Clinical symptoms and diagnostic tools that are related to infertility and hydrosalpinx formation in women with advanced stage endometriosis complicated by endometrioma

Objawy kliniczne i narzędzia diagnostyczne w niepłodności i wodniaku jajowodu u kobiet z zaawansowanym stadium endometriozy powikłanym torbielą endometrialną

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Abstract

Objectives: *The study included patients suffering from stage III-IV endometriosis complicated by an endometrioma (OMA). We investigated the association between age, presence of dysmenorrhea/dyspareunia, preoperative CA 125 level, size of OMA on ultrasonographic exam and infertility, as well as the risk of intraoperative detection of hydrosalpinx that was not suspected on pre-operative assessment.*

Materials and Methods: *The study included patients with stage III-IV endometriosis complicated by OMA who underwent a laparoscopic or open surgery due to pre-diagnosis of infertility or adnexal mass.*

Results: *Dysmenorrhea had statistically significant association with infertility (p=0.031). There was no statistically significant relation between age, dyspareunia, preoperative CA 125 level, size of OMA on ultrasonographic exam and infertility (p=0. 203, p=0.561, p=0.561 and p=0.668, respectively). No statistically significant relation was found between age, CA 125 level, dysmenorrhea, dyspareunia and detection of an unilateral/bilateral hydrosalpinx, that was not suspected on pre-operative assessment (p=0.179, p=0.295, p=0.895, p=0.424, respectively). There was an association between OMA size (p=0.023) and detection of unilateral/bilateral hydrosalpinx.*

Conclusions: *Patients who desire to have children but suffer from severe dysmenorrhea must be preoperatively informed about the possibility of having stage III-IV endometriosis. Infertile patients who are about to undergo an operation, especially due to a large OMA, may turn out to have hydrosalpinx. These patients should be informed preoperatively about the possibility of having salpingectomy or the proximal tubal surgery for improving fertility.*

Key words: **endometriosis** / **endometrioma** / **hydrosalpinx** / **infertility** /

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Otrzymano: **06.05.2013**
Zaakceptowano do druku: **30.07.2013**

Streszczenie

Cel: *Do badania włączono pacjentki cierpiące na endometriozę w stopniu III-IV powikłaną torbielą endometrialną (OMA). Zbadano powiązania między wiekiem, obecnością bolesnego miesiączkowania/dyspareunii, przedoperacyjnym poziomem CA125, rozmiarem OMA w USG a niepłodnością. Oceniono również ryzyko śródoperacyjnego rozpoznania wodniaka jajowodu, którego nie podejrzewano przed operacją.*

Materiał i metoda: *Do badania włączono pacjentki z III-IV stopniem endometriozy powikłanym OMA, które przeszły laparoskopię lub operację metodą otwartą z powodu niepłodności lub guza jajnika.*

Wyniki: *Bolesne miesiączkowanie miało istotny związek z niepłodością (p=0,031). Nie znaleziono istotnego związku pomiędzy wiekiem, dyspareunia, przedoperacyjnym poziomem CA125, rozmiarem OMA w USG a niepłodnością (p=0,203; p=0,561; p=0,561 i p=0,424, odpowiednio). Rozmiar OMA miał istotny związek z rozpoznaniem jedno/obustronnego wodniaka jajowodu (p=0,023).*

Wnioski: *Kobiety, które chcą zajść w ciążę ale cierpią z powodu bolesnych miesiączek powinny być poinformowane przed operacją o możliwej endometriozie III-IV stopnia. Niepłodne pacjentki, które mają się poddać leczeniu operacyjnemu, zwłaszcza z powodu dużych torbieli endometrialnych, mogą w rzeczywistości mieć wodniaka jajowodu. Te pacjentki powinno się informować przed operacją o konieczności wykonania usunięcia jajowodu lub chirurgii proksymalnego odcinka jajowodu celem poprawy płodności.*

Słowa kluczowe: **endometrioza** / **endometrioma** / **wodniak jajowodu** / **niepłodność** /

List of abbreviations:
endometrioma, **OMA**; revised endometriosis scoring of the American Fertility Society, **R-AFS**; in vitro fertilization, **IVF**; ultrasonography, **USG**; deep infiltrating endometriosis, **DIE**; peritoneal superficial endometriosis, **SUP**; nerve growth factor, **NGF**; protein gene product 9.5, **PGP9.5**.

