shown in Table1. The mean serum AMH were significantly lower in the endometriosis group (p<0.01). Previous ovarian surgery and ovarian adhesion rates and total gonadotropin dose administered were also higher in the endometriosis group. All procedures were performed under general anesthesia.

Forty-five out of 58 (77.6%) patients with endometriosis had OMAs. Thirty-one (68.9%) patients had unilateral OMAs and 14 patients had bilateral OMAs (31.1%). The median diameter of the OMAs was 4 cm (2-11). In two patients, endometriomas were inadvertently punctured to gain access to the follicles lying behind.

In the control group, male factor infertility was the leading indication (n=33, 54%) for the procedure, the other factors were diminished ovarian reserve, tubal factor, polycystic ovarian syndrome, hypogonadotropic hypogonadism, fertility preservation, and unexplained infertility.

The median total number of punctures per patient was comparable between the two groups (p=0.45). Procedure performance rates, defined as the number of oocytes retrieved per needle entry, were higher in the control group (p=0.001). The need for manual assistance was significantly higher in the control group (57.4% vs 27.6%, p=0.001). A similar proportion of women needed analgesia after TVOR in the endometriosis and control groups (10.3% vs 16.4%, p=0.33). No significant intergroup difference was found in all-cause hospital readmission rates; two patients from the control group and 5 patients from the endometriosis group presented with pelvic irritation symptoms (p=0.22) (Table 2).

Conditions requiring intervention or treatment such as suturing of the vaginal wall to control bleeding, intravenous antibiotics to treat pelvic infections, and injuries to adjacent organs were accepted as complications. Complications associated with the procedure are presented in Table 3.

Vaginal wall suturing had to be performed due vaginal bleeding that was unresponsive to local pressure in a total of seven

Table 1. Baseline characteristics

Characteristics	Endometriosis n=58	Control n=61	p value
Age (years)	32 (29-35)	31 (29-34)	0.369[a]
Nulliparity (%)	47 (81)	44 (72.1)	0.25[c]
BMI (kg/m^2)	23.98±3.84	25.83±5.5	0.17[b]
AMH (ng/mL)	1.76±1.95	3.27±3.11	**<0.01**[a]
Infertility duration (years)	5.35±3.59	7.02±3.59	0.09[a]
Previous ovarian surgery (%)	26 (44.8%)	3 (4.9%)	**<0.01**[c]
Presence of ovarian adhesions (%)	21 (36.2%)	3 (4.9%)	**<0.01**[c]
Total gonadotrophin dose (IU)	3100 (2400:4050)	2325 (1750:3300)	**<0.01**[b]
Serum estradiol value on hCG day (pg/mL)	1497.9±1207.1	1768±1301.4	0.25[a]

Data were presented as median (interquartile range), mean (± standard deviation) and n (%); [a]: Independent-samples t-test; [b]: Mann-Whitney U test; [c]: Chi-square test; hCG: Human chorionic gonadotropin; AMH: Anti-Müllerian hormone; BMI: Body mass index

Table 2. Properties of TVOR

Characteristics	Endometriosis n=58	Control n=61	p value
Performance rate *(Retrieved oocyte number/ per vaginal puncture)*	0.34±0.15	0.59±0.53	**0.001**[a]
Total number of needle entries	4.1±1.85	4.9±2.57	0.45[a]
Manual assistance (%) *(Abdominal pressure to gain access to the ovaries)*	16 (27.6%)	35 (57.4%)	**0.001**[c]
Requirement for analgesia (%)	6 (10.3%)	10 (16.4%)	0.33[c]
Hospital readmission rate (%)	5 (8.6%)	2 (3.3%)	0.22[c]

Data were presented as median (interquartile range), mean (±standard deviation) and n (%); [a]: Independent-samples t-test; [c]: Chi-square test

patients (5.8%). Five of these patients were in the control group (p=0.28) (Table 3). Two women in the control group had intraabdominal bleeding and were hospitalized for observation, none of whom required any additional interventions. All three patients who were readmitted due to pelvic peritoneal irritation and leukocytosis after OPU and treated for pelvic infections were in the endometriosis group. Two of these patients were those who had their OMA punctured during the TVOR procedure. One patient who presented with macroscopic hematuria was diagnosed as having a bladder injury after a cystoscopy exam. She was in the endometriosis group without OMA. The TVOR procedure of this patient was ordinary.

The number of oocytes retrieved per needle entry did not significantly correlate with OMA diameters (r=0.28; p=0.68) in the endometriosis group.

The rate of ovarian adhesions detected with ultrasound was found to be higher in the endometriosis group (p<0.01). However, no significant associations were found between ovarian adhesions and the total number of oocytes retrieved per needle entry (p=0.99).

When the results were analyzed according to BMI scores, a positive correlation was found between BMI scores and total number of needle entries and higher BMI scores (>30 kg/m^2) were associated with higher total number of needle entries (p<0.001).

Discussion

In this prospective study, we evaluated whether the presence of endometriosis had an unfavorable effect on TVOR procedures and we concluded that endometriosis could have an unfavorable effect on the performance (total number of oocytes retrieved per needle entry) of TVOR procedures during IVF/ICSI treatment. Furthermore, obesity was defined as another factor that may present a challenge for the procedure.

Oocyte retrieval procedures should be performed with the highest possible safety and attention because these patients are actually healthy individuals. Effectiveness and success of an oocyte retrieval procedure depends on the least amount of interference and complication rates with an adequate number of oocytes retrieved during the procedure. TVOR procedure is simple and efficient in terms of a better visualization of smaller follicles and therefore, more oocytes could be harvested (4).

Table 3. Complications

Complications	Endometriosis n=58	Control n=61	p value
Bleeding from the ovary (%)	-	2 (3.3%)	-
Minimal vaginal bleeding (%) *Local compression*	15 (25.9%)	9 (14.8%)	0.13[c]
Necessity of sutures to stop vaginal bleeding (%)	2 (3.4%)	5 (8.2%)	0.28[c]
Pelvic infections (%)	3 (5.2%)	-	-
Injuries to adjacent organs	1	-	-
Data were presented as n (%); [c]: Chi-square test			

Although TVOR is accepted as a safe and straightforward variations and absence of clear, unique definitions for the surgical approach makes it complicated to define certain difficulty parameters for evaluation. As a parameter that has not been evaluated previously, we evaluated the need for assistance as a difficulty parameter in our study. In endometriosis, assistance may be considered because access to the ovaries can be challenging owing to higher prevalences of adnexal adhesions. In our study, when considering the need for manual abdominal compression to fix the ovaries during OPU, the need for assistance was found to be at significantly higher rates in the control group (p=0.001), and it was correlated with BMI scores. In the assessment of the need for assistance by the prevalence of ovarian adhesions, no significant associations were found between ovarian adhesions and total number of oocytes retrieved per needle entry (p=0.99). In another study, it was suggested that, TVOR procedure might be easier to perform due to limited ovarian mobility, in the presence of adherent ovaries (9). In line with this study, higher ovarian adhesion rates in the endometriosis group (p<0.001) could explain the restricted ovarian mobility and easier oocyte collection in our study. Restricted ovarian mobility might also have reduced the need for manual fixation of the ovaries in the patients with endometriosis.

The number of oocytes retrieved, which is sign of success, was evaluated in a meta-analysis of five studies that compared the mean number of oocytes collected in patients with OMA to those in control subjects. In this meta-analysis, it was concluded that a lower number of oocytes could be collected in patients with OMA than controls (10). However, at this point, the debate about OMA and ovarian reserve continued.

In endometriomas, an important issue that has not been evaluated until now is the visible oocytes that cannot be reached and cannot be collected because of OMA. In this case, retrieved oocyte percentage (visualized follicles /retrieved oocyte number) can be evaluated. As a novel approach, in our study we evaluated the number of oocytes retrieved per needle entry, which is defined as TVOR performance. Performance rates were higher in the control group than those in the endometriosis group. However, no correlation was found between OMA diameters and number of oocytes collected (p=0.68).

Furthermore, obesity was found to be another factor that might present a challenge in reaching the ovaries in our study population. This finding was also supported by the fact that the number of needle penetrations was particularly high in patients

with higher BMI (>30 kg/m^2). Moreover, an increased number of needle entries alone may suggest that the procedure is challenging. A variety of factors were found to be responsible for the increased number of needle entries, especially in obese patients and patients with endometriosis patients in our study's population. In patients with endometriosis, the number of needle penetrations could be increased particularly in order to avoid passing through an endometrioma while in the control group, especially in the obese patients, the prominent reason was the difficulty accessing the ovaries.

Complication rates did not increase in parallel with the increased number of needle penetrations in our study's population. However, this is a potential issue of debate. There are no direct rational studies showing that complication rates increase as the number of needle penetrations increases, and further studies with larger sample sizes are required to provide statistical evidence to make a definitive conclusion. It is generally recommended to collect as many oocytes as possible with a minimal number of punctures (5).

The sole available meta-analysis also highlighted the lack of data about potential complications that might occur during IVF treatment and especially during the OPU procedure (10). Although there are limited data on OPU complications, notably, of those that may occur during the TVOR procedure, hemorrhages and infections have been known to be the most prominent complications with incidences ranging from 0.2% to 9% and from 0.2% to 0.6%, respectively (9,11). The most common complication was bleeding at the puncture site as a result of direct trauma (7). Simple compression is usually adequate to control local bleeding and it should be done without using a speculum. Rarely, sutures are needed to stop bleeding (8,12). In a study, it was suggested that an average blood loss of 230 mL might be considered as normal for a 24-hour period after an uncomplicated OPU. Moreover, no associations were found between blood loss and the number of follicles collected during the procedure or duration of the procedure (13). It is difficult to know and exactly foresee which patients are at risk. In our study, vaginal bleeding occurred in patients who underwent vaginal punctures at lower numbers.

Intraabdominal bleeding can be detected by a pulsatile flow and pelvic accumulation of blood. Large vessels are unlikely to be injured during ultrasound-guided procedures. However, it may not always be possible to pass through a safe area in order to avoid endometriomas and sometimes this necessitates passing through the uterus, even through the endometrium. Two patients who were followed up for intraabdominal hemorrhage were in the control group. They did not need any additional interventions. Three control patients who required uterine passage did not develop any complications.

