

Clinical review

Diagnosis and management of dysmenorrhoea

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The prevalence of dysmenorrhoea (painful menstrual cramps of uterine origin) is difficult to determine because of different definitions of the condition—prevalence estimates vary from 45% to 95%. However, dysmenorrhoea seems to be the most common gynaecological condition in women regardless of age and nationality.^{1 2} Absenteeism from work and school as a result of dysmenorrhoea is common (13% to 51% women have been absent at least once and 5% to 14% are often absent owing to the severity of symptoms).³ Dysmenorrhoea, especially when it is severe, is associated with a restriction of activity and absence from school or work. Yet despite this substantial effect on their quality of life and general wellbeing, few women with dysmenorrhoea seek treatment as they believe it would not help.^{w1}

Sources and selection criteria

We used Medline (1966 to March 2006) to conduct a literature search of the Cochrane Database of Systematic Reviews on the Cochrane Library, issue 1, 2006, and we searched citation lists of relevant publications, including studies for randomised controlled trials (RCTs) and review articles. We used the following subject headings and keywords: dysmenorrhoea, dysmenorrhea, menstrual pain, period pain, and pelvic pain.

What types of dysmenorrhoea are there?

Dysmenorrhoea is commonly divided into two categories based on pathophysiology (table). Primary dysmenorrhoea is menstrual pain without organic disease, and secondary dysmenorrhoea is menstrual pain associated with an identifiable disease. Common causes of secondary dysmenorrhoea include endometriosis, fibroids (myomas), adenomyosis, endometrial polyps, pelvic inflammatory disease, and the use of an intrauterine contraceptive device.

What causes dysmenorrhoea?

Until recently, many medical and gynaecological texts ascribed the source of dysmenorrhoea to emotional or psychological problems—for example, anxiety, emotional instability, a faulty outlook on sex and menstruation, and imitation of the mother's feelings about menstruation.^{w2} However, experimental and clinical research has identified a physiological reason for dysmenorrhoea—the production of uterine prostaglandins.^{w3} During endometrial sloughing, endometrial

Summary points

Dysmenorrhoea is a common gynaecological condition that is underdiagnosed and undertreated

Simple analgesics and non-steroidal anti-inflammatories are effective in up to 70% of women

Oral contraceptives can be considered for women who wish to avoid pregnancy

For women seeking alternative therapies heat, thiamine, magnesium, and vitamin E may be effective

cells release prostaglandins as menstruation begins. Prostaglandins stimulate myometrial contractions and ischaemia. Women with more severe dysmenorrhoea have higher levels of prostaglandins in menstrual fluid and these levels are highest during the first two days of menstruation.^{w3} Prostaglandins are also implicated in secondary dysmenorrhoea; however, anatomical mechanisms can also be identified, depending on the type of accompanying pelvic disease.

How should dysmenorrhoea be investigated?

A focused history and physical examination are usually sufficient to diagnosis primary dysmenorrhoea. Information about the onset, location, duration, and characteristics of pain, plus any aggravating or relieving factors, should be sought from the patient. The initial onset of primary dysmenorrhoea is usually six to 12 months after menarche, with the onset of ovulatory cycles. Lower abdominal or pelvic pain often occurs for eight to 72 hours and is usually associated with the onset of menstrual flow. Back and thigh pain, headache, diarrhoea, nausea, and vomiting may also be present.

Secondary dysmenorrhoea can occur at any time after menarche, but may arise as a new symptom when a woman is in her 30s or 40s, after the onset of an underlying causative condition. Women may complain of a



Further references (w1-w16) are on bmj.com

change in timing or intensity of pain. Other gynaecological symptoms, such as dyspareunia, menorrhagia, intermenstrual bleeding, and postcoital bleeding, may also be present depending on the underlying condition. If any of the following conditions are present then secondary dysmenorrhoea may be indicated: dysmenorrhoea during the first one or two cycles after menarche; first occurrence of dysmenorrhoea after age 25; late onset of dysmenorrhoea after no history of pain with menstruation; pelvic abnormality on physical examination; infertility (consider endometriosis, pelvic inflammatory disease, or other causes of scarring); heavy menstrual flow or irregular cycles (consider adenomyosis, fibroids, polyps); dyspareunia; and little or no response to treatment with non-steroidal anti-inflammatory drugs (NSAIDs), oral contraceptives, or both.^{w4} In addition, the patient's family history (for example, endometriosis in first degree relatives) may be helpful in differentiating secondary dysmenorrhoea from primary dysmenorrhoea.

