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ORIGINAL ARTICLE

The effect of new cross linked hyaluronan gel on quality of life of patients after deep infiltrating endometriosis surgery: a randomized controlled pilot study

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ABSTRACT

In this prospective randomised placebo-controlled study, we aimed to evaluate the effect of New Cross linked Hyaluronan Gel (NCH gel) on the quality of life of patients who underwent laparoscopic surgery due to Deep Infiltrating Endometriosis (DIE). The intervention group received 40 mL of NCH gel, and the control group had a 40 mL sterile saline solution instilled into the peritoneal cavity following standard laparoscopic procedures. The patients were called in the third and sixth postoperative months and requested to fill the Visual Analogue Scale (VAS), Endometriosis Health Profile (EHP-5), and Short Form for Mental and Physical Health (SF-12) questionnaires. There was a significant reduction in dysmenorrhoea, dyschezia, dyspareunia VAS scores at 3rd, and 6th-month visits in NCH gel group. The postoperative 6th-month EHP-5 scores were significantly lower (1.16 ± 1.51, p-value: .02) in NCH gel group. Besides, NCH gel group had higher SF-12 mental and SF-12 physical scores.

Clinical Trials registration number: NCT04023383

IMPACT STATEMENT

- **What is already known on this subject?** Application of solid or liquid physical barriers is believed to be a promising strategy to reduce adhesions after laparoscopic endometriosis surgery. However, comparable data regarding the effects of adhesion barriers are still lacking.
- **What the results of this study add?** We revealed that there was a significantly higher decrease in VAS and EHP-5 scores and an increase in SF-12 physical-mental ratings after surgery in NCH gel group.
- **What are the implications of these findings for clinical practice and/or further research?** Using NHC gel in addition to standard surgical procedure improves postoperative VAS scores, and provides better quality of life scores.

KEYWORDS

Endometriosis; hyaluronic acid; quality of life; tissue adhesions; adhesion barriers

Introduction

Endometriosis is defined as the presence of endometrial glands and stroma outside of the uterine cavity. Endometriosis is one of the most common diseases of women during their reproductive period, with a prevalence of 7–10% (Laufer et al. 1997; Eskenazi and Warner 1997). The lesions are typically observed in the peritoneal cavity, ovaries, and tubes. Still, it can also be found in the rectum, rectosigmoid colon, bladder, ureter, and other pelvic structures such as the uterine ligaments and vagina (Jansen and Russell 1986; Vercellini et al. 2014). The patients with endometriosis have a low quality of life (QoL) due to dysmenorrhoea, dyspareunia, chronic pelvic pain, and infertility as a result of inflammation and adhesion formation.

Surgery is required for patients who failed to respond to medical therapy and those who develop acute abdominal pain or suspicion of malignant adnexal mass (Singh and Suen 2017). The surgical technique may vary from simple laparoscopic excision of endometrial foci to complex procedures including extensive adheziolysis, ureterolysis, partial resection of bladder, ureter, and bowel to treat deep infiltrative endometriosis (DIE) (Arcoverde et al. 2019).

One of the significant postoperative concerns is the high recurrence rate of the symptoms due to de novo pelvic adhesions that are associated with endometriosis-related pain (Al-Jabri and Tulandi 2011). Immunohistochemical analyses also confirmed that there were nerve fibres in the adhesions that had been removed from patients with pelvic pain (Hammoud et al. 2004). Administrating solid or liquid physical barriers is believed to be a promising strategy to reduce postoperative adhesions and to separate peritoneal injuries from each other (Ahmad et al. 2008). Ideal barriers should be absorbable, safe, deliverable by either laparotomy or laparoscopic approaches, and broadly efficacious to reduce both de novo and reformed adhesions in the abdominopelvic cavity (Chen and Abatangelo 1999).

Hyaluronan, a glycosaminoglycan found in connective tissues and extracellular matrix, has been thought to reduce

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postoperative adhesions, because of its biological functions in tissue repair. However, its fluid nature causes rapid degradation, and it cannot affect long enough to work as an adhesion barrier (Chen and Abatangelo 1999; Wiseman et al. 2000). For this reason, a new cross-linked hyaluronan (NCH) gel, with a higher viscosity than natural hyaluronan has been developed. It is gradually absorbed within 1–2 weeks *in vivo*, which is the required period for tissue repair and adhesion formation. Although it has already known that endometriosis has a serious impact on the quality of life of women; comparable data regarding the effects of adhesion barriers on patients who have had laparoscopic DIE surgery is lacking.

