Systematic Review

Comparing the Efficacy of Surgery and Medical Therapy for Pain Management in Endometriosis: A Systematic Review and Meta-analysis

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Background: Pain is considered as one of the main symptoms of endometriosis. The treatment for endometriosis remains controversial.

Objectives: The aim of this study is to compare the effect of medical or surgical treatments for pain-relief in patients with endometriosis.

Study Design: Systematic review and meta-analysis.

Setting: Published papers about evaluating pain treatment in endometriosis in PubMed, Scopus, and Google Scholar.

Methods: After searching all studies evaluating pain treatment in endometriosis in PubMed, Scopus, and Google Scholar, there were 23 related studies, containing 1,847 patients enrolled in our study. We used a variety of tests: fixed and random effects models, Q Cochrane test and I2 index, Egger and Begg tests, forest and funnel plots, Trim and fill method, and meta-regression in our analysis.

Results: There was no statistically significant difference in pain improvement between surgical and medical treatment. Interestingly, pain relief was more prominent longer after treatment. Both clinical trials and cross sectional studies showed higher improvement in pain than cohort studies. High quality studies and lower body mass index (BMI) had a greater effect on pain relief. All studies were heterogeneous, but there was no publication bias.

Limitations: There was a higher probability of risk of bias in blinding, random sequence generation, and selective outcome reporting in clinical trial studies entered in our meta-analysis.

Conclusions: Our results could not demonstrate the preference of each medical or surgical treatment effect for dysmenorrhea in endometriosis. Additional data is required before a standardized medical protocol can be offered, but we believe this study may encourage clinicians to consider a less invasive alternative for treating their patients' chronic pelvic pain in the near future.

Key words: Endometriosis, pain, meta-analysis, therapy, disease management

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Endometriosis is an inflammatory, estrogen-dependent condition in which tissue that normally grows inside the uterus grows outside it (1). About 20 – 25% of women with endometriosis have no symptoms (2). Pelvic pain and infertility are considered the main symptoms (3,4).

In a study conducted by Abbas et al in Germany (5), the standardized prevalence and incidence rates of endometriosis were 8.1 and 3.5 per 1000 women, respectively. Also, according to their results, the highest prevalence was observed in women aged 35 to 44 with 12.8 per 1000 women. Endometriosis is a relatively prevalent disease with 10% frequency among women of reproductive age (6). Based on a systematic review study, the overall prevalence of visually confirmed endometriosis is 62% in all adolescent girls undergoing laparoscopic investigation due to chronic pelvic pain (7).

The prevalence of chronic cyclical pelvic pain (CCPP) in the general population was found to be very high (14.7% to 24%) in women aged 18 to 49 (8,9).

The goal of treatment in women of reproductive age is to provide pain relief and to restrict the progression of the process and to restore or preserve fertility where indicated (2). Depending upon the patient situation, several treatment modalities may be used to manage endometriosis: hormonal and pain medication for a woman who is still fertile or a combination of surgery and fertility treatment after surgery for an infertile woman (10). The long list of different medications (11) shows that there is no definite cure for endometriosis yet.

In general, medicinal and surgical interventions produce approximately comparable pain relief benefits, and recurrence of pain was found to be 53% and 44% with surgical and medicinal interventions, respectively (12). Although, each approach has strengths and limitations, there is insufficient evidence on the efficacy of medication for relieving pain associated with endometriosis.

As mentioned above, there are many approaches to treatment for pain in endometriosis. One of the most important concerns is the ovarian damage caused by the surgery and the recurrent nature of the disease. In addition, determining the efficacy of each approach used for relieving endometriosis-associated pain needs to be addressed. Therefore, it seems that we need to do studies with high levels of evidence in this context for selecting the best treatment approach.

The intent of this systematic review is to compare the results of medicinal intervention versus surgical procedures in treating pain in endometriosis. Potential confounding factors were also identified during this meta-analysis.

