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Review Article

Ovarian Hormones and Migraine Headache: Understanding Mechanisms and Pathogenesis—Part 2

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Migraine headache is strongly influenced by reproductive events that occur throughout the lifespan of women. Each of these reproductive events has a different "hormonal milieu," which might modulate the clinical course of migraine headache. Estrogen and progesterone can be preventative or provocative for migraine headache under different circumstances depending on their absolute serum levels, constancy of exposure, and types of estrogen/progesterone derivatives. Attacks of migraine with and without aura respond differently to changes in ovarian hormones. Clearly a greater knowledge of ovarian hormones and their effect on migraine is essential to a greater understanding of the mechanisms and pathogenesis of migraine headache.

Key words: menstrual migraine, migraine headache, estrogen, progesterone, menstrual cycle, menarche, pregnancy, menopause, lactation

Abbreviations: GnRH gonadotropin-releasing hormone, HRT hormone replacement therapy, OCPs oral contraceptives, PROGINS progesterone receptor allele, CVA cerebrovascular accident, CNS central nervous system, CI confidence intervals, HR hazard ratio, MAO-B monoamine oxidase-B, NMDA *N*-methyl-d-aspartate, AUC area-under-the-curve, TNC trigeminal nucleus caudalis, GABA gamma aminobutyric acid

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During part 1 of this series, we reviewed the genomic and nongenomic effects of ovarian hormones on the central nervous system as well as the current basic science studies linking them to the pathogenesis of migraine headache. These studies clearly indicate that ovarian hormones can alter neurotransmitter systems theorized to play an important role in the pathogenesis of migraine headache. Numerous clinical studies also exist to provide clues to how ovarian hormones might modulate migraine headaches. Migraine headaches are likely influenced by the different "hormonal milieus" encountered during reproductive life events that begin during menarche and continue through menopause. The purpose of this manuscript will be to review existing clinical studies examining the course of migraine headache during reproductive life events (eg, menarche, menstrual cycles, pregnancy, lactation, and menopause) as well as after administration of exogenous hormones (eg, oral contraceptives [OCPs] and hormone replacement therapy [HRT]). We will also define the specific serum levels of ovarian hormones encountered during the different reproductive life events and postulate mechanisms through which they might affect migraine headache.

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MENARCHE

Menarche refers to the onset of menstruation during puberty. The typical age range of menarche is 9.1 to 17.7 years with a median age of 12.8 years within American girls.[1,2] The initial menstrual cycles are often anovulatory and may remain so for the first 12 to 18 months after the onset of menarche. Serum estradiol levels range from 10 to 156 pg/mL during puberty prior to the onset of ovulatory menstrual cycles; serum levels of estrogen and progesterone similar to those encountered during the adult menstrual cycle may not be reached until several years after the onset of menarche.[3]

The prevalence of migraine is similar in preadolescent boys and girls, but diverges at the time of menarche.[4] After menarche, the prevalence is 2 to 3 times higher in girls than in boys and remains so throughout most of the reproductive years. The age of onset of migraine tends to differ between girls experiencing attacks of migraine with and without aura. Stewart et al[5] reported the peak incidence of migraine was 12 to 13 years of age for girls experiencing migraine with aura (MWA) (14.1 cases per 1000 person years) and 14 to 17 years of age for those experiencing migraine without aura (MWoA) (18.9 cases per 1000 person years). Thus MWoA most commonly begins after the onset of menarche, while MWA usually begins shortly before or at the time of menarche. Since ovulation and regular menstrual cycles may not develop for 1 to 2 years after menarche, it is likely that the onset of MWoA is associated with the establishment of the female menstrual cycle.

MENSTRUAL CYCLE

Migraine headaches could theoretically be influenced by changes in ovarian hormones that occur throughout the female menstrual cycle. Knowledge of the different "hormonal milieus" encountered during different phases of the menstrual cycle is essential to an understanding of the effects of ovarian hormones on migraine headache. Therefore, in the next several sections, we will review the endocrinology of the menstrual cycle as well as the potential mechanisms through which ovarian hormones could modulate menstrual and nonmenstrual migraine headaches.

ENDOCRINOLOGY OF THE MENSTRUAL CYCLE

The menstrual cycle is divided into follicular and luteal phases. The follicular phase includes all days from the first day of menstrual bleeding to the day before ovulation and the luteal phase includes all days from the first day of ovulation to the last day before the next menstrual period. The follicular and luteal phases can further be subdivided into early, mid, and late time intervals. Serum estradiol levels typically are low during the early to mid-follicular phases (eg, 25 to 50 pg/mL range), peak during the late follicular and early luteal phase (eg, 100 to 400 pg/mL range), plateau during the mid-luteal phase (200 to 300 pg/mL range), and fall precipitously to levels of 25 to 50 pg/mL just prior to menstruation. Serum progesterone levels are extremely low during the follicular phase (<1 ng/mL range), peak during the mid-luteal phase at levels ranging from 6 to 10 ng/mL, and then fall precipitously to levels <2 ng/mL during the late luteal phase (Figure 1).

MENSTRUAL MIGRAINE

Menstrual migraine has recently been defined by the International Headache Society in the appendix of their diagnostic criteria for headache and has been divided into 2 subcategories: "menstrually related MWoA" and "pure menstrual MWoA." The criteria for "menstrually related MWoA" include:

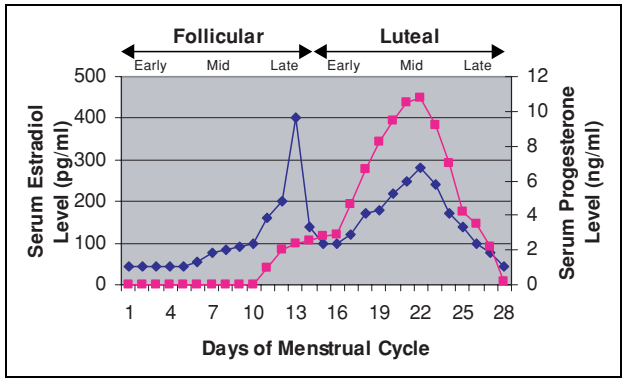

Fig 1.—Changes in serum estrogen and progesterone levels during a native menstrual cycle. Day 1 is the first day of menses and day 27 is the last day before the next menstrual period. The follicular phase includes all days prior to ovulation and the luteal phase includes all days after ovulation. The follicular and luteal phases can be divided into early, mid, and late time periods.

(1) predictable migraine attacks occurring during the perimenstrual time period (2 days before to 3 days after the onset of menstruation), (2) migraines also occur at other times of the month, and (3) the association with menses must be confirmed in 2/3 menstrual cycles. "Pure menstrual MWoA" is similar to the above criteria, except that migraine headaches are strictly limited to the perimenstrual time period and do not occur at other times of the menstrual cycle. For the sake of this review, we will refer to both types of migraine as "menstrual migraine."

Epidemiology.—The overall prevalence of menstrual migraine in the general population is approximately 3%, but it is much higher within populations of migraineurs[6]; 35% to 51% of female migraineurs have "menstrually related MWoA," while 7% to 19% have "pure menstrual MWoA"[7-13] (Table 1).

Attack Characteristics.—Population-based studies of nonselected female migraineurs demonstrate little difference between the attack characteristics of menstrual and nonmenstrual migraine.[14,15] Studies within subspecialty-based clinics, however, suggest that menstrual migraine is more severe, disabling, and associated with greater abortive medication use than nonmenstrually related migraine.[16-18] The discrepancies between specialty- and population-based studies most likely can be explained by their selection of patients. Subspecialty-based studies may have included a greater percentage of "hormonally sensitive" patients than population-based studies, thus allowing a greater chance of identifying differences between menstrually related and nonmenstrually related attacks.

Effect on MWoA.—Interestingly only attacks of MWoA occur during the perimenstrual time period. Stewart et al[15] reported that attacks of MWoA were 2.04 times more likely during the first 2 days of menstruation, while attacks of MWA occurred with equal frequency throughout the menstrual cycle. Johannes

Table 1.—Prevalence of Menstrual Migraine in Female Migraineurs*

Author/Year (n)	Study Population	Method of Ascertainment of Menstrual Migraine	Prevalence of PMM	Prevalence of MRM
MacGregor/1990 (n = 55)†	Headache clinic	Prospective diary study		
All migraines			7%	35%
Granella/1993 (n = 1277)‡	Headache clinic	Retrospective chart review		
All migraines			9%	51%
Culpini/1995 (n = 268)†	Headache clinic	Prospective diary study		
Migraine with aura			4%	33%
Migraine without aura			14%	56%
All migraines			10%	49%
Granella/2000 (n = 300)†	Headache clinic	Physician interview		
Migraine with aura			4%	14%
Migraine without aura			3.5%	54%
All migraines			3.7%	41%
Dzolijic/2002 (n = 1298)	Female students	Written questionnaire		
All migraines			12%	49%
Mattsson/2003 (n = 728)§	General population	Physician interview		
Migraine with aura			4%	NA
Migraine without aura			21%	NA
All migraines			19%	NA
Koseoglu/2003 (n = 1146)	General population	Structured interview		
All migraines			NA	36%

*Prevalence represents the proportion of female migraineurs with MRM or PMM; Data from references[8-13,130]; Adapted with permission from Martin, V. Curr Pain Headache Rep 2004;8:229-237.
†The perimenstrual time period was defined as –2 to + 3 days relative to menstruation.
‡The perimenstrual time period was defined as –3 to +3 days relative to menstruation.
§MRM defined as 76% to 100% of attacks –2 to +3 days relative to menstruation.
MRM = menstrually related migraine without aura; NA = not available; PMM = pure menstrual migraine without aura.

et al[14] found that attacks of MWoA were 1.66 times more common during the first 3 days of menstruation. Mattsson et al[12] reported that 21% of patients experiencing MWoA reported >75% of attacks occurring during the perimenstrual time period as compared to only 4% of patients with MWA. These data could suggest that ovarian hormones differentially modulate these two subtypes of migraine headache.

Ovarian Hormone Levels.—Several studies have compared serum levels of ovarian steroids between patients with and without menstrual migraine. Davies et al[19] measured serum estrogen and progesterone for the 7 days before menses as well as during 1 midcycle day in menstrual migraineurs, nonmenstrual migraineurs, and controls and found similar levels of ovarian hormones between the groups. Epstein et al[20] demonstrated no differences between serum estrogen levels during the follicular and luteal phases of the menstrual cycle between women with and without menstrual migraine. They did, however, find significantly higher serum progesterone levels during the early follicular phase in menstrual migraineurs, but the clinical significance of this finding is questionable, since progesterone levels are typically quite low at this time of the menstrual cycle. Therefore, the predominance of evidence indicates that levels of ovarian hormones are similar between menstrual and nonmenstrual migraineurs. This would suggest that menstrual migraine is likely the result of an "abnormal response" of the central nervous system to normal fluctuations in ovarian steroids.

