Review paper

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Specificity of Migraine Treatment in Women

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Abstract - The prevalence of migraine is higher in women than in men, with female to male ratio 3:1 in reproductive age. It is believed that sex hormones play significant role in migraine pathogenesis. Therefore, treatment of migraine in women has some specificities due to hormonal differences between sexes and due to hormonal fluctuations during menstrual cycle, pregnancy, lactation and perimenopause. Treatment of migraine during pregnancy depends on safety profile of the therapy. NSAID-s like naproxen and ibuprofen are being considered safe during the second trimester, but during the first and third trimester they may have adverse effects on pregnancy and foetus. CGRP antagonists should be avoided during pregnancy. Acetaminophen, ibuprofen, and diclofenac are considered to be safe acute therapy during breastfeeding and for preventive treatment propranolol should be used as first line therapy. Women with severe menstrual and menstrual related migraine without aura may be treated with hormonal therapy, whereas it should be avoided among patients with aura due to increased risk of stroke.

Key words: menstruation; migraine disorders; therapeutics; pregnancy; women

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Introduction

The prevalence of migraine in women is higher than in men, with female to male ratio 3:1 in reproductive age [1-3]. Characteristics of migraine also differ between sexes. In women attacks are more severe, more often accompanied with associated symptoms, have longer duration and greater disability. There are beneficial effects of pregnancy on migraine and during menopause migraine attacks most often improve [4,5]. Based on these facts it is believed that sex hormones play a role in migraine pathogenesis [6]. However, exact effects and precise role in pathogenesis are still not fully understood, which warrants further research. Considering hormonal differences between sexes and hormonal fluctuations during menstrual cycle, pregnancy, lactation and perimenopause, treatment of migraine in women has numerous specificities.

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Migraine treatment in pregnancy

Acute migraine treatment in pregnancy

Acetaminophen is recommended as initial treatment. There is no clear evidence of an increased risk of adverse effects on pregnancy

or the foetus. Metoclopramide can be added to enhance effect of acetaminophen and to treat nausea [7]. Non-steroidal anti-inflammatory drugs including ibuprofen and naproxen are considered safe for use during the second trimester as second line therapy. During the first trimester their use may increase the risk of miscarriage, and use in the third trimester can lead to premature closure of the foetal ductus arteriosus, persistent pulmonary hypertension of the newborn, oligohydramnios, necrotizing enterocolitis, renal dysfunction or failure, and intracranial haemorrhage [7,8].

Triptans during pregnancy

In women who do not respond to firsts and second line drugs and have severe pain and disabling attacks, triptans can be offered [9]. Triptans can be used if benefit outweighs the risk in the first trimester. Use of ergotamine is absolutely contraindicated during pregnancy because it can cause hypertonic uterine contractions and vasospasm, which could cause adverse foetal effects [7,10].

Preventive treatment in pregnancy

Preventive therapy in pregnancy is generally not recommended because migraines are less frequent and less severe during pregnancy. Life style changes can be useful. Adjusting meals, preventing dehydration and enough rest is recommended. In rare cases when preventive therapy is required it should be used under specialist surveillance. Non-pharmacological treatment is preferred in pregnancy (relaxation, biofeedback, etc.). Among pharmacological treatment propranolol and amitriptyline are considered the least harmful. Treatment for status migrainous include fluid replacement, metoclopramide, steroids and acetaminophen [11].

CGPR antagonists during pregnancy

The safety of monoclonal antibodies to calcitonin gene-related peptide or its receptor (CGRP mAbs) during pregnancy has not been determined in randomized clinical trials. Although animal studies did not show any increased risk data in humans are lacking. Animal and human studies suggest that CGRP levels may affect the development of preeclampsia and women with migraine are at higher risk for preeclampsia. The CGRP may also play a role in cardiovascular adjustment in pregnancy and in uteroplacental circulation. Since the effect of inhibiting CGRP during pregnancy is not known those medications should be avoided during pregnancy. Because of their long half-life they should be withheld starting 4-6 months prior to plan conception [8].

Migraine treatment during lactation

During breastfeeding, acetaminophen, ibuprofen, and diclofenac are considered to be safe acute therapy [8]. Aspirin should be avoided due to risk of haemolyses and bleeding conditions in the newborn, although risk is minimal for low dose preparations [8]. Data on the use of triptans during lactation are limited. Sumatriptan is recommended as the preferred triptane for use in breastfeeding women [12]. For preventive treatment first line therapy is propranolol. Amitriptyline can be used as second line treatment with risk of sedation of infants. Topiramate was associated with infant diarrhoea in one case report and was otherwise well tolerated by breastfeeding infants [8]. The use of Onabotulinum toxin A is considered safe during breastfeeding [11,13-16]. Clinical data on the use of CGRP mAbs during lactation are limited and it is recommended not to use them during lactation [17].

