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This document has been approved by the Council of the Society of Obstetricians and Gynaecologists of Canada.

THE CANADIAN CONSENSUS CONFERENCE ON ENDOMETRIOSIS

HOW SHOULD ENDOMETRIOSIS BE TREATED MEDICALLY?

OBJECTIVES OF MEDICAL THERAPY

The goals of medical therapy for endometriosis are pain relief and cytoreduction. Numerous recent studies have documented the efficacy of hormonal treatment in relieving pain and reducing the endometriosis score. This can be achieved as a primary mode of treatment, or as a pre- or postoperative adjuvant. The pathophysiological mechanisms underlying endometriosis-associated infertility remain obscure, and improved pregnancy rates following medical therapy for endometriosis have not been documented. Therefore, the indications for medical therapy for endometriosis include pain, the presence of a mass and progressive anatomical distortion.

RATIONALE FOR MEDICAL THERAPY

The aetiology and natural history of endometriosis are poorly understood, and no factor, including the disease stage, can accurately predict spontaneous improvement or deterioration. All forms of medical therapy may, therefore, be considered somewhat empirical.

The goal of pain relief can be often be accomplished by simple measures which provide symptomatic relief. However, cytoreduction frequently requires complex endocrine manipulations to induce amenorrhea and remove the cyclic steroidal stimulation of the endometrial deposits. The central dogma underlying hormonal treatment of endometriosis is the belief that steroid hormones regulate growth and function of both normal endometrium and ectopic endometriotic tissue. Several studies have reported different concentrations of estrogen, progesterone, and androgen receptors in various endometriotic tissues. In general, estrogen stimulates the growth of endometriotic implants while pharmacologic concentrations of androgens induce atrophy. The effect of progesterone, which normally induces secretory changes...
on an adequately estrogen-primed endometrium or endometnotic tissue has not been described. The synthetic 19-norprogestogens, which are derivatives of testosterone and have androgenic properties, appear to inhibit the growth of endometriotic tissue. This pharmacologic knowledge can be used to create an acyclic endocrine environment which mimics one of the two naturally occurring conditions under which endometriosis is thought to regress: pregnancy and the menopause.

**STRATEGIES FOR MEDICAL THERAPY**

Factors influencing the decision to treat endometriosis include the extent of the disease, associated pelvic pathology, age of the patient, her desire for fertility, the severity of her pain and previous attempts at therapy. The risks and benefits of treating an asymptomatic patient with minimal or mild disease remain unknown.

Several options exist for the medical management of endometriosis. While conservative therapy such as nonsteroidal anti-inflammatory drugs (NSAIDs) or oral contraceptives may be used empirically, more complex therapy, such as danazol and GnRH analogs should only be used in the presence of a surgical or histological diagnosis. The presence of occult disease, nonpigmented lesions, or atypical presentations should be considered at the time of laparoscopy, as should the functional status of the endometriotic implants.

GnRH agonists or danazol are generally considered the first line of therapy in patients whose symptoms and disease severity are rated as moderate to severe. They can be used alone, or as pre- or postoperative adjuncts, with the caveat that medical therapy alone is likely to have little effect on large endometriomas.

Continuous progestins or estrogen-progestin combinations are often considered second line agents, but are well suited for use in selected women with mild symptoms, recurrent disease, or chronic pain requiring long term treatment.

**THERAPEUTIC OPTIONS**

1. **EXPECTANT MANAGEMENT**

Expectant management may be an appropriate form of therapy (or nontherapy), particularly in women with mild endometriosis and few symptoms. Expectant management for 6 to 18 months, combined with identification and correction of other infertility factors, has been shown to produce pregnancy rates comparable to medical or surgical therapy in women with minimal and mild endometriosis.\(^{12-15}\)

2. **ANALGESICS**

Paradoxically, the severity of the pelvic pain may not correspond to the extent of the disease. Prostaglandin (PG) production from endometriotic deposits may be responsible for many of the symptoms of endometriosis, including dysmenorrhea, pelvic pain, and cyclic gastrointestinal
symptoms. NSAIDs inhibit PG biosynthesis and antagonize PGs at the target level.16 As they are generally safe, well-tolerated, and inexpensive, they usually constitute the first line of symptomatic management. Less conventional approaches, such as acupuncture, biofeedback, or transepidermal nerve stimulation, may be used for pain control and symptomatic relief. While these approaches may be particularly useful in the management of the chronic pain patient, little prospective documentation of their efficacy is available.

