

# Primary Dysmenorrhea Consensus Guideline

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## Abstract

**Methods:** Members of this consensus group were selected based on individual expertise to represent a range of practical and academic experience both in terms of location in Canada and type of practice, as well as subspecialty expertise along with general gynaecology backgrounds. The consensus group reviewed all available evidence through the English and French medical literature and available data from a survey of Canadian women. Recommendations were established as consensus statements. The final document was reviewed and approved by the Executive and Council of the SOGC.

**Results:** This document provides a summary of up-to-date evidence regarding the diagnosis, investigations, and medical and surgical management of dysmenorrhea. The resulting recommendations may be adapted by individual health care workers when serving women who suffer from this condition.

**Conclusions:** Dysmenorrhea is an extremely common and sometimes debilitating condition for women of reproductive age. A multidisciplinary approach involving a combination of lifestyle, medications, and allied health services should be used to limit the impact of this condition on activities of daily living. In some circumstances, surgery is required to offer the desired relief.

**Outcomes:** This guideline discusses the various options in managing dysmenorrhea. Patient information materials may be derived from these guidelines in order to educate women in terms of their options and possible risks and benefits of various treatment strategies. Women who find an acceptable management strategy for this condition may benefit from an improved quality of life.

**Key Words:** Primary dysmenorrhea, pelvic pain, menstrual pain, crampy suprapubic pain, endometriosis, menorrhagia, menstrual cramps, length of cycles, regularity of cycles, duration of menses, pelvic examination, management of dysmenorrhea

**Evidence:** MEDLINE and Cochrane databases were searched for articles in English and French on subjects related to primary dysmenorrhea, menstrual pain and pelvic pain from January 1990 to December 2004 in order to prepare a Canadian consensus guideline on the management of primary dysmenorrhea.

**Values:** The quality of evidence is rated using the criteria described in the Report of the Canadian Task Force on the Periodic Health Examination. Recommendations for practice are ranked according to this method.

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## Recommendations

### Section 3: Diagnosis / Differential Diagnosis / Investigations

1. In adolescents experiencing dysmenorrhea in the first 6 months from the start of menarche, and when an anovulatory patient complains of dysmenorrhea, the diagnosis of obstructing malformation of the genital tract should be considered. (III-A)
2. The diagnosis of secondary dysmenorrhea should be considered when symptoms appear after many years of painless menses. (III-A)
3. In view of the high prevalence of dysmenorrhea, and evidence that many women do not seek medical attention for this problem, health care providers should include specific questions regarding menstrual pain when obtaining a woman's medical history. (III-B)
4. In an adolescent who has never been sexually active and has a typical history of mild to moderate dysmenorrhea, a pelvic examination is not necessary. (III-D)
5. A pelvic examination is indicated in all patients not responding to conventional therapy of dysmenorrhea or when an organic pathology is suspected. (III-B)

### Section 4: Non-medicinal Therapeutic Options

1. Unlike low-frequency TENS, high-frequency TENS provides more effective dysmenorrhea pain relief compared with placebo. High-frequency TENS may be considered as a supplementary treatment in women unable to tolerate medication. (II-B)
2. Women who inquire about alternatives to relieve dysmenorrhea, may be instructed that, at the present time, there is limited evidence that acupuncture may be of benefit (II-B), there is no evidence to support spinal manipulation as an effective treatment (II-D), and there is limited evidence to support topical heat therapy (II-B).

### Section 5: Medicinal Therapeutic Options

1. Women suffering from primary dysmenorrhea should be offered NSAIDs as a first-line treatment for the relief of pain and improved daily activity unless they have a contraindication to the use of NSAIDs. (I-A)

**These guidelines reflect emerging clinical and scientific advances as of the date issued and are subject to change. The information should not be construed as dictating an exclusive course of treatment or procedure to be followed. Local institutions can dictate amendments to these opinions. They should be well documented if modified at the local level. None of these contents may be reproduced in any form without prior written permission of the SOGC.**

**Table 1. Criteria for quality of evidence assessment and classification of recommendations**

Level of evidence*	Classification of recommendations†
I: Evidence obtained from at least one properly designed randomized controlled trial.	A. There is good evidence to support the recommendation for use of a diagnostic test, treatment, or intervention.
II-1: Evidence from well-designed controlled trials without randomization.	B. There is fair evidence to support the recommendation for use of a diagnostic test, treatment, or intervention.
II-2: Evidence from well-designed cohort (prospective or retrospective) or case-control studies, preferably from more than one centre or research group.	C. There is insufficient evidence to support the recommendation for use of a diagnostic test, treatment, or intervention.
II-3: Evidence from comparisons between times or places with or without the intervention. Dramatic results from uncontrolled experiments (such as the results of treatment with penicillin in the 1940s) could also be included in this category.	D. There is fair evidence not to support the recommendation for a diagnostic test, treatment, or intervention.
III: Opinions of respected authorities, based on clinical experience, descriptive studies, or reports of expert committees.	E. There is good evidence not to support the recommendation for use of a diagnostic test, treatment, or intervention.

