A bout de souffle
My mum was a smoker, and watching her struggle to breathe as chronic obstructive pulmonary disease (COPD) took hold was heartbreaking. The treatment options are limited and increasingly ineffective as the condition progresses. Low dose opioids are commonly tried for symptom control, but evidence is sparse.

A small but notable Australian trial of 156 people with COPD and chronic breathlessness found that a week of daily, low dose, oral, extended release morphine (8 or 16 mg/day) didn’t significantly improve the intensity of worst breathlessness compared with placebo. The daily step count didn’t improve either, even at higher doses of up to 48 mg/day. More people who received morphine had serious adverse events such as increased breathlessness, morphine related symptoms, and respiratory failure than those taking placebo (33% v 12%).

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Organ rally
Bike weeks are huge events in the US, with the Sturgis Motorcycle Rally in South Dakota attracting over 400 000 people a year. This cross sectional study using the US national transplant registry for 2005 to 2021 of more than 10 000 organ donors and 35 000 recipients, found that there were 21% more donors and 26% more recipients per day in the regions around seven mass motorbike rallies compared with the four weeks before and after the rallies. Several factors could be at play here; there may have been greater general motorbike use during rallies in the same way that many of us brush off our tennis rackets during Wimbledon; the risks associated with any large scale event such as road congestion; tired bikers travelling long distances to attend a rally being more likely to have a crash; or health services gearing up to register potential donors and do more transplants.

In the US in 2021, 84% of all donated solid organs came from the recently deceased, with motorbike accidents accounting for 11% of them. The injury risk associated with motorbikes is well known, but this is the first study to report on deaths in rallies and the impact on transplant rates. JAMA Intern Med doi:10.1001/jamainternalmed.2022.5431

Thin pickings
When weight loss is important to control diabetes, GLP-1 agonists and SGLT-2 inhibitors are often prescribed, though the weight loss is modest at best.

A novel drug—LY3437943—that combines two incretins (gut hormones that stimulate insulin production in the pancreas), GIP and GLP-1, and a glucagon receptor agonist has shown some promise in lipid, glucose, and weight control. This 12 week, phase 1b, multiple ascending dose study found that a weekly subcutaneous dose of LY3437943 was safe with only mild and transient gastrointestinal side effects and a dose-dependent increase in pulse rate. Glucose levels, body weight, and blood pressure all fell significantly compared with dulaglutide (a GLP-1 receptor agonist) alone. Bigger, longer studies are needed to find out whether the drug’s positive impact on weight and diabetes control can be reproduced and sustained.

Masking the answer
Are N95 masks, which provide a tighter fit and more particle filtration, better than the disposable type of medical masks in protecting healthcare workers from covid-19? This multicentre, randomised, non-inferiority trial of just over a thousand healthcare workers in Canada, Israel, Pakistan, and Egypt who provided routine direct care to patients with covid-19 between 2020 and 2022, found that, over a 10 week period, covid occurred in similar numbers in the medical mask group compared with the N95 group (10.46% v 9.27%).

The overall estimates ruled out a doubling in the chance of getting covid-19 when using medical masks instead of N95 respirators, but heterogeneity between countries (including baseline antibody levels, circulating variants, and vaccination levels) limits the reliability of these findings.

Attention all drivers
This study of 152 registered US drivers aged 16-19 years with attention deficit hyperactivity disorder (ADHD) evaluated a computerised skills-training program to reduce long glances of more than 2 seconds away from the road, something that is known to contribute to accidents. In simulated driving after the training, people in the intervention group took their eyes off the road less than those in the control group, and there was less veering out of lane. In real world driving in the year after training, the trained group had lower rates of long glances away from the road during bursts of acceleration and lower rates of collisions and near collisions.

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Ann Robinson, NHS GP and health writer and broadcaster
EASILY MISSED?

Endometriosis

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This is one of a series of occasional articles highlighting conditions that may be more common than many doctors realise or may be missed at first presentation. To suggest a topic for this series, please email us at practice@bmj.com.

Within this article, we use the terms “women” and “women’s health.” However, we acknowledge that all people assigned female at birth, including those whose gender identity does not align with the sex they were assigned, need access to evidence based care in order to maintain their gynaecological health and reproductive wellbeing.

A 24 year old woman presents to a new GP with three years of pain during sexual intercourse and increasingly painful periods affecting her mood, relationships, and work. Simple analgesia was ineffective and pelvic ultrasound imaging within three months was normal. She has presented five times in the past two years but has received no diagnosis or effective management.

What is endometriosis?