3. CYCLIC ORAL CONTRACEPTIVES

The reduction in ante-and retrograde menstrual flow associated with cyclic oral contraceptive (OC) use has been advocated for the treatment and prophylaxis of endometriosis, but lacks prospective documentation. One retrospective study reported a decreased prevalence of OC use among women with endometriosis,17 while another reported a higher risk of endometriosis among women using OCs containing more than 50 μg of estrogen, and no increased risk with lower dose pills.18 However, safety, cost (Table 1), and acceptability make these an excellent choice for the symptomatic management of selected women with mild to moderate symptoms.

4. CONTINUOUS ORAL CONTRACEPTIVES

In 1958, R.W. Kistner first reported the use of a pseudopregnancy regime with continuous estrogen-progestin OCs.19 Since then, at least ten studies have reported symptomatic relief in 36 to 100 percent of cases, due predominantly to decidualization of the endometriotic tissue.20 However, the cytoreductive efficacy of this approach has not been well documented or compared with newer forms of therapy, such as danazol or GnRH analogues.

While progestins alone may theoretically be more effective in treating endometriosis, oestrogen may also be required to induce progesterone cellular receptors. Qualitative and quantitative abnormalities in progesterone receptors have been described in endometriotic tissue, rendering the deposits potentially incapable of responding to progestins.20 Affected patients may experience increased pain during OC use, as their endometriotic lesions only respond to the growth-promoting properties of the estrogenic component.

Side effects from this form of therapy include nausea, oedema, weight gain, breakthrough bleeding, breast tenderness, pelvic pain, and rarely, thromboembolic disease. The recent tendency to use pills with a lower estrogen content and a relatively higher progestin component has reduced the incidence of side effects. This may provide an appropriate alternative for short- or long-term symptomatic relief for selected women in whom cost or side effects preclude the use of other agents.

5. CONTINUOUS PROGESTINS

Continuous progestin therapy can produce amenorrhoea and an histological pattern showing marked glandular atrophy, pseudodecidualization of the stroma, and increased vascularity.20 At least six studies have reported symptomatic relief in 57 to 100 percent of patients treated with various progestins, including oral medroxy-progesterone acetate (MPA), Depo-MPA, and megestrol acetate.1 Two studies have demonstrated cytoreductive efficacy comparable to 600 mg
of danazol, as determined by laparoscopic scoring after six months of treatment. One retrospective study described good symptomatic relief from megestrol acetate therapy in women previously treated with other medical or surgical approaches. While depo-MPA is frequently used to treat endometriosis, there is no objective or comparative documentation of its efficacy.

Lipoprotein levels should be monitored during long-term therapy, as parental administration of MPA may significantly decrease HDL-cholesterol. The prolonged anovulation and amenorrhea associated with this regime may make it advantageous for long term use in older women who do not want to conceive and who wish to avoid surgery. Oral administration may be preferable in the younger patient desiring conception because of the long delay in the return of fertility, after the last injection (up to one year).

Side effects of progestational drugs are similar to, but less severe than, those of continuous estrogen-progestin therapy.

6. CYPROTERONE ACETATE

Cyproterone acetate (CPA) is a 17-OH-progesterone derivative having antigonadotropic, antiandrogenic, and progestational activities. Cyproterone acetate (27mg) plus ethynil estradiol (0.035 mg/day) was as effective as danazol (600 mg) in producing pain relief and cytoreduction in a small group of 11 patients. Cyproterone acetate lacks the androgenic side effects of danazol, but may cause fatigue, loss of libido, depression, weight gain, and mastalgia.

