HEADACHE IN SPECIAL GROUP

Dr. Aye Aye Sann
Professor/ Sr. Consultant Neurologist

CASE SCENARIO

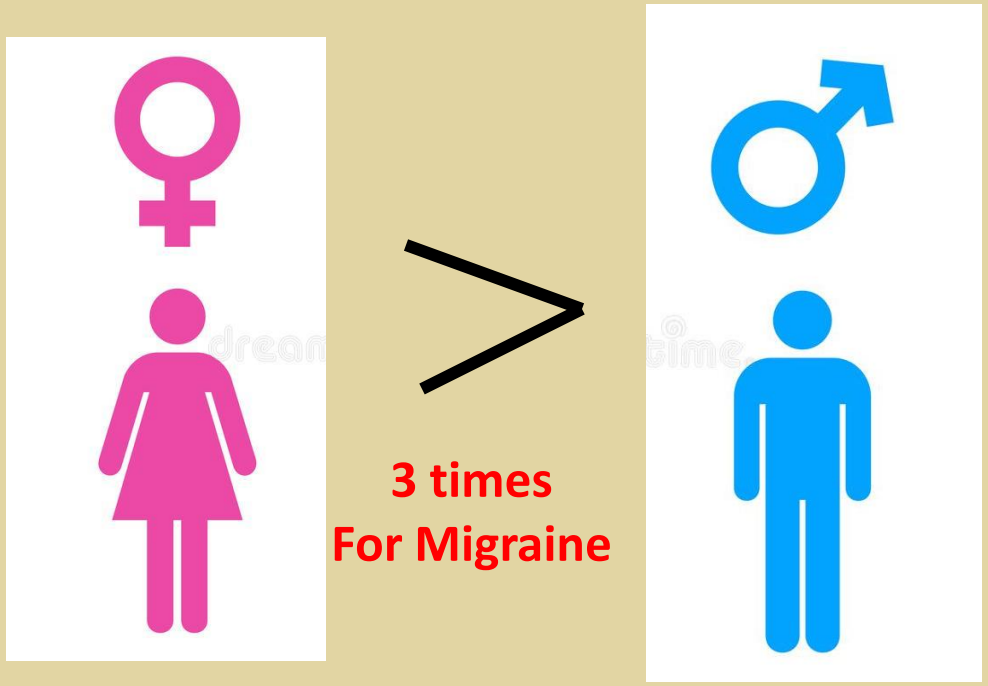
27 year old lady in her 32 weeks pregnancy came for continuous headache for 5 consecutive days. She has history of episodic migraine without aura since 18 years of age that had been treated effectively with naproxen and additional zolmitriptan during her menstrual periods.

She intentionally became pregnant for first time and her migraine frequency reduced in 1st trimester. After 24 weeks gestational age, her headache frequency increased again; 1-2 days per week and acetaminophen and metoclopramide effectively relieved her acute attacks.

