Endometriosis - Management

Scenario: Diagnosis of endometriosis

When should I suspect endometriosis?

- **Suspect endometriosis in women who present with:**
  - Secondary dysmenorrhoea (which may be severe) — usually before or during menstruation.
  - Deep dyspareunia.
  - Chronic pelvic pain.
  - Ovulation-related pain.
  - Cyclical or peri-menstrual bowel or bladder symptoms, with or without abnormal bleeding or pain.
  - Subfertility.
  - Pain on defecation (especially during menses).
  - Painful Caesarean-section scar.
  - Painful micturition (especially during menses). This is very rare.
- In adolescents, consider endometriosis if pain is unresponsive to the combined oral contraceptive pill and to nonsteroidal anti-inflammatory drugs.
- **Examination is likely to be normal,** as most endometriosis is mild or moderate in severity. However, more extensive endometriosis should be suspected if, on a speculum and bimanual pelvic examination:
  - There is localized pelvic tenderness, a fixed retroverted uterus, tenderness of the uterosacral ligaments, or enlargement of the ovaries (due to cystic lesions).
  - There are palpable nodules on the uterosacral ligaments (like a string of beads) or in the pouch of Douglas. Nodules are more likely to be felt during menstruation but pelvic examination at this time is not acceptable to many women.
  - Lesions are visible in the vagina or on the cervix.
- **Consider referring all women with suspected endometriosis,** as laparoscopy is usually required to confirm the diagnosis.

Basis for recommendation

These recommendations are based on expert advice in guidelines published by the Royal College of Obstetricians and Gynaecologists [RCOG, 2006] and the European Society of Human Reproduction and Embryology [Kennedy et al, 2005], and two non-systematic reviews [Brosens, 1997; Farquhar, 2007].

- A non-systematic review found that [Laufer et al, 2003]:
  - Endometriosis in adolescents may present with acyclic, cyclic, or continuous pelvic pain.
  - Several studies have shown that between 50% and 70% of adolescents undergoing laparoscopy for pelvic pain unresponsive to nonsteroidal anti-inflammatory drugs and the combined oral contraceptive pill have endometriosis.

What else might it be?

- Consider other conditions that may present with similar symptoms:
  - Uterine causes, such as adenomyosis or uterine fibroids.
  - Adhesions.
  - Interstitial cystitis or recurrent urinary tract infections.

- Irritable bowel syndrome or other bowel pathology.
- Pelvic inflammatory disease.
- Primary dysmenorrhoea.
- Musculoskeletal disorders, such as referred pain from degenerative disc disease of the spine.
- Malignancy (of the cervix, uterus, ovary, rectum, or bladder).
- Congenital anomalies of the reproductive tract.

Basis for recommendation

- These recommendations are based on expert advice in two textbooks [Edmonds, 1999; Drife and Magowan, 2004b] and a non-systematic review [Practice Committee of the American Society for Reproductive Medicine, 2008].

Endometriosis - Management

Scenario: Endometriosis

How should I manage a woman with suspected endometriosis?

- **Consider referring all women with suspected endometriosis** to a gynaecologist (especially women with severe symptoms or subfertility) to confirm the diagnosis by laparoscopy, and for medical or surgical management.
- The choice regarding referral and treatment depends on:
  - The wishes of the woman.
  - The severity and duration of symptoms.
  - Requirements for fertility.
  - Previous treatment.
  - Abnormalities identified on pelvic ultrasound or clinical examination.
- Prescribe analgesia for women who are awaiting referral or who do not wish to be referred, if symptoms are troublesome and the women does not require contraception or does not wish to take hormonal treatment.
  - A nonsteroidal anti-inflammatory drug (NSAID, such as ibuprofen, naproxen, mefenamic acid, or diclofenac) is recommended first-line. Ibuprofen may be preferred because of its more favourable risk–benefit ratio.
  - Offer paracetamol if an NSAID is poorly tolerated or contraindicated, or in addition to an NSAID if the response is insufficient. Regular use may be more effective than as-required use.
  - Codeine (15 mg or 30 mg) may be added to paracetamol and/or an NSAID if the response is insufficient.
- **If symptoms are troublesome and are not sufficiently controlled with analgesics or contraception is required,** consider prescribing hormonal treatment.
  - Consider an ultrasound scan to rule out a pelvic mass (such as an endometrioma) before prescribing hormonal treatment.
  - Consider the combined oral contraceptive (COC) pill, first-line.
  - Monophasic COCs containing 30–35 micrograms of ethinylestradiol, and either norethisterone or levonorgestrel, are usually the first choice.
  - It is not known whether the COC should be taken conventionally, continuously without a break, or in a tricycling regimen to control endometriosis.
  - CKS suggests a three month trial of conventional treatment, then switching to tricycling after three months if necessary. Some women may find continuous use helpful.
  - Consider a progestogen if the COC is contraindicated:

- A 3-month course of medroxyprogesterone (not contraceptive).
- A 4–6-month course of norethisterone (not contraceptive).
- A progestogen-only contraceptive is a further alternative.
- Not all women will achieve amenorrhoea with this method.
- If symptom relief is not obtained after a 3–6 month trial, consider switching to an alternative hormonal method or refer.
- Suitable progestogen-only contraceptives include the levonorgestrel-releasing intra-uterine system (Mirena®), Cerazette® (a progestogen-only pill), depot medroxyprogesterone acetate (Depo-Provera®), or the etonogestrel subdermal contraceptive implant (Nexplanon® [formely Implanon®]).
- See the CKS topic on Contraception for detailed information on prescribing hormonal contraceptives. Whilst licensed for contraceptive use, the COC, Cerazette®, Depo-Provera®, Mirena®, and Implanon® are not specifically licensed for the treatment of endometriosis.