Effect of Medical Oophorectomy.—Menstrual migraine can be significantly improved by medical oophorectomy, which would imply that ovarian hormones are directly responsible for its development. Lichten et al[21] administered depo-leuprolide to create a medical oophorectomy in 29 women with severe menstrual migraine and noted that 17 of the participants had a >50% improvement in the headache index when compared to a placebo run-in phase. Murray et al[22] gave depo-leuprolide to 5 women with pure menstrual migraine and demonstrated a 74% decrease in the headache index during a 2-month treatment phase when compared to baseline. Therefore, hormonal therapies which minimize fluctuations in ovarian hormones can improve menstrual migraine.

Estrogen Withdrawal Theory.—The most plausible theory to explain the pathophysiology of menstrual migraine is that of "estrogen withdrawal." The estrogen withdrawal theory was advanced by Somerville, who demonstrated that the intramuscular injection of estradiol valerate administered shortly before menstruation could delay the onset of menstrual migraine by artificially raising serum estradiol levels during the late luteal and early follicular phases of the menstrual cycle[23,24] (Figure 2). Intramuscular administration of progesterone prior to menstruation did not affect the time of onset of menstrual migraine.[25] He later administered an intramuscular injection of a short-acting estrogen preparation to menstrual migraineurs during the mid-follicular phase of the menstrual cycle, but this did not trigger an attack. This experiment suggested that several days of estrogen priming prior to estrogen withdrawal was necessary in order to provoke a migraine headache.[26]

The estrogen withdrawal theory is further supported by studies that demonstrate perimenstrual treatment with estrogen can prevent the development of menstrual migraine. de Lignieres et al[27] reported that menstrual migraine occurred in 96% of a placebo group and 31% of a group treated with percutaneous estradiol gel during the perimenstrual time period. In an open label study, Calhoun[28] administered 0.9 mg of conjugated estrogens during the placebo week of OCPs to menstrual migraineurs and noted a 77% reduction in the number of headache days per cycle. Pradalier et al[29] showed that a 100-mcg transdermal estradiol patch applied perimenstrually was effective in the prevention of menstrual migraine, while a 50-mcg patch was ineffective. These data suggested that it may be necessary to maintain serum estradiol levels above the 45 pg/mL range during the perimenstrual time period to prevent menstrual migraine because the 100-mcg estradiol patch maintains serum estradiol levels in a range of 45 to 75 pg/mL.

Prostaglandin Release Theory.—Prostaglandins are released into the systemic circulation by a shedding endometrium during the perimenstrual time period secondary to the withdrawal of progesterone. Several lines of evidence suggest that "prostaglandin release" plays a role in the pathophysiology of menstrual migraine.[30] First, migraine-like headaches can

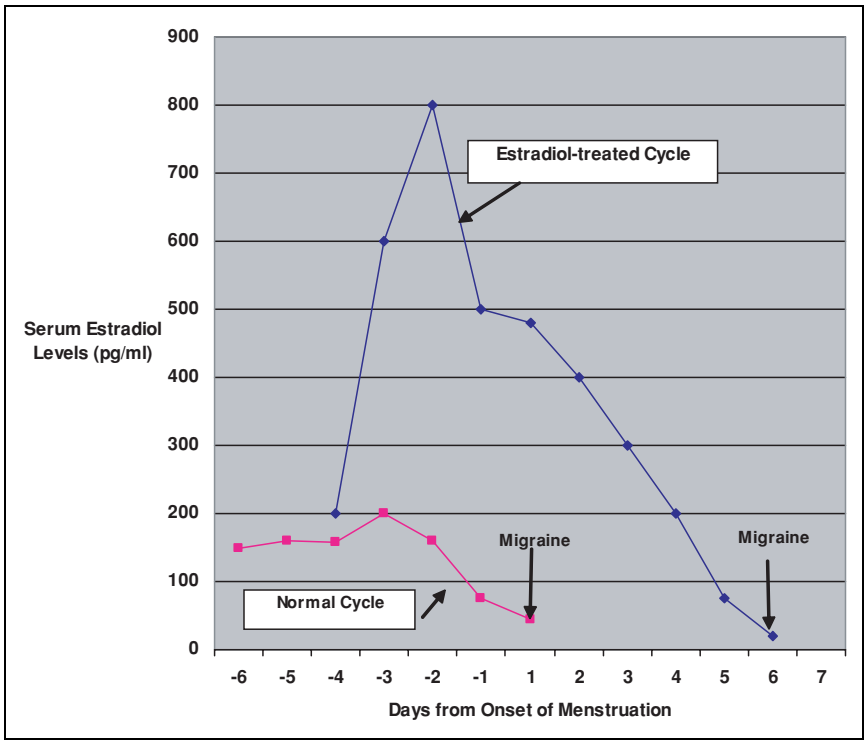

Fig 2.—Onset of menstrual migraine during estradiol-treated and native menstrual cycles. In a representative patient, menstrual migraine breaks through on day 1 when the serum estradiol levels fall below 50 pg/mL during a normal menstrual cycle. In the estradiol-treated patient, the serum estradiol levels are artificially increased during the perimenstrual time period and therefore menstrual migraine is delayed until day 6 of the menstrual cycle. Day 1 of the menstrual cycle is the first day of menstrual bleeding. (Reproduced with permission from Somerville B. JAMA 1972;221:845-846.)

be triggered by injections of prostaglandin E_2 in nonmigraineurs.[31] Second, serum taken from women during menstruation and later infused back to them at a later time can induce headache.[32] Third, medications that are prostaglandin inhibitors have been used to prevent menstrual migraine.[33]

Magnesium Deficiency Theory.—Magnesium ions are essential to a number of functions within the cerebral arteries and central nervous system. They regulate the tone of cerebral arteries, modulate release of nitric oxide (NO) from blood vessels, control the release of serotonin, block influx of calcium through *N*-methyl-D-aspartate (NMDA) receptors, and are essential cofactors for a number of enzymes.[34] Ramadan et al[35] measured brain magnesium using 31-phosphorus nuclear magnetic resonance spectroscopy and demonstrated that magnesium levels were low during a migraine attack. Therefore, magnesium deficiency could theoretically play a role in migraine.

Some authors have proposed that the low magnesium levels may be a trigger for menstrual migraine. Mauskop et al[36] reported a deficiency in ionized magnesium in 45% of attacks of menstrual migraine, while only 15% of nonmenstrually related attacks had a deficiency. They also demonstrated that attacks associated with low ionized magnesium could be aborted by intravenous magnesium infusions.[37] Facchinetti et al[38] demonstrated that menstrual migraine could be prevented by administration of oral magnesium during the last 15 days of the menstrual cycle.

Alterations of Neurotransmitter Systems.—Hormone withdrawal, prostaglandin release, or magnesium deficiency during the late luteal and early follicular phases of the menstrual cycle could alter the function of neurotransmitter systems relevant to migraine pathophysiology. Opiatergic and serontonergic neurotransmitter systems as well as the production of NO within platelets have been demonstrated to be

modulated by the phase of the menstrual cycle in menstrual migraineurs.

Central opiatergic tone may change during different phases of the menstrual cycle in menstrual migraineurs. The release of β-endorphin and corticotropin-releasing factor is under negative control from the opiatergic system. Therefore, administration of naloxone, an opioid antagonist, should increase levels of β-endorphin and cortisol levels. Facchinetti et al[39] found little increase in the serum levels of cortisol and β-endorphin after administration of naloxone during the late luteal phase of the menstrual cycle in menstrual migraineurs, while their response during the follicular phase was similar to controls. This would suggest a failure of central opioid tonus during the late luteal phase in women with menstrual migraine.

Serotonergic function both within the central nervous system and platelets may be influenced by the phase of the menstrual cycle. Cassidy et al[40] found a hypersensitivity of 5-HT1A receptors during the early follicular phase (eg, first 5 days of the menstrual cycle). This hypersensitivity of 5-HT1A receptors was reduced or absent in those with chronic migraine or menstrual status migrainosis.[41,42] D'Andrea et al[43] showed that platelet serotonin levels were highest during the mid-cycle phase (late follicular and early luteal) and lowest during early follicular and late luteal time periods in migraine patients with and without aura. Fioroni et al[44] demonstrated that platelet monoamine oxidase-B (MAO-B) activity and 5-hydroxyindole acetic acid levels are increased and platelet serotonin levels are decreased during the late luteal phase as compared with the follicular phase in menstrual migraine patients. If platelet serotonin and MAO-B levels reflect serotonergic activity within the central nervous system, then patients with menstrual migraine could have decreased serotonergic tone during the late luteal and early follicular phases secondary to decreased synthesis, increased release, and/or increased catabolism of serotonin.

Sarchielli et al[45] found increased amounts of collagen-induced NO formation and cGMP production within platelets during the luteal phase of the menstrual cycle as compared to the follicular phases in women with menstrual migraine. Controls and patients with nonmenstrually related migraine experienced the greatest amounts of NO and cGMP production during the late follicular time period. They postulated that enhanced NO production during the luteal phase of the menstrual cycle could play a role in menstrual migraine if platelet abnormalities reflect events within the CNS or vascular endothelium.

Theorized Pathogenesis.—Neurotransmitter systems could be directly affected through "withdrawal" of ovarian hormones or indirectly modulated through other chemical mediators (eg, prostaglandins, magnesium, NO). When compared to other phases of the menstrual cycle, the serotonergic/opiatergic systems seem to be suppressed during the late luteal and early follicular phases. These systems have been theorized to represent important inhibitory neurotransmitter systems for trigeminal pain pathways.

One could hypothesize that menstrual migraine develops secondary to a delicate balance of excitatory and inhibitory neurotransmission. As mentioned during part 1 of this review, animal studies suggest that estrogen enhances excitatory neurotransmission of glutamatergic synapses secondary to sprouting of dendritic spines and formation of NMDA receptors.[46-48] We postulate that the presence of estrogen induces similar structural changes within the trigeminal nucleus caudalis (TNC), but that neuroexcitation is dampened during the "high estrogen milieu" of the late follicular and early to mid-luteal phases of the menstrual cycle secondary to activation of inhibitory neurotransmitter systems (eg, serotonergic, opiatergic, GABAergic) in particular the GABAergic system. Recently, it has been established that high levels of sex hormones cause formation of GABA-A receptors that contain δ subunits.[49] These receptors are located in the extrajunctional sites and are more efficient in producing inhibitory responses to GABA. However, during the perimenstrual time period (late luteal and early follicular periods), a decline in serum estradiol levels leads to inactivation of these neuroinhibitory systems. These changes along with a delayed recovery of the neuroexcitatory glutamatergic system (because the structural changes within the TNC induced by estrogen may not reverse as fast) could render the perimenstrual time a particularly vulnerable period for migraine headache. (Figure 3; see part 1 of review for further details.) Obviously these hypotheses are speculative and will need to be confirmed in future studies.

