ORIGINAL ARTICLE

Menstrual cycle-related exacerbation of common medical conditions such as migraine, epilepsy, asthma, irritable bowel syndrome, and diabetes, is a well-recognized phenomenon. Accurate documentation of symptoms on a menstrual calendar allows identification of women with cyclic alterations in disease activity.

Menstrual Cycle Effects on Common Medical Conditions

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INTRODUCTION

The menstrual cycle is an event which punctuates the lives of most women, and may be associated with diverse physical, psychological, and behavioural 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.

There are many examples of psychological and behavioural changes associated with the menstrual cycle. Medical hospitalizations and consultations, accidents, work absenteeism, criminal behaviour, and suicides are all more common during the second half of the cycle.[1,2] Mothers also report minor illnesses in their children more frequently during the luteal and menstrual phases.[3] Premenstrual syndrome (PMS) is another well-documented example of menstrual cycle-related psychological and behavioural effects.

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

Several theories exist to explain these menstrual cycle-related effects on existing disease processes. These include 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.

REPRINTS

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THE MENSTRUAL CYCLE

Normal menstrual cyclicity requires coordination of the hypothalamus, pituitary gland, and ovaries. Gonadotropin-releasing hormone is secreted in a pulsatile fashion from the hypothalamus, stimulating the release of follicle-stimulating hormone (FSH) and luteinizing hormone (LH) from the anterior pituitary.[4]

During the follicular phase, there is progressive growth of an ovarian follicle. Estrogen secretion increases, at first gradually, and then exponentially in the 5–6 days leading up to ovulation. The luteal phase is characterized by production of both estrogen and progesterone from the corpus luteum. 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 and hypothalamus, and a new cycle of ovarian stimulation begins.[4]

GONADOTROPIN-RELEASING HORMONE (GNRH) AGONISTS

Gonadotropin-releasing hormone (GnRH) agonists, by binding to GnRH receptors in the anterior pituitary, initially cause an increase in FSH and LH secretion, the so-called "flare" effect. However, after about one week, down-regulation and desensitization of the pituitary produces a hypogonadal state, sometimes likened to a "medical oophorectomy".[5]

Side effects of GnRH agonist treatment are related to hypoestrogenism. They include hot flushes, headache, vaginal dryness, and sleep disturbances. The side effect of greatest concern is accelerated bone loss. Prolonged administration of GnRH agonists (i.e., > 6 months) increases the patient's risk for osteoporosis. This effect, and the hypoestrogenic symptoms, can be prevented by the addition of steroid "add-back" therapy, very similar to postmenopausal hormone replacement therapy. Patients on GnRH agonists take a small dose of estrogen daily (0.625–1.25 mg conjugated estrogens or 1–2 mg estradiol). A progestational agent (medroxyprogesterone acetate 5 mg or oral micronized progesterone 200 mg) is administered on a cyclic schedule for 12–14 days every 1–3 months to induce a withdrawal bleed and minimize the risk of endometrial hyperplasia.[5,6] Sometimes the addition of a progestin will create symptoms attributable to the steroid itself, or may exacerbate the pre-existing medical condition. Since endometrial hyperplasia would be very unlikely to develop with six months of unopposed estrogen, estrogen add-back may be used on its own during a brief (3–6 months) diagnostic trial.

In gynecology, GnRH agonists are used to temporarily suppress ovarian steroid secretion in order to treat such conditions as endometriosis, precocious puberty, uterine leiomyomas, PMS,[7] and for prevention of menstruation in specific clinical situations (e.g. thrombocytopenia, leukemia).[6] They can also be used as diagnostic tools to confirm the relationship of the menstrual cycle to conditions such as PMS and menstrual migraine.[6] 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 GnRH agonists or after surgical oophorectomy. GnRH agonists have also been used to treat a variety of medical conditions with severe, potentially life-threatening, menstrual cycle-related exacerbations, examples of which will be discussed in this review.

