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Critical Appraisal of Endometriosis Management for Pain and Subfertility

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Introduction

Endometriosis can be seen as a continuum that is only considered pathological when a certain threshold of severity has been reached.¹ Minimal or mild endometriosis is increasingly viewed as part of normal physiologic process, whereas the more severe forms - ovarian cysts and deeply infiltrating lesions- are considered 'endometriotic disease.'² Estimates from asymptomatic fertile subpopulations undergoing tubal ligation have varied greatly, from 0.7 to 43% around a mean of 4%.³ However, up to 90% of these women were diagnosed with minimal or mild endometriosis.

Understanding the environmental and genetic epidemiology of endometriosis is essential for identification of appropriate subjects and effective therapy. Our understanding of endometriosis is severely compromised as studies failed to take account of basic epidemiological principles in their design. Of 100 studies of environmental risk-factors reviewed by Eskenazi and Warner³, only six met the following basic criteria for adequate study design:

- (i) cohort or case-control design;
- (ii) surgically confirmed cases;
- (iii) clearly described criteria for control selection; and (iv) adjustment for confounding factors in the analysis.

There is now good evidence that the assessments patients make about their health differ from the proxy reports other health professionals make about their patients' well-being.⁴ It is important therefore to evaluate from the patients' perspective the ways in which treatments are affecting their health-related quality of life. The areas of well-being and functioning that may be important to women, with endometriosis that can lead to a diminished quality of life, have been identified as: feelings of control and powerlessness, unable to conceive, ineffectiveness of treatments, lack of social support, impaired sexual functioning, lack of self image, lack of emotional well-being, pain, relationship with children, performance at work place and dissatisfaction with medical professionals.⁵ These dimensions have previously been overlooked but are specific to the experiences of women with endometriosis and should be taken in account when deciding about modality of treatment. In this clinical review we will focus on treatment of pain and infertility ascribable to endometriosis as they also influence other areas of well-being and functioning which are important to women with endometriosis.

Methods

Our electronic searches targeted all therapeutic modalities among studies on treatment of endometriosis. We searched general bibliographic databases: Medline (1966-2001) and specialist computer databases: the Cochrane Library⁶, Bandolier⁷, Clinical Evidence⁸, Database of Abstracts of Review of Effectiveness (DARE)⁹ and National Guideline Clearinghouse (NGC).¹⁰ We also checked reference lists of known reviews and primary articles to identify cited articles not captured by electronic searches.

The selection criteria were systemic reviews and randomized controlled trials (RCTs) in treatment of pain and subfertility ascribable to endometriosis. Electronic searches were scrutinised and full manuscripts were obtained of all citations that were likely to meet the predefined criteria. Final inclusion or exclusion decisions were then made after examining these manuscripts. In cases of duplicate publication we selected the most recent and complete versions. Due to logistic reasons we restricted our search to English language. In presenting this critical appraisal, we adopted the evidence-based approach of formulating answerable clinical questions¹¹ for different clinical possibilities.

Pain ascribable to endometriosis

Question 1.

In women with pain ascribable to endometriosis, does hormonal treatment at diagnosis compared with placebo reduce pain?

Assessment of Search

See Table 1 for details.

Outcomes and Interventions examined

For relief of pain, 6 months of continuous ovulation suppression was done using Danazol, Gestrinone, Depot medroxyprogesterone acetate (DMPA), Dydrogesterone, Oral contraceptives or GnRH-analogues

Critically appraised results

1. Dydrogesterone given at two different doses in the luteal phase, showed no evidence of effect.
2. Combined oral contraceptives (COC) vs GnRH-analogues, no significant difference in pain reduction was found.
 1. Danazol (200 mg/day) vs Gestrinone (2.5 mg twice weekly), no significant difference in pain reduction was found.
 2. DMPA (150 mg q 3 months) vs COC+Danazol (50 mg/day), DMPA was more effective at reducing dysmenorrhoea.

Answer

All hormonal treatments at diagnosis, except for dydrogesterone, reduce pain ascribable to endometriosis compared with placebo, and are equally effective at 6-months

Question 2.

In women with pain ascribable to endometriosis, does laparoscopic uterine nerve ablation (LUNA) compared with laparoscopic treatment without LUNA reduces pain?

Assessment of Search

See Table 1 for details.

Outcomes and Interventions examined

For relief of pain, LUNA was compared with laparoscopic treatment without LUNA in 132 women, age range 18-40 years, with endometriosis of stages I-III in two RCTs.

Critically appraised results

1. No significant difference in pain relief between both groups.
2. Patient satisfaction was high in both groups (68 v 73%)

Answer

There is insufficient evidence at present on the effects of LUNA in women with pain ascribable to endometriosis.(results awaited of ongoing study).

Question 3.

In women with pain ascribable to endometriosis, does laparoscopic ablation of endometriotic deposits along with laparoscopic uterine nerve ablation (LUNA) compared to diagnostic laparoscopy reduce pain?

Assessment of Search

See Table 1 for details.

Outcomes and Interventions examined

Reduced pain at 6 months after laparoscopic ablation plus LUNA was compared with diagnostic laparoscopy in 63 women with mild to moderate endometriosis.

Critically appraised results

1. No RCT evaluating laparoscopic ablation of endometriotic deposits was found.
2. Median decrease in pain score of 2.85 for ablation was seen versus 0.05 for diagnostic laparoscopy, $p=0.01$

Answer

Combined treatment with ablation of deposits plus LUNA reduces pain more than diagnostic laparoscopy at 6 months.

Question 4.