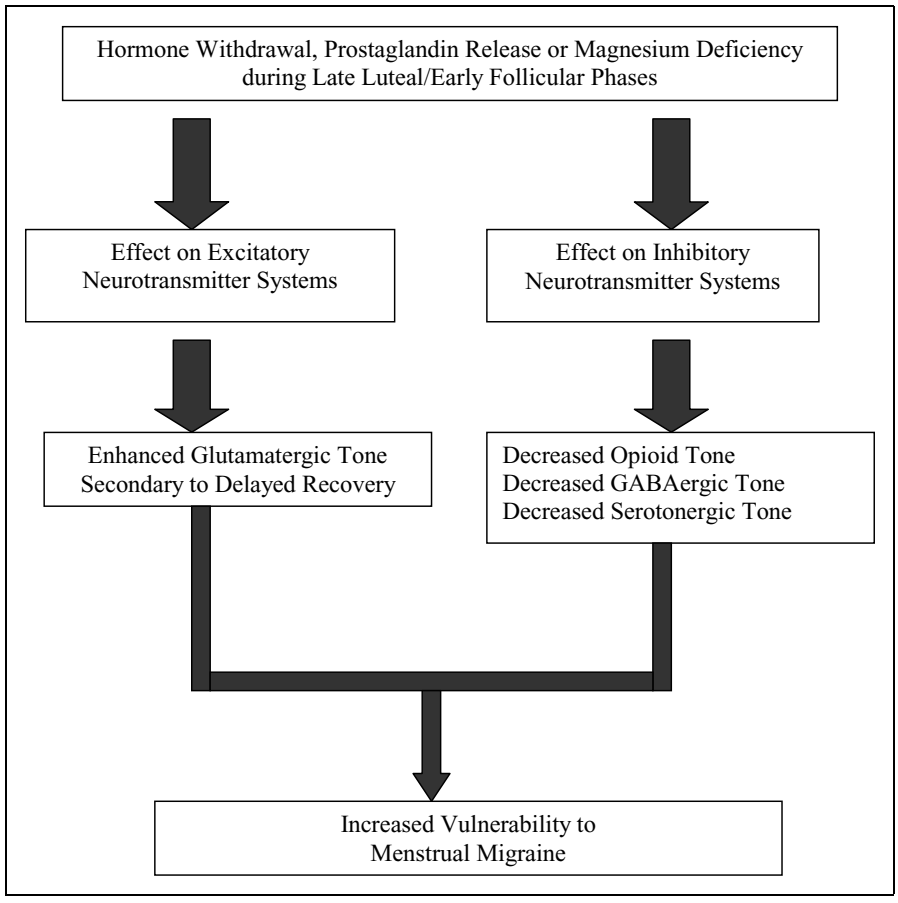

Fig 3.—Theorized pathogenesis of menstrual migraine. Estrogen and progesterone withdrawal, prostaglandin release, or magnesium deficiency during the late luteal and early follicular phases of the menstrual cycle lead to effects on excitatory and inhibitory neurotransmitter systems that increase the vulnerability to menstrual migraine.

NONMENSTRUAL MIGRAINE

The effect of ovarian hormones on attacks of nonmenstrual migraine is less clear. Studies have not convincingly shown an increased frequency of migraine headache during the mid-cycle or ovulatory time period of the menstrual cycle. Two past studies[14,15] have attempted to identify the day of ovulation by counting back 14 days from the onset of menstruation from the next cycle. They did not find an increased incidence of migraine headache at that time when compared with the rest of the menstrual cycle, but they may not have accurately identified the ovulatory time period, since no independent hormonal monitoring was performed.

Studies[16,50] suggest that the mid-luteal intervals of the menstrual cycle might represent times of less frequent, severe, and disabling migraine headache. Martin et al[16] reported that the headache index was highest during the early follicular, intermediate during mid-cycle, and lowest during mid-luteal intervals. There was a trend toward lower headache outcome measures in mid-luteal intervals when compared with all other outcome measures ($P < .04$). Beckham et al[50] also reported that the headache index was lowest during luteal time intervals in 14 female migraineurs (11 had menstrual migraine). These data could suggest that the hormonal milieu of the mid-luteal time period (eg, high progesterone/high estrogen levels) could play a preventative role for migraine headache, possibly secondary to agonism of neuroinhibitory GABA-A receptors by progesterone and/or its metabolites within trigeminal pain pathways.[51,52]

ORAL CONTRACEPTIVES

OCPs are commonly used in women of child bearing age to prevent pregnancy. They are primarily composed of ethinyl estradiol and a progestin

(a derivative of 19-nortestosterone). Ethinyl estradiol is a synthetic estrogen that has a high potency to inhibit gonadotropin release from the anterior pituitary gland. In the 1970s OCPs contained 50 to 100 mcg of ethinyl estradiol, while more recent pills contain 15 to 35 mcg.[53] Progestins also inhibit gonadotropin release and have been categorized as first (eg, norethisterone), second (eg, norgestrel, levonorgestrel), third (eg, desogestrel, gestodene, norgestimate), and fourth generation (eg, drospirenone). Third generation progestins are less androgenic and have less effect on plasma lipid levels than first or second generation progestins. Fourth generation progestins are less androgenic and also have an antimineralocorticoid effect similar to spironolactone.

OCPs exist in monophasic, triphasic, and extended duration formulations as well as those that contain progestins only. Monophasic OCPs have a fixed dosage of synthetic hormones for the first 3 weeks followed by a placebo week for the last week. Triphasic OCPs change the dose of synthetic hormones on a weekly basis for 3 consecutive weeks and then a placebo week follows. Extended duration OCPs contain a fixed dosage of synthetic hormones for 3 months followed by a placebo week. Progestin-only pills have a fixed dose of a progestin for 4 weeks.

Preexisting Migraine Headache.—Most of the past studies evaluating the effect of OCPs on preexisting migraine headache were conducted during the 1970s with the higher dose estrogen pills (eg, 50 to 100 mcg of ethinyl estradiol). Studies using the higher dose estrogen OCPs have generally demonstrated a worsening of migraine headache. Ryan[54] reported that headaches worsened in 70% and improved in 30% during treatment with OCPs (50 mcg of ethinyl estradiol/0.5 mg of norgestrel) in a randomized placebo-controlled crossover trial. Other case series[55,56] have reported that migraine headaches typically occur during the placebo week of the OCP, which would be expected if "estrogen withdrawal" triggers migraine in susceptible patients.

More recent studies have evaluated the impact of OCPs containing lower dosages of estrogen on migraine headache.[9,11,57] They have reported that the clinical course of migraine was unchanged in 44% to 67%, worse in 24% to 35%, and improved in 5% to 8% after administration of OCPs. These results suggest that migraine is most often unaffected by the use of OCPs. None of the above trials specified the type of OCP (eg, monophasic or triphasic) or the dosage of estrogen/progestin used, but they likely used monophasic OCPs with 30 to 35 mcg of ethinyl estradiol, since these were the predominant OCPs used at the time of these studies.

Headache Complaints in Contraceptive Trials.—Loder et al[58] performed a literature review of existing OCP trials to determine if the incidence of "headache complaints" (not migraine) was higher in those taking monophasic OCPs when compared to a placebo group. They concluded the following: (1) most contraceptive trials do not demonstrate statistically significant differences in "headache complaints" between treatment and control groups, (2) women with a history of migraine or "troublesome" headaches may be at increased risk of "headache complaints" with OCPs, (3) the type and dosage of progestin does not influence headache activity, and (4) if headaches begin or worsen during the first month of OCP use, they will often improve during subsequent months. Others have demonstrated that the incidence of "headache complaints" may be reduced through the use of extended duration OCPs, which decrease the frequency of "estrogen withdrawal" by having only 1 placebo week every 3 months. Cachrimanidou et al[59] reported an incidence of headache complaints of 9.7% in participants receiving extended duration OCPs and 17.3% in those receiving standard OCPs.

Effect on MWA.—Patients experiencing attacks of MWA are more likely to worsen with administration of OCPs than those with MWoA. Two past trials[10,11] noted that 50% to 57% of patients with MWA worsened with OCPs as compared to 25% to 35% of those with MWoA. In addition, case reports[11,60-62] have demonstrated that visual, sensory, and motor aura may develop for the first time in those receiving OCPs. Some patients with "new onset aura" or a "crescendo pattern" to their migraines after the start of OCPs have progressed to develop cerebrovascular accidents (CVAs).[62]

Pathogenesis.—Scant research exists to explain the mechanisms through which migraine (particularly MWA) could be triggered by OCPs in some patients.

Hanington et al[63] reported decreases in "platelet aggregation" after cessation of OCPs in patients who had developed "new onset migraine" with OCPs. The decreases in platelet aggregation seemed to parallel improvements in migraine headache. These data suggest that increased "platelet aggregation" induced by OCPs might play a role in the development of migraine headache. Another mechanism through which OCPs might trigger attacks of MWoA could be "estrogen withdrawal" during the placebo week of the pill.

Risk of CVA.—Past studies[64-68] have reported an increased risk of CVAs in patients with migraine headache, particularly in young women and those with MWA. A recent meta-analysis[69] reviewed 14 studies (11 case control and 3 cohort studies) to determine the relationship between migraine and risk of ischemic CVA. They found relative risks of 2.27 (95% confidence intervals [CI] 1.61, 3.19) for patients with MWA and 1.83 (95% CI 1.06, 3.15) for those with MWoA, while migraineurs taking OCPs had a relative risk of 8.72 (95% CI 5.05, 15.05). Other studies[70,71] have suggested an increased risk of CVA in OCPs with higher estrogen dosages (eg, 30 to 50 mcg vs. 20 mcg) and those containing second and third generation progestins, while progestin-only pills were not associated with an increased risk. Cardiovascular risk factors (eg, smoking, hypertension) as well as prothrombotic conditions (eg, factor V Leiden, prothrombin, and methylenetetrahydrofolate mutations) may further increase the risk of CVAs in those consuming OCPs.[67,72,73] One study[67] reported an odds ratio of 34 for stroke in female migraineurs who smoked and used OCPs. These data has led some groups to recommend that OCPs not be used in patients experiencing MWA or in those with cardiovascular risk factors.[74-76]

PREGNANCY

The human placenta produces the majority of estrogen and progesterone necessary for a successful pregnancy. Serum levels of estradiol and progesterone begin to rise in the mother during the 6th to 8th weeks of pregnancy as the placenta begins to produce steroids and they continue to gradually increase to their highest levels during the third trimester.[77] During the third trimester, serum estradiol levels are

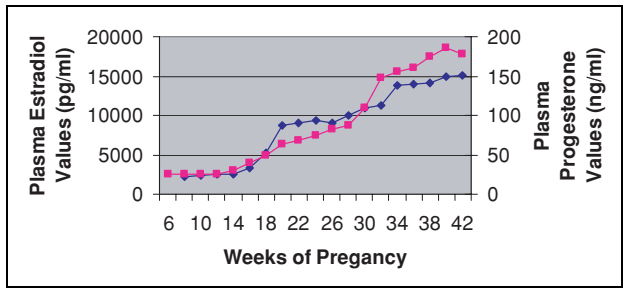

Fig 4.—Mean plasma estrogen and progesterone levels during pregnancy. Plasma estradiol (-♦-) and progesterone (-■-) levels rise abruptly during the second and third trimesters (weeks 14 to 40) of pregnancy. Note that serum estradiol levels during the third trimester of pregnancy are 30 to 40 times higher and progesterone levels are 20 times higher than their peak levels during natural menstrual cycles. (Adapted with permission from Tulchinsky D. Am J Obstet Gynecol 1972;112(8):1095-1100.)