\*The quality of evidence reported in these guidelines has been adapted from the Evaluation of Evidence criteria described in the Canadian Task Force on the Periodic Health Exam.<sup>126</sup>

†Recommendations included in these guidelines have been adapted from the Classification of Recommendations criteria described in the Canadian Task Force on the Periodic Health Exam.<sup>126</sup>

- Oral contraceptives may be recommended for the treatment of primary dysmenorrhea. The added contraceptive advantage may make oral contraceptives a first-line therapy for some women. (1-A)
- Consideration may be given to continuous use of oral contraceptive pills for withdrawal bleeding and the associated dysmenorrhea. (1-A)
- Depot medroxyprogesterone acetate and levonorgestrel intrauterine system have been shown to be effective in the treatment of dysmenorrhea and therefore can be considered as treatment options in the management of primary dysmenorrhea. (II-B)

**Section 6: Surgical Options**

- Surgery constitutes the final diagnostic and therapeutic option in the management of dysmenorrhea. Laparoscopy should be considered in women who have persistent dysmenorrhea despite medical therapy of NSAIDs and/or oral contraceptives. (III-C)
- Hysterectomy may be considered for the management of dysmenorrhea when medical alternatives have been refused or failed and fertility is no longer possible or desired. (II-B)
- As there is limited evidence for use of presacral neurectomy in the management of primary dysmenorrhea, the risks must be carefully weighed against the expected benefits. (III-C)
- Laparoscopic uterosacral ligament resection has not been shown to reduce dysmenorrhea and therefore should not be advocated as a mainstream treatment option. (III-C)

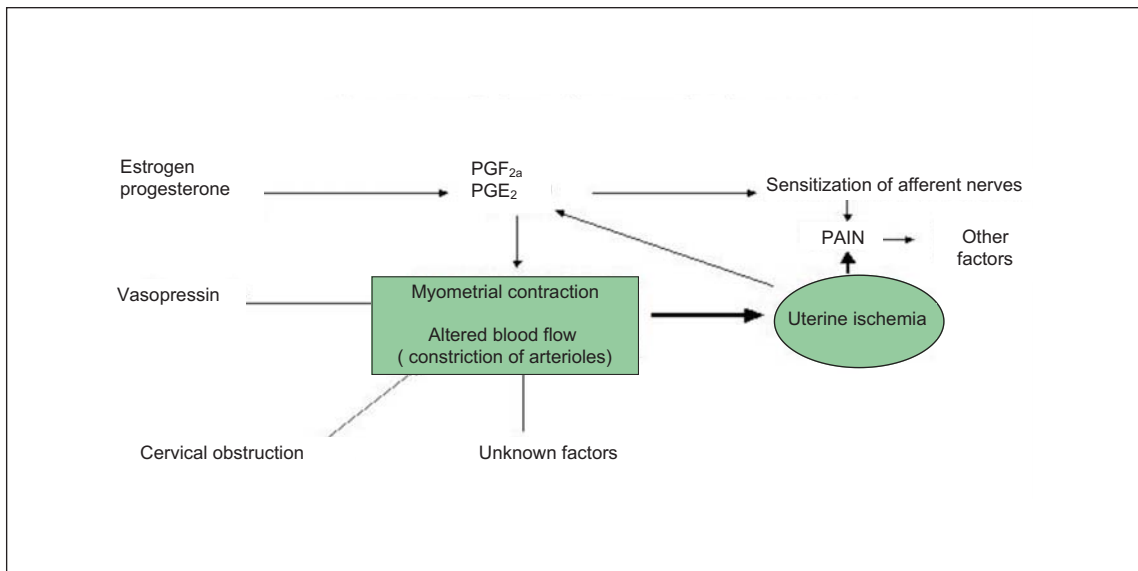
**Section 7: Complementary and Alternative Medicine (CAM)**

- The following CAM has limited support and may be considered in the treatment of primary dysmenorrhea, though further study is required:
    - Vitamin B1 (I-B)
  - The following CAMs showed an initial positive response for the treatment of primary dysmenorrhea and merit further study:
    - Vitamin E (I-C)
    - Fish oil / Vitamin B12 combination (I-C)
    - Magnesium (II-1 C)
    - Vitamin B6; (II-1 C)
    - Toki-shakuyaku-san (II-1 C)
    - Fish oil (II-3 C)
    - Neptune krill oil (II-3 C)
  - The following CAMs have not been shown to have any benefit in the treatment of primary dysmenorrhea and may need further study:
    - Vitamin B6 / Magnesium combination (II-1)
    - Vitamin E (daily) in addition to Ibuprofen (during menses) (II-3)
    - Fennel (II-3)
- J Obstet Gynaecol Can 2005;27(12):1117–1130

**SECTION 1: DEFINITION AND PATHOPHYSIOLOGY**

“Dysmenorrhea” is derived from a Greek root translating to difficult menstrual flow. Dysmenorrhea can be divided into 2 broad categories of primary and secondary. Primary dysmenorrhea is defined as recurrent, crampy pain occurring with menses in the absence of identifiable pelvic pathology. Secondary dysmenorrhea is menstrual pain associated with underlying pelvic pathology such as endometriosis. Primary dysmenorrhea usually begins in

adolescence after the establishment of ovulatory cycles.<sup>1,2</sup> Primary dysmenorrhea is caused by myometrial activity resulting in uterine ischemia causing pain.<sup>1</sup> This myometrial activity is modulated and augmented by prostaglandin synthesis (Figure 1). Uterine contractions can last many minutes and may produce uterine pressures greater than 60 mm Hg. Multiple other factors may play a role in the perception and the severity of the pain.