Endometriosis is a condition defined by the presence of endometrial-like tissue outside the uterus.1 It typically occurs in women of reproductive age but prepubertal endometriosis has been reported. Endometriosis is also reported in women after menopause but is thought to have developed prior to menopause.2 3 Globally, it affects 190 million women but a UK survey in 2017 reported that only 20% of the general public had ever heard of it.4 Subtypes include superficial peritoneal (as visualised at laparoscopy, and the most common type); deep (depth of penetration ≥5 mm); and ovarian (ovarian cysts with endometriosis content, also known as endometriomas). In women with endometriosis, 17-44% have an ovarian endometrioma.5 6 Less frequently, endometriosis occurs at other anatomical locations such as the thorax or previous surgical incision sites.7

Long term consequences include impaired quality of life, anxiety, depression, and self-harm.8 9 Central pathway sensitisations may also lead to chronic pain syndromes.10 Symptom severity is frequently discordant between disease subtype and extent1 and data pertaining to natural history are limited, particularly when disease is found incidentally at laparoscopy.

Prevalence estimates vary widely (box, see bmj.com) because of inconsistent presentation and reliance on laparoscopy for diagnosis, access to which varies globally.15 16

Although endometriosis can coexist with other causes of pelvic pain, explicit discussion of these comorbidities, as well as infertility associated with endometriosis, is beyond the scope of this paper.
Why is it missed?

Clinical diagnosis is difficult, partly because the symptoms are often non-specific and may be attributed to other conditions. For example, endometriosis may mimic or cause irritable bowel syndrome. Symptoms may also be misdiagnosed as functional or psychosomatic or dismissed or normalised (for example, as painful periods). Women consistently report difficulties in convincing doctors about the severity of their symptoms; however, some women may also believe that their menstrual symptoms are normal. Despite increased public awareness and clinical education, early recognition of endometriosis remains uncommon, possibly as a result of gaps in evidence about the clinical relevance of mild disease at laparoscopy, poor correlation between symptoms and extent of disease, the need for histological confirmation, limited laparoscopy access, and/or laparoscopy cost.

The average diagnostic delay has been reported as seven years from symptom onset to definitive diagnosis, with variation between countries (approximately eight years in both the UK and Australia). Retrospective data analysis in the UK showed that one third of patients had consulted their GP six times or more before referral, with 39% having two or more gynaecological referrals before receiving a definitive diagnosis. Diagnostic delay is even more common in adolescents, possibly because of the unfounded belief that endometriosis takes time to cause symptoms after menarche.

Cultural barriers to discussing menstruation and sexual symptoms still exist and may cause reluctance or difficulty in reporting them. The lack of reliable non-invasive tests likely also contributes to delays. This is intensified by the variation and methodological quality of endometriosis guidelines, which suggest different diagnostic criteria.

Data analysis showed a third of patients had consulted a GP six times or more before referral

Why does it matter?

Although it is unknown whether earlier treatment affects the course of endometriosis or reduces the incidence of chronic pain syndromes, endometriosis, and associated delays in diagnosis, can cause considerable suffering, distress, impaired quality of life, economic hardship, reduced productivity, and reduced workforce participation.

In the UK, work absenteeism and healthcare costs related to endometriosis cause economic losses of around £8.2bn a year (direct treatment costs are comparable to those for type 2 diabetes and rheumatoid arthritis). Earlier diagnosis and prompt treatment might reduce psychosocial and economic burdens.

According to retrospective population linked data, delayed diagnosis was associated with a reduced chance of pregnancy by 33% in those who required assisted reproductive technology.

Endometriosis poses a diagnostic dilemma in primary care settings, and uncertainty at initial consultations is common. Definitive diagnosis is only possible with laparoscopy in secondary care. However, we encourage GPs to empower patients to advocate for themselves by having early, open discussions about endometriosis as a possible or likely cause of their symptoms, and about consequences and treatment options. Some women may wish to avoid definitive diagnosis with laparoscopy for mild symptoms or when their symptoms are controlled on hormonal therapies.

Improving diagnosis and non-invasive screening tools are among the top 10 research priorities for endometriosis in the UK.

Clinical features

No consensus exists about how to diagnose endometriosis clinically; however, typical gynaecological presentations include painful periods and infertility. Other common symptoms include pelvic pain (which may be cyclical) that occurs with sex, defecation, or urination, gastrointestinal symptoms which may be associated with menstruation, and systemic manifestations such as fatigue. Some patients have no pain symptoms, particularly those with infertility, which may be the presenting complaint or primary concern for some women.