Methods

Search Strategy

We systematically reviewed PubMed, Scopus, and Google Scholar with different combinations of these words: endometriosis AND pain AND (treatment OR therapy OR surgery) on May 3, 2014. We found 6,717 papers. There were 931 duplicate papers which were deleted. After reading titles and abstracts, a total of 476 related papers remained. We contacted with authors for regarding their information in some papers when we did not find their full texts. Review of full texts showed only 114 papers related to our interest (Fig. 1). Two trained reviewers (KR and MM) evaluated and selected studies independently. Any disagreement was assessed by both and if a consensus was not reached, a third author (AK) evaluated the study. Two independent reviewers (AK and SC) extracted data according to a predefined Excel sheet which was prepared by all authors. Moreover, quality assessment (using STROBE and CONSORT according to the type of study) and risk of bias (using Newcastle Ottawa form) were also determined by the same data extractor for each study. A data extraction form was created based on group discussion, and was piloted according to 10 different types of studies. Then, it was modified and used by the data extractor. Some small changes were also made in the data extraction form during data extraction after confirming with the research team. Such added/modified variables were again filled/corrected for previous extracted studies. We considered 20 common studies for both data extractors and computed kappa, which was more than 96% for all variables.

Eligibility Criteria

Our eligibility criteria included any trial (every type), cohort, case-control, cross-sectional, and case series/report study or even papers of review articles or final original selected papers enrolling women with endometriosis-related pain undergoing any medical or surgical procedure evaluating pain as their primary or secondary (accessory) outcome. We included women with any stage or severity of endometriosis, diagnosed by visualization (for example laparoscopy or laparotomy) or suspected diagnosis based on the history and pelvic examination, and other tests such as ultrasound