**Figure 1. Pathophysiology of primary dysmenorrhea**

## SECTION 2: RISK FACTORS

Dysmenorrhea is the most common gynaecological symptom reported by women. Ninety percent of women presenting for primary care suffer from some menstrual pain.<sup>3</sup> Population surveys suggest that, although prevalence rates vary considerably by geographical location, complaints of dysmenorrhea are widespread in diverse populations.<sup>4-10</sup> Furthermore, one third to one half of these women report moderate or severe symptoms. Symptoms are frequently associated with time lost from school, work, or other activities.<sup>11</sup> In spite of the frequency and severity of dysmenorrhea, most women do not seek medical treatment for this condition.<sup>4,12</sup>

Age is a determinant of menstrual pain<sup>12</sup> with symptoms being more pronounced in adolescents than in older women.<sup>9,12,13</sup> Associated factors for more severe episodes of dysmenorrhea may include early menarche,<sup>6,14,15</sup> heavy

and increased duration of menstrual flow<sup>14,15</sup> and family history.<sup>15</sup> There is some evidence that parous women have less severe dysmenorrhea.<sup>6,13,14,16</sup>

The evidence that smoking worsens primary menstrual pain is convincing.<sup>12,13,15-17</sup> One recent prospective study found that dysmenorrhea is also associated with increased exposure to environmental tobacco smoke.<sup>18</sup>

There is some suggestion that more frequent life changes, fewer social supports, and stressful close relationships may be associated with increased dysmenorrhea.<sup>19</sup> There may be an increased prevalence of dysmenorrhea in lower socioeconomic groups.<sup>3</sup>

There is controversy about the association of obesity,<sup>6,14,17</sup> physical activity,<sup>14,17</sup> and alcohol<sup>6,14,16,17</sup> with primary dysmenorrhea.

## SECTION 3: DIAGNOSIS / DIFFERENTIAL DIAGNOSIS / INVESTIGATIONS

### DIAGNOSIS OF PRIMARY DYSMENORRHEA

Typically, primary dysmenorrhea is characterized by a crampy suprapubic pain that begins somewhere between several hours before and a few hours after the onset of the menstrual bleeding. Symptoms peak with maximum blood flow<sup>20</sup> and usually last less than one day, but the pain may persist up to 2 to 3 days. Symptoms are more or less reproducible from one menstrual period to the other.<sup>21</sup> The pain is characteristically colicky and located in the midline of the

lower abdomen but may also be described as dull and may extend to both lower quadrants, the lumbar area, and the thighs. Frequently associated symptoms include diarrhea, nausea and vomiting, fatigue, light-headedness, headache, dizziness and, rarely, syncope and fever.<sup>20,22-25</sup> These associated symptoms have been attributed to prostaglandin release.<sup>1,2</sup>

Onset of dysmenorrhea soon after menarche or in a patient who is clearly anovulatory should alert the physician to the

possibility of an obstructing malformation of the genital tract. Occasionally adolescents may experience menstrual pain with their first periods without any demonstrable underlying cause, especially when the bleeding is heavy and accompanied by clots.<sup>22</sup> Menstrual pain appearing after several years of painless periods is suggestive of secondary dysmenorrhea.

### **Differential diagnosis**

The differential diagnosis of primary dysmenorrhea is summarized in Table 2. Endometriosis is certainly one of the most frequent causes of secondary dysmenorrhea and is a disease that can also affect younger patients. In adolescent girls undergoing laparoscopy for chronic pelvic pain not responding to NSAIDs and oral contraceptives, endometriosis is found with a prevalence of approximately 70%.<sup>26,27</sup> In parous women, adenomyosis should be considered as a possible diagnosis, especially in the presence of menorrhagia and of a uniformly enlarged uterus. Pedunculated submucosal leiomyomas and endometrial polyps may cause obstruction of the cervical canal and trigger painful menstrual cramps. In patients with a history of surgical procedures of the cervix such as a cerclage, a cryotherapy, or a conization, cervical stenosis is a possibility. When dysmenorrhea occurs suddenly in patients who normally have no or mild menstrual pain, pelvic inflammatory disease or pregnancy complications should be ruled out. Congenital obstructing malformations of the müllerian ducts should be considered when dysmenorrhea appears before the establishment of ovulatory menstrual cycles.<sup>21,24</sup> Other causes of chronic pelvic pain (chronic pelvic inflammatory disease, pelvic adhesions, bowel inflammatory diseases, irritable bowel syndrome, interstitial cystitis) may be symptomatic during menses.<sup>28</sup>

## **CLINICAL APPROACH**

### **History**

Many women consider menstrual pain, even severe and incapacitating, as inevitable. Women suffering from primary dysmenorrhea may not seek medical assistance and frequently do not make use of the prescription therapies that are available.<sup>12,22</sup>

When a health care provider identifies menstrual pain on history, an attempt should then be made to differentiate between primary and secondary dysmenorrhea. The history should focus on menstrual history, including age at menarche, length and regularity of cycles, dates of last two menses, and duration and amount of the bleeding. The length of time elapsed between menarche and the beginning of dysmenorrhea should be established. The pain should be clearly defined in terms of type, location, radiation, and

associated symptoms, as well as the chronology of the onset of pain in relation to onset of menstrual bleeding. The severity and duration of symptoms, the progression over time, and the degree of the patient's disability should be established. Significant gastrointestinal or urinary symptoms or the presence of pelvic pain not related to the menstrual cycle may suggest other causes of pelvic pain.

In obtaining a thorough history, it is important to inquire about sexual activity, dyspareunia, and contraception. Many adolescents use dysmenorrhea as a pretext to obtain contraception.<sup>24</sup> Past obstetric and gynaecologic history, in particular, sexually transmitted infections, pelvic infection, infertility, and pelvic surgery, as well as other medical problems should be recorded. A family history of endometriosis should also be sought.

