ABSTRACT

Approximately 60% of migraine headaches in women are associated with the menstrual cycle, with 25% of menstrually related migraines occurring exclusively during the perimenstrual period and 75% occurring during this period as well as at other times during the cycle. Both types of menstrually associated migraine fall under the broader classification of migraine without aura, and typically last longer and may require more treatment than migraines with aura.

This article reviews the hormonal fluctuations that occur during the natural menstrual cycle, pregnancy, perimenopause, and menopause, as well as their relationship to migraine attacks. Epidemiology, impact, characteristics, and complex pathophysiology of menstrually related migraine are reviewed along with diagnostic criteria and a discussion of the links between migraine and numerous comorbid conditions. Whereas comorbidities can confound the diagnosis, they more directly influence choice of medication for treatment.

(Migraine is a common disabling primary headache disorder that affects 28 million men and women in the United States. It has considerable impact on daily life functions and productivity at work and in school. As noted in the American Migraine Study II, 53% of migraineurs reported impairment severe enough to require bed rest and 31% reported missing at least 1 day of work or school in a 3-month period because of migraine. Other studies report increased work-related disability due to migraine, billions of dollars of disability and economic costs, and a 4-fold increased risk for stroke in women with migraine who are younger than age 45.

Although the prevalence of migraine peaks between the ages of 25 and 55, it is 3× more common in women during their reproductive years than it is in men. Migraine occurring in women during these years is believed to be associated with hormonal fluctuations because no comparable fluctuations in androgens are observed in men and because prevalence in women rises after puberty and falls after menopause. Moreover, 51% to 55% of women with migraine report menstruation as a headache trigger. Two main types of estrogen-mediated migraine have been identified: estrogen withdrawal and migraine without aura, and high-estrogen states and migraine with aura.

Among women with migraine, 11% experience onset of migraine at the onset of menarche and are...
migraine associated with menstruation than they are other migraine types; 14% have migraine only with menses (defined as pure menstrual migraine, or MM), and 46% have migraine with menses as well as at other times during the menstrual cycle (defined as menstrually related migraine, or MRM). Risk of a migraine attack is higher during the first 3 days of menstruation than during ovulation. Depending on the definition of menstrual migraine (ie, whether it occurs only with menses or with menses as well as at other times during the cycle), its prevalence ranges from 4% to 73%. The wide range alone reflects the paucity of solid epidemiologic data on MM and MRM.

### Classification and Characteristics

In revising its standardized definitions of headache disorders, the International Headache Society (IHS) provided separate classifications for MM and MRM, as outlined in Table 1. Citing the need for additional epidemiologic evidence, however, the IHS placed these definitions in the Appendix rather than in the main body of classification codes.

With these classifications in mind, Mannix et al determined that 14% of women with migraine have pure MM, 46% have MRM, and 40% have nonmenstrual migraine. MacGregor and Hackshaw analyzed diary data to assess the association between migraine and menses in a total of 698 cycles in 155 women. They found the overall relative risk (RR) of migraine was highest during the first 3 days of menses (2.5), followed by the 2 days preceding menses (1.71); and the RR of severe migraine and migraine with vomiting was higher during the first 3 days of menses (3.41 and 4.69, respectively). These findings support the new IHS definitions and diagnostic criteria.

Both pure MM and MRM are included under the broader classification of migraine without aura (A1.1), and both subcategories apply only to menstruating women. Other characteristics of MM and MRM are severe intensity, long duration (up to 72 hours), high recurrence rate, greater work-related disability compared with nonmenstrual migraine, and predictable timing.

Figure 1 shows the incidence of 3 types of headache—migraine without aura, tension-type, and migraine with aura—in relation to the menstrual cycle. The high incidence of migraine without aura during the perimenstrual period supports the relationship of MM and MRM to menstruation, whereas the smaller but noticeable upswing in tension-type headache during this same time interval suggests that tension-type headache may represent a milder form of migraine. It should be noted, however, that this study was small, including only 81 women.