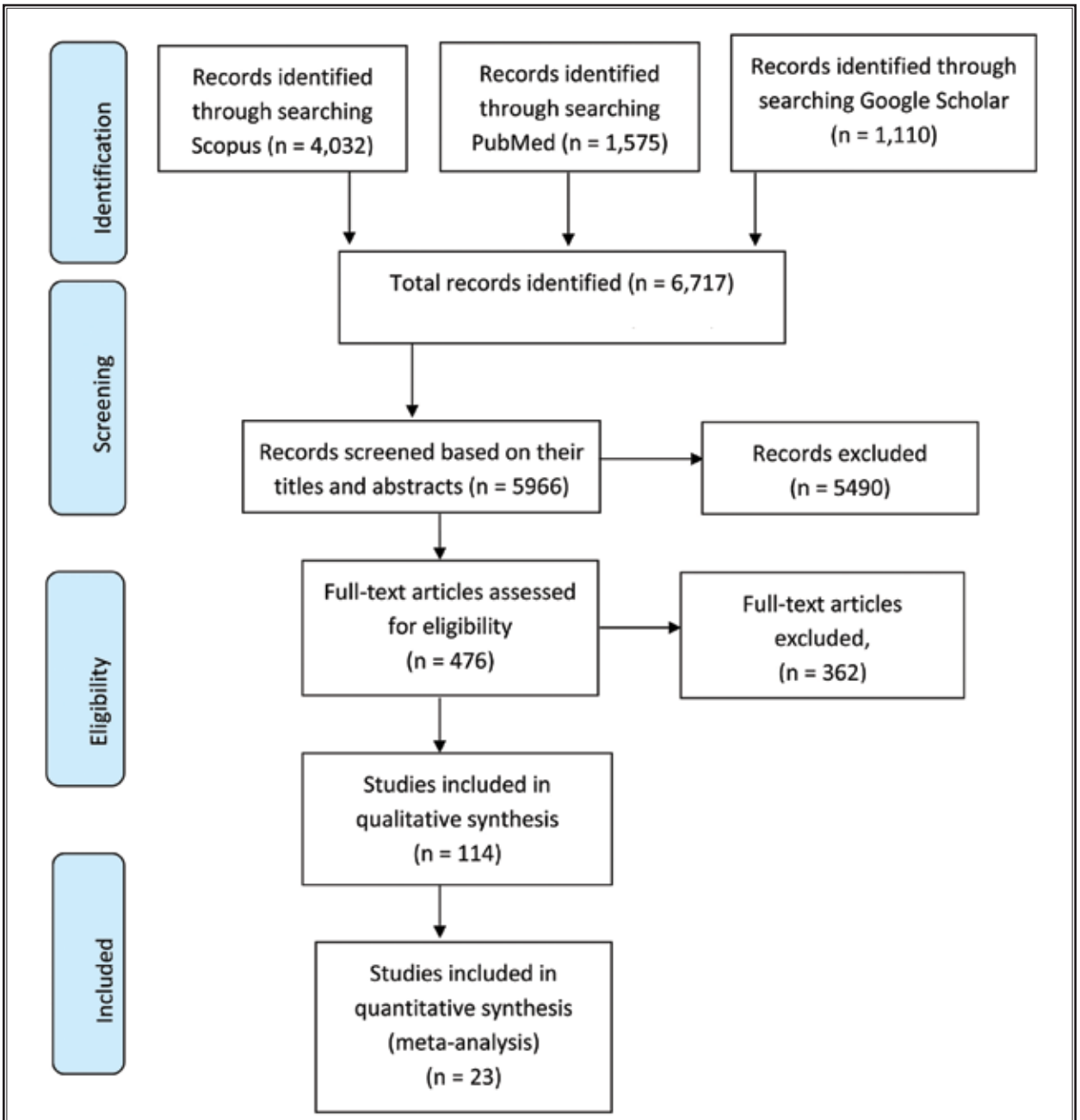

Fig. 1. *Searched and selected studies for systematic review of treatment of pain in endometriosis.*

and magnetic resonance imaging (MRI). We excluded all studies with more than 20% loss to follow-up or studies on women with chronic pelvic pain due to other specific known causes. Participants were women over 18 years old. At least one of the following outcomes had to be measured for a study to be included: pain relief (measured by visual analogue scale [VAS], other validated scales or as a dichotomous outcome, for example improved or not improved), unintended effects of treatment (duration and type of side effects), propor-

tion of satisfaction with treatment, and proportion of requiring more treatment. There was not any limitation in language of selected papers.

Variables

The following characteristics were assessed: type of study; presence and type of randomization; allocation concealment; different sources of selection and information bias, and percentage of loss to follow-up; study design in trials; date of the study (not the year of publication); sample size of the treatment and control group; age; ethnicity; marital status; stage of endometriosis; body mass index (BMI); American Fertility Society (AFS) scores from laparoscopy; pain measurement tool; pain score at baseline and after treatment; type of endometriosis; endometriosis diagnostic criteria; inclusion and exclusion criteria; types of interventions in each group; types of treatments (medical or surgery); type, dose, and duration of pain medication (such as nonsteroidal anti-inflammatory drugs [NSAIDS] and opioids); type, dose, and duration of hormone therapy (oral contraceptives, progesterone and progestin, GnRH agonists, Danazol); type of surgical treatment (laparoscopy or laparotomy); need for supplementary analgesia; unintended effects of treatment; reoperation; and recurrence of pain, if any.

According to the European Society of Human Reproduction and Embryology (ESHRE) guideline, dysmenorrhea is the most prevalent clinical symptom and the most important predictive factor of endometriosis; therefore, in this study we only evaluated dysmenorrhea. Data about other types of pain (deep dyspareunia and non-cyclic chronic pelvic pain) were extracted and will be evaluated in our future studies, but not in the present manuscript.

Data Synthesis

All pain scores, before and after treatment, were recalculated in a range of values between 0 and 10.

Data Analysis

Our main summary measure was mean difference of pain, which was calculated by subtracting the after treatment score from its previous value.

We considered quality score of the included papers in analysis for assessment of subgroup analysis based on their quality. Risk of bias was also used for determining the probability of bias in determining measurements and outcome in studies entered in our meta-analysis. Each study was considered low risk of bias if all key domains were low risk of bias. Definition of unclear and high risk of bias for each individual study is based on unclear or high risk of bias for at least one key domain of the risk of bias assessment form (13).

Mean and standard deviation (SD) were used to describe quantitative variables with normal distribution. We used fixed and random effects models based on the absence or presence of heterogeneity, respectively. Heterogeneity was assessed using the Q Cochrane test and I2 index. A forest plot was implemented for showing results of the individual and pooled effect of all studies. Egger and Begg tests and a funnel plot were used for evaluating the presence of publication bias. The trim and fill method was also used for overcoming the publication bias. Different subgroup analyses were implemented for finding different sources of heterogeneity. Sensitivity analysis was done for determining the effect of risk of bias on the value of pain relief after treatment in various studies. Meta-regression was also used for finding the most important independent factor in evaluation of response to pain relief treatments while omitting the confounder effect of other variables. *P*-values of all statistical tests were considered significant at 0.05 except for the Q Cochrane, meta-regression, Begg and Egger tests, which were set at less than 0.1. All statistical tests and figures were implemented using Stata12.0 (STATA Corp. LP).