Introduction

Endometriosis is defined as the localization of endometrial-like tissue outside the uterus. Endometriosis causes infertility, dyspareunia and chronic pelvic pain in women during their reproductive years [1]. In advanced endometriosis cases, i.e. stages III (moderate; score 16-40) and IV (severe; score, >40), the adhesions, fimbrial distortion, tubal contraction or occlusion (proximal/distal tubal obstruction) which disrupts or distorts the structure of the pelvis, are responsible for infertility [2]. Jasović and Jasović-Siveska reported pregnancy rates to be substantially lower in patients with stage III and IV endometriosis, even if they attempted assisted reproductive techniques [3].

The presence of an ovarian endometrioma (OMA), an endometriotic cyst of 1 cm or more on the ovary, means that patients shall be diagnosed with stage III (moderate) disease or higher, according to the revised endometriosis scoring of the American Fertility Society (R-AFS) [4]. OMAs can be easily overlooked in conventional ultrasonography and increase the disease stage, possibly leading to hydrosalpinx and fertility problems related to tubal occlusion.

In most patients, advanced stage endometriosis (III-IV) leads to dysmenorrhea and dyspareunia due to deep pelvic invasion, recto-uterine obliteration, and recto-vaginal involvement [1]. Dysmenorrhea is associated with the stage of endometriosis [5]. It was noted in another study that patients with advanced stage (III-IV) endometriosis suffer from severe dyspareunia [6]. According to the Polish Gynecological Society Expert Group, the correlation between the stage of endometriosis and pain intensity is not always proportional [7].

An increase in pregnancy rates is observed after patients with hydrosalpinx have undergone proximal tubal occlusion or salpingectomy before in vitro fertilization (IVF). Also, surgical procedures increase the spontaneous pregnancy ratio in patients with unilateral hydrosalpinx and normal contralateral tubes [8]. In a large study, 1143 benign adnexal masses were examined, and the positive likelihood ratio (LR+) for diagnosing hydrosalpinx in the preoperative grey-scale ultrasonography (USG) was only 58.2% [9].

Objectives

This study included patients suffering from stage III-IV endometriosis complicated by OMA. We investigated the association between age, presence of dysmenorrhea/dyspareunia, preoperative CA 125 level, size of OMA on ultrasonographic exam and infertility, as well as the risk of intraoperative detection of hydrosalpinx that was not diagnosed on preoperative assessment.

Material and Methods

The study included patients with stage III-IV endometriosis complicated by OMA, who underwent a laparoscopic or open surgery due to pre-diagnosis of infertility or adnexal mass between November 2009 and February 2013, at the Obstetrics and Gynecology Department, Düzce University School of Medicine.

The study participants were selected from among the patients in their reproductive period (16-50 years of age), not pregnant and with regular cycles. Exclusion criteria included i) history of the medical treatment of endometriosis, pelvic surgery and pelvic inflammatory disease, ii) the diagnosis of an infectious disease and a gynecological or non-gynecological

malignancy, iii) cases where uterine leiomyoma, adenomyosis, endometrial polyps, endometrial hyperplasia or borderline ovarian tumors were detected in the surgical specimens. On USG performed preoperatively, patients with i) dilated fallopian tube as a thin- or thick-walled tubular fluid-filled structure which was elongated or folded, ii) thickened longitudinal folds in the fallopian tube, iii) dilated fallopian tube showing longitudinal folds, or iv) multilocular cystic mass with multiple septa creating multiple compartments were excluded as these were traditional pathognomonics of a hydrosalpinx on USG [10].