- Review after 10–12 weeks (earlier if symptoms are troublesome). Refer if there is no improvement.

Basis for recommendation

Referral for diagnosis

- Establishing a diagnosis of endometriosis on the basis of symptoms alone is difficult because symptoms are variable and overlap with other conditions (for example pelvic inflammatory disease and irritable bowel syndrome).
- There are no investigations in primary care that are helpful in making a diagnosis of endometriosis. However, CKS expert reviewers commented that:
  - A normal ultrasound scan of the pelvis does not exclude endometriosis but can be reassuring, particularly as it can exclude ovarian endometrioma with good certainty.
  - A successful trial of hormonal suppression therapy (for example COC or oral progestogens), in the presence of normal pelvic ultrasound, is suggestive that at least mild endometriosis may be present.
- Laparoscopy is the gold standard diagnostic test.
  - The Royal College of Obstetrician and Gynaecologists [RCOG, 2006] and the European Society of Human Reproduction and Embryology Special Interest group for Endometriosis and Endometrium guideline development group [Kennedy et al, 2005] recommend visual inspection of the pelvis by laparoscopy as the gold standard diagnostic test [RCOG, 2006] except, rarely, when the disease is visible (such as in the posterior vaginal fornix).
- Other tests are less useful:
  - Transvaginal ultrasound has no value in diagnosing peritoneal deposits but is useful to confirm or exclude an ovarian endometrioma [RCOG, 2006].
  - There is insufficient evidence to recommend magnetic resonance imaging as a useful diagnostic test for endometriosis [Kennedy et al, 2005; RCOG, 2006].
  - Although serum CA-125 may be elevated in endometriosis, it has no value as a diagnostic tool [Kennedy et al, 2005].

Nonsteroidal anti-inflammatory drugs

- Although there is good evidence that NSAIDs are effective in the treatment of primary dysmenorrhoea, there is less evidence regarding their use in women with secondary dysmenorrhoea or confirmed endometriosis. A Cochrane systematic review (that included only one small randomized controlled trial) showed:
  - Naproxen may be no more effective than placebo in the management of endometriosis-associated pain.
  - Insufficient evidence to indicate whether one NSAID is more effective than any other for the treatment of endometriosis.
- Despite the lack of evidence to support their use, NSAIDs are widely prescribed for the treatment of endometriosis-associated pain and seem to be effective for many women.

- Ibuprofen, diclofenac, naproxen, and mefenamic acid are recommended in the treatment of endometriosis-associated pain because:

  - Ibuprofen is considered to have a lower risk of gastrointestinal adverse effects than other NSAIDs [García Rodríguez and Hernández-Díaz, 2001; BNF 57, 2009].

  - Naproxen and diclofenac are associated with an intermediate risk of gastrointestinal adverse effects; mefenamic acid, having a short half-life, is likely to be associated with a low-to-intermediate risk [García Rodríguez and Hernández-Díaz, 2001; BNF 57, 2009].

Paracetamol

- CKS found no trials on the use of paracetamol to treat endometriosis-associated pain.
- There is only very limited evidence from one small (n = 35) randomized controlled trial for its use in the relief of primary dysmenorrhoea. This trial showed paracetamol (at a sub-therapeutic dose) to be no better than placebo.

Codeine

- CKS found no direct evidence on the use of codeine in the treatment of endometriosis-associated pain. However, the addition of codeine seems reasonable in women who are unable to take an NSAID or who do not get adequate pain relief from paracetamol plus an NSAID.

Hormonal treatments

- Hormone treatments aim to induce atrophy of ectopic endometrium, either by altering the effect of oestrogen on endometriotic tissue or by reducing circulating oestrogen levels. They reduce endometriosis-associated pain by reducing menstrual blood flow or by inducing amenorrhoea. CKS expert reviewers agreed that although this may alter the laparoscopic appearance of the disease, in practice this was not a concern.

The combined oral contraceptive pill

- The limited evidence available suggests that there is no difference between the effectiveness of the low-dose COC taken cyclically and goserelin in relieving endometriosis-associated pain.
- There is a lack of evidence to guide which COC or treatment regimen to use [Kennedy et al, 2005; RCOG, 2006] therefore, CKS recommends the preparations that are usually used first-line for contraception. See the CKS topic on Contraception for more information. Different treatment regimens may be considered:

  - Conventional use of COCs. There is evidence from a small randomized trial supporting the effectiveness of low-dose oral contraception, used cyclically.

  - Tricycling COCs (using COCs continuously for 3 months followed by 1 week without pills) has not been studied in women with endometriosis, but as it reduces the frequency of menstrual bleeding it may improve quality of life [Nasir and Bope, 2004]. This practice is an off-label use. The regimen is regarded as having a good safety profile, and is well tolerated and acceptable to women (although this does not specifically relate to women with endometriosis) [FFPRHC, 2005].

