Effects of the Menstrual Cycle on Medical Disorders

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Exacerbation of certain medical conditions at specific phases of the menstrual cycle is a well-recognized phenomenon. We review the effects of the menstrual cycle on medical conditions, including menstrual migraine, epilepsy, asthma, rheumatoid arthritis, irritable bowel syndrome, and diabetes. We discuss the role of medical suppression of ovulation using gonadotropin-releasing hormone agonists in the evaluation and treatment of these disorders. Peer-reviewed publications from English-language literature were located via MEDLINE or from bibliographies of relevant articles. We reviewed all review articles, case reports and series, and therapeutic trials. Emphasis was placed on diagnosis and therapy of menstrual cycle-related exacerbations of disease processes. Abrupt changes in the concentrations of circulating ovarian steroids at ovulation and premenstrually may account for menstrual cycle-related changes in these chronic conditions. Accurate documentation of symptoms on a menstrual calendar allows identification of women with cyclic alterations in disease activity. Medical suppression of ovulation using gonadotropin-releasing hormone agonists can be useful for both diagnosis and treatment of any severe, recurrent menstrual cycle-related disease exacerbations.

Arch Intern Med. 1998;158:1405-1412

The menstrual cycle, an event that punctuates the lives of most women, may be associated with diverse physical, psychological, and behavioral changes. Not surprisingly, it plays a significant role in women's health and disease. Conversely, menstrual cyclicity can be easily disrupted by disease, both physical and psychological.

Exacerbation of certain medical conditions at specific menstrual cycle phases is a well-recognized phenomenon. Accurate documentation of symptoms on a menstrual calendar allows identification of women with cyclic alterations in disease activity. The majority of these effects occur during the luteal and menstrual phases of the cycle. Diseases most often affected are those characterized by relapsing and remitting courses, and those that are easily triggered by external factors; for example, migraine, asthma, and epilepsy.

Several theories have been proposed to explain these menstrual cycle-related effects on existing disease processes, including fluctuations in levels of sex steroids, cyclic alterations in the immune system, and changing perceptions of disease severity brought about by premenstrual alterations in mood, as seen in premenstrual syndrome.

THE MENSTRUAL CYCLE

Normal menstrual cyclicity requires coordination of the hypothalamus, pituitary gland, and ovaries. Gonadotropin-releasing hormone is released in a pulsatile fashion from the hypothalamus. Its secretion is modulated by a variety of neurotransmitters, including norepinephrine, serotonin, and endogenous opioids. Gonadotropin-releasing hormone
stimulates the release of follicle-stimulating hormone and luteinizing hormone from the anterior pituitary.³

The follicular phase, or the time of oocyte development before ovulation, is marked by progressive growth of an ovarian follicle. This phase is characterized by estrogen secretion, at first gradual, and then exponential in the 5 to 6 days leading up to ovulation. An abrupt transient decline in estrogen level occurs coincident with ovulation. Recovery in the luteal phase results from corpus luteal production of estrogen and progesterone.

The lifespan of the corpus luteum is fixed at approximately 12 days. If fertilization of the ovum does not occur, the corpus luteum involutes, levels of estrogen and progesterone fall dramatically, and menstruation occurs. Falling levels of ovarian hormones remove the negative feedback from the pituitary gland and hypothalamus, and a new cycle of ovarian stimulation begins.¹

GONADOTROPIN-RELEASING HORMONE AGONISTS

Gonadotropin-releasing hormone agonists are analogues of gonadotropin-releasing hormone, the hypothalamic hormone that binds to specific receptors in the anterior pituitary gland, stimulating the release of gonadotropins. Gonadotropin-releasing hormone agonists, by binding to gonadotropin-releasing hormone receptors, cause an initial increase in follicle-stimulating hormone and luteinizing hormone secretion, the so-called flare effect. After about 1 week however, down-regulation and desensitization of the pituitary gland produces a hypogonadal state, sometimes likened to a “medical oophorectomy.”²