Thirty-three patients with stage III (moderate; score 16-40) and IV (severe; score, >40) endometriosis complicated by OMA, classified is a wide as late stage endometriosis according to the revised endometriosis scoring of the American Fertility Society (R-AFS), were enrolled in the study [4]. Düzce University School of Medicine Ethics Committee for Non-invasive Clinical Research gave an approval for the study (Decision No: 2013/391). Patient data were obtained from the medical records of Düzce University School of Medicine and analyzed retrospectively. All patients provided an informed written consent before the surgery.

Before operations, patients were checked for the presence of dysmenorrhea and dyspareunia. Nulligravidas who, despite unprotected sex, could not become pregnant in the curse of 12 months, were regarded as infertile. Dyspareunia was defined as 'pain during sexual intercourse' [11]. Dysmenorrhea was described as 'menstrual pain which can be accompanied with headache, nausea, vomiting, cold sweats, or additional symptoms' [12]. Hydrosalpinx was described as 'fallopian tube which is blocked at its end and swollen with fluid'. When the presence of an unilateral or bilateral hydrosalpinx was found in the histopathological examination, the presence of hydrosalpinx was confirmed.

Three cc peripheral venous blood drawn from the operated patients was put into sterile tubes and, without delay, centrifuged in the laboratory for 15 min at 3000 g. The obtained serum samples were measured on the Roche Hitachi Cobas 6000 E 601, and CA 125 level was determined by the electrochemiluminescence method. Values were denominated in IU/ml. The upper limit for normal level of CA 125 serum was determined as 35 IU/ml.

Statistical Method

Patient data were recorded using the SPSS v19.0 program. Descriptive statistics of the digital data were obtained by using average, standard deviation, and minimum and maximum values. Variables were analyzed by t test for parametric data. Pearson chi-square test was used for nonparametric variables and t-test for comparison of the groups. $P < 0.05$ was regarded as statistically significant.

Results

Average patient age, CA 125 level measured preoperatively, number of patients suffering from dysmenorrhea and dyspareunia, history of infertility, sizes of preoperatively detected OMAs, stage of disease and number of patients with hydrosalpinx are shown in Table I.

Dysmenorrhea had statistically significant association with infertility in patients with advanced endometriosis and OMA (p=0.031) (Table II). However, there was no statistically significant relation between age, dyspareunia, preoperative CA 125 level and the size of OMA on ultrasonographic exam and infertility (p =0. 203, p=0.561, p=0.561 and p=0.668, respectively). (Table II).

No statistically significant relation between intraoperative detection of a unilateral/bilateral hydrosalpinx that was not suspected on pre-operative assessment and patient age (p=0.179), preoperatively measured CA 125 level (p=0.295), symptoms of dysmenorrhea (p=0.895) and dyspareunia (p=0.424) was found. (Table III). We found an association between OMA size on ultrasonographic exam (p=0.023) and detection of unilateral/bilateral hydrosalpinx that was not diagnosed on pre-operative assessment. We used the Receiver Operating Characteristic curve analysis to determine an optimal size of OMA cut-off for the detection of hydrosalpinx that was not suspected on pre-operative assessment. Nevertheless, we were not able to obtain a statistically significant cut-off value.

Discussion

Patients with moderate and severe endometriosis suffer from pelvic pain symptoms such as dysmenorrhea and dyspareunia more frequently. Treating OMAs as the only cause in severe dysmenorrhea and dyspareunia cases would be an oversimplification of the disease; because such patients generally suffer from deep infiltrating endometriosis (DIE), with lesions invading 5mm or deeper under the peritoneal surface, peritoneal superficial endometriosis (SUP) and tubo-peritoneal adhesive/ obstructive lesions along with OMA [6,13].

Oscillation of the mast cell and the nerve growth factor (NGF), the pain mediator in endometriosis, increases in different endometriotic lesions such as OMA, DIE and SUP [14]. The protein gene product 9.5 and stained nerve fibers have a role in the pain mechanism of endometriosis. Zhang et al., indicated that the intensity of protein gene product 9.5 (PGP9.5)-positive nerve fibers increased through OMA in patients diagnosed with late-stage (stage III-IV) endometriosis, who suffered from pelvic pains such as dysmenorrhea and dyspareunia [15].