Results

Main and Subgroup Analyses

Twenty-three studies with 40 arms, consisting of 1,847 cases were enrolled in our analysis (14-36). The studies described different stages of endometriosis. The patients mean (SD) age, and BMI was 31.6 (3.2) and 24.9 (2.0) kg/m^2, respectively. Among these 23 studies, there were 7 (14-20) and 16 (21-36) studies with surgical and medical treatments, respectively. The numbers of arms with surgical and medical treatment were 12 and 28, respectively. Most of studies were trials and were of high quality but also had a high risk of bias (Table 1).

There was no statistically significant difference in pain improvement between surgical and medical treatments, although the results with the surgical approach were slightly better for patients (Table 2). Interestingly, this minimal difference between these 2 methods decreased as the time of follow-up increased.

Both clinical trials and cross sectional studies showed a higher improvement in pain than cohort studies. However, clinical trials and cross sectional stud-

Table 1. *Basic characteristics of the included studies in meta-analysis.*

Author, median year of doing study, treatment modality	Type of study	Sample	Total risk of bias	Quality percentage
Keltz MD, 1996, Paracolic Adhesions Lysed vs Not Lysed	CT	25	U	78.8
Kaser DJ, 2001, Norethindrone Acetate	CT	194	U	58.3
Alborzi S, 2003, Pentoxifylline vs Placebo	CT	88	U	84.8
Bayoglu Tekin Y, 2006, Gosareline Acetate vs Levonorgestrel-Releasing Intrauterine System	CT	40	H	78.8
Deng S, 2006, Levonorgestrel-Releasing Intrauterine System	CT	33	H	63.6
Diamond MP, 2008, Elagolix 250 mg vs 150 mg Daily vs Placebo	CT	155	H	72.7
Koninckx PR, 2008, Infliximab	CT	21	U	75.8
Wayne PM, 2008, Acupuncture vs Placebo	CT	18	H	69.7
Carr B, 2009, Elagolix 150 mg daily vs Placebo	CT	137	H	72.7
Ferrero S, 2009, Letrozole and Norethisterone Acetate vs Norethisterone Acetate	CT	82	U	81.8
Strowitzki T, 2010, Leuprolide Acetate vs Dienogest	CT	252	H	93.9
Rubi-Klein K, 2010, Non-Specific Acupuncture vs Verum-Acupuncture	CT	101	U	72.7
Muzii L, 2011, Cyclic vs Continuous Estroprogestins	CT	57	U	72.7
Wickstrom K, 2012, Pertubation with Lignocaine vs Ringer	CT	34	H	90.9
Maia Jr H, 2013, Gestodene/Ethinylestradiol Alone or with Pycnogenol vs Drospirenone/ Ethinylestradiol Alone or with Pycnogenol	CT	45	U	60.6
Ott J, 2010, Laparoscopic Ventrosuspension	CS	63	H	87.9
Kapural L, 2006, Spinal Cord Stimulation	CS	6	L	63.9
Ferrero S, 2010, Norethisterone Acetate	C	40	U	72.2
Meissner K, 2010, Systemic Autoregulation Therapy	C	47	L	91.7
Hidaka T, 2012, Removal of Deep Endometriotic Lesion vs Adhesionotomy and Cystectomy	C	198	L	72.2
Morelli M, 2013, Estradiol Valerate with Dienogest vs Levonorgestrel-Releasing Intrauterine-Device	C	92	L	86.1
Madny EH, 2013, Letrozole	C	20	U	86.1
Berner E, 2013, Laparoscopic Supracervical Hysterectomy	C	113	L	55.6

C: cohort, CS: cross sectional, CT: clinical trial, H: high, L: low, Ref: reference, U: unclear

ies demonstrated no difference (Table 2). Interestingly, pain relief improved the longer the follow-up in all situations (Table 2). Type of treatment, qualitative quality of the paper (low: < 40%, middle: 40 – 70%, and high: ≥ 70%), previous surgery for endometriosis, previous medical treatment for endometriosis, and continent were not significant factors for pain relief in cases with endometriosis (Table 2). All studies were heterogeneous even in different subgroups (Table 2). There was no temporal pattern for reducing pain with different lengths of follow-ups (3 – 24 months after treatment).