Guidance from the National Institute for Health and Care Excellence (NICE) suggests considering a diagnosis of endometriosis in women and girls presenting with one or more of the following symptoms or signs:

- Chronic pelvic pain
- Period related pain (dysmenorrhea) affecting daily activities and quality of life
- Deep pain during or after sexual intercourse
- Period related or cyclical gastrointestinal symptoms, in particular, painful bowel movements or rectal pain
- Period related or cyclical urinary symptoms, in particular, blood in the urine or pain passing urine
- Infertility in association with one or more of the above

Isolated pelvic examination in primary care is often uninformative but, especially in deep disease, may reveal masses or signs such as reduced organ mobility and enlargement, tender nodularity in the posterior vaginal
who are subsequently diagnosed with superficial or deep sensitivity of 79% and specificity of 94% has been reported pouch of Douglas, site specific tenderness and nodularity (a such as loss of mobility of the ovaries and, within the endometriotic cysts and adenomyosis. Advanced TVUS endometriomas and exclude diff erentials such as non-endometriosis; however, it can reliably identify those with for the identifi cation of deep endometriosis with TVUS by experienced sonographers). 42 The sensitivity of 3D ultrasound fi rst line investigation. 37 TVUS is often normal in those histology is the gold standard for diagnosis 21 37; however, NICE and ESHRE guidance suggests that laparoscopy with Laparoscopy with histological conf ormation NICE and ESHRE guidance suggests that laparoscopy with histology is the gold standard for diagnosis21,37; however, many researchers and clinicians believe that clinical and radiographical features (as above) are suffi cient for diagnosis, particularly for ovarian and deep subtypes.23,37 Similarly, some guidelines (including those from ESHRE39) suggest that laparoscopy may not be indicated for patients with symptoms controlled by medical treatment if the patient is in agreement with a working diagnosis of endometriosis.44

Investigations
No relevant biomarkers
Although it is an active area of research, there are no biomarkers with adequate specifi city or sensitivity to identify endometriosis29-40 (including CA125), according to NICE37 and the European Society of Human Reproduction and Embryology (ESHRE).41

Radiology
NICE recommends transvaginal ultrasound (TVUS) as the fi rst line investigation. 37 TVUS is often normal in those who are subsequently diagnosed with superficial or deep endometriosis; however, it can reliably identify those with endometriomas and exclude diff erentials such as non-endometriotic cysts and adenomyosis. Advanced TVUS specialists might assess for subtle features of endometriosis such as loss of mobility of the ovaries and, within the pouch of Douglas, site specific tenderness and nodularity (a sensitivity of 79% and specifi city of 94% has been reported for the identifi cation of deep endometriosis with TVUS by experienced sonographers).41 The sensitivity of 3D ultrasound for deep endometriosis is 87%.40,41 However, access to specialist ultrasonography is limited in most settings. When TVUS is declined, inappropriate, or unavailable, offer trans-abdominal ultrasound (although sensitivity and specifi city is lower).37 Ovarian and deep endometriosis may be visible on magnetic resonance imaging (MRI), but normal MRI does not exclude endometriosis.40

Laparoscopy with histological conf ormation
NICE and ESHRE guidance suggests that laparoscopy with histology is the gold standard for diagnosis21,37; however, many researchers and clinicians believe that clinical and radiographical features (as above) are suffi cient for diagnosis, particularly for ovarian and deep subtypes.23,37 Similarly, some guidelines (including those from ESHRE39) suggest that laparoscopy may not be indicated for patients with symptoms controlled by medical treatment if the patient is in agreement with a working diagnosis of endometriosis.44

How is it managed?
Primary care management
NICE recommends an initial three month trial of paracetamol or non-steroidal anti-infl ammatory drugs (alone or with a combined oral contraceptive pill or continuous progestogen) in primary care for pain suggestive of endometriosis.17,45

In parallel, offer holistic management for symptoms and psychological support, individualised to patient wishes and fertility priorities, and, after asking about experience with hormonal treatment, the need for contraception, and future pregnancy planning, make shared decisions about trialling hormonal treatment (combined oral contraceptive pill or continuous oestrogen).17 Patient decision aids can support choice of hormonal preparation.46

When to refer
NICE recommends not excluding the possibility of endometriosis if abdominal/pelvic examination, ultrasound, or MRI are normal. When clinical suspicion remains, symptoms persist, or initial management with analgesia persist, consider referral to gynaecology specialists (if available, a specialist endometriosis centre).37

Secondary and tertiary care management
Medical treatments such as gonadotrophin releasing hormone agonists and antagonists, alone or in addition to surgery (pre and post-operatively), may be considered to manage pain and reduce recurrence.31-48 Laparoscopic excisional/ablative surgery is the mainstay of surgical treatment. Complex surgery for deep endometriosis involving the bowel, bladder, or ureter is best managed within a specialist endometriosis centre.49 Surgery may not be definitive and up to 50% of patients who have had surgery report persistent symptoms at five years.49-51 Clinical trials are examining the risks and benefi ts of subtype specific surgery to improve pain, quality of life, and fertility further to inform evidence based and shared decision making.