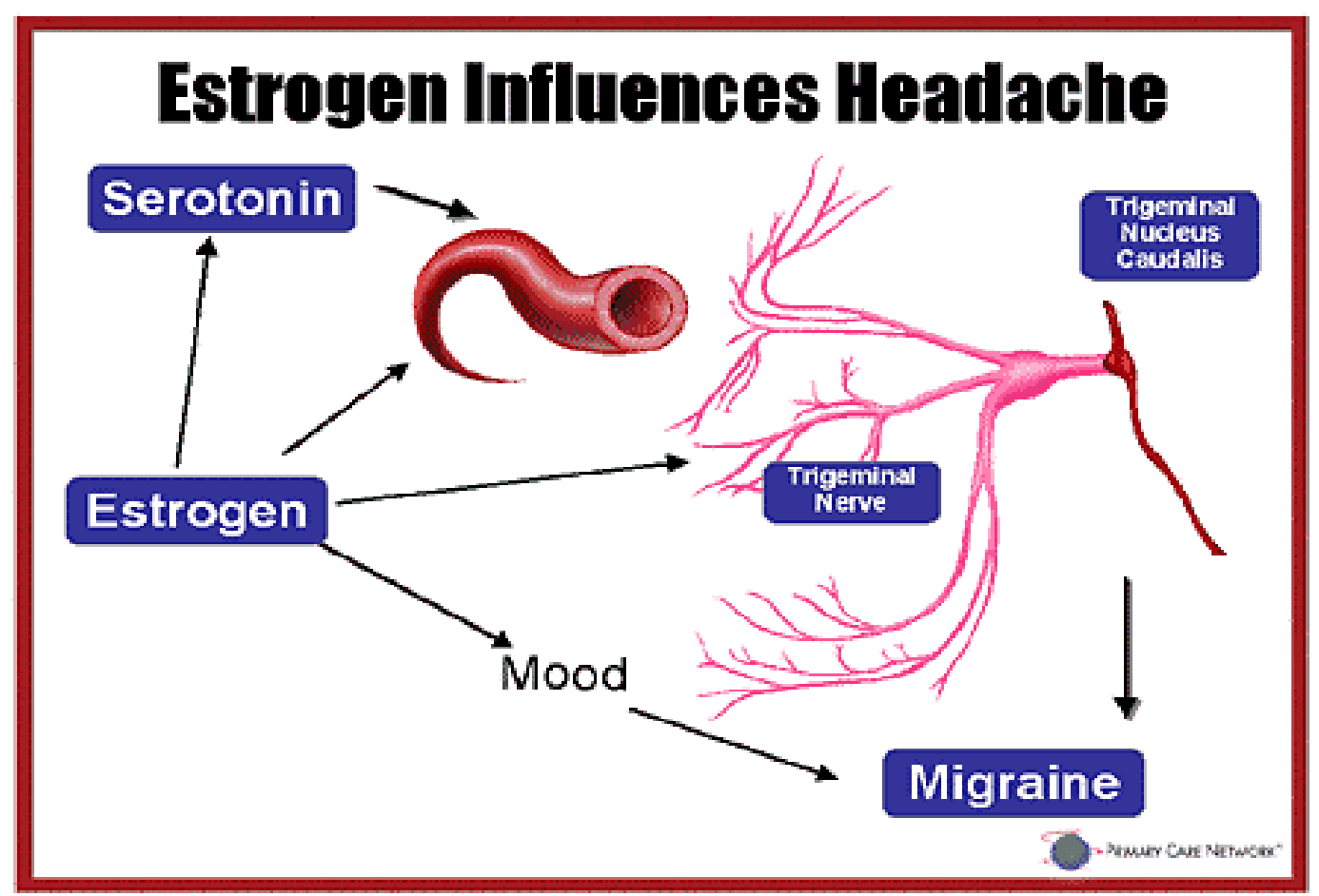
Her recent symptoms were similar to previous migraine attacks but with increased severity, prolonged duration and not relieved by acetaminophen.

How would you approach and manage this case?