7. RU 486

RU486 is a synthetic steroid with antiprogesterone and antiglucocorticoid activities. It can antagonize the endometrial effects of exogenous estrogen. Preliminary data from six women receiving 100 mg/day revealed good pain relief but little cytoreduction after six months of therapy. Serum cortisol and ACTH levels were increased during treatment. Further studies are required before this investigational drug can be considered for clinical use.

8. GESTRINONE

Gestrinone (R-2323) is a 19-nortestosterone derivative which acts as progesterone and androgen agonist/antagonist. It is not currently available in Canada or the United States, but shows efficacy comparable to danazol with the advantage of only requiring twice weekly oral administration.

9. DANAZOL

Danazol is an isoxazol derivative of 17a-ethinyl testosterone which has an agonist effect on the androgen and glucocorticoid receptors and agonist/antagonist action on the progesterone receptor. Danazol partially decreases luteinizing hormone (LH) and follicle stimulating hormone (FSH) concentrations, inhibits multiple enzymes involved in estrogen synthesis, and displaces testosterone from sex hormone-binding globulin (SHBG), thus increasing the free testosterone concentration. The acyclic, hypoestrogenic, high androgen environment induces atrophy of endometriotic tissue.
Doses range from 100 to 800 mg/day and result in symptomatic improvement in 70 to 95 percent of patients, and laparoscopically observed improvement in 85 to 95 percent of patients. Daily dosages of less than 800 mg however, are associated with variable results.

The most frequent side effects are of an androgenic and anabolic nature, and include weight gain, muscle cramps, decreased breast size, oily skin, and acne. Hypoestrogenic side effects, such as hot flushes, vaginal dryness and mood changes, are not prominent. Most side effects are mild, tolerable, or respond to dose adjustments, but result in medication discontinuation in some five to ten percent of individuals.

Danazol’s androgenic properties probably contribute to the decrease in HDL-and increase in LDL-cholesterol levels observed during treatment. The resulting increase in the atherogenic index (cholesterol: HDL-cholesterol) may pose an unacceptable risk for some women, particularly those with dyslipidaemias. Danazol also alters the production rates of several liver proteins and produces mild elevations of serum transaminase (SGOT and SGPT) levels. Danazol is contraindicated in the presence of hepatic dysfunction, and may have to be discontinued if an elevation of serum liver enzyme level occurs. Other relative contraindications include obesity, acne, hirsutism, and renal or cardiac impairment.

10. GONADOTROPHIN RELEASING HORMONE (GnRH) AGONISTS

Agonistic analogues of gonadotrophin-releasing hormone (GnRH) induce reversible down-regulation of pituitary gonadotrophin secretion. The gonadotroph normally secretes LH and FSH in a pulsatile manner in response to episodic hypothalamic GnRH release. It rapidly becomes refractory to continuous exposure to a long-acting GnRH agonist. After an initial phase of pituitary-gonadal stimulation lasting three to 14 days, estradiol levels decrease to the peri- or postmenopausal range.

Five generic compounds are available (buserelin, goserelin, leuprolide, nafarelin, and tryptorelin) which can be administered by multiple daily nasal sprays, daily subcutaneous (SC) injection, or monthly SC or intramuscular (IM) injection. Each formulation produces effective inhibition of ovarian steroidogenesis, although the suppression is more profound and constant with the monthly injections.

The effect of GnRH agonist treatment on pain relief and cytoreduction has been documented in some 36 pilot studies, three multicentre trials, and four randomized danazol comparative studies. Pelvic pain was almost completely relieved after two months of either GnRH analogue or danazol therapy. A significant reduction in AFS scoring (34 percent to 51 percent for total score and 38 percent to 81 percent for implant score) was observed after six months of either treatment. A partial reduction was obtained in large endometriomas and the mitotic index in the ovarian endometriotic tissue was reduced.