A pelvic examination may be necessary for assessing dysmenorrhoea if information on the onset and duration of pain suggests secondary dysmenorrhoea or if previous drug treatments have been unsuccessful. Consider pelvic ultrasound if secondary dysmenorrhoea is suspected. Patients who are at risk of sexually transmitted infection should have the appropriate swabs taken.

Which patients should be referred?

Referral for laparoscopy is indicated if initial measures, such as oral contraceptives and NSAIDs, have not improved symptoms. Referral is also indicated if secondary dysmenorrhoea is suspected (for example, associated menstrual symptoms, such as menorrhagia, intermenstrual or postcoital bleeding, dyspareunia, and/or abnormal pelvic examination) or if the patient has pain management problems with disruption to daily living.

What are the risk factors for dysmenorrhoea?

The severity of dysmenorrhoea is significantly associated with duration of menstrual flow, younger average menarche, smoking, obesity, and alcohol consumption.^{w5} High levels of stress can also greatly increase the incidence of dysmenorrhoea,^{w6} as can depression, anxiety, and disruption of social networks.^{w7} Primary dysmenorrhoea often improves in the third decade of a woman's reproductive life and after childbirth.^{3 w5} The relation between the prognosis of secondary dysmenorrhoea and the severity of underlying disease is unclear.

How is it treated?

Treatment for dysmenorrhoea aims to relieve pain or symptoms either by affecting the physiological mechanisms behind menstrual pain (such as prostaglandin production) or by relieving symptoms. Treatments such as paracetamol, aspirin, and NSAIDs work by reducing the activity of cyclo-oxygenase pathways, thus inhibiting prostaglandin production.^{w8} Treatments such as oral contraceptives work by inhibiting ovulation.

Differential diagnosis of primary and secondary dysmenorrhoea

Primary dysmenorrhoea	Secondary dysmenorrhoea
Onset shortly after menarche	Onset can occur at any time after menarche (typically after 25 years of age)
Lower pelvic or abdominal pain is usually associated with onset of menstrual flow and lasts 8-72 hours	Women may complain of change in time of pain onset during menstrual cycle or in intensity of pain
Back and thigh pain, headache, diarrhoea, nausea, and vomiting may be present	Other gynaecological symptoms (such as dyspareunia, menorrhagia) may be present
No abnormal findings on examination	Pelvic abnormality on physical examination

Simple analgesics

Simple analgesics, such as aspirin and paracetamol, may be useful as a starting point especially when NSAIDs are contraindicated. Two systematic reviews (one of eight RCTs, the other of two such trials) found no significant difference in pain relief between paracetamol and placebo, aspirin, or naproxen, although some of the trials may have been too small to detect clinically important differences.^{1 4 5}

Non-steroidal anti-inflammatory drugs

The different formulations of NSAIDs have similar efficacy for dysmenorrhoea, and pain relief is achieved in most women. Between 17% and 95% (mean 67%) of women achieve pain relief with an NSAID.⁵ Compared with placebo treatment, the number needed to treat is 2.1 for at least moderate pain relief over three to five days.⁵ Gastrointestinal effects (nausea, vomiting, and/or diarrhoea) are of particular concern with NSAIDs. Effects are generally tolerable, but when treating women with risk factors for NSAID induced ulceration, the potential risks and benefits of using an NSAID should be considered. If an NSAID is offered in this situation, a gastroprotective agent may be useful. Women with a history of gastroduodenal ulcer, gastrointestinal bleeding, or gastroduodenal perforation should probably seek alternatives.

COX 2 specific inhibitors

A review of the newest generation of anti-inflammatories has shown that COX 2 (cyclo-oxygenase-2) specific inhibitors are effective for dysmenorrhoea.^{w9} Questions about the cardiovascular and cardioprotective safety of COX 2 inhibitors^{w10} remain unresolved, however, and these drugs have been withdrawn from use in many countries.