MENSTRUAL MIGRAINE

Migraine headaches are two to three times more common in women than men,[8] and their frequency increases considerably after menarche.[9] While 60% of migrainous women link attacks to menstruation,[10] only 7% of women have true "menstrual migraine," defined as "attacks of migraine without aura that occur regularly on day one of menstruation, ± 2 days, and at no other time," implicating the existence of an exclusive hormonal trigger for migraine in these particular women.[11]

Migraines are vascular headaches, associated with a vasoconstrictive phase followed by vasodilatation.[12] Estrogen withdrawal is likely responsible for initiating some or all of these vascular effects on intracranial vessels.[9,13-15] In women with menstrual migraine, the onset of headache appears to be triggered by an abrupt decline in serum estrogen levels, rather than by any absolute level. Estrogen administration can preclude the expected migraine attack until the estrogen is discontinued.[16]

Several clinical observations support the association between menstrual migraine and estrogen withdrawal. Many women taking the combined oral contraceptive experience migraine headaches during the pill-free or placebo week.[17] Migraine tends to improve during pregnancy, but may recur postpartum associated with falling estrogen levels.[9,18] Migraine also tends to improve following menopause when menstrual cyclicity ceases, resulting in low estrogen levels with little fluctuation.[19]

Effective treatment of menstrual migraine depends first on accurate diagnosis of migraine, and

establishing a link between attacks and menstruation. This is best accomplished by prospective recording of migraine attacks and menstrual periods by the patient herself for at least three months. During this time, symptomatic relief of acute migraine attacks with the usual migraine therapies (ergotamine, analgesics, antiemetics) can be offered.

Prophylactic therapy is indicated for women with menstrual migraine who do not experience adequate relief from symptomatic treatment. Hormonal prophylaxis to stabilize estrogen levels may be useful.[21-24] Estrogen can be administered either orally, or percutaneously as a 25 µg or 50 µg transdermal patch or 1.5 mg of percutneous estradiol gel.[25] Percutaneous estrogen may be more effective as there is less variation in serum estrogen levels compared to oral preparations.[26] Estrogen should be started in the late luteal phase, at least 48 hours prior to the anticipated onset of migraine, and continued for four to six days. Estradiol (1 mg) taken sublingually immediately at the onset of the headache may interrupt the usual progression to migraine.[27]

Medications which suppress the hypothalamic-pituitary-ovarian (H-P-O) axis have been successful for treatment of women whose menstrual migraines are refractory to the usual therapies. The combined oral contraceptive (OC) can be given continuously for three to four months, followed by a withdrawal bleed and symptomatic treatment of any resulting migraine attack. A new 28-day OC which maintains continuous, albeit lower, estrogen administration, rather than placebo for the last seven days is currently being developed, and may be very useful for women experiencing menstrual migraine, or migraine on the OC during the usual pill-free or placebo week.

GnRH agonists are a useful tool for both diagnosis and treatment of menstrual migraine, but should be tried only after all other possible treatments have been exhausted. A recent report demonstrated dramatic success in treating menstrual migraine with GnRH agonists, combined with continuous low-dose estrogen replacement therapy.[28] Women who respond to this treatment typically can expect to experience long-term relief following surgical oophorectomy with low dose estrogen replacement therapy. Concomitant 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. This "definitive" therapy should only be offered to the woman with recalcitrant menstrual migraine who has completed her childbearing. Individualized counselling regarding the potential risks of a permanent menopausal state, and the consequent need for estrogen replacement therapy (ERT) to maintain long-term health is essential, as is long-term postoperative follow-up to maintain patient compliance with ERT. For the few women who experience exacerbation of migraine headaches on ERT, 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.[20]

CATAMENIAL EPILEPSY

Catamenial epilepsy is observed in 10%–70% of epileptic women.[29,30] As in menstrual migraine, the wide range in reported incidence is due to the lack of a generally accepted definition.[30] Strictly defined, catamenial epilepsy is epilepsy which occurs at or worsens around menstruation. While up to 70% of epileptic women claim that their seizures are exacerbated by menstruation,[30] true catamenial epilepsy can be objectively demonstrated in approximately 12%.[30] Menstrual exacerbations occur with all types of seizures.[31] Accurate prospective documentation of seizures in relation to menstrual periods is essential for diagnosis, and prior to specific treatment.

Catamenial epilepsy is believed to result from cyclic alterations in both ovarian hormone levels and drug metabolism. Seizure threshold is increased by progesterone and decreased by estrogen.[32] A decrease in the progesterone level, or in the progesterone:estrogen ratio, correlates with increased seizure activity.[33] Seizure frequency has been shown to increase during two specific times in the menstrual cycle. The first corresponds to the rapid decrease in progesterone just prior to menses, and the second to the elevation of estrogen prior to ovulation.[32,34] An increase in seizure frequency has also been demonstrated during anovulatory cycles when progesterone levels are relatively low.[35] Menopause or oophorectomy may lead to significant improvement in epilepsy.[2]

