ORIGINAL RESEARCH PAPER

General Medicine

STUDY OF RISK OF MIGRAINE DURING MENSTRUATION

KEY WORDS: Migraine - Hormones ,Pregnancy, Menopause

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ABSTRACT

Migraine is a predominantly female disorder. Menarche, menstruation, pregnancy, and menopause, may in uence migraine occurrence. Migraine usually starts after menarche, occurs more frequently in the days just before or during menstruation, and ameliorates during pregnancy and menopause. Those variations are mediated by uctuation of estrogen levels through their influence on cellular excitability or cerebral vasculature.

INTRODUCTION

Migraine is a predominantly female disorder. Women, compared with men, have a 1-year migraine prevalence nearly threefold higher and lifetime incidence more than twofold higher [1, 2]. Moreover, menarche, menstruation, pregnancy, and menopause may in uence migraine occurrence. Until puberty, migraine affects both sexes equally [3]. After the menarche there is an increasing prevalence of migraine in women [4, 5]. The mechanism for the gender difference in migraine is not clear even if endogenous sex steroids are considered to play a relevant role.

Migraine during women's life

The woman's reproductive cycle is regulated by the hypothalamic-hypophyseal-ovarian axis through the release of estrogen and progesterone. Variations in the levels of these hormonesandoftheirfeedbackcontrolregulatethemenstrual cycle, pregnancy, puerperium, and menopause (Fig. 1). A normal menstrual cycle lasts about 28 days and consists of two phases: the follicular or the proliferative phase and the luteal or ovulatory phase. The rst day of menstruation is considered the start of follicular phase and bleeding occurs after estrogen and progesterone levels decrease at the end of the previous cycle. At this time, the pituitary follicular stimulating hormone (FSH) level increases slightly, stimulating the development of several ovarian follicles. Each follicle contains an oocyte; only one follicle proceeds through ovulation producing increased levels of estrogens, which result in a drop of the FSH production, preventing the additional development offollicles, and in the stimulation of the hypophysis to release the luteinizing hormone (LH). Progesterone remains low during the follicular phase except for a small rise just prior to ovulation. At the time of ovulation, a mature follicle ruptures in response to a surge of LH, releasing a mature oocyte. The luteal phase starts just after ovulation and during this phase the follicle, denominated corpus luteum, secretes progesterone and estrogen, which stimulate the endometrium to prepare a thick layer of blood vessels for possible fertilization. If no pregnancy occurs, the corpus luteum persists for about 14 days and then degenerates with a fall in blood estrogen and progesterone levels and a shedding of the top layers of endometrium for the beginning of a new menstrual cycle. When pregnancy occurs, the trophoblast releases the human chorionic gonadotropin (hCG) which allows the corpus luteum to continue to produce estrogen and progesterone until the formation of the placenta. The placenta, from that point on, produces the majority of estrogen and progesterone necessary for the pregnancy. Serum levels of estradiol and progesterone begin to rise in the mother during the 6th to 8th week of pregnancy and continue to gradually increase to their highest levels during the third trimester; serum estradiol levels during the third trimester of pregnancy are 30–40 times higher and progesterone levels are 20 times higher than their peak levels during natural menstrual cycles. The hormonal levels drop sharply during the puerperium that is de ned as the time from delivery of the placenta through the rst few weeks after the delivery (usually 6 weeks) and represents the phase in which the woman's body returns back to prepregnancy condition. The transition from the reproductive to the non-reproductive phase occurs over a period of years and is the result of a reduction in female hormonal production by the ovaries. Although the perimenopausal period is characterized by considerable uctuations of estrogen and progesterone levels, higher than during the normal phases of menstrual cycle in the fertile period, the menopause is characterizedby hormonal stability due to decline of estrogen and progesterone production by the ovaries. The average age of menopause is 51 years, within an age range of 40–60 years [6].

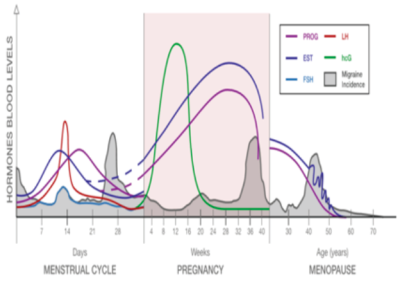

Fig. 1 Hormonal changes and incidence of migraine without aura in women

Menstrual cycle

Throughout the reproductive years, menstruation is one of the most significant events related to the occurrence of migraine attacks [7, 8] (Fig. 1). Compared with all other phases of the menstrual cycle, incidence of migraine without aura (MwA) is greatest during a 5-day window that starts 2 days before the onset of menstruation and continues through the first 3 days of menstruation [9–12].

