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LITERATURE REVIEW**Migraine And Pregnancy: What Should We Know**

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Abstract

Migraine is a common headache characterized by unilateral throbbing-like headache and pulsating in nature and sometimes associated with aura. Migraine is a disabling disorder that among adults is more prevalent among women than men. It is primary headache that is often found in pregnancy. Migraine is a common disorder in women of childbearing age, and usually requires pharmacological treatment. Migraine can be considered an important risk factor for hypertensive and vascular diseases during pregnancy. Migraine therapy in pregnancy is very challenging, it must taken into a consideration about the health of the mother and fetus. Several effective antimigraine medications are reasonably safe for use by pregnant and breastfeeding women. Prophylactic therapy should be given to patient with recurrent migraine attacks in pregnancy. Nonpharmacological strategies are always first-line treatment options for mild migraine, and should also be used complementarily whenever pharmacological treatment is required. Women with migraine should be offered periconceptional counselling to promote a safe and healthy pregnancy.

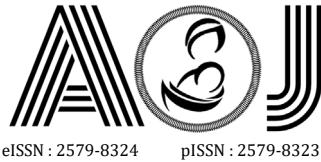
Keywords: migraine, pregnancy, therapy

INTRODUCTION

Headache is the seventh highest cause of years lived with disability according to The Global Burden of Disease in 2013.¹ The World Health Organisation has listed migraine as one of top 20 causes of disability.² The international headache society (IHD) classifies headaches as either primary or secondary. The first one are benign and have no underlying medical problems while the latter occurs as a result of medical conditions such as hypertension, preeclampsia, idiopathic intracranial hypertension, subarachnoid hemorrhage, cerebral venous thrombosis, and reversible cerebral vasoconstriction syndrome.³

In most cases it is considered as a primary disorder, meaning there are no organic or functional causes. Primary headache including migraine with or without aura, tension type headache, and cluster—the first two are the more frequent conditions that affect people, mostly women, in seeking medical help. In pregnancy, it is not sparse that patient come with such disorder. A pattern change from migraine without aura to migraine with aura and vice versa or migraine without aura to tension type headache and vice versa can be found.¹

Migraine is a common neurological disorder, ranked among the world's leading causes of years lived with disability by the World Health Organization. Migraine is a disabling



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disorder that among adults is more prevalent among women than men. The burden of migraine is highest in women of reproductive age.^{4,5} Migraine is primary headache that is often found in pregnancy. Migraine attacks are reportedly reduced in the second and third trimesters.^{5,6}

Migraine has long been mentioned as a possible predictor of complications in pregnancy. Several associations have been proposed, including miscarriage, pre-eclampsia, congenital anomalies, and low birth weight.⁷ Prophylactic therapy should be given to patient with recurrent migraine attacks in pregnancy. Avoid trigger, good sleep, exercise and always relax must be done. Pharmacological and non pharmacological prophylactic therapy should be given to pregnant migraine patients with due regard to side effects on the mother and fetus.^{3,6}

In this paper we will review correlation between migraine in pregnancy and how it might affect the pregnancy itself.

DEFINITION

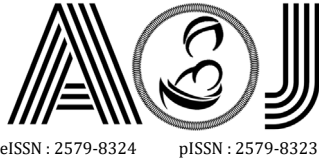
Migraine is a common headache characterized by unilateral throbbing-like headache and pulsating in nature and sometimes associated with aura.³ We must be able to diagnose migraines by taking a good history the illness based on ICHD criteria. Because in migraines patients the no clinical neurological deficits were found. The following migraine criteria that must be recognized.⁸⁻⁹

Table 1. Criteria of Migraine⁹

Migraine without aura	Migraine with Aura
At least 5 attacks (4-72 hours) Pain features (at least 2) <ul style="list-style-type: none"> • Unilateral • Pulsating • Moderate to severe intensity • Aggravated by activity • Associated features (at least 1) <ul style="list-style-type: none"> • Nausea and/or vomiting • Photo and phonophobia • No organic disease 	At least 2 attacks Aura consisting of at least one of the following <ul style="list-style-type: none"> • Fully reversible visual symptoms • Fully reversible sensory symptoms • Fully reversible dysphasic symptoms • At least 2 of the following <ul style="list-style-type: none"> • Hemifield or hemisensory symptoms • Development over 5 minutes • Each symptom last >5 and <60 minutes • Headache fulfilling criteria for Migraine without aura begins during or follows aura within 60 minutes