Infections associated with TVOR were another complication reported with an incidence of 0.02% (14). Inoculation of vaginal bacteria was the most apparent elucidation. The number of vaginal punctures has been implicated as a risk factor (15). Although there are no specific trials, endometriosis and especially puncture of endometriomas has been suggested to be associated with higher infection rates (16). Our results provided further support to this suggestion because pelvic infections developed in only three patients with endometriosis in our study; one whom had bilateral endometriomas 7-8 cm in diameter and the surgeon had to puncture the endometrioma to gain access and collect follicles. Another patient who had her endometrioma punctured also developed a pelvic infection. Based on this information, dimensions and location of endometriomas may be crucial for gaining access to follicles. The third patient, who had early-stage endometriosis with an ovary adherent to the posterior wall of the uterus, underwent multiple vaginal punctures and presented with peritoneal irritation findings and leukocytosis two days after the TVOR procedure. However, the small numbers of events prevent reliable statistical comparison between the patients. Although there are some case reports supporting associations between endometriomas and infection (17), many of them failed to prove such associations (6). In a retrospective analysis of 19 patients in whom it was required to pass through an endometrioma during the procedure, no patients developed infections (18). Nevertheless, endometrioma punctures should not be encouraged and we also paid attention to avoid passing through any endometriomas. There are reports indicating that perioperative prophylactic antibiotic use may also help reduce the risk for infections (19). Without endometrioma puncture, follicular contamination with endometrioma content is unusual but possible. We observed only one case of follicular contamination with endometrioma content without cyst puncture. There are limited data on follicular contamination and its frequency has been reported as 2.8% (18).

The exact number of patients with pelvic pain who needed administration of additional analgesics therapy after OPU was comparable between the groups (p=0.33). A number of potential mechanisms could be suggested. Enlarged ovaries with multiple follicles can cause irritation.

As a much rarer complication, any accidental injury to adjacent organs is also possible and should be kept in mind (20). In a study in 2670 patients who underwent TVOR procedures, no injuries to adjacent organs were reported (9). However, there is no consensus at to whether these injuries are really so rare or simply under-recognized. We had only one patient with endometriosis who presented with gross hematuria four days after TVOR. Her TVOR procedure was performed as usual without any suspicious or unexpected finding. Bladder

injury was diagnosed through a cystoscopy examination, which revealed a needle entry hole in the bladder. Although adhesions found in patients with endometriosis may raise concern, it is also suggested that TVOR may be easier due to limited ovarian mobility in case of adherent ovaries (9). Limiting the number of needle entries and careful visualization under ultrasound guidance should be kept in mind because injuries are the result of punctures. Pelvic adhesions due to endometriosis or infections are suggested to increase the risk of such injuries secondary to distorted anatomy. Although unproven, practically, it can be recommended to maintain the needle guidance in a lateral position during punctures, away from the anterior structures (21,22).

In conclusion, endometriosis could have unfavorable effects on the performance of TVOR procedure during IVF/ICSI. Also, obesity could present a further challenge for TVOR procedures with an increased number of interventions, which should be evaluated in future studies. The low prevalence of major complications may prevent reliable statistical intergroup comparisons, especially in the case of infections; the probability of false- negative results should be taken in consideration. It is worth considering a trend toward higher infectious complication rates observed in patients with endometriosis after TVOR procedures, in comparison with controls. Taking care not to puncture OMAs actually awakens the conscience, so it makes the procedure special. However, proper preoperative evaluation before contemplating TVOR is a must for all patients for the safest attention possible.

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New insights on the pathogenesis of endometriosis and novel non-surgical therapies

Anom Suardika, Tjokorda Gede Astawa Pemayun
Department of Obstetrics and Gynecology, Udayan University, Sangah Hospital, Bali, Indonesia

Abstract

Endometriosis is a disease of theories, but none has succeeded to explain the whole picture. Most widely available drugs for endometriosis aim to relieve symptoms and improve fertility. Unfortunately, many short and long-term side-effects are associated with the treatments. To overcome this problem, researchers have developed many novel therapeutic agents, including non-invasive technique. We aim to provide new insights on pathogenesis model and novel non-surgical treatments for endometriosis, including drugs already available in the market and also drugs which are still under research. Seven novel treatment modalities are recognized, namely dienogest, aromatase inhibitor (AI), gonadotrophine-releasing hormone (GnRH) antagonist, anti tumor necrosing factor (TNF)-α, selective estrogen receptor modulator (SERM), selective progesterone receptor modulator (SPRM), and high-intensity focused ultrasound (HIFU). Dienogest, AI, and GnRH antagonists are effective novel treatments with good tolerance and safety. SERM and SPRM show inconsistent results, while anti-TNF-α is still in the animal experimental stage. HIFU is a potential futuristic treatment. However, it is still a long way until this technology is truly applicable. (J Turk Ger Gynecol Assoc 2018; 19: 158-64)

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Impacts of Practice

• Knowledge on new pathogenesis and pathophysiologic models of endometriosis may modify clinicians' perspective on therapy

• Implementing new therapeutical options may help to improve patients' satisfaction

Introduction

Endometriosis is an estrogen-dependent chronic inflammatory disease associated with chronic pelvic pain and infertility. Endometriosis causes a wide spectrum of symptoms and inflicts heavy socio-economic burden to patients. Endometriosis occurs in about 2-10% of women of reproductive age (1,2) and approximately in 50% of infertile women (3). The economic burden was reported 69,4 billion dollars in United States every year (4,5).

Clinical diagnosis of endometriosis is often difficult due to the wide spectrum of symptoms which most are non-spesific. Visual observation through laparoscopy and hystopathological sampling are the gold-standards (2,6). The most common complaints in endometriosis patients are dysmenorrhea (79%) and chronic pelvic pain (69%) (1). Many theories have been proposed as the basis for medical treatment (7-10). Conventional medical treatments include progesterone, danazole, combined oral contraceptive (COC), gonadotrophine-releasing hormone (GnRH) agonist, and non-steroid anti-inflammatory drugs (NSAIDs). The aim of these conventional therapies are suppression of inflammatory reaction, reduction of serum estrogen level, or increasing serum progesterone level (1,9,10). The efficacies of conventional therapies are good, but when given for a longer period, some aspects should be considered: 1) significant potential side-effects, especially for reproductive-aged women as the result of hipoestrogenic environment; 2) high relapse rate despite optimal medical therapy, and 3) costly treatments (9,10). Along with the massive development in the etiopathogenesis theories, many treatment modalities emerge, aiming at specific molecular mechanism and to avoid

Address for Correspondence: *Tjokorda Gede Astawa Pemayun*
e.mail: tjokgedeap@gmail.com ORCID ID: orcid.org/0000-0002-9936-9128

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previous generations of drugs'side-effects (1,11). In this paper, we present novel therapies for endometriosis and their specific mechanisms of action.

Overview of Endometriosis Pathogenesis

Among existing theories on endometriosis pathogenesis, Sampson's retrograde menstruation theory is the most popular, because it is scientifically proven, easy to understand and widely acceptable. The theory is supported by laparoscopic findings from women on perimenstrual period, of which menstrual blood components were found in peritoneal cavity on 90% of patients (12-15). In 1960s, Ferguson proposed that mesothelial cells from peritoneal and ovarian surfaces may undergo metaplasia and transform into endometrial tissue (12,15-17). Consistently, mullerian remnant theory also describes that primordial cells spread accross posterior pelvic wall may transform into endometrial tissue when exposed to high-level estrogenic stimulus (12,16). Stem cell potential to differentiate into endometrial tissue under hyperesterogenic influence has also been studied (15,18).

In endometriosis, various biomolecular changes are involved in the development of lesions, including: impaired immune system response, increased cytokines and pro-inflammatory mediators, increased angiogenic activity, excessive estrogen production, and progesterone resistance. Ectopic tissues may avoid normal apoptotic and phagocytosis mechanisms, presumably due to decreased expression of metalloproteinases, CD36 and increased production of dissolved intercellular adhesion molecule-1 (19).

Increased inflammatory activity is also present in endometriosis, through the overproduction of Interleukin (IL)-1, IL-6, IL-8, monocyte chemo-attractant protein-1, RANTES, tumor necrosis factor (TNF)-α and TNF-β. These mediators will further stimulate the prostaglandins production and triggers the release of vascular endothelial growth factor that serves as pro-angiogenic agent (19).

The most important factor in the pathophysiology of endometriosis is the estrogen hormonal dysregulation and progesterone resistance. Hypomethylation of the CpG cluster changes the balance of estrogen receptors, from alpha subtypes (ERα) dominance into beta subtypes (ERβ) dominance. In endometrial tissue, ERβ binds to the promoter of ERα, suppressing the production of ERα, thereby reducing the formation of progesterone (PR) receptor, resulting in resistance to progesterone. ERβ regulates cell cycle progression, and contributes to the proliferation of endometriotic cells (20,21). Prostaglandins are also known to increase the activity of steroidogenic proteins especially aromatase (p450arom) and the production of tissue estrogens, thereby aggravating the condition (22,23). We can see the summary of biomolecular process of endometriosis in Figure 1.

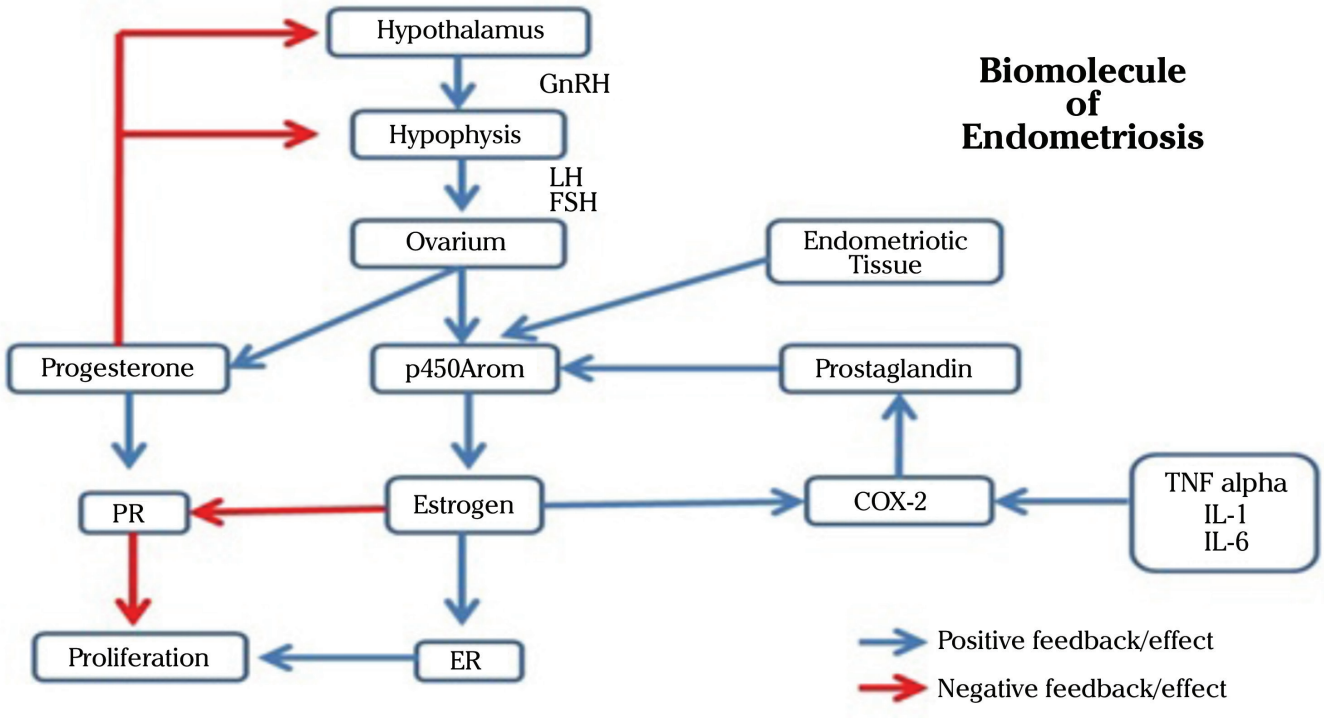

Figure 1. Biomolecular processes in endometriosis

PR: Progesterone receptor; ER: Estrogen receptors; IL: Interleukin; COX: Cyclooxygenase; LH: Luteinizing hormone; FSH: Follicle-stimulating hormone, GnRH: Gonadotrophine-releasing hormone; TNF: Tumor necrosing factor

An understanding of the biomolecular processes in endometriosis has now brought about the possibility of potential new therapies. These new therapies aim specific pathophysiologic mechanisms that have not been targeted by conventional methods. Although promising, some has not been fully tested in humans, and some are still in the early phase of clinical trials (24,25).