Menstrual and menstrual related migraine

Menstruation is a common migraine trigger. Oestrogen and progesterone receptors are expressed in the trigeminovascular system. The role of hormone fluctuations mainly falling in oestrogen levels before menstruation is believed to have important role in migraine triggering. Studies suggest that falling of oestrogen increase the susceptibility of blood vessels to prostaglandins that are associated with neurogenic inflammation. In addition, ovar-

ian hormonal fluctuations modulate calcitonin gene-related peptide and serotonin in the trigeminovascular system. In animal models gonadal hormones modulate cortical spreading depression susceptibility [18].It is well known that menstrual migraine attacks are usually longer lasting, more debilitating and less responsive to acute treatment than non-menstrual migraine attacks [19]. The first goal in treating menstrual migraine is to establish efficacy of acute therapy, menstrual cycle regularity, and possible need for contraception. Preventive therapy can be standard like in migraine in general (preferred for women with irregular cycles) or perimenstrual in women with regular cycles [11,14,15].

Acute treatment

Since menstrual migraine attacks are usually more debilitating and have higher intensity of pain, non-steroidal anti-inflammatory drugs alone are not very effective but they can be combined with triptans to enhance efficacy. Many attacks of menstrual migraines respond well to triptans. For acute treatment triptans and pharmacologic doses of oestrogen in hormonal preparations are contraindicated in patients suffering from uncontrolled hypertension, stroke, cardiovascular disease and complicated migraine with aura, such as hemiplegic migraine. Those patients may use over-the-counter analgesics, antiemetic drugs, ditans, and CGRP antagonists as well as non-pharmacological interventions for acute treatment [20].

Preventive treatment

In women with regular menstrual cycle and menstrual migraine short-term treatment with long-lasting triptans (frovatriptan, naratriptan), naproxen or oestrogen administered some days before or during menses is preferred. There is a risk of medication overuse with use of triptans and long-lasting nonsteroidal anti-inflammatory drugs. In women with irregular cycles a continuous preventive treatment is used and it include standard preventive drugs (as for migraine prevention in general) and hormonal therapy [11].

Hormonal therapy

Women with severe menstrual migraine or menstrual related migraine without aura can be offered hormonal therapy with oestrogen-progestin contraceptives in order to suppress ovarian activity and hormonal fluctuations, especially if they want effective contraception. Hormonal therapy can be used orally or locally. In order to prevent the fall in oestrogens in perimenstrual period oestrogens are given as short-term preventive medication in females with pure menstrual migraine and with regular cycles, however this approach is not very useful since oestrogen level fall follows the end of the oestrogen treatment and this can possibly trigger migraine attack. Oestrogen can also be administered at low doses continuously to counterbalance physiological hormonal fluctuations. Oestrogen combined with progestogens are used to stabilize hormonal levels and ensure contraception [21]. Women suffering from menstrual migraine and menstrual related migraine with aura should avoid pharmacologic levels of oestrogen-containing products for preventive therapy due to increased risk of stroke [20]. Due to increased risk of stroke in women with migraine use of hormonal preparations must be carefully considered. Other possible cardiovascular risk factors should be identified like hypertension, smoking, increased body weight, increased levels of serum cholesterol etc. and in such cases combined hormonal therapy is not recommended. Only gestagen preparations or low doses of oestrogens (20 mcg ethinylestradiol) can be used, as well as topical preparations of oestrogen. Further research is needed to understand the mechanisms that contribute to neuroendocrine vulnerability in some women. This will enable new and more effective treatment options for menstrual migraine.

Migraine treatment in menopause

Perimenopause is the time of peak migraine prevalence due to hormonal fluctuations. During this period women should be asked about presence of headaches so they

can be appropriately treated. Hormonal preparations in menopause can have ameliorating or aggravating effects on migraine so individual approach is recommended. Stable oestrogen levels that can benefit migraine can be achieved with contraceptive hormonal preparations which suppress ovarian activity or with oestrogen replacement therapy. The most favourable outcomes are associated with non-oral administration and with using the lowest effective dose. Transdermal administration of oestrogen with the levonorgestrel intrauterine system can be used both in perimenopause and postmenopause. In postmenopause continuous combined transdermal hormonal replacing therapy can be used. In migraine with aura synthetic oestrogens are contraindicated because they are an independent risk factor for ischemic stroke. Physiological doses of transdermal oestrogens can be used in such patients. Vasomotor symptoms are common in perimenopause and can be treated by adding venlafaxine, sertraline, pregabaline or gabapentin. There is evidence for use of escitaloprame or venlafaxine for both migraine prophylaxis and management of vasomotor symptoms if oestrogens are contraindicated [22].

Conclusion

Neurologist, gynaecologists and anaesthesiologists who are treating migraine must be aware of specificity in migraine treatment in women in order to treat migraine successfully and to avoid problems associated with potential harmful effects of treatment. We suggest combining pharmacological and non-pharmacological therapies and multidisciplinary approach to optimize migraine treatment in women.

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Conflict of Interest

None to declare.

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