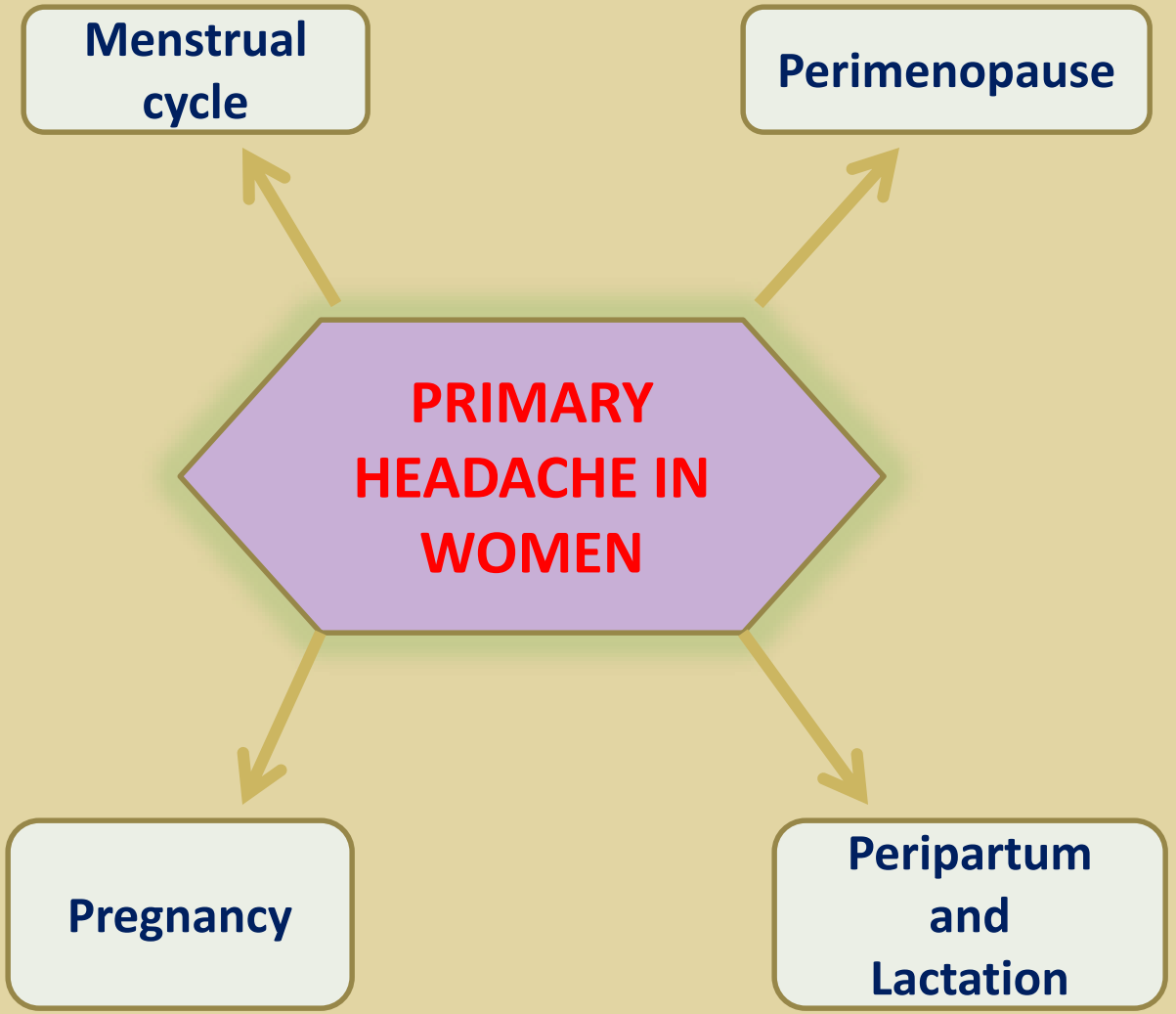
Primary Headache Disorders

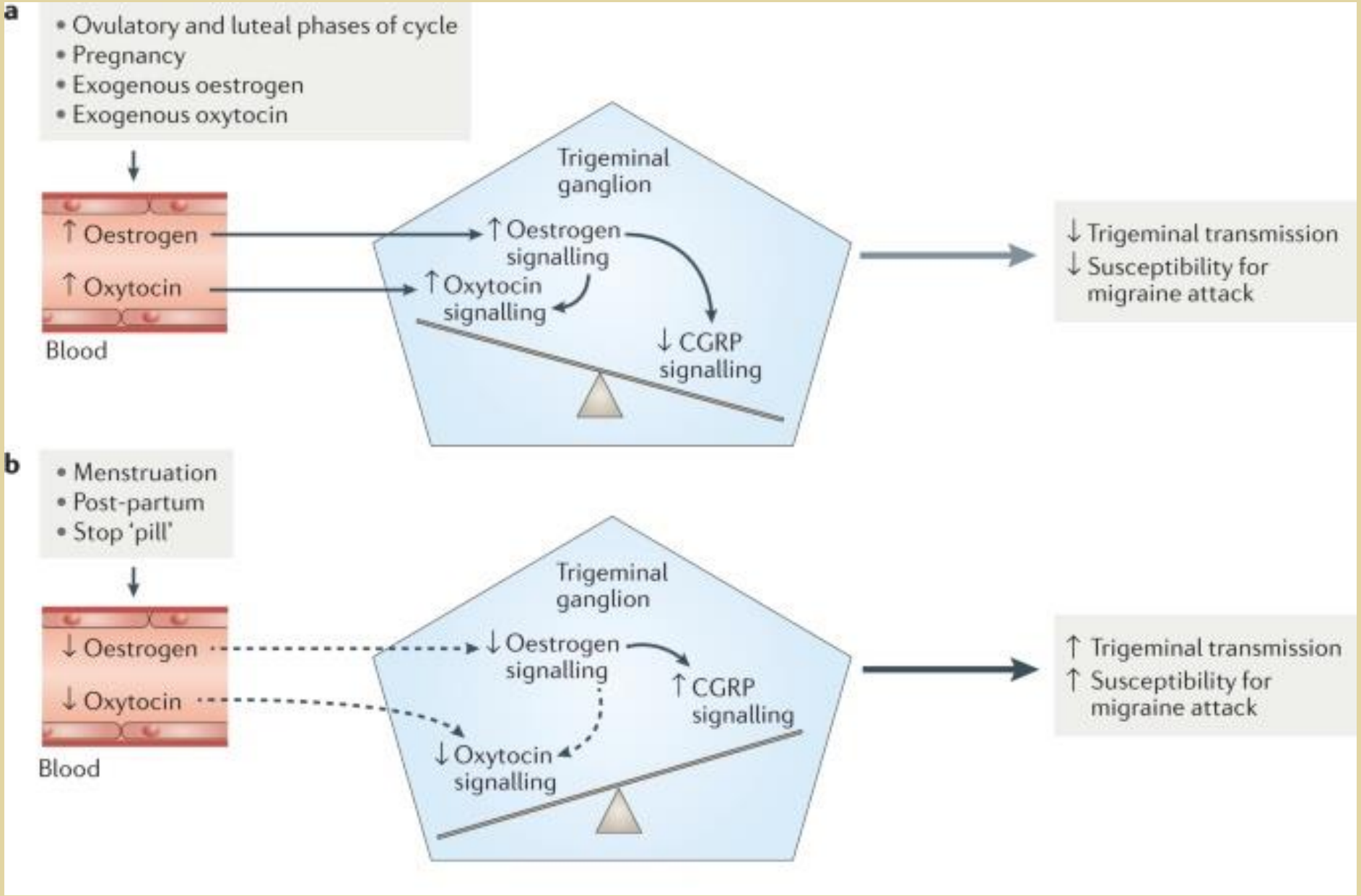


CONTINUUM 2021:27 (3, HEADACHE) American Academy of Neurology



Hormonal fluctuations can have significant impact on occurrence of both migraine and tension type headache


Menstrual cycle
Perimenopause
PRIMARY HEADACHE IN WOMEN
Pregnancy
Peripartum and Lactation


a
• Ovulatory and luteal phases of cycle
• Pregnancy
• Exogenous oestrogen
• Exogenous oxytocin
↑ Oestrogen
↑ Oxytocin
Blood
Trigeminal ganglion
↑ Oestrogen signalling
↑ Oxytocin signalling
↓ CGRP signalling
↓ Trigeminal transmission
↓ Susceptibility for migraine attack
b
• Menstruation
• Post-partum
• Stop 'pill'
↓ Oestrogen
↓ Oxytocin
Blood
Trigeminal ganglion
↓ Oestrogen signalling
↑ CGRP signalling
↓ Oxytocin signalling
↑ Trigeminal transmission
↑ Susceptibility for migraine attack