Novel Medical Therapies

Dienogest

Dienogest (DNG) is an oral progestin that has been recognized as single-drug therapy for endometriosis in Europe, Japan, Australia and Singapore (26,27). DNG is a 19-nortestosterone derivative with the advantage of short plasma half-life, strong progestin effect on endometrium, high bioavailability, anti-androgenic activity, and moderate gonadotropin secretion inhibition, with no interference with p450 cytochrome in the liver (28,29). Inhibition of gonadotropin secretion is not as high as GnRH agonist, with mean estrogen level maintained at 30-60 pg/mL (28).

DNG 2 mg/day has been shown to significantly inhibit the expression of genes and proteins associated with aromatase and cyclooxygenase (COX)-2, as well as prostaglandin E2 (PGE2) production (30,31). DNG administration also increases the PR-β/PRα ratio, as well as decreases the ERβ/ERα ratio; thus, minimizing progesterone resistance in endometriosis patients (32). Provision of long-term DNG has been proven to be effective, safe, tolerable, as well as low incidence of adverse events and drop-out rates (26,33). DNG administration, when compared to GnRH agonists, provides a similar improvement in the intensity of complaints, but lower decrease in estrogen level or negative impact on bone mass (26). DNG can be tolerated in long-term administration due to negligible antiestrogenic, glucocorticoid, and mineralocorticoids effects (26,29). The most frequent side effects are breast pain (4.2%), nausea (3.0%), and irritability (2,4%) (27,34).

Aromatase inhibitor

The administration of aromatase inhibitors (AI) in endometriosis patients may directly decrease aromatase activity in endometriotic tissue and estrogen level, thereby suppressing COX-2 activity, decreasing PGE2 level, and breaking the positive feedback loop (35-38). When given to premenopausal women, AI suppresses estrogen production and increases the follicle stimulating hormone (FSH) production by the pituitary gland; dosage of 0.5 mg decreases estrogen up to 97-99% (35). The third-generation AIs are selective, reversible, and potent triazole derivatives, making it suitable for use in clinical practice (35). The recommended daily dose is 1 mg for anastrozole, 2.5 mg for letrozole and 25 mg for exemestane, with the lowest decrease in E2 levels caused by exemestane (52-72%) (39).

AIs when combined with progestogen, COC, or GnRH agonist significantly decrease endometriotic pain intensity, thereby improving patient's quality of life. AI is superior in preventing postoperative recurrence when compared to GnRH or Danazol, within 6 months period (40,41). AI is equivalent to clomiphene citrate in increasing pregnancy rates (42). In post-menopausal patients, AI shows exellent performance (43). Side effects are mostly mild (ie mild headache, joint pain or stiffness, nausea, diarrhea, hot flashes, mild bone density decrease) (40,41).

GnRH antagonist

GnRH antagonists act by competitively block GnRH receptor. When compared to GnRH agonist, this class of drugs shows no-flare period, faster therapeutic onset, and unchanged pituitary sensitivity to GnRH after discontinuation of therapy (44-48). Single dose elagolix of 25-400 mg will decrease luteinizing hormone up to 22-35%, FSH 62-71%, and estradiol 42-65% (46). Administration of Elagolix 150 mg per day (75 mg twice daily) improves pelvic pain as measured with Biberoglu and Behrman pain scale, comparable to DMPA injection (47). The highest improvement on patient's quality of life as measured by Endometriosis Health Profile-5 attained at dosage 150 mg per day (49,50).

The most common side effects are hot flush, nausea and headache. With long-term use up to 6 months, these side effects are increased by 10%. Approximately 25% of patients become amenorrhea after 8 weeks of therapy with a dose of 150 mg per day, but this number decreases to 7.6% after 24 weeks (44). Elagolix causes a mild decrease in axial bone density (44,47). The rate of pregnancy increases by 5% at a dose of 150 mg per day (47). No teratogenic effect was found from elagolix treatment (44).

Anti-TNF-α

As noted earlier, TNF-α has a major role in the pathogenesis and survival of endometriosis lesions. Thus, targeting this molecule is a rational approach to treat endometriosis. Drugs classified as anti-TNF-α are either monoclonal antibodies (infliximab) or soluble TNF-α receptors (etanercept, TNF recombinant human protein bindings) (51-53). In baboons, anti-TNF-α inhibits the development of lesions significantly, but fails to increase pregnancy rates, fecundity levels per cycle, time to pregnancy, and cumulative pregnancy rates (54,55). *In vitro* studies have shown that regression of lesion

size, as well as decreased expression of inflammatory cytokines after anti-TNF-α administration (56-61). Mild side-effects may include headache and allergic reactions during intravenous administration, whereas long-term administration is associated with serious infections and tuberculosis reactivation (51,62).

Selective Estrogen Receptor Modulator

The selective estrogen receptor modulator (SERMs) are agents that have the effect of estrogen antagonists on the target organ, and the agonistic effects on bones and blood vessels (63,64). There are three types of SERM: triphenylethylene (tamoxifen), benzothiophene (raloxifen), and steroid (63). In animal models, raloxifene showed comparable benfits with anastrozole (AI) in reducing the size of lesion (65). In humans, the results are still unsatisfactory (64,66). Newer generation SERM, bazedoxifen (BZA), is being extensively studied for endometriosis therapy (47,64). The decrease in the size of lesions & reduced expression of various genes involved in tissue proliferation are significantly found after the administration of BZA 3 mg/kg/day (64,67). BZA administration alone (3 mg/kg/day) or BZA-conjugated-estrogen combination led to lesion size reduction and decreased ER expression (68).

Selective Progesterone Receptor Modulator

Selective progesterone receptor modulator (SPRMs) are PR ligands with specific clinical effects: agonists, antagonist, or agonist-antagonist combination on progesterone target tissues *in vivo* (69). The ideal SPRM for therapy is capable of triggering antiproliferative effects on the endometrium and breast, but retains the protective effects of estrogen on bone and cardiovascular systems (69-71). Histologic observation shows that SPRM administration results in reduced endometrial thickness, loss of mitotic activity, and increased stromal density (71,72). In animals, SPRM does not produce ovarian estrogen production suppression. It seems like the suppressive effects are stronger on endometrial tissue compared to hypothalamus-pituitary-gonad axis (71).

Experimental study on primates by giving asoprisnil and asoprisnil ecamate, resulted in amenorrhoea, endometrial proliferative suppression, and endometrial atrophy (69). In phase II studies, asoprisnil of 5, 10 and 25 mg doses significantly improved the non-menstrual pelvic pain scores (69,73). In a study on rats, ulipristal administration reduced endometriotic focci by at least 50% and is associated with a decrease in the number of cells exhibiting proliferative activity (70,74,75). In humans, administration of ulipristal acetate (doses 10, 50 or 100 mg) in the mid-luteal phase inhibits endometrial maturation, decreases endometrial thickness, and induces endometrial atrophy. Also, endometrial glands shows mixed secretory and proliferative characteristics (76,77).

Non-Invasive Therapy

High-Intensity Focused Ultrasound

High-intensity focused ultrasound (HIFU) is a new technique that utilizes local heating phenomenon. This technique was first introduced by Zhang and Wang (78) in 1940 (79). Currently, HIFU can be performed with the guidance of ultrasound (USgHIFU) or magnetic resonance imaging (78). The physical basis of HIFU technique is by focusing the ultrasonic wave so that high intensity acoustic energy will be absorbed and then converted into heat at a designed focal point, resulting in thermal coagulation. Other mechanisms that may be involved are acoustic cavitation (interaction of sound waves with microscopic gas formation) and radiation forces (microflow of liquid around the bubbles) (80,81).

Abnormal tissue ablation with USgHIFU in the case of adenomyosis provides good safety and effectiveness as well as significant improvement of clinical symptoms (82). HIFU has also been proven effective for ablation of endometriotic lesions. In one study, cyclic pain disappeared in all patients after 3-31 months (mean 18.7 months) (83). Some of the HIFU weaknesses are as follow: 1) ultrasonic waves can not penetrate hollow viscera, 2) time-consuming in certain cases, 3) movement during procedure is not allowed, thus, it needs additional regional anesthesia, which is the policy in many centers (79). Severe complications ever reported are post-procedure vaginal bleeding, and unexplained tumor enlargement that causes discomfort (84).

Endometriosis is a gynecologic disorder highly associated with chronic pelvic pain and infertility. Dienogest, AI, and GnRH antagonists have been proven effective as endometriosis therapy in many clnical studies, with good tolerance and safety. Studies on SERM and SPRM are mostly still in phase I and II clinical trials, that show inconsistent results. Anti-TNF-α is still studied in the animal model. HIFU is a potential futuristic treatment. However, it is still a long way until this technology is truly applicable.

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What is your diagnosis?