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Endometriosis: a guide to management

Andrew W Horne,1 Stacey A Missmer2,3

STATE OF THE ART REVIEW

Endometriosis is often chronic, inflammatory, gynaecological disease marked by the presence of endometrial-like tissue outside the uterus, that affects approximately 10% of women during their reproductive years—190 million women worldwide.1 In many, it is associated with chronic painful symptoms and other comorbidities, including infertility.2

Although more than 50% of adults diagnosed with endometriosis report onset of severe pelvic pain during adolescence,3 most young women do not receive timely treatment for endometriosis. Almost 60% of women will see three or more clinicians before a diagnosis of endometriosis is made, after an average of seven years with symptoms.4 Much of endometriosis knowledge is based on concepts in early stages of evidence development or on sparse literature. It is associated with other comorbidities, including infertility.5

Management of pain

A critical aspect of care for those with endometriosis is that associated symptoms progress and recede over the life course, sometimes in response to treatment and sometimes with age or altered environment in pathways that we do not yet understand. For example, pain remediation is often a priority among adolescents,6 while older women may be focused on fertility or on life impacting fatigue.6,100 Furthermore, it has long been believed erroneously that endometriosis and its symptoms did not occur in adolescents and ended at menopause. However, the years of perimenopause101-102 can be a time of increased pelvic pain, with particular attention needing to be paid to symptom management, such as an unexpected return of pain in those patients for whom a treatment regimen had been successful during premenopause.103 Clinicians should focus across the life course on patient centred care, engaging in a dialogue to capture evolving symptomatology but also to collaborate on what symptoms are of most importance to the patient at their life stage.100

In women with a high suspicion of endometriosis, where imaging has not shown obvious pelvic pathology and a laparoscopy has not been performed or is awaited, it can be helpful to give a “working diagnosis” of probable endometriosis and instigate early medical treatment without waiting for a more definitive diagnosis. This is an emerging concept, for which some use “working” and “clinical” diagnosis interchangeably. The growing recognition that endometriosis-associated pain has a mixed pain phenotype (or occupies different points on a continuum) supports a personalised, multimodal, interdisciplinary treatment approach,12 which might include surgical ablation/ excision of lesions, analgesics, hormonal treatments, non-hormonal treatments including neuromodulators, and non-drug therapies (or a combination of the above) (figure).12

Surgical management of endometriosis associated pain

The most recent guidelines for managing endometriosis from the National Institute for Health and Care Excellence and the European Society of Human Reproduction and Embryology (ESHRE) recommend surgery as a treatment option to reduce pain associated with endometriosis.113-114 However, only a limited number of randomised controlled trials (RCTs) have assessed pain outcomes after surgery (and most are small, offer little detail on endometriosis sub-phenotypes visualised at surgery, and have a follow-up period of less than 12 months).

Surgery for superficial peritoneal endometriosis

Little evidence shows that surgery to treat isolated superficial peritoneal endometriosis improves overall symptoms and quality of life.136-138 The uncertainty around surgical management of this subtype is compounded by the limited evidence to allow an informed selection of specific surgical modalities to remove the lesions (for example, laparoscopic ablation versus laparoscopic excision).139-140

Surgery for ovarian endometriosis

To our knowledge, no RCTs have compared cystectomy versus no treatment in women with endometrioma and measured the effect on painful symptoms. Also, no published data indicate a threshold cyst size below which surgery may be safely withheld in the absence of suspicious features on imaging (surgery is the only means by which a tissue specimen can be obtained to rule out ovarian malignancy). Thus, surgical excision is generally considered the optimal treatment for ovarian endometriosis.