Oral contraceptives

Good quality clinical trials of oral contraceptives for dysmenorrhoea are lacking.⁶ One recent RCT found that low dose (or combined) oral contraceptives significantly reduced pain compared with placebo.^{w11} Another recent trial found, however, that although a reduction in dysmenorrhoea was reported in the group who received the oral contraceptive, a similar reduction occurred in the group who took placebo, with no significant differences between the two groups.^{w12} In an open clinical trial of a combined oral contraceptive involving 100 000 women, 65% (23 500 women) of those who had dysmenorrhoea as a pre-existing condition felt relief from dysmenorrhoea as a result of treatment.^{w13} Therefore, despite a lack of many high quality RCTs in this area, there is some evidence in general populations that combined oral contraceptives can effectively treat dysmenorrhoea.

One small trial comparing a combined oral contraceptive with a gonadotrophin releasing hormone for

pain associated with endometriosis showed that it is also effective for secondary dysmenorrhoea.⁷ If a woman also wants to avoid pregnancy, then a combined oral contraceptive may well be a worthwhile treatment option. Adverse effects such as headache, nausea, abdominal pain, bloating, anxiety, loneliness, weight gain, and acne have all been reported in association with combined oral contraceptives, and very rarely such contraceptives can cause serious health problems, such as venous thrombosis, heart attack, and stroke. Women who are already at higher risk of these conditions are generally advised to avoid oral contraceptives. Smoking increases the chances of these more serious adverse effects. However, combined oral contraceptives may also confer health benefits—for example, a reduction in the risk of endometrial and ovarian cancers. Placebo controlled double blind studies have shown that many adverse effects can also occur with similar frequency in placebo control groups, and even in the general population.⁸

Levonorgestrel releasing intrauterine system

The levonorgestrel releasing intrauterine system releases levonorgestrel (20 µ/day) into the uterine cavity for at least five years, thus preventing the thickening of the lining of the uterus. Up to 50% of women using it become amenorrhoeic after 12 months, and reduction in dysmenorrhoea was spontaneously reported by women in non-randomised studies.⁹ The levonorgestrel releasing intrauterine system has also been shown to be effective in reducing dysmenorrhoea in an RCT of women with endometriosis after one year.¹⁰ It should be noted that non-hormone intrauterine devices may result in dysmenorrhoea and may require removal if adequate pain relief is not provided with analgesics.

Combined drug treatments and less common drug treatments

A combination of analgesics and the oral contraceptive or the Mirena intrauterine device is also an option in cases that do not respond to a single treatment. For the small percentage of patients who do not respond to these treatments or to combination treatment, other options exist.

Herbal products or medicines, and dietary supplements: the evidence^{1 16}

Thiamine

One study has shown that 100 mg of thiamine (vitamin B-1) taken daily may be an effective cure for dysmenorrhoea: 87% of patients were cured up to two months after treatment.

Pyridoxine and magnesium

Some evidence also exists that pyridoxine (vitamin B-6) supplements, taken alone or with magnesium, can reduce pain, but more research is needed to confirm this. Magnesium may also be an effective treatment. Women in some trials of magnesium experienced a reduction in period pain and a lowering of prostaglandins in their blood. The therapeutic dose is unclear, however, as magnesium supplements were used several ways (daily or during pain). In addition, some women stopped taking magnesium during the trials, possibly owing to lack of benefit or due to adverse effects such as constipation.

Fish oil

The use of fish oil capsules (omega 3 fatty acids) may also reduce pain, although more research is needed; adverse effects associated with fish oil treatment were mild and included nausea and worsening of acne.

