

Extracts from "Clinical Evidence"

Endometriosis

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Interventions

In women with pain attributed to endometriosis

Beneficial:

Hormonal treatments (danazol, medroxyprogesterone, gestrinone, gonadotrophin releasing hormone analogues)
Combined ablation of endometrial deposits and uterine nerve
Postoperative hormonal treatment
Cystectomy for ovarian endometrioma (better than drainage)

Likely to be beneficial:

Oral contraceptive pill

Unknown effectiveness:

Dydrogesterone
Laparoscopic uterine nerve ablation (LUNA)
Laparoscopic ablation of endometrial deposits
Preoperative hormonal treatment

In women with subfertility attributed to endometriosis

Beneficial:

Laparoscopic ablation or excision of endometrial deposits
Cystectomy for ovarian endometrioma (better than drainage)

Unlikely to be beneficial:

Hormonal treatment
Postoperative hormonal treatment

diagnostic criteria used and the populations studied.¹⁻⁴ In women with dysmenorrhoea, the incidence of endometriosis ranges from 40% to 60%, and in women with subfertility it ranges from 20% to 30%.^{2 5 6} The severity of symptoms and the probability of diagnosis increase with age.⁷ Incidence peaks at about age 40.⁸ Symptoms and laparoscopic appearance do not always correlate.⁹

Aetiology The cause is unknown. Risk factors include early menarche and late menopause. Embryonic cells may give rise to deposits in the umbilicus, while retrograde menstruation may deposit endometrial cells in the diaphragm.^{10 11} Oral contraceptives reduce the risk of endometriosis, and this protective effect persists for up to a year after their discontinuation.⁹

Prognosis We found one small randomised controlled trial (RCT) in which repeat laparoscopy was performed in the women treated with placebo. Over 12 months, endometrial deposits resolved spontaneously in a quarter, deteriorated in nearly half, and were unchanged in the remainder.¹²

Aims To relieve pain (dysmenorrhoea, dyspareunia, and other pelvic pain) and to improve fertility, with minimal adverse effects.

Outcomes American Fertility Society scores for size and number of deposits; recurrence rates; time between stopping treatment and recurrence; rate of adverse effects of treatment. In women with pain: relief of pain, assessed by visual analogue scale and subjective improvement. In women with subfertility: cumulative pregnancy rate, live birth rate. In women undergoing surgery: ease of surgical intervention (rated as easy, average, difficult, or very difficult).¹³

Methods

Clinical Evidence search and appraisal for systematic reviews, January 1999. We sought RCTs by electronic searching of databases, handsearching of 30 key journals, searching the reference lists of other RCTs, and identifying unpublished studies from abstracts, proceedings, and pharmaceutical companies. We used the search strategy and database of the Cochrane Menstrual Disorders and Subfertility Group to identify RCTs on Medline and Embase. We included RCTs that used adequate diagnostic criteria for inclusion of participants (endometriosis diagnosed either by laparoscopy or laparotomy in association with dysmenorrhoea, dyspareunia, other pelvic pain, or infertility) and

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Background

Definition Endometriosis is characterised by ectopic endometrial tissue, which can cause dysmenorrhoea, dyspareunia, non-cyclical pelvic pain, and subfertility. Diagnosis is made by laparoscopy. Most endometrial deposits are found in the pelvis (ovaries, peritoneum, uterosacral ligaments, pouch of Douglas, and rectovaginal septum). Extrapelvic deposits, including those in the umbilicus and diaphragm, are rare. Endometriomas are cysts of endometriosis within the ovary.

Incidence/prevalence In asymptomatic women, the prevalence ranges from 2% to 22%, depending on the



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clinical outcomes. Studies of assisted reproductive technologies were not included.

Question: What are the effects of hormonal treatments?

Four small systematic reviews found that all hormonal treatments except dydrogesterone were equally effective, compared with placebo, in reducing pain attributed to endometriosis. One systematic review of small RCTs found no evidence that hormonal treatments improved fertility. RCTs have found that six months' postoperative treatment with gonadotrophin releasing hormone analogues or a combination of danazol plus medroxyprogesterone reduces pain and delays the recurrence of pain significantly better than placebo. They found no evidence of an effect of postoperative gonadotrophin releasing hormone analogues on fertility.