Although it is accepted that OMA, DIE and SUP are painful endometrial lesions [16], it has not been proven yet whether hydrosalpinx developing in endometriosis has a net correlation with the pain symptoms. In patients with advanced stage endometriosis (stage III-IV), hydrosalpinx significantly affects the fertility due to its mechanical, gametotoxic and embryotoxic effects, the avb3 integrin disrupting the endometrial receptivity, its negative effect on other integrins and the intrauterine fluid accumulation [17]. Conservative laparoscopic surgery, laparotomy, or IVF are recommended for infertile patients with stage III-IV endometriosis (AFS-R) [18]. The present study examined the preoperative risk factors for infertility and detection of hydrosalpinx in patients with advanced stage disease.

OMA and severe pelvic pains are associated with advanced stage endometriosis [6]. In the present study we demonstrated a correlation between dysmenorrhea and infertility, what is consistent with the literature (p=0.031). On the other hand, Vercellini et al., reported that frequency and severity of pelvic pain symptoms did not change in patients diagnosed with advanced-stage endometriosis, including DIE and vaginal endometriosis [18]. In 2013, Dubuisson et al., indicated that dyspareunia developing in late-stage endometriosis disappeared after surgical treatment [19]. We found no correlation between infertility and dyspareunia, which is the other major factor of

Table I. Demographics and characteristics.

	N=33(100%)	Minimum	Maximum	Mean+/-Std. Dev.
Age	33(100%)	20	58	34.76+/-9.00
ca125 level	33(100%)	4.25	200.00	50.86+/-46.72
size of OMA(mm)*	33(100%)	25	84	52.52+/-16.06
dysmenorrhea	17(51.5 %)			
dyspareunia	14(42.4 %)			
hydrosalpinx positive	12(36.3 %)			
infertility positive	10(30.3%)			
Total	33(100%)			

* millimeters , **mm.**

Table II. Examination of the factors affecting infertility.

	infertile	fertile	p value*
Age	35.96+/-9.584	32.00+/-7.165	0. 203
dysmenorrhea	0.43+/-0.50	0.80+/-0.42	***0.031***
dyspareunia	0.43+/-0.50	0.80+/-0.42	0.561
Ca125 level	52.42+/-54.34	47.29+/-22.84	0.705
size of OMA(mm)*	50.50+/-18. 24	53.39+/-15.37	0.668

* millimeters , **mm.**

Table III. Examination of the factors affecting detection of hydrosalpinx.

	hydrosalpinx positive	hydrosalpinx negative	p value*
Age	33.24+/-9.52	37.42+/-7.645	0.179
dysmenorrhea	0.52+/-0.51	0.50+/-0.52	0.895
dyspareunia	0.47+/-0.51	0.33+/-0.49	0.424
Ca125 level	43.47+/-38.28	63.80+/-58.30	0.295
size of OMA(mm)*	54.29+/-24.81	47.92+/-17.51	***0.023***

* millimeters , **mm.**

pelvic pain (p=0.561). Dyspareunia is a subjective symptom and may change depending on several factors such as age, mental condition, social characteristics and educational background [20].

CA 125, along with ultrasonography, is the most commonly used marker for the diagnosis of OMAs [9]. CA 125 level is higher in patients with advanced-stage endometriosis. Today, there is a clear consensus that infertility frequency is specifically high in patients with stage III-IV endometriosis [18].

In our study, the preoperative CA 125 level (p=0.705) did not differ between fertile and infertile patients. Patrelli et al,. reported the correlation between CA 125 level and the surgical and pathologic findings of ovarian and deep endometriosis to be statistically significant. However, the location did not affect the fertility rate [21].

It is debatable whether infertility originates from OMA, or is related to common tubo-peritoneal lesions associated with OMA in advanced stage endometriosis. Whether the excision of OMAs contributes to the infertility of the patient remains to be elucidated [22]. So far, it has been discovered that the presence of OMA does not affect the number of oocytes in the IVF applications, in which tubo-peritoneal factors are ruled out [23]. In our study, we found no statistically significant association between the size of OMA and infertility (p=0.668).