### Table 1. Distinguishing Between Pure Menstrual and Menstrually Related Migraine

<table>
<thead>
<tr>
<th></th>
<th>Migraine Without Aura (A1.1)</th>
<th>Menstral Migraine</th>
<th>Menstrually Related Migraine</th>
</tr>
</thead>
<tbody>
<tr>
<td>IHS classification code</td>
<td>A1.1.1</td>
<td>A1.1.2</td>
<td></td>
</tr>
<tr>
<td>Terminology</td>
<td>Pure menstrual migraine without aura</td>
<td>Menstrually related migraine without aura</td>
<td></td>
</tr>
<tr>
<td>Pattern of occurrence</td>
<td>Exclusively during 5-day perimenstrual period (days -2 to +3) of menstruation in at least 2 of 3 menstrual cycles</td>
<td>During perimenstrual period and at other times of the month in at least 2 of 3 menstrual cycles</td>
<td></td>
</tr>
</tbody>
</table>

Data from International Headache Society classification of headache disorders.
HORMONAL CHANGES THROUGHOUT LIFE

Several distinct changes in the hormonal environment occur during 3 chronologic stages of a woman’s life—birth to menarche, menarche to perimenopause, and perimenopause to menopause—as well as during temporary states such as pregnancy, the postpartum period, and lactation. An artificial hormonal environment also can be created by exogenous influences such as oral contraceptive pills (OCPs), estrogen replacement therapy (ERT), and hormone replacement therapy (HRT).

Because migraine headaches can occur during any of these stages and circumstances, issues are raised that are addressed in this article and elsewhere in this monograph. Specifically, do hormonal fluctuations observed at different times in a woman’s life increase the likelihood of migraine? Does the risk of migraine increase or decrease during pregnancy? Does use of OCPs, ERT, or HRT affect likelihood of migraine? Are there factors other than hormonal changes that are responsible for increasing or decreasing migraine attacks during the years of normal menstrual cycling, pregnancy, perimenopause, and menopause?

THE MENSTRUAL CYCLE

The menstrual cycle begins at menarche and ends at menopause. The first day of menses is defined as the first day of the menstrual cycle, and the day before the next menses is defined as the end of the menstrual cycle. The average menstrual cycle is 28 days, but can be as short as 21 days or as long as 35 days.

The 28-day cycle shown schematically in Figure 2 depicts the primary hormonal changes that occur each month in the absence of pregnancy. Estradiol rises during the follicular phase, falls prior to ovulation, and then rises again during the luteal phase. Progesterone, however, does not begin to rise until after ovulation and the surge in luteinizing hormone (LH) and follicle-stimulating hormone (FSH). Unless pregnancy occurs, levels of both estradiol and progesterone fall during the latter half of the luteal phase and menstruation begins anew.

PERIMENOPAUSE AND MENOPAUSE

The menstrual cycle continues to occur until perimenopause, which is defined as the transition between having monthly cycles and the menopause. Menopause occurs between the ages of 43 and 57 (mean age 50 to 51 years) and is defined as having no menses for 1 year.

Perimenopause may last 4 years or longer, and during this interval fluctuations in estradiol, progesterone, and FSH may be considerably more pronounced than those observed during the regular menstrual cycle. By contrast, the hormonal state seen at menopause is essentially the same as that seen in the premenarchal female. The absence of ovarian follicles, oocytes, and ovarian secretion of estradiol and progesterone results in very low levels of these hormones and a very stable hormonal milieu, at least theoretically. However, FSH and particularly LH levels continue to fluctuate and are higher during menopause than they are premenopausally.

PREGNANCY, POSTPARTUM, AND LACTATION

The most dramatic hormonal changes occur during pregnancy. The normal menstrual cycle is interrupted at fertilization. Implantation begins 7 days later, or on approximately day 21 of the menstrual cycle, and the trophoblastic tissue begins to secrete human chorionic gonadotropin (hCG). Levels of hCG then begin to rise to stimulate and maintain the function of the corpus luteum, which is needed to sustain the pregnancy for the first 8 to 12 weeks. Progesterone levels do not fall during this period. Instead, they remain elevated for the duration of the pregnancy, with the placenta serving as the source of progesterone after 12 weeks.

Estrogen levels are at their highest during pregnancy, with concentrations of the 3 major estrogens—estrone (E₁), estradiol (E₂), and estriol (E₃)—continuing to rise as pregnancy progresses (Figure 3). Levels of progesterone and 17-hydroxyprogesterone also continue to rise.

