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### ASSOCIATION OF MIGRAINE AND HORMONES DURING MENSTRUATION, PREGNANCY AND MENOPAUSE

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#### ABSTRACT

Migraine is primarily a female disorder that has been associated with sex hormones. Throughout the reproductive years, the migraine prevalence is about three times more in women than in men. The occurrence of migraine may be influenced by menarche, menstruation, pregnancy, and menopause. Migraine usually starts after menarche, and occurs few days before or during menstrual cycle. The period of highest chances for migraine in susceptible women corresponds to estrogen withdrawal in the late luteal and early follicular phases of the menstrual cycle. This review concludes that migraine particularly affects women due to the hormonal changes throughout their lifecycle.

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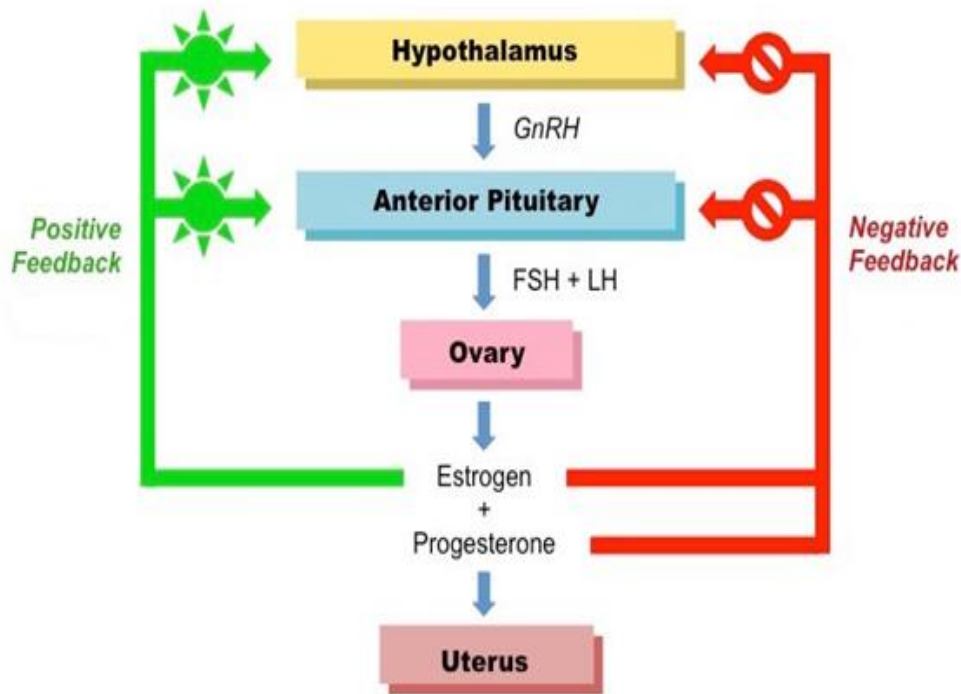
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## INTRODUCTION

Migraine is one of the neurovascular conditions which is influenced by the hormones. Global Burden of Disease Study, updated in 2013, showed that the migraine was found to be the sixth highest cause worldwide for years lost due to disability (YLD).<sup>[1]</sup> Throughout the reproductive years, the incidence of migraine is approximately three times greater in females than in males.<sup>[2]</sup> 70% of the migraine sufferers are women. Up to puberty, migraine can affect both the genders. Prevalence of migraine in women is increased after the menarche and the gender difference in migraine is not clear.<sup>[3]</sup> Menarche, menstruation, pregnancy, and menopause, may also have an impact on migraine occurrence. Migraine generally begins after menarche, arises commonly in the days just before or during menstruation, and recovers during pregnancy and menopause.<sup>[3]</sup> For the majority of women with migraine, headache attacks are more expected during 2 days prior to the beginning of menstrual bleeding and for the first 3 days of menses.<sup>[4]</sup> The period of highest risk for migraine in susceptible women corresponds to withdrawal of estrogen in the late luteal and early follicular phases of the menstrual cycle. Menstrual attacks are typically migraine without aura and, in some women, they can be more severe, of longer duration, and are more disabling than migraines starting outside the perimenstrual window.<sup>[3]</sup>