Hypoestrogenic side effects of GNRH agonists are common and include hot flushes, vaginal dryness, and less frequently, decreased libido, fatigue, headache, and emotional lability. In contrast to danazol, GnRH analogues have no adverse effects on triglyceride and cholesterol metabolism, although a potentially beneficial, but unexplainable, increase in HDL-cholesterol
levels occurs.\textsuperscript{35,47,51}

The major potential drawback of GnRH agonist therapy is the accelerated hypoestrogenic bone loss. Lumbar trabecular bone density decreases by minus two to minus eight percent after six months of \textit{treatment}.\textsuperscript{52-60} This demineralization appears readily reversible after discontinuation of treatment, although complete recovery could not be demonstrated in all subjects. This loss should not be detrimental to an \textit{eumenorrhoeic} woman with otherwise normal bone mass, but precludes treatment for more than six months. Unless bone recovery is complete, treatment should not be repeated for fear of a detrimental cumulative bone loss.

GnRH agonists are not recommended in patients with depressive illnesses or those with an increased risk of osteoporosis (malabsorption, glucocorticoid use, metabolic bone disease, long-standing irregular menses, strong family history of osteoporosis).

\textbf{MONITORING DURING TREATMENT}

Hormonal therapy is usually started during the menses after pregnancy has been excluded. Liver function studies and a lipid profile are recommended, especially prior to danazol, continuous OCs, Depo-MPA use, and in those requiring long-term therapy. As routine bone density assessments are generally not feasible, clinical risk factors for osteoporosis may be used to identify women at \textbf{risk} for undesirable bone loss during GnRH analog therapy (poor calcium intake, malabsorption, glucocorticoid use, metabolic bone disease, irregular menses, strong family history of osteoporosis, and high intake of alcohol, caffeine, or cigarettes).

Although ovulation during treatment is unlikely, neither GnRH analogs nor danazol are approved as contraceptives, so barrier methods should be used to avoid inadvertant fetal exposure.

Temporary worsening of clinical symptoms may occur during the initial stimulation phase of GnRH analogue therapy. This is usually followed by an estrogen withdrawal bleed after two to four weeks, and amenorrhea, hot flushes, and symptomatic relief. If bleeding continues or hypoestrogenic symptoms fail to appear, an estradiol level $<130\ \text{pmol/L}$ may be used to confirm adequate suppression of the pituitary-ovarian axis.

Light, painless, breakthrough bleeding may occur in up to 25 percent of danazol treated patients, and may \textbf{respond to dose increases of up to 800 mg/day}. \textbf{Breakthrough bleeding} occurs frequently during continuous progestin and OC treatment and may respond to \textbf{temporary doubling of the OC dose}, or to small supplemental doses of oral estrogen.

Follow-up visits during danazol and GnRH analogue therapy are suggested after one, three, and six months of treatment to evaluate the degree of symptomatic relief and medication side effects.

\textbf{DURATION OF TREATMENT}

Danazol, continuous progestin, and estrogen-progestin therapy is usually administered for six months. Longer term therapy can be considered in selected patients who are tolerant of the side effects, and not affected by adverse lipid, liver function, or blood pressure changes.
Studies should be re-evaluated. GnRH analog therapy should not be extended beyond six months due to the potential for significant or irreversible bone loss. However, various low-dose estrogen-progestin and addback protocols are being evaluated and may ultimately facilitate long term therapy. Several ongoing studies are evaluating the efficacy of a three-to-four month preoperative course of medical therapy with danazol and GnRH analogs.

**OUTCOME MEASURES**

1. **PAIN RELIEF**

The main benefit of hormonal treatment of endometriosis is relief of dysmenorrhoea, intermenstrual pain, and dyspareunia. However, superficial dyspareunia may occur due to vaginal dryness during GnRH analog therapy. Failure to obtain significant pain relief after two to three months of therapy may signal the need for an alternate form of therapy, particularly if a continuous progestin or estrogen-progestin preparation was used, as described previously.