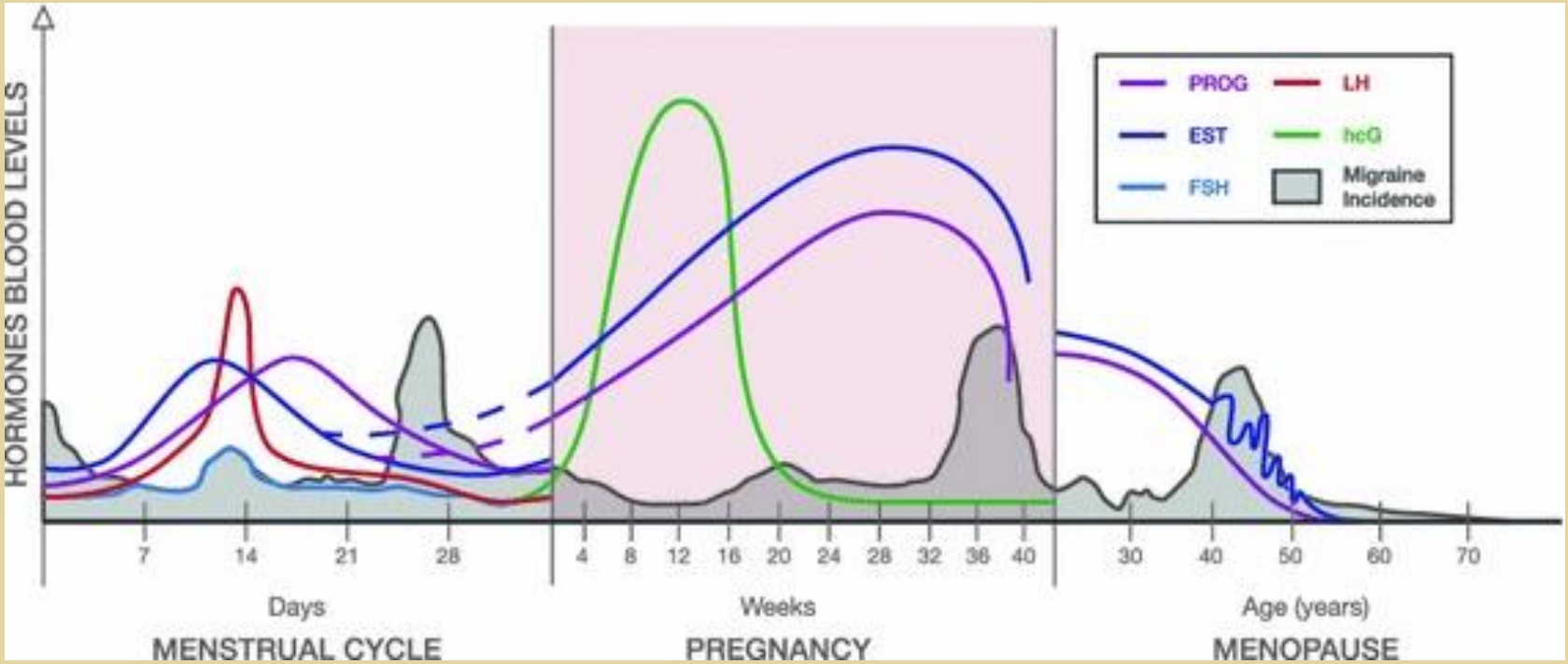
Headache in Pregnancy

- Challenge in diagnosis and management
- May be pre-existing primary headache or can also happen de novo during pregnancy, peripartum, post partum periods
- 50 to 80% of women with migraine experience a reduction in headache frequency or even complete remission during second and third trimesters

CONTINUUM 2021:27 (3, HEADACHE) American Academy of Neurology

- Emergence of new headache or change in characteristics of preexisting headache disorders during pregnancy and peripartum period should be viewed with a high index of caution
- Prothrombotic state can put mother at risk of secondary headache
- Migraine during peripartum period can be associated with increased risk of ischaemic stroke, ICH, MI, venous thromboembolism, pulmonary embolism and thrombophilia

Migraine and tension type headache are found to be more severe and increase in frequency in perimenstrual and perimenopausal periods and generally improve during pregnancy



Menstrually related migraine without aura

Confirmation of primary headache disorder

- Among women with a history of headache
  - changed feature or a longer duration was associated with secondary headache disorder

1st Need to Exclude

- Reversible cerebral vasoconstriction syndrome(RCVS)
- Preeclampsia/eclampsia
- Cerebral venous sinus thrombosis
- Cervical artery dissection
- Posterior reversible encephalopathy syndrome (PRES)
- Stroke
- SOL

CONTINUUM 2021:27 (3, HEADACHE) American Academy of Neurology

Management of Migraine in pregnancy

- Treatment has unique challenges of balancing risks and benefits of treatment with the health of mother and fetus

  Non Pharmacological Treatment
- Episodic nature of attacks in majority, strategy is often to delay or avoid treatment
- Use non pharmacological treatment; relaxation, medical message, mindfulness or biofeedback
- All patients with primary headache disorders may benefit from a discussion of lifestyle modifications; sleep optimization, stress management, adequate hydration and regular healthy meals