Figure 2. Hormonal Changes Occurring During the Menstrual Cycle

![Figure 2](image-url)
Hormone secretion during pregnancy reflects a complex interaction among the fetus, the placenta, and the maternal adrenals and ovaries. The placenta does not utilize cholesterol to produce estrogens and progesterone, but fetal and maternal precursors such as dehydroepiandrosterone and pregnenolone. The placenta and pituitary also produce large amounts of several other hormones during pregnancy, including prolactin, human placental lactogen, and hCG.

Hormone levels decline rapidly after delivery and expulsion of the placenta. In the absence of breastfeeding, prolactin levels return to normal after 7 days. The time line for return to normal of other hormone levels and resumption of ovulation and menses is summarized in Table 2. Resumption of ovulation and menses after delivery depends on whether breast-feeding occurs and, if it does, on the intensity and frequency of feeding. Interestingly, progesterone secretion is diminished during the luteal phase of the initial menstrual cycles after delivery.

When a woman is fully breast-feeding and amenorrheic, the hormonal milieu is similar to that seen during premenarche and menopause. Hormone levels are low and unchanging. However, as ovulation resumes, the hormonal milieu is similar to that seen during the perimenopause, with fluctuating levels of progesterone and estradiol.

**ARTIFICIAL HORMONAL MILIEU**

OCPs, ERT, and HRT induce an artificial hormonal milieu. OCPs act on the pituitary to suppress ovulation and the secretion of ovarian estradiol, progesterone, and androgens. They contain ethinyl estradiol (or mestranol, which is converted to ethinyl estradiol) and one of several different progestins such as norethindrone acetate.

ERT (estrogen only) is reserved for women who no longer have a uterus and HRT (estrogen plus progestin) is indicated for women with an intact uterus, to protect the uterus from endometrial malignancy. Conjugated equine estrogens and other estrogens are used in ERT formulations, and esterified estrogens and estradiol are used in HRT formulations. Medroxyprogesterone acetate, norethindrone acetate, and micronized progesterone are the most commonly used progestins for HRT.

**Table 2. Hormone Levels and Return to Menses After Delivery**

<table>
<thead>
<tr>
<th>Hormone</th>
<th>Time</th>
</tr>
</thead>
<tbody>
<tr>
<td>Human chorionic gonadotropin</td>
<td>Up to 2 weeks</td>
</tr>
<tr>
<td>Human placental lactogen</td>
<td>1–2 days</td>
</tr>
<tr>
<td>Estradiol</td>
<td>At follicular phase levels within 1–3 days</td>
</tr>
<tr>
<td>Estriol</td>
<td>1–3 days</td>
</tr>
<tr>
<td>Progesterone</td>
<td>At follicular phase levels within 1–3 days</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Resumption of Ovulation and Menses</th>
<th>Average Time</th>
<th>Range</th>
</tr>
</thead>
<tbody>
<tr>
<td>No breast-feeding</td>
<td>4–6 weeks</td>
<td>3–10 weeks</td>
</tr>
<tr>
<td>Suppression of lactation</td>
<td>3 weeks</td>
<td>2.5–4 weeks</td>
</tr>
<tr>
<td>Induced pregnancy loss</td>
<td>4 weeks</td>
<td>2–6 weeks</td>
</tr>
<tr>
<td>Full breast-feeding</td>
<td>27 weeks</td>
<td>3+ months</td>
</tr>
</tbody>
</table>
**Pathophysiology**

This section explores 2 concepts underlying migraine pathophysiology in women: that migraine and its evolution from episodic to chronic headache involves a disorder of neuromodulatory systems of pain perception; and that interaction between ovarian steroids and the modulating components of nociceptive systems may explain the clinical features of migraine in women.

In migraine with aura, a wave of cortical spreading depression invades the trigeminal terminals surrounding the penetrating pial arterial vessels, depolarizing them and initiating an axon reflex. In this way, vasodilation of the meningeal vessels takes place, as does a cascade of events culminating in a sterile inflammatory change mediated through release of calcitonin gene-related peptide, substance P, and various neurokinins. This peripheral inflammatory change initiates antidromic impulses along the trigeminal nerve, relaying the trigeminal nucleus via a brain stem reflex. The parasympathetic nervous system also is activated via a brain stem reflex to promote further dilatation.