Altered metabolism of anticonvulsants at different times in the cycle is well established.[36] 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.[36] Treatment of catamenial epilepsy should include measurement of serum levels of anticonvulsants during times of seizure exacerbation.[33] A supplemental daily dose of seizure medication at the time of exacerbation may improve seizure control.[37]

TABLE 1

Mechanisms and Management of Menstrual Cycle-related Effects on Common Medical Conditions

Medical Condition	Mechanism	Management
Menstrual Migraine *Migraines occuring only on day 1 of menstruation, ± 2 days*	Estrogen withdrawal	1. Symptomatic • Ergotamine, analgesics, antiemetics 2. Prophylactic • Estrogen (percutaneous patch or gel; oral) • Cycle suppression (continuous OC, GnRH agonist)
Catamenial Epilepsy *Epilepsy that worsens, or occurs exclusively at menstruation*	1. ↓ progesterone = ↓ seizure threshold 2. Altered drug metabolism	1. Symptomatic • Measure anticonvulsant levels and alter dose accordingly 2. Prophylactic • Progesterone (p.o., i.m.) • Continuous combined OC • Progestin-only OC
Premenstrual Asthma *Premenstrual &/or menstrual asthma exacerbations*	Progesterone-induced hyperventilation and alterations in airway responsiveness	1. Symptomatic • Optimize usual asthma medications 2. Prophylactic • GnRH agonist (if life-threatening)
Irritable Bowel Syndrome *Premenstrual &/or menstrual exacerbations*	Progesterone-induced changes in gut motility	1. Symptomatic • Antispasmodics, promotility agents, bulk-forming laxatives 2. Prophylactic • GnRH agonist (severe cases)
Diabetes *Premenstrual &/or menstrual alterations in glycemic control*	1. Changes in carbohydrate metabolism—? mechanism 2. Altered eating control/ patterns	1. Symptomatic • Adjust insulin accordingly 2. Prophylactic • Awareness of altered control; adjust insulin accordingly

OC, oral contraceptive; GnRH, gonadotropin-releasing hormone

Many investigators have shown progesterone therapy to be beneficial.[33-35,38-40] Medroxyprogesterone acetate given orally (10–40 mg o.d.) or intramuscularly (150 mg q 6–12 weeks) has been the most widely tested.[33,35] In addition to its antiepileptic properties, progesterone given in this fashion may also reduce seizure frequency by suppressing gonadotropin release which, in turn, lowers estrogen levels.[34,39] The effects of combined OCs on seizure frequency have been inconsistent, with seizure exacerbation occurring on the pill-free days in some reports.[33] Uninterrupted combined OCs or the progestin-only OC may be preferable in women with epilepsy as they result in continuous progestin exposure.[41]

The use of ovarian suppressive agents such as danazol and GnRH agonists with steroid add-back for seizure control 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

There are numerous reports of increased frequency and severity of asthma attacks occurring premenstrually or at menstruation in some women.[42,43]

Gibbs[44] objectively confirmed the worsening of asthmatic symptoms premenstrually by documenting significant decreases in peak expiratory flow rates (PEFR). The precise etiology may be related to changing levels of progesterone or prostaglandins. Progesterone increases steadily after ovulation, and falls abruptly in the days prior to menstruation. Its relaxant effect on smooth muscle contractility may contribute to cyclic changes in airway responsiveness.[29] Progesterone-stimulated hyperventilation may further influence asthma leading to symptomatic deterioration and dyspnea. Menstrual cycle-related alterations in immune mechanisms have also been suggested.[45]

Treatment for premenstrual asthma consists of the usual asthma medications: β-adrenergic agonists, anticholinergics and corticosteroids.[29] Intramuscular progesterone was shown to be effective in three women with severe, refractory premenstrual asthma, eliminating the decrease in peak flow rate, as well as reducing total corticosteroid requirement.[46] There is one report of the use of a GnRH agonist in a woman with reccurrent menstrually-related status asthmaticus.[47]

IRRITABLE BOWEL SYNDROME

Irritable bowel syndrome (IBS) is a common gastrointestinal (GI) disorder, diagnosed clinically by the triad of chronic or recurrent abdominal pain, altered bowel habits, and the absence of a structural or biochemical abnormality.[48,49] 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.[50,51] Ovulatory women frequently report constipation in the progesterone dominant luteal phase, with loose stool or diarrhea at, or immediately preceding, the onset of menstruation.