2. **CYTOREDUCTION**

GnRH analogs, danazol, and MPA cause a significant reduction in endometriotic lesions after six months of therapy, although rapid regrowth may occur in some women within the first few months after treatment. Active lesions may decrease by 50 to 80 percent although little effect is obtained on adhesions or endometriomas. Depot formulations of GnRH analogs may be more effective in reducing the size of large endometriomas.

**RECURRENCE RATE**

Normal ovulatory cycles usually return within one to three months after cessation of danazol or GnRH agonist treatment. Reported recurrence rates following danazol treatment range from ten to 60 percent and are difficult to interpret due to the variation in the length of follow-up. Two danazol studies reported recurrence of symptoms in 33 percent of patients over follow-up periods of 60 and 78 months. When stratified by stage of the disease, the recurrence rates were 22 percent for stage I, 41 percent for stage II, 33 percent for stage III, and 50 percent for stage IV. In the most recent studies comparing danazol with GnRH analogue treatment, 22 percent and 15 percent of patients, respectively, required further retreatment within 12 months. Of the remaining patients, symptoms were absent or mild in 67 percent and 77 percent, respectively, at 12 months after discontinuing treatment. Symptom scores increased throughout the 12-month follow-up period, but always remained less than pretreatment pain scores.

**FERTILITY POST MEDICAL TREATMENT**

Fertility was appropriately evaluated in five cohort studies comparing danazol or MPA with placebo, five randomized controlled studies comparing danazol, gestrinone, and MPA with placebo, and five randomized controlled trials comparing gestrinone, GnRH agonists, or OC to danazol. The results of these studies suggest no significant benefit of medical treatment over no treatment. In addition, there appears to be no significant benefit of a GnRH agonist or progestin when compared to danazol.
TABLE 1

SUMMARY OF MEDICAL TREATMENT OF ENDOMETRIOSIS*

<table>
<thead>
<tr>
<th>Medication</th>
<th>Route of Administration</th>
<th>Generic Name</th>
<th>Recommended Dosage</th>
<th>Cost of Drug Intervention per Month</th>
<th>Drug Cost per Su-Month Course</th>
</tr>
</thead>
<tbody>
<tr>
<td>Lupron Depot 3.75 mg. Monthly intramuscular injection (2)</td>
<td></td>
<td>Leuprolide acetate. For depot suspension.</td>
<td>3.75 mg monthly.</td>
<td>$304</td>
<td>$1,824</td>
</tr>
<tr>
<td>Suprefact. Nasal spray (1). Three times daily nasal insufflation.</td>
<td></td>
<td>Buserelin acetate.</td>
<td>600 to 1200 ug per day.</td>
<td>$171 to $226</td>
<td>$1,026 to $1,388</td>
</tr>
<tr>
<td>Suprefact. Subcutaneous injection</td>
<td></td>
<td>Buserelin acetate.</td>
<td>0.2 ml (200 ug per day).</td>
<td>$137</td>
<td>$822</td>
</tr>
<tr>
<td>Synarel. Nasal Spray. Twice daily nasal insufflation (2).</td>
<td></td>
<td>Nafarelin acetate.</td>
<td>400 ug per day</td>
<td>$308</td>
<td>$1,848</td>
</tr>
<tr>
<td>Zoladex (1). Monthly subcutaneous injection.</td>
<td></td>
<td>Goserelin acetate.</td>
<td>3.6 mg monthly.</td>
<td>$381</td>
<td>$2,286</td>
</tr>
<tr>
<td>Cyclopropane. Oral. (2)</td>
<td></td>
<td>Danazol</td>
<td>200 to 800 mg per day</td>
<td>$50 to $200</td>
<td>$300 to $1,200</td>
</tr>
<tr>
<td>Monophasic combined Oral contraceptive</td>
<td></td>
<td>Ethynyl estradiol and norgestrel or norethindrone.</td>
<td>One daily.</td>
<td>$10 to $12</td>
<td>$60 to $72</td>
</tr>
<tr>
<td>Triphasic combined Oral Contraceptive</td>
<td></td>
<td>Ethynyl estradiol and norgestrel or norethindrone.</td>
<td>One daily.</td>
<td>$11.50</td>
<td>$69</td>
</tr>
<tr>
<td>Provera. Oral.</td>
<td></td>
<td>Medroxyprogesterone acetate</td>
<td>10 to 40 mg per day</td>
<td>$15 to $58</td>
<td>$90 to $348</td>
</tr>
<tr>
<td>Depo-Provera. Intramuscular Injection.</td>
<td></td>
<td>Medroxyprogesterone acetate</td>
<td>100 to 150 mg every two to six weeks</td>
<td>$88 to $89</td>
<td>$408 to $534</td>
</tr>
<tr>
<td>Megace. Oral.</td>
<td></td>
<td>Megestrol acetate.</td>
<td>40 mg per day</td>
<td>$40</td>
<td>$240</td>
</tr>
<tr>
<td>Androcur. Oral.</td>
<td></td>
<td>Cyproterone acetate</td>
<td>25 to 50 mg per day</td>
<td>$34 to $68</td>
<td>$204 to $408</td>
</tr>
</tbody>
</table>