A 25-year-old gravida 4, parity 1, abortion 2 patient was referred to our clinic during the 24th gestational week due to abdominal echogenicity and intestinal cyst. An ultrasound examination revealed a cystic structure with minimal intestinal dilatation at the umbilical cord entry level of the fetal abdomen (Figure 1). Fetal growth was compatible with the gestational week, and amniotic fluid index and placental constitution were normal. Additional anomalies or fetal ascites were not detected on the detailed ultrasonography of the fetal anatomy. Antenatal chromosomal screening tests were normal. TORCH and parvovirus studies were negative. Cytogenetic analysis was suggested, but the patient did not accept the amniocentesis. Magnetic resonance imaging (MRI) T2-weighted images at 24 weeks of gestation showed a 30×29×22-mm cystic mass with internal septations and calcifications at the umbilical cord entry level of the lower fetal abdomen, which was evaluated as a meconium pseudocycst (Figure 2). The remaining abdominal organs and urinary system were normal. At the 28th gestational week, we observed dilated bowel loops with the widest diameter of 20 mm, containing intraabdominal calcified areas on ultrasonographic examination (Figure 3). Meconium pseudocycst with meconium peritonitis secondary to jejunoileal atresia was considered. Pregnancy follow-ups were continued with weekly fetal well-being tests. Preoperative ultrasonographic examination showed a 370-mm fetal abdominal circumference and an enlarged intestinal ring of 30 mm in diameter with intraabdominal calcifications (Figure 4). Pregnancy was terminated by cesarean section at 38 gestational weeks after consulting with the pediatric surgery and neonatology departments. The newborn was delivered with meconium-stained amniotic fluid and the abdomen was distended. A few meconium passage was observed in the rectal examination. On the first day of labor, laparotomy was performed by pediatric surgery due to intestinal atresia. Intraoperative diffuse intestinal adhesions were detected. Jejunoileal atresia at 70 cm distal to the ligament of Trietz was accompanied with meconium peritonitis and bowel reanastomosis was performed (Figure 5). The neonate tolerated feeding very well and defecated. Current follow-ups continued successfully in the neonatal intensive care unit and the baby was discharged after one week. When the newborn was at two months of age, genetic analysis for cystic fibrosis (CF) was performed, and the result was negative.

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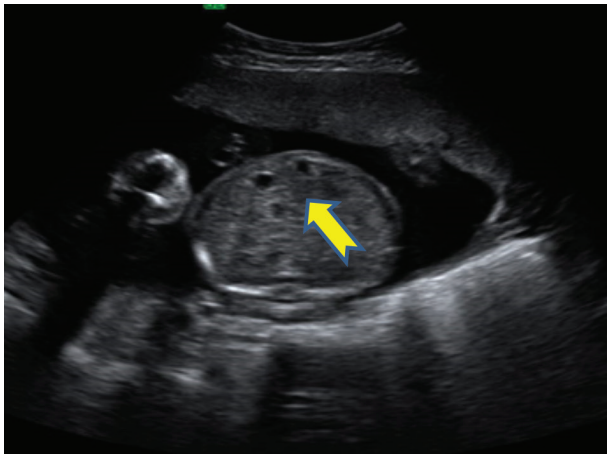

Figure 1. Ultrasound examination revealed a cystic structure with minimal intestinal dilatation at the umbilical cord entry level of the fetal abdomen

Address for Correspondence: *Seyit Ahmet Erol*
e.mail: gyn.aerol@gmail.com ORCID ID: orcid.org/0000-0002-2494-4896

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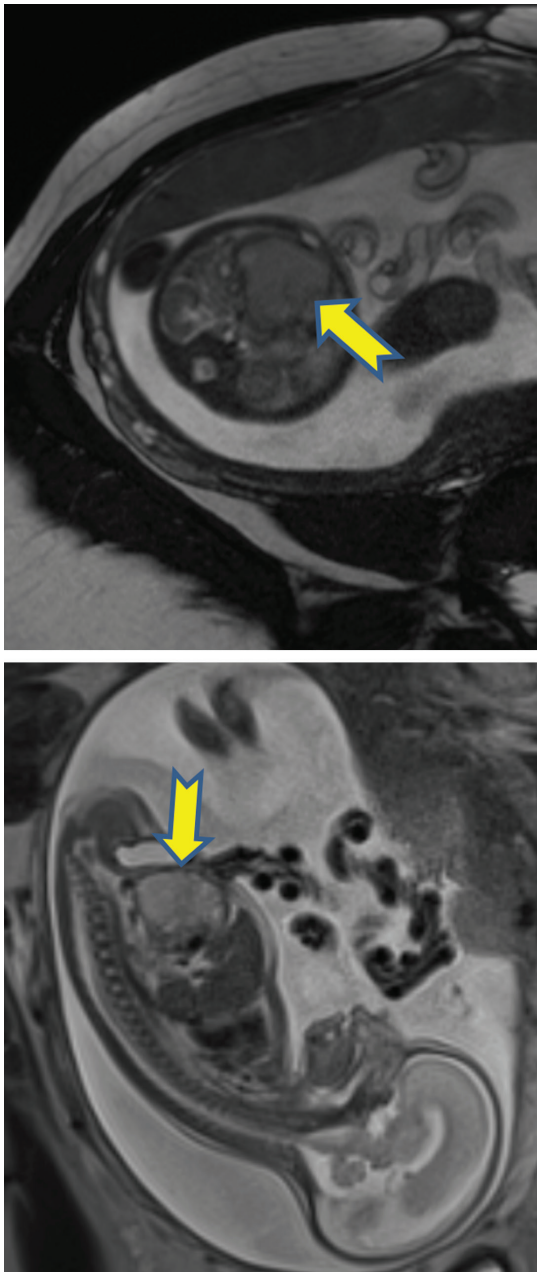

Figure 2. Magnetic resonance imaging T2-weighted images at 24 weeks of gestation showed a 30×29×22 mm cystic mass with internal septations and calcifications at umbilical cord entry level of fetal lower abdomen which was evaluated as meconium pseudocycst

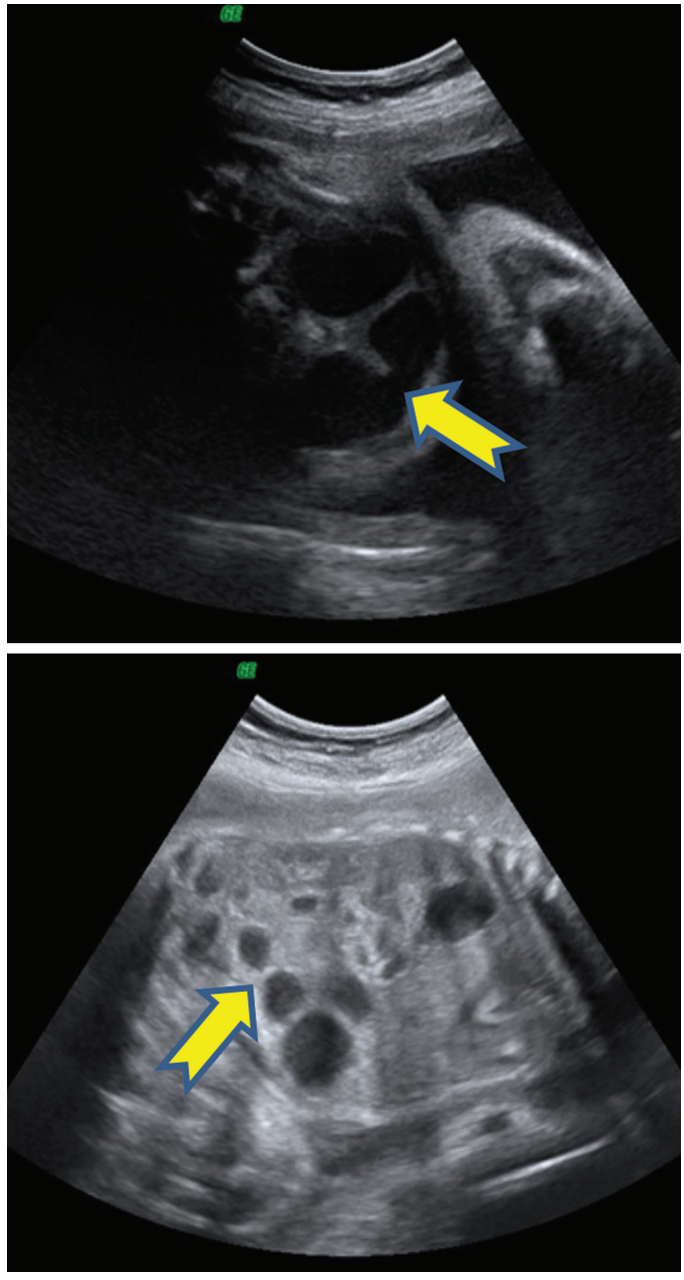

Figure 3. At the time of the 28th gestational weeks, we observed dilated bowel loops with the widest diameter of 20 mm, containing intraabdominal calcified areas on ultrasonographic examination

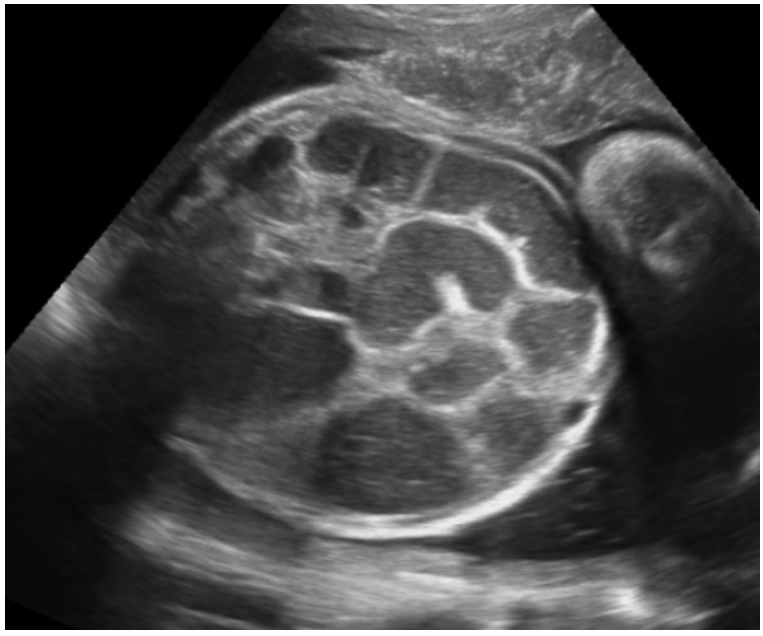

Figure 4. Preoperative ultrasonographic examination showed a 370 mm fetal abdominal circumference and an enlarged intestinal ring of 30 mm in diameter with intraabdominal calcifications at 38th gestational weeks