Cystectomy, instead of drainage and coagulation, is the preferred surgical approach as it reduces recurrence of endometrioma and endometriosis associated pain.133 Cystectomy should be chosen with caution for women who desire fertility, as a risk of fertility affecting diminished ovarian reserve exists, and a highly skilled conservative approach should be applied to minimise ovarian damage.142
Surgery for deep endometriosis

Surgical treatment to excise deep disease completely is generally considered to be the treatment of choice. Nevertheless, most of the studies that have reported improvements in quality of life following surgical excision of deep endometriosis (typically involving the bowel) have been done in small cohorts of women, usually from single centres, without a comparator arm, and this affects the precision and generalisability of the results. The largest multicentre prospective non-randomised study published to date reported the six, 12, and 24 month follow-up outcomes on nearly 5000 women undergoing laparoscopic excision of deep rectovaginal endometriosis. This showed clinically and statistically significant reductions in premenstrual, menstrual, and non-cyclical pelvic pain, deep dyspareunia, dyschezia, low back pain, and bladder pain at 24 months (data from 524-560 participants for each symptom) with a corresponding improvement in quality of life (575 participants, median score on EuroQol-5D 76, 95% confidence interval 75 to 80). Although the results should be interpreted with caution, because data were missing for >70% of patients at 24 months, assigned score methods suggest that evidence of improvement remained statistically significant.

Most of the studies reporting improvements in quality of life following surgical excision of deep endometriosis have been done in small cohorts

Flowchart for a step-by-step approach to patients with suspected endometriosis (adapted from flowcharts in the NICE114 and ESHRE13 endometriosis guidelines). Imaging does not rule out endometriosis; if "negative" imaging but symptoms highly suggestive of endometriosis, consider "working diagnosis" of probable endometriosis. General practitioners should monitor for emergence of signs of conditions associated with endometriosis and involve/refer to appropriate specialist (eg, gastroenterologist, cardiologist, rheumatologist, psychologist, oncologist). Ideally within accredited specialist endometriosis centre.
Hysterectomy for endometriosis

No RCTs on hysterectomy for the treatment of endometriosis associated pain have been done. Most published articles are retrospective case series, and only a few prospective studies have been reported. Hysterectomy (with or without oophorectomy) with removal of all visible endometriosis lesions should be reserved for women who no longer wish to conceive and who have not responded to more conservative management.

Women with endometriosis should be informed that hysterectomy is not a “cure” for endometriosis and that it is best reserved for women with coexisting adenomyosis (which does occur inside the uterus) or for women with severe pain who have exhausted all other options to improve their symptoms.145 Women should be informed that hysterectomy is associated with long term morbidity,146 including cardiovascular disease,147 among those with and without surgically induced menopause.148 149

Recurrence or progression of endometriosis after surgery

The reported recurrence rate of painful symptoms attributed to endometriosis is high, estimated as 21.5% at two years and 40-50% at five years.146 147 However, although a purist’s definition of “endometriosis recurrence” calls for “second look” laparoscopy, it is most often diagnosed in the real world on the basis of recurrence of symptoms alone. In addition, no robust evidence exists to support an ordered progression of endometriotic lesions. In prospective studies of repeat surgeries, lesions progressed (in 29% of cases), regressed (in 42%), or were static (in 29%).148 Surgical treatment of certain subtypes of endometriosis could also exacerbate painful symptoms.149 150

Pharmacological management of endometriosis pain

Analgesics

Most women with suspected or known endometriosis use over-the-counter drugs, such as non-steroidal anti-inflammatory drugs (NSAIDs). However, the available evidence to support their use is scarce. The data on the benefit of NSAIDs are limited to one small RCT.151 They can be useful as “breakthrough medication” in the management of a pain flare.

Hormonal treatments

Hormone treatments for endometriosis include combined contraceptives, progestogens, gonadotrophin releasing hormone (GnRH) agonists, GnRH antagonists, and aromatase inhibitors (table ). All of these hormone treatments (except the newer GnRH antagonists, which have not been so extensively studied) have been included in a multivariate network meta-analysis of the outcomes “menstrual pain” and “non-menstrual pelvic pain” (pain relief on VAS; total of 1680 participants).114 All treatments led to a clinically significant reduction in pain on theVAS compared with placebo.

The magnitude of this treatment effect is similar for all treatments, suggesting that little difference exists between them in their capacity to reduce pain. Furthermore, symptoms return after cessation of treatment and hormone treatments used to manage endometriosis all have side effects. In addition, although the contraceptive properties of the hormones may be welcome if the woman does not wish to become pregnant, they may be unwanted if fertility is desired.