Progestogens and antiprogestogens

Progestogens such as medroxyprogesterone acetate and gestrinone induce anovulation with resulting amenorrhoea and therefore can successfully treat the symptoms of dysmenorrhoea in women with endometriosis.^{11 12}

Gonadotrophin releasing hormones and danazol

Gonadotrophin releasing hormones and danazol confer the same degree of pain relief.¹³ The side effect profiles of these treatments are different, however, with danazol having more androgenic side effects, while gonadotrophin releasing hormones tend to produce more hypo-oestrogenic symptoms. Further studies are also required to establish the optimal supplementation or “add back” regimen of oestrogen for limiting adverse effects.¹⁴

Calcium channel blockers

Calcium antagonists can reduce myometrial activity and relieve dysmenorrhoea by controlling the cytoplasmic concentration of free calcium and thereby the contractions of the uterine muscle. None, however, are licensed for this indication.¹⁵

Alternative therapies

In all, 10-20% of women with primary dysmenorrhoea do not respond to treatment with NSAIDs or oral contraceptives. In addition, some women have contraindications to these treatments. Consequently, researchers have investigated many alternatives to drug treatments.

Herbal products or medicines, and dietary supplements

Herbal and dietary therapies are popular as they can be self administered and are available from health shops, chemists, and supermarkets. This availability, although helpful, can create problems with the control of dosage, quality, and drug interactions. Systematic reviews and RCTs of herbal and dietary supplements have shown that thiamine, pyridoxine, magnesium, and fish oil may be effective in relieving pain, although some of these may be associated with adverse effects (see box).¹⁶ A Bandolier review found evidence from three small RCTs that vitamin E was effective in treating dysmenorrhoea, but it advises caution in use owing to potential adverse effects when used in high doses.¹⁷

Dietary changes

One RCT has shown a significant association between a low fat vegetarian diet and a reduction in symptoms (perhaps by influencing prostaglandin metabolism), but the trial was too small (33 women) to give conclusive results.¹⁸

Exercise

Physical exercise may reduce dysmenorrhoea. Current studies have too many methodological flaws, however, to be able to confirm results.¹⁴ It is hypothesised that exercise works by improving blood flow at the pelvic level as well as stimulating the release of β endorphins, which act as non-specific analgesics.

Transcutaneous electrical nerve stimulation

Transcutaneous electrical nerve stimulation (TENS) involves stimulation of the skin using current at various pulse rates (frequencies) and intensities to provide pain



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Information for patients

Handout on painful menstrual periods. *American Family Physician* 2005;71(2). www.aafp.org/afp/20050115/292ph.html (accessed 25 Apr 2006).

Prodigy patient information leaflet. Department of Health. www.prodigy.nhs.uk/ProdigyKnowledge/PatientInformation/Content/pils/PL54.htm (accessed 25 Apr 2006).

What treatments can we expect in the future?

Current research into treatments for dysmenorrhoea include vasopressin antagonists, nitroglycerin, and magnets.

Vasopressin antagonists

Overproduction of vasopressin, a hormone that stimulates the contraction of muscular tissue, has been identified as a contributing factor to dysmenorrhoea. An RCT of vasopressin antagonist given as a dose of 300 mg/day starting between four hours to three days before the onset of pain and/or bleeding significantly reduced pain compared with placebo.²⁴ No serious adverse effects were noted.

Nitroglycerin

Nitric oxide can relax the uterine muscle. Nitroglycerin formulations are currently used to relax the uterus for various pregnancy problems, so it may have implications for dysmenorrhoea. One study, in patients with dysmenorrhoea, used 0.1-0.2 mg of nitroglycerin taken hourly during first few days of the menstrual cycle and found that pain was reduced in most patients.²⁵ However, 20% of women reported headaches as an adverse effect and more research is needed.

Magnets

An RCT of a static magnet of 0.27 T attached over the pelvic area, compared with a placebo magnet in women with primary dysmenorrhoea showed a significant reduction in pain and irritability symptoms.¹⁵ A larger study to confirm results is planned.

Current research

RCTs are ongoing or currently recruiting for the following interventions for dysmenorrhoea: vitamin K, antispasmodics (drotaverine hydrochloride), TENS, high frequency TENS, extended-regimen oral contraceptives, low dose oral contraceptives, and sildenafil citrate.¹⁶

What is the role of the general practitioner?

A general practitioner should seek from a patient with dysmenorrhoea a history that covers the onset,

Tips for general practitioners

- Adolescents are unlikely to have underlying disease and so do not usually require a pelvic examination
- First line treatment for dysmenorrhoea should be oral contraceptives and/or non-steroidal anti-inflammatory drugs
- Specialist referral is indicated if oral contraceptives and non-steroidal anti-inflammatory drugs fail
- The levonorgestrel intrauterine system is useful in managing secondary dysmenorrhoea

relief. A Cochrane systematic review found limited evidence from small trials that high frequency transcutaneous electrical nerve stimulation reduces pain¹⁹; 42-60% of patients had at least moderate relief, and less use of additional analgesics was needed in one RCT.