  - Continuous use (also off-label) could be considered if tricycling does not provide sufficient symptom relief.

  - Evidence for continuous use of COCs comes from a prospective, non-randomized, self-controlled trial of women (n = 50) who had experienced recurrence of dysmenorrhoea within a year of having surgery for endometriosis despite taking the COC cyclically [Vercellini et al, 2003]. Women were offered ethinyl estradiol 0.02 mg and desogestrel 0.15 mg daily for 2 years but could choose at each 6 monthly review whether they wanted to continue daily treatment, revert to the standard 21-day cycle, or discontinue treatment. Forty one women completed the study: 80% were either satisfied (54%) or very satisfied (27%) with the treatment. The following adverse effects were reported: amenorrhoea (38%), spotting (36%), and breakthrough bleeding (13%).

  - The Faculty of Sexual and Reproductive Healthcare (FSRH), formerly the Faculty of Family Planning and Reproductive Healthcare (FFPRHC), does not report on the safety of this regimen, but other authors [Miller and Hughes, 2003] have commented that it is unlikely that the loss of the pill-free week will greatly alter the safety profile.

Oral progestogens that are not contraceptives

- Progestogens induce endometrial atrophy and reduce oestrogen levels by inhibiting ovulation.
- CKS expert reviewers commented that treatment with oral progestogens (medroxyprogesterone or norethisterone) could be started by primary healthcare professionals provided that the symptoms were suggestive of endometriosis. Some expert reviewers suggested an ultrasound scan, to rule out pathology such as an endometrioma, before prescribing.

- Evidence is limited due to lack of data, but continuous high-dose progestogen (medroxyprogesterone acetate) appears to be effective for the treatment of endometriosis-associated pain.
- Luteal phase dydrogesterone does not appear to be effective and is no longer available.
- There is limited evidence for the use of norethisterone.

Progestogen-only contraceptives

- CKS expert reviewers commented that not all women achieve amenorrhoea with these methods.
- Some expert reviewers stressed that a pelvic examination should be normal before prescribing progestogen-only contraception. They also suggested an ultrasound scan to rule out pathology such as an endometrioma.

- Most CKS expert reviewers recommended that the levonorgestrel-releasing intrauterine system (LNG-IUS) could be initiated by a GP, particularly if the woman needed contraception or had experienced good symptom relief from this method in the past.
- There is limited evidence from two small randomized controlled trials and three small prospective observational studies that the LNG-IUS reduces endometriosis-associated pain, with symptom control maintained over 3 years.
- There is limited evidence from a Cochrane systematic review that found one small open-label study for its use following surgery for endometriosis.
- Most CKS expert reviewers recommended that depot medroxyprogesterone (Depot-Provera®) could also be initiated by a GP, particularly if the woman needed contraception or had experienced good symptom relief from this method in the past, but that not all women would achieve amenorrhoea.
- There is limited evidence from one small randomized trial that depot medroxyprogesterone is effective in the treatment of pelvic pain associated with endometriosis.
- Some CKS expert reviewers also recommended that Cerazette® (a progestogen-only pill) or the etonogestrel subdermal implant (Implanon®) were alternatives if the woman needed contraception or had experienced good symptom relief from this method in the past.
- Note that from mid-October 2010, Nexplanon® will replace Impanon®. Nexplanon® is bioequivalent to Implanon®. The main differences are that Nexplanon is radio-opaque, and the insertion technique is different [FSRH, 2010].
- CKS found no evidence assessing the effectiveness of Cerazette® for endometriosis.
- Very limited evidence from a small randomized controlled trial, an open-label study, and five case studies suggests that the etonogestrel subdermal implant might be useful in relieving endometriosis-associated pelvic pain.

Referral if no response to treatment

- Referral if symptoms do not resolve after 3 months' treatment with oral progestogens is based on expert opinion.

What hormonal treatments are available for confirmed endometriosis?

- Treatment for endometriosis may be initiated by a specialist. Follow the specialist management plan if available.
- The following hormonal treatments are used to treat the pain associated with endometriosis and may be initiated in primary or secondary care. They are *not* used to treat subfertility:

- Combined oral contraceptive pill.

- Progestogens:
- Medroxyprogesterone or norethisterone (not contraceptive). See prescribing information on Progestogens.
- Cerazette®.
- Depot medroxyprogesterone acetate (Depo-Provera®).
- The levonorgestrel-releasing intrauterine system (Mirena®).
- The etonogestrel subdermal contraceptive implant (Nexplanon® [formerly Implanon®]).

- See the CKS topic on Contraception for detailed information on prescribing hormonal contraceptives.
- The following hormonal treatments are used to treat the pain associated with endometriosis and may be initiated in secondary care. They are *not* used to treat subfertility:

- Androgens — danazol and gestrinone are not commonly used now.
- See prescribing information on Androgens.
- Gonadotrophin-releasing hormone (GnRH) analogues. See prescribing information on Gonadotrophin-releasing hormone (GnRH) analogues.