Therefore, in this study, we aimed to conduct a pilot randomised controlled study to evaluate the effect of NCH gel on short term quality of life in patients who had undergone laparoscopic surgery due to DIE.

Materials and methods

A prospective, 1:1, randomised, placebo-controlled study was conducted in University of Health Sciences Bakirkoy Dr. Sadi Konuk Hospital, Istanbul, which serves as a tertiary referral hospital between January 2017 and January 2019. The study protocol was approved by the local ethics committee of our hospital (approval number: 2017/04/35).

The inclusion criteria for this study were as follows; women aged 18–45 years, undergoing laparoscopic surgery for suspicion of DIE, and having persistent pain unresponsive to any medical treatment.

The exclusion criteria for the study were as follows; the presence of an acute or severe infection, autoimmune disease, use of a systemic anti-inflammatory or hormonal drug at least three months before the planned surgery, having clinical evidence of cancer. Also, patients with known/suspected hypersensitivity against hyaluronan or its derivatives, use of any anticoagulant agents, fibrin glue, or other anti-adhesion agents, patients with bowel involvement proven via ultrasound or MRI, and those who want to receive postoperative hormonal treatment were excluded.

One hundred twenty-four patients who were admitted to the endometriosis outpatient clinic, corresponding inclusion/exclusion criteria were informed and asked to anticipate to the study. The patients who were scheduled to undergone laparoscopic surgery for the treatment of deep infiltrating endometriosis without bowel involvement were enrolled. Sixty patients were enrolled in the study after written and signed informed consent was obtained. The same surgical team who experienced in minimally invasive DIE surgery performed all of the procedures. The patients were called for follow-up visits in the 3rd and 6th postoperative months.

Participants were allowed to withdraw from the study for any reason at any time, and the study was decided could be terminated by investigators in case of safety concerns, violations of inclusion/exclusion criteria, or presence of pregnancy. None of the participants lost during the study period, and the study was completed with the planned number of patients.

Surgical procedure

Patients were randomly assigned to either the NCH gel or control group in a 1:1 ratio through a computer-based programme. A standardised laparoscopic approach was conducted consisting of removal of all the endometriotic foci. After hemostasis, 40 mL of NCH gel (HyaRegen, BioRegen Biomedical, Changzhou, China) was administered into the peritoneal cavity of the intervention group. In contrast, the control group received a 40 cc of sterile saline solution. The operators were not blind to the type of treatment due to the nature of the study, but the questionnaire assessors and the patients were blinded to the kind of treatment applied.

Preoperative and postoperative assessment of pain and quality of life (QoL)

A research assistant recorded the scores of Visual Analogue Scale (VAS), Endometriosis Health Profile (EHP-5), and Short Form for Mental and Physical Health (SF-12) of patients before the day of the surgery.

A validated, Likert fashion, VAS score form was used. The scoring varied between 0 and 10 that 0 was referred to as no pain, and ten was the worst pain that they had ever experienced. Then, the VAS and QoL questions were asked in the 3rd and 6th months of their follow up visits. A QoL form SF-12, which assesses physical functioning, bodily pain, general health, vitality, social functioning, role limitations due to physical and mental health problems, was used. The scores were analysed to obtain both physical and mental scores.

A validated form of EHP-5 questionnaire was used to determine endometriosis-related QoL (Selcuk et al. 2015). EHP-5 consists of two parts. The first part evaluates parameters, namely; pain, control and powerlessness, emotional well-being, social support, and self-image; and the second part measures the sexual life, work, relationship with children, feelings about medical professional, treatment, and infertility.