Expectant therapy is not recommended in infertile patients with hydrosalpinx or tubal occlusion. It is certain that surgical treatments increase the pregnancy rate [8, 16]. Although hydrosalpinx is typically recognized on the USG, it is hard to diagnose it preoperatively when it has an atypical character or is

associated with another mass. Preoperative CA 125 level is not useful for the diagnosis of hydrosalpinx in all circumstances [9]. According to the results of our study, there was no statistically significant association between preoperatively measured CA 125 level (p=0.295) and the presence of unilateral/bilateral hydrosalpinx.

In many cases, even an experienced sonographer is not able to correctly differentiate a hydrosalpinx from other adnexal pathologies [24]. Ultrasound examiners may misdiagnose 10% of hydrosalpinges [25]. There is always the risk of finding a hydrosalpinx in patients with fertility problems and advance staged endometriosis (stage III-IV). We examined the relationship between clinical properties and the risk of intraoperative detection of a hydrosalpinx that was not suspected on pre-operative assessment. It was shown in our study that age, dysmenorrhea and dyspareunia symptoms did not have a statistically significant relation to the risk of hydrosalpinx detection (p=0.179, p=0.895, p=0.424, respectively), but the size of OMA on preoperative sonography had an association with the risk of intraoperative detection of hydrosalpinx (p=0.023). There are two types of patho-physiological pathways for the formation of hydrosalpinx in endometriosis. Intralesional hemorrhage and fibrosis developing in functional serosal or subserosal endometriotic implants leading to the formation of peritubal adhesions and hydrosalpinx. According to another default theory, the intraluminal tubal endometriotic tissue causes hydrosalpinx by obstructing passages, especially in intramural and isthmic area by leading to the disruption of normal tubal function [26]. Donnez et al., described that adhesions were the causes of OMA by shedding of active superficial implants [27]. Probably, as the active endometriotic lesion known as OMA enlarges, it deteriorates the tubal structure.

Conclusions

Despite the low number of study participants, we were able to find that dysmenorrhea was associated with infertility in patients diagnosed with advanced-stage endometriosis. The risk of hydrosalpinx detection, not diagnosed on pre-operative assessment, was linked with the size of OMA. Patients who desire to have children but suffer from severe dysmenorrhea should be preoperatively informed about the possibility of having stage III-IV endometriosis. Infertile patients, undergoing an operation especially due to a large OMA, may turn out to have hydrosalpinx. They should be informed about salpingectomy or the proximal tubal surgery that might be performed intraoperatively. These patients must provide a written consent preoperatively, regardless of whether the hydrosalpinx can be seen on preoperative USG, to avoid a second operation due to hydrosalpinx in the future.