Adverse effects of gonadotropin-releasing hormone agonist treatment are related to hypoestrogenism, including hot flushes, headache, vaginal dryness, and sleep disturbances. The adverse effect of greatest concern however, is accelerated bone loss, putting the patient at increased risk for osteoporosis if continued for prolonged periods (>6 months). This effect, and the hypoestrogenic symptoms, can be prevented by the addition of estrogen “add-back” therapy, similar to postmenopausal hormone replacement therapy. Patients receiving gonadotropin-releasing hormone agonists take a small dose of estrogen daily (0.625-1.25 mg of conjugated estrogens or 1-2 mg estradiol). A prophylactic agent (5 mg of medroxyprogesterone acetate or 200 mg of oral micronized progesterone) is administered on a cyclic schedule for 12 to 14 days every 1 to 3 months to induce a withdrawal bleed and minimize the risk of endometrial hyperplasia.²,³ Sometimes the addition of a progestin will create symptoms attributable to the steroid itself, or may exacerbate the preexisting medical condition. Since endometrial hyperplasia would be unlikely to develop with 6 months of unopposed use of estrogen, estrogen add-back may be used on its own during a brief (3-6 months) diagnostic trial.

In gynecology, gonadotropin-releasing hormone agonists are used to temporarily suppress ovarian steroid secretion to treat such conditions as endometriosis, precocious puberty, uterine leiomyomas, premenstrual syndrome,⁴ and for prevention of menstruation in specific clinical situations (eg, thrombocytopenia or leukemia).³ They can also be used as diagnostic tools to confirm the relationship of the menstrual cycle to conditions such as premenstrual syndrome and menstrual migraine.⁵ If symptoms or cyclic exacerbations resolve with elimination of the ovarian cycle, a link to the menstrual cycle is confirmed. These patients generally have excellent symptomatic relief with continued use of gonadotropin-releasing hormone agonists or after surgical oophorectomy. Gonadotropin-releasing hormone agonists have also been used to treat a variety of medical conditions with severe, potentially life-threatening menstrual cycle-related exacerbations, examples of which are discussed in this review.

MENSTRUAL MIGRAINE

The evidence supporting a relationship between estrogen withdrawal and migraine headache is compelling. Migraine headaches are 2 to 3 times more common in women than men,⁵ a sex difference that does not exist in prepubertal children.⁶,⁷ The frequency of migraine headaches in women increases considerably after menarche.⁸-¹⁰ Sixty percent of women with migraine link attacks to menstruation. True menstrual migraine, however, occurs in the 8% to 14% of women who experience migraines exclusively at the time of menstruation, and are virtually free of migraine at other times of the cycle, with the exception of the small percentage of these women who experience a brief exacerbation associated with ovulation.⁸,¹¹

Seventy percent to 90% of women with menstrual migraine experience improvement during pregnancy, especially during the second and third trimesters.⁹,¹⁰,¹²,¹³ These women may experience migraine attacks in the postpartum period, associated with falling estrogen levels.¹⁴ Oral contraceptives have a variable effect on migraine, causing headaches to worsen, improve, or show no change.¹⁵ Analogous to women with menstrual migraine, some users of oral contraceptives experience headaches only during tablet-free or placebo days.¹⁶ Although the prevalence of migraine headaches decreases with advancing age, migraine can either regress or worsen at menopause.¹⁷

Migraines are vascular headaches, associated with a vasospastic phase followed by vasodilatation.¹⁸ Factors thought to trigger these vascular changes include abnormal platelet aggregation, altered platelet content of serotonin, aberrant neurotransmitter activity, and central opioid disregulation.¹⁹-²² In menstrual migraine, estrogen withdrawal is likely responsible for initiating some or all of these vascular effects on intracranial vessels. Estrogen regulation of prostaglandin production may also be directly or indirectly involved with the pathogenesis of menstrual migraine.²¹,²³

Several investigators²⁴-²⁷ have demonstrated an effect of estrogen on the vasculature. It has been proposed that in women with menstrual migraine, estrogen may sensitize intracranial vessels, making these vessels more responsive to hormonal changes, leading to vasoconstriction associated with estrogen withdrawal.²⁸ Estrogen administra-
tion to women with menstrual migraine can preclude the expected migraine attack until the use of estrogen is discontinued. The response to estrogen withdrawal is triggered by the abrupt decline in estrogen levels, rather than by any absolute level. Progesterone administration, while delaying menstrual flow, does not prevent the occurrence of migraine at the expected time.

Treatment of menstrual migraine may be symptomatic or prophylactic. Ergotamine tartrate, analgesics, and antiemetics will provide symptomatic relief in most women. Nonsteroidal anti-inflammatory agents are occasionally effective in women with menstrual migraine.