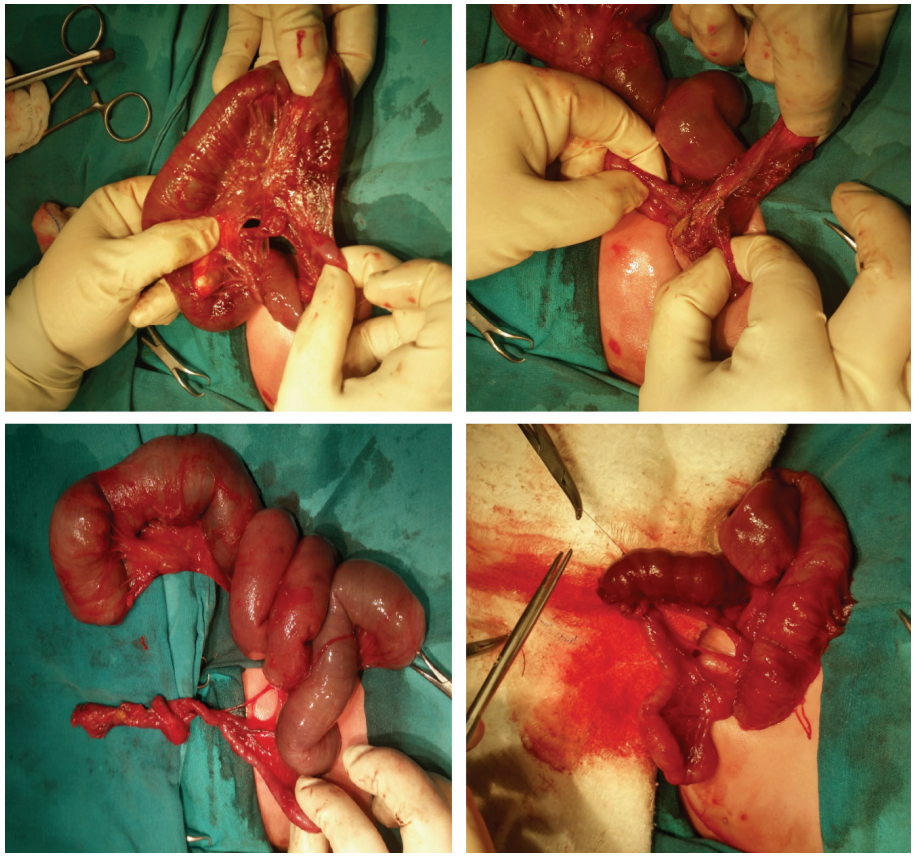

Figure 5. Jejunoileal atresia at 70 cm distal to the ligament of Trietz was located with meconium peritonitis and bowel reanastomosis was performed

Answer

Other than meconium pseudocyst, possible diagnosis of abdominal cysts contains a wide range of diseases such as omental and mesenteric cysts, intestinal duplication cysts, obstructive uropathy, choledochal, pancreatic, urachal, renal and ovarian cysts, hydrometrocolpos, imperforate anus, Meckel diverticulum, ureterocele and sacrococygeal teratomas (1). Meconium ileus, volvulus, intestinal stenosis, atresia, intussusception and mesenteric vascular insufficiency could be a reason for intestinal perforation (2). Meconium pseudocyst occurs as a consequence of meconium extravasation secondary to intestinal perforation during the antenatal period, and it is observed as a hypoechoic mass attached to the extraluminal meconium (3,4). Meconium pseudocyst can rupture during pregnancy, albeit rarely (5). Meconium peritonitis is a chemical, sterile peritonitis induced by meconium spilling in the peritoneal cavity secondary to intrauterine intestinal perforation. Its prevalence is about 1 per 35,000 live births. Meconium peritonitis presents with common ultrasonographic signs as ascites, calcifications, polyhydramnios, meconium pseuodocysts, and bowel dilatation clinically (6). Meconium ileus occurs in about 10% to 15% of newborn with CF. Genetic analysis of CF is important and recommended (7). Magnetic resonance imaging (MRI) findings of meconium pseudocyst have been presented infrequently but it could be useful and valuable in the differentiation from other abdominal cystic masses (8-10). In the present case, both ultrasonographic and MRI scans revealed a hypoechoic mass with calcified echogenic organization in lower fetal abdomen. Progression of ileal atresia may occur with the rupture of meconium pseudocyst during pregnancy (5). In conclusion, meconium pseudocyst should be considered in the differential diagnosis when abdominal cystic mass is accompanied by intraabdominal calcifications. Therefore, prenatal diagnosis and follow-ups are important to diagnose likely intestinal atresia accompanied with meconium pseudocyst.

Seyit Ahmet Erol[1], Cem Yaşar Sanhal[1], Yavuz Yılmaz[2], Dilek Şahin[1]

[1]Clinic of Perinatology, University of Health Sciences, Zekai Tahir Burak Women's Health Practice and Research Center, Ankara, Turkey

[2]Clinic of Pediatric Surgery, University of Health Sciences, Zekai Tahir Burak Women's Health Practice and Research Center, Ankara, Turkey

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The opinions and thoughts of women who underwent hysterosalpingography for the first time: Letter to the editor

To the Editor;

We read the article "The effect of a preprocedural informative video on anxiety levels in patients undergoing hysterosalpingography: A prospective case-control study" by Erkılınç et al. (1) with great interest, which mentioned the effect of a preprocedural informative video on anxiety levels in patients undergoing hysterosalpingography (HSG). They found the Beck Anxiety scores to be significantly lower in the study group compared with the control group. In the literature, there are many intervention studies for pain and anxiety during HSG procedures (2). However, in order to determine the effectiveness of interventions, we believe that the determination of the experiences, opinions, and thoughts of women and information on the procedure before HSG is important (3).

As for our experience, we designed a qualitative study to determine the thoughts and experiences of women towards HSG. This was conducted on 20 women who presented for the first time to have an HSG procedure in Gülhane Training and Research Hospital. Individual interviews were conducted before and after the procedure for each participant.

We used a questionnaire of 14 questions including the sociodemographic and obstetric data of the women. Also, “before and after the procedure” questions were asked to determine the thoughts of the women towards HSG and their answers were recorded using a voice recorder. Before the operation, their sources of information and current feelings were questioned through face-to-face interviews. After the HSG, the interview was recorded again, asking how the overall experience was, and how they would share their experiences with other women, as well as their recommendations to them. The main answers and concerns of women were concentrated around why HSG was done, the pain associated with the procedure, and anxiety caused by the unknown procedure.

After the interviews, we concluded that the knowledge of women was not sufficient on HSG and that they needed to be informed. Women reported that they had gained information about HSG mostly from the internet and from women who had undergone the procedure previously. We determined that the information acquired by women with their own efforts increased their anxiety toward the process. Therefore, it is important to ensure accurate and reliable information provided by health professionals to women who are going to undergo HSG. By doing so, it would be possible to prevent the prejudices, anxiety, and false perceptions/information of women regarding HSG. Therefore, we appreciate the work of Erkılınç et al. (1) because it will have a real positive effect on patients.

Mehmet Ferdi Kıncı[1], İlknur Yeşilçınar[2], Gamze Acavut[1], Kazım Emre Karaşahin[1]

[1]Clinic of Obstetrics and Gynecology, University of Health Sciences, Gülhane Training and Research Hospital, Ankara, Turkey

[2]Batman University, Health Sciences, Batman, Turkey

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Address for Correspondence: *Mehmet Ferdi Kıncı*
e.mail: drferdikinci@gmail.com ORCID ID: orcid.org/0000-0003-0487-1201

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Author's Response

Dear Editor,

We thank the authors for their valuable comments on our manuscript that "The effect of preprocedure informative video on anxiety levels in patients undergoing hysterosalpingography: A prospective case-control study". Hysterosalpingography causes anxiety in patients with infertility and several methods are presented in the literature. Our study showed the benefit of a preprocedural informative video that a simple implementation in clinical practice on reducing anxiety. The authors finding that the main concern of the hysterosalpingography was anxiety caused by the unknown procedure confirmed importance of the management of anxiety during procedure (1). In addition to our study evaluating the patients in a before and after fashion may provide quantity of the change in anxiety levels. So, future studies may be designed in the way that the authors described. The finding of their study that information on procedure mostly obtained from other than health professionals (internet, friends) is interesting. Furthermore, it may cause increase in levels of anxiety. Although a preprocedural informed consent is a standard of care the study concluded that knowledge of patients was insufficient. So, this critic added a perspective to us that a preprocedural informative video may reduce anxiety levels and the main cause of the anxiety was insufficient knowledge of the patients.

Selçuk Erkılınç[1], Nazlı Aksoy Kala[2], Ali İrfan Güzel[3], Mehmet Çınar[3], Nafiye Yılmaz[3]

[1]Clinic of Gynecologic Oncology, University of Health Sciences, Tepecik Training and Research Hospital, İzmir, Turkey

[2]Clinic of Obstetrics and Gynecology, University of Health Sciences, Ankara Numune Tarining and Research Hospital, Ankara, Turkey

[3]Clinic of Obstetrics and Gynecology, University of Health Sciences, Zekai Tahir Burak Women's Health Tarining and Research Hospital, Ankara Turkey

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Is corona mortis a historical myth? A perspective from a gynecologic oncologist

To the Editor;

Corona mortis is the vascular anastomosis between the obturator and external iliac or inferior epigastric vessels. It is also known as the 'crown or circle of death' because massive bleeding may occur due to an injury.

The obturator artery arises from the internal iliac artery and lies longitudinally to the obturator foramen on the medial part of obturator internus muscle. Anatomically, the corona mortis is on the retro-pubic part of the superior pubic rami lateral to the symphysis pubis, where a pubic artery or vein in this field may arise from the inferior epigastric or external iliac vessels, lie to the obturator foramen, and be damaged during surgical procedures. The incidence of venous corona mortis is between 27% (1) and 100% (2). On the other hand, the incidence of arterial corona mortis is between 14.8% (3) and 36% (4).

The corona mortis may have several anatomic variations. The vascular supply of the pelvis has many connections and variations, as such, the clinical role of the corona mortis in surgical practice is a matter of importance to prevent significant, uncontrolled bleeding for general surgeons, gynecologists, urologists and orthopedic surgeons during femoral hernia operations, urogynecologic operations such as transvaginal tape procedures, pelvic lymphadenectomies or pelvic fracture operations (5).

During procedures with an anterior approach to the pelvis such as hernioplasty, femoral hernia repair or sometimes transvaginal tape operations, the surgeon may not recognize or see the vascular connections on the retro-pubic area, which is on the posterior parts of the surgically exposed field. However, during operations where the surgeon opens the retroperitoneal area such as in pelvic lymph node dissection, the retro-pubic vascular anastomoses are easily seen after a careful and tiny dissection over the external iliac artery below the inguinal ligament. The corona mortis will be noted over the superior pubic ramus, on the medial part of ligamentum teres uteri, where it enters the inguinal canal. The Figure 1 shows the pubic vein below the inguinal ligament on the posterior part of superior pubic rami. This large area of exposure will maintain quick maneuvers during abnormal bleeding to control the hemorrhage. Our clinical practice of 96 pelvic lymphadenectomies showed an incidence of 2.01% (2/96) arterial anastomoses and we had a total of 4 hemorrhages (4.1%) from the pubic vein (venous corona mortis), which were easily controlled. In that manner, the term *corona mortis* is questionable in gynecologic oncology practice. Nevertheless, the amount of bleeding and the ability to control hemorrhage from an arterial corona mortis could not be foreseen.