References

1. D'Hooghe T, Mohali A, Sims P, [et al.]. Why we need a noninvasive diagnostic test for minimal to mild endometriosis with a high sensitivity. *Gynecol Obstet Invest.* 2006, 62, 136–138.
2. Hassa H. Endometriosis-İnfertilite ilişkisi ve tedavi sınırları. *J Turk Soc Obstet Gynecol.* 2004, 3,181-187.
3. Jasović V, Jasović-Siveska E. Success rate of intra uterine insemination in patients with unknown infertility. *Vojnosanit Pregl.* 2012, 69, 301-307.
4. ASRM (1997): American Society for Reproductive Medicine: Revised American Society for Reproductive Medicine classification of endometriosis: 1996. *Fertil Steril.* 1997, 67, 817–821.
5. Chapron C, Fauconnier A, Dubuisson J, [et al.]. Deep infiltrating endometriosis: relation between severity of dysmenorrhea and extent of disease. *Hum Reprod.* 2003, 18, 760-766.
6. Chapron C, Santulli P, de Ziegler D, [et al.]. Ovarian endometrioma: severe pelvic pain is associated with deeply infiltrating endometriosis. *Hum Reprod.* 2012, 27, 702-711.
7. Basta A, Brucka A, Górski J, [et al.]. The statement of Polish Society's Experts Group concerning diagnostics and methods of endometriosis treatment. *Ginekol Pol.* 2012, 83, 871-876.
8. Sagoskin A, Lessey B, Mottla G, [et al.]. Salpingectomy or proximal tubal occlusion of unilateral hydrosalpinx increases the potential for spontaneous pregnancy. *Hum Reprod.* 2003, 18, 2634-2637.
9. Alcázar J, Guerriero S, Mínguez J, [et al.]. Adding cancer antigen 125 screening to gray scale sonography for predicting specific diagnosis of benign adnexal masses in premenopausal women: is it worthwhile? *J Ultrasound Med.* 2011, 30, 1381-1386.
10. Benjaminov O, Atri M. Sonography of the abnormal fallopian tube. *AJR Am J Roentgenol.* 2004, 183,737-742.
11. American College of Obstetricians and Gynecologists. Sexual dysfunction. Technical bulletin no. 211. *Int J Gynecol Obstet.* 205, 51, 265-277.
12. French L. Dysmenorrhea. *American Family Physician.* 2005, 71, 285–292.
13. Chapron C, Pietin-Vialle C, Borghese B, [et al.]. Associated ovarian endometrioma is a marker for greater severity of deeply infiltrating endometriosis. *Fertil Steril.* 2009, 92, 453–457.
14. Anaf V, Chapron C, El Nakadi I, [et al.]. Pain, mast cells, and nerves in peritoneal, ovarian, and deep infiltrating endometriosis. *Fertil Steril.* 2006, 86, 1336–1343.
15. Zhang X, Yao H, Huang X, [et al.]. Nerve fibres in ovarian endometriotic lesions in women with ovarian endometriosis. *Hum Reprod.* 2010, 25, 392–397.
16. A Committee Opinion The Practice Committee of the American Society for Reproductive Medicine Birmingham, Alabama. Endometriosis and Infertility. *Fertil Steril.* 2012, 98, 591–598.
17. Parihar M, Mirge A, Hasabe R. Hydrosalpinx functional surgery or salpingectomy? The importance of hydrosalpinx fluid in assisted reproductive technologies. *J Gynecol Endosc Surg.* 2009, 1, 12-16.
18. Vercellini P, Trespidi L, De Giorgi O, [et al.]. Endometriosis and pelvic pain: relation to disease stage and localization. *Fertil. Steril.* 1996, 65, 299-304.
19. Dubuisson J, Pont M, Roy P, [et al.]. Female sexuality after surgical treatment of symptomatic deep pelvic endometriosis. *Gynecol Obstet Fertil.* 2013, 41, 38-44.
20. Laumann E, Paik A, Rosen R. Sexual dysfunction in the United States: prevalence and predictors. *JAMA.* 1999, 281, 537–544.
21. Patrelli T, Berretta R, Gizzo S, [et al.]. CA 125 serum values in surgically treated endometriosis patients and its relationships with anatomic sites of endometriosis and pregnancy rate. *Fertil Steril.* 2011, 95, 393-396.
22. Vercellini P, Somigliana E, Viganò P, [et al.]. Surgery for endometriosis-associated infertility: a pragmatic approach. *Hum Reprod.* 2009, 24, 254-269.
23. Almog B, Shehata F, Sheizaf B, [et al.]. Effects of ovarian endometrioma on the number of oocytes retrieved for in vitro fertilization. *Fertil Steril.* 2011, 95, 525-527.
24. Timor-Tritsch I, Monteagudo A, Tsymbal T. Three-dimensional ultrasound inversion rendering technique facilitates the diagnosis of hydrosalpinx. *J Clin Ultrasound.* 2010, 38, 372-376.
25. Sokalska A, Timmerman D, Testa A, [et al.]. Diagnostic accuracy of transvaginal ultrasound examination for assigning a specific diagnosis to adnexal masses. *Ultrasound Obstet Gynecol.* 2009, 34, 462-470.
26. Clement P. Diseases of the peritoneum. In: Blaustein's pathology of the female genital tract. 2nd ed. Ed. Blaustein A. New York, NY: Springer-Verlag.1984, 729–789.
27. Donnez J, Nisolle M, Gillet N,[et al.]. Large ovarian endometriomas. *Hum Reprod.* 1996, 11,641-646.