Prophylactic therapy is indicated for women with menstrual migraine who do not experience adequate relief from symptomatic treatment. The occurrence of migraine headaches at predictable times each month permits tailored use of prophylactic medications such as ergotamine, β-blockers, calcium channel blockers, and antidepressants. Because estrogen withdrawal is implicated in the pathogenesis of menstrual migraine, it may be more physiologic to treat these women prophylactically with estrogen. Estrogen, which can be administered in either oral or percutaneous form, is started 48 hours before the anticipated onset of headache at midcycle or at menstruation, and is continued for 3 and 6 days, respectively. Estradiol (1 mg) taken sublingually immediately at the onset of aura may interrupt the usual progression to migraine headache.

Tamoxifen citrate is reported to relieve menstrual migraine. Recent reports indicate that sumatriptan succinate, a 5-hydroxytryptamine1 receptor agonist, is also effective. There is no evidence to support the use of progesterone in the treatment of menstrual migraine.

Use of medications that suppress the hypothalamic-pituitary-ovarian axis have been successful for treatment of women whose menstrual migraines are refractory to the usual therapies, or in whom migraines are problematic at times other than at midcycle or at menstruation (usually luteal). Danazol, an androgen derivative, has shown variable effectiveness. A recent report demonstrated dramatic success in treating menstrual migraine with gonadotropin-releasing hormone agonists, combined with continuous low-dose estrogen replacement therapy. Women who respond to this treatment typically can expect to experience long-term relief following surgical oophorectomy with low-dose estrogen replacement therapy. Comitant hysterectomy, while unnecessary for migraine prevention, simplifies subsequent hormone replacement therapy, allowing replacement with estrogen alone and avoiding the need for progestin, which at times triggers recrudescence of migraine. For the few women who experience exacerbation of migraine headaches while receiving estrogen replacement therapy, several strategies have been suggested including reduction of estrogen dose, continuous rather than cyclic estrogen administration, and changing the type or route of administration of estrogen.

CATAMENIAL EPILEPSY

Catamenial epilepsy is observed in 10% to 70% of women with epilepsy. The wide range in reported incidence is because of the lack of a generally accepted definition of catamenial epilepsy. Up to 70% of women with epilepsy claim that most of their seizures are exacerbated by menstruation. Strictly defined, however, catamenial epilepsy is epilepsy that occurs at or worsens around menstruation, and can be objectively demonstrated in approximately 12% of women with epilepsy. A strict definition is important as it has implications for management of seizure. Menstrual exacerbations occur with all types of seizures. Catamenial epilepsy is believed to result from cyclic alterations in both ovarian hormone levels and drug metabolism.

The evidence that ovarian steroid fluctuations are involved is compelling. In women who develop catamenial epilepsy, seizures frequently start at or shortly after menarche. Patients with mixed seizure types show increased electroencephalographic activity during menstruation. Seizure threshold is increased by progesterone and decreased by estrogen, an effect presumably caused by alterations in brain excitability. A decrease in the progesterone level, or in the progesterone-estrogen ratio, correlates with increased seizure activity. Frequency of seizure has been shown to increase during 2 specific times in the menstrual cycle. The first corresponds to the rapid decrease in progesterone just before menses, and the second to the elevation of estrogen before ovulation. An increase in frequency of seizure has also been demonstrated during anovulatory cycles when progesterone levels are relatively low. Finally, menopause or oophorectomy may lead to significant improvement in epilepsy.

Menstrual abnormalities and gynecologic syndromes such as polycystic ovaries, hypogonadotropic and hypergonadotropic hypogonadism, oligomenorrhea, and amenorrhea are more common in women with epilepsy. This could result directly from the effects of anticonvulsant medications on the hypothalamic-pituitary axis, or indirectly through alterations in the metabolism of sex steroids. Women with temporal lobe epilepsy are particularly prone to anovulation. Dysfunction of the limbic cortex, which is extensively interconnected with the hypothalamus, appears to alter the release of hypothalamic hormones and pituitary gonadotropins, resulting in anovulation.