Basis for recommendation

Hormone treatments aim to induce atrophy of ectopic endometrium, either by altering the effect of oestrogen on endometriotic tissue or by reducing circulating oestrogen levels.

Androgens

- Androgens (danazol and gestrinone) inhibit secretion of pituitary gonadotrophins. They have androgenic, anti-oestrogenic, and anti-progestogenic activity, and usually cause amenorrhoea and induce a reversible postmenopausal state. Their use is limited by androgenic adverse effects.

- Evidence is limited due to lack of data, but gestrinone appears to be effective for the treatment of pain associated with endometriosis.
- There is limited evidence from a Cochrane systematic review (of two randomized, double-blind, placebo-controlled trials) that danazol is effective at treating the symptoms of endometriosis when compared with placebo, but its use is limited by the occurrence of androgenic adverse effects.

GnRH analogues

- The GnRH analogues (buserelin, goserelin, nafarelin, leuprorelin, and triptorelin) initially stimulate pituitary secretion and then rapidly inhibit secretion due to pituitary down-regulation. This is followed by anovulation, markedly reduced oestrogen levels, and amenorrhoea, inducing a reversible postmenopausal state and regression of endometriotic deposits.
- There is limited evidence, due to poor quality data, that GnRH analogues are as effective as other medical treatments in relieving the pain associated with endometriosis.
- There is evidence from one prospective, double-blind, randomized controlled trial (n = 179) [Hornstein et al, 1995] that 3 months of treatment with nafarelin may be as effective as 6 months of treatment, for pain relief [RCOG, 2006].

Add-back therapy

- GnRH analogues reduce bone mineral density, typically by 4–6% during 6 months of treatment [DTB, 1999]; this bone loss may not be entirely reversible [RCOG, 2006]. They can also cause postmenopausal symptoms. These adverse effects may be reduced by the use of additional add-back therapy.
- Tibolone, or combined progestogen plus oestrogen can be used as add-back therapy for women taking GnRH analogues.

- There is good evidence that both combined progestogen plus oestrogen add-back therapy or danazol add-back therapy are protective of bone mineral density in women treated with GnRH analogues. Progestogen alone is not effective. However, danazol has significant adverse effects that limit its use.
- We have recommended tibolone because most CKS expert reviewers agree that tibolone (2.5 mg daily) is the preferred treatment. There is evidence from a small trial that tibolone is more effective than placebo.

What surgical treatments are available for confirmed endometriosis?

- Surgical treatment aims to remove (excise) or destroy (ablate) areas of endometriosis in order to improve symptoms, and increase the chance of pregnancy.
- Ideally, endometriosis should be removed or destroyed at the time of diagnosis.
- However this may not be possible as symptoms do not always relate to severity: unexpectedly severe disease may be discovered at laparoscopy.
- Surgery for severe endometriosis should only be performed in a specialized tertiary endometriosis centre.
- Surgical treatment may be conservative (minimally invasive when continued fertility is required) or radical (when continuing fertility is no longer required).
- Conservative surgery is generally carried out laparoscopically and includes techniques such as diathermy, laser ablation or excision of deposits, ovarian cystectomy, denervation procedures, and helium plasma coagulation.
- Radical surgery (such as total abdominal hysterectomy or salpingo-oophorectomy) is reserved for women who have completed their families and in whom other treatments have failed.
- Relapse is common after surgical procedures for endometriosis; it may be as high as 50% at 1-year follow up.

Basis for recommendation

Treatment at the time of diagnosis

- The recommendation for laparoscopic surgery at the time of diagnosis is based on guidelines from the Royal College of Obstetricians and Gynaecologists and the European Society of Human Reproduction and Embryology [Kennedy et al, 2005; RCOG, 2006]. There is widespread consensus for treating endometriosis at the time of surgical diagnosis, depending on the experience and competency of the surgeon and the severity of disease present [Varma, Personal Communication, 2009].

Surgery for the treatment of pain associated with mild-to-moderate endometriosis

- The recommendation that laparoscopic ablation of endometrial deposits may relieve pain in some women is based on guidelines from the Royal College of Obstetricians and Gynaecologists and the European Society of Human Reproduction and Embryology [Kennedy et al, 2005; RCOG, 2006].
- Ablation of endometriotic lesions reduces the pain associated with endometriosis compared with diagnostic laparoscopy. There is limited evidence from a Cochrane systematic review (of one small randomized controlled trial [RCT]) that laser ablation, adhesiolysis, and uterine nerve ablation performed together are beneficial in the treatment of pain due to mild or moderate endometriosis compared with diagnostic laparoscopy alone. There is limited evidence from one RCT that women who have a laparoscopy with excisional surgery are likely to have less pain and an improved quality of life at 1 year compared with women who have had a diagnostic laparoscopy alone.
- The Royal College of Obstetricians and Gynaecologists guidelines state that there is no evidence that it is necessary to add laparoscopic uterine nerve ablation (LUNA, which aims to interrupt the nerve pathways that conduct pain sensation from the pelvic area to the brain) to laser ablation. Used in isolation, LUNA has no effect on endometriosis-associated dysmenorrhoea [RCOG, 2006].

- Laparoscopic helium plasma coagulation is a more recent minimally-invasive procedure used to vaporize endometriotic deposits. Current evidence on the safety and efficacy of this procedure is not adequate to recommend its use without special arrangements for consent [NICE, 2006].