Statistical analysis

Data analysis was performed by using SPSS (IBM SPSS Statistics for Windows, version 20.0. Armonk, NY: IBM Corp.). One-sample Kolmogorov–Smirnov test was performed to analyse the distribution of clinical variables. The frequency and percentage of the categorical variables and the mean, standard deviation, median, and range values of the continuous and ordinal variables were presented. The study groups were compared using Student *t*-test for parametric variables and Mann Whitney *U* test for the non-parametric variables. A post-hoc sample size calculation was performed via a two-sided *Z* test ($\alpha = 0.05$, $\beta = 0.20$) for each study group to obtain VAS scores as the primary outcome. A *p*-value of $<.05$ was considered statistically significant for all calculations.

Results

There was no significant difference between the study groups in terms of age, BMI, gravidity, parity, size of adnexal

Table 1. Baseline characteristics of the study population.

	Control group	NCH† gel group	*p* Value	95% Confidence interval(CI)
Age (years)	36.43 ± 8	34.36 ± 7.58	0.23	0.23–0.25
Gravidity	1.33 ± 1.1	0.86 ± 0.97	0.1	0.1–0.11
Parity	1.16 ± 0.9	0.76 ± 0.85	0.09	0.09–0.11
BMI (kg/m^2)	26.27 ± 3.94	24.39 ± 3.4	0.06	0.060–0.069
Size of adnexal mass (mm)	61 ± 20.56	66 ± 22.06	0.28	0.26–0.30
Laterality				
Unilateral	14 (46.7%)	8 (26.7%)	0.09	0.17–0.18
Bilateral	16 (53.3%)	22 (73.3%)		
Number of intra/postoperative complication	2 (6.7%)	0	0.49	0.48–0.51
Number of recurrence	2	4	0.67	0.66–0.68
Type of operation				
Cystectomy	16	22	0.11	0.17–0.18
Oophorectomy	14	8		
Preoperative Hb g/dL	12.46 ± 1.59	12.16 ± 1.17	0.38	0.38–0.4
Preoperative Hct %	38.06 ± 3.96	37.86 ± 2.94	0.8	0.79–0.81
Postoperative Hb g/dL	10.46 ± 1.53	10.43 ± 1.47	0.99	0.99–1
Postoperative Hct %	33.03 ± 4.27	33.13 ± 3.96	0.97	0.97–0.98
Decrease in Hb	2 ± 1.28	1.73 ± 0.98	0.31	0.316–0.334
Decrease in Hct %	5.03 ± 3.63	4.73 ± 2.81	0.82	0.819–0.834
Duration of surgery (min.)	135.83 ± 56.32	166.5 ± 58.28	0.06	0.059–0.069
Duration of hospital stay (days)	2.83 ± 0.91	2.83 ± 0.64	0.66	0.64–0.66

†NCH: New cross linked hyaluronan.

Table 2. Preoperative and postoperative VAS‡ scores of the study population.

	Control group	NCH† gel group	*p* Value	95% Confidence interval(CI)
Preoperative VAS dysmenorrhea dysmenorrhoea	8.06 ± 0.9	8.13 ± 1.63	0.71	0.71–0.73
3rd month VAS dysmenorrhea dysmenorrhoea	3.1 ± 2.39	1.26 ± 1.99	**0.001**	**0–0.002**
6th month VAS dysmenorrhea dysmenorrhoea	2.46 ± 1.75	1 ± 1.33	**0.001**	**0–0.001**
Decrease in VAS dysmenorrhea dysmenorrhoea	5.6 ± 1.92	7.13 ± 2.17	**0.007**	**0.005–0.008**
Preoperative VAS dyschezia	2.9 ± 2.1	2.43 ± 2.29	0.33	0.333–0.352
3rd month VAS dyschezia	2.2 ± 1.5	1.13 ± 1.27	**0.006**	**0.004–0.007**
6th month VAS dyschezia	2.13 ± 1.54	0.76 ± 1.01	**<0.001**	**0–0.001**
Decrease in VAS dyschezia	0.76 ± 0.93	1.66 ± 1.71	0.067	0.062–0.071
Preoperative VAS dyspareunia	3.23 ± 2.25	3.26 ± 2.59	0.91	0.919–0.929
3rd month VAS dyspareunia	2.43 ± 1.69	1.03 ± 1.42	**0.001**	**0–0.002**
6th month VAS dyspareunia	2.2 ± 1.56	0.8 ± 1.06	**<0.001**	**0.000–0.000**
Decrease in VAS dyspareunia	1.03 ± 1.27	2.46 ± 2.08	**0.01**	**0.009–0.01**
Pre-op VAS dysuria	2.33 ± 1.6	2.6 ± 2.38	0.6	0.601–0.620
3rd month VAS dysuria	1.7 ± 1.14	1.4 ± 1.32	0.39	0.391–0.410
6th month VAS dysuria	1.26 ± 0.94	0.93 ± 0.94	0.18	0.165–0.180
Decrease in VAS dysuria	1.06 ± 1.11	1.66 ± 1.82	0.38	0.379–0.398
Preoperative VAS pelvic pain	2.93 ± 2.16	3.03 ± 3.02	0.85	0.853–0.867
3rd month VAS pelvic pain	2.26 ± 1.61	1.6 ± 1.84	0.21	0.211–0.227
6th month VAS pelvic pain	1.5 ± 1.16	0.8 ± 1.03	**0.01**	**0.010–0.014**
Decrease in VAS pelvic pain	1.43 ± 1.47	2.23 ± 2.41	0.36	0.351–0.370