Benefits

In women with pain attributed to endometriosis: We found four systematic reviews (search dates 1998, 1996, 1997, 1997) comparing six months' continuous suppression of ovulation (using danazol, gestrinone, medroxyprogesterone acetate, dydrogesterone, oral contraceptives, or gonadotrophin releasing hormone analogues) and placebo.¹⁴⁻¹⁷ None of the reviews included more than 200 women. They found that except for dydrogesterone, which was given at two different dosages in the luteal phase, with no evidence of effect, all treatments were equally effective at reducing severe and moderate pain at six months. We found no placebo controlled RCTs of oral contraceptives. One RCT compared oral contraceptives and gonadotrophin releasing hormone analogues in 49 women.¹⁸ It found no differences in rate of relief for all types of pain except menstrual pain, for which oral contraceptive was better. **In women with subfertility attributed to endometriosis:** We found one systematic review (search date 1996), which identified four RCTs in a total of 244 women.¹⁹ The trials evaluated six months' treatment with danazol, medroxyprogesterone, or gonadotrophin releasing hormone analogues compared with placebo. They found no evidence of an effect on the probability of pregnancy (odds ratio for pregnancy compared with placebo 0.83; 95% confidence interval 0.50 to 1.39). **In women who have undergone surgery:** We found no systematic review. We found three placebo controlled RCTs of gonadotrophin releasing hormone analogues in a total of 443 women who had undergone surgery for endometriosis.²⁰⁻²² The smallest trial (n=65) evaluated three months' treatment and found no difference in pain relief; the two larger trials (n=109, n=269) evaluated six months' treatment and found that gonadotrophin releasing hormone analogues significantly reduced pain scores (P=0.008)²¹ and delayed the recurrence of pain by more than 12 months.^{21 22} Two of the trials evaluated fertility (n=65, n=269) and found no difference in pregnancy rates or time to conception.^{20 22} One RCT in 60 women found that postoperative treatment with a combination of danazol (600 mg/day) and medroxyprogesterone (100 mg/day) reduced pain more than placebo six months after surgery.²³

Harms

Gonadotrophin releasing hormone analogues: Adverse effects occurred in 11% of women taking gonadotrophin releasing hormone analogues,¹⁴ which are associated with hypo-oestrogenic symptoms such as hot flushes and vaginal dryness. RCTs have found that adding oestrogen, progesterone, or tibolone significantly relieves hot flushes caused by gonadotrophin releasing hormone analogues (by 50% or more on symptom scores).^{13 24 25} **Danazol:** Adverse effects occurred in 15% of women taking danazol.¹⁵ Danazol is associated with androgenic symptoms of acne, weight gain, and hirsutism and with decreased breast size, muscle cramps, and hunger. **Gestrinone** is associated with a higher frequency of hot flushes than are gonadotrophin releasing hormone analogues, and also with greasy skin and hirsutism.¹⁵ **Medroxyprogesterone:** The trials gave no information on adverse effects of medroxyprogesterone.

Comment

The trials were mainly small, with no long term follow up. Most trials compared gonadotrophin releasing hormone analogues with danazol. No summary statistics could be calculated because the trials compared different drugs with placebo or with no treatment.

Question: What are the effects of surgical treatments?

Option: Laparoscopic uterine nerve ablation (LUNA)

We found insufficient evidence on the effects of laparoscopic uterine nerve ablation in women with pain attributed to endometriosis.

Benefits

We found one systematic review (search date 1998), which identified two small RCTs in women with endometriosis. These found no difference in pain relief between women treated with laparoscopic uterine nerve ablation and those who were not.²⁶

Harms

The trials gave no information on adverse effects. Potential harms include denervation of pelvic structures and uterine prolapse.²⁶

Comment

The trials may have been too small to rule out a beneficial effect.²⁶

Option: Laparoscopic ablation of endometrial deposits

We found insufficient evidence on the effects of laparoscopic ablation of deposits on its own. One RCT found that at six months ablation of deposits combined with laparoscopic uterine nerve ablation reduced pain more than diagnostic laparoscopy. One RCT found that laparoscopic surgery increased fertility more than diagnostic laparoscopy.

Benefits

In women with pain attributed to endometriosis: We found no systematic review and no RCTs evaluating laparoscopic ablation of deposits alone. We found one

RCT comparing the combination of ablation of deposits plus laparoscopic uterine nerve ablation with diagnostic laparoscopy in 63 women.²⁷⁻²⁸ This found that combined ablation reduced pain at six months (median decrease in pain score 2.85 for ablation, 0.05 for diagnostic laparoscopy; $P=0.01$). **In women with subfertility attributed to endometriosis:** We found no systematic review. We found one RCT comparing laparoscopic ablation or excision of endometriotic deposits and diagnostic laparoscopy in 341 women with subfertility attributed to mild or moderate endometriosis.²⁹ This found that laparoscopic surgery increased cumulative pregnancy rates (relative risk of pregnancy after 36 weeks 1.7, 1.2 to 2.6; NNT 8). **Laser versus diathermy ablation:** We found no RCTs.

Harms

The trials gave no information on adverse effects.²⁷⁻²⁹ Potential harms include adhesions, reduced fertility, and damage to other pelvic structures.

Comment

Further RCTs comparing ablation alone and ablation plus laparoscopic uterine nerve ablation are under way (C Sutton and R Dover, personal communication). A systematic review of laser versus diathermy ablation is planned (C Farquhar and N Johnson, personal communication).

Question: What are the effects of preoperative hormonal treatment?

One RCT found no evidence that preoperative treatment with gonadotrophin releasing hormone analogues facilitated surgery.