The patient should also be asked about all types of therapy tried in the past. Since many patients do not use medication in adequate dose, it is essential to inquire about the way every medication was utilized. Campbell and McGrath report that in a group of high school girls aged 14 to 21 years using over-the-counter medications for menstrual discomfort, only 31% took them at the recommended daily dosage. Of those using a prescription drug, 13% reported using less than the prescribed dose. In the same study, participants waited a median of 30 minutes after the onset of dysmenorrhea before taking their medication and only 16% of them took it prophylactically.<sup>29</sup> Many patients who state that oral contraceptives are ineffective did not try them for a long enough period to obtain the maximum effectiveness in pain relief.

## **PHYSICAL EXAMINATION**

Women suffering from primary dysmenorrhea are expected to have a normal pelvic examination. However, a normal pelvic examination does not systematically rule out the presence of a pelvic pathology.

An abdominal examination should be done in every patient to rule out palpable pathology. In an adolescent who has never been sexually active and presents with a typical history of mild to moderate primary dysmenorrhea, pelvic examination is not necessary.<sup>21,22-24</sup> However, some authors recommend inspecting the external genitalia of all patients to exclude an abnormality of the hymen.<sup>23</sup> On the other hand, when history is suggestive of organic disease or congenital malformation of the genital tract, or when the patient does not respond to the conventional therapy of primary dysmenorrhea, a complete pelvic examination is indicated.

**Table 2. Differential diagnosis of dysmenorrhea**

Primary dysmenorrhea
Secondary dysmenorrhea
Endometriosis
Adenomyosis
Uterine myomas
Endometrial polyps
Cervical stenosis
Obstructive malformations of the genital tract
Other causes of pain
Chronic pelvic inflammatory disease
Pelvic adhesions
Irritable bowel syndrome
Inflammatory bowel disease
Interstitial cystitis
Sudden onset of dysmenorrhea
Pelvic inflammatory disease
Unrecognized ectopic pregnancy or spontaneous abortion

## INVESTIGATIONS

Laboratory testing or imaging is not required to make a diagnosis of primary dysmenorrhea. Complementary investigations may be ordered when secondary dysmenorrhea is suspected.

There is no evidence for the routine use of ultrasound in the evaluation of primary dysmenorrhea. For women who suffer from dysmenorrhea refractory to first-line therapy, or in women who have a clinical abnormality on pelvic examination, ultrasound may identify causes of secondary dysmenorrhea. In adolescents in whom a pelvic examination is impossible or unsatisfactory, ultrasound may uncover a pelvic mass or an obstructing müllerian malformation. Ultrasonography cannot detect subtle signs of organic diseases such as uterosacral ligament tenderness or nodules and cervical motion tenderness. Ultrasound will not replace a thorough bimanual examination.

Magnetic resonance imaging has been shown to be an interesting diagnostic tool for adenomyosis but since a precise diagnosis of this pathology is rarely essential to therapeutic

decisions, this expensive test has limited clinical usefulness.<sup>28,30</sup>

Hysteroscopy and saline sonohysterography are helpful in the diagnosis of endometrial polyps and submucosal leiomyomas.<sup>30,31</sup>

Laparoscopy is the only procedure that will establish a definite diagnosis of endometriosis, pelvic inflammatory disease, or pelvic adhesions. It should be performed when these pathologies are strongly suspected or when first-line therapy has failed. In adolescent girls who do not respond to therapy, a diagnostic laparoscopy should not be postponed unduly because the prognosis of endometriosis may be improved by an early diagnosis.<sup>32</sup> Gynaecologists are usually experienced with the laparoscopic diagnosis of endometriosis in adult women. In adolescents, however, the appearance of endometriotic implants may have variable morphology. In these younger patients, red flame, white, and clear lesions are more frequently seen than the classical blue-black and powder burn lesions found in adults.<sup>33</sup> Laufer has proposed that using fluid as a distension medium during laparoscopy facilitates the identification of clear lesions that can be easily missed when doing the conventional technique of laparoscopy.<sup>34</sup> This has not been advocated traditionally. Biopsies of visible lesions, especially when atypical, are recommended in order to have histological confirmation of the diagnosis.

## Recommendations

1. In adolescents experiencing dysmenorrhea in the first six months from the start of menarche, and when an anovulatory patient complains of dysmenorrhea, the diagnosis of obstructing malformation of the genital tract should be considered. (III-A)
2. The diagnosis of secondary dysmenorrhea should be considered when symptoms appear after many years of painless menses. (III-A)
3. In view of the high prevalence of dysmenorrhea, and evidence that many women do not seek medical attention for this problem, health care providers should include specific questions regarding menstrual pain when obtaining a woman's medical history. (III-B)
4. In an adolescent who has never been sexually active and has a typical history of mild to moderate dysmenorrhea, a pelvic examination is not necessary. (III-D)
5. A pelvic examination is indicated in all patients not responding to conventional therapy of dysmenorrhea or when an organic pathology is suspected. (III-B)

## SECTION 4: NON-MEDICINAL THERAPEUTIC OPTIONS

Non-medicinal approaches such as exercise, heat, behavioural interventions, and dietary/herbal supplements are commonly utilized by women in an effort to relieve dysmenorrhea.<sup>35</sup> The data on the effectiveness of such interventions remain inconclusive and controversial.