‡VAS: visual analogue scale.
†NCH: new cross linked hyaluronan.
Bold values indicates statistically significant ($p < 0.05$).

cyst, laterality of the mass, peri/postoperative complications and recurrence rates, type of operation, pre and postoperative Hb/Hct levels, duration of surgery, and duration of postoperative hospital stay (Table 1). There was a statistically significant reduction in dysmenorrhoea, dyschezia, dyspareunia at 3rd and 6th month, and in VAS scores at 6th month in NCH gel group compared to the control group (Table 2). No significant difference for preoperative EHP-5 and postoperative 3rd-month EHP-5 results between the study groups was noted. However, postoperative 6th-month EHP-5 scores were significantly lower (1.16 ± 1.51, *p*-value: .02) in NCH gel group. Preoperative SF-12 mental and physical parameters and postoperative 3rd-month physical scores were not statistically different between the study groups. On the other hand, significantly higher scores of the postoperative 3rd month mental SF-12 and postoperative 6th month SF-12 physical and mental ratings (50.43 ± 11.09, 51. 92 ± 11.21, and 51.55 ± 10.93, respectively) found in NCH gel group (Table 3).

Discussion

It is a well-known fact that endometriosis itself progresses with the formation of postoperative adhesions despite definitive radical excisional surgeries and hormonal therapies. So far, the studies had focussed on the effect of surgery alone on QoL of patients, recurrence, and postoperative adhesion formation rates. However, there is still a lack of evidence on the impact of adhesion barriers on postoperative pain and QoL (Chen and Abatangelo 1999; Garry et al. 2000).

To enlighten the relation between adhesion barriers and postoperative de novo adhesions, diZerega et al. compared patients who had surgery only (*n*: 17, control patients with

Table 3. Preoperative and Postoperative SF-12[§], EHP5[¶], QoL[°] assesment scores of the study population.

	Control group	NCH gel group	*p* Value	95% Confidence interval(CI)
Preoperative EHP-5	5.46 ± 3.13	7.83 ± 4.98	0.06	0.065–0.075
3rd month EHP-5	2.66 ± 1.56	1.93 ± 1.74	0.07	0.066–0.076
6th month EHP-5	2.16 ± 1.91	1.16 ± 1.51	**0.02**	**0.017–0.022**
Decrease in EHP-5	3.3 ± 3.19	6.6 ± 5.12	**0.009**	**0.007–0.011**
Preoperative SF 12 physical score	43.15 ± 10.11	39.99 ± 9.45	0.21	0.216–0.233
Preoperative SF 12 mental score	44.89 ± 9.31	40.38 ± 11.41	0.06	0.066–0.076
3rd month SF 12 physical score	49.34 ± 7.43	50.11 ± 11.16	0.18	0.182–0.197
3rd month SF 12 mental score	46.41 ± 7.93	50.43 ± 11.09	**0.005**	**0.004–0.006**
6th month SF 12 physical score	49.24 ± 7.89	51.92 ± 11.21	**0.004**	**0.002–0.004**
6th month SF 12 mental score	49.21 ± 7.07	51.55 ± 10.93	**0.01**	**0.010–0.014**
Decrease in SF 12 physical score	6.09 ± 10.02	11.93 ± 14.61	**0.03**	**0.027–0.034**
Decrease in SF 12 mental score	4.32 ± 11.29	11.17 ± 14.76	**0.01**	**0.015–0.020**