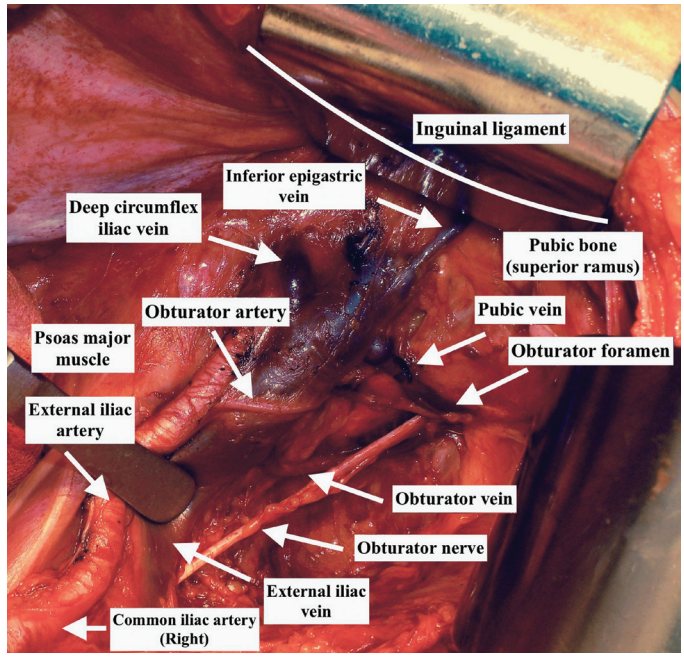

Figure 1. Pubic vein from the obturator vein to the external iliac vein arising from obturator foramen

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Address for Correspondence: *İlker Selçuk*
e.mail: ilkerselcukmd@hotmail.com ORCID ID: orcid.org/0000-0003-0499-5722

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İlker Selçuk[1], İlkan Tatar[2], Ayşegül Fırat[2], Emre Huri[3], Tayfun Güngör[1],

[1]Department of Gynecologic Oncology, University of Health Sciences, Zekai Tahir Burak Woman's Health, Health Practice and Research Center, Ankara, Turkey

[2]Department of Anatomy, Hacettepe University School of Medicine, Ankara, Turkey

[3]Department of Urology, Hacettepe University School of Medicine, Ankara, Turkey

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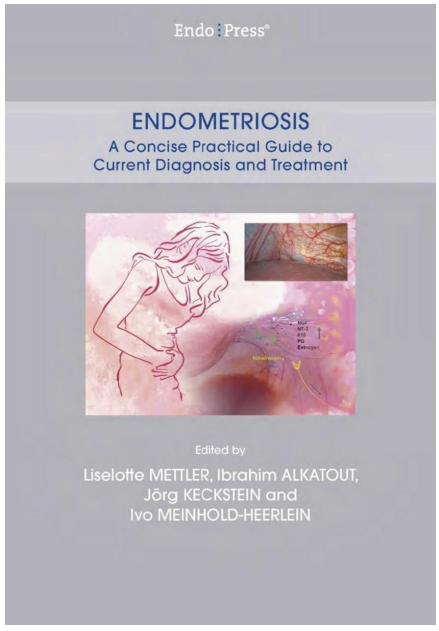
Endometriosis: A concise practical guide to current diagnosis and treatment

İbrahim Alkatout[1], Ivo Meinhold-Heerlein[2], Jörg Keckstein[3], Liselotte Mettler[1]

[1]Department of Gynecology and Obstetrics, Kiel School of Gynecological Endoscopy, University Hospitals Schleswig-Holstein, Kiel, Germany

[2]Department of Obstetrics and Gynecology, RWTH Aachen University Faculty of Medicine, Aachen, Germany

[3]Department of Obstetrics and Gynecology, Certified Clinical-Scientific Level III Center for State Hospital of Villach, Carinthia, Austria



Book Details

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Abstract

This book addresses the management of endometriosis from a holistic approach, including theoretical principles, conservative treatment of the condition, diagnostic and surgical procedures, as well as the outcome of research. Endometriosis and its treatment are complex issues. We believe that a combination of treatment modalities is needed in order to effectively address the pain, infertility, and other difficulties associated with endometriosis. In addition to theory and scientific principles, minimally invasive surgical procedures for the treatment of endometriosis are described in a stepwise manner. Separate sections of the books are devoted to specific conditions, urological procedures, and general surgical procedures because the condition is ideally treated on an interdisciplinary basis. Areas of overlap with other specialties are also addressed.

Keywords: Endometriosis, laparoscopy, robotic surgery, pain, infertility

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Address for Correspondence: *İbrahim Alkatout*
e.mail: ibrahim.alkatout@uksh.de ORCID ID: orcid.org/0000-0002-7194-6034

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Introduction

Despite a large number of reports on endometriosis, a practical guide for endoscopic surgical treatment does not exist. The integration of traditional procedures with alternative methods of treatment has also not been addressed satisfactorily. To resolve this problem, the editors of the present book requested a group of expert researchers and physicians to describe their view of the management of endometriosis (1). A team of dedicated surgeons wrote separate chapters on the existing surgical approaches for the treatment of the condition.

In view of the fact that endometriosis is a benign but chronic estrogen-dependent disease and a lifelong problem for the patient, its early identification and appropriate treatment are essential. In addition to traditional theories concerning the pathogenesis of various types of endometriosis, the recent published literature suggests that a variety of additional factors play a role in the development and spread of the disease, such as genetic predisposition, an abnormal peritoneal environment, stem cells, immune dysfunction, and inflammation (2,3). A number of therapies have been suggested and are, in part, effective. However, surgery - usually endoscopic surgery - still is the principal procedure for the diagnosis and treatment of endometriosis. Therefore, the present work focuses on the individual steps of surgical procedures.

The purpose of the book is two-fold: a) improve the patient's comprehension of the problems that may arise and are resolved during surgery; b) guide surgeons in performing the appropriate surgical procedure in an efficient manner (4,5). All forms of endometriosis must be managed by surgery in order to treat the condition effectively.

It should be noted that the majority of treatments currently used for endometriosis are based on surgery. The large majority of medical therapies rely on manipulating ovarian steroid hormones, but fail to achieve a complete response in every patient. The authors of this book hope that continued research will disclose new perspectives for the development of novel treatment strategies (2,6). The extensive support from the industry in terms of technology, instruments, optical aids, and healthcare has made endoscopic surgery safer, simpler, less invasive, and decidedly more effective.

Outline of the book

The book addresses theoretical principles, clinical experience, and scientific conclusions. A variety of surgical techniques for different manifestations of endometriosis are discussed; illustrations and tables are provided. This work serves as a reliable guide for beginners as well as experts. The above mentioned aspects - background, diagnosis, and treatment options for endometriosis - are divided as follows:

1. Theoretical Principles, Research Results and Conservative Treatment
2. Diagnostic Workup and Preparation for Surgery
3. Surgical Procedures for Various Manifestations of Endometriosis
4. Specific Situations
5. Urological Approaches
6. General Surgical Approach

Gynecologists concerned with conservative treatment and surgery will be able to widen their perspectives. This book should enhance their ability to provide state-of-the-art diagnostic investigation and treatment strategies for endometriosis.

The historical background is followed by the etiology, pathogenesis, and pathology of endometriosis. The anatomy of the region, and the reasons for radical treatment are addressed. These sections are followed by internationally accepted classification systems. One chapter addresses medical treatments and the currently undervalued measures of rehabilitation and appropriate nutrition.

The book offers a complete overview of diagnostic investigation and surgical techniques for various forms of endometriosis. The approaches include conventional laparoscopic and robot-assisted approaches, as well as urologic and general surgical procedures (7). The management of endometriosis in patients with infertility is also addressed in detail.

This work has been produced by an Austrian-German group of scholars, associates, and experts at the Kiel School of Gynecological Endoscopy. The latter is a gynecologic training center located at the department of obstetrics and gynecology at Campus Kiel, which is one of the University Hospitals of Schleswig-Holstein in Germany.

One of the foremost aims of the book was to enhance and promote effective cooperation between patients, medical experts, researchers, as well as producers and developers of medical technology (8). This was the reason for publishing the book through Endo Press GmbH, Tuttlingen, Germany, and the KARL STORZ Company. Thanks to these publishers, the book can be downloaded free of cost from the Karl Storz media library.

Highlights

This book mainly addresses the actual procedure of endoscopic surgery, based on conventional laparoscopic and robotic-assisted techniques. Procedures performed within the anatomical scope of gynecology, as well as urologic and general surgical procedures are included.

The chapter on the origin of the disease summarizes currently-known aspects of the pathogenesis of endometriosis, with specific attention given to the mechanisms underlying the

vascularization of lesions and the role of immune factors. Furthermore, the importance of hormones, immune cells, and cytokine signaling is addressed. Current pharmaceutical options for the management of pain in women with this persistent but potentially manageable disease are described. Internationally known and accepted classifications of the disease are highlighted. Fertility treatment and endometriosis are also given attention (9,10).

Evaluation of the book

This book encompasses a large number of overlapping medical specialties, as such the editors regard it as a comprehensive answer to the need for interdisciplinary treatment of endometriosis. Specialists of visceral surgery, urology, and internal medicine will be able to identify the interdisciplinary aspects of the condition and their treatment.

In view of the currently extensive communication among the various specialties of medicine, we invited a number of leading surgeons, scientists, and teachers from all over the world to contribute to this book. It presents the newest treatment strategies for endometriosis. Furthermore, the open access e-Book version meets the global demands of unlimited exchange and is freely available online to the international community. Last but not least, this textbook aims to improve the standard of healthcare for women.

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Congress report of the 23rd AGE annual meeting from 26th - 28th April 2018 in Hamburg

İbrahim Alkatout[1], Bernd Holthaus[2]

[1]Department of Obstetrics and Gynecology, University Hospitals Schleswig-Holstein, Campus Kiel, Kiel, Germany
[2]Clinic of Obstetrics and Gynecology, St. Elisabeth Hospital, Damme, Germany

Abstract

The Study Group of Gynecological Endoscopy (AGE) has a growing number of members each year. This is an acknowledgment as well as a challenge for the study group. The challenges were faced in the form of exemplary cooperative work by the core members of AGE, the Velen Study Group for Ambulant Surgery (VAAO), the Foundation of Endometriosis Research (SEF), the Study Group of Urogynecology and Plastic Pelvic Floor Reconstruction (AGUB), the Study Group for Robotic-assisted Surgery in Gynecology (ARC^{Gyn}), and the Study Group of Gynecological Oncology (AGO). More than 1500 AGE members have been able to create significant effects preemptively by designing a Congress program that was prepared interactively. The program of live surgery was designed in the course of two days on the basis of an online inquiry. The first transmission of laparoscopy on a body donor and anatomic demonstrations on formalin-fixed specimens were especially significant in this context. Sessions of general gynecology, including myoma therapy, endometriosis and infertility treatment, and gynecologic oncology and urogynecology covered the entire spectrum of minimally invasive surgical techniques. Individual topics were addressed in specific courses. The Congress was preceded by an optional certified basic course (MIC I) of the AGE. Far more than 500 congress attendees from all German-speaking countries were spirited away to a paramedical steep face, which was ascended together with a renowned German extreme climber. The keynote lecture was especially impressive and held by the pioneer and founder of the neuropelveology. The world's leading expert in this field described the responsibilities of our specialty in a visionary manner and motivated all of the listeners strongly in regard of their actions and efforts.