### EXERCISE

In a review of 4 randomized controlled trials and 2 observational studies, exercise was associated with a reduction in dysmenorrhea symptoms.<sup>36</sup> A more recent study found that vigorous exercisers (more than 3 times per week) reported less physical symptoms during menstruation in comparison with sedentary counterparts.<sup>37</sup> In contrast, results from a retrospective questionnaire completed by a cohort of nurses indicated that although exercise was associated with an improvement in mood and stress, it was also associated with a 30% increase in dysmenorrhea symptom severity.<sup>36,38</sup> The majority of these early studies had numerous methodological flaws (non-blinded, confounding factors, lack of objective measurements for pain or level of activity), making it inappropriate to draw definitive conclusions regarding the use of exercise as a supplementary treatment for dysmenorrhea. A Cochrane review on exercise and primary dysmenorrhea is currently being compiled and recommendations are expected in 2005.<sup>39</sup>

### TRANSCUTANEOUS ELECTRICAL NERVE STIMULATION (TENS) / ACUPUNCTURE

TENS involves use of electrodes to stimulate the skin at various frequencies and intensities in an attempt to diminish pain perception. TENS may be divided into high and low frequency. Low-frequency TENS involves pulses delivered between 1 and 4 Hz and high-frequency TENS consists of pulses delivered between 50 and 120 Hz.<sup>40,41</sup> Acupuncture also involves stimulating nerve fibre receptors in an attempt to block pain impulses. A Cochrane review examined 9 randomized controlled trials on the use of TENS or acupuncture for the treatment of primary dysmenorrhea.<sup>42</sup> Overall data indicated that high-frequency TENS provides more effective pain relief when compared with placebo TENS.<sup>40,41,43</sup> Adverse outcomes associated with high-frequency TENS including muscle tightness, headaches, nausea, redness or burning of skin were reported in over 10% of participants.<sup>40</sup> Two trials compared TENS with medical treatment. Ibuprofen was found to be significantly better in relieving pain in comparison than high-frequency TENS.<sup>40</sup> In contrast, no difference in pain relief scores was demonstrated between naproxen and high-frequency

TENS.<sup>41,44</sup> Overall results indicate no significant differences between low-frequency TENS and placebo TENS or placebo pill for relief of dysmenorrhea.<sup>41,43,45-47</sup>

Significantly greater pain relief in the acupuncture group compared with the sham acupuncture group was reported.<sup>48</sup> Due to the limited evidence (only 1 randomized controlled trial), recommendations regarding acupuncture as a treatment for dysmenorrhea must be guarded.

### SPINAL MANIPULATION

A Cochrane review included 5 trials examining spinal manipulation for the treatment of dysmenorrhea. Overall results provided no evidence that spinal manipulation relieves dysmenorrhea.<sup>49</sup> No significant differences in adverse effects were reported by the spinal manipulation group in comparison to the sham treatment group.<sup>50</sup>

### BEHAVIOURAL INTERVENTIONS

Behavioural interventions used in the treatment of dysmenorrhea include procedures such as biofeedback, desensitization, Lamaze exercise, hypnotherapy, and relaxation training.<sup>51</sup> Case studies suggest that behavioural interventions may be effective in treating dysmenorrhea.<sup>51</sup> Because of the limited studies no recommendation can be formulated at this time. A Cochrane protocol examining behavioural interventions for primary and secondary dysmenorrhea was published in 2000, but has since been withdrawn from publication.<sup>52</sup>

### TOPICAL HEAT

A randomized placebo-controlled trial compared the effectiveness of topically applied heat for dysmenorrhea with the use of oral ibuprofen and placebo treatments. Results indicate that the 3 treatment groups – heated patch plus ibuprofen, heated patch plus placebo pill, and unheated patch plus ibuprofen – demonstrated significantly greater pain relief than the unheated patch plus placebo pill control ( $P < 0.001$ ). Low-level topical heat therapy was as effective as ibuprofen for the treatment of dysmenorrhea. Furthermore, there was faster improvement in pain relief when heat was applied with ibuprofen compared with the ibuprofen and unheated patch control.<sup>53</sup>

## Recommendations

1. Unlike low-frequency TENS, high-frequency TENS provides more effective dysmenorrhea pain relief than placebo. High-frequency TENS may be considered as a supplementary treatment in women unable to tolerate medication. (II-B)

2. Women who inquire about alternatives to relieve dysmenorrhea may be instructed that, at the present time, there is limited evidence that acupuncture may be of benefit (II-B), there is no evidence to support spinal manipulation as an effective treatment (II-D), and there is limited evidence to support topical heat therapy. (II-B)

## SECTION 5: MEDICINAL THERAPEUTIC OPTIONS

### 5.1 NON-HORMONAL MEDICAL TREATMENT

Many drugs are commercially available and approved for the use in treatment of primary dysmenorrhea.

#### *Over-the-counter (OTC) medications*

OTC medications available to treat dysmenorrhea in Canada include acetaminophen (Tylenol), acetaminophen plus pamabrom (Midol), acetylsalicylic acid (Aspirin), and ibuprofen (Advil, Motrin).

Acetaminophen is an analgesic/antipyretic drug, not a peripheral prostaglandin synthetase inhibitor, and is a weak cyclooxygenase (COX) inhibitor in the presence of high peroxide concentrations that are present in inflammatory tissues. Acetaminophen produces analgesia by raising the pain threshold. It is a safe drug when used in therapeutic dosages with a good gastrointestinal tolerance and no effect on hemostasis. Acetaminophen can cause liver damage after three or more alcoholic drinks per day<sup>54</sup> and can cross-react with ASA to produce analgesic-induced asthma.<sup>55</sup> The one randomized controlled trial of acetaminophen showed it to be no better than placebo, but the trial was small and also failed to show aspirin to be effective.<sup>56</sup> In many analyses of effectiveness of medications for relief of primary dysmenorrhea, acetaminophen is used as the control.