The International Classification of Headache Disorders, II edition (ICHD-II) identifies in Appendix the:

(a) menstrually related migraine, which is MwA that regularly occurs on or between days -2 to+3 of menstruation, with additional attacks of migraine with aura (MA) or MwA at other times of the cycle;

(b) pure menstrual migraine (MM), which is MwA that occurs only on or between days -2 to+3, with no attacks at any other time of the cycle [13] (Table 1). Pure MM is uncommon with respect to menstrually related migraine. Fewer than 10–20% of women report migraine exclusively with menstruation and

at no other time of the month [9, 14–17]. Generally, the term MM includes both types of those attacks. MM attacks occur almost invariably without aura even in MA patients [7, 18, 19]. According to the majority of the available studies, compared with migraine at other times of the cycle, menstrual attacks last longer, are more severe, more likely to relapse, less responsive to treatment, and associated with greater disability [11, 12, 18, 20–24]. According to some studies, MM attacks are accompanied by nausea and vomiting more than non-menstrual attacks [18, 19] although this nding is not unanimously shared by all the studies [12, 22, 24, 25]. Correlations have been identi ed between premenstrual syndrome and MM [26, 27]. The association of migraine with ovulation is controversial but generally not supported despite some women may report attacks during this phase[19]. While MwA is clearly associated with menstruation, MA is generally unrelated to them [4]. Even in patients with aura accompanying their migraine attacks during the remaining of the month, the MM attacks are without aura [10, 12].

Pregnancy and puerperium

Most epidemiological studies have demonstrated that the majority of women suffering from migraine note remarkable and increasing improvement of their attacks during pregnancy, from the first to the third trimester [7, 15, 28– 30] (Fig. 1). Improvement is more likely in women with a history of MM [7, 30, 31]. If migraine does not improve by the end of the first trimester, it is likely to continue throughout the pregnancy [32]. In fact, a small number of pregnant women experience a worsening of their migraine [7, 15], while a few others may even develop de novo migraine symptoms [33]. The worsening usually occurs during the first trimester [34] and involves women suffering from MA rather than from MwA; also de novo migraines during pregnancy mostly consist of MA [14, 35]. Nearly all women report the return of migraine attacks after delivery [15, 32]. Factors accelerating the return of migraine attacks in the postpartum include bottle-feeding and age of 30 years or less [30]. Women suffering from migraine are also at higher risk of developing gestational hypertension, preeclampsia, or vascular complications related to pregnancy including ischemic stroke and other vascular events in the peripartum period [36, 37]. The risk is particularly evident in those women not showing remission or amelioration of migraine attacks. Even neonatal outcomes may be affected by the persistence of migraine [38, 39]. For all the above reported reasons, migraine should be considered a potential risk factor in obstetric care.

Menopause

During the transition to menopause some women may experience a worsening of the migraine attacks [40], but usually, postmenopause is also associated with respite [41] (Fig. 1). The type of menopause has a substantial effect on migraine: natural menopause is associated with a lower prevalence of migraine compared to surgical menopause [15, 40, 42]. The longer is the time interval from menopause onset, the greatest is the association with improvement [41, 43]. Whether migraine is associated with other menopause symptoms is unclear since data from available studies are conflicting [43, 44]. In contrast to the effects of menopause on MwA, prevalence of MA does not improve with menopause [43].

Table 1 Diagnostic criteria according to the International Classification of Headache Disorders, II edition, for pure menstrual migraine without aura and menstrually related migraine without aura

A1.1.1 Pure menstrual migraine without aura

Diagnostic criteria

A. Attacks, in a menstruating woman, ful lling criteria for 1.1. Migraine without aura

B. Attacks occur exclusively on day 1 ± 2 (i.e., days -2 to+3)a of menstruationb in at least two out of three menstrual cycles at no other times of the cycle

A1.1.2 Menstrually related migraine without aura

Diagnostic criteria

A. Attacks, in a menstruating woman, fulfilling criteria for 1.1. Migraine without aura

B. Attacks occur on day 1 ± 2 (i.e., days -2 to+3)a of menstruationb in at least two out of three menstrual cycles and additionally at other times of the cycle

a The first day of menstruation is day 1 and the preceding day is -1; there is no day 0

b For the purposes of this classification, menstruation is considered to be endometrial bleeding resulting from either normal menstrual cycle or from the withdrawal of exogenous progestogens, as in the case of combined oral contraceptives and cyclical hormone replacement therapy

Study

In a prospective study,doneat PMCH department of medicine and department of neurology of 50 cases between 1 january 2018 to 1 december 2019 , we noted a significantly elevated risk of migraine without aura on the first two days of menstruation [odds ratio (OR) 2.0; 91% confidence interval (CI) 1.45–2.78]. The lowest risk for headache was around the expected time of ovulation [OR 0.41; 90% CI 0.22–0.70]. Headache duration appeared to be significantly longer for migraine headaches in the 3 to 7 day period before onset of menses.Menstrual migraine is also associated with increased menstrual distress and disability.

CONCLUSION

Migraine in women often is associated with hormonal changes throughout the life cycle, from menarche to postmenopause. Hormonal changes, whether endogenous or exogenous, can be unpredictable. Many women experience more severe and debilitating migraines during menses than at other times. Menstrual migraine may be treated with acute therapies, intermittent prophylaxis, or long-term prophylaxis. Hormone-based therapy for menstrual migraine can result in withdrawal headache, but is shown to decrease overall headache burden. Treatment choices should be individualized based on the patient's needs regarding headache severity and frequency and on where she is in her life cycle, also taking into account contraception concerns or pregnancy.

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