Keywords: Congress, report

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Program

The Study Group of Gynecological Endoscopy (AGE) registers a growing number of members each year. This is an acknowledgement as well as a challenge. It is an acknowledgement of the fact that the needs of its members have been fulfilled satisfactorily over the years. At the same time, the growing technical and formal demands of the German and international gynecologic societies in terms of clinical, scientific and training activities could also be fulfilled. However, it is also a challenge because rapid and complex developments in medicine, medical technology, and the pharmaceutical industry present major responsibilities and tasks in clinical routine. Furthermore, the increasing level of enlightenment among patients and their sense of entitlement, as well as the low level of tolerance in terms of medicolegal action, have become the focus of our actions.

The 23rd Annual Meeting of the Study Group of Gynecological Endoscopy (AGE) was held from April 26th to 28th, 2018, at the Radisson Blue Hotel in Hamburg. The Congress marked the 25th anniversary of the founding of the study group. Some aspects of the program were based on the three essential pillars of a doctor's life, analogous to the integration of conservative and innovative methods in hybrid technology (Figure 1).

After the inauguration of the Congress by Dr. Bernd Holthaus, Congress President and First Chairman of the AGE, and Prof. Diethelm Wallwiener, Past President of the AGE and the German Society of Obstetrics and Gynecology (DGGG), two people were awarded an honorary membership. The first of these was Prof. Klaus Kolmorgen who was commended for his lifework and his commitment to minimally invasive surgery (1,2). In his laudatory speech, Dr. Rüdiger Müller from Königswusterhausen

Address for Correspondence: *İbrahim Alkatout*
e.mail: kiel.school@uksh.de ORCID ID: orcid.org/0000-0002-7194-6034

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emphasized Dr. Kolmorgen's pioneering work in the era of the German Democratic Republic (Figure 2).

The second honorary membership was awarded post mortem to the Past President of the AGE, Associate Professor Thoralf Schollmeyer. In an evocative and emotional speech, Dr. Liselotte Mettler reminded us of the significance of Thoralf Schollmeyer's achievements for the AGE and the continuation of the Semm legacy at the Kiel School of Gynecological Endoscopy in Kiel (3-5).

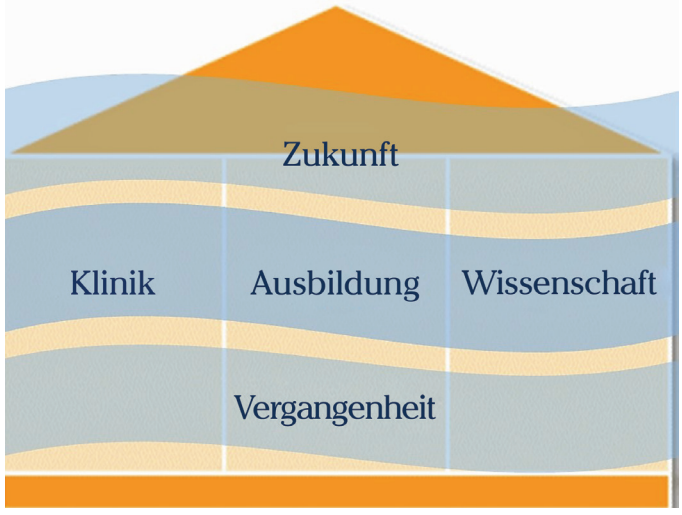

Figure 1. Concept of the three essential pillars - health services at the clinic, training, and science - which have always onstituted the foundations of our medical work and will always do so in the future. Training is one of the essential concerns of the Study Group of Gynecological Endoscopy, indivisibly linked with health care and science, anchored in the experiences of the past and the visions of the future

Figure 2. The president of the German Society for Gynecological Endoscopy (left) hands over the honorary membership to two laureates

Golden Scope Science Prizes

The Golden Scope (sponsored by Karl Storz Company) for outstanding achievements in gynecologic endoscopy was awarded to Dr. Claus Peter Möller from Hamburg. Claus Möller was Acting President of the AGE from 2012 to 2013.

The science prizes are listed in Table 1.

Key Science Aspects of the AGE Annual Meeting

1. MIC – Basic Course

At the preliminary program of the actual Annual Meeting, an MIC Basic Course certified by the AGE was held under the leadership of the AGE training centers of Damme, Hamburg and Kiel. On great demand, 30 attendees were supervised most competently by staff members of the three training centers as well as Karl Storz and Richard Wolf Company. The attendees had the opportunity to practice on the traditional pelvitrainer as well as the virtual hysteroscopy trainer. The basic course was headed by Peter Biel in a familiar atmosphere.

2. Intensive Courses

Without complication upon the schedule of the main program, 8 courses, which focused on individual topics, were held for small groups. Selected tutors made it possible for colleagues to exchange their knowledge and gain close insights into specialized fields.

- Reproduction Medicine and Surgery
- Multidisciplinary Surgery
- VAAO and Hysteroscopy
- Complication Management
- Complex Operations Explained Step by Step
- Myoma Treatment

Table 1. Science Prizes at the 25th Annual Meeting of the AGE from 26 to 28 April 2018 in Hamburg

Prize	Name	City	Subject
Hans Frangenheim Prize	Julia C. Radosa	University Clinic of Gynecology of Saarland, Homburg	Prospective randomized trial comparing the impact of two different intraoperative CO_2 pressure levels (10 und 15 mm Hg) during laparoscopic hysterectomy due to benign uterine pathologies
Kurt Semm Prize	Bashar Haj Hamoud	University Clinic of Gynecology of Saarland, Homburg	Laparoscopic cerclage

3. Scientific Sessions

In line with the trend towards highly individualized yet strictly guideline-based treatment concepts, the main program offered scientific sessions on the subjects of general gynecology, (including myoma, endometriosis and infertility treatment), gynecologic oncology, and urogynecology.

The session on General Gynecology addressed the procedure for the treatment of complex myomas, a niche after caesarean sections and hysteroscopy techniques, and the session on Urogynecology was focused on current problems in descensus and incontinence. The session was held jointly by the AGE and the Study Group of Urogynecology and Plastic Pelvic Floor Reconstruction (AGUB). Core aspects included the differentiation between vaginal and laparoscopic access, the treatment of recurrent disease after mesh placement, and the avoidance of complications following extensive ultrasound diagnostic investigation. The session on endometriosis, held jointly with the Foundation of Endometriosis Research, presented current efforts to impose meaningful limitations on extensive surgery (6).

The session on Laparoscopy in Oncology was held together with the Study Group of Gynecological Oncology (AGO). Here the role of laparoscopy in oncology was addressed in detail, along with the current body of data on the subject. Options for the use of laparoscopy in ovarian cancer, its role in endometrial cancer, the role of the robot, and the technique of compartment-based surgery founded by Höckel (7,8) were discussed. It became evident that endoscopy plays a role in all relevant malignant diseases. It is the gold standard for endometrial cancer, and its role in cervical cancer is being discussed anew because of recent data concerning the prognosis of the disease in patients who undergo endoscopic versus open surgery. In ovarian cancer, endoscopic surgery is regarded internationally as an option for staging, along with the use of preoperative reaction scores (9).

The session on hysterectomy (10) was focused on the extent of resection, access in borderline situations, and the question of in-bag morcellation systems (11,12). The session 'My Special Case' was very well accepted despite the advanced time of the day. The purpose of the session was to conduct an open discussion of complications and their management, as well as exceptional cases and their specific challenges.

The scientific sessions were complemented by industrial symposia on the subjects of fluorescence-based diagnostic imaging (indocyanine green) by Olympus Company, myoma therapy (Gedeon Richter), and hysteroscopy (Karl Storz).

4. Scientific highlights of the last day of the Congress

The last day of the Congress was focused on training but was as well attended as the preceding days, thus reflecting the attendees' sense of responsibility towards future generations. Videos of operations were presented at this session. Entire operation sequences were re-edited and accompanied by live commentaries. The didactic framework offered adequate opportunity for the exchange of knowledge. The session included a panel discussion on training, which was marked by a lively discussion on the concerns of advanced training assistants.

5. Live surgery on two days at two locations

Live transmissions are the soul of the annual meeting of a society focused on surgery. Therefore, the time for live transmissions was extended to two days by the Congress Committee, but there were fewer operations than in the past. For the first time, all AGE members participated actively in planning live operations. Prior to the Congress, all AGE members were sent an online questionnaire and requested to join in the selection of the operations. More than 30% responded. Thus the attendees could indirectly influence the surgery program. The result was a surgery program consisting of urogynecologic, oncologic, and laparoscopic operations for myoma and endometriosis as well as hysteroscopic operations. On April 26th and 27th, robotic-assisted operations were transmitted for the first time at an annual meeting of the AGE, in addition to laparoscopic surgery (Figure 3) (13).

At the live transmissions, experienced surgeons demonstrated the innovative management of various diseases, taking the most recent developments in medical technology into account. This included, in an educational atmosphere, an exchange of information with the attendees in the auditorium. Based on the medical-ethical principles of autonomy, beneficence, non-maleficence, and justice (righteousness, fairness, justness), this approach was reviewed critically and repeatedly; possible equivalent alternatives to this approach were discussed (Figure 4) (14).

All the same it should be noted that the benefits of training and teaching under safe medical and ethical conditions have been

Figure 3. Impressions during the live transmission

comprehensively established in clinical and anatomic curricula (15-18).

For the first time at a live surgery demonstration in Germany, a body donor was investigated by laparoscopy. For the purpose of teaching, this anatomic presentation was complemented by a video demonstration of selective formalin-fixed specimens (Figure 5, 6).

The implementation and transmission of the operations were rendered possible by the assistance of Karl Storz SE & Co. KG Company, Olympus Deutschland Private Limited Company, Richard Wolf, and Intuitive Surgery, and were executed technically by TV-Studios Leonberg Company.