Ovarian hormone treatment

Preoperative and postoperative hormone treatment

Preoperative hormone treatment has not been shown to improve the immediate outcome of surgery for pain, or reduce recurrence, in women with endometriosis.155 A meta-analysis of 340 participants found that, compared with surgery alone, postoperative hormone treatment of endometriosis reduced pelvic pain after 12 months (standardised mean difference on VAS −0.79, −1.02 to −0.56), but the evidence is very low quality.155 Women with endometriosis who undergo hysterectomy with oophorectomy should be advised to start continuous combined hormone replacement therapy for at least the first few years after surgery.156 This may be changed later to oestrogen alone, but this needs to be balanced with the theoretical risk of reactivation and malignant transformation of any residual endometriosis, which can occur many years later.

Non-hormonal treatments

Analgesic tricyclic antidepressants (for example, amitriptyline, nortriptyline), selective serotonin uptake inhibitors (for example, duloxetine), and anticonvulsants (for example, gabapentin and pregabalin) are sometimes used clinically in the treatment of endometriosis associated pain without a strong evidence base.157 These “neuromodulatory drugs” differ from conventional analgesics, such as NSAIDs, in that they primarily affect the central nervous system’s modulation of pain rather than peripheral mediators of inflammation. However, in a recent RCT for the management of chronic pelvic pain (in the absence of endometriosis), gabapentin was not shown to be superior to placebo and was associated with dose limiting side effects.158

<table>
<thead>
<tr>
<th>Hormone treatments</th>
<th>Treatment</th>
<th>Administration</th>
<th>Potential side effects</th>
<th>Comments</th>
</tr>
</thead>
<tbody>
<tr>
<td>Combined contraceptives</td>
<td>Oral (COC, patch, vaginal ring)</td>
<td>Nausea, headaches</td>
<td>Continuous COC use may be superior to cyclical use for dysmenorrhea114 (no difference in safety profiles115)</td>
<td></td>
</tr>
<tr>
<td>Progestogens</td>
<td>Oral, intramuscular, subcutaneous; intrauterine system</td>
<td>Weight gain, bloating, acne, unscheduled vaginal bleeding; amenorrhea common after prolonged depot use</td>
<td>Cochrane review concluded that continuous progestogens (and gestrinone) are effective therapies for treatment of endometriosis associated pain149</td>
<td></td>
</tr>
<tr>
<td>GnRH agonists</td>
<td>Intranasal, subcutaneous; intramuscular</td>
<td>Vaginal dryness, hot flushes, reduced bone mineral density</td>
<td>Cochrane review suggests GnRH against is more effective than placebo (but inferior to levonorgestrel releasing intrauterine system) in treating endometriosis associated pain150</td>
<td></td>
</tr>
<tr>
<td>GnRH antagonists</td>
<td>Oral</td>
<td>Reserved for women with endometriosis associated pain refractory to other medical or surgical treatment</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Aromatase inhibitors</td>
<td>Oral</td>
<td>May be prescribed in combination with other hormone treatments</td>
<td></td>
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</tbody>
</table>

COC=combined oral contraceptive; GnRH=gonadotrophin releasing hormone; HRT=hormone replacement therapy.
Non-drug management of endometriosis associated pain

Pelvic physiotherapy

An increasing number of women with endometriosis report anecdotal benefit from pelvic physiotherapy. Physiotherapists may support women with activity management (for example, exercises, pacing strategies, and goal setting) and/or use complementary approaches to manage their pelvic pain symptoms (for example, massage and trigger point release therapy).

Establishing the independent benefit of standalone physiotherapy is difficult, because most studies have assessed it in combination with psychological and medical management. Two small pilot studies assessed the outcome of manipulations and massage for relief of endometriosis associated pain specifically, but they included specific patient groups and need expansion and replication to support recommendations for care of endometriosis patients.

Psychology

The most common psychologically based intervention for chronic pain is cognitive behavioural therapy (CBT). Most of the studies of CBT in women with endometriosis are of low quality, designed using different methods, and based on different psychological frameworks (making separation of effects difficult). However, given that CBT has been evaluated across a spectrum of other chronic pain disorders and was shown to be effective for developing pain coping strategies, it should be integrated into individualised treatment plans when needed.

Dietary intervention

Diet has been postulated to affect symptoms of endometriosis. However, very few studies (all of limited quality) have evaluated the benefit of dietary interventions and their effect on endometriosis symptoms. Supplements, such as omega-3 polyunsaturated fatty acids (O-PUFAs), have been investigated as such as omega-3 polyunsaturated fatty acids (O-PUFAs), have been investigated as a way of reducing inflammation and pain in endometriosis. In a recent review, decreased pain scores were observed in women with endometriosis after use of O-PUFAs, which were not seen in controls.