Acupuncture

Acupuncture excites receptors or nerve fibres, which, through a complicated interaction with serotonin and endorphins, block pain impulses. A Cochrane systematic review found one RCT showing that acupuncture significantly reduces pain, but more research is needed to confirm this finding.¹⁹

Heat

Heat therapy has been a traditional home remedy for dysmenorrhoea. One RCT has compared its use with the NSAID ibuprofen.²⁰ The heat patch (39°C) used for 12 hours a day was found to be as effective as ibuprofen (400 mg three times a day) and more effective than placebo in reducing pain. Women using both the heat patch and ibuprofen experience the most pain relief. Another RCT found a heat wrap was better than paracetamol for pain relief over an eight hour period.²¹

Spinal manipulation

A Cochrane systematic review of five RCTs found no significant difference between spinal manipulation and placebo manipulation.²²

Surgery

In recent years uterine nerve ablation and presacral neurectomy have been increasingly used when diagnostic laparoscopy has been indicated for dysmenorrhoea. These two surgical procedures interrupt most of the cervical sensory nerve fibres (thus diminishing uterine pain). However, a Cochrane systematic review of nine RCTs found insufficient evidence to recommend the use of nerve interruption in the management of dysmenorrhoea, regardless of cause.²³

Unanswered research questions

Research is needed to determine whether there are features of dysmenorrhoea in adolescence that predict whether a woman will have fertility problems and endometriosis in her 20s and 30s

Further RCTs should focus on comparing oral contraceptives combined with non-steroidal anti-inflammatory drugs (NSAIDs) with NSAIDs alone or with the levonorgestrel intrauterine system

Future RCTs should also consider the effectiveness of the alternative and complementary therapies

location, duration, and characteristics of pain, plus any aggravating or relieving factors. A physical examination including pelvic examination is not generally indicated in adolescent women but should be done in all other women.

NSAIDs relieve symptoms in up to 70% of women, so should be the first line treatment⁵ unless there are contraindications (for example, history of hypersensitivity to aspirin or other NSAIDs, serious comorbidity, and gastrointestinal ulcers or bleeding).

Paracetamol may offer some relief in women who cannot tolerate NSAIDs, although there is less evidence for its efficacy. If contraceptives are required then the combined oral contraceptive may be considered. It may be helpful to give the patient additional information on alternative treatments that evidence supports (for example, heat, thiamine, magnesium, and vitamin E) and information about risk factors that increase the severity of dysmenorrhoea (for example, smoking, obesity, and alcohol consumption). Menstrual cycle suppressants, such as progestogens, danazol, and gonadotrophin releasing hormone analogues, may be considered for resistant dysmenorrhoea, but should normally be used only on specialist advice.

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Corrections and clarifications

Vaccines against cervical cancer provoke US controversy
In this news article by Janice Hopkins Tanne (*BMJ* 2006;332:814, 8 Apr), we gave the wrong name for the GlaxoSmithKline vaccine submitted for approval to the European Agency for the Evaluation of Medicinal Products. The correct name is Cervarix.

Minerva

We misspelt one of the authors' names in the photo item in this Minerva (*BMJ* 2006;332:862, 8 Apr). Emma Thomson does not spell her name with a "p".

Short cuts

More than one reader spotted that we slipped up in the third item of these Short Cuts by Alison Tonks (*BMJ* 2006;332:1025-6, 29 Apr). Candesartan is an angiotensin II receptor antagonist, not an angiotensin converting enzyme inhibitor as we stated.

Hypertension and ethnic group

A mix-up in drug types went uncorrected in this Practice review by Morris J Brown (*BMJ* 2006;332:833-6, 8 Apr). In the second paragraph of the "Treatment" section (p 835) we stated that AB drugs include calcium blockers. They don't—we should have said they include β blockers. Calcium blockers are in fact CD drugs, as we had stated earlier in that paragraph.