In MM and MRM, which are infrequently characterized by aura, cyclic hormonal influences further compromise pain modulation; estrogen dysmodulation of neuronal systems may be an important cause of MM and MRM. Possibly, inability to modulate the mismatch between cyclic changes in estrogen levels and the neuronal systems involved in pain perception triggers the MM or MRM attack. In essence, migraine attacks may be caused by failure of homeostatic adjustment in brain physiology necessary to respect the primacy of estrogen cycling for reproductive function.

Although MM seems to be triggered by a precipitous fall in estrogen levels alone, both MM and MRM also are dependent on fluctuating estrogen levels throughout the cycle, especially the luteal phase, which appears to be critical (Figure 4).

At the very least, variations in estradiol levels are extremely important in the different clinical expressions of hormonally influenced migraine. Somerville showed that treatment with estradiol delayed the MM attack but not the menses, whereas treatment with progesterone delayed the menses but not the migraine attack.

Although migraine without aura is the most common presentation of MM and MRM, estrogen levels at ovulation are considerably higher in women with migraine with aura compared with controls (Table 3). It has been proposed that this priming—the sustained elevation of the estrogen level prior to its fall—and/or the magnitude of the fall may be a key factor in triggering a migraine attack. This may explain, to some extent, why MRM often worsens in perimenopausal women who experience erratic and often more pronounced hormonal fluctuation.

As for the overwhelming preponderance of migraine without aura in women with MM and MRM, experts in brain hyperexcitability surmise that it is the lack of an excitatory response when estrogen levels fall that allows the brain to “skip” the initial aura phase.

Mismatch may be the dual effect of estrogen in the relatively slow nuclear transcriptional activation and the more rapid direct nonnuclear action on cell membranes that promote neuronal excitability. The latter,

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**Table 3. Estrogen Levels at Menses and Ovulation in Migraine With and Without Aura**

<table>
<thead>
<tr>
<th></th>
<th>Menses</th>
<th>Ovulation</th>
</tr>
</thead>
<tbody>
<tr>
<td>Control</td>
<td>28.9 ± 9.2 pg/mL</td>
<td>72.4 ± 12.6 pg/mL</td>
</tr>
<tr>
<td>Migraine without aura</td>
<td>21.3 ± 1.7 pg/mL</td>
<td>65.6 ± 11.9 pg/mL</td>
</tr>
<tr>
<td>Migraine with aura</td>
<td>28.1 ± 8.2 pg/mL</td>
<td>149.7 ± 39.4 pg/mL</td>
</tr>
</tbody>
</table>

Data from Nagel-Leiby et al.
which affects mitogen-activated protein kinases, is more immediate than the former. The effects of estrogen on receptor activation are illustrated schematically in Figure 4.20

This and other aspects of nuclear/nonnuclear mismatch are germane to treatment of MM and MRM, which can be more difficult to treat than other types of migraines. The mismatch also serves as a reminder that treatment has to overcome changes in membrane excitability as well as changes in nuclear actions.

The sequence of events leading to a hormonally influenced migraine attack can be summarized as follows:

- Increased excitability and homeostatic gene regulation of excitability in the cortex, the nociceptive and trigeminal systems in the brain stem, and the peripheral trigeminal system occurs when estrogen levels are at their highest;
- Mismatch in homeostatic gene regulation unmasks nonnuclear hyperexcitability effects of estrogen, resulting in a trigger-sensitized cortex and activated trigeminal system or brain stem center, and occurs when estrogen levels decline; and
- Up-regulation of mitogen-activated protein kinases and other inflammatory genes, increased peptide-modulated central sensitization, and increased pain and disability occur when estrogen levels continue to decline.

In short, estrogen regulates genes to counteract propagation and complications of aura and diminish estrogen-induced excitability of the trigeminal system. A precipitous fall in estrogen at menstruation or when excitability is induced by an estrogen imbalance promotes dysmodulation of neuronal systems that favor trigeminal peptide release, central nervous system inflammation, and central sensitization.

**DIAGNOSIS AND COMORBIDITIES**

The diagnosis of MM and MRM is based largely on the diagnostic criteria in the IHS classification. However, other hormonally influenced headaches and headaches with features similar to those of MM and MRM can confound the diagnosis. Therefore, it is important to focus on the patient, her headache symptoms, her history, and any comorbid conditions she may have before assessing how closely she fulfills the IHS diagnostic criteria.