[§]SF 12: Short form-12 health survey for mental-physical health.
[¶]EHP-5: Endometriosis health profile-5.
[°]QoL: Quality of life.
Bold values indicates statistically significant ($p < 0.05$).

total 30 adnexal involvement) and the other group received Oxiplex/AP gel (approximately 12 mL; range, 4–60 mL in 90 s) in addition to standard surgery (*n*: 20 patients with total 35 adnexal involvement) (diZerega et al. 2007). They concluded that Oxiplex/AP gel was effective in the reduction of adhesion formation scores obtained in second-look surgery since increased scores were observed in patients with stage I and stage II disease in the control group. They also indicated that, especially in cases of red endometriotic lesions, which are indicative of early endometriosis, intraoperative administration of gel might provide additional benefits in reducing endometriotic lesions (diZerega et al. 2007).

To date, Adept (4% icodextrin solution; Baxter Bio-Surgery, Deerfield, IL) has been approved in Europe for abdominal surgery and in the US for laparoscopic gynaecologic adhesiolysis (Darai et al. 2010; Mabrouk et al. 2012). However, in a pivotal randomised controlled study in the US, Adept was found to be ineffective in reducing the extent and severity of adhesions. There was only an 11% difference (49% in the Adept group vs. 38% in the control group which lactated Ringer's solution was used.) in terms of clinical success, which was basically considered as the reduction in adhesions (Tanmahasamut et al. 2012). To evaluate the anti-adhesion effect of barriers, in a randomised study with 215 patients by Liu et al. 160 mL of NCH gel (107 of 108) was instilled into the peritoneal cavity following standard laparoscopic procedures, and the patients in control group had 160 mL of saline (108 of 108) instillation (Liu et al. 2015). They concluded that NCH gel could significantly reduce postoperative adhesion formation, severity, and modified American Fertility Society (mAFS) scores compared to the control group (Liu et al. 2015). In contrast to our study, patients in this trial underwent a laparoscopic surgery due to a variety of indications such as pelvic adhesions, uterine fibroids, simple ovarian cysts, and endometriotic cysts.

These results confirm that NCH gel is efficient in reducing postoperative adhesion formation in the abdominopelvic cavity. A 160 mL of NCH gel can be applied to the abdominopelvic cavity to provide broad coverage on the surfaces of organs and tissues with a high safety threshold. However, like the previous studies, we also used 40 mL of gel in our research. (Garry et al. 2000; Sintonen 2001). We believe that 40 mL NCH gel is adequate to cover the ovaries, fallopian tubes, and pouch of Douglas as it has a cross-linked molecular structure. Its high viscosity allows expansion and slow degradation, which provides enough time interval to prevent adhesions at the surgical area.

Recently, Pang et al. have demonstrated that NCH gel inhibits migration, invasion, and proliferation of ovarian cancer cells *in vitro*. It can also suppress implantation *in vivo* by blocking the activation of epidermal growth factor receptor (EGFR) in implantation nude mice model of ovarian cancer (Pang et al. 2018). Also, a marked increase of epidermal growth factor (EGF) concentrations has been previously demonstrated in the peritoneal fluid of women with endometriosis (Rakhila et al. 2016). Therefore, one of the reasons why NCH gel may have a positive effect on the quality of life scores can be explained by its anti-proliferative effects on endometriotic implants.

Hyaluronan has distinctive functions on scar-free healing by reducing inflammation and improving peritoneal re-epithelialization (Ribeiro et al. 2014). We believe that adhesion formation is an inherited defect of the peritoneal healing process; thus, better tissue hemostasis and enhancement of routine healing may reduce adhesion formation. In our study, we used the EHP-5 questionnaire, which is a condition-specific scale and health-related QoL questionnaire, which is less burdensome for respondents to complete (Jones et al. 2004). There are few studies that assessed the efficacy of laparoscopic surgery on improving the QoL of women with endometriosis (Minas and Dada 2014). In a study by Minas and Dada, 40 out of the 49 women (81.6%) completed the EHP-5 questionnaires. They reported that there was an improvement in the QoL after surgery, as lower scores were seen in the post-surgery EHP-5 scale. Specifically, the mean score before surgery was 46.9, and after surgery was 27.5 with a reduction by 41.3% (Minas and Dada 2014). In our study, we also used the EHP-5 questionnaire to evaluate disease-specific QoL scores. Although a significant reduction was observed regarding postoperative scores compared with preoperative scores in both groups, a significantly higher decrease was observed in NCH gel group.