Surgery for the treatment of subfertility

- There is evidence that laparoscopic surgery for the treatment of minimal and mild endometriosis may improve the chance of pregnancy, but the evidence is conflicting and limited to two RCTs.
- The role of surgery in improving pregnancy rates in women with moderate-to-severe endometriosis is uncertain. A review from the Practice Committee of the American Society for Reproductive Medicine concluded that women who have moderate or severe endometriosis, without other identifiable infertility factors, may improve their chance of conceiving with conservative surgical treatment such as laparoscopy and possibly laparotomy [Practice Committee of the American Society for Reproductive Medicine, 2006].
- There is evidence from a Cochrane systematic review [Hart et al, 2008] of six non-randomized trials of women with endometrioma that excision of the endometrioma is preferable to drainage and ablation in regard to recurrence of symptoms, recurrence of an endometrioma, and spontaneous pregnancy rates.

Treatment of severe endometriosis

- The Royal College of Obstetricians and Gynaecologists guidelines recommend radical surgery for severe and deeply-infiltrating endometriosis [RCOG, 2006]. There is high morbidity associated with these procedures, and therefore surgery for severe endometriosis should only be conducted by gynaecologists accredited in advanced laparoscopy, and should be performed in specialized tertiary endometriosis centres, where the volume of work and level of expertise ensures the best care for the woman. Multidisciplinary input in the treatment pathway for women with severe endometriosis may involve gynaecologists, radiologists, colorectal surgeons, urologists, anaesthetic pain specialists, and psychologists [Varma, Personal Communication, 2009].

Relapse rate

- A systematic review included three RCTs and found that the absolute benefit on pain relief at short-term follow up (6 months or 1 year) was 30–40% in women with mild to severe endometriosis. Data from case series also analysed in this review suggested that 50% of women still needed analgesics or hormonal treatment at 1 year. One study in the review reported long-term follow up (12–14 years) and found that the repeat surgery rate was 52% in the excision group and 48% in the observational laparoscopic group [Vercellini et al, 2009].

Use of hormonal treatment before or after surgery

- There is insufficient evidence to suggest that hormonal suppression in association with surgery for endometriosis will significantly benefit eradication of endometriosis, improvement of symptoms, pregnancy rates, and overall tolerability. The Royal College of Obstetricians and Gynaecologists does not recommend its use [RCOG, 2006].

How should I manage relapse?

- If the woman has been successfully treated for endometriosis, but the symptoms have returned:
  - Exclude other conditions with similar symptoms.
  - Explain that relapse is common.

- Management options include:
- Treatment with a nonsteroidal anti-inflammatory drug, simple analgesia, and/or medical treatment (such as combined oral contraception for symptomatic relief; particularly if this has worked well in the past and contraception is required). Refer the woman if such strategies prove ineffective.
- Referral, if subfertility is a problem.
- Further hormonal treatment under specialist supervision (referral required) or on specialist advice.
- Surgery.

Basis for recommendation

Relapse rate

- Relapse is common once hormonal treatment is discontinued. In trials of treatment with a gonadotrophin-releasing hormone (GnRH) analogue or danazol, approximately 10–20% of women required further treatment within 12 months. Uncontrolled cohort studies report relapse in about half of women at 5 years [Farquhar and Sutton, 1998].
- Relapse is also common after surgical procedures, and up to 50% of women may require analgesics or hormonal treatment 1 year later [Vercellini et al, 2009].

Further medical treatment

- There is a lack of trial evidence regarding the safety and effectiveness of repeat courses of hormonal treatment for endometriosis. Specialist advice is therefore recommended. Several CKS expert reviewers advised that it would be reasonable to prescribe medical treatment such as combined oral contraception if this had been effective in the past, if subfertility was not an issue, and in the absence of findings that the disease had significantly worsened (such as ovarian endometriomas or deeply infiltrating nodules).

Surgery

- Repeat surgery may also be considered.

What advice should I give about contraception?

- If the woman is currently taking hormonal treatment for endometriosis that does *not* provide contraception, advise her to use a non-hormonal method of contraception to prevent pregnancy.
- Non-contraceptive hormonal treatments include oral medroxyprogesterone, norethisterone, danazol, gestrinone, and gonadotrophin-releasing hormone analogues.
- Contraceptive methods that can be used in women with endometriosis, provided there are no contraindications, include:
- Combined oral contraceptive.
- The levonorgestrel-releasing intrauterine system (Mirena®).
- Depot medroxyprogesterone acetate (Depot-Provera®).
- Progestogen-only pill (such as Cerazette®).
- Etonogestrel-only implant (Nexplanon® [formerly Implanon®]).
- Barrier methods — male or female condom, diaphragm (with spermicide), and cervical cap.
- A copper intrauterine device may worsen dysmenorrhoea but the advantages of this method generally outweigh the risks in women with endometriosis.

- Sterilization should only be undertaken by an experienced surgeon, as severe endometriosis may make access to the fallopian tubes difficult and may increase the risk of complications.

Basis for recommendation

These recommendations are based on the UK medical eligibility criteria for contraceptive use [FFPRHC, 2006].

