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Endometriosis is a painful condition caused by displaced cells from the lining of the womb, causing inflammation and scarring inside the body. It affects 6-10% of women and there is no permanent cure. Medical and laparoscopic surgical treatments are available, but about 28% of patients do not get the hoped-for pain relief after surgery.
Currently there is no way of predicting who gets better and who does not. We systematically searched the world literature to establish who may get better, in order to improve counselling when women choose treatment options. We identified 5 studies of variable quality showing: More complex disease (in specialist hands) responds better to surgery then less, but more studies needed.

Systematic review of patient-specific pre-operative predictors of pain improvement to endometriosis surgery

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Running title: Success of endometriosis surgery

Twitter: #SystematicReview of endometriosis surgery: more complex disease responds better to surgery then less, but more studies needed

Abstract

Background: Up to 28% of endometriosis patients do not get pain relief from therapeutic laparoscopy but this subgroup is not defined.

Objectives: To identify any prognostic patient-specific factors (such as but not limited to patients' type or location of endometriosis, sociodemographics and lifestyle) associated with a clinically meaningful reduction in post-surgical pain response to operative laparoscopic surgery for endometriosis.

Search strategy: PubMed, Cochrane and Embase databases were searched from inception to 19th May 2020 without language restrictions. Backward and forward citation tracking was used.

Selection criteria, data collection and analysis: Cohort studies reporting prognostic factors, along with scores for domains of pain associated with endometriosis before and after surgery, were included. Studies that compared surgeries, or laboratory tests, or outcomes without stratification were excluded. Results were synthesised but variation in study designs and inconsistency of outcome reporting precluded us from doing a meta-analysis.

Main results: Five studies were included. Quality assessment using the Newcastle Ottawa Scale graded three studies as high, one as moderate and one as having a low risk of bias. Four of five included studies separately reported that a relationship exists between more severe endometriosis and stronger pain relief from laparoscopic surgery

Conclusion: Currently there are few studies of appropriate quality to answer the research question. We recommend future studies report core outcome sets to enable meta-analysis.

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Introduction

Endometriosis is a chronic inflammatory condition affecting 6–10% of women of reproductive age, defined by the presence of endometrial-like tissue outside the uterus, commonly affecting the peritoneum, ovaries and other pelvic organs (Viganò et al., 2004).

Endometriosis impacts on many aspects of daily life and is associated with considerable costs to health services and society (Simoens et al., 2012). Commonly, women with endometriosis experience infertility and fatigue as well as pain, the latter often worsening during menses (dysmenorrhoea) and sexual intercourse (dyspareunia). In addition, pain may occur during bowel movements (dyschezia) or in a non-cyclical fashion.

There is no cure for endometriosis and current established treatments show an inconsistent response. Laparoscopic removal of endometriosis (therapeutic laparoscopy) remains the mainstay of treatment for endometriosis-associated pain (as described above) as a stand-alone intervention (Zanelotti and Decherney, 2017), after failure of or in conjunction with medical treatment (Duffy et al., 2014).

There is a distinction between diagnostic and therapeutic laparoscopies, and clinicians are advised to use a combined 'see and treat' approach for most cases (Ball et al., 2008). A recent meta-analysis (Leonardi et al., 2020), which included two studies also reviewed in this paper (Sutton et al., 1994, Abbott, 2004 #12), demonstrated that operative laparoscopy was more effective for pain relief at 6 months than diagnostic laparoscopy (n=102; RR 2.65; 95% confidence interval 1.61-4.34 p<0.001).

Unfortunately, between 20% (Abbott et al., 2004) and 28% (Sutton et al., 1994) of women with endometriosis pain do not respond to therapeutic laparoscopy (pre- and post-operative pain scores are not different), but it is not known which subgroup of women will respond and which will not. A recent meta-analysis (Leonardi et al., 2020) entitled "When to Do Surgery and When Not to Do Surgery for Endometriosis" failed to identify sufficient evidence to answer this question.

The location and the severity of endometriosis (commonly staged 1-4 using the revised American Fertility Society grading system (r-AFS)) (1985) may correlate with patients' symptoms (Fauconnier et al., 2002, Sinaii et al., 2008) and it could be hypothesized that these factors may also have prognostic value for treatment response.

If clinicians knew which subgroup of endometriosis patients benefitted from laparoscopic surgery, they would be better able to counsel their patients and manage their expectations. Access to therapeutic laparoscopy, which is a costly, limited resource associated with anaesthetic and surgical risks, could be better managed.

This review aims to determine which women will benefit from therapeutic laparoscopy for endometriosis.

Methods

A systematic review was performed using a prospectively registered protocol as part of a more extensive investigation (PROSPERO CRD42018108604, 04. sept. 2018) within the CRESCENDO project (peer and Patient and Public Involvement (PPI)-reviewed, NIHR PB-PG-0317-20018). Findings are reported in line with PRISMA guidelines. The search was performed on PubMed, Cochrane and Embase databases from inception to 19th May 2020 without language restrictions. At the time of protocol writing no relevant core outcomes were published, though one has since been developed (Duffy et al., 2020). In the absence of predictor variables associated with a favourable surgical outcome published in reviews or guidelines, we chose an inclusive search strategy. The search is detailed in appendix S1. A manual search of reference lists of included articles as well as backward and forward citation tracking supplemented the database search. When clarification on data was required, authors were also contacted.

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Two reviewers (EB and BK) screened titles and abstracts separately for eligible articles and reviewed the full-texts of these articles for final study selection. Disagreements were resolved by discussion between reviewers and with a third reviewer (JA).

Our interest was in prognostic factors that can be used to identify women most likely to experience pain relief from laparoscopic surgery for the treatment of endometriosis-related pain. Only patient-specific pre-operative factors were explored, surgery-specific factors were beyond the remit of this review, as the former would be the most relevant for patient counselling before surgery. Thus, our inclusion criteria, using the PECO format (Morgan et al., 2018), were:

Patients: Women with endometriosis

Exposure: Women, for whom the presence of any type of prognostic patient-specific factor was reported (this could be any sociodemographic, lifestyle and disease-related factors). We did not specify the prognostic factor before a priori, but approached the search with an open mind and recorded the prognostic factors that were available in the literature and where the pain outcomes were stratified by those predictors.

Comparison: Women without the prognostic factor of interest (e.g. parous women (exposure) nulliparous women (non- exposure))

Outcomes: Improved dysmenorrhoea, dyspareunia, non-cyclical pelvic pain and dyschezia or global pain reported after at least 6 months on the visual analogue score (VAS) or as ‘better’ or ‘improved’ versus ‘not better’ or ‘not improved’

Pain relief after surgery had to be reported stratified by the prognostic factor, to allow, if data were available, for the construction of a 4x4 table. This means that studies without a comparative element were not included.

We excluded: Recurrence and re-operation rates as measures for surgical outcomes, fertility outcomes, a postoperative follow up time of less than six months (the minimum the research

group agreed necessary to judge genuine surgical outcomes), studies comparing different surgical techniques, or laboratory tests as predictor variables, reports without predictor variables, abstracts, case reports, conference proceedings, and review articles.

EB and CM independently extracted the data on pre- and post-operative pain scores stratified by risk factors. EB and CR assessed the quality of studies using the Newcastle-Ottawa scale (Wells et al.).

Findings were reported as a qualitative synthesis due to a paucity of data and variation in reporting, which precluded meta-analysis.