Garry et al. conducted a study on 57 patients who underwent laparoscopic excision of invasive endometriosis and

determined QoL by using the SF-12 questionnaire (Garry et al. 2000). They reported a significant improvement in SF-12 physical score (44.8 vs. 51.9) four months after radical laparoscopic excision of deep endometriosis. Still, the mental health score of SF-12 failed to show any statistical improvement (47.1:48.4) (Garry et al. 2000). In our study, we observed no difference in preoperative SF-12 mental and physical parameters and postoperative 3rd-month physical scores between the study groups. On the other hand, significantly higher scores were found in favour of NCH gel group in the postoperative 3rd month SF-12 mental scores and postoperative 6th month SF-12 physical and mental scores. According to the preoperative VAS assessment, Garry et al. showed that the patients were experiencing a significant degree of pain (Garry et al. 2000). The mean VAS score of 53 patients who complained of dysmenorrhoea was eight preoperatively and four postoperatively. Non-menstrual pelvic pain improved 7–2 in 4 months. A similar reduction in the level of dyspareunia and rectal symptoms were reported as VAS scores decreased from 6 to 0 and 4 to 0, respectively (Garry et al. 2000).

In a recent review, dysmenorrhoea, chronic pelvic pain (CPP), and dyspareunia scores were evaluated preoperatively and in postoperative 3rd and 12th months by using VAS (Marqui 2015). The results show a significant improvement in pain symptoms after three months, and this remained significant throughout 12 months postoperatively. Furthermore, at the end of the study, 79% of the patients reported general satisfaction regarding pain relief. In our study, there was a significant reduction in dysmenorrhoea, dyschezia, dyspareunia at 3rd, and 6th months after surgery. Pelvic pain parameters in the 6th month were observed significantly lower in NHC gel group compared to the control group (Marqui 2015).

Limitations of the study include that we could not perform a second-look laparoscopy to evaluate the postoperative adhesions, and we should have increased the size of the study.

In conclusion, laparoscopic surgery alone or with saline instillation may provide improvement in postoperative pain scores and QoL. However, using NHC gel improves postoperative VAS scores. It provides better QoL scores by preventing possible adhesions that occurred after surgical denudation, ischaemia, desiccation, abrasion, and peritoneal trauma during laparoscopic DIE surgery.