Acetaminophen and pamabrom are indicated to provide temporary relief of dysmenorrhea. Pamabrom is a mild and short-acting diuretic that relieves water retention. The available information concerning the efficacy of acetaminophen in primary dysmenorrhea is limited and not conclusive with respect to other non-steroidal anti-inflammatory drugs (NSAIDs) or even placebo. The clinical evidence regarding the association with pamabrom is even more scarce.<sup>57</sup>

Adolescents who experience less menstrual discomfort, shorter duration of menstrual discomfort, and less severe disability were more likely to be associated with the use of OTC medications. More than half (56%) of the adolescents who used OTC medications took the pills less often than the maximum daily recommendation.<sup>29</sup> There was a greater

frequency of OTC medication use among young women aged 16 to 21 years than among girls aged 12 to 14 years.<sup>58</sup>

#### NSAIDs

##### *Non-selective NSAIDs*

Research has identified the over-production of uterine prostaglandins (higher levels of prostaglandins F<sup>2</sup>  $\alpha$  and E<sup>2</sup>) as a contributing factor to primary dysmenorrhoea. NSAIDs are analgesics which inhibit the cyclooxygenase (COX) enzymes, thereby inhibiting the production of prostaglandins.

A meta-analysis of 56 trials<sup>59</sup> confirms beyond doubt that all 4 NSAIDs evaluated (naproxen, ibuprofen, mefenamic acid and aspirin) are effective in primary dysmenorrhea. In the systematic review, both naproxen and ibuprofen appeared to be better than aspirin. On a risk-benefit assessment, ibuprofen was better than naproxen because of the side effects of naproxen. All 4 NSAIDs reduced restriction of daily life better than placebo, but only with ibuprofen and naproxen was this statistically significant.

In a review of 63 randomized controlled trials<sup>60</sup> in women with primary dysmenorrhea, NSAIDs were found significantly more effective for pain relief than placebo (OR 7.91; 95% CI 5.65–11.09), although overall adverse effects were also significantly more common (OR 1.52; 95% CI 1.09–2.12). When NSAIDs were compared with each other or with acetaminophen, there was little evidence of superiority of any NSAIDs with regard to either efficacy or safety. Women taking NSAIDs were significantly less likely to report restriction of daily activities and absenteeism from work or school than women taking placebo.

Effective treatment is initiated with the onset of bleeding and/or associated symptoms and should not be necessary for more than 2 to 3 days. Recommended maximum dosing includes starting with an initial loading dose followed by divided doses over 24 hours.

The adverse effects of NSAIDs can include gastrointestinal intolerance, headaches, and drowsiness. It is important for women taking NSAIDs to be aware of the need to take the

**Table 3 Examples of NSAIDs**

Class of NSAIDs	Medications
Acetic acid derivatives (including indole derivatives)	Diclofenac potassium (Voltaren Rapide) Indomethacin (Indocid)
Cyclooxygenase-2 (COX-2) inhibitors	Celecoxib (Celebrex) Meloxicam (Mobicox)
Fenamates	Mefenamic acid (Ponstan, Mefenamic)
Oxicams	Meloxicam (Mobicox)
Propionic acid derivatives	Ibuprofen (Advil, Motrin) Naproxen (Naprosyn) Naproxen sodium (Anaprox)
Salicylic acid derivatives	Acetylsalicylic acid (Aspirin)

medications with food. Aspirin is not recommended for children and adolescents with influenza or chicken pox because of its association with the onset of Reyes syndrome.<sup>61</sup>

**COX-2 inhibitors**

Prostaglandin synthesis is mediated primarily by 2 distinct isoforms of cyclooxygenase (COX-1 and COX-2), which catalyze the metabolism of arachidonate to prostaglandin H<sup>2</sup>. Conventional NSAIDs are non-selective inhibitors of both isoforms of COX. It has been proposed that the therapeutic efficacy of NSAIDs is primarily the result of cyclooxygenase-2 (COX-2) inhibition, whereas their well-recognized gastrointestinal toxicity and disruption of platelet function is derived from inhibition of the cyclooxygenase-1 (COX-1) activity.

In a double-blind study<sup>62</sup> comparing meloxicam 7.5 mg and 15 mg once a day with mefenamic acid 500 mg three times a day, both of the daily doses of meloxicam were comparable to mefenamic acid t.i.d. in relieving dysmenorrhea symptoms, and meloxicam had a better gastrointestinal tolerability profile.

Both rofecoxib (Vioxx) and valdecoxib (Bextra) have been withdrawn from the market because of cardiovascular concerns (rofecoxib, valdecoxib) and potentially life-threatening skin reactions (valdecoxib).

**Transdermal glyceryl trinitrate**

Transdermal glyceryl trinitrate has a relaxing effect on myometrium. In a study comparing glyceryl trinitrate patch with diclofenac,<sup>63</sup> both treatments significantly reduced the pain intensity score by 30 minutes. However, diclofenac continued to be effective in reducing pelvic pain for 2 hours whereas glyceryl trinitrate did not. Headache was significantly increased by glyceryl trinitrate. This study indicates that glyceryl trinitrate has a reduced efficacy and

tolerability by comparison with diclofenac in the treatment of primary dysmenorrhea.