Meta-regression

Our meta-regression showed that among all quantitative variables, percentage of quality of studies and BMI were related to our main outcome (difference of pain in different visits [3-6, 6-12, and 12-24 months] from baseline) in univariate analysis. High quality studies and lower BMI indicated a higher effect on pain relief (Table 3). Multivariable meta-regression showed that neither of these 2 variables are predictors of this outcome. Mean age and percentage of cases with stage 1, 2, 3, or 4 were not related to variance in pain during different visits (3-6, 6-12, and 12-24 months) from baseline. This may be due to the low number of studies in each treatment option with cases with different stages of endometriosis. So, none of studied variables could explain the source of heterogeneity except quality of studies and BMI. Since, there were different types of medical or surgical treatments, probably the main source of high heterogeneity in this study, we separately compared the effect of each therapeutic regimen on dysmenorrhea-related pain. The order of treatment effect from the most to the least effective option 3 – 6 months after treatment is pertubation with lignocaine, alternative medicine, spinal cord stimulation, hysterec-

Table 2. *Subgroup analyses of pain relief in cases that received treatment for endometriosis with different follow-up times.*

		Difference of diffuse pain from baseline after 3 – 6 months from treatment		Difference of diffuse pain from baseline after 6 – 12 months from treatment		Difference of diffuse pain from baseline after 12 – 24 months from treatment	
		Value*	Heterogeneity, § Sig	Value*	Heterogeneity, § Sig	Value*	Heterogeneity, § Sig
Type of treatment	Medication	-3.6 (-4.3, -2.9)	100, < 0.001	-4.9 (-5.8, -3.9)	100, < 0.001	-5.0 (-5.9, -4.0)	100, < 0.001
	Surgery	-4.5 (-5.4, -3.6)	100, < 0.001	-5.0 (-6.3, -3.8)	100, < 0.001	-5.2 (-6.0, -4.4)	100, < 0.001
Quality of paper	≥ 70%	-3.8 (-4.5, -3.1)	100, < 0.001	-4.4 (-5.8, -2.9)	100, < 0.001	-4.5 (-6.1, -3.0)	100, < 0.001
	40 – 70%	-4.3 (-5, -3.5)	99.8, < 0.001	-6.5 (-7.6, -5.4)	100, < 0.001	-6.4 (-7.5, -5.4)	100, < 0.001
Previous surgery for endometriosis	Yes	-2.9 (-3.6, -2.3)	100, < 0.001	-3.6 (-5.7, -1.5)	100, < 0.001	-4.0 (-5.8, -2.3)	100, < 0.001
	No	-5.3 (-7.4, -3.2)	99.4, < 0.001	-5.3 (-7.4, -3.2)	100, < 0.001	-5.3 (-7.4, -3.2)	99.4, < 0.001
Previous medical treatment for endometriosis	Yes	-5.2 (-5.6, -4.9)	78.9, < 0.001	-8.8 (-10.2, -7.3)	96.6, < 0.001	-8.8 (-10.2, -7.3)	96.3, < 0.001
	No	-5.3 (-7.4, -3.2)	99.4, < 0.001	-5.3 (-7.4, -3.2)	99.4, < 0.001	-5.3 (-7.4, -3.2)	99.4, < 0.001
Continent	America	-3.3 (-4.2, -2.4)	100, < 0.001	-5.8 (-6.4, -5.2)	100, < 0.001	-6.5 (-7.1, -6.0)	100, < 0.001
	Europe	-4.8 (-5.7, -3.8)	100, < 0.001	-4.9 (-6.0, -3.7)	100, < 0.001	-4.4 (-5.8 -3.1)	100, < 0.001
	Asia	-3.3 (-5.0, -1.6)	100, < 0.001	-3.6 (-8.3, 1.1)	100, < 0.001	-4.4 (-8.2, 0.5)	100, < 0.001
	Middle East	-2.2 (-3.1, -1.4)	100, < 0.001	-2.2 (-3.1, -1.4)	100, < 0.001	-2.2 (-3.1, -1.4)	100, < 0.001
	Africa	-1.6 (-1.7, -1.4)	-	-3.6 (-3.8, -3.5)	-	-7.6 (-7.8, -7.5)	-
Study design	Clinical trial	-4.2 (-4.9, -3.5)	100, < 0.001	-5.3 (-6.2, -4.3)	100, < 0.001	-4.6 (-5.6, -3.7)	100, < 0.001
	Cohort	-2.5 (-3.4, -1.6)	100, < 0.001	-3.2 (-4.7, -1.8)	100, < 0.001	-5.8 (-6.9, -4.8)	100, < 0.001
	Cross sectional	-4.7 (-4.8, -4.6)	62.7, 0.101	-7.2 (-8.7, -5.8)	96.4, < 0.001	-7.2 (-8.7, -5.8)	96.1, < 0.001