## MENSTRUAL CYCLE

Gonadotropin-releasing hormone (GnRH) is synthesized by hypothalamus and they secrete the hormone in a pulse like manner with varying rate all throughout the menstrual cycle. Anterior pituitary is stimulated by GnRH to synthesise and to secrete follicle-stimulating hormone (FSH) and luteinizing hormone (LH). FSH is essential for stimulating the growth of ovarian follicles and LH is critical for ovulation and production of sex steroid. When FSH and LH act upon the ovaries, estrogen and progesterone are produced. Estrogen sends a negative feedback signal to hypothalamus and anterior pituitary to stop FSH and LH secretion (Fig 1).



**Fig 1. Hormonal actions during menstrual cycle.**

Phases of menstrual cycle: the follicular phase, ovulation, and the luteal phase (Fig 2).

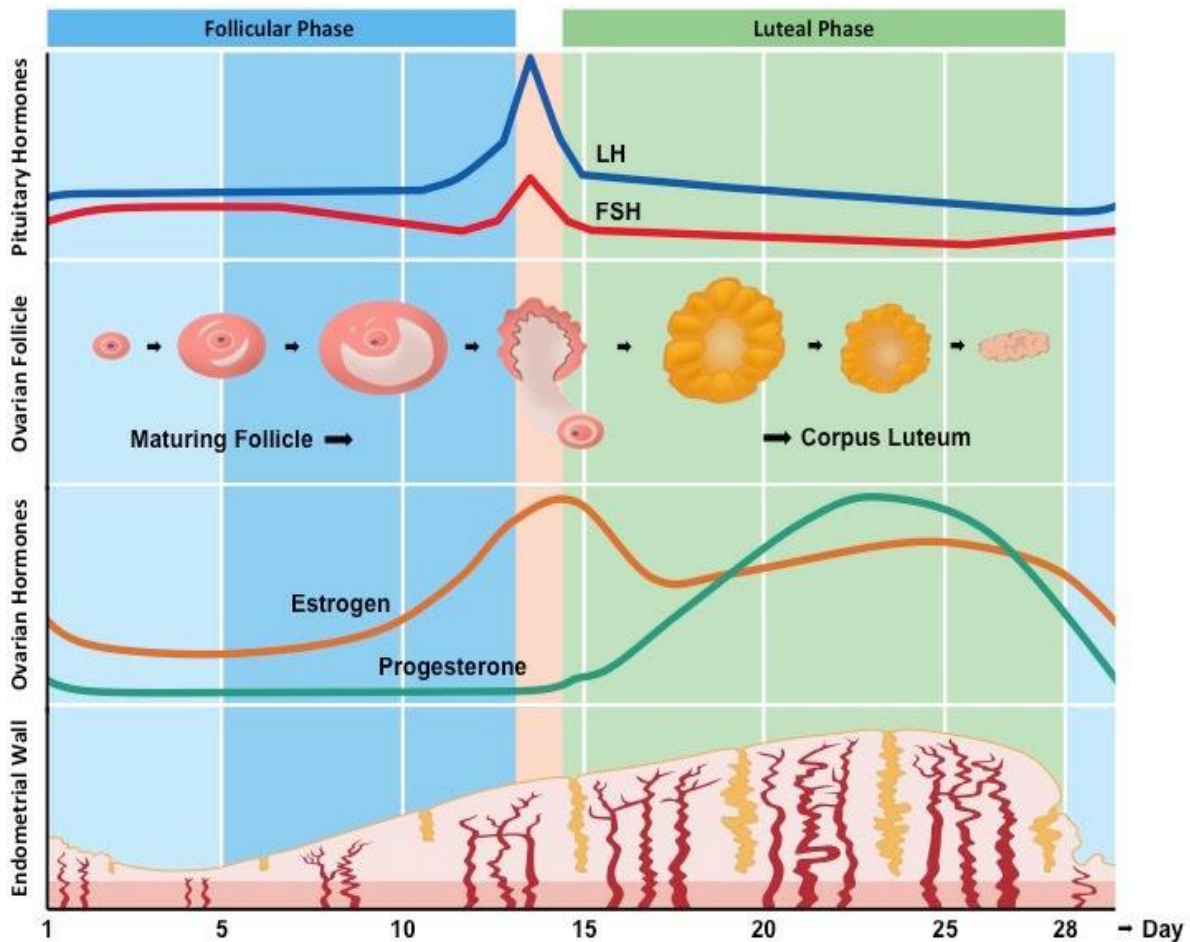


Fig 2: Stages of Menstrual cycle.