Progesterone has well-documented effects on the GI system, including a reduction in lower esophageal sphincter tone and delayed gastric emptying.[52] Delayed GI transit time in women, particularly during the luteal phase, has also been demonstrated.[53] Abrupt progesterone withdrawal may trigger an increase in bowel activity.

Fifty percent of women with IBS report an increase in GI symptoms such as abdominal pain, diarrhea, and constipation in association with the menstrual cycle.[54-56] The most dramatic changes in bowel symptoms occur at the start of menstrual flow, a time when the levels of progesterone fall, and prostaglandin E_2 and $F_{2\alpha}$, powerful stimulants of colonic contractility, rise.[50] Patients with IBS, in whom the colon is hyperresponsive to a variety of stimuli, may have an exaggerated colonic response to prostaglandins released during menstruation.[50]

Treatment of IBS is generally symptomatic, including antispasmodic and promotility agents, and bulk-forming laxatives. There have also been several reports of successful treatment of severe, menstrually-related IBS with GnRH agonists.[51]

DIABETES

Menstrual cycle-related alterations in glycemic control during the luteal and premenstrual phases in some insulin-dependent diabetics have been reported.[2,57,58] Deterioration in glycemic control, diabetic ketoacidosis, severe insulin reactions, and hypoglycemic episodes may occur more frequently around menstruation.[59] In one exceptional case, insulin resistance and ketoacidosis recurred exclusively during menstruation.[60]

Menstrual cycle-related changes in carbohydrate metabolism have been attributed to a variety of factors, including altered insulin receptor binding and affinity,[61] and impaired glucose tolerance.[62] Loss of eating control, such as bingeing or increased intake of sweets, is described by many women in the luteal phase and premenstrually,[63] and is another possible cause for loss of glycemic control. Diabetic women should be counseled regarding the possibility of altered control, and the need to recognize changes in their eating patterns and adjust insulin dosages accordingly.

MISCELLANEOUS DISORDERS

The previous discussion describes the effects of the menstrual cycle on several relatively common disorders. Several rare conditions show menstrual variation in severity. There are numerous case reports of catamenial pneumothorax, the occurrence of recurrent spontaneous pneumothorax exclusively associated with menses, possibly the result of pleural or diaphragmatic endometriosis.[64,65] This condition has been successfully treated with GnRH agonists.[66]

There is some evidence that acute appendicitis presents more frequently in the luteal phase,[67,68] although this could be due to the misdiagnosis of right lower quadrant pain resulting from corpus luteal cysts, leading to unnecessary appendectomy. Other disorders exacerbated by the post-ovulatory and premenstrual phases of the menstrual cycle include acne, endocrine allergy and anaphylaxis, hereditary angioedema, erythema multiforme, urticaria, aphthous ulcers, Behçet syndrome, acute intermittent porphyria, paroxysmal supraventricular tachycardia, glaucoma, and multiple sclerosis.[29,69-73] GnRH agonists have been used for some of these

conditions, in particular for recurrent anaphylaxis and acute intermittent porphyria, when symptoms are severe or disabling.[74-76] In contrast to these disorders, myasthenia gravis generally improves premenstrually.[77] Although one early report indicated better outcomes if breast surgery was performed in the luteal phase,[78] subsequent investigators have been unable to confirm this finding.[79]

AN APPROACH TO MENSTRUAL CYCLE-RELATED EXACERBATIONS OF MEDICAL CONDITIONS

Exacerbation of certain medical conditions at specific times during the menstrual cycle is a well-recognized phenomenon. The importance of prospective recording of symptoms in relation to the menstrual cycle to facilitate the diagnosis and treatment of menstrual cycle-related exacerbations cannot be overestimated. Where appropriate, cyclic alteration of symptomatic therapy may be sufficient for treatment. If such measures prove ineffectual, a trial of medical ovulation suppression may be warranted. If a dramatic benefit results, consideration should be given to ongoing therapy with a GnRH agonist and steroid add-back, or to a cheaper alternative such as medroxyprogesterone acetate or danazol. If these medical approaches are impractical due to cost or side effects, and the woman's fertility aspirations have been met, consideration of hysterectomy and bilateral oophorectomy with ongoing estrogen replacement therapy is a final option.

CONCLUSION

The recognition of recurrent menstrual cycle-related exacerbations of a medical disorder allows consideration of innovative treatments that alter or suppress ovarian hormone production. Elimination of ovarian cyclicity may provide dramatic relief for some women in whom standard therapies prove less than ideal. **CT**

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