Clinicians should be aware that women with endometriosis have an increased risk of co-presenting with irritable bowel syndrome concomitant with endometriosis associated dyschezia. Patients are not uncommonly referred for gastroenterology evaluation without consideration of potential endometriosis.

Treatment of infertility

Hormonal/medical therapies

No evidence exists of benefit of suppression of ovarian function in women with endometriosis associated infertility who wish to conceive. Following surgery for endometriosis, women seeking pregnancy should not be treated with postoperative hormone suppression with the sole purpose of enhancing future pregnancy rates.

Surgery to increase chance of natural pregnancy

Moderate quality evidence from a Cochrane meta-analysis of three RCTs in 528 participants shows that laparoscopic treatment (ablation or excision) of superficial peritoneal endometriosis increases viable intrauterine pregnancy rates compared with diagnostic laparoscopy only (odds ratio 1.89, 95% confidence interval 1.25 to 2.86). We found no data on live birth rates, and the effect on ectopic pregnancy and miscarriage rates is unclear. No published RCTs have assessed fertility outcomes after surgery for ovarian or deep disease, and surgery is generally recommended only in the presence of painful symptoms. Use of the Endometriosis Fertility index to support decision making for the most appropriate option to achieve pregnancy after surgery (for example, women who may benefit from medically assisted reproduction) has been suggested.

Medically assisted reproduction

Low quality evidence shows that viable intrauterine pregnancy rates are increased in women with superficial peritoneal endometriosis if they undergo intrauterine insemination with ovarian stimulation, instead of expectant management or intrauterine insemination alone. In one RCT of 103 participants randomly assigned either to ovarian stimulation with gonadotrophins and intrauterine insemination treatment or to expectant management, the live birth rate was 5.6 (95% confidence interval 1.18 to 17.4) times higher in the treated couples. In women with ovarian or deep endometriosis, the benefit of ovarian stimulation with intrauterine insemination is unclear. No RCTs have evaluated the efficacy of assisted reproductive technology (ART) versus no intervention in women with endometriosis. Recommendations in guidelines suggesting that ART may be effective for endometriosis associated infertility have been based on meta-analyses of observational studies comparing the outcomes of ART in women with and without endometriosis. Doing surgery before ART for infertility associated with superficial peritoneal endometriosis is not recommended, as the evidence suggesting benefit is based on a single retrospective study of low quality and is not supported by indirect evidence from multiple studies comparing outcomes in women with surgically treated endometriosis and those managed without surgery. Doing surgery for ovarian endometrioma before ART to improve live birth rates is also not recommended. Current evidence shows no benefit, and surgery is likely to have a negative effect on ovarian reserve.

In addition, no evidence shows that doing surgical excision of deep endometriosis before ART improves reproductive outcomes, and this should be reserved for women with concomitant painful symptoms.

Long term monitoring of endometriosis

Follow-up, including psychological support, should be considered in women with confirmed endometriosis, with renewed evaluation and revised treatment plan if symptoms emerge, recur, or worsen over time. However, there is currently no evidence of benefit of regular long term monitoring (eg, imaging) for early detection of endometriotic lesion recurrence, complications, or malignant transformation—in the absence of complex ovarian masses or deep bowel-impacting endometriosis. Given growing evidence of risk of multisystem involving conditions, patient centred whole healthcare dictates that general practitioner monitoring for emergence of signs and symptoms of mental health conditions, cardiovascular disease, immunological and autoimmune disorders, gastrointestinal conditions, or multifocal pain conditions be heightened and referral to non-gynaecological specialist be considered as needed.

Competing interests: See bmj.com.

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CASE REVIEW
Annular scaly erythematous plaque on the right chest

A woman in her 80s presented to dermatology with a three year history of a persisting, mildly pruritic, annular, infiltrated, erythematous plaque with crusts and scales on the right side of her chest (fig 1). She said this area was frequently exposed to the sun in the summer, when she would usually wear vests. Despite treatment with topical corticosteroids and antifungal ointment for various periods over the three years, the lesion persisted with only slight improvement. Microscopic examination of scales for fungi (potassium hydroxide test) was negative.

1 What is the most likely diagnosis?
2 What are the differential diagnoses?
3 What are the therapeutic options?

Submitted by Tian Chen and Dong-Lai Ma
Patient consent obtained.
Cite this as: BMJ 2022;379:e071572

LEARNING POINTS
• Consider Bowen’s disease when presented with a longstanding, well defined, hyperkeratotic, erythematous scaly plaque, which expands slowly in an area of skin exposed to sunlight and shows no obvious effect to topical treatment for eczema or tinea.
• Progression to invasive squamous cell carcinoma of the skin may occur.