How do I manage a woman who is considering hormone replacement therapy?

- **For women who are considering hormone replacement therapy (HRT) for menopausal symptoms** and who are not currently prescribed hormonal treatment for endometriosis, discuss treatment options with a specialist. It is important to discuss the risks of HRT and balance the potential benefits against the risks.
  - If HRT is prescribed, monitor for symptoms that may indicate reactivation of the disease. If these occur, either stop the HRT or seek specialist advice.
- **HRT is recommended for young women who have had a bilateral oophorectomy.**
  - Seek specialist advice about whether to prescribe combined HRT, unopposed HRT, combined-continuous HRT, or tibolone.
  - Unless there are contraindications, this should be continued until 50 years of age, when a decision should be made to either stop or continue the HRT.
  - Monitor for symptoms that may indicate reactivation of the disease. If these occur, seek specialist advice.

Basis for recommendation

Seek specialist advice

- CKS recommends seeking specialist advice as it is not clear what type of hormone replacement therapy (HRT) is best for women who have endometriosis, whether or not they have had a total hysterectomy or oophorectomy. The decision should be made on an individual basis taking the following into account:
  - The woman's family history.
  - Unopposed oestrogen may reactivate any residual disease and combined HRT may protect against this [RCOG, 2006].
  - Adenocarcinomas arising from pelvic endometriosis have been reported in women treated with unopposed oestrogen [Van Gorp and Neven, 2002]. Limited evidence suggests that combined HRT is associated with a lower risk of malignant change than treatment with unopposed oestrogens [Oxholm et al, 2007].
  - The risk of breast cancer appears to be increased by all HRT regimens (unopposed oestrogen, combined HRT, and tibolone) but seems to be greatest with combined HRT [Rees and Purdie, 2006].
  - Tibolone may slightly increase the risk of endometrial cancer [Rees and Purdie, 2006].
  - CKS expert reviewers stressed the importance of explaining the risks and benefits to the woman.

Women who have had bilateral oophorectomy

- The Royal College of Obstetricians and Gynaecologists recommend HRT in young women who have had a bilateral oophorectomy, because of the overall health benefits and the small risk of recurrence of endometriosis whilst taking HRT [RCOG, 2006].
- A Cochrane systematic review concluded that although there is a risk that HRT might cause recurrence of endometriosis in women who have had a bilateral oophorectomy for severe endometriosis, the available evidence (from two small randomized controlled trials) is not strong enough to deprive severely symptomatic women of treatment.

- There is no good evidence on whether to recommend an unopposed HRT regimen, a combined-continuous regimen, or tibolone [Rees and Purdie, 2006].
- Prescribing combined HRT after hysterectomy may protect against the unopposed action of the oestrogen on any residual disease [RCOG, 2006]. However the small risk of avoiding reactivation of the endometriosis or malignant transformation should be balanced against the increased risk of breast cancer reported with combined HRT regimens and with tibolone [RCOG, 2006].

When should I refer?

- **If there is a palpable abdominal or pelvic mass on examination that is not obviously uterine fibroids, or not of gastrointestinal or urological origin:**
  - Refer urgently for a scan.
  - If the scan is suggestive of cancer or an urgent ultrasound is not available, refer urgently to a gynaecologist.
- **If endometriosis is suspected** (especially if symptoms are severe or there is difficulty conceiving), consider referral to a gynaecologist to confirm the diagnosis by laparoscopy, and for medical or surgical management.
- **If the woman has been successfully treated for endometriosis, but the symptoms have returned,** seek advice or refer to gynaecologist for consideration of further hormonal treatment or surgery.
- **If there are suspected complications** in a woman with known endometriosis (such as rupture of an endometriotic cyst, or symptoms of bowel obstruction), consider urgent admission.
- **Seek specialist advice regarding prescribing hormone replacement therapy (HRT) or tibolone:**
  - As add-back treatment for women receiving gonadotrophin-releasing hormone analogues.
  - For women who have menopausal symptoms and are not currently prescribed hormonal treatment for endometriosis.
  - For young women who have had a bilateral oophorectomy.

Basis for recommendation

Referral if there is a palpable abdominal or pelvic mass

- These recommendations are based on referral guidelines for suspected cancer from the National Institute for Health and Clinical Excellence [NICE, 2005].

Referral for suspected endometriosis

- Referral is recommended because establishing a diagnosis on the basis of symptoms alone is difficult and laparoscopy is the gold standard diagnostic test [RCOG, 2006].

Referral for subfertility

- CKS found no evidence that hormonal treatment improves the chance of pregnancy in women with endometriosis-associated subfertility. Use of the combined oral contraceptive pill, progestogens, androgens, and gonadotrophin-releasing hormone analogues in women with subfertility may cause adverse effects and delay the use of treatment such as surgery, or assisted reproductive techniques.
- Laparoscopic surgery in women with endometriosis-associated subfertility and minimal or mild disease may improve the chance of pregnancy. However, the evidence is conflicting and limited to two small randomized controlled trials.

- Specialized subfertility treatments, such as in vitro fertilization (IVF), may need to be considered in some women. For further information, see the CKS topic on Infertility.

When to consider urgent admission

- The advice on when to admit urgently is based on expert opinion in standard textbooks [Edmonds, 1999; Jewell, 2003].