30 to 40 times higher and progesterone levels are 20 times higher than peak levels during native menstrual cycles (Figure 4). Other hormones may also be increased during pregnancy and include human chorionic gonadotropin, human placental lactogen, inhibin, atrial natriuretic peptide, and α-fetoprotein as well as others.[78]

Preexisting Migraine Headache.—Preexisting migraine most often improves with pregnancy. Sances et al[79] conducted a prospective study of 47 female migraineurs to investigate the course of migraine headache during pregnancy. Migraine improved in 46.8% of women during the first trimester, 83% during the second trimester, and 87% during the third trimester. The complete remission rate increased from 11% during the first trimester to 53% and 79% during the second and third trimesters, respectively. Other retrospective studies have also confirmed that 48% to 79% of women with a history of preexisting migraine improve during pregnancy, particularly during the second and third trimesters[9,80-83] (Table 2). Aura symptoms in particular appear to occur quite frequently during pregnancy in those with a past history of migraine. Ertresvag et al[84] demonstrated that 40.9%, 20.3%, and 15.5% of migraineurs, respectively, had visual, sensory, or motor symptoms during pregnancy.

Effect on MWA.—Migraine has also been reported to develop for the first time during pregnancy in 1.3% to 18% of migraineurs.[9,81] Several studies[85,86] have reported "new onset" visual, sensory, and motor

Table 2.—The Course of Migraine During Pregnancy*

Parameter	Somerville 1972	Ratinahirana 1990	Granella 1993	Rasmussen 1993	Chen 1994	Maggioni 1995	Sances 2003
Number with migraine	38	116	943	80	508	80	49
New onset of migraine	18%	11%	5%	NR	NR	1%	17%
Prior migraine improved	77%	69%	67%	48%	79%	80%	87%
Prior migraine unchanged or worsened	23%	14%	33%	52%	21%	20%	23%
Type of study	R, I	R, I	R, I	R, I	R, I	R	P, D

*Data obtained from references[9,79-83,131]. Table adapted with permission from Silberstein S. Pregnancy, breast-feeding and headache. In: *Headache in Clinical Practice*. Oxford, UK: Isis Medical Media; 1998:192.
D = Diary; I = Interview; NR = not reported; P = Prospective; R = Retrospective.

aura during pregnancy. Some of the patients had experienced complicated pregnancies with accompanying thrombocytopenia, pre-eclampsia, and threatened abortions.[85] One might postulate that the "high estrogen milieu" of pregnancy could play a role in initiating attacks of MWA.

Clinical Predictors for Improvement.—Studies have attempted to identify clinical predictors that would allow identification of migraineurs more or less likely to experience improvement during pregnancy. Granella et al[9] reported that a complete remission with pregnancy was more likely in those with a history of onset of migraine during menarche. Sances et al[79] found that a pathological pregnancy course (eg, toxemia) and prior history of menstrual migraine were negative predictors of improvement during the first and the third trimesters. Kelman[87] noted that female migraineurs with "exclusively" MWA were less likely to have an improvement in migraine during pregnancy.

Pathogenesis.—Pregnancy induces a state of antinociception that has been termed the "analgesia of pregnancy." The "analgesia of pregnancy" is likely mediated through the opiatergic system as intrathecal administration of antagonists of κ and δ opioid receptors can abolish this antinociception within pregnant rats.[88] Spinal cord levels of enkephalin and dynorphin levels are also increased in pregnant rats.[88] High serum levels of *both* estrogen and progesterone are necessary to produce the "analgesia of pregnancy," as administration of either hormone alone fails to induce antinociception. It is not known if similar mechanisms exist within the trigeminal pain pathways of female migraineurs to explain an improvement in migraine headache during pregnancy.

LACTATION

Lactation commonly inhibits ovulation during the postpartum period. The mean time to ovulation after delivery is 189 days in breast-feeding women and 45 days in nonbreast-feeding women.[89] The duration of anovulation may be influenced by the intensity and the frequency of breast-feeding. Seventy percent of women that practice full or partially full breast-feeding will remain amenorrheic for 6 months.[90]The "hormonal milieu" during lactation depends on the presence or absence of ovulatory cycles.

Lactation generally leads to an improvement in the clinical course of migraine headache during the postpartum time period. Sances et al[79] reported that migraine recurred within the first postpartum month in 100% of women who bottle-fed and in 43.2% of those who breast-fed ($P = .0003$). Marcus et al[91] found that the headache index during the first 3 postpartum months was similar for patients who breast-fed to that obtained during the second trimester of pregnancy. These data likely suggest that the improvement of migraine commonly seen during the second trimester of pregnancy continues into the postpartum time period if breast-feeding is maintained.

PERIMENOPAUSE

The World Health Organization has defined the perimenopause as the time period 2 to 8 years prior

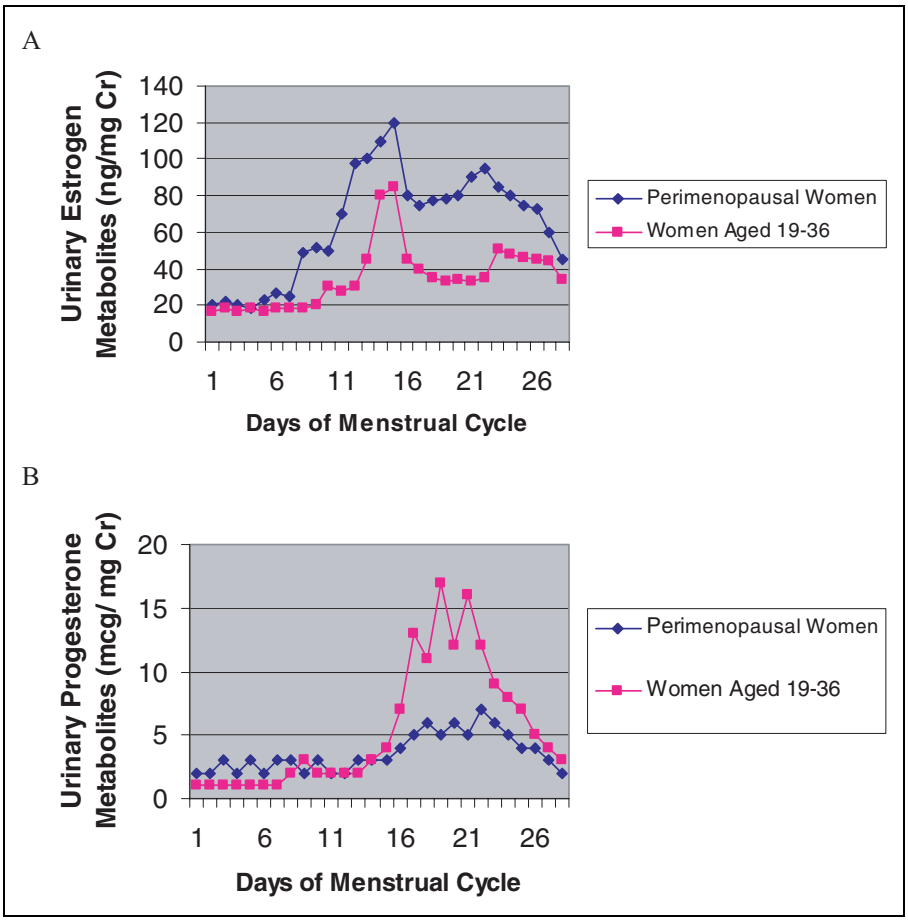

Fig 5.—Urinary estrogen and progesterone metabolites during natural menstrual cycles in perimenopausal and younger cycling women. Note that urinary estrogen metabolites are higher and progesterone metabolites are lower in perimenopausal women than in younger cycling women aged 19 to 38 (Graphs A and B, respectively). Day 1 is the first day of menstruation and day 28 is the last day before the next menstrual cycle. All urinary hormone values are divided by creatinine to correct for variations in concentrations within urine samples. (Reproduced with permission from Santoro N. J Clin Endocrinol Metab 1996;81:1495-1501.)

to menopause as well as the year after cessation of menses.[92,93] Women experience variable lengths of their menstrual cycles, heavier menstrual bleeding, anovulation, and intermittent amenorrhea during this time. Levels of ovarian hormones during native menstrual cycles may differ between perimenopausal and younger women. Santoro et al[94] found that the urinary estrogen metabolites were higher and progesterone metabolites were lower throughout the menstrual cycle in perimenopausal than younger women (Figure 5). Such a "hormonal milieu" might be provocative for migraine during the perimenopausal time period if higher levels or greater fluctuations in estrogen provoke migraine. If mid-luteal progesterone is preventative for migraine, then anovulation encountered during the perimenopause could be provocative for migraine.

No longitudinal diary studies have been conducted to determine the exact effect of the perimenopausal time period on migraine headache. Two cross-sectional studies,[12,95] however, have suggested that the prevalence of migraine headache is higher during the perimenopausal transition than during early menopausal time periods. The increased prevalence of migraine, however, was only encountered in those with a past history of MWoA and premenstrual syndrome. Therefore, these two subgroups of migraineurs may be more prone to the hormonal effects of the perimenopause.

MENOPAUSE

The World Health Organization has defined menopause as the "permanent cessation of menstruation, determined retrospectively after 12 consecutive months of amenorrhea without any pathological or physiological cause."[92] Menopause represents a time period during which women have depleted their supply of follicles from the ovaries resulting in a permanent cessation of ovulation. Serum levels of estradiol typically range from 10 to 20 pg/mL in most postmenopausal women. Postmenopausal women often experience symptoms such as hot flashes, fatigue, forgetfulness, loss of memory, inability to concentrate, anxiety, depression, irritability, and headache.[96] Many of these symptoms can be improved with estrogen replacement therapy.[97,98]

Preexisting and New Onset Migraine.—The clinical course of migraine headache is quite variable at the time of menopause. Unfortunately, there have been no longitudinal cohort studies of migraine patients transitioning through menopause to determine the true effect of menopause on migraine. Most past studies have been retrospective questionnaire studies querying patients of the effect of menopause on their headaches. These studies suggest that preexisting migraine improves in 8% to 36%, worsens in 9% to 42%, and remains unchanged in 27% to 64% at the time of menopause[9,11,57,99-101] (Table 3). Eight to 13% of female migraineurs may develop migraine for the first time during menopause.[9,11] Patients with a surgical menopause may fare worse than those with a natural menopause, with 38% to 87% experiencing a worsening of existing migraine.[9,101] These data could suggest that an *abrupt* withdrawal of estrogen such as that occurring with surgical oophorectomy may be more provocative for migraine headache than a gradual withdrawal such as that occurring with a natural menopause. Another potential explanation may be that the dose of estrogen replacement therapy used in surgically oophorectomized patients was too low to prevent migraine (see below).