Day 1 or the first day of bleeding is referred to as the first day of the menstrual cycle. Bleeding usually occurs from day 1 to day 5 of the cycle, although in few women it may be prolonged. The follicular phase begins at the onset of menstruation and lasts nearly for 10 to 14 days. At the beginning of the follicular phase several follicles begin to develop in the ovaries. In the second half of the follicular phase most of the developing follicles atrophy, while the dominant follicle develops further and produces estrogen in increasing amounts.

This elevated estradiol levels during the ovulatory phase leads to a surge in LH and FSH. The LH rush plays a major role in the final-stage growth and maturation of the follicles, ovulation, and the formation of the corpus luteum. Ovulation occurs 14 days prior to the last day of the cycle which is followed by the luteal phase. The least variable part of the human reproductive cycle is the luteal phase which last for about 13-15 days. During this progesterone-dominant phase, progesterone and estrogen are secreted by the corpus luteum. Endometrium is prepared by the progesterone to implant the fertilized ovum.

If fertilization happens, the developing embryo will get implanted in the endometrium and release the hormones to preserve the corpus luteum. Corpus luteum degenerates when fertilization does not take place which results in the decline of estrogen and progesterone levels. When there is a decrease in these hormone levels, the endometrium cannot be maintained and is sloughed off (menstrual phase). Using the average 28-day cycle as an example, the day before to the bleeding and the last day of the cycle (day 28) and begins again for the next menstrual cycle.<sup>[5]</sup>

## IMPACT OF HORMONES IN MIGRAINE

The migraine risk is remarkably high during the first three days of menstruation that is when a notable changes in estrogen level takes place.<sup>[6]</sup> In 1972, Somerville and colleagues proposed the "Estrogen withdrawal hypothesis", stating that the decline in estrogen level before menstruation can trigger the attacks of menstrual migraine. Increased sensitivity to prostaglandins and release of neuropeptides such as CGRP, substance P and neurokinins can be caused when there is a drop in estrogen level which could result in neurogenic inflammation.<sup>[7]</sup> Decreased estrogen concentrations which takes place during the late luteal phase of the menstrual cycle can be correlated to reduced serotonin production and increased elimination of estrogen. This leads to vasodilation of cranial vasculature and sensitization of trigeminal nerves, which can trigger migraine in few women.<sup>[8,9]</sup>

During the initial bleeding phase and the late luteal phase of the menstrual cycle, migraine attacks can be increased due to prostaglandins released during the endometrial shedding.<sup>[10]</sup>

Increased incidence of aura is associated with high concentration of estrogen. Conversely, low estrogen concentration which occurs in menstruation are so unlikely associated with aura, whereas the ICHD describes that the menstrual migraine is without aura.<sup>[11]</sup> Migraine will not be precipitated by steady or increasing concentrations of estrogen, while the steep decline in estrogen level that occurs prior to menstruation can induce unusually severe attacks known as menstrual - related migraine.<sup>[12,13]</sup> By eliminating estrogen withdrawal in the perimenstrual window, estrogen supplements can be used to prevent menstrual migraine.<sup>[3]</sup>

## MENSTRUAL MIGRAINE

Migraine affects more in women than men. Approximately 14% of female migraine sufferers experience migraine only during menstruation, while 60% of female migraineurs have migraine both in menses and at other times during the menstrual cycle.<sup>[6]</sup> The International Headache Society (IHS) classifies menstrual migraine into two Menstrually related migraine and Pure menstrual migraine (Table 1).<sup>[11]</sup>

Approximately 50% of the women who suffer from migraine report an association between their migraine and monthly cycle.<sup>[14]</sup> Development of migraine attacks can be linked with the menstruation which is the most significant event during the reproductive years. While comparing with the other phases of the menstrual cycle, frequency of migraine without aura is highest during a period of 5-day window which begins 2 days prior to the menstruation and continues over the first 3 days of menstruation.<sup>[15-17]</sup>