Altered metabolism of anticonvulsants at different times in the cycle is well established. Decreased serum levels of phenytoin demonstrated during menses in women with catamenial epilepsy correlate with increased seizure activity. The decrease in estrogen and progesterone at menstruation is believed to stimulate the release of hepatic monooxygenase enzymes, which accelerates anticonvulsant metabolism, and increases the risk for breakthrough seizures. Treatment of catamenial epilepsy requires measurement of serum levels of anticonvulsants during times of seizure exacerbation, with alterations in dosing as appropriate to improve seizure control.

Many investigators have shown progesterone therapy to be
beneficial. Medroxyprogesterone acetate given orally (10-40 mg once daily) or intramuscularly (150 mg every 6-12 weeks) has been the most widely tested. In addition to its antiepileptic properties, progesterone given in this fashion may also reduce frequency of seizure by suppressing gonadotropin release which, in turn, lowers estrogen levels. The effects of combined oral contraceptives on frequency of seizure have been inconsistent, with seizure exacerbation occurring on the pill-free days according to some reports. Uninterrupted combined use of oral contraceptives or the progestin-only oral contraceptive may be preferable in women with epilepsy as they result in continuous progesterone exposure. Since efficacy of oral contraceptives may be decreased in patients with epilepsy receiving anticonvulsant therapy because of accelerated metabolism of the contraceptive steroids, a higher dose (30 μg) of oral contraceptive pills are recommended. The use of ovarian suppressive agents such as danazol and gonadotropin-releasing hormone agonists with steroid add-back for control of seizure has not been described in the literature. It may be worthwhile to consider these medications in patients refractory to the anticonvulsant and hormonal therapies previously discussed.

ASTHMA

The observation that asthma is influenced by gonadal steroids is supported by the fact that asthma is more common in females after puberty. In many women there is an increased frequency and severity of attacks premenstrually or at menstruation. Gibbs et al. objectively confirmed the worsening of asthmatic symptoms premenstrually by documenting significant decreases in peak expiratory flow rates. Women are also more likely to be hospitalized premenstrually for asthma complications, including respiratory failure.

The precise cause of premenstrual asthma remains elusive, but may be related to changing levels of progesterone or prostaglandins. Progesterone, increases steadily after ovulation, and falls abruptly in the days before menstruation. Its relaxant effect on smooth muscle contractility may contribute to cyclic changes in airway responsiveness in women with menstrual cycle-related exacerbations of asthma. Progesterone-stimulated hyperventilation may further influence asthma leading to symptomatic deterioration and dyspnea. Although a luteal increase in asthma symptoms and decrease in peak expiratory flow rates have been demonstrated, an associated deterioration in airway reactivity has not been shown. There is also no relationship between airway function and absolute levels of progesterone. Although some prostaglandins have bronchoconstrictive effects, endogenous prostaglandin synthesis has shown no correlation with premenstrual asthma. The lack of definitive evidence for either progesterone or prostaglandin mediation has led to the theories that premenstrual asthma may in part be due to altered perception, or heightened awareness of symptoms. Menstrual cycle-related alterations in immune mechanisms have also been suggested.

Treatment for premenstrual asthma includes the usual medications for asthma: β-adrenergic agonists, anticholinergics, and corticosteroids. Intramuscular progesterone was shown to be effective in 3 women with severe, refractory premenstrual asthma, eliminating the decrease in peak flow rate, as well as reducing total corticosteroid requirement. The use of danazol, intramuscular me-adoxyprogesterone acetate (Depo-Provera), or gonadotropin-releasing hormone agonists to suppress menstrual cyclicity remains a promising area for investigation.

RHEUMATOID ARTHRITIS

Symptoms of rheumatoid arthritis often improve in the luteal phase when gonadal steroid production is maximal. Similarly, improvement is seen during pregnancy, with exacerbation postpartum. A subjective increase in morning stiffness and arthritic pain during menstruation and the early follicular phase has been shown. Rudge et al. objectively documented menstrual cycle-related variations in rheumatoid arthritis by demonstrating a significant decline in mean grip strength at the start of menstruation. Similarly, the size of finger joints peaked within 6 days of the start of menstruation, corresponding in many cases with increased body weight.