Pathogenesis.—"Estrogen withdrawal" and its effects on the central nervous system are thought to be the primary mechanism through which symptoms are provoked during the menopausal time period (eg, hot flashes, headaches, etc.). In fact, many of the same neurotransmitter systems altered during menstrual migraine secondary to "estrogen withdrawal" may also be affected by menopause. Decreased opioid tonus within hypothalamic nuclei, decreased blood serotonin levels, and up-regulation of certain serotonin receptors (eg, 5-HT 2A) have been demonstrated within studies of postmenopausal women.[102-105]

While the effects of a natural menopause on migraine headache can be quite variable, there appears to be a subgroup of women in which migraine arises "de novo" or worsens with the onset of menopause. These headaches have been termed "estrogen withdrawal" headaches and share some common features with hot flashes. "Estrogen withdrawal" headaches and hot flashes may not resolve for months to years after a natural menopause and both improve with estrogen treatment. This could suggest that the changes in the central nervous system induced by "estrogen withdrawal" during a natural menopause may not resolve immediately after removal of the offending stimulus. A long-standing menopause (>2 years), however, generally leads to an improvement in the clinical course of migraine headache.

HORMONE REPLACEMENT THERAPY

HRT refers to the administration of estrogens and/or progestins to women to ameliorate the symptoms encountered during perimenopausal or menopausal time periods. The estrogen preparations are categorized as those that contain natural, conjugated, and synthetic estrogens. Natural estrogen preparations contain estrogens normally found with women (eg, β-estradiol). Conjugated estrogens are produced from animal and/or plant sources, while synthetic estrogens are synthesized estrogen derivatives (eg, ethinyl estradiol). Both conjugated and synthetic estrogens are primarily composed of estrogen derivatives that are not typically found within humans. The estrogens within HRT have a much lower potency than those generally found in OCPs. The oral progestins include natural progesterone (eg, micronized progesterone) as well as synthetic progestins (eg, medroxyprogesterone). Oral progestins may be administered daily or for 10 to 12 days each month to prevent endometrial hyperplasia. The routes of delivery of HRT include pills, transdermal patches/gels, subcutaneous implants or injections, and vaginal suppositories.

Table 3.—Effects of Natural Menopause and Hormone Replacement Therapy on Migraine*

	Effect of Natural Menopause			Effect of Hormone Replacement		
Author/Year	Improved	Unchanged	Worsened	Improved	Unchanged	Worsened
Whitty/1968	8%	69%	23%	NR	NR	NR
Neri/1993	67%	24%	9%	NR	NR	NR
Granella/1995	25%	45%	29%	NR	NR	NR
Culpini/1995	30%	27%	42%	NR	NR	NR
Hodson/2000	36%	48%	16%	22%	57%	21%
Mueller/2000	24%	40%	36%	76%	IMP or UC	23%

*Data taken from references[9,11,57,99-101].
IMP = improved; NR = not reported; UC = unchanged.

Preexisting Migraine Headache.—HRT has been reported to improve migraine in 22% to 23%, worsen migraine in 21%, and leave it unchanged in 57%[100] (Table 3). Hodson et al[100] reported that HRT was more likely to have no effect on migraine headache if a natural menopause left migraine unchanged. The PEPI trial[97] showed an improvement in headache with oral conjugated estrogens when compared with placebo in those with a history of headache at baseline, whereas if there was no history of headache they were more likely to develop headache as a side effect. In a cross-sectional study of 17,107 postmenopausal women from the Women's Health Study, Misakian et al[106] demonstrated that a diagnosis of migraine was 1.44 times more likely in current HRT users as compared to nonusers. This study could not ascertain, however, if the use of HRT led to the increased migraine prevalence or if migraine patients were simply more likely to be prescribed HRT.

Effect on MWA.—Case reports have suggested that aura symptoms can develop secondary to estrogen replacement therapy in some patients.[107,108] They may develop "de novo" or may increase the frequency of existing attacks of MWA. Higher dosages of estrogen replacement therapy may be more prone to lead to the development of aura symptoms. MacGregor[108] reported that lowering the dosage or changing to another type of estrogen replacement may lead to an abatement of aura symptoms.

Dosage of Estrogen Replacement Therapy.—The dosage of estrogen replacement therapy may have an influence on the clinical course of migraine in postmenopausal women. Martin et al[109] reported that a 100-mcg transdermal estradiol patch produced a modest preventative benefit for migraine headache in 21 women (15 with MWoA; 6 with MWA) who had a medical menopause induced by a gonadotropin-releasing hormone agonist. A subsequent study[110] randomized the same group of patients to two different doses of transdermal estradiol (either 50 or 100 mcg) and found that only the 100-mcg dose was preventative of migraine. Since the 100-mcg patch maintains serum levels of estradiol in the 45 to 75 pg/mL range, these data could imply that a critical range of estradiol levels is necessary to prevent migraine headache.

Type and Route of Administration.—The type and route of administration of estrogen replacement therapy could have an effect on migraine headache. Nappi et al[111] demonstrated that headache outcome measures worsened in headache patients receiving an oral conjugated estrogen and medroxyprogesterone, while they did not change as compared to baseline in those receiving a 50-mcg transdermal estradiol patch and medroxyprogesterone. These data could suggest that HRTs containing conjugated estrogens are provocative for migraine, while those containing natural estrogens have less effect on migraine. Alternatively, transdermal routes of delivery may be superior to oral routes, since they maintain a more constant serum estradiol level, which could prove advantageous if fluctuating estrogen levels trigger headache.[112]

Table 4.—Influence of Reproductive Events and Hormonal Therapies on Migraine Headache

Hormonal Event	Hormonal Milieu	Effect on MWA	Effect on MWoA
Menarche	Anovulation for first 12 to 18 months	Onset before or at onset of menarche	Onset after menarche
Menstrual migraine	↓ in serum estradiol levels from 300 to 50 pg/mL	No effect	Triggers migraine attacks
Pregnancy	Serum estradiol levels 15,000 pg/mL, serum progesterone levels 150 to 200 ng/mL	No improvement; rare new onset aura	Improvement during second and third trimesters
Lactation	Anovulation variable during first 6 months	Unknown	Improvement compared to before pregnancy
Perimenopause	↑ estrogen and ↓ progesterone serum levels compared with younger women	No effect	↑ prevalence of migraine compared with early menopause
Menopause	Serum estradiol levels in 10 to 20 pg/mL range	Effect variable	Effect variable; rare new onset migraine
OCP	Synthetic estrogen and progestin	More likely to worsen; rare new onset aura	Mostly unchanged; may worsen during placebo week
HRT			
Estradiol patch 100 mcg	Serum estradiol levels of 45 to 75 pg/mL	Rare new onset aura	Improvement in some
Conjugated estrogens	Numerous estrogen metabolites	Unknown	Unchanged or worsens

HRT = hormone replacement therapy; MWA = migraine with aura; MWoA = migraine without aura; OCPs = oral contraceptives.

Dosing Regimens.—The dosing regimens of combined estrogens/progestin therapy can also influence migraine headache. Facchinetti et al[113] found that patients receiving regimens of daily continuous HRT (eg, daily oral estrogens and progestins) had lower headache outcome measures than those receiving HRT regimens with intermittent dosing regimens (eg, regimens with no HRT for 1 week per month or those that gave progestins for only 2 weeks per month). These data would imply that HRT regimens using the same dosage of estrogens and progestins on a daily basis are superior to those using intermittent dosing of HRT.

Risk of HRT.—HRT does carry some risk to postmenopausal women. The Women's Health Initiative[114] reported that oral conjugated estrogens administered daily along with a progestin significantly increased the risk of breast cancer (hazard ratio [HR], 1.26), stroke (HR, 1.41), pulmonary embolus (HR, 2.13), and coronary heart disease (HR, 1.29). This data has led several expert panels to discourage use of HRT for the prevention of chronic disease.[115-119] They recommended HRT for short-term use (<2 years) during the early menopausal time period to manage symptoms of hot flashes, but to discourage long-term use for other indications.

REPRODUCTIVE LIFE EVENTS AND HORMONAL THERAPIES

Reproductive life events as well as hormonal therapies can be preventative or provocative for migraine depending on the "hormonal milieu" to which the patient is exposed. A decline of serum estradiol levels of the magnitude experienced prior to menstruation (eg, decline from 250 to 300 pg/mL to 25 to 50 pg/mL) is clearly provocative for patients with menstrual migraine. It is unknown if a similar "magnitude" of decline at higher serum levels would be provocative for migraine. More stable levels of estrogen (eg, serum levels maintained within a 45 to 75 pg/mL range) as administered in the form of a 100-mcg transdermal estradiol patch are preventative for migraine in some postmenopausal women. A complete remission of attacks of MWoA can be induced during the third trimester of pregnancy with serum estradiol levels ranging from 13,000 to 15,000 pg/mL and progesterone levels ranging from 150 to 200 ng/mL.[79] Therefore, different hormonal milieus can have vastly different effects on the clinical course of migraine (Table 4).

Reproductive life events affect MWA differently than MWoA (Table 4). The onset of MWoA occurs after the development of menarche suggesting that the

development of the female menstrual cycle could play a role in its initiation, while MWA generally begins prior to menarche or at least prior to development of consistent menstrual cycles. Falling estradiol levels at the time of menstruation seem to trigger attacks of MWoA, but not attacks of MWA. MWoA tends to improve with pregnancy, but patients with pure MWA may not.[79,87] The prevalence of migraine increases during the perimenopausal time period in patients experiencing MWoA, but remains unchanged in those with MWA. Therefore, patients with MWoA seem to be more responsive to the effects of changing ovarian hormones. Interestingly, symptoms of premenstrual syndrome and menopause (eg, hot flashes) have also been reported in some studies to be more common in patients with MWoA.[12,87]

There may be different subgroups of migraineurs that are more sensitive to the changes in hormones encountered with reproductive events. For example, women with migraine onset during menarche are more likely to have improvement in their migraines during pregnancy, while those with menstrual migraine are less likely to improve during the first and third trimesters of pregnancy.[9,79] Women who experience hot flashes during the perimenopause or those with a history of premenstrual syndrome may be more likely to experience migraine during the perimenopause.[12,95] Therefore, a history of menstrual migraine, premenstrual syndrome, hot flashes, or onset of migraine during menarche may signify that a given patient is "hormonally sensitive" and thus more likely to be affected, either positively or negatively, by other hormonal events.

ESTROGEN AND MIGRAINE

Estrogen in particular appears to modulate the frequency, severity, and disability of migraine headache. The effects of estrogen appear to be strongly influenced by the *specific levels* of serum estradiol levels. A decline in estrogen levels during the perimenstrual time period will trigger menstrual migraine, but only when serum levels fall below a threshold of 45 to 50 pg/mL. Sustained moderate-to-high serum estradiol levels such as these experienced with pregnancy and HRT seem to be preventative for some patients with MWoA. High serum levels of estrogen such as those experienced with pregnancy and HRT or high potency estrogens (eg, OCPs) may worsen MWA in some patients. Thus moderate-to-high levels of serum estradiol seem to be preventative for some patients with MWoA while provocative for others with MWA.

How sensitive might some migraineurs be to changes in serum estradiol levels? The above mentioned medical oophorectomy study[109] found that headache outcome measures were 45–50% higher during the first 2 days after application of a transdermal estradiol patch when compared to the fifth and sixth days after a patch change while no differences were seen between patch days in the placebo group. Within the estradiol treated group, serum estradiol levels were maintained in a very narrow range varying from 50 pg/mL during the first 2 patch days to 42 pg/mL during the last 2 days of the patch. Therefore, despite an "overall" preventative effect with the transdermal estradiol patch compared with placebo, a small rise (eg, 11 pg/mL) in serum estradiol levels on the first 2 days of the patch might be provocative for migraine headache. These results emphasize how exquisitely sensitive some migraineurs may be to small changes in serum estradiol levels and demonstrate that estrogen can be preventative in some situations and provocative in others.