When the glyceryl trinitrate patch was compared with a placebo patch, the pain intensity differences from 1 to 6 hours were statistically significant in favour of the active treatment. The incidence of headache was 26% for the active drug and 6.1% for placebo.<sup>64</sup>

**5.2 HORMONAL MEDICAL TREATMENT**

**Combined oral contraceptive (COC)**

As early as 1937, researchers showed that dysmenorrhea responds favourably to inhibition of ovulation.<sup>65</sup> Research suggests that the COC suppresses ovulation and endometrial tissue growth, thereby decreasing menstrual fluid volume and prostaglandin secretion<sup>66-68</sup> with subsequent decrease in intrauterine pressure<sup>67</sup> and uterine cramping.<sup>69</sup>

COCs are considered an effective treatment for primary dysmenorrhea. Observational studies support an association between COC use and decreased dysmenorrhea.<sup>12,70-77</sup> The lack of a placebo control group is a major limitation of all of these studies. Only five double-blinded, randomized, placebo-controlled trials have examined the effectiveness of COCs in the treatment of primary dysmenorrhea. A 2003 Cochrane Collaborative Review, which included 4 of these studies in its analysis, determined that COCs with more than 35 mcg of ethinyl estradiol were more effective than placebo for pain relief during menses (OR 2.01; 95% CI 1.17-3.33).<sup>66</sup> However, when data were analyzed with a random effects model, the results were not statistically significant (OR 1.68; 95% CI 0.29-9.81). Treatment with COCs compared with placebo did appear to significantly decrease absences from work or school (OR 0.43; 95% CI 0.19-0.99). Only 1 randomized, double-blinded, placebo-controlled study has been conducted using a low-dose COC



preparation. Hendrix et al. found a significant reduction in painful menstrual cramping in users of a COC containing 20 µg of ethinyl estradiol compared with placebo ( $P < 0.001$ ).<sup>78</sup>

When given in a continuous fashion, the COC may have a number of advantages, including a decreased incidence of dysmenorrhea.<sup>79,80,81</sup>

### **Progestin regimens**

Depot medroxyprogesterone acetate (DMPA) works primarily by suppressing ovulation.<sup>82</sup> It also can induce endometrial atrophy.<sup>83</sup> One of its non-contraceptive benefits is amenorrhea with a resultant reduction in the incidence of dysmenorrhea. Amenorrhea rates are 55% to 60% at 12 months and 68% at 24 months.<sup>84</sup> For this reason, DMPA may be considered in the treatment of dysmenorrhea.<sup>85–87</sup>

The progestin only pill (POP) may decrease menstrual flow, and up to 10% of POP users will develop amenorrhea. Menstrual cramping may be decreased; however, no studies have been done to date.

### **Levonorgestrel intrauterine system (LN-IUS)**

LN-IUS (Mirena) is an intrauterine device that releases progestin locally inside the uterine cavity. Although

ovulation is not suppressed, the LN-IUS has a local effect on the endometrium, which becomes atrophic and inactive.<sup>88</sup> Menstrual blood loss is reduced by 74% to 97%<sup>89–92</sup> and 16% to 35% of LN-IUS users will become amenorrheic after 1 year of use.<sup>93–96</sup> Dysmenorrhea has been shown to improve in LN-IUS users.<sup>90,97</sup>

### **Recommendations**

1. Women suffering from primary dysmenorrhea should be offered NSAIDs as a first-line treatment for the relief of pain and improved daily activity unless they have a contraindication to the use of NSAIDs. (I-A)
2. Oral contraceptives may be recommended for the treatment of primary dysmenorrhea. The added contraceptive advantage may make oral contraceptives a first-line therapy for some women. (I-A)
3. Consideration may be given to continuous use of oral contraceptives for withdrawal bleeding and associated dysmenorrhea. (I-A)
4. Depot medroxyprogesterone acetate and levonorgestrel intrauterine system have been shown to be effective in the treatment of dysmenorrhea and therefore can be considered as treatment options in the management of primary dysmenorrhea. (II-B)

## **SECTION 6: SURGICAL OPTIONS**

For a small number of women, the dysmenorrhea will persist despite medical management, and in this group of women it is appropriate to consider surgical options. Surgery therefore constitutes the final diagnostic and therapeutic option in the management of dysmenorrhea.<sup>98,99</sup>

### **LAPAROSCOPY**

In women who do not obtain adequate pain relief with NSAIDs and oral contraceptives, the likelihood of pelvic pathology such as endometriosis is high. In one study of 100 women with pelvic pain who did not have adequate pain relief with NSAIDs, 80% were found to have endometriosis at laparoscopy.<sup>100</sup>

Endometriosis is present at laparoscopy in 12% to 32% of women undergoing laparoscopy to determine the cause of pelvic pain,<sup>101,102</sup> but it is found in up to 50% of teenagers undergoing laparoscopy for evaluation of chronic pelvic pain or dysmenorrhea.<sup>103,104</sup> The lesions of endometriosis may be cauterized or resected at the time of laparoscopy followed by medical suppressive therapy.

In women who experience relief of their dysmenorrhea with NSAIDs or oral contraceptives, there is a possibility of

underlying endometriosis, but the risks of laparoscopic documentation of the disease must be weighed against the predicted advantages of having a diagnosis of endometriosis when the symptoms are controlled without surgery.