Fig 1 | Annular, infiltrated, erythematous plaque with crusts and scales on the right side of the chest

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Fig 2 | Hyperkeratosis, parakeratosis, dyskeratosis, acanthosis, full-thickness atypical keratinocytes with pleomorphic, enlarged nuclei, loss of polarity in the epidermis, and without dermal invasion. (Hematoxylin and eosin stain, original magnification, ×200)
A corneal snowflake in hyperuricaemia

This is an anterior slit lamp photograph showing crystalline keratopathy in a man in his 60s. The patient had a three year history of blurred vision and redness in both eyes. Slit lamp examination found bilateral-peripheral dense corneal deposits in the peripheral cornea with numerous snowflake-like needle shaped crystals extending centrally. Serum uric acid level was raised at 484 μmol/L (reference range 240-420 μmol/L) and serum calcium levels were normal.

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Circulating tumour DNA

Liquid biopsy—the detection and analysis of tumour derived DNA from peripheral blood—has potential for diagnosis and for guiding treatment. In a large series of patients with non-small cell lung cancer, it also had prognostic significance. Three quarters of patients with extrapulmonary disease had detectable amounts of circulating tumour DNA levels, compared with less than half of those with intrapulmonary disease. DNA detection was associated with shorter survival independently of clinical features and tumour volume (Nat Med doi:10.1038/s41591-022-02047-z).

Wilms’ tumour

Nephroblastoma, or Wilms’ tumour, is the most important kidney tumour of childhood, accounting for 5% of paediatric malignancies. Although treatment with a combination of surgery, chemotherapy, and radiotherapy has greatly improved outcomes, evaluation of nearly 300 survivors, median age 30, reveals that chronic endocrine and cardiopulmonary disease, neurocognitive deficits, and impairments in physical function are substantially commoner than in an age and sex matched comparison group (Pediatrics doi:10.1542/peds.2022-056918).

Herpes zoster and cardiovascular disease

Post herpetic neuralgia is the commonest chronic complication of shingles, but data from three large US cohorts also show a raised long term risk of stroke and coronary heart disease. The increase was modest—around 20% to 30% greater than in members of the cohort without a history of shingles—but it persisted for at least 12 years after the rash (JAHA doi:10.1161/JAHA.122.027451).

Metaphors in medicine

All language depends on metaphor, and the lingo that both patients and doctors use to talk about illness is no exception. The imagery is often military. Cancer cells don’t simply multiply but invade and overwhelm the body’s defences. Treatment is targeted. People win or lose battles with their diseases. An essay in the Postgraduate Medical Journal (doi:10.1136/pmj-2022-142074) emphasises the need to listen carefully to the metaphors used by patients. Sometimes the line between the semantic and the somatic is fine.

Dietary supplements and lipid levels

Numerous dietary supplements are promoted as lowering cholesterol levels and improving cardiovascular health. A short trial suggests that none has any useful effect compared with a low dose statin. Participants were randomised to receive daily doses of one of the following: rosuvastatin, placebo, fish oil, cinnamon, garlic, turmeric, plant sterols, or red yeast rice. After 28 days, low density lipoprotein cholesterol levels in those taking rosuvastatin had fallen by more than 30% compared with those taking placebo. None of the dietary supplements led to a decrease (J Am Coll Cardiol doi:10.1016/j.jacc.2022.10.013).

Psoriasis

Drinking alcohol and cigarette smoking have both been thought to increase the likelihood of psoriasis and to make the condition worse in patients with existing disease. A mendelian randomisation study finds that this is only half right. Using data from genome-wide association studies, analyses showed that cigarette smoking roughly doubled the risk of psoriasis. On the other hand, no causal relation was seen with alcohol consumption (BJD doi:10.1111/bjd.21718).

The essay emphasises the need for doctors to listen carefully to the metaphors used by patients about their condition

Pain relief

An intravenous opioid was slightly better at relieving pain than intravenous acetaminophen (paracetamol), according to a randomised study carried out in two US emergency departments among adults aged 65 and over. The mean difference between the two drugs was only 1.0 on a 0-10 pain scale, which was judged too small to matter. Perhaps the most important finding was that pain relief was inadequate for many patients, regardless of which drug they received. Nearly half needed additional analgesic medication (Ann Emerg Med doi:10.1016/j.annemergmed.2022.06.016).