Benefits

We found no systematic review. We found one RCT comparing three months' preoperative treatment with a gonadotrophin releasing hormone analogue and no treatment in 75 women with moderate or severe endometriosis.³⁰ There was no difference in ease of surgery between the two groups.

Harms

See above under hormonal treatments.

Comment

The trial may have been too small to rule out a clinically important effect.

Question: What are the effects of treatments for ovarian endometrioma?

Option: Laparoscopic drainage or laparoscopic cystectomy

One RCT found that pain and fertility improved more with cystectomy than with drainage, and there was no evidence of a difference in complication rates.

Benefits

We found no systematic review. We found one RCT comparing laparoscopic cystectomy and laparoscopic drainage in 64 women.³¹ **In women with pain attributed to endometrioma:** The trial found that cystectomy reduced recurrence of pain at two years (odds ratio 0.2, 0.05 to 0.77) and increased the pain free interval after

Key messages

Four small systematic reviews found that all hormonal treatments except dydrogesterone were equally effective, compared with placebo, in reducing pain attributed to endometriosis

One systematic review of small RCTs found no evidence that hormonal treatments improved fertility

Six months' postoperative treatment with gonadotrophin releasing hormone analogues or a combination of danazol and medroxyprogesterone significantly reduces pain and delays the recurrence of pain compared with placebo, but there is no evidence of an effect of postoperative gonadotrophin releasing hormone analogues on fertility

We found insufficient evidence on the effects of laparoscopic uterine nerve ablation in women with pain attributed to endometriosis and on the effects of laparoscopic ablation of deposits on its own

One RCT found no evidence that preoperative treatment with gonadotrophin releasing hormone analogues facilitated surgery

One RCT found that pain and subfertility caused by ovarian endometrioma were improved more by cystectomy than by drainage

operation (median interval 19 months *v* 9.5 months; $P<0.05$). **In women with subfertility attributed to endometrioma:** Cystectomy increased the pregnancy rate (66.7% *v* 23.5%; odds ratio 8.25, 1.15 to 59; $P<0.05$).

Harms

The trial reported no intraoperative or postoperative complications in either group.

Comment

None.

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A memorable patient Check, check, and check again

A well known author came in at the end of our tuberculosis clinic with an x ray which suggested tuberculosis. He was well but his contact was a man with AIDS and tuberculosis on the ward. He had no symptoms and the physical examination was normal so, as is customary, I asked him to provide some sputum, which he managed with great perseverance, and blood and arranged to see him a few days later.

He had a partner and child, and I called them to the contact clinic for Heaf tests and chest x ray examinations, which turned out to be negative. His blood tests were normal and the sputum was negative on direct examination, but I was so sure that his chest x ray film showed active tuberculosis that I was quite ready to embark on bronchoscopy and treatment. All the normality made me suspicious and, before committing the act of writing the prescription, I asked him to have another chest x ray examination.

Surprisingly, this was completely normal. So at least he did not have tuberculosis and I could send him on his way with sincere apologies for the inconvenience, unnecessary investigations, and anxiety caused by a monumental error. But he was pleased that he had not had a bronchoalveolar lavage.

His chest x ray film had his name typed on a label stuck over the top right hand corner. Peeling it off I found another name which I later identified as belonging to a man who had attended the cardiology clinic on the same morning as the tuberculosis clinic. I rang him at home and got his mother who was sufficiently surprised that I decided to confide the reason for my call.

He was a postgraduate geology student living at university, but he was due in town the next day and I managed to meet him. He had done his MSc in Paris the previous year and been afflicted by a severe flu-like

illness with anorexia, weight loss, cough, and haemoptysis which resolved after six weeks or so. His Parisian doctor had been so excited by a mitral murmur that he had quite forgotten to arrange a chest x ray examination. So, 16 months later, he had eventually come to the cardiology clinic at our hospital for follow up and had been sent for a routine examination.

His repeat x ray examination was abnormal and his sputum was full of acid-fast bacilli, so the diagnosis was not in doubt. One further complication: he was just about to embark on an expedition up to 19 000 feet in the Himalayas. A straw poll of expert tuberculologists was exactly divided as to whether he should be forbidden or allowed to go.

The explanation for the extraordinary error: the radiographer could not believe that the abnormal x ray film could have been of the fit young man who bounced in from the cardiology clinic, but she felt that it must have come from the man who told her all about his contact with a tuberculous patient on the AIDS ward so she swapped the names.

Never believe what you see if it does not make sense. Check, check, and check again.

Geoff Scott *consultant clinical microbiologist, London*

We welcome articles of up to 600 words on topics such as *A memorable patient*, *A paper that changed my practice*, *My most unfortunate mistake*, or any other piece conveying instruction, pathos, or humour. If possible the article should be supplied on a disk. Permission is needed from the patient or a relative if an identifiable patient is referred to. We also welcome contributions for "Endpieces," consisting of quotations of up to 80 words (but most are considerably shorter) from any source, ancient or modern, which have appealed to the reader.