Seeking advice before prescribing HRT

- There is a lack of evidence about the risks of HRT in perimenopausal women who have endometriosis: HRT may increase the risk of reactivation of the endometriosis, unopposed HRT may increase the risk malignant change in endometriotic deposits, and combined HRT increases the risk of breast cancer. There is also a lack of evidence about the best type of HRT to prescribe (tibolone, continuous-combined HRT, unopposed HRT, or combined HRT). Therefore, CKS recommends seeking specialist advice before initiating HRT. See HRT for more information.
- HRT can also be used as add-back therapy to manage the adverse effects of gonadotrophin-releasing hormone analogues. This is generally prescribed on the advice of a specialist.

Prescriptions

For information on contraindications, cautions, drug interactions, and adverse effects, see the electronic Medicines Compendium (eMC) (http://emc.medicines.org.uk), or the British National Formulary (BNF) (www.bnf.org).

Nonsteroidal anti-inflammatory drugs

Age from 16 years onwards

Ibuprofen tablets: 400mg three or four times a day when required

Ibuprofen 400mg tablets
Take one tablet three or four times a day when required for pain relief. Do not exceed the stated dose.
Supply 84 tablets.

Age: from 16 years onwards
NHS cost: £1.72
OTC cost: £3.30
Licensed use: yes

Naproxen tablets: 250mg to 500mg twice a day when required

Naproxen 250mg tablets
Take one or two tablets twice a day when required for pain relief. Do not exceed the stated dose.
Supply 112 tablets.

Age: from 16 years onwards
NHS cost: £5.32
Licensed use: yes

Mefenamic acid tablets: 500mg three times a day when required

Mefenamic acid 500mg tablets
Take one tablet three times a day when required for pain relief. Do not exceed the stated dose.
Supply 84 tablets.

Age: from 16 years onwards
NHS cost: £5.94

Licensed use: yes

Diclofenac sodium e/c tablets: 25mg three times a day when required

Diclofenac sodium 25mg gastro-resistant tablets
Take one tablet three times a day when required for pain relief. Do not exceed the stated dose.
Supply 84 tablets.

Age: from 16 years onwards
NHS cost: £1.14
Licensed use: yes

Diclofenac sodium e/c tablets: 50mg three times a day when required

Diclofenac sodium 50mg gastro-resistant tablets
Take one tablet three times a day when required for pain relief. Do not exceed the stated dose.
Supply 84 tablets.

Age: from 16 years onwards
NHS cost: £1.31
Licensed use: yes

Paracetamol

Age from 16 years onwards

Paracetamol tablets: 500mg to 1g up to four times a day

Paracetamol 500mg tablets
Take one or two tablets every 4 to 6 hours when required for pain relief. Maximum of 8 tablets in 24 hours.
Supply 50 tablets.

Age: from 16 years onwards
NHS cost: £0.78
OTC cost: £1.35
Licensed use: yes

Codeine

Age from 16 years onwards

Add on if severe pain: codeine 30-60mg 4-6 hourly if needed

Codeine 30mg tablets
Take one to two tablets every 4 to 6 hours when required for additional pain relief. Maximum of 8 tablets in 24 hours.
Supply 28 tablets.

Age: from 16 years onwards
NHS cost: £1.19
Licensed use: yes

Combined oral contraceptive pill

Age from 16 to 50 years

Microgynon 30: levonorgestrel 150mcg+ethinylestradiol 30mcg

Microgynon 30 tablets
Take one tablet once a day for 21 days. Start the next packet after a 7-day break. See package insert for full instructions.
Supply 63 tablets.

Age: from 16 years to 50 years
NHS cost: £2.99
Licensed use: yes

Patient information: Take the pill at the same time each day. If you forget one or more pills or experience diarrhoea or vomiting and are unsure what to do, seek the advice of a health professional.

Ovranette: levonorgestrel 150mcg + ethinylestradiol 30mcg

Ovranette tablets
Take one tablet once a day for 21 days. Start the next packet after a 7-day break. See package insert for full instructions.
Supply 63 tablets.

Age: from 16 years to 50 years
NHS cost: £2.29
Licensed use: yes

Patient information: Take the pill at the same time each day. If you forget one or more pills or experience diarrhoea or vomiting and are unsure what to do, seek the advice of a health professional.

Levest: levonorgestrel 150mcg + ethinylestradiol 30mcg

Levest 150/30 tablets
Take one tablet once a day for 21 days. Start the next packet after a 7-day break. See package insert for full instructions.
Supply 63 tablets.

Age: from 16 years to 50 years
NHS cost: £2.64
Licensed use: yes

Patient information: Take the pill at the same time each day. If you forget one or more pills or experience diarrhoea or vomiting and are unsure what to do, seek the advice of a health professional.

Rigevidon: levonorgestrel 150mcg+ethinylestradiol 30mcg

Rigevidon tablets
Take one tablet once a day for 21 days. Start the next packet after a 7-day break. See package insert for full instructions.
Supply 63 tablets.

Age: from 16 years to 50 years
NHS cost: £1.89
Licensed use: yes

Patient information: Take the pill at the same time each day. If you forget one or more pills or experience diarrhoea or vomiting and are unsure what to do, seek the advice of a health professional.