The above data also suggest that migraine with and without aura are triggered by different mechanisms. Attacks of MWoA are triggered by declines in serum estradiol, while attacks of MWA are triggered by sustained high levels of estradiol. The mechanisms through which estrogen triggers these two subtypes of migraine are largely speculative. One might hypothesize that moderate-to-high serum levels of estrogen trigger attacks of MWA through enhancement of cortical glutamatergic neurotransmission or development of platelet microemboli, which could then trigger attacks on a vascular or ischemic basis. In regard to MWoA, declining levels of estradiol might trigger migraine through effects on excitatory and inhibitory neurotransmission within trigeminal pain pathways.

PROGESTERONE AND MIGRAINE

Progesterone and/or its metabolites as well as progestins can have a variable effect on migraine. There is preliminary evidence to suggest that mid-luteal

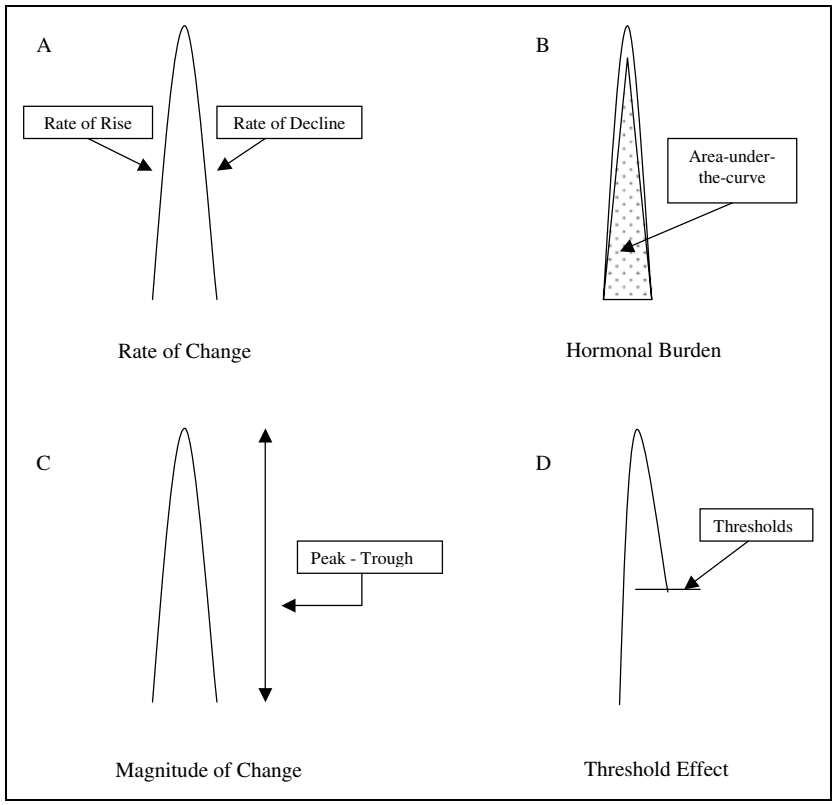

Fig 6.—Theorized mechanisms through which ovarian hormones could modulate migraine headaches. (A) "Rate of change" is calculated by the slope of the rise or decline in serum hormone levels. (B) "Hormonal burden" is determined by measuring the area-under-the-curve of hormone peaks. (C) "Magnitude of change" signifies the absolute difference in peak and trough hormone levels. (D) The "threshold effect" indicates that a certain level of ovarian hormone exists above or below which migraine is triggered.

elevations of progesterone and/or its metabolites could be preventative for migraine when compared to other times of the cycle.[16] Past studies[120-123] have also reported that daily oral progestins could be preventative for migraine headache in *premenopausal* women. Their preventative effect in premenopausal women may be secondary to induction of anovulation along with a preventative benefit of the particular progestin used. Side effects such as breakthrough bleeding and mastalgia may, however, limit their use. Injectable depot medroxyprogesterone and levonorgestrel implants, which are contraceptive agents, can trigger headache as a side effect in susceptible patients.[124,125] Progestins administered episodically for 10 to 12 days each month along with estrogen replacement therapy have been reported to trigger migraine in some *postmenopausal* women.[113,126] Therefore, progesterone and progestins can prevent or trigger migraines in different clinical situations.

MECHANISMS OF OVARIAN HORMONES

Ovarian hormones, whether encountered during menstrual cycles or with hormonal therapies, could modulate migraine headache through a number of mechanisms including the "rate of change," "magnitude of change," "hormonal burden," or a "threshold effect." The "rate of change" of ovarian hormones is calculated by determining the "slope of a rise or fall" in hormone levels around a hormonal peak. "Magnitude of change" is defined as the absolute difference between peak and trough hormone levels of a hormonal peak. The "hormonal burden" is calculated by measuring the area-under-the-curve of hormones during hormone peaks. There could also be a "threshold effect" of ovarian hormones, which refers to a level of serum hormones above or below which migraine may be triggered or prevented (Figure 6).

A recent study[16] did *not* find that "rates of change," "magnitude of change," or "total hormonal

burden" of urinary estrogen metabolites influenced headache outcome measures during menstrual cycles in premenopausal female migraineurs. Higher "hormonal burdens" of urinary progesterone metabolites, however, were associated with *worse* headache outcome measures during mid-luteal time periods. This might appear to be contrary to the above mentioned hypothesis that progesterone could be preventative for migraine during the mid-luteal phase of the menstrual cycle, but could suggest that a threshold of serum progesterone levels exists above which migraine is provoked and below which it is prevented. There may also be a "threshold" of serum estradiol levels below which migraine might be triggered after a decline of estrogen. Sommerville[24] and Lichten[127] noted that menstrual migraine was triggered when serum levels of estradiol fell below 45 to 50 pg/mL during the perimenstrual time period. Therefore, preliminary evidence would suggest that a "threshold effect" may be the most relevant mechanism through which ovarian hormones modulate migraine headache.

GENETICS OF OVARIAN HORMONES RECEPTORS

Migraine may only be influenced by ovarian hormones in those with a specific genetic predisposition. Colson et al[128] demonstrated that G594A polymorphism of the α-estrogen receptor occurred more frequently in migraineurs than controls within an Australian cohort. They later reported that a 306 base pair insertion within intron 7 of the progesterone receptor gene (PROGINS allele) was overrepresented within migraine patients.[129] The G594A α-estrogen receptor and the PROGINS alleles may act synergistically to increase the prevalence of migraine. Individuals possessing both risk alleles were 3.2 times more likely to have migraine headache than those possessing no alleles while those possessing just the PROGINS allele were only 1.8 times more likely to have migraine. Therefore, polymorphisms of estrogen and progesterone receptors genes may influence migraine prevalence in some populations.

CONCLUSIONS

Migraine headache is strongly influenced by reproductive events that occur throughout the lifespan of women. Each of these reproductive events has a different "hormonal milieu," which might modulate the clinical course of migraine headache. Estrogen and progesterone can be preventative or provocative for migraine headache under different circumstances depending on their absolute serum levels, constancy of exposure, and types of estrogen/progesterone derivatives. Attacks of migraine with and without aura respond differently to changes in ovarian hormones. Clearly, a greater knowledge of ovarian hormones and their effect on migraine is essential to a greater understanding of the mechanisms and pathogenesis of migraine headache.

REFERENCES

1. Zacharias L, Rand WM, Wurtman RJ. A prospective study of sexual development and growth in American girls: The statistics of menarchie. *Obstet Gynecol Surv.* 1976;31(4):325-337.
2. Harlan WR, Harlan EA, Grillo GP. Secondary sex characteristics of girls 12 to 17 years of age: The U.S. Health Examination Survey. *J Pediatr.* 1980;96(6):1074-1078.
3. Jenner MR, Kelch RP, Kaplan SL, Grumbach MM. Hormonal changes in puberty. IV. Plasma estradiol, LH, and FSH in prepubertal children, pubertal females, and in precocious puberty, premature thelarche, hypogonadism, and in a child with a feminizing ovarian tumor. *J Clin Endocrinol Metab.* 1972;34(3):521-530.
4. Stewart WF, Lipton RB, Celentano DD, Reed ML. Prevalence of migraine headache in the United States. Relation to age, income, race, and other sociodemographic factors. *JAMA.* 1992;267(1):64-69.
5. Stewart WF, Linet MS, Celentano DD, Van Natta M, Ziegler D. Age- and sex-specific incidence rates of migraine with and without visual aura. *Am J Epidemiol.* 1991;134(10):1111-1120.
6. Couturier EG, Bomhof MA, Neven AK, van Duijn NP. Menstrual migraine in a representative Dutch population sample: Prevalence, disability and treatment. *Cephalalgia.* 2003;23(4):302-308.
7. Martin VT. Menstrual migraine: A review of prophylactic therapies. *Curr Pain Headache Rep.* 2004;8(3):229-237.
8. MacGregor EA, Chia H, Vohrah RC, Wilkinson M. Migraine and menstruation: A pilot study. *Cephalalgia.* 1990;10(6):305-310.