*: mean difference (95% confidence interval), §: I^2 percentage

Table 3. *Univariate meta-regression of quantitative variables for evaluating their relationship with pain relief in cases that received treatment for endometriosis.*

Dependent variable	Independent variable	Beta	Standard error	Sig.
Difference of diffuse pain from baseline after 12 – 24 months from treatment	Quality of studies (%)	0.15	0.05	0.010
	BMI (kg/m2)	-2.0	.75	0.022

tomy, ventrosuspension, hormonal treatment, surgery in combination with paracolic adhesiolysis, placebo, removal of deep endometriotic lesion, immunologic drugs, and adhesiotomy in combination with cystectomy; their effect ranging from 7.36 to 1 score decrease in pain, a wide range of treatment effect. Relatively similar patterns were also found after 6 – 12 and 12 – 24 months of follow-up.

Publication Bias

There was no publication bias according to the Begg and Egger test and funnel plot in evaluating the effect of medical or surgical treatment of endometriosis for reducing pain in the first and third follow up period. However, pain relief in the second follow-up period showed publication bias ($P = 0.026$). After running the meta trim and fill method for correcting this bias, the results did not change.

Risk of Bias

Clinical trial studies were at risk of bias more than cohort and cross sectional studies (Figs. 2 and 3). There was a higher probability of risk of bias in blinding, random sequence generation, and selective outcome reporting in clinical trial studies entered in our meta-analysis. Among the 23 studies included in the quantitative synthesis, 6 studies had at least 2 parts with high risk of bias, meaning that there was 26.1% of risk of

bias in the included published studies in our meta-analysis.

According to risk of bias, the sensitivity analysis showed that studies with low and high risk of bias have the highest and lowest improvement in pain. However, these differences were not statistically significant (data are not shown).

Discussion

In this systematic review and meta-analysis, there was no statistically significant difference between surgery and medical therapy in the treatment of pain in all stages of endometriosis. Also, the results of this analysis showed that there were some differences in results based on study design. Studies with clinical trial and cross sectional designs had a higher improvement in pain in comparison with cohort studies, but clinical trials and cross sectional studies showed no difference. Apart from the disparities in results from the differently designed studies, since the analysis of diffuse pain from baseline was carried out in 3 follow-up periods (3 – 6, 6 – 12, and 12 – 24 months), the results indicated that relief of endometriosis-associated pain was better after longer follow-up periods in all situations. These results were also reported in some earlier studies (12,37-39). Interestingly, the difference between medical and surgical methods decreases with the length of the follow-up period. One failure of most studies is that the time to conclude that treatment was successful is relatively short. This fits with the data here