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Results

Search results and risk of bias

The search returned 14 366 citations; additional backward and forward citation tracking returned one additional paper. After removal of duplicates 34 full-text papers were obtained. Of these, 29 were excluded after inclusion and exclusion criteria were applied (Figure 1; Table S1). We included five studies (n=606) (Chopin et al., 2005, Abbott et al., 2003, Milingos et al., 2006, Banerjee et al., 2006, Ghai et al., 2020), two retrospective (Chopin et al., 2005, Ghai et al., 2020), three prospective. All were from specialist clinics from the global north and included all endometriosis stages (study details Table 1).

Considering risk of bias for the five studies, one scored low (Chopin et al., 2005), one medium (Ghai et al., 2020), and four (Abbott et al., 2003, Banerjee et al., 2006, Milingos et al., 2006, Ghai et al., 2020) high using the Newcastle Ottawa tool (Table 2). While scoring highly in other domains, three studies scored low on 'comparability' which may be the result of poor reporting rather than poor study design.

We found reports which stratified postsurgical pain relief by disease severity and anatomical site. There were no reported data on the predictive role of sociodemographic factors (for instance age and parity).

Study participants

Chopin (Chopin et al., 2005) retrospectively reported data from a continuous series of women (age not stated) from a French university-affiliated hospital who reported pain (dysmenorrhoea, deep dyspareunia, chronic pelvic pain (CPP) or a pain combination) and deep endometriosis (DE) affecting at least a uterosacral ligament (USL). Of the 241 recruited women with laparoscopy-proven DE, 132 were included with complete follow-up. Only women with a histological lesion of $\geq$ 5mm depth were included.

Banerjee (Banerjee et al., 2006) recruited women (age not stated), with symptoms suggestive of endometriosis from CPP clinics in a district hospital with tertiary level endometriosis care.

One hundred and eight women were recruited; 88 women had histologically confirmed endometriosis, two women had no endometriosis. Of the 88 with endometriosis, 44 women had complete datasets and were analysed.

Milingos (Milingos et al., 2006) recruited 274 women with CPP of ≥ 6 months from university fertility and laparoscopy clinics, of whom 258 underwent laparoscopy, excluding women with pouch of Douglas obliteration or requiring hysterectomy. One hundred and one women were visually diagnosed with endometriosis during laparoscopy.

Abbott (Abbott et al., 2003) reported 254 women referred with pain symptoms suggestive of endometriosis to two specialist units of whom 132 were included in the analysis. The mean age was 31 years (20-48), 6% were nulliparous, 70% had required analgesia for pain and 73% had hormonal treatment. Seventy percent had at least one prior diagnostic or operative laparoscopy.

Ghai (Ghai et al., 2020) reported a secondary analysis of existing databases (Kent et al., 2014, Kent et al., 2016) of 198 women who had endometriosis surgery. In the group with severe endometriosis, 2.9% were converted to laparotomy. The authors do not report demographics but state no difference between responders and non-responders in age and stage of endometriosis within superficial and deep endometriosis (Ghai et al., 2020). Three studies recruited in England (Abbott et al., 2003, Banerjee et al., 2006) (Ghai et al., 2020) one in Greece (Milingos et al., 2006) and one in France (Chopin et al., 2005).

Authors state CPP as an indicator for surgery; one study also includes fertility (Ghai et al., 2020). In studies that stated the data (Chopin et al., 2005, Abbott et al., 2003), women averaged 31 years and a large proportion were childless (Table 1). Ethnicity and other sociodemographic factors were not reported. All studies reported dropouts (Table 1). In one study (Banerjee et al., 2006), this involved half of the women who had laparoscopically confirmed endometriosis. Apart from Banerjee (Banerjee et al., 2006), all other authors listed previous surgical and medical treatments (see Table 1).

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In all studies the aim was for complete laparoscopic endometriosis removal. The surgical approach depended on the depth and location. Milingos' [Milingos et al., 2006] described ablation of implants (not further specified), lysis of adhesions and excision of fibrosis / endometrioma. Six cases of 'frozen pelvis' were converted to open hysterectomy with bilateral oophorectomy and were excluded. Banerjee [Banerjee et al., 2006] described excision with monopolar diathermy; rectovaginal and bilateral USL lesions were removed en-bloc, ovarian endometrioma drained and excised, vaginal and bladder endometriosis fully excised and bowel endometriosis treated with shaving or disc resection. Chopin [Chopin et al., 2005] described a 'see and treat approach' and excision of all endometriosis lesions +/- ureterolysis. Endometrioma were excised; superficial implants were coagulated. Bladder and USL lesions were excised, and vaginal endometriosis was treated with laparoscopically–assisted resection. Intestinal lesions were treated by laparoscopy or laparotomy (n= 16 not further specified). Abbott [Abbott et al., 2003] reported a previously published excisional technique without hormonal pre-treatment [Garry et al., 2000]. Ghai [Ghai et al., 2020] described laser ablation or ultrasonic excision of superficial endometriosis. All DE patients had bowel involvement treated with bowel shaving, disc excision or anterior resection. Women received six months of reoperative gonadotropin-releasing hormone antagonist.

In two studies [Chopin et al., 2005, Milingos et al., 2006], a proportion of complex cases were either converted to or planned as laparotomies. Milingos [Milingos et al., 2006] excluded six cases due to conversion to open surgery.

Apart from Millingos [Milingos et al., 2006] and Ghai [Ghai et al., 2020], who included ablation of endometriosis, all others report histological confirmation. The duration of follow up ranged from 6 months [Milingos et al., 2006] to 9 years [Abbott et al., 2003]. Three studies scheduled follow up at a single timepoint: Milingos [Milingos et al., 2006] 6, Ghai [Ghai et al., 2020] 12 and Banerjee [Banerjee et al., 2006], at 18 months. Chopin [Chopin et al., 2005] reported a mean follow-up of 3.3 years (range 1.0-

9.1) and Abbott [Abbott et al., 2003] a mean follow-up of 3.7 years (range 2-5). Follow-up rates were 94% [Banerjee et al., 2006], 76% [Abbott et al., 2003], 72% [Ghai et al., 2020] for severe endometriosis, 54% [Chopin et al., 2005] and 52% [(Milingos et al., 2006)].

Dysmenorrhoea, dyspareunia, and also non-menstrual pelvic pain or CPP (used synonymously) were measured in all studies. Additional symptoms were menstrual and non-menstrual dyschezia, menstrual and non-menstrual backache and lower urinary tract symptoms. Apart from Ghai [Ghai et al., 2020] and Banerjee [Banerjee et al., 2006], researchers used the 10 cm VAS for pain. Banerjee used a 0-5 cm VAS for pain and calculated one global score for each participant. Milingos [Milingos et al., 2006] grouped the VAS results measured as 0 cm, 1-5 cm, 6-7 cm and 8-10 cm, when testing the correlation between pain and endometriosis severity. Furthermore, they created the binary measurement 'improved' vs 'non-improved' (reduction of ≥2 points) when comparing the post-operative pain reduction of minimal/mild with moderate/severe endometriosis. Ghai [Ghai et al., 2020] measured pain changes using the EPH-30 questionnaire, defining any pain decrease as improvement.

Endometriosis severity

Regarding endometriosis severity (Table 1), all studies included all endometriosis stages. The proportion of moderate and severe endometriosis combined is highest in Milingos 71.6% [Milingos et al., 2006], followed by Abbott 58% [Abbott et al., 2003] and Chopin [Chopin et al., 2005] and Banerjee [Banerjee et al., 2006], who both report 45%. Ghai [Ghai et al., 2020] reports DE (excluding moderate severity endometriosis) at 48%. The high proportion of severe endometriosis is likely due to recruitment from specialised centres. The two predictor variables by which outcomes were stratified were endometriosis severity and anatomical site. Within the group of severe endometriosis, Ghai [Ghai et al., 2020] reported higher pre-operative pain and lower feeling of control scores associated with response to surgery. Study results are shown in Table 6.

All five included studies reported endometriosis severity; four considered either AFS stages 1-4 [Chopin et al., 2005, Abbott et al., 2003] or depth of invasion (superficial / deep) in the relevant

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analysis (Banerjee et al., 2006) [Ghai et al., 2020]. Milingos [Milingos et al., 2006] dichotomised severity into minimal/mild (AFS scores < 16) and moderate/severe endometriosis (≥16), Ghai reported superficial (stage 1-3) versus severe disease (stage 4).

Endometriosis-related pain and disease severity

Abbott [Abbott et al., 2003] reported the median and interquartile ranges of the pre-operative and post-operative pain scores for different pain types and compared pain scores for endometriosis stage 1 to 4 before and after surgery. This study did not compare pain reduction before and after surgery between different stages of endometriosis (such as a test for trend). The reduction in dysmenorrhoea is consistently highly statistically significant ($p<0.001$) across all endometriosis stages, but women with stage 4 endometriosis showed the highest magnitude in pain reduction across the pain types (dyspareunia <0.0001, non-menstrual pelvic pain <0.0001, dyschezia 0.002). Other stages, while still showing significant reduction in pain (Table 2) showed lower levels of statistical significance. Only patients with stage 3 endometriosis showed no evidence of pain reduction from dyschezia ($p=0.12$).

Milingos [Milingos et al., 2006] reported higher pre-operative scores for dysmenorrhea and dyspareunia in moderate/severe (group 2) than minimal / mild endometriosis (group 1) ($p = 0.014$ and $p < 0.0001$ respectively). The authors compared changes in pain scores pre- to post-operatively in two analyses. Firstly, 'change in pain score' was depicted graphically for minimal/ mild and moderate/severe endometriosis. Without providing numerical data, the authors reported the magnitude for pain score reduction for dyspareunia to be higher in the group with moderate/severe endometriosis ($p=0.04$). Differences for dysmenorrhoea and for non-menstrual pelvic pain were not statistically significant ($p=0.082$ and $p=0.56$, respectively). For dysmenorrhoea, the differences may have been clinically significant, as the authors reported a benefit.

Secondly, the authors looked at subgroups of women, who had 'improved' pain scores for dysmenorrhoea (n=52), dyspareunia (n=38), and non-menstrual pain (n=30) after surgery

(≥2cm VAS reduction) and compared the proportions with minimal/mild and moderate/severe endometriosis. Regarding women with improved dysmenorrhea (n=52), 43% had minimal/mild and 66% moderate/severe endometriosis (p = 0.0037). Of the women reporting improved deep dyspareunia (n=38), 33% had minimal/mild and 67% had moderate/severe endometriosis ('not significant') and for non-menstrual pain (n=30) 67% had minimal/mild and 56% had moderate/severe endometriosis ('not significant').

Banerjee (Banerjee et al., 2006) reported a global pain score for three groups of women: no endometriosis, isolated superficial endometriosis and DE +/- superficial endometriosis. Global scoring was 35 maximum points, the sum of 0-5 points for each of dysmenorrhoea, dyspareunia, non-cyclical pelvic pain, menstrual dyschezia, non-menstrual dyschezia, menstrual backache, non-menstrual backache. The surgeon visually distinguished between superficial peritoneal and deep infiltrating/nodular lesions. Data indicate a correlation between deep /superficial classification and AFS staging (chi square test of association: $X^2_{(3)}$=25.8 p<0.001).Pre- and post-operative global pain scores were compared using a paired T-test in all three groups, women without endometriosis (n=2; p=0.30), with only superficial endometriosis (n=17; p=0.43), and with DE+/-superficial endometriosis (n=27; p=0.004). The authors concluded surgery did not reduce pain scores in superficial endometriosis but was valuable in DE. We agree but note the small group size.

Ghai (Ghai et al., 2020) reported a significantly higher proportion of women treated for severe endometriosis responding to surgery (n=86/96) than for superficial disease (77/102; p=0.0089). Women with severe endometriosis were more likely to respond if they had higher pre-operative EPH-30 pain scores (median 66, range 24-83) vs lower scores (median 50; range 20.5-63.6) and lower scores for 'feeling of control' (60.25; range 47.7- 72.7 versus 62.5, range 45.8-70.8).

Endometriosis-related pain and disease location

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All authors, apart from Ghai [Ghai et al., 2020], detailed endometriosis location; USL endometriosis was listed in four studies, ovarian endometrioma in three [Abbott et al., 2003, Banerjee et al., 2006, Milingos et al., 2006] and rectovaginal septum [Milingos et al., 2006] and intestinal endometriosis in two [Banerjee et al., 2006, Chopin et al., 2005].

Chopin [Chopin et al., 2005] reported pre- and post-operative pain scores stratified by location: USL, vagina, bladder and intestine. Pre- and post-operative differences in pain scores were compared for each location, but locations were not compared with each other. Removal of USL endometriosis (n=78) resulted in highly significant reduction across all five pain types (dysmenorrhoea $p<0.001$, deep dyspareunia $p<0.001$, dyschezia $p=0.001$, lower urinary tract symptoms $p=0.011$, and non-cyclical pelvic pain $p<0.001$). Vaginal (n=25) and intestinal (n=16) endometriosis excision was associated with significant reduction of four pain types (dysmenorrhoea $p=0.001$ and $p=0.004$ respectively, deep dyspareunia $p=0.001$ and $p=0.015$ respectively, dyschezia $p=0.007$ and $p=0.033$ respectively and non-cyclical pelvic pain $p=0.022$ and $p=0.027$ respectively), but not lower urinary tract symptoms ($p=0.0679$ and $p=0.0697$ respectively). Removal of bladder endometriosis (n=13) resulted in a significant reduction in dysmenorrhoea $p=0.022$, deep dyspareunia $p=0.0117$ and lower urinary tract symptoms $p=0.022$, but not dyschezia $p=0.0697$. Non-cyclical pelvic pain reduction could not be ascertained due to missing data.

Excluded studies

Two excluded studies for which we obtained full texts merit further discussion. Sutton [Sutton et al., 1994] was excluded due to limited presentation of results. Seventy-four women from gynaecology clinics with symptoms suggesting endometriosis were included. Visual assessment at laparoscopy showed minimal (n=29), mild (n=28) and moderate (n=6) endometriosis, which was destroyed with laser and not histologically confirmed. Follow-up was 3 and 6 months post-operatively. Of the 74 recruited women 63 completed the study.

Women recorded the intensity of global pain on a 10cm VAS and also 'how pain had changed'. The proportion of women with pain alleviation stratified by endometriosis stage was graphically displayed, without numerical values or significance testing. The proportion of women with stage 3 endometriosis is depicted at 100 'percentage better' whereas the percentage in stage 1 endometriosis is depicted below 50 'percentage better'. The authors were unsuccessfully contacted for their raw data. However, they concluded that the severity of pain experienced by endometriosis patients may be used to predict their response to surgery.

A retrospective cohort study by Harris (Harris et al., 2020) recruited 972 women who underwent therapeutic laparoscopy for confirmed endometriosis. In total 398 women had complete follow-up reported 6/52 weeks post-operatively. This study was excluded because of short follow-up. Global pain was recorded as 'pain improvement/resolution' versus 'no improvement'.
The proportion of women with improvement/resolution was higher if women: were 'not Caucasian' (n=188, 67.7%) versus 'Caucasian' (n=90, 32.4%) - OR 0.60, CI 0.37-0.99 p=0.046; were operated on by a specialised endoscopic gynaecologist (n=75, 83.0%) versus not (n=15, 16.7%) - OR 0.42, CI 0.18-0.94 p=0.036; had a history of CPP (n=29, 55.8%) versus not (n=23, 44.2%) - OR 2.0, CI 1.14-3.76 (p=0.02)); had stage 3-4 endometriosis (n=128, 83.1%) versus stage 1-2 (n=26, 16.9%) - OR 0.35, CI 0.21-0.57 p<0.001.

Discussion

Main Findings: Four of the five included studies indicate that stronger pain relief after endometriosis surgery was related to more severe disease prior to surgery (Chopin et al., 2005; Banerjee et al., 2006; Milingos et al., 2006; Ghai et al., 2020). Although the current review returned a limited quantity and quality of evidence, the 'theme' 'severity of endometriosis' is consistent across

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studies and warrants further investigation to determine whether it may be used in the future to counsel women about laparoscopic surgery for endometriosis. Endometriosis severity may be only fully understood during laparoscopy. Nonetheless, there are clinical pointers to DE, such as severity of symptoms (Fedele et al., 1992 , Ferrero et al., 2005), USL nodularity, and the 'kissing ovary' sign on scan, which may be used as surrogate markers for disease severity . More research is needed to quantify the value of using these in treatment decision making (Ghezzi et al., 2005, Matorras et al., 1996).

Strengths and Limitations: The strengths of this systematic review include a thorough literature review following PRISMA guidelines and assessment of studies using the Newcastle Ottawa quality tool. However, due to the limitations of the available data and the high risk of bias scores we are unable to make definitive conclusions about predictors of surgical success.

Interpretation: It was surprising to find so few studies focussing on patient-specific predictors of favourable surgical outcomes, given the large number of series that report evidence of a reduction of endometriosis-related pain scores after surgery (Garry et al., 2000, Ford et al., 2004, Wykes et al., 2006, Angioli et al., 2014, De la Hera-Lazaro et al., 2016, Byrne et al., 2018, Rindos et al., 2020) and the large numbers of affected patients.

Reviewed studies included women with advanced endometriosis, treated in specialist centres and with reported complete excision.

Surgical factors that could influence operative outcomes – such as whether excision is complete - are highly relevant to future research. Studies show less pain reduction in incomplete compared to complete surgery (Hidaka et al., 2012, Cao et al., 2015, Angioni et al., 2015). Thus a systematic review of three randomised controlled trials (RCTs) with 335 women indicates superior reduction of dysmenorrhea (mean difference [MD] = 0.99; 95% confidence interval [CI], -0.02 to 2.00; p = .05) and dyschezia (MD = 1.31; 95% CI, 0.33-2.29; p = .009) using excision compared to ablation, but not in dyspareunia (MD = 0.96; 95% CI, -0.07 to 1.99; p = .07) (Pundir et al., 2017). Conversely, a later RCT of 73 women with endometriosis ablation and

excision showed no difference in dysmenorrhoea but a difference in dyspareunia at 6 months (Mean Change -22.96; 95% CI, -39.06 to -6.86; p = .01) (Riley et al., 2019).

The studies included in the present review used the r-AFS scoring or a score deduced from it. Whilst the AFS score was designed to predict fertility and puts strong weighting on endometriotic cysts, it may correlate less well with pain(Vercellini et al., 1996), whereas the ENZIAN score (Haas et al., 2013, Montanari et al., 2019) may have stronger correlation in pain in DE.

The location of endometriosis in the USL and its removal may have a special role in pain relief after surgery (Chopin et al., 2005, Chapron and Dubuisson, 1996), and appears to be closely associated with the symptom of dyspareunia (Porpora et al., 1999, Fauconnier et al., 2002, Montanari et al., 2019). The presence of endometriosis is specifically associated with tenderness of the cul-de-sac or USL during examination (Yong et al., 2017). This can help indicate the presence of DE.

Debate remains whether surgical removal of endometriosis can relieve non-cyclical pelvic pain. Abbott (Abbott et al., 2003), Chopin (Chopin et al., 2005), and Banerjee (Banerjee et al., 2006), but not Milingos (Milingos et al., 2006) reported evidence of improvement of non-cyclical pelvic pain. Pain scores for non-cyclical back pain and non-cyclical dyschezia failed to show evidence of improvement after removal of endometriosis in one paper that included these outcomes (Banerjee et al., 2006). These symptoms may have causes other than endometriosis, as also can non-cyclical CPP that is resistant to laparoscopic endometriosis treatment.

The use of post-operative adjuvant hormone treatment (such as the oral contraceptive pill or levonorgestrel intrauterine device) could have been a confounding variable for pain improvement, especially dysmenorrhoea. However, this detail is not provided in the studies included.

Conclusion: The current systematic review identified severity of endometriosis as a possible predictor for surgical response based on a small number of studies, mostly assessed as having a 'high risk of bias'. The review has also shown there is a knowledge gap that needs to be filled. A multicentre RCT to clarify if low stage endometriosis removal causes any improvement in pain scores is planned (Horne et al., 2019). We are also currently producing an algorithm to predict surgical success in women with confirmed or suspected

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endometriosis (CRESCENDO, NIHR PB-PG-0317-20018) using pre-existing databases (Daniels et al., 2009, Byrne et al., 2018, Khan KS, 2018). Given the review findings we recommend that future studies should be designed more robustly and less heterogeneously. An important element is the reporting of pre-defined core outcome sets for endometriosis treatment (Hirsch et al., 2016, Duffy et al., 2019). With standardised reporting, studies can be adequately compared, synthesised and meta-analysed. A core outcome set for endometriosis has recently been published (Duffy et al., 2020) that includes overall pain, improvement in the most troublesome symptom and quality of life, and its adoption may create more substantive evidence in the future.

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Disclosure of Interests

None of the authors declare financial, personal, political, intellectual or religious interests relating to the current paper. Andrew Horne is a Co-Editor-in-Chief of Reproduction and Fertility. Andrew Horne was not involved in the review or editorial process for this paper, on which he is listed as an author.

Details of Ethics Approval

Given this study was a systematic review on data in the public domain it is exempt from ethics approval

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Contribution to authorship

I confirm that all authors made a substantial contribution to conception and design, or acquisition of data, or analysis and interpretation of data; AND in drafting the article or revising it critically for important intellectual content; AND in the final approval of the version to be published; AND All authors agree to be accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved.

In addition, the authors carried out the following tasks:

EB: Conception, planning, carrying out systematic review, analysing and writing

BK: Carrying out systematic review, analysing and writing

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JA: Conception, planning, carrying out systematic review, analysing and writing

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SB: Conception, planning and writing

JD: Conception and writing

Abbreviations

Chronic pelvic pain (CPP)

Deep endometriosis (DE)

National Health Service (NHS)

Revised American Fertility Society grading system, (r-AFS)

Uterosacral ligaments (USL)

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Table 1 Characterisation of studies.

Reference	Design	Cohort studied	Average Age (y)	Parity	Setting	Study size and Attrition			EM location	EM stages	Prev. treatment	Operative approach	Hist. confirm.	Follow up time from baseline, y	Pre- and Post-operative Outcome measures
						LAP ‡	EM	Follow-Up							
Abbott *et al*. (2003)	POC	ES 1-4	31 (20-48)	0: 80/175 (60%)	2 UK UH	261	176	135	OE: 38%; USL 88%	Stage 1: 28%; Stage 2: 28%; Stage 3: 17%; Stage 4: 41%	Analgesia: 70%; HT: 70% Prev. LAP: 70%	CLET: 100%	yes	5 (3.2 (2-5) ⁑)	VAS (10cm) presented as median and IQR for dysmenorrhoea, dyspareunia, non-menstrual PP, dyschezia)
Chopin *et al*. (2005)	ROC	DE†	31.7 ± 5.4	0.3± 0.61 (0-3)	1 French UAH	241	241	132	USL: 59.9%; vagina: 18.9%; bladder: 9.8%; intenstine:12.1%; multiple locations: 39.4%	Stage 1: 20.5%; Stage 2: 34.1%; Stage 3: 24.2%; Stage 4: 21.2%	HT: 56%; Prev. LAP: 0.9+-1	CLET: 87.1%; LT: 12.9%	yes	3.7±2.0 (median: 3.3)	VAS (10 cm) for each pain type (dysmenorrhoea, dyspareunia, CPP, dyschezia, lower urinary tract symptoms)
Banerjee *et al*. (2006)	POC	ES 1-4 and no EM	NS		1 UK tertiary EM centre in DGH	108	88	46	OE: 14%; USL: 59%; recto-vaginal: 43%; pouch of Douglas: 43%; intestine: 47%	Stage 1: 39%; Stage 2: 16%; Stage 3: 9%; Stage 4: 36%	NS	CLET: 100%	yes	18 months post-surgery	Pre- and post-operative global pain scores; theses are a sum of VAS (0-5) for dysmenorrhoea, dyspareunia, non-cyclical pelvic pain, menstrual dyschezia, non-menstrual dyschezia, menstrual backache, non-menstrual backache
Milingos *et al*. (2006)	POC	ES 1-4	NS		1Greek UH	258	101	95	OE:61.8%; USL: 59%; recto-vaginal septum: 10.3%	Minimal and mild: 21.4%; moderate and severe: 71.6%	Prev. LAP: 14.7%	CLET; LT: 6.3%	no	6 months post-surgery	VAS (10) for each pain type dysmenorrhoea, dyspareunia, non-menstrual pelvic pain. Pain scores grouped as 0, 1-5, 6-7, 8-10
Ghai *et al*. (2020)	RS*	ES 1-4	NS		1 UK tertiary EM centre in DGH	102	96	100	ND	Stage 1-3 "superficial": 48%; stage 4 with bowel involvement "severe": 52%	GRA: 6/12	Stage 1-3: laser destruction or excision; Stage 4: excision (97.1 % CLEP); LT: 2.9%	Severe: yes; superficial: NS	12 months post-surgery	Pre- and post-operative pain component measured with EPH30 questionnaire

* Analysis of data from previous databases (1, 2); † with infiltration of USL or Bladder/ intestine/ vagina; ‡women with CPP who had laparoscopy; ⁑ mean (range)

POC, prospective observational cohort; ROC, retrospective observational cohort; RS, retrospective secondary; EM, endometriosis; ES, endometrial stage; NS. Not stated; ND, not detailed; UH, university hospital; UAH, university affiliated hospital; DGH, district general hospital; LAP, laparoscopy; OE, ovarian endometrioma; HT, hormonal treatment; Prev. previous; GRA; gonadotropin receptor antagonist; CLET, complete laparoscopic excisional treatment; LT, laparotomy; Hist. confirm., histological confirmation;

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Author	Outcomes stratified by risk factors	Presented as	Findings	Author's conclusions
Abbott 2003	Outcomes of dysmenorrhoea, dyspareunia, non- menstrual PP, Dyschezia pre and postop scores stratified by Endometriosis AFS staging 1-4 QOL measures reported but not stratified	Median, IQR and P	Pain scores (median VAS baseline versus follow-up 2-5 years) were all significantly reduced for: Dysmenorrhoea all stages 9 versus 3.3 (P < 0.0001), Stage I endometriosis 8 versus 2 (P < 0.0001), Stage II endometriosis 8 versus 4.5 (P < 0.0001), Stage III endometriosis 9 versus 3.5 (P < 0.0001), Stage IV endometriosis 9 versus 2 (P < 0.0001 Non-menstrual pelvic pain all stages 8 versus 3 (P < 0.0001), Stage I endometriosis 6 versus 3 (P=0.036), Stage II endometriosis 6 versus 3.3 (P < 0.0001), Stage III endometriosis 6 versus 2.9 (P =0.046), Stage IV endometriosis 7 versus 2.4 (P < 0.0001) Dyspareunia all stages 7 versus 0 (P < 0.0001), Stage I endometriosis 7 versus 2.6 (P=0.002), Stage II endometriosis 5.5 versus 1.7 (P=0.005), Stage III endometriosis 6 versus 0 (P=0.004), Stage IV endometriosis 6 versus 0 (P < 0.0001) Dyschezia all stages 7 versus 2 (P < 0.0001), Stage I endometriosis 6 versus 3.1 (P=0.035), Stage II endometriosis 6 versus 2.7 (P=0.006), Stage III endometriosis 4 versus 0 (P=0.12), Stage IV endometriosis 5 versus 2 (P=0.002)	The results from sub-analysis examining pain scores by stage suggested a reduction in pain for all four parameters examined.
Chopin 2005	Outcomes of dysmenorrhoea, dyspareunia, CPP, Dyschezia, lower Urinary tract symptoms pre and postop scores stratified by anatomical location (USL, Vagina, bladder, intestine)	Mean and SD and P	USL (n=78) Dysmenorrhea (n=68) preop mean 7.68; SD 2.08; range 0-10; postop mean 3.31; SD 3.31; range 0-10; Delta 4.36 ± 3.61; p=0.0001 Deep dyspareunia (n=61) preop mean 6.41; SD 2.47; range 0-10; postop mean 2.12; SD 2.71; range 0-10; Delta 4.30 ± 3.29; p=0.0001 Dyschezia (n=39) preop mean 6.44; SD 2.59; range 0-10; postop mean 2.72; SD 3.12; range 0-10; Delta 3.72 ± 4.00; p=0.0001 Lower urinary tract symptoms (n=21) preop mean 5.52; SD 0.69; range 2-8; postop mean 2.29; SD 3.23; range 0-8; Delta 3.24 ± 3.02; p=0.0011 CPP (n=36) preop mean 7.36; SD 1.46 range 3-10; postop mean 3.25; SD 3.83; range 0-10; Delta 4.11 ± 3.34; p=0.0001 Vagina (n=25) Dysmenorrhea (n=23) preop mean 8.00; SD 1.48; range 5-10; postop mean 2.82; SD 3.33; range 0-9; Delta 5.17 ±3.70; p=0.0001 Deep dyspareunia (n=21) preop mean 6.77; SD 1.73; range 4-10; postop mean 1.62; SD 3.03; range 0-9; Delta 5.14 ± 2.97; p=0.0001 Dyschezia (n=17) preop mean 6.77; SD 2.17; range 4-10; postop mean 2.35; SD 3.10; range 0-8; Delta 4.41 ± 3.20; p=0.0007 Lower urinary tract symptoms (n=4) preop mean 4.50; SD 1.73; range 3-7; postop mean 0.00; SD 0.00; range 0-0; Delta 4.50 ± 1.73; p=0.0679	The results presented show that for each location in the surgical classification, the mean scores for the five symptoms according to the numerical rating scale were significantly lower postoperatively. This result is nearly significant when the group-specific sample sizes of patients are very small.

			CPP (n=8) preop mean 7.63; SD 1.60; range 5-10; postop mean 1.62; SD 3.11; range 0-9; Delta 6.00 ± 3.25; p=0.0171 Bladder (n=13) Dysmenorrhea (n=13) preop mean 9.23; SD 1.09; range 7-10; postop mean 2.23; SD 2.95; range 0-7; Delta 7.00 ± 3.27; p=0.0022 Deep dyspareunia (n=9) preop mean 7.56; SD 2.13; range 4-10; postop mean 2.44; SD 2.60; range 0-7; Delta 5.11 ± 3.76; p=0.0117 Dyschezia (n=4) preop mean 7.50; SD 2.08; range 5-10; postop mean 0.00; SD 0.00; range 0-0; Delta 7.50 ± 2.08; p=0.0679 Lower urinary tract symptoms (n=12) preop mean 7.50; SD 2.24; range 3-10; postop mean 0.00; SD 0.00; range 0-0; Delta 7.50 ± 2.24; p=0.022 CPP (n=1) preop mean 5.0; range 5-5; postop mean 0.00; range 0-0 Delta 5.0 Intestine (n=16) Dysmenorrhea (n=16) preop mean 9.00; SD 0.97; range 8-10; postop mean 1.94; SD 2.77; Range 0-8; Delta 7.06 ± 2.82 .0004 Deep dyspareunia (n=13) preop mean 6.77; SD 2.13; range 3-10; postop mean 2.08; SD 2.75; range 0-9; Delta 4.69 ± 2.32 .0015 Dyschezia (n=11) preop mean 6.91; SD 2.55; range 3-10; postop mean 1.09; SD 2.07; range 0-6; Delta 5.82 ± 2.71 .0033 Lower urinary tract symptoms (n=4) preop mean 7.00; SD 1.83; range 5-9; postop mean 1.00; SD 2.00; range 0-4; Delta 6.00 ± 3.16 .0679 CPP (n=6) preop mean 9.17; SD 0.98; range 8-10; postop mean 3.50; SD 3.89 range 0-8; Delta 5.67 ± 4.13 .0277	
Banerjee 2006	global pain score stratified by no endometriosis, only superficial endometriosis, deep +_ superficial endometriosis	Mean pain score and SD	Difference pre to postoperative scores: 5.2 points +/- 3.6 for dysmenorrhea, 4.6 points +/- 3.1 for deep dyspareunia, 4.4 points +/- 3.7 for painful defecation during menstruation, 4.9 +/- 3.2 for lower urinary tract symptoms during menses, and 4.6 points +/- 3.4 for noncyclic chronic pelvic pain. Comparable results observed for patients in each group according to the surgical classification of their DIE lesions: USL (n = 78 patients); vagina (n = 25 patients); bladder (n = 13 patients); and intestine (n = 16 patients).	This small study suggests that surgical therapy does not reduce pain scores in superficial endometriosis but is valuable in the treatment of deep or infiltrating disease.
Milingos 2006	Outcomes for dysmenorrhoea, deep dyspareunia and non-menstrual pain stratified by 1. number of improved patients (reduction ≥2cm VAS was considered significant) 2. change in pain scores (graph) for severity AFS score <16 (group 1) and 16+	Graphics : changes in pain scores with p	Postoperatively dysmenorrhea improved in 43% of cases in group 1 (superficial endometriosis), vs. 66% of cases in group 2 (deep endometriosis) (p = 0.0037). For deep dyspareunia, improvement was reported by 33% in group 1, vs. 67% in group 2 (p =0.074). Scores for Improvement in non-menstrual pain was not significantly different between the two groups (67% vs. 56%). Global pain scores (SD, pre versus post-operative) were 17.5 (7.8) versus 16.1 (6.7), p= 0.43 for superficial endometriosis, and 19.2 (7.2) versus 14.5 (8.9), p=0.004 for deep endometriosis +/- superficial (figures not given for deep alone).	Cases with advanced disease seem to benefit the most

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	(group2)	Proportion improved patients an p		
Ghai 2020	Outcome is any reduction of EPH 30 pain score reduction (responders): 1. comparison between the proportion of responders among women with severe and superficial endometriosis 2. stratification within the superficial and severe groups by anxiety and depression HADS scores, feeling of control, emotional wellbeing, sexual relationship and pain EPH30 scores, VAS for dysmenorrhoea, dyspareunia, CPP, dyschezia	1. proportion of non-responders in severe and superficial endometriosis with p value 2. median and range for HADS, EPH30 domains and for VAS with p value for superficial and severe endomet	Higher proportion of women with severe endometriosis (n=86/96) than women with superficial endometriosis (77/102; p=0.0089) respond to surgery. Women with severe endometriosis were more likely to respond to surgery of they have higher preoperative EPH 30 pain scores (median 66, range 24-83) as compared to lower scores (median 50; range 20.5-63.6). In this group response to surgery was associated with lower scores for 'feeling of control' (60.25; range 47.7- 72.7 versus 62.5 versus 45.8-70.8)	Severity of disease and pain and pain may be used to predict response to surgery

		riosis		

Table 2: Study results

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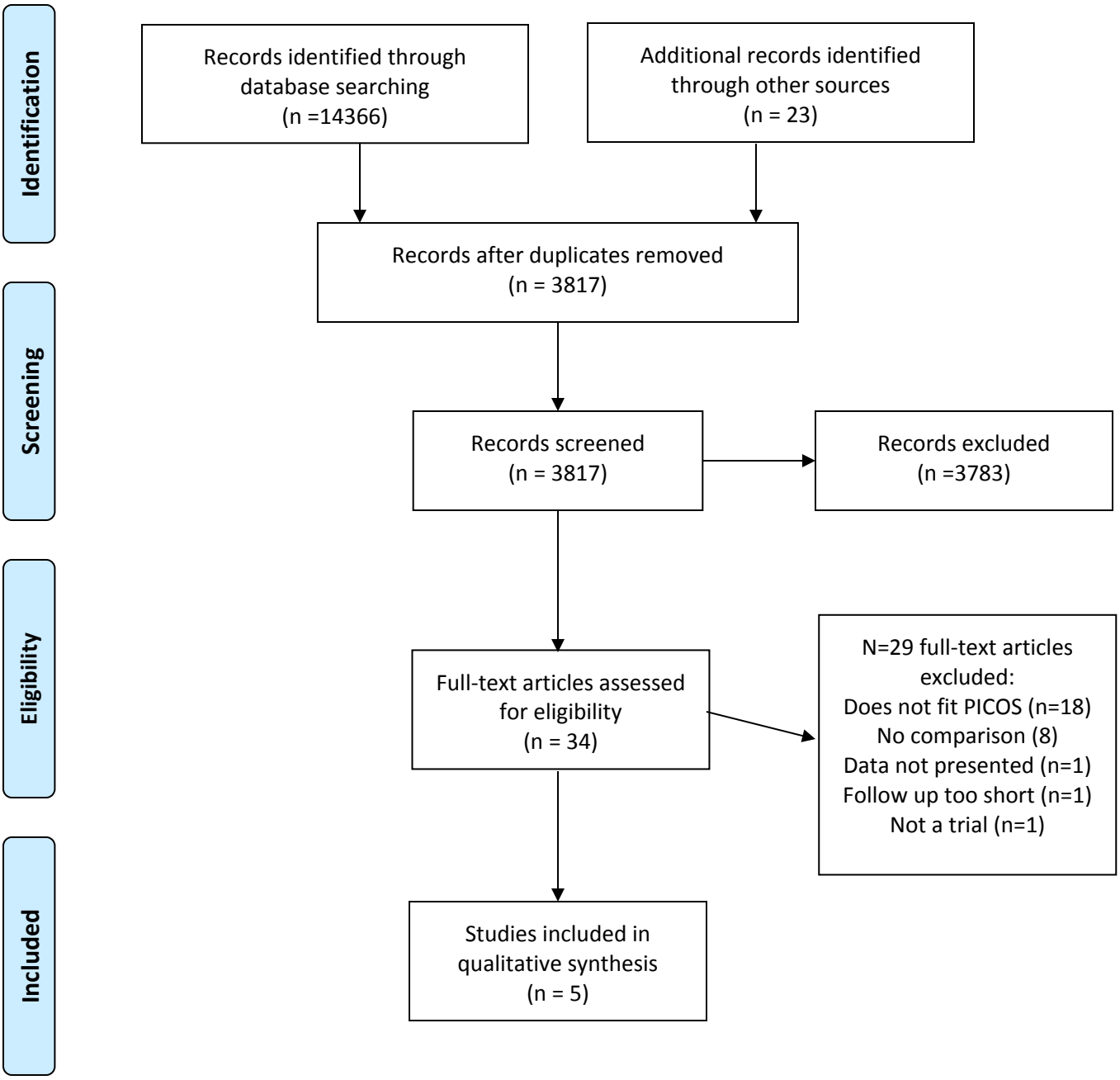
Figure 1: PRISMA Flow Diagram



From: Moher D, Liberati A, Tetzlaff J, Altman DG, The PRISMA Group (2009). *P*referred *R*eporting *I*tems for *S*ystematic Reviews and *M*eta-*A*nalyses: The PRISMA Statement. PLoS Med 6(7): e1000097. doi:10.1371/journal.pmed1000097

Appendix S1

Details of search strategy used in the systematic review on predictors of pain improvement after laparoscopic surgery for endometriosis

MEDLINE search strategy

1. (Validat* OR Predict* OR Rule*).ti,ab
2. (Predict* AND (Outcome* OR Risk* OR Model*)).ti,ab
3. ((Clinic* OR Presentation OR symptom* OR sign* OR History OR Variable* OR Criteria OR Scor* OR Characteristic* OR Finding* OR Factor*) AND (Predict* OR Model* OR Decision* OR Identif* OR Prognos* OR causality OR etiology OR odds ratio OR risk OR risk factor* OR odds OR cause)).ti,ab
4. (Decision* AND (Model* OR Clinical* OR Logistic Model*)).ti,ab
5. (Prognostic AND (History OR Variable* OR Criteria OR Scor* OR Characteristic* OR Finding* OR Factor* OR Model*)).ti,ab
6. ("risk score" OR "prediction model" OR "prediction rule" OR "risk assessment" OR "algorithm").ti,ab
7. (1 OR 2 OR 3 OR 4 OR 5 OR 6)
8. (endometrios*).all fields
9. (7 AND 8)

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Table S1
Included and excluded studies

Included studies	
Author	Title and reference
Abbott 2003	The effects and effectiveness of laparoscopic excision of endometriosis: a prospective study with 2-5 year follow-up. Hum Reprod. 2003;18(9):1922-7.
Chopin 2005	Chopin N, Vieira M, Borghese B, Foulot H, Dousset B, Coste J, et al. Operative management of deeply infiltrating endometriosis: results on pelvic pain symptoms according to a surgical classification. J Minim Invasive Gynecol. 2005;12(2):106-12.
Banerjee 2006	Banerjee S, Ballard KD, Lovell DP, Wright J. Deep and superficial endometriotic disease: the response to radical laparoscopic excision in the treatment of chronic pelvic pain. Gynecological Surgery. 2006;3(3):199-205.
Milingos 2006	Milingos S, Protopapas A, Kallipolitis G, Drakakis P, Loutradis D, Liapi A, et al. Endometriosis in patients with chronic pelvic pain: is staging predictive of the efficacy of laparoscopic surgery in pain relief? Gynecol Obstet Invest. 2006;62(1):48-54.
Ghai 2020	Ghai V, Jan H, Shakir F, Kent A. Identifying Preoperative Factors Associated with Nonresponders in Women Undergoing Comprehensive Surgical Treatment for Endometriosis. J Minim Invasive Gynecol. 2020;27(1):141-7.

Excluded studies	
Noventa M, Saccardi C, Litta P, et al. Ultrasound techniques in the diagnosis of deep pelvic endometriosis: algorithm based on a systematic review and meta-analysis. *Fertil Steril*. 2015;104(2):366-83	does not fit PICOS
Soriano D, Schonman R, Nadu A. et al. Multidisciplinary team approach to management of severe endometriosis affecting the ureter: long-term outcome data and treatment algorithm. J Minim Invasive Gynecol. 2011;18:483–488	no comparison group
Cocco A, Borghero A, Saccardi C, Guidetti G, Conte L, Litta P. Deep pelvic endometriosis: From diagnosis to wellness. Gynecological Surgery. 2009;6(SUPPL. 1):S39.	no comparison group, conference abstract
Daraï E, Dubernard G, Coutant C, Frey C, Rouzier R and Ballester M. Randomized trial of laparoscopically assisted versus open colorectal resection for endometriosis: morbidity, symptoms, quality of life, and fertility. Ann Surg 2010; 251:1018–1023.	does not fit PICOS
Daraï E, Thomassin I, Barranger E. et al. Feasibility and clinical outcome of laparoscopic colorectal resection for endometriosis. Am J Obstet Gynecol. 2005;192:394–400	does not fit PICOS
Deng S, Leng J, Lang J, Dai Y, Li X. [Clinicopathological characteristics of recurrent endometriosis and the outcomes of secondary surgery]. Zhonghua fu chan ke za zhi. 2011;46(11):809-12.	no comparison group
Dibi R, Pinho De Oliveira MA, Nogueira M, Muller M, Soares T, Souza C, et al. How many surgeries are necessary for definitively treatment of deep endometriosis. Journal of Minimally Invasive Gynecology. 2012;19(6 SUPPL. 1):S98.	does not fit PICOS, conference abstract
Dowaji J, Jaenicke F. Long-term results of laparoscopic resection of deep pelvic endometriosis with rectosigmoid involvement. Gynecological Surgery. 2010;7(SUPPL. 1):S160.	no comparison group

Dubernard G, Piketty M, Rouzier R, Houry S, Bazot M, Darai E. Quality of life after laparoscopic colorectal resection for endometriosis. Human reproduction (Oxford, England). 2006;21(5):1243-7.	no comparison group
Duffy JMN, Arambage K, Correa FJS, Olive D, Farquhar C, Garry R, et al. Laparoscopic surgery for endometriosis. The Cochrane database of systematic reviews. 2014 (4):CD011031.	not a trial
Grundstrom H, Alehagen S, Bertero C, Kjolhede P. Impact of Pelvic Pain and Endometriosis on Patient-Reported Outcomes and Experiences of Benign Hysterectomy: A Study from the Swedish National Register for Gynecological Surgery. Journal of Women's Health. 2018;27(5):691-8.	does not fit PICOS
Healey M, Ang C, Cheng C. Surgical treatment of endometriosis: a prospective randomized double-blind trial comparing excision and ablation. Fertil Steril 2010; 94: 2536–	does not fit PICOS
Ianieri MM, Mautone D, Ceccaroni M. Recurrence in Deep Infiltrating Endometriosis: A Systematic Review of the Literature. Journal of Minimally Invasive Gynecology. 2018;25(5):786-93.	does not fit PICOS
Jarrell J. Annual repeat rates of laparoscopic surgery: a marker of practice variation. American journal of medical quality : the official journal of the American College of Medical Quality. 2010;25(5):378-83.	does not fit PICOS
Kalu E, McAuley W, Richardson R. Teenagers, adolescents, endometriosis and recurrence: A retrospective analysis of recurrence following primary operative laparoscopy. Gynecological Surgery. 2008;5(3):209-12.	does not fit PICOS
Kayani S, Nightingale A. Laparoscopic surgery for endoemtriosis: A systematic review. Gynecological Surgery. 2009;6(SUPPL. 1):S85-S6.	does not fit PICOS
Li H-j, Leng J-h, Lang J-h, Wang H-l, Liu Z-f, Sun D-w, et al. [Correlative factors analysis of recurrence of endometriosis after conservative surgery]. Zhonghua fu chan ke za zhi. 2005;40(1):13-6.	does not fit PICOS
Martin CE, Johnson E, Wechter ME, Leserman J, Zolnoun DA. Catastrophizing: a predictor of persistent pain among women with endometriosis at 1 year. Human reproduction (Oxford, England). 2011;26(11):3078-84.	does not fit PICOS
Martin DC. Hysterectomy for treatment of pain associated with endometriosis. J Minim Invasive Gynecol 2006; 13:566–572.	does not fit PICOS
Meuleman C, Tomassetti C, D'Hooghe T M. Clinical outcome after laparoscopic radical excision of endometriosis and laparoscopic segmental bowel resection. Curr Opin Obstet Gynecol. 2012	does not fit PICOS
Moini A, Arabipoor A, Ashrafinia N. Risk factors for recurrence rate of ovarian endometriomas following a laparoscopic cystectomy. Minerva medica. 2014;105(4):295-301.	does not fit PICOS
Renner S P, Rix S, Boosz A. et al. Preoperative pain and recurrence risk in patients with peritoneal endometriosis. Gynecol Endocrinol. 2009 (2010 on file);28:1–6	does not fit PICOS
Saleh A, Tulandi T. Reoperation after laparoscopic treatment of endometriomas by excision and fenestration. Fertil Steril. 1999	does not fit PICOS
Sutton CJ, Ewen SP, Whitelaw N and Haines P. Prospective, randomized, double-blind, controlled trial of laser laparoscopy in the treatment of pelvic pain associated with minimal, mild, and moderate endometriosis. Fertil steril 1994; 62:696–700.	data not presented
Ford J, English J, Miles W A. et al. Pain, quality of life and complications following the radical resection of rectovaginal endometriosis. Br J Obstet Gynaecol. 2004;111:353–356.	no comparison group

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Abbott J, Hawe J, Hunter D. et al. Laparoscopic excision of endometriosis: a randomized, placebo-controlled trial. Fertil Steril. 2004;82:878–884	no comparison group
Chapron C, Dubuisson JB. Laparoscopic treatment of deep endometriosis located on the uterosacral ligaments. Hum Reprod 1996;11:868–73.	no comparison group
Vercellini P, Fedele L, Aimi G, De Giorgi O, Consonni D and Crosignani PG. Reproductive performance, pain recurrence and disease relapse after conservative surgical treatment for endometriosis: the predictive value of the current classification system. Hum Reprod 2006a; 21:2679–2685	does not fit PICOS
Harris A, McCaughey T, Tsaltas J, Davies-Tuck M, Ratner R, Najjar H, et al. Endometriosis-related pelvic pain following laparoscopic surgical treatment J Endometr Pelvic Pain Disord [Internet]. 2020.	follow up too short

PRISMA 2009 Checklist

Section/topic	#	Checklist item	Reported on page #
TITLE			
Title	1	Identify the report as a systematic review, meta-analysis, or both.	
ABSTRACT			
Structured summary	2	Provide a structured summary including, as applicable: background; objectives; data sources; study eligibility criteria, participants, and interventions; study appraisal and synthesis methods; results; limitations; conclusions and implications of key findings; systematic review registration number.	
INTRODUCTION			
Rationale	3	Describe the rationale for the review in the context of what is already known.	
Objectives	4	Provide an explicit statement of questions being addressed with reference to participants, interventions, comparisons, outcomes, and study design (PICOS).	
METHODS			
Protocol and registration	5	Indicate if a review protocol exists, if and where it can be accessed (e.g., Web address), and, if available, provide registration information including registration number.	
Eligibility criteria	6	Specify study characteristics (e.g., PICOS, length of follow-up) and report characteristics (e.g., years considered, language, publication status) used as criteria for eligibility, giving rationale.	
Information sources	7	Describe all information sources (e.g., databases with dates of coverage, contact with study authors to identify additional studies) in the search and date last searched.	
Search	8	Present full electronic search strategy for at least one database, including any limits used, such that it could be repeated.	
Study selection	9	State the process for selecting studies (i.e., screening, eligibility, included in systematic review, and, if applicable, included in the meta-analysis).	
Data collection process	10	Describe method of data extraction from reports (e.g., piloted forms, independently, in duplicate) and any processes for obtaining and confirming data from investigators.	
Data items	11	List and define all variables for which data were sought (e.g., PICOS, funding sources) and any assumptions and simplifications made.	
Risk of bias in individual studies	12	Describe methods used for assessing risk of bias of individual studies (including specification of whether this was done at the study or outcome level), and how this information is to be used in any data synthesis.	
Summary measures	13	State the principal summary measures (e.g., risk ratio, difference in means).	
Synthesis of results	14	Describe the methods of handling data and combining results of studies, if done, including measures of consistency (e.g., I^2) for each meta-analysis.	

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PRISMA 2009 Checklist

Section/topic	#	Checklist item	Reported on page #
Risk of bias across studies	15	Specify any assessment of risk of bias that may affect the cumulative evidence (e.g., publication bias, selective reporting within studies).	
Additional analyses	16	Describe methods of additional analyses (e.g., sensitivity or subgroup analyses, meta-regression), if done, indicating which were pre-specified.	
RESULTS			
Study selection	17	Give numbers of studies screened, assessed for eligibility, and included in the review, with reasons for exclusions at each stage, ideally with a flow diagram.	
Study characteristics	18	For each study, present characteristics for which data were extracted (e.g., study size, PICOS, follow-up period) and provide the citations.	
Risk of bias within studies	19	Present data on risk of bias of each study and, if available, any outcome level assessment (see item 12).	
Results of individual studies	20	For all outcomes considered (benefits or harms), present, for each study: (a) simple summary data for each intervention group (b) effect estimates and confidence intervals, ideally with a forest plot.	
Synthesis of results	21	Present results of each meta-analysis done, including confidence intervals and measures of consistency.	
Risk of bias across studies	22	Present results of any assessment of risk of bias across studies (see Item 15).	
Additional analysis	23	Give results of additional analyses, if done (e.g., sensitivity or subgroup analyses, meta-regression [see Item 16]).	
DISCUSSION			
Summary of evidence	24	Summarize the main findings including the strength of evidence for each main outcome; consider their relevance to key groups (e.g., healthcare providers, users, and policy makers).	
Limitations	25	Discuss limitations at study and outcome level (e.g., risk of bias), and at review-level (e.g., incomplete retrieval of identified research, reporting bias).	
Conclusions	26	Provide a general interpretation of the results in the context of other evidence, and implications for future research.	
FUNDING			
Funding	27	Describe sources of funding for the systematic review and other support (e.g., supply of data); role of funders for the systematic review.	

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