Major non-scientific aspects of the AGE Annual Meeting

1. Keynote Lecture Alexander Huber

Analogy of mountaineering and work. The professional mountaineer and extreme climber Alexander Huber (www.huberbuam.de) addressed subjects like motivation, courage, creativity, planning, risk and risk management in a uniquely comprehensible manner with the aid of impressive pictures, videos and personal experiences (Figure 7).

These subjects constitute everyday challenges or play a key role in the medical profession as well, but medical professionals are rarely prepared for these challenges in an adequate manner.

2. Keynote lecture of Mark Possover

A very special highlight was Mark Possover's keynote lecture, which provided an overview, a retrospective view, and a future view of the options of neuropelveology. His creative work is rooted in the AGE and in gynecological endoscopy. Through his extraordinary vision, pioneering spirit and courage, Professor Mark Possover was able to expand his therapies to include the treatment of the loss of spinal cord functions. As a visionary, he eventually led the entire auditorium into spheres that were known so far only in the field of aerospace technology (Figure 8) (19,20).

The next Congress will be held in 2020 in Berlin under the leadership of the designated President Prof. Dr. Uwe A. Ulrich.

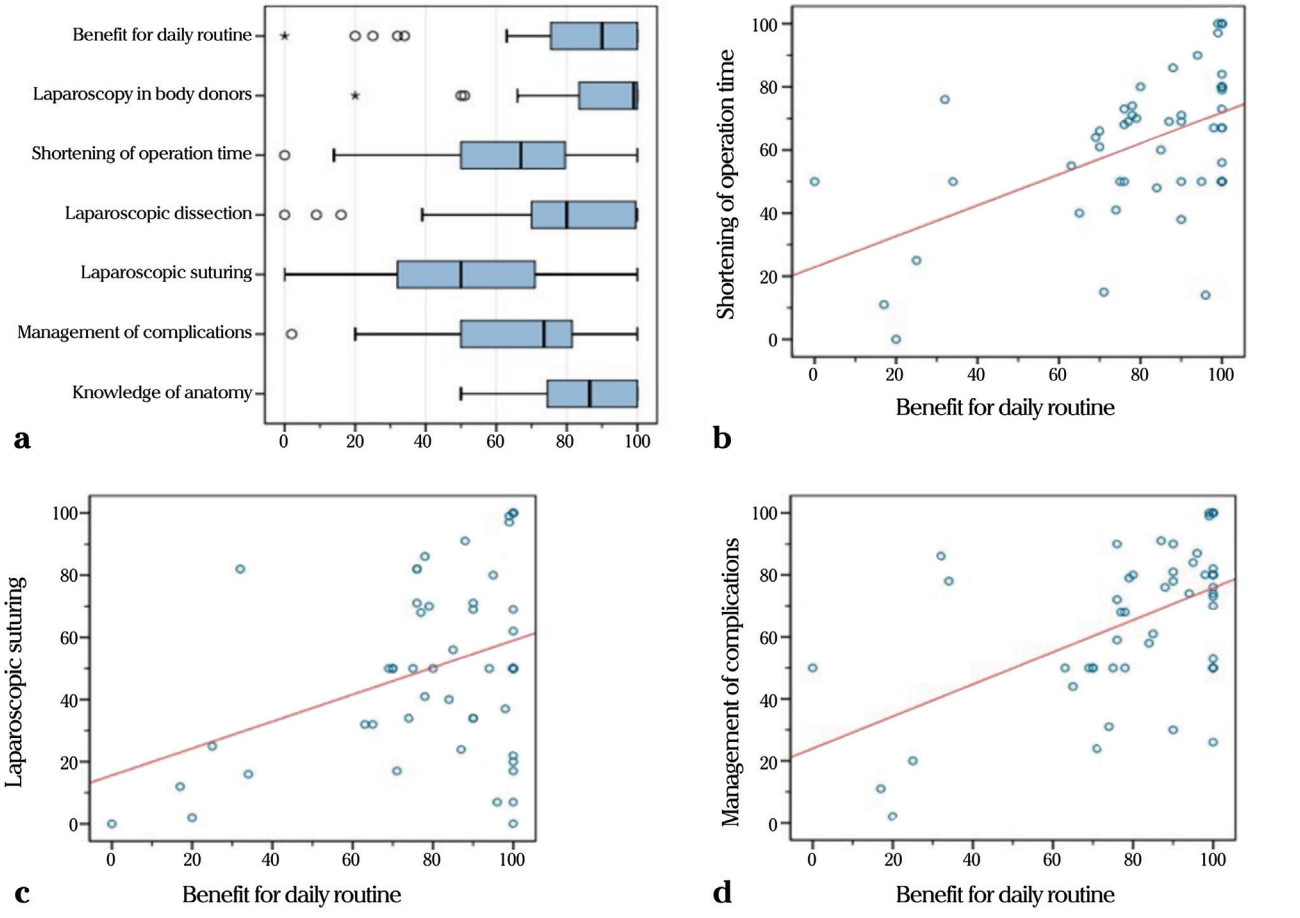

Figure 4. Results of a face validation survey among members of the training course on Laparoscopy. The results (a-d) confirm that a laparoscopic training course helps the attendees in all essential aspects of their daily work (such as operating time, suture techniques, and complication management)

Figure 5. Live demonstration of formalin-fixed body donors into the auditorium of the AGE Annual Meeting in Hamburg. This figure shows the topographical anatomy in the lesser pelvis
AGE: Gynecological Endoscopy

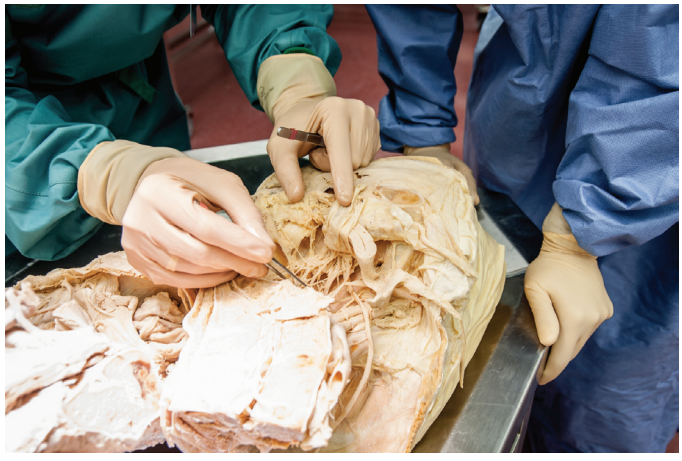

Figure 6. Live demonstration of formalin-fixed body donors into the auditorium of the AGE Annual Meeting in Hamburg. This figure shows the course of vessels in the lesser pelvis
AGE: Gynecological Endoscopy

Figure 7. The German extreme climber in his element - the unification of man and mountain

Figure 8. The pioneer and founder of the neuropelveology appeals to the attendees' individual sense of responsibility and the practical application of the Hippocratic Oath in our times; he raises both hands upward while doing so

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CONGRESS CALENDER

INTERNATIONAL MEETINGS

(for detailed International Meeting please go website:
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September 5-8, 2018	**26th European Congress of Perinatal Medicine 2018, Saint Petersburg, Russia**
September 7-9, 2018	**International Society for the Study of Vulvovagınal Disease 24th Congress 2018, Chicago, United States**
September 20-22, 2018	**32nd Annual Fall Conference on High Risk Obstetrics 2018, San Francisco, United States**
September 27-29, 2018	**Society of European Robotic Gynecological Surgery 10th Annual Meeting 10 Years of Robotic Surgery 2018, Milano, Italy**
October 3-6, 2018	**North American Menopause Society 29th Annual Meeting 2018, San Diego, United States**
October 6-10, 2018	**American Society for Reproductive Medicine Annual Meeting 2018, Denver, United States**
October 7-10, 2018	**European Society for Gynecological Endoscopy 27th Annual Congress 2018, Vienna, Austria**
October 9-13, 2018	**American Urogynecologic Society Pelvic Floor Disorders Week 2018, Chicago, United States**
October 14-19, 2018	**22nd FIGO World Congress of Gynecology and Obstetrics 2018, Rio De Janeiro, Brazil**
October 18-21, 2018	**International Pelvic Pain Society Annual Meeting 2018, Chicago, United States**
October 20-24, 2018	**28th World Congress on Ultrasound in Obstetrics and Gynecology 2018, Singapore**
October 25-27, 2018	**11th Annual Congress of the European Urogynecological Association | Leading Lights in Urogynecology 2018, Milano, Italy**
October 26-27, 2018	**Comprehensive Laparoscopic Gynecology Course 2018, Hamilton, Ontario, Canada**
November 11-15, 2018	**47th AAGL Global Congress on Minimally Invasive Gynecology 2018, Las Vegas, United States**

CONGRESS CALENDER

NATIONAL MEETINGS

(for detailed International Meeting please go website:
http://www.kongre2017.com)

September 6-9, 2018	**6. Uluslararası Ürojinekoloji Kongresi, İstanbul, Turkey**
September 20-21, 2018	**36. Zeynep Kamil Jineko-Patoloji Kongresi, İstanbul, Turkey**
September 27-30, 2018	**10. Ulusal Obstetrik ve Jinekolojik Ultrasonografi Kongresi, Muğla, Turkey**
September 27-30, 2018	**1. Uluslararası Rekonstruktif - Estetik Genital Cerrahi & Seksoloji Kongresi, İstanbul, Turkey**
October 3-5, 2018	**Anne Sütü ve Emzirme Kongresi, İzmir, Turkey**
October 4-7, 2018	**Ovülasyon İndüksiyonu ve İnfertilitede Güncel Yaklaşımlar, Muğla, Turkey**
October 5-7, 2018	**2. Uluslararası Katılımlı Health 4.0 Sağlıkta Yenilikler Kongresi, İstanbul, Turkey**
October 25-28, 2018	**Kozmetoloji ve Kozmetik Jinekoloji Kongresi, İstanbul, Turkey**
November 8-11, 2018	**TSRM Kongresi, Antalya, Turkey**
November 17-18, 2018	**2. Türk-Rus Ürojinekoloji Sempozyumu, İstanbul, Turkey**
November 21-25, 2018	**Ulusal Jinekolojik Onkoloji Kongresi, Antalya, Turkey**

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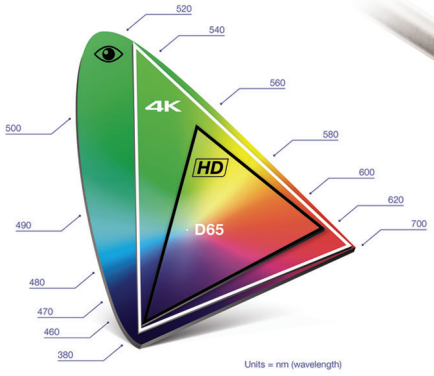

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- Şiddetli adet kanaması endikasyonu[6,7]
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