9. Granella F, Sances G, Zanferrari C, Costa A, Martignoni E, Manzoni GC. Migraine without aura and reproductive life events: A clinical epidemiological study in 1300 women. *Headache.* 1993;33(7):385-389.
10. Granella F, Sances G, Pucci E, Nappi RE, Ghiotto N, Napp G. Migraine with aura and reproductive life events: A case control study. *Cephalalgia.* 2000;20(8):701-707.
11. Cupini LM, Matteis M, Troisi E, Calabresi P, Bernardi G, Silvestrini M. Sex-hormone-related events in migrainous females. A clinical comparative study between migraine with aura and migraine without aura. *Cephalalgia.* 1995;15(2):140-144.
12. Mattsson P. Hormonal factors in migraine: A population-based study of women aged 40 to 74 years. *Headache.* 2003;43(1):27-35.
13. Koseoglu E, Nacar M, Talaslioglu A, Cetinkaya F. Epidemiological and clinical characteristics of migraine and tension type headache in 1146 females in Kayseri, Turkey. *Cephalalgia.* 2003;23(5):381-388.
14. Johannes CB, Linet MS, Stewart WF, Celentano DD, Lipton RB, Szklo M. Relationship of headache to phase of the menstrual cycle among young women: A daily diary study. *Neurology.* 1995;45(6):1076-1082.
15. Stewart WF, Lipton RB, Chee E, Sawyer J, Silberstein SD. Menstrual cycle and headache in a population sample of migraineurs. *Neurology.* 2000;55(10):1517-1523.
16. Martin V, Wernke S, Mandell K, Grumbach MM. Defining the relationship between ovarian hormones and migraine headache. *Headache.* 2005;45:1190-1201.
17. MacGregor EA, Hackshaw A. Prevalence of migraine on each day of the natural menstrual cycle. *Neurology.* 2004;63(2):351-353.
18. Granella F, Sances G, Allais G, Nappi RE, Tirelli A, Benedetto C, et al. Characteristics of menstrual and nonmenstrual attacks in women with menstrually related migraine referred to headache centres. *Cephalalgia.* 2004;24(9):707-716.
19. Davies PT, Eccles N, Steiner TJ, Leathard H, Rose F. Plasma estrogen, progesterone and sex hormone binding globulin levels in the pathogenesis of migraine. *Cephalalgia.* 1989;9:143 [abstract].
20. Epstein MT, Hockaday JM, Hockaday TD. Migraine and reproductive hormones throughout the menstrual cycle. *Lancet.* 1975;1(7906):543-548.
21. Lichten EM, Lichten J, Whitty A, Peiper D. The use of leuprolide acetate in the diagnosis and treatment of menstrual migraine: The role of artificially induced menopause. *Headache Q.* 1995;6:313-317.
22. Murray SC, Muse KN. Effective treatment of severe menstrual migraine headaches with gonadotropin-releasing hormone agonist and "add-back" therapy. *Fertil Steril.* 1997;67(2):390-393.
23. Somerville BW. Plasma estradiol level linked to migraine during menstrual period. *JAMA.* 1972;221:845-846.
24. Somerville BW. The role of estradiol withdrawal in the etiology of menstrual migraine. *Neurology.* 1972;22(4):355-365.
25. Somerville BW. Estrogen-withdrawal migraine. II. Attempted prophylaxis by continuous estradiol administration. *Neurology.* 1975;25(3):245-250.
26. Somerville BW. Estrogen-withdrawal migraine. I. Duration of exposure required and attempted prophylaxis by premenstrual estrogen administration. *Neurology.* 1975;25(3):239-244.
27. de Lignieres B, Vincens M, Mauvais-Jarvis P, Mas JL, Touboul PJ, Bousser MG. Prevention of menstrual migraine by percutaneous oestradiol. *Br Med J (Clin Res Ed).* 1986;293(6561):1540.
28. Calhoun AH. A novel specific prophylaxis for menstrual-associated migraine. *South Med J.* 2004;97(9):819-822.
29. Pradalier A, Vincent D, Beaulieu P, Baudesson G, Launay J. Correlation between oestradiol plasma level and therapeutic effect on menstrual migraine. In: Rose C, ed. *New Advances in Headache Research: 4.* London: Smith-Gordon, 1994, pp. 129-132.
30. Silberstein SD, Merriam GR. Estrogens, progestins, and headache. *Neurology.* 1991;41(6):786-793.
31. Carlson LA, Ekelund LG, Oro L. Clinical and metabolic effects of different doses of prostaglandin E1 in man. Prostaglandin and related factors. *Acta Med Scand.* 1968;183(5):423-430.
32. Irwin J, Morse E, Riddick D. Dysmenorrhea induced by autologous transfusion. *Obstet Gynecol.* 1981;58(3):286-290.
33. Sances G, Martignoni E, Fioroni L, Blandini F, Facchinetti F, Nappi G. Naproxen sodium in menstrual migraine prophylaxis: A double-blind placebo controlled study. *Headache.* 1990;30(11):705-709.
34. Li W, Zheng T, Altura BM, Altura BT. Sex steroid hormones exert biphasic effects on cytosolic magnesium ions in cerebral vascular smooth muscle cells:

Possible relationships to migraine frequency in premenstrual syndromes and stroke incidence. *Brain Res Bull.* 2001;54(1):83-89.
35. Ramadan NM, Halvorson H, Vande-Linde A, Levine SR, Helpern JA, Welch KM. Low brain magnesium in migraine. *Headache.* 1989;29(7):416-419.
36. Mauskop A, Altura BM. Role of magnesium in the pathogenesis and treatment of migraines. *Clin Neurosci.* 1998;5(1):24-27.
37. Mauskop A, Altura BT, Cracco RQ, Altura BM. Intravenous magnesium sulphate relieves migraine attacks in patients with low serum ionized magnesium levels: A pilot study. *Clin Sci (Lond).* 1995;89(6):633-636.
38. Facchinetti F, Sances G, Borella P, Genazzani AR, Nappi G. Magnesium prophylaxis of menstrual migraine: Effects on intracellular magnesium. *Headache.* 1991;31(5):298-301.
39. Facchinetti F, Martignoni E, Fioroni L, Sances G, Genazzani AR. Opioid control of the hypothalamus-pituitary-adrenal axis cyclically fails in menstrual migraine. *Cephalalgia.* 1990;10(1):51-56.
40. Cassidy EM, Tomkins E, Dinan T, Hardiman O, O'Keane V. Central 5-HT receptor hypersensitivity in migraine without aura. *Cephalalgia.* 2003;23(1):29-34.
41. Nappi RE, Sances G, Brundu B, Ghiotto N, Detaddei S, Biancardi C, et al. Neuroendocrine response to the serotonin agonist M-chlorophenylpiperazine in women with menstrual status migrainosus. *Neuroendocrinology.* 2003;78(1):52-60.
42. Cassidy EM, Tomkins E, Sharifi N, Dinan T, Hardiman O, O'Keane V. Differing central amine receptor sensitivity in different migraine subtypes? A neuroendocrine study using buspirone. *Pain.* 2003;101(3):283-290.
43. D'Andrea G, Hasselmark L, Cananzi AR, Alecci M, Perini F, Zamberlan F, et al. Metabolism and menstrual cycle rhythmicity of serotonin in primary headaches. *Headache.* 1995;35(4):216-221.
44. Fioroni L, Andrea GD, Alecci M, Cananzi A, Facchinetti F. Platelet serotonin pathway in menstrual migraine. *Cephalalgia.* 1996;16(6):427-430.
45. Sarchielli P, Tognoloni M, Russo S, Vulcano MR, Feleppa M, Mala M, et al. Variations in the platelet arginine/nitric oxide pathway during the ovarian cycle in females affected by menstrual migraine. *Cephalalgia.* 1996;16(7):468-475.
46. Smith CC, McMahon LL. Estrogen-induced increase in the magnitude of long-term potentiation occurs only when the ratio of NMDA transmission to AMPA transmission is increased. *J Neurosci.* 2005;25(34):7780-7791.
47. Woolley CS. Estrogen-mediated structural and functional synaptic plasticity in the female rat hippocampus. *Horm Behav.* 1998;34(2):140-148.
48. Martin V, Behbehani M. Ovarian hormones and migraine headache: Understanding mechanisms and pathogenesis—Part 1. *Headache.* 2006.
49. Stell BM, Brickley SG, Tang CY, Farrant M, Mody I. Neuroactive steroids reduce neuronal excitability by selectively enhancing tonic inhibition mediated by delta subunit-containing GABAA receptors. *Proc Natl Acad Sci U S A.* 2003;100(24):14439-14444.
50. Beckham JC, Krug LM, Penzien DB, Johnson CA, Mosley TH, Meeks GR, et al. The relationship of ovarian steroids, headache activity and menstrual distress: A pilot study with female migraineurs. *Headache.* 1992;32(6):292-297.
51. Cutrer FM, Moskowitz MA. Wolff Award 1996. The actions of valproate and neurosteroids in a model of trigeminal pain. *Headache.* 1996;36(10):579-585.
52. Limmroth V, Lee WS, Moskowitz MA. GABAA-receptor-mediated effects of progesterone, its ring-A-reduced metabolites and synthetic neuroactive steroids on neurogenic oedema in the rat meninges. *Br J Pharmacol.* 1996;117(1):99-104.
53. Allais G, De Lorenzo C, Mana O, Benedetto C. Oral contraceptives in women with migraine: Balancing risks and benefits. *Neurol Sci.* 2004;25 (suppl 3):S211-S214.
54. Ryan RE. A controlled study of the effect of oral contraceptives on migraine. *Headache.* 1978;17(6):250-251.
55. Whitty CW, Hockaday JM, Whitty MM. The effect of oral contraceptives on migraine. *Lancet.* 1966;1(7442):856-859.
56. Dalton K. Migraine and oral contraceptives. *Headache.* 1976;15:247-251.
57. Mueller L. Predictability of exogenous hormone effect on subgroups of migraineurs. *Headache.* 2000;40(3):189-193.
58. Loder EW, Buse DC, Golub JR. Headache and combination estrogen-progestin oral contraceptives:

Integrating evidence, guidelines, and clinical practice. *Headache.* 2005;45(3):224-231.
59. Cachrimanidou AC, Hellberg D, Nilsson S, Waldenstrom U, Olsson SE, Sikstrom B. Long-interval treatment regimen with a desogestrel-containing oral contraceptive. *Contraception.* 1993;48(3):205-216.
60. Mousa GY. Migraine and oral contraceptives. *Am J Optom Physiol Opt.* 1982;59(10):821-823.
61. Horenstein S. Neurological disorders associated with oral contraceptives. *Trans N Engl Obstet Gynecol Soc.* 1967;21:159-172.
62. Gardner JH, Horenstein S, Van den Noort S. The clinical characteristics of headache during impending cerebral infarction in women taking oral contraceptives. *Headache.* 1968;8(3):108-111.
63. Hanington E, Jones R, Amess J. Platelet aggregation in response to 5HT in migraine patients taking oral contraceptives. *Lancet.* 1982;1:967-968.
64. Stang PE, Carson AP, Rose KM, Mo J, Ephross SA, Shahar E, et al. Headache, cerebrovascular symptoms, and stroke: The Atherosclerosis Risk in Communities Study. *Neurology.* 2005;64(9):1573-1577.
65. Tzourio C, Bousser MG. Migraine: A risk factor for ischemic stroke in young women. *Stroke.* 1997;28(12):2569-2570.
66. Tzourio C, Iglesias S, Hubert JB, Visy JM, Alperovitch A, Tehindrazanarivelo A, et al. Migraine and risk of ischaemic stroke: A case–control study. *BMJ.* 1993;307(6899):289-292.
67. Chang CL, Donaghy M, Poulter N. Migraine and stroke in young women: Case–control study. The World Health Organisation Collaborative Study of cardiovascular disease and steroid hormone contraception. *BMJ.* 1999;318(7175):13-18.
68. Velentgas P, Cole JA, Mo J, Sikes CR, Walker AM. Severe vascular events in migraine patients. *Headache.* 2004;44(7):642-651.
69. Etminan M, Takkouche B, Isorna FC, Samii A. Risk of ischaemic stroke in people with migraine: Systematic review and meta-analysis of observational studies. *BMJ.* 2005;330(7482):63.
70. Lidegaard O, Kreiner S. Contraceptives and cerebral thrombosis: A five-year national case–control study. *Contraception.* 2002;65(3):197-205.
71. Lidegaard O, Edstrom B, Kreiner S. Oral contraceptives and venous thromboembolism. A case–control study. *Contraception.* 1998;57(5):291-301.
72. Slooter AJ, Rosendaal FR, Tanis BC, Kemmeren JM, van der Graaf Y, Algra A. Prothrombotic conditions, oral contraceptives, and the risk of ischemic stroke. *J Thromb Haemost.* 2005;3(6):1213-1217.
73. Tzourio C, Tehindrazanarivelo A, Iglesias S, Alperovitch A, Chedru F, d'Anglejan-Chatillon J, et al. Case–control study of migraine and risk of ischaemic stroke in young women. *BMJ.* 1995;310(6983):830-833.
74. World Health Organization. *Improving Access to Quality Care in Family Planning: Medical Eligibility Criteria for Contraceptive Use*, 2nd ed. Geneva: World Health Organization, 2000.
75. Bousser MG, Conard J, Kittner S, de Lignieres B, MacGregor EA, Massiou H, et al. Recommendations on the risk of ischaemic stroke associated with use of combined oral contraceptives and hormone replacement therapy in women with migraine. The International Headache Society Task Force on combined oral contraceptives & hormone replacement therapy. *Cephalalgia.* 2000;20(3):155-156.
76. The use of hormonal contraceptives in patients with coexisting medical conditions: ACOG practice bulletin no. 18. *Int J Gynecol Obstet.* 2001;75:93-106.
77. Tulchinsky D, Hobel CJ, Yeager E, Marshall JR. Plasma estrone, estradiol, estriol, progesterone, and 17-hydroxyprogesterone in human pregnancy. I. Normal pregnancy. *Am J Obstet Gynecol.* 1972;112(8):1095-1100.
78. Speroff L, Glass R, Kase N. *Clinical Endocrinology and Infertility*, 5th ed. Baltimore: Williams & Wilkins, 1994.
79. Sances G, Granella F, Nappi RE, Fignon A, Ghiotto N, Polatti F, et al. Course of migraine during pregnancy and postpartum: A prospective study. *Cephalalgia.* 2003;23(3):197-205.
80. Chen TC, Leviton A. Headache recurrence in pregnant women with migraine. *Headache.* 1994;34(2):107-110.
81. Somerville BW. A study of migraine in pregnancy. *Neurology.* 1972;22(8):824-828.
82. Rasmussen BK. Migraine and tension-type headache in a general population: Precipitating factors, female hormones, sleep pattern and relation to lifestyle. *Pain.* 1993;53(1):65-72.
83. Ratinahirana Y, Darbois Y, Bousser MG. Migraine and pregnancy: A prospective study in 703 women. *Neurology.* 1990;40(suppl 1):437.
84. Ertresvag J, Zwart J, Helde G, Johnsen H, Bovim G. Headache and transient focal neurological symptoms during pregnancy, a prospective cohort. *Acta Neurol Scand.* 2005;111:233-237.