(1) Currently approved for the palliative treatment of advanced carcinoma of the prostate.
(2) Approved for the treatment of endometriosis.

* The cost per drug intervention refers to drug costs to pharmacist as of December, 1992. The cost of the drugs have been rounded to the nearest dollar, and does not include the pharmacists dispensing fee or mark-up.
Current evidence does not favour the use of danazol therapy after surgical treatment of the infertile woman with endometriosis. No significant difference in clinical pregnancy rates was demonstrable in five of six studies comparing danazol alone with danazol prior to conservative surgery performed by laparoscopy or laparotomy. However, only one study reports that danazol used preoperatively resulted in a slightly higher pregnancy rate than when conservative surgery alone was employed for all stages of the disease. Preliminary data after a year of follow-up indicates a higher pregnancy rate in patients pretreated with a GnRH analog prior to laparoscopic surgery as compared to those receiving danazol or gestrinone. In addition, one recent study demonstrated an increase in clinical pregnancy rates following GnRH agonist pretreatment in patients with severe endometriosis undergoing in vitro fertilization.

THE CONSENSUS COMMITTEE AGREED THAT

1. IF THE PELVIC EXAMINATION IS NORMAL AND ENDOMETRIOSIS IS SUSPECTED, A THERAPEUTIC TRIAL OF ANALGESICS, COMBINED ORAL CONTRACEPTIVES, OR PROGESTINS IS JUSTIFIED.

2. IF THE PELVIC EXAMINATION IS ABNORMAL, OR THE THERAPEUTIC TRIAL FAILS, FURTHER TREATMENT SHOULD BE WITHHELD UNTIL THE DIAGNOSIS OF ENDOMETRIOSIS HAS BEEN CONFIRMED.

3. BOTH DANAZOL AND GnRH AGONISTS AFFECT CYTOREDUCTION AND PAIN RELIEF IN THE SHORT TERM. RECURRENCE IS NOT UNCOMMON.

4. CHRONIC PAIN MAY REQUIRE LONG-TERM OR REPEATED COURSES OF THERAPY WITH AGENTS OTHER THAN GnRH AGONISTS ALONE.

REFERENCES


64. Levinson CJ. Endometriosis therapy: rationale for expectant or minimal therapy in minimal/mild cases (AFSI). Unpublished data.


The Canadian Consensus Conference Committee was composed of Dr. Glenn Brimacombe (CMA Economics Department), Dr. Stan Brown, Dr. David Cumming, Dr. Margo Fluker, Dr. Victor Gomel, Dr. Gillian Graves, Dr. Ellen Greenblatt, Dr. Philippe Laberge, Dr. André Lalonde, Executive Vice-president of the SOGC, Dr. Art Leader, Dr. André Lemay, Dr. Bruno Lemieux, Barbara Mains (Endometriosis Association), Dr. Pierre Miron Dr. Timothy Rowe, Guest Editor, Dr. Patrick Taylor, Editor-in-Chief of the SOGC Journal, and Dr. Ian Tummon.

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