The abrupt decline of ovarian steroidogenesis resulting from involution of the corpus luteum is thought to be responsible for “menstrual arthritis,” a rare condition in which arthritis occurs exclusively at the time of menses. Cyclic alterations in rheumatoid arthritis may be attributable to menstrual cyclicity in the immune response. Cyclic changes in local antibody release and in white blood cell subpopulations have been described. Both estrogen and progesterone have anti-inflammatory properties that may ameliorate arthritic symptoms. Premenstrual exacerbation of symptoms has also been attributed to altered pain perception associated with premenstrual alterations in mood.

Estrogen, either alone or in the combination oral contraceptive pill, has proved beneficial for some women with rheumatoid arthritis. Oral contraceptives may delay onset of disease, but do not prevent its occurrence. Although not as thoroughly studied, estrogen replacement therapy in postmenopausal women appears not to protect against the occurrence of rheumatoid arthritis.

IRRITABLE BOWEL SYNDROME

Irritable bowel syndrome is a common gastrointestinal disorder, diagnosed clinically by the triad of chronic or recurrent abdominal pain, altered bowel habits, and the absence of a structural or biochemical abnormality. Symptoms of irritable bowel syndrome appear in late adolescence and affect women 3 to 20 times more frequently than men. In women, symptoms tend to recur and become cyclic, with exacerbation during the postovulatory and premenstrual phases of the menstrual cycle, suggesting a hormonal influence. Women in the ovulatory phase frequently report constipation in the progesterone-dominant luteal phase, with loose stool or diarrhea at, or
releasing hormone agonists.98 It is of their symptoms during the women experienced transient recur-
toms. Interestingly, many of these experience significant and progres-
pletely eliminated, these women
n with the menstrual cycle
adotropin-releasing hormone
agonists. With the menstrual cycle
 Bundes, and delayed gastric emptying.99,100 De-
ayed gastrointestinal transit time in
women, particularly during the lu-
teal phase, has also been demon-
strated.101-103 Progesterone may act as an endogenous antagonist of en-
teric nerve function.98 Abrupt pro-
gesterone withdrawal may trigger an increase in bowel activity.

Gastrointestinal symptoms such as abdominal pain, diarrhea, and constipation are consistently reported by women with irritable bowel syn-
drome, in association with the men-
strual cycle.104-108 The most dramatic changes in bowel symptoms occur at
the start of menstrual flow, a time when the levels of progesterone fall, and prostaglandin E2 and F2 alpha, powerful stimulants of colonic con-	ractility, rise.104,105,109 Patients with ir-
ritable bowel syndrome, in whom the colon is hyperresponsive to a variety of stimuli, may have an exaggerated colonic response to prostaglandins released during menstruation.97

Treatment of irritable bowel syndrome is generally symptomatic, including antispasmodic and promo-
tility agents, and bulk-forming laxa-\ntives. The theory of prostaglandin in-
volve in menstrual-related exacerbations of irritable bowel syn-
drome raises the possibility of treat-
ment with prostaglandin synthesis inhibitors.

There have been several re-
ports of successful treatment of ir-
ritable bowel syndrome with go-
adotropin-releasing hormone agonists. With the menstrual cycle completely eliminated, these women experience significant and progres-
sive improvement in bowel symp-
toms. Interestingly, many of these women experienced transient recur-
rence of their symptoms during the progesterone phase of the estrogen and progesterin add-back therapy, given to minimize the long-term adverse ef-
fects associated with gonadotropin-
releasing hormone agonists.98 It is likely that gonadotropin-releasing hormone agonists have direct ef-
fects on the enteric nervous system, in addition to their indirect effects on the gut, mediated through ovarian hormone suppression.114 This possi-
bility is supported by limited evi-
dence that gonadotropin-releasing hormone agonists provide relief from irritable bowel syndrome in men and in menopausal women.111 The ex-
pense and potential adverse effects of these medications will preclude pro-
longed use in most circumstances. Rarely, if dramatic relief results from a trial of ovarian suppression, ovar-
ectomy and low-dose estrogen re-
placement may have a therapeutic role.