**DIAGNOSIS**

Diagnosis begins with a careful patient history, including headache history, family history, medication history, relationship to the menstrual cycle, and a range of headache and other features.

The IHS classification identifies 6 types of headache that are related to the menstrual cycle, related to changes in estrogen/progesterone levels, or sharing features with menstrually related headaches. In addition to MM (A1.1.1) and MRM (A1.1.2), these headaches are nonmenstrual migraine without aura (A1.1.3), exogenous hormone-induced headache (8.3.1), estrogen-withdrawal headache (8.4.3), and other cycle-linked miscellaneous headaches such as tension-type headache that may occur with greater frequency in susceptible women (Figure 1).

The diagnostic criteria for MM and MRM include the features noted in Table 1. Both occur in relation to the natural menstrual cycle or in response to the withdrawal of progestins in combination OCPs and cyclic HRT. Other diagnostic criteria for MM, MRM, and nonmenstrual migraine without aura, which occurs without relation to the menstrual cycle in women of reproductive age, are those for migraine without aura (A1.1), as outlined in Table 4. Fulfillment of these criteria and the use of a headache diary or calendar for at least 3 months to confirm the association between migraine and menses in at least 2 out of 3 cycles are considered diagnostic of MM and MRM.

<table>
<thead>
<tr>
<th>Table 4. International Headache Society Diagnostic Criteria for Migraine Without Aura (A1.1)*</th>
</tr>
</thead>
<tbody>
<tr>
<td>A. At least 5 attacks fulfilling criteria 1, 2, and 3</td>
</tr>
<tr>
<td>1. Headache attacks lasting 4 to 72 hours if untreated or unsuccessfully treated</td>
</tr>
<tr>
<td>2. Headache has at least 2 of the following characteristics:</td>
</tr>
<tr>
<td>a. Unilateral location</td>
</tr>
<tr>
<td>b. Pulsating quality</td>
</tr>
<tr>
<td>c. Moderate or severe pain intensity</td>
</tr>
<tr>
<td>d. Aggravation by or causing avoidance of routine physical activity such as walking or climbing stairs</td>
</tr>
<tr>
<td>3. At least 1 of the following is present during the headache:</td>
</tr>
<tr>
<td>a. Nausea and/or vomiting</td>
</tr>
<tr>
<td>b. Photophobia and phonophobia</td>
</tr>
<tr>
<td>B. Headache is not attributed to another disorder</td>
</tr>
</tbody>
</table>

*Migraine without aura often has a strict menstrual relationship.
Data from International Headache Society classification of headache disorders.
Dysmenorrhea also may be present during MM and MRM attacks. Features of premenstrual dysphoric disorder, such as mood change, backache, nausea, and breast tenderness and swelling—whereas not part of migraine—may precede a migraine attack.21

Exogenous hormone-induced headache can develop or worsen shortly after starting OCPs, ERT, or HRT. It is seen less commonly today than in the past, when OCPs and ERT/HRT regimens contained higher doses of estrogen. By definition, this type of headache abates within 3 months of discontinuation of the exogenous hormones.

Estrogen-withdrawal headache is difficult to diagnose as an entity unto itself because it must overlap diagnostically with MRM. It occurs in women who are taking OCPs formulated to provide active estrogen for 3 weeks and placebo (or no estrogen) for 1 week. It also can occur in women on a limited course of ERT.

Headache develops within the first 5 days of the pill-free or inactive drug interval and resolves within 3 days. It resolves completely if OCP or ERT use is discontinued. The diagnosis of estrogen-withdrawal headache is reserved for women who have not had estrogen-related headaches prior to OCP or ERT use.

**COMORBID CONDITIONS**

Migraine, whether related to the menstrual cycle or not, is associated with a broad range of comorbid conditions, including numerous cardiovascular, cerebrovascular, gastrointestinal, neurologic, psychiatric, respiratory, and metabolic disorders.

Cardiovascular and cerebrovascular conditions that frequently coexist with migraine include hypertension or hypotension, Raynaud’s disease, mitral valve prolapse, angina and myocardial infarction, stroke, carotid artery disease, and patent foramen ovale.