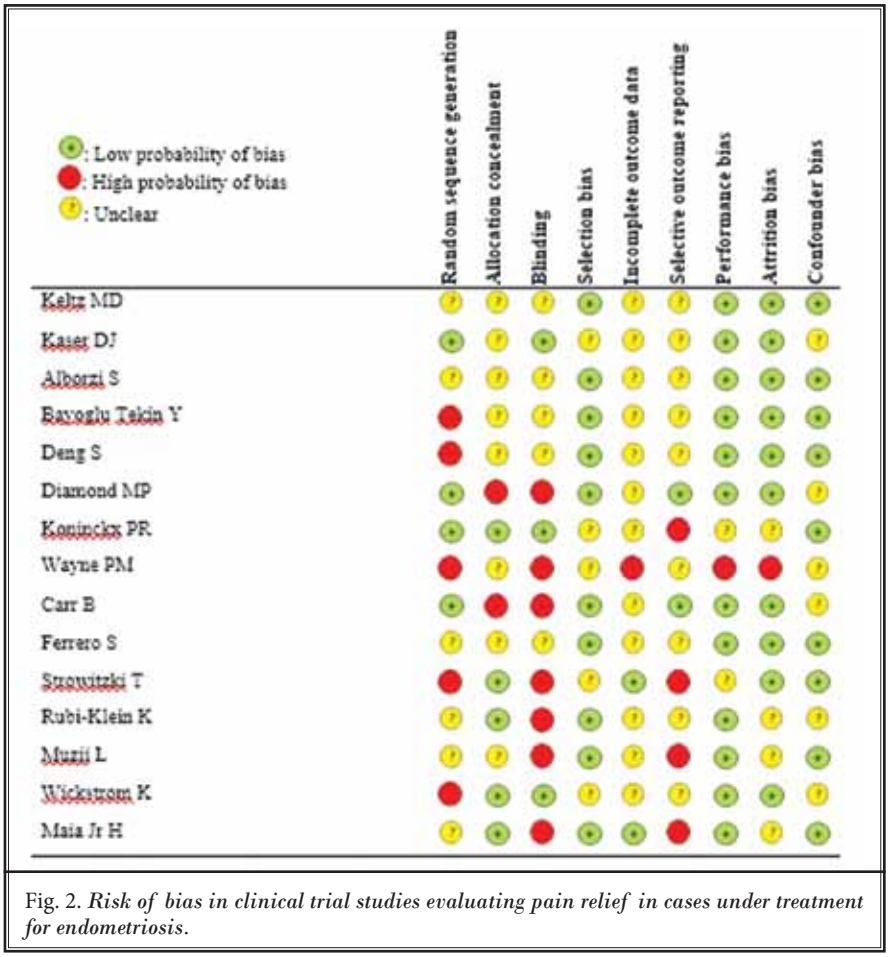

Fig. 2. *Risk of bias in clinical trial studies evaluating pain relief in cases under treatment for endometriosis.*

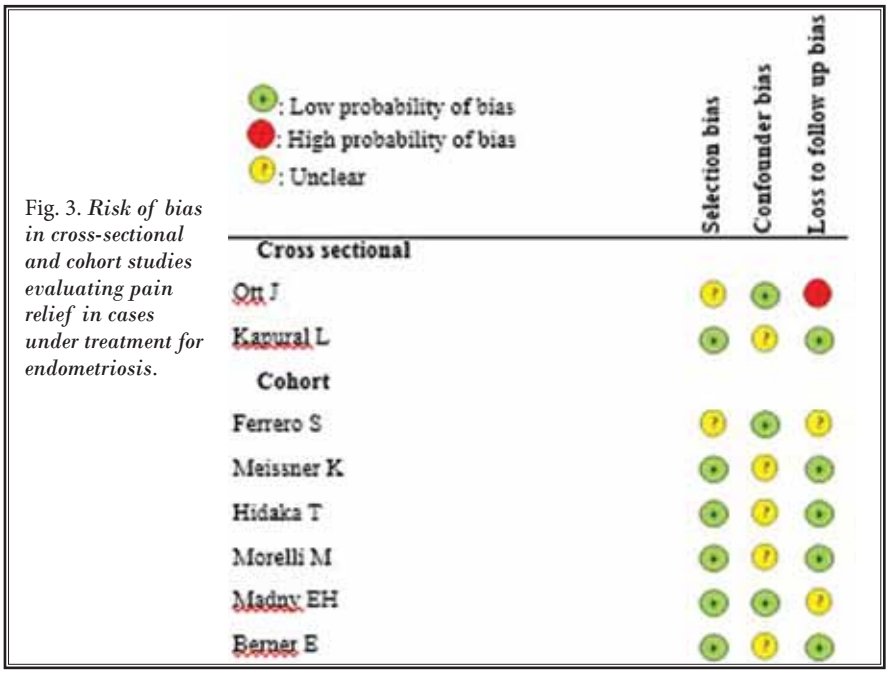

Fig. 3. *Risk of bias in cross-sectional and cohort studies evaluating pain relief in cases under treatment for endometriosis.*

that suggest that success had the lowest rate in cohort studies compared to cross-sectional ones. In addition, most studies have a fatal flaw, most likely evidenced by the observation of greater pain relief after longer follow-up. None of these studies implemented methods for systematically tracking all patients. Thus, only those patients still in contact with their treating clinician are included in the analyses, and these patients are most often those returning with a complaint of lack of pain remediation. In all of these studies, those lost to follow-up were considered to be cured, when in fact, a portion of them – perhaps a sizable portion – will seek treatment from another clinic or give up on medical intervention altogether. However, we did not find any difference between medical and surgical treatment groups on this issue.

Another important result of this study was that the assessment of potentially influential factors in endometriosis, such as type of treatment, previous surgery or medical treatment for endometriosis, and continent, had no significant effect on pain relief. Improvement in pain was more associated with the follow-up period than other factors. In a study conducted by Harris et al (40), it was mentioned that the greater predicted plasma 25 (OH) D levels and higher intake of dairy foods are associated with a decreased risk of endometriosis. In another study by Latthe et al (41), pelvic inflammatory disease, previous caesarean section, drug or alcohol abuse, miscarriage, heavy menstrual flow, pelvic pathology, physical abuse, and psychological comorbidity were associated with an increased risk of non-cyclical pelvic pain.