85. Chancellor AM, Wroe SJ, Cull RE. Migraine occurring for the first time in pregnancy. *Headache.* 1990;30(4):224-227.
86. Wright GD, Patel MK. Focal migraine and pregnancy. *Br Med J (Clin Res Ed).* 1986;293(6561):1557-1558.
87. Kelman L. Women's issues of migraine in tertiary care. *Headache.* 2004;44(1):2-7.
88. Medina VM, Dawson-Basoa ME, Gintzler AR. 17 beta-estradiol and progesterone positively modulate spinal cord dynorphin: Relevance to the analgesia of pregnancy. *Neuroendocrinology.* 1993;58(3):310-315.
89. Campbell OM, Gray RH. Characteristics and determinants of postpartum ovarian function in women in the United States. *Am J Obstet Gynecol.* 1993;169(1):55-60.
90. Labbok MH, Hight-Laukaran V, Peterson AE, Fletcher V, von Hertzen H, Van Look PF. Multicenter study of the Lactational Amenorrhea Method (LAM): I. Efficacy, duration, and implications for clinical application. *Contraception.* 1997;55(6):327-336.
91. Marcus DA, Scharff L, Turk D. Longitudinal prospective study of headache during pregnancy and postpartum. *Headache.* 1999;39(9):625-632.
92. World Health Organization Scientific Group. *Report of WHO Scientific Group: Research on the Menopause in the 1990's*. Geneva, Switzerland: World Health Organization; 1996.
93. Greendale GA, Lee NP, Arriola ER. The menopause. *Lancet.* 1999;353(9152):571-580.
94. Santoro N, Brown JR, Adel T, Skurnick JH. Characterization of reproductive hormonal dynamics in the perimenopause. *J Clin Endocrinol Metab.* 1996;81(4):1495-1501.
95. Wang SJ, Fuh JL, Lu SR, Juang KD, Wang PH. Migraine prevalence during menopausal transition. *Headache.* 2003;43(5):470-478.
96. Fettes I. Migraine in the menopause. *Neurology.* 1999;53(4 suppl 1):S29-S33.
97. Greendale GA, Reboussin BA, Hogan P, Barnabei VM, Shumaker S, Johnson S, et al. Symptom relief and side effects of postmenopausal hormones: Results from the Postmenopausal Estrogen/Progestin Interventions Trial. *Obstet Gynecol.* 1998;92(6):982-988.
98. Nelson AL. Extended-cycle oral contraception: A new option for routine use. *Treat Endocrinol.* 2005;4(3):139-145.
99. Whitty C, Hockaday JM. Migraine: A follow-up of 92 patients. *BMJ*. 1968;1:735-736.
100. Hodson J, Thompson J, al-Azzawi F. Headache at menopause and in hormone replacement therapy users. *Climacteric.* 2000;3(2):119-124.
101. Neri I, Granella F, Nappi R, Manzoni GC, Facchinetti F, Genazzani AR. Characteristics of headache at menopause: A clinico-epidemiologic study. *Maturitas.* 1993;17(1):31-37.
102. Genazzani AR, Petraglia F, Volpe A, Facchinetti F. Estrogen changes as a critical factor in modulation of central opioid tonus: Possible correlations with post-menopausal migraine. *Cephalalgia.* 1985;5(suppl 2):212-214.
103. Gonzales GF, Carrillo C. Blood serotonin levels in postmenopausal women: Effects of age and serum oestradiol levels. *Maturitas.* 1993;17(1):23-29.
104. Blum I, Vered Y, Lifshitz A, Harel D, Blum M, Nordenberg Y, et al. The effect of estrogen replacement therapy on plasma serotonin and catecholamines of postmenopausal women. *Isr J Med Sci.* 1996;32(12):1158-1162.
105. Berendsen HH. The role of serotonin in hot flushes. *Maturitas.* 2000;36(3):155-164.
106. Misakian AL, Langer RD, Bensenor IM, Cook NR, Manson JE, Buring JE, et al. Postmenopausal hormone therapy and migraine headache. *J Womens Health (Larchmt).* 2003;12(10):1027-1036.
107. Kaiser HJ, Meienberg O. Deterioration or onset of migraine under oestrogen replacement therapy in the menopause. *J Neurol.* 1993;240(3):195-196.
108. MacGregor A. Estrogen replacement and migraine aura. *Headache.* 1999;39(9):674-678.
109. Martin V, Wernke S, Mandell K, Zoma W, Bean J, Pinney S, et al. Medical oophorectomy with and without estrogen add-back therapy in the prevention of migraine headache. *Headache.* 2003;43(4):309-321.
110. Martin V, Liu J, Wernke S, Mandell K, Bean J, Rebar R. The dose of transdermal estradiol and its role in migraine headache. *Headache.* 2003;43:547-548 [abstract].
111. Nappi RE, Cagnacci A, Granella F, Piccinini F, Polatti F, Facchinetti F. Course of primary headaches during hormone replacement therapy. *Maturitas.* 2001;38(2):157-163.
112. Stumpf PG. Pharmacokinetics of estrogen. *Obstet*

Gynecol. 1990;75(4 suppl):9S-14S; discussion 15S-17S.
113. Facchinetti F, Nappi RE, Tirelli A, Polatti F, Nappi G, Sances G. Hormone supplementation differently affects migraine in postmenopausal women. *Headache.* 2002;42(9):924-929.
114. Rossouw JE, Anderson GL, Prentice RL, LaCroix AZ, Kooperberg C, Stefanick ML, et al. Risks and benefits of estrogen plus progestin in healthy postmenopausal women: Principal results from the women's health initiative randomized controlled trial. *JAMA.* 2002;288(3):321-333.
115. Hormone therapy for the prevention of chronic conditions in postmenopausal women: Recommendations from the U.S. Preventive Services Task Force. *Ann Intern Med.* 2005;142(10):855-860.
116. Abramson BL. Postmenopausal hormone replacement therapy for primary prevention of cardiovascular and cerebrovascular disease. Recommendation statement from the Canadian Task Force on Preventive Health Care. *CMAJ.* 2004;170(9):1388-1389.
117. Wathen CN, Feig DS, Feightner JW, Abramson BL, Cheung AM. Hormone replacement therapy for the primary prevention of chronic diseases: Recommendation statement from the Canadian Task Force on Preventive Health Care. *CMAJ.* 2004;170(10):1535-1537.
118. Mosca L, Appel LJ, Benjamin EJ, Berra K, Chandra-Strobos N, Fabunmi RP, et al. Evidence-based guidelines for cardiovascular disease prevention in women. *Circulation.* 2004;109(5):672-693.
119. Recommendations for estrogen and progestogen use in peri- and postmenopausal women: October 2004 position statement of the North American Menopause Society. *Menopause.* 2004;11(6 Pt 1):589-600.
120. Somerville BW, Carey HM. The use of continuous progestogen contraception in the treatment of migraine. *Med J Aust.* 1970;1(21):1043-1045.
121. Singh I, Singh I, Singh D. Progesterone in the treatment of migraine. *Lancet.* 1947;1:745-747.
122. Bradley W, Hudgson P, Foster J, Newell D. Double-blind controlled trial of a micronized preparation of flumedroxone (Demigran) in prophylaxis of migraine. *BMJ.* 1968;3:531-533.
123. Davies P, Fursdon-Davies C, Rees MC. Progestogens for menstrual migraine. *J Br Menopause Soc.* 2003;9(3):134.
124. Kaunitz AM. Injectable depot medroxyprogesterone acetate contraception: An update for U.S. clinicians. *Int J Fertil Womens Med.* 1998;43(2):73-83.
125. Sivin I. International experience with NORPLANT and NORPLANT-2 contraceptives. *Stud Fam Plann.* 1988;19(2):81-94.
126. Greenblatt RB, Bruneteau DW. Menopausal headaches—psychogenic or metabolic? *J Am Geriatr Soc.* 1974;22(4):186-190.
127. Lichten EM, Lichten JB, Whitty A, Pieper D. The confirmation of a biochemical marker for women's hormonal migraine: The depo-estradiol challenge test. *Headache.* 1996;36(6):367-371.
128. Colson NJ, Lea RA, Quinlan S, MacMillan J, Griffiths LR. The estrogen receptor 1 G594A polymorphism is associated with migraine susceptibility in two independent case/control groups. *Neurogenetics.* 2004;5(2):129-133.
129. Colson NJ, Lea RA, Quinlan S, MacMillan J, Griffiths LR. Investigation of hormone receptor genes in migraine. *Neurogenetics.* 2005;6(1):17-23.
130. Dzoljic E, Sipetic S, Vlajinac H, Marinkovic J, Brzakovic B, Pokrajac M, et al. Prevalence of menstrually related migraine and nonmigraine primary headache in female students of Belgrade University. *Headache.* 2002;42(3):185-193.
131. Maggioni F, Alessi C, Maggino T. Primary headache and pregnancy. *Cephalalgia.* 1995;15:54 [abstract].