INCIDENT MIGRAINE IN PREGNANCY

Primary headache disorders reach a prevalence peak among women of childbearing age due to hormonal influence and particularly oestrogen fluctuations.¹⁰ By the end of their reproductive life cycle, roughly 40% of women have experienced migraine. Women have



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certain times of vulnerability for migraine that relate to abrupt declines in estrogen levels.¹¹ Migraine affects mostly women during their reproductive years with prevalence around 15% for women and 6% for men within 1 year of migraine with or without aura. The overall 1 year prevalence of migraine with aura is around 5% for women and 2% for men. Its prevalence varies with age, rising through early adult life and peaking at 30 – 40 years and declined in the late 40s and after 50s in both males and females.¹²

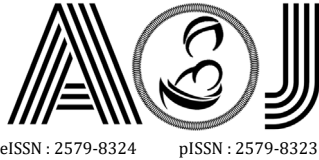
Headache is common in the week following delivery, affecting around 30 – 40% of women.¹² During childbearing years, migraine prevalence is estimated to be around 25% and its incidence peaks at nearly 20 per 1000 person-years according to American Migraine Prevalence and Prevention Study. Migraine without aura typically improves or remits simultaneously in pregnant women, with improvement or remission observed in nearly 47% of women during the first trimester, 83% during the second trimester, and 87% in the third trimester. Migraine improvement during pregnancy is related to increasing levels of estradiol during gestational period as well as the lack of cycling related to the menstrual cycle where estrogen withdrawal can serve as major trigger for migraine. However, more than 26% of pregnant women who suffers from migraine do report some degree of moderate or severe headache related disability during their early pregnancy.¹³

Up to 80–90% of women with migraine experience a progressive improvement of symptoms during pregnancy, and some even experience complete remission.¹⁴ A study that was conducted 2015 addressed acute headache diagnosis in pregnancy and included 140 women who presented to acute care with severe headache requiring inpatient neurologic consultation. In this sample, primary headache was diagnosed in 65% of patients. The most common diagnosis was migraine at 59,3%.¹³ In pregnancy, migraine attacks are known to decrease significantly during the second and third trimesters.^{5,6,15}

ETHIOPATOGENESIS MIGRAINE IN PREGNANCY

The pathogenesis of migraine is largely correlated with cerebral vasculature vasodilation, serotonin release and stimulation of nociceptors. Migraine can be precipitated by a single or combination of trigger factors, including dietary triggers such as chocolate, cheese, stress, and hormonal influences.³

Differ from migraine without aura, migraine with aura is less likely to improve during pregnancy. New-onset migraine with aura and even aura without headache may occur in the later stage of pregnancy. In one study, it is reported that among 91 women who had any primary headache disorder, 39,6% presented with aura while pregnant and 69,4% of these women had no previous aura attack. Potential mechanisms driving the different prognosis of migraine with aura relative to migraine without aura include increased endothelial reactivity



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during pregnancy as well as a high estrogen to progesterone ratio, which may actually lower the threshold for cortical spreading depression.¹³

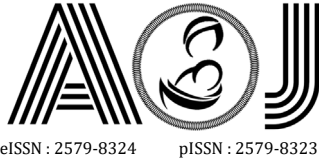
About one half to three fourths of female migraineurs experienced a marked improvement in migraine during pregnancy with a significant reduction in frequency and intensity of their attacks, if not a complete resolution.¹ Among women with a history of headache, a changed feature of a longer attack duration was associated with a secondary headache disorder diagnosis in this group. Acute attack features associated more with primary headache included phonophobia only. Attack features associated with secondary headache included the presence of seizures, elevated blood pressure, fever, and an abnormal neurologic examination. Women presenting with acute headache in the peripartum and postpartum period also require high diagnostic vigilance for secondary headache causes.¹³