The presence of defined cardiovascular or cerebrovascular disease, or the presence of significant risk factors for either or both, influences the choice of acute and prophylactic migraine medications. For example, triptans should be avoided in these circumstances.

Mood disorders such as depression, bipolar disorder, panic disorder, and anxiety, as well as respiratory conditions such as asthma and allergies, also are major comorbidities of migraine. As with cardiovascular and cerebrovascular disease, comorbid respiratory conditions influence the choice of therapy, albeit to a lesser extent. Irritable bowel syndrome also has long been associated with migraine.

Fibromyalgia, a poorly defined rheumatologic disorder, is associated with migraine and chronic daily headache.22,23 Metabolic disorders such as obesity24,25 and celiac disease also are associated with migraine.26,27 Here, the therapeutic view is long term rather than acute.

The association between migraine and stroke is of particular concern, primarily because migraine is the leading cause of stroke in women under the age of 45.28-32 In this population, which reflects much of the population with MM and MRM, the RR of stroke is increased.

Odds ratios are 1.8 to 5 for women with migraine without aura, 2.2 to 8.3 for women with migraine with aura, 5 to 17 for those with migraine with aura plus OCP use (which is related to the estrogen dose), and 34 in those with migraine with aura plus OCP use plus smoking.

However, when the contribution of migraine per se is extrapolated from the broad range of odds ratios calculated for the 4 subgroups, the absolute risk is considerably lower than the RR (0.9-19/100 000), or about twice the risk (5-10/100 000) seen in women under age 45 without migraine.26-32 Higher Framingham risk scores, hypertension, hypercholesterolemia, decreased alcohol use, and a positive family history of coronary artery disease have been implicated as contributors to increased stroke risk in young women with migraine.13 There is no evidence that migraine is a risk factor for stroke in women older than age 45.

Epilepsy has long been linked to migraine. Two studies exploring this link are of particular importance.24,35 The first, a population study, involved 1948 adults with epilepsy and 1411 of their parents and siblings.26 The investigators found that the rate ratio for migraine was 2.4 in the adults with epilepsy and 2.4 among relatives with epilepsy compared with relatives.
without epilepsy. Migraine risk was highest in probands with epilepsy due to head trauma. In addition, the age-specific incidence of migraine among the probands rose to a greater extent after the onset of epilepsy.

The second study, a follow-up to the first, looked for shared genetic tendencies but failed to detect any change in RR in genetic vs nongenetic epilepsy. The investigators also examined relatives of probands with and without migraine, but again failed to detect a change in RR. The investigators concluded that, although the comorbidity of migraine and epilepsy was increased, the linkage did not appear to be genetic.

Several studies have demonstrated an association between migraine and behavioral disorders, such as depression and anxiety. One such study found that migraine was 2× to 5× more common than no migraine in patients with major depression, bipolar disorder, generalized anxiety, and social phobia.

Another study that examined the epidemiology of migraine and major depression found that persons with migraine were 3.2× more likely than the general population to develop depression and that persons with depression were 3.1× more likely to develop migraine. The bidirectional association argues against unidirectional theories and suggests a common biology. Another finding was that depression and migraine contribute separately to decrements in health-related quality of life.

**CONCLUSION**

Approximately 60% of migraine headaches in women are associated with the menstrual cycle. Most of these headaches occur during menses and at other times during the cycle; a smaller proportion occur only during menses. These attacks are induced by fluctuations in estrogen and progesterone levels that normally occur during the natural menstrual cycle. Headaches may worsen when hormonal fluctuations are more pronounced, as they often are during perimenopause.

The pathogenesis of migraine in women is complex. Migraine involves a disorder of the neuromodulatory systems of pain perception, and the interaction between ovarian steroids and the modulatory components of nociceptive systems may explain the clinical features of migraine. In MM and MRM, which are not characterized by aura, cyclic hormonal fluctuations further compromise the brain’s ability to modulate pain perception. Diagnosis is based on a thorough history, including a headache, medication, and family history, and the IHS diagnostic criteria for each of these headache types.

Migraine, whether menstrually related or not, is associated with a broad range of comorbidities, including cardiovascular, cerebrovascular, gastrointestinal, neurologic, psychiatric, respiratory, and metabolic disorders. These comorbid conditions must be taken into account when choosing acute or prophylactic medications to treat migraine.

**REFERENCES**