With our current knowledge, medical treatment is one of the main options of chronic pelvic pain, especially because we may use it recurrently, with different drugs, and in many situations, such as in adolescent patients, before and after surgical treatments, for the prevention and treatment of recurrent disease, and during postpartum period with no fear of loss of ovarian function; however, few studies, specifically randomized clinical trials (RCTs), have evaluated this method (42-45). Moreover, there are many confounders such as side effects associated with medications in RCTs comparing different agents. In previous studies, placebo effects have been reported in 40% to 45% of cases (46). These findings lead to difficulties in assessing the success of medical treatments. Our meta-regression indicated that a higher BMI is associated with a lower response to pain-relief therapy. Previous studies have shown that higher BMI is associated with metabolic diseases. So, medical treatment should be used cautiously because of changes in blood pressure and lipid profile with steroid hormones. Surgery may seem safer in cases with metabolic diseases or concomitant related diseases precipitated by medical therapy. Steroid therapy should be avoided in cases with higher BMI. Moreover, the risk of surgery in women with a high BMI should not be underestimated.

In addition to drug therapy procedures, there are other approaches for dealing with endometriosis-related pain, including surgical procedures (4,12,47). Apart from some of the advantages of surgical methods, such as definite diagnosis, long-term cure, and no need to use medications in some cases, they have several disadvantages, including risks associated with surgeries, higher expenses, recurrence of endometriosis (in 30% of cases that had laparoscopy), and decrease in ovarian reservoir and infertility (48). In addition, the outcome of either surgery or medication in patients with endometriosis pain is influenced by psychological factors related to personality, marital, and psychosexual issues. Because of these varying factors, it is difficult to evaluate the real difference between surgical or medical methods.

There are many treatment methods to deal with endometriosis pain. Prior studies suggest that avoiding repeated surgical procedures and maximizing the use of medical treatments are essential principles (3,49-51). Even though the use of hysterectomy and bilateral salpingo-oophorectomy are acceptable treatments for endometriosis, they must be reserved for women with debilitating symptoms and failure of previous therapies who have completed their family (52).

High quality studies and studies with lower risk of bias showed an increased effect on pain improvement that may be due to the low quality papers having weak pain assessment and obscure differences before and after intervention, or between different methods.

Limitation

There is a methodological concern specific to those studies that began as an RCT for infertility treatment but then the cohort of participants was later analyzed with pain as the outcome. For most of these, the statistical analyses continued to treat the study design as an RCT because the treatment at baseline was randomized. However, the goal was pregnancy. In the case of effective treatment, then the treated arm would have a higher proportion of parous women than the untreated arm. We know that pregnancy and lactation are ben-

eficial for endometriosis-associated pain. Therefore, to evaluate the association between treatment and pain, the study must be analyzed as a non-randomized prospective cohort study and apply methods to account for confounding – including confounding by parity and lactation. Those studies have not been considered and we unfortunately have no access to their main data.

Conclusion

In general, our study results could not demonstrate a definite preference for a medical or surgical treatment approach. We further noticed that the gap between these 2 treatment modalities was even smaller if we continued our study for a longer duration. Although, our study shows some significant differences between some modalities like pertubation with lignocaine or alternative medicine which claim that they are superior to removal of deep endometriotic lesion, immunologic drugs, or adhesiolysis in combination with cystectomy, the number of studies for a precise conclusion is very low. As figures show, when the number of studies is higher there is a tendency of the total effect to be centralized to the mean. We understand that additional data is required before a standardized medical protocol can be reached, but we believe this manuscript will provide our colleagues a data set that may encourage them consider a less invasive alternative for treating their patients' pain in the near future, considering only effectiveness of the treatment, irrespective of side effects and costs. Therefore, further studies specifically those with a randomized clinical trial design, are required to better clarify the differences between surgical and medical treatment for chronic pelvic pain therapy. Our multivariable meta-regression showed that age, stage of endometriosis, and previous medical/surgical treatment for endometriosis were not related to pain relief. High quality papers with lower risks of bias in patients with lower BMI showed better response to pain treatment in our meta-analysis.

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