CONTINUUM 2021:27 (3, HEADACHE) American Academy of Neurology

Acute abortive therapy

- No therapy is totally devoid of risk to developing fetus
- Inadequate treatment of headache in pregnant women result in work absenteeism and presenteeism
- Risk should be discussed thoroughly among patients and patient's obstetrician

First line agents

Acetaminophen

- Premature closure of ductus arteriosus with use in third trimester
- Childhood respiratory disorders with frequent use
- Association of ADHD if use in third trimester or prolonged use
- Reasonable to continue occasional use during pregnancy
- Thoughtful discussion of benefits and risks is warranted

Metoclopramide

- caution with use around delivery due to extrapyramidal S.E

Diphenhydramine

- useful indirect role via its sedating properties

Ondensetron

- as an adjunctive in preventing severe nausea and vomiting

Nerve blocks

- Limited data in humans but frequently used, no teratogenicity in animal studies

Second line agents

Triptans

- effective and relatively safe

Ibuprofen

- Avoid in 1st trimester because of spontaneous miscarriage risk and 3rd trimester because of premature closure of ductus arteriosus

Prednisone and methylprednisolone

- For status migrainosus
- Increased risk of cleft palate and low birth weight with chronic use

Treatment that should be avoided

- Butalbital containing medications
- Opiates
- Direct CGRP receptor antagonists; ubrogepant, rimegepant
- Serotonin-1F agonist- lasmitidan
- Aspirin – risk of premature closure of ductus arteriosus in late pregnancy, neonatal hemorrhage, perinatal mortality and IUGR with chronic higher dose

Absolutely contraindicated

- Dihydroergotamine – oxytocic effects and IUGR

TABLE 4-4 Safety and Effectiveness of Acute Medications in Pregnancy

Medication	Safety[a]	Effectiveness[a]
Metoclopramide	More safe	Moderately effective
Lidocaine (subcutaneous, intranasal)	More safe	Moderately effective
Acetaminophen	More safe	Moderately effective
Cyclobenzaprine	More safe	Moderately effective
Diphenhydramine (adjunct for sedation)	More safe	Least effective
Ondansetron (adjunct for nausea)	Between safest and moderate safety categories	Most effective
Triptans	Between safest and moderate safety categories	Most effective

CONTINUUM 2022:28 (1, NEUROLOGY OF PREGNANCY) American Academy of Neurology

TABLE 4-4 Safety and Effectiveness of Acute Medications in Pregnancy

Medication	Safety[a]	Effectiveness[a]
Ibuprofen (only for use during second trimester)	Moderate safety	Moderately effective
Prednisone	Moderate safety	Moderately effective
Prochlorperazine	Moderate safety	Moderately effective
Oxycodone (generally not recommended for migraine)	Moderate safety	Least effective
Butalbital (generally not recommended for migraine)	Moderate safety	Least effective
Lasmiditan	Least safe	Most effective
Gepants (rimegepant, ubrogepant)	Least safe	Most effective
Magnesium sulfate (IV)	Least safe	Least effective
Ergots	Least safe	Moderately effective

Preventive therapy

- If pharmacotherapy is indicated , can start with one of following preferred medications; *propranolol, cyclobezaprine* or *mementine* or *oral magnesium*
- Intermittent occipital nerve blocks for severe headache

- Second line therapy

  onabotulinum toxin A injections, *CoQ10*, *venlafaxine*, *riboflavin*, *amitriptyline/nortriptyline*, *verapamil* and *gabapentin*

Medications that should avoid in pregnancy

- *CGRP*
- *Topiramate* – risk of cleft palate and lip, IUGR and metabolic acidosis
- *ACEI and ARB*

Medicines that are absolutely contraindicated

- *Valproric acid*
- *Feverfew*

Medical devices

- Single pulse transcranial magnetic stimulation
- Vagus nerve stimulation
- Trigeminal nerve stimulation
- Many headache specialists feel to use these devices preferable to oral medications with established or unknown teratogenic potential