Brevinor: norethisterone 500mcg + ethinylestradiol 35mcg

Brevinor 500microgram/35microgram tablets

Take one tablet once a day for 21 days. Start the next packet after a 7-day break. See package insert for full instructions.
Supply 63 tablets.

Age: from 16 years to 50 years
NHS cost: £1.99
Licensed use: yes

Patient information: Take the pill at the same time each day. If you forget one or more pills or experience diarrhoea or vomiting and are unsure what to do, seek the advice of a health professional.

Loestrin 30: norethisterone 1.5mg + ethinylestradiol 30mcg

Loestrin 30 tablets
Take one tablet once a day for 21 days. Start the next packet after a 7-day break. See package insert for full instructions.
Supply 63 tablets.

Age: from 16 years to 50 years
NHS cost: £3.90
Licensed use: yes

Patient information: Take the pill at the same time each day. If you forget one or more pills or experience diarrhoea or vomiting and are unsure what to do, seek the advice of a health professional.

Norimin: norethisterone 1mg + ethinylestradiol 35mcg

Norimin 1mg/35microgram tablets
Take one tablet once a day for 21 days. Start the next packet after a 7-day break. See package insert for full instructions.
Supply 63 tablets.

Age: from 16 years to 50 years
NHS cost: £2.28
Licensed use: yes

Patient information: Take the pill at the same time each day. If you forget one or more pills or experience diarrhoea or vomiting and are unsure what to do, seek the advice of a health professional.

Ovysmen: norethisterone 500mcg + ethinylestradiol 35mcg

Ovysmen 500microgram/35microgram tablets
Take one tablet once a day for 21 days. Start the next packet after a 7-day break. See package insert for full instructions.
Supply 63 tablets.

Age: from 16 years to 50 years
NHS cost: £1.58
Licensed use: yes

Patient information: Take the pill at the same time each day. If you forget one or more pills or experience diarrhoea or vomiting and are unsure what to do, seek the advice of a health professional.

Cilest: norgestimate 250mcg + ethinylestradiol 35mcg

Cilest 250microgram / 35microgram tablets
Take one tablet once a day for 21 days. Start the next packet after a 7-day break. See package insert for full instructions.
Supply 63 tablets.

Age: from 16 years to 50 years
NHS cost: £5.97
Licensed use: yes

Patient information: Take the pill at the same time each day. If you forget one or more pills or experience diarrhoea or vomiting and are unsure what to do, seek the advice of a health professional.

Progestogens

Age from 16 to 60 years

Medroxyprogesterone acetate 150mg syringe (Depo-Provera®)

Medroxyprogesterone 150mg/1ml suspension for injection pre-filled syringes
Give 150mg (1ml) by deep intramuscular injection.
Supply 1 1ml prefilled syringe.

Age: from 16 years to 60 years
NHS cost: £5.01
Licensed use: yes

Patient information: You may experience altered bleeding patterns whilst you are using this injection.

Levonorgestrel 20mcg/24hrs intra-uterine system (Mirena®)

Levonorgestrel 20micrograms/24hours intrauterine system
For insertion into the uterine cavity.
Supply 1 device.

Age: from 16 years to 60 years
NHS cost: £83.16
Licensed use: yes

Patient information: You may experience irregular bleeding for about 6 months after insertion of the device. Seek medical advice if this persists.

Desogestrel 75micrograms (Cerazette®)

Cerazette 75microgram tablets
Take one tablet once a day. See package insert for full instructions.
Supply 84 tablets.

Age: from 16 years to 60 years
NHS cost: £8.85
Licensed use: yes

Patient information: Take the pill at the same time each day. If you forget a pill, take it as soon as you remember, and the next one at your normal time. If you are more than 12 hours late with any Cerazette pill, it may not work. Take it as soon as you remember, and the next one at your normal time. You must use an extra contraceptive method for the next 2 days (48 hours) or you may become pregnant. You should also do this if you vomit within 2 hours of taking the pill or if you have very severe diarrhoea.

Etonogestrel 68mg implant (Nexplanon®)

Etonogestrel 68mg implant
For subdermal implantation.
Supply 1 implant.

Age: from 16 years to 60 years
NHS cost: £90.00
Licensed use: yes

Age from 16 years onwards

Medroxyprogesterone: 10mg three times a day (not contraceptive)

Medroxyprogesterone 10mg tablets
Take one tablet three times a day.
Supply 90 tablets.

Age: from 16 years onwards
NHS cost: £22.16
Licensed use: yes

Patient information: Begin the course of tablets on the first day of your period. Use a non-hormonal (barrier) contraception method whilst you are taking these tablets.

Norethisterone tablets: 5mg twice a day (not contraceptive)

Norethisterone 5mg tablets
Take one tablet twice a day.
Supply 60 tablets.

Age: from 16 years onwards
NHS cost: £5.22
Licensed use: yes

Patient information: Begin the course of tablets on the fifth day of your period. If 'spotting' occurs and does not settle within a few weeks, you may increase to 4 or 5 tablets daily, but reduce to 2 tablets daily once this bleeding between periods has stopped. Use a non-hormonal (barrier) contraception method whilst you are taking these tablets.