**DIABETES**

Menstrual cycle–related alterations in glycemic control during the luteal and premenstrual phases in some in-
sulin-dependent individuals with dia-
abetes have been reported.50,112-115 Most women describe a deterioration in glycemic control, although improve-
ments have also been noted.113,114 Dia-
abetic ketoacidosis, severe insulin re-
actions, and hypoglycemic episodes also occur more frequently around menstruation.111,114 In one excep-
tional case, insulin resistance and ke-
toadicosis occurred exclusively dur-
ing menstruation.116

Altered insulin receptor bind-
ing and affinity at different times dur-
ing the menstrual cycle have been re-
ported in some,117-119 but not all120 studies. Attempts to identify the hor-
mones responsible for menstrual cy-
cle–related changes in carbohydrate metabolism have produced conflicting results. Impaired glucose toler-
ance during the luteal phase is re-
ported in healthy women without di-
abetes.120-122 In studies,123-125 on the ef-
effects of oral contraceptive, phys-
ologic levels of estrogen were found to have minimal effects on carbo-
hydrate metabolism in women without diabetes. Studies126-128 of progesterational agents have also demon-
strated variable effects. It is pos-
sible that even small effects of pro-

gestosterone on glucose homeostasis are exaggerated in women with diabetes, in whom the normal feedback regulation between plasma glucose levels and in-
sulin secretion is lost.112 Loss of eat-
ing control, such as binging or increased intake of sweets, is de-
scribed by many women in the lu-
teal phase and premenstrually,120-122 and is another possible cause for loss of glycemic control in women with diabetes during this time.

The exact mechanism of men-
strual cycle–related effects on glu-
cose homeostasis in women with diabetes is enigmatic. In practical terms however, women with diabe-
tes should be counseled regarding the possibility of altered control. They need to recognize changes in their eating patterns and adjust in-
sulin dosages accordingly. Ovarian suppression with gonadotropin-
releasing hormone agonists has been used in women with recurrent life-
threatening complications, such as recurrent severe insulin reactions or ketoacidosis associated with spe-
cific phases of the menstrual cycle, with good effect.113

**MISCELLANEOUS DISORDERS**

The previous discussion describes the effects of the menstrual cycle on se-
veral relatively common disorders. Several rare conditions show men-
strual variation in severity. There are numerous case reports of catame-
nial pneumothorax, the occurrence of recurrent spontaneous pneumo-
thorax exclusively associated with menses, possibly the result of pleu-
r al or diaphragmatic endometrio-

There is some evidence that acute appendicitis presents more fre-
frequently in the luteal phase,50,114-119 although this could be because of the misdiagnosis of pain in the right lower quadrant resulting from corpus luteum cysts, leading to un-
necessary appendectomy. Other dis-
orders exacerbated by the postovu-
lary and premenstrual phases of the menstrual cycle include acne, en-
docrine allergy and anaphylaxis, he-
reditary angioedema, erythema multiforme, urticaria, aphthous ulcers, Behc¸et syndrome, acute intermittent porphyria, paroxysmal supra-
ventricular tachycardia, glaucoma, and multiple sclerosis.41,144-149 Go-
adotropin-releasing hormone ago-
nists have been used for some of these conditions, in particular for re-
current anaphylaxis and acute in-
termittent porphyria, when symp-
toms are severe or disabling. In contrast to these disorders, myasthenia gravis generally improves premenstrually. Although one early report indicated better outcomes if breast surgery was performed in the luteal phase, but subsequent investigators have been unable to confirm this finding.

**AN APPROACH TO MENSTRUAL CYCLE–RELATED EXACERBATION OF MEDICAL DISORDERS**

Exacerbation of certain medical conditions at specific times during the menstrual cycle is a well-recognized phenomenon. If a woman's history is suggestive of significant deterioration of the underlying condition, then accurate documentation should be obtained using a menstrual calendar. Where appropriate, cyclic modulation of therapy may overcome any deleterious menstrual cycle–related changes in the disease process. If such measures prove ineffectual, a trial of medical ovolution suppression may be warranted. If a dramatic benefit results, consideration should be given to ongoing therapy with a gonadotropin-releasing hormone agonist and steroid add-back, or to a cheaper alternative such as intramuscular mecloxyprogesterone acetate or dana- zol. If these medical approaches are impractical because of cost or adverse effects, and the woman’s fertility aspirations have been met, consideration of hysterectomy and bilateral oophorectomy with ongoing estrogen replacement therapy is appropriate.

**CONCLUSIONS**

The recognition of recurrent menstrual cycle–related exacerbations of a medical disorder opens the door to innovative treatments that alter or suppress gonadal steroid production. Elimination of ovarian cyclicity may provide dramatic relief for some women in whom standard therapies prove less than ideal.

Accepted for publication November 17, 1997.

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