Migraine represents one of the most common neurological disorders in adult, with a female predominance and peak incidence ages in the second and third decades of life. This age range corresponds to childbearing years for women, with such the association between headache and pregnancy is common.^{2,16} Some studies have also stated that women who suffers from migraine is at increased risk of developing preeclampsia, therefore it is important to monitor their blood pressure and obtain urine dipstick.³ Preeclampsia complicates about 3% of all pregnancies and is a leading cause of maternal and perinatal morbidity as well as mortality worldwide. A correlation between migraine and an increased risk of preeclampsia has been suggested, particularly because they share common pathogenic mechanisms such as endothelial dysfunction, activation of inflammatory response, and enhanced platelet function and clotting.³

Although migraine is reported to improve or disappear during pregnancy in approximately 70% of women and mostly occurs in the first semester, some authors report persistence or even worsening of migraine episodes in 4 – 8% women. Those whose migraine persists or even worsened have a higher risk of developing preeclampsia than those who experienced migraine relief. It is also suggested that the disappearance of recurrent migraine episode is a protective factor against the risk of developing pregnancy complications, particularly preeclampsia and stroke.^{16,17} A study suggested that a diagnostic strategy for acute headache in pregnant women should feature liberal use of non-contrast MRI and monitoring for preeclampsia, particularly in those with an elevated blood pressure and without a headache history.^{1,13}

MIGRAINE AND ITS IMPACT TOWARDS PREGNANCY

Generally speaking, a preexisting migraine does not represent a risk factor for negative outcome and no increase rate of fetal malformations could be detected in pregnant women



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suffering from migraine. However, migraine can be considered an important risk factor for hypertensive and vascular diseases during pregnancy.¹

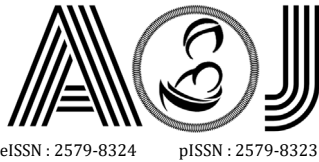
There are a number of case reports that have found an association between migraines and an increased risk of preeclampsia in pregnancy. Notably, migraines and preeclampsia are known to have similar pathogenesis mechanisms, such as endothelial dysfunction, activation of the inflammatory response, and increased platelet function and blood clotting.^{1,13,16} In addition, several studies have also suggested that there is an association between migraine in pregnancy with increased vascular complications, including stroke and gestational hypertension. Pregnant women with severe gestational hypertension or preeclampsia are at high risk for preterm delivery, and placental abruption.¹⁸

In various studies, it is known that migraines have improved or even disappeared during pregnancy, especially during the second and third trimesters.³ Where about 70% of women with migraines have improved, and usually occurs in women with menstrual migraine.^{16,19} However, some researchers report the incidence of persistent migraine episodes or even worsening episodes in 4-8% of pregnant women. Patients with migraine who do not experience improvement during pregnancy have a higher risk for experiencing preeclampsia.¹⁶

One of its impact toward pregnancy is challenge in treating it because it concerns both maternal and fetal well-being as no single medication is entirely free of any potential teratogenic effects.^{2,13,20} Hence, nonpharmacological approach is preferred. A pregnant woman who has an intractable migraine attack or status migrainosus should know what a backup plan might be during pregnancy to minimize worry and to have a safe and effective treatment strategy in place. But it is need to be noted that all medications can be graded by a milk to plasma ratio and generally, a less than 10% value is safe threshold for drugs that do not concentrate in breastmilk.¹³

MIGRAINE AND ITS IMPACT TOWARDS PREGNANCY

Management of migraines in pregnancy by using drugs is very challenging, in which there is no single drug that has no teratogenic effect at all.¹² The US Food and Drug Administration has abolished the system of drug risk categories for drugs pregnant women and replace it with a new labeling algorithm, which provides a qualitative description of the risks to pregnancy and breastfeeding.^{13,2}



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Table 2. Safety commonly used antimigraine medications over the course of pregnancy and lactation¹⁴