### **HYSTERECTOMY**

Pelvic pain should be carefully investigated prior to considering a hysterectomy. There is a case for hysterectomy when an underlying disease, amenable to hysterectomy, is demonstrated and the patient has completed her family. Hysterectomy may offer permanent relief for the woman who has pain confined to her menses, and therefore there is good evidence for excellent patient satisfaction following hysterectomy in this context.<sup>105–108</sup>

### **PRESACRAL NEURECTOMY**

Presacral neurectomy (PSN) involves the total transection of the presacral nerves lying within the boundaries of the interiliac triangle. PSN seems to be the method of pelvic denervation that is associated with the major long-term effectiveness in pain relief.<sup>109,110</sup> In one study, 126 women underwent laparoscopic management for pain associated

with endometriosis: 63 were randomized to undergo PSN; the other women underwent conservative ablation of visible endometriosis lesions. No difference in intraoperative complications was observed between groups. The 6- and 12-month follow-up visits revealed improved relief with regard to the severity of dysmenorrhea in patients who were treated with laparoscopic PSN.<sup>111</sup> This improved relief was also present and statistically significant ( $P < 0.05$ ) at 24 months following treatment.<sup>111</sup> Some of the complications of this procedure may include constipation as well as urinary urgency which is unlikely to respond to medical treatment. This adverse event was observed in 5% of women treated with PSN.<sup>112</sup>

### LAPAROSCOPIC UTEROSACRAL NERVE ABLATION (LUNA)

Resection of the uterosacral ligaments achieves in theory a more complete uterine denervation than presacral neurectomy. The intervention carries the risk for complications such as bleeding, ureteral lesions, and pelvic support disorders. The efficacy of relieving pain associated with endometriosis was not confirmed in a recent meta-analysis.<sup>112,113</sup> In one study involving 180 women scheduled to undergo laparoscopy for pain and endometriosis, 78

women had uterosacral ligament resection. One year later, 29% of women in this group had persistent dysmenorrhea. Of the 78 women who had conservative surgery only, 27% had recurrent dysmenorrhea. Addition of uterosacral ligament resection did not appear to reduce dysmenorrhea.<sup>114</sup>

### Recommendations

1. Surgery constitutes the final diagnostic and therapeutic option in the management of dysmenorrhea. Laparoscopy should be considered in women who have persistent dysmenorrhea despite medical therapy of NSAIDs and/or oral contraceptives. (III-C)
2. Hysterectomy may be considered for the management of dysmenorrhea when medical alternatives have been refused or failed and fertility is no longer possible or desired. (II-B)
3. As there is limited evidence for use of presacral neurectomy in the management of primary dysmenorrhea, the risks must be carefully weighed against the expected benefits. (III-C)
4. Laparoscopic uterosacral nerve resection has not been shown to reduce dysmenorrhea and therefore should not be advocated as a mainstream treatment option. (III-C)

## SECTION 7: COMPLEMENTARY AND ALTERNATIVE MEDICINES (CAM)

In considering complementary and alternative medicine (CAM) treatments for primary dysmenorrhea, a search of the conventional medical literature was undertaken. Though there may be CAMs other than those mentioned below which are used for dysmenorrhea, we are not aware of well-designed, published studies that demonstrate efficacy. When advising patients about CAM for primary dysmenorrhea, care should be taken to consider uncertainty about long-term efficacy, interactions, and possible harm. Evidence is limited by small study sizes.

According to one large randomized controlled trial, vitamin B1 at 100 mg daily is an effective treatment for primary dysmenorrhea.<sup>114</sup>

Vitamin E taken 2 days before and 3 days after onset of menses (500 mg/day) significantly improved primary dysmenorrhea in a small study of adolescents.<sup>115</sup> Daily vitamin E, however, taken with ibuprofen during menses only, showed no significant difference.<sup>116</sup>

A small trial showed that fish oil (2.5 g/day) in combination with vitamin B12 (7.5 mg/day) may be helpful in reducing dysmenorrhea.<sup>117</sup> There is some suggestion that both fish oil and Neptune krill oil (2 g/day) may produce improvement from baseline with the Neptune krill oil requiring

fewer additional analgesics.<sup>118</sup> Other small studies of fish oil have shown promise<sup>119,120</sup> and further studies are recommended.

Overall, magnesium was more effective than placebo in improving pain control in primary dysmenorrhea.<sup>121,122</sup> Results are tempered by high participant withdrawal from the studies as well as different doses prescribed differently.

In a small study, vitamin B6 alone (200 mg/day) was helpful and even better than a combination of vitamin B6 (200 mg/day) with magnesium (500 mg/day) in reducing dysmenorrhea and the use of additional medications. No differences were seen between vitamin B6 alone (200 mg/day) and magnesium alone (500 mg/day).<sup>123</sup>

One study of 40 participants showed that Tokishakuyaku-san, a combination Japanese herbal remedy (7.5 mg/day in divided doses), reduced pain and decreased additional diclofenac use during a 2-month treatment period and a further 2-month untreated follow-up. These findings may be limited by differences between Eastern and Western diagnostic techniques.<sup>124</sup>

In a small study, mefenamic acid (250 mg q6h) was superior to essence of Fennel/E's fruit ([2%] 25 gts po q4h). There was, however, no placebo group in this study.<sup>125</sup>

## Recommendations

- The following CAM has limited support and may be considered in the treatment of primary dysmenorrhea, though further study is required:
  - Vitamin B1 (I-B)
- The following CAMs showed an initial positive response for the treatment of primary dysmenorrhea and merit further study:
  - Vitamin E (I-C)
  - Fish oil / Vitamin B12 combination (I-C)
  - Magnesium (II-1 C)

- Vitamin B6 (II-1 C)
  - Toki-shakuyaku-san (II-1 C)
  - Fish oil (II-3 C)
  - Neptune krill oil (II-3 C)
- The following CAMs have not shown to have any benefit in the treatment of primary dysmenorrhea and may need further study:
    - Vitamin B6/magnesium combination (II-1)
    - Vitamin E (daily) in addition to ibuprofen (during menses) (II-3)
    - Fennel (II-3)

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