Studies suggest that during the late luteal phase of the menstrual cycle there is an increased risk of menstrually related migraine due to the withdrawal of estrogen.<sup>[14]</sup> For majority of women, menstrual migraines are more painful, long standing, and more resistant to acute therapy when compared with migraines which happens at other times.<sup>[16,18]</sup>

**Table 1 IHS classification (ICHD-3) for pure menstrual and rnensturually-related migraine.**

<b>PURE MENSTRUAL MIGRAINE</b>	<b>MENSTRUALLY-RELATED MIGRAINE</b>
Attacks, in a menstruating woman, fulfilling criteria	Attacks, in a menstruating woman, fulfilling criteria
for migraine without aura.	for migraine without aura.
Attacks occurring exclusively on day 1 ± 2 (i.e. days –	Attacks occurring on day 1 ± 2 (i.e. days -2 to +3) <sup>a</sup> of
2 to +3) <sup>a</sup> of menstruation in at least two out of three menstrual	menstruation in at least two out of three menstrual cycles, and
cycles and at no other times of the cycle.	additionally at other times of the cycle.

<sup>a</sup>The first day of menstruation is day 1 and the preceding day is day 1; there is no day 0

<sup>b</sup>For the purpose of this classification, menstruation s considered to be endometrial bleeding resulting from either the normal menstrual cycle or from withdrawal of exogenous, as in the case of combined oral contraceptives and cyclical hormone replacement therapy<sup>[11]</sup>

## MIGRAINE IN PREGNANCY

It was demonstrated in various studies that during pregnancy, mainly in the second and third trimesters nearly one-half to three fourths of female migraineurs experience reduced frequency or complete cessation of migraine attacks. If migraine is not improved by the end of first trimester it might continue throughout the pregnancy and postpartum.<sup>[19]</sup> During the first trimester elevated estrogen levels can provide an improvement and this normally continues throughout the second and third trimesters. Females who are suffering migraine with aura are less probable to rehab than those who are suffering with migraine without aura.<sup>[6]</sup> Improvement of migraine has been reliably reported around in the early stages of pregnancy in 50 % of women and greater than three quarters of women in the further stages of pregnancy.<sup>[20]</sup> In a large proportion of women during pregnancy the levels of estrogen are continuously high in both migraine with aura and without aura which may disappear or diminish.<sup>[21]</sup>

## MIGRAINE IN MENOPAUSE

Menopausal status of the female life cycle can be divided into 5 categories: premenopause, early perimenopause, late perimenopause, spontaneous menopause, and surgical menopause.<sup>[22]</sup> Migraine attacks may be exacerbated in some women during their shift to menopause.<sup>[23]</sup> When combined with menopausal symptoms, migraine during perimenopause is a common problem which can result in considerable disability. While comparing to surgical menopause, natural menopause reduce the frequency of migraine.<sup>[22]</sup>

A cross-sectional community based study was conducted by Wang et al among 1436 Chinese women aged 40 to 54 years to study the effect of menopausal transition on the frequency of migraine. It was found that the presence of low estrogen and increased levels follicle-stimulating hormone showed lower migraine prevalence, while a history of hysterectomy was related to higher prevalence.<sup>[23]</sup>

## CONCLUSION

Menstruation is known to be a powerful trigger for migraine. Migraine associated with menstruation can be more recurrent, severe and is related with significant disability. Most of the woman suffers from migraine few days before menstrual cycle, during the menstrual cycle or during ovulation period. The number of migraine attacks can increase when there is a drop in estrogen level. Most of the woman experience complete termination or decreased frequency of migraine attacks during pregnancy. Migraine can worsen during perimenopause and can get inactivate during late menopause.

Recommended future research.

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## CONFLICT OF INTEREST

There is no conflict of interest between the authors.

## ABBREVIATIONS

YLD- : Years lost to disability  
 GnRH : Gonadotropin-releasing hormone  
 FSH : Follicle stimulating hormone  
 LH : Luteinizing hormone  
 ICHD : International classification of headache disorders  
 HIS : International headache society  
 CGRP : Calcitonin gene-related peptide

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