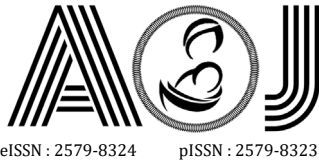
Medication	Close to conception	First trimester	Second trimester and early third trimester	Late third trimester	During lactation
Acute treatment*					
Paracetamol	Considered safe	Considered safe	Considered safe	Considered safe	Considered safe
Sumatriptan	No evidence of increased fetal or maternal risk	No evidence of increased risk of malformations	No evidence of increased fetal or maternal risk	No evidence of increased fetal or maternal risk	Considered safe
Other triptans	No evidence of increased fetal or maternal risk, but data are limited	No clear evidence of malformations, but data are limited	No evidence of increased fetal or maternal risk	No evidence of increased fetal or maternal risk	Most triptans are probably compatible with breastfeeding
NSAIDs: ibuprofen, diclofenac, naproxen	Possibly increased risk of miscarriage	Possibly increased risk of malformations	Single doses considered safe in second trimester; occasional use of single doses up to week 32 in the third trimester should not pose any risk to the fetus	Risk of harmful fetal and maternal effects if used after week 32	Generally compatible with breastfeeding, with ibuprofen being the drug of choice
Preventive treatment					
β-blockers: metoprolol, propranolol	No evidence of increased fetal or maternal risk	Occasional reports of increased risk of some malformations, but causality not established. In general, no notable teratogenic effects demonstrated	Risk of adverse effects in the fetus, for example bradycardia	Risk of adverse effects in the newborn infant, for example bradycardia, hypotension and hypoglycaemia	Adverse effects in the infant are unlikely
Tricyclic antidepressants: amitriptyline	No evidence of increased fetal or maternal risk	Few data exist; no evidence for teratogenic effects for tricyclic antidepressants in general	Very few data exist; increased risk of pre-eclampsia in one study	Adverse effects and withdrawal symptoms in the newborn infant cannot be excluded	Low excretion in milk, but few data available. Impaired elimination in premature and newborn infants might cause accumulation
Antiepileptics: valproate	Increased risk of neural tube defects in the fetus	Increased risk of a variety of malformations	Risk of unfavourable long-term neurodevelopmental effects	Risk of unfavourable long-term neurodevelopmental effects	No risk for the breastfed infant, but an obvious risk of teratogenic effects if the mother should become pregnant again
Antiepileptics: topiramate	No data exist, but experience with other antiepileptic drugs suggests it is wise to avoid use	Increased risk of orofacial clefts	Few data exist, but unfavourable mental and neuromotor effects in the child cannot be excluded	Few data exist, but unfavourable mental and neuromotor effects in the child cannot be excluded	Generally considered compatible with breastfeeding, but in premature and newborn infants, drug levels might accumulate to cause adverse effects
<small>Overview of the safety of commonly used antimigraine medications related to stage of pregnancy and lactation. Dark green pills indicate drugs that are considered safe. Light green pills indicate drugs that are generally considered safe, but uncertainty exists owing to, for example, risks associated with specific drugs in a class or with a certain time period during pregnancy, or because of the limited data. Yellow pills indicate drugs for which increased risk of harm cannot be excluded, either because of studies revealing harmful effects or a lack of data supporting safety. Red pills indicate contraindicated drugs, for which the risk to the fetus or infant exceeds the therapeutic benefit to the mother. *Classification presupposes occasional use; risks may increase with frequent or excessive use.</small>					

MIGRAINE THERAPY IN PREGNANCY

Migraine is a common disorder in women of childbearing age, and usually requires pharmacological treatment.²⁰ Migraine therapy in pregnancy is very challenging, it must taken into a consideration about the health of the mother and fetus. Counseling and understanding should be given to pregnant women before starting migraine therapy, besides, all women of reproductive age who get migraine therapy should also be educated about the risks that can occur in future pregnancy.^{13,21}

Non-pharmacological therapy is the main therapy in the management of migrain in pregnancy. Non-pharmacological therapy already have a proven effectiveness and safety from many studies. Prevention and recognition of precipitating factors and factors that aggravate the migraine is very important as a non-pharmacological management. Precipitating factors and risk factors such as diet (excessive caffeine consumption), obesity, sleep disorders, medication overuse, and other comorbidities such as psychiatric disorders and pain are one of the factors that can be modified in preventing the progressivity and worsening of the disease. Therapeutic strategies which included are relaxation therapy, adequate sleep duration, stress management, biofeedback, adequate nutrition, acupuncture, use of ice packs and cognitive-behavioral therapy.^{13,18,21,22}

Non-pharmacological therapy is the highly recommended therapy during pregnancy, but if the pharmacological therapy is needed, the treatment needs to consider the risk to the fetus later, since there is no migraine therapy which completely free from potential teratogenic effects. Migraine medical therapy is divided into acute therapy and prophylaxis.



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Acute therapy is given in stages, while migraine prophylactic therapy may not be needed in pregnancy because in general, migraine in pregnancy has a good prognosis and also administration of these drugs should be avoided because of its teratogenic concerns.^{13,21}

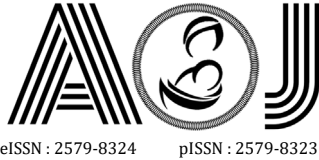
Table 3. Acute and preventive migraine therapy²³

Acute Migraine Medications		Migraine preventive medications	
Medication (Evidence)	FDA pregnancy rating	Medication (Evidence)	FDA pregnancy rating
Acetaminophen (A*)	B	Sodium valproate (A)	D
Ibuprofen, Naproxen (A)	C (D after 30 weeks)	Topiramate (A)	D
Aspirin (A)	D (high dose)	Amitriptyline (B)	C
Triptans (A)	C	Venlafaxine (B)	C
Butorphanol (A, C*)	C	Propranolol (A)	C
Butalbital (C)	C	Metoprolol (A)	C
Prochlorperazine (B*)	C	Timolol (A)	C
Metoclopramide (B*)	B	Atenolol (B)	D

Among of various therapeutic options for migraine therapy, analgesics are the initial choice of therapy which more frequently chosen to treat migraine attacks. Acetaminophen is the first choice in acute migraine therapy during pregnancy because it has minimal teratogenic effects, but in severe migraine conditions, the administration of this therapy may not effective.^{21,22} Metoclopramide is also an acute migraine therapy that is considered safe for pregnant women, it can be given orally or parenterally.¹⁸ However, these therapies still have potential risks including the later development of attention deficit hyperactivity disorder in children with antepartum exposure to acetaminophen and changes in maternal cardiac conduction and extrapyramidal symptoms due to metoclopramide exposure.^{13,21}

Opiate therapy as an analgesic is usually not indicated in migraine therapy, but if needed, oxycodone is probably the safest drug to use. However, in every opioid administration, the safety must be considered because it can cause neonatal and even internal respiratory suppression and fetal dependence. Butalbital components that are usually used in combination with acetaminophen and caffeine are related to congenital heart abnormalities in fetus, so it is not recommended to use in pregnancy.^{13,21}

Meanwhile, the administration of NSAIDs, such as ibuprofen, has a specific teratogenic profile in each trimester, which is forbidden in the first and third trimesters, while administration in the second trimester may be given and must be prescribed with the knowledge of an obstetrician. The administration of this drug in the first trimester can cause cardiac abnormalities while its administration in the final trimester can increase the risk of antepartum hemorrhage, closure of the fetal ductus arteriosus and fetal pulmonary arterial hypertension (included in category D).^{13,21}



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In general, migraine symptoms usually accompanied by nausea and vomiting. Drugs such as clorpromazine (Category C), promethazine (Category B), metoclopramide 10 mg (Category B), ondansetron IV 8 mg to 3 doses per day (Category B), are the drugs which can be given to treat these symptoms.^{11,13,21,24}

Serotonin receptor antagonists, such as sumatriptan, are commonly used in non-pregnant populations for migraine therapy. However, its administration safety in pregnant women has a very limited evidence. The use of triptan therapy in pregnant women is considered if has a greater benefits beside the risks that can occur. The administration of sumatriptan in some cases is attributed to severe migraine that does not respond to simple analgesic administration. Meanwhile, domperidone therapy is not recommended and the use of ergotamine is prohibited in pregnant women (categories D and X). The use of ergotamine and dihydroergotamine is restricted in the management of migraine in pregnancy because it has an uterotonic effect.^{3,21}

CONCLUSION

Migraine is a common neurological disorder, ranked among the world's leading causes of years lived with disability by the World Health Organization. The burden of migraine is highest in women of reproductive age. Migraine is primary headache that is often found in pregnancy. Migraine attacks are reportedly reduced in the second and third trimesters. Non-pharmacological therapy is the highly recommended therapy during pregnancy, but if the pharmacological therapy is needed, the treatment needs to consider the risk to the fetus later, since there is no migraine therapy which completely free from potential teratogenic effects.

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