TMS

Vagus nerve stimulation

Trigeminal nerve stimulation

TABLE 4-3 Safety and Effectiveness of Preventive Treatments in Pregnancy

Medication	Safety[a]	Effectiveness[a]
Propranolol ←	More safe	Most effective
Magnesium	More safe	Least effective
Memantine ←	More safe	Moderately effective
Coenzyme Q_{10}	More safe	Least effective
Venlafaxine ←	Moderate safety	Moderately effective
OnabotulinumtoxinA	Moderate safety	Most effective
Amitriptyline/nortriptyline ←	Moderate safety	Most effective
Riboflavin	Moderate safety	Least effective
Verapamil	Moderate safety	Least effective[b]
Gabapentin	Moderate safety	Least effective

CONTINUUM 2022:28 (1, NEUROLOGY OF PREGNANCY) American Academy of neurology

TABLE 4-3 Safety and Effectiveness of Preventive Treatments in Pregnancy

Medication	Safety[a]	Effectiveness[a]
Calcitonin gene-related peptide targeting treatments (erenumab, fremanezumab, galcanezumab, eptinezumab, rimegepant, atogepant)	Least safe	Most effective
Topiramate	Least safe	Most effective
Lisinopril	Least safe	Moderately effective
Candesartan	Least safe	Moderately effective
Valproic acid	Least safe	Most effective
Feverfew	Least safe	Least effective

CONTINUUM 2022:28 (1, NEUROLOGY OF PREGNANCY) American Academy of neurology

Treatment during lactation and puerperium

Acute treatment

Safe 1st line options

- *Acetaminophen* and *Ibuprofen*
- *Triptans*

  Eletriptan has lowest milk to plasma ratio and sumatriptan has most safety data available for breast feeding
- *Metoclopramide* – increase milk supply but use caution because of sedation effect
- *Promethazine* can interfere with establishment of lactation

Medications that should be avoided

- *Urbogepant*, *rimegepant* and *lasmiditan*

TABLE 4-5 **Safety and Effectiveness of Medications During Lactation**

Medication	Hale's risk category[a,66]	Safety[a]	Effectiveness[a,b]
Acute therapies			
Acetaminophen/ibuprofen	L1 ←	More safe	Moderately effective
Triptans (eletriptan/sumatriptan preferred)	L2/L3 ←	More safe	Most effective
Lidocaine (subcutaneous/intranasal)	L2	More safe	Moderately effective
Prednisone (short term)	L2 ←	More safe	Moderately effective
Ondansetron (adjunct for nausea)	L2	More safe	Most effective
Antiemetics	L2/L3	Moderate safety	Moderately effective
Lasmiditan	Not rated	Least safe	Most effective
Gepants (ubrogepant, rimegepant)	Not rated	Least safe	Most effective
Ergots	L4	Least safe	Most effective

CONTINUUM 2022:28 (1, NEUROLOGY OF PREGNANCY) American Academy of neurology

Preventive therapy

Medications compatible with breast feeding

- *Amitriptyline* , *nortriptyline*
- *Propranolol*, *riboflavin* and *magnesium*
- *Verapamil*
- *Onabotulinumtoxin A*
- *Topiramate* should be used at lower doses and with caution given possibility of lethergy and diarrhoeain infants

TABLE 4-5 Safety and Effectiveness of Medications During Lactation

Medication	Hale's risk category[a,66]	Safety[a]	Effectiveness[a,b]
Preventive therapies[c]			
Amitriptyline/nortriptyline	L2	More safe	Most effective
Candesartan	L3	Moderate safety	Moderately effective
Gepants (atogepant, rimegepant)	Not rated	Least safe	Most effective
Propranolol	L2	More safe	Most effective
Topiramate	L3	Moderate safety	Most effective
OnabotulinumtoxinA	L3	Moderate safety	Most effective
Riboflavin/magnesium	L1	More safe	Least effective
Valproic acid	L2	Moderate safety	Most effective
Venlafaxine	L3	Moderate safety	Moderately effective
Verapamil	L2	More safe	Moderately effective
Calcitonin gene-related peptide targeting treatments (erenumab, fremanezumab, galcanezumab, eptinezumab)	Not rated	Least safe[d]	Most effective

KEY MESSAGE

- Women with migraine with aura may be less likely