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References

Ahmad G, Duffy JM, Farquhar C, Vail A, Vandekerckhove P, Watson A, et al. 2008. Barrier agents for adhesion prevention after gynaecological surgery. Cochrane Database Systematic Review 2:CD000475.
Al-Jabri S, Tulandi T. 2011. Management and prevention of pelvic adhesions. Seminars in Reproductive Medicine 29:130–137.
Arcoverde FVL, Andres MP, Borrelli GM, Barbosa PA, Abrão MS, Kho RM. 2019. Surgery for endometriosis improves major domains of quality of life: a systematic review and meta-analysis. Journal of Minimally Invasive Gynecology 26:266–278.
Chen WY, Abatangelo G. 1999. Function of hyaluronan in wound repair. Wound Repair and Regeneration 7:79–89.
Darai E, Dubernard G, Coutant C, Frey C, Rouzier R, Ballester M. 2010. Randomized trial of laparoscopically assisted versus open colorectal resection for endometriosis: morbidity, symptoms, quality of life, and fertility. Annals of Surgery 251:1018–1023.
diZerega GS, Coad J, Donnez J. 2007. Clinical evaluation of endometriosis and differential response to surgical therapy with and without application of Oxiplex/AP* adhesion barrier gel. Fertility and Sterility 87:485–489.
Eskenazi B, Warner ML. 1997. Epidemiology of endometriosis. Obstetrics and Gynecology Clinics of North America 24:235–258.
Garry R, Clayton R, Hawe J. 2000. The effect of endometriosis and its radical laparoscopic excision on quality of life indicators. BJOG: An International Journal of Obstetrics and Gynaecology 107:44–54.
Hammoud A, Gago LA, Diamond MP. 2004. Adhesions in patients with chronic pelvic pain: a role for adhesiolysis? Fertility and Sterility 82:1483–1491.
Jansen RP, Russell P. 1986. Nonpigmented endometriosis: clinical, laparoscopic, and pathologic definition. American Journal of Obstetrics and Gynecology 155:1154–1159.
Pang J, Jiang P, Wang Y, Jiang L, Qian H, Tao Y, et al. 2018. Cross-linked hyaluronan gel inhibits the growth and metastasis of ovarian carcinoma. Journal of Ovarian Research 11:2–8.
Jones G, Jenkinson C, Kennedy S. 2004. Development of the short form Endometriosis Health Profile questionnaire: the EHP-5. Quality of Life Research 13:695–704.
Laufer MR, Goitein L, Bush M, Cramer DW, Emans SJ. 1997. Prevalence of endometriosis in adolescent girls with chronic pelvic pain not responding to conventional therapy. Journal of Pediatric and Adolescent Gynecology 10:199–202.
Liu C, Lu Q, Zhang Z, Xue M, Zhang Y, Zhang Y, et al. 2015. A randomized controlled trial on the efficacy and safety of a new cross-linked hyaluronan gel in reducing adhesions after gynecologic laparoscopic surgeries. Journal of Minimally Invasive Gynecology 22:853–863.
Mabrouk M, Spagnolo E, Raimondo D, D'Errico A, Caprara G, Malvi D, et al. 2012. Segmental bowel resection for colorectal endometriosis: is there a correlation between histological pattern and clinical outcomes? Human Reproduction 27:1314–1319.
Marqui AB. 2015. Evaluation of endometriosis-associated pain and influence ofconventional treatment: a systematic review. Revista da Associação Médica Brasileira 61:507–518.
Minas V, Dada T. 2014. Laparoscopic treatment of endometriosis and effects on quality of life: a retrospective study using the short form EHP-5 endometriosis specific questionnaire. Journal of Obstetrics and Gynaecology 34:336–340.
Rakhila H, Al-Akoum M, Bergeron ME, Leboeuf M, Lemyre M, Akoum A, et al. 2016. Promotion of angiogenesis and proliferation cytokines patterns in peritoneal fluid from women with endometriosis. Journal of Reproductive Immunology 116:1–6.
Ribeiro PA, Sekula VG, Abdalla-Ribeiro HS, Rodrigues FC, Aoki T, Aldrighi JM. 2014. Impact of laparoscopic colorectal segment resection on quality of life in women with deep endometriosis: one year follow-up. Quality of Life Research 23:639–643.

Selcuk S, Sahin S, Demirci O, Aksoy B, Eroglu M, Ay P, et al. 2015. Translation and validation of the Endometriosis Health Profile (EHP-5) in patients with laparoscopically diagnosed endometriosis. European Journal of Obstetrics & Gynecology and Reproductive Biology 185: 41–44.

Singh SS, Suen MW. 2017. Surgery for endometriosis: beyond medical therapies. Fertility and Sterility 107:549–554.

Sintonen H. 2001. The 15D instrument of health-related quality of life: properties and applications. Annals of Medicine 33:328–336.

Tanmahasamut P, Rattanachaiyanont M, Angsuwathana S, Techatraisak K, Indhavivadhana S, Leerasiri P. 2012. Postoperative levonorgestrel-releasing intrauterine system for pelvic endometriosis-related pain: a randomized controlled trial. Obstetrics & Gynecology 119:519–526.

Vercellini P, Viganò P, Somigliana E, Fedele L. 2014. Endometriosis: pathogenesis and treatment. Nature Reviews Endocrinology 10:261–275.

Wiseman DM, et al. 2000. Adhesion prevention: past the future. In: DiZerega GS, DeCherney AH, Diamond M, et al, editors. Peritoneal surgery. New York (NY): Springer-Verlag. p. 401–417.