In women with pain ascribable to endometriosis, does postoperative hormonal treatment

compared with placebo significantly reduces pain?

Assessment of Search

See Table 1 for details.

Outcomes and Interventions examined

Reduced pain at 6 months

Critically appraised results

1. Postoperative danazol (600mg/day) v placebo for 3 months, No significant difference in pain relief 6 months after finishing treatment
2. Danazol 100 mg/day for 6 months v expectant management (after conservative surgery followed by monthly injections of decapeptyl for 6 months), danazol significantly reduced pain at 12 months and 24 months
3. Postoperative Danazol (600 mg/day) or Medroxyprogesterone (100 mg/day) for 180 days v placebo, more reduction in pain at 6 months with danazol
4. GnRH-analogues 6 months v placebo, significantly reduced pain scores and delayed recurrence of pain by more than 12 months with GnRH-analogues.

Answer

Six-months of postoperative hormonal treatment verses placebo significantly reduces pain and delays the recurrence of pain while treatment for 3 months did not seem to be effective.

Question 5.

In women with pain ascribable to endometrioma, does laparoscopic cystectomy compared with laparoscopic drainage of ovarian cyst significantly reduces pain?

Assessment of Search

See Table 1 for details.

Outcomes and Interventions examined

1 RCT evaluating comparison of laparoscopic cystectomy with laparoscopic drainage of ovarian cyst was found.

Reduced recurrence of pain

Increased pain free interval after operation Critically appraised results

1. Laparoscopic cystectomy reduced pain at 2 years.
2. Laparoscopic cystectomy increased the pain free interval after operation (median interval 19 months v 9.5 months; p value <0.05)

Answer

Laparoscopic cystectomy reduces pain more than laparoscopic drainage of endometriomas. The recurrence rate of endometriomas after drainage /aspiration was high.

Subfertility ascribable to endometriosis

Question 1.

In women with subfertility ascribable to endometriosis, does hormonal treatment at diagnosis compared with placebo improve fertility?

Assessment of Search

See Table 2 for details.

Outcomes and Interventions examined

Attempting conception for more than 12 months following 6 months treatment with Danazol, Medroxyprogesterone, or Gonadorelin (GnRH) analogues.

Critically appraised results

1. Danazol vs Placebo, no significant effect on the likelihood of pregnancy was found.
2. Medroxyprogesterone vs Placebo, no significant effect on the likelihood of pregnancy was found.

Answer

No evidence that hormonal treatments at diagnosis improve fertility.

Question 2.

In women with subfertility ascribable to endometriosis, does laparoscopic ablation/excision of endometriotic deposits compared with diagnostic laparoscopy improve fertility?

Assessment of Search

See Table 2 for details.

Outcomes and Interventions examined

Relative risk of pregnancy after 36 weeks or pregnancy rates at end of 12 months following laparoscopic ablation/excision of mild to moderate endometriotic deposits.

Critically appraised results

1. In larger trial of 341 women, laparoscopic surgery significantly increased cumulative pregnancy rates (follow-up of 36 weeks)
2. In a smaller more recent trial of 101 women, no significant difference in pregnancy rates was found (follow-up of 12 months)

Answer

Laparoscopic ablation/excision of endometriotic deposits may improve fertility. (results

awaited of ongoing trials)

Question 3.

In women with moderate or severe endometriosis, does postoperative hormonal treatment compared with placebo improve fertility?

Assessment of Search

See Table II for details.

Outcomes and Interventions examined

Pregnancy rates and time to conception.

Critically appraised results

1. For all stages of endometriosis no effect of postoperative hormonal therapy was found on pregnancy rates and time to conception

Answer

No evidence of an effect of postoperative hormonal treatment on fertility.

Question 4.

In women with subfertility ascribable to endometrioma, does laparoscopic cystectomy compared with laparoscopic drainage of ovarian cyst significantly improves fertility?

Assessment of Search

See Table 2 for details.

Outcomes and Interventions examined

Pregnancy rates.

Critically appraised results

1. 1 RCT evaluating comparison of laparoscopic cystectomy with laparoscopic drainage of ovarian cyst was found.
2. Laparoscopic cystectomy improved pregnancy rates after operation (67% v 24 %; p value <0.05).

Answer

Laparoscopic cystectomy improves fertility more than laparoscopic drainage of endometriomas.

Conclusions

Surgical resection of endometriosis, previously possible only by means of laparotomy, can now be accomplished through laparoscopic techniques. There is a learning curve to achieve these skills which can be accomplished. Treatment of adnexal masses by

operative laparoscopy can be performed safely, with reduced morbidity and patient disability, and at a reduced cost.³³ Although randomised control trials are lacking, a recent critical appraisal showed laparoscopic surgery to be equivalent to laparotomy for ovarian endometriosis.³⁴ In a comparison of two surgical series for recurrent endometriosis³⁵ rate of recurrence of dyspareunia and need for third surgery was higher in laparotomy series. While no significant difference was found between the cumulative pregnancy rates at 24 months in the two groups.

Our review of current best available evidence for the management of endometriosis strongly suggests an urgent need to modify conventional clinical practices in favour of evidence-based practice recommendations.

Best Practice Points

1. Hormonal treatments (combined oral contraceptives, Danazol or Depot medroxyprogesterone acetate) for pain are effective but should be used for six months.
2. Surgical treatments (ablation of endometriosis and LUNA) are effective treatments for pain.
3. Pre or post hormonal treatments for subfertility are not useful - they do not improve pregnancy rates.
4. The most effective treatment for endometriomas is Cystectomy or ablation of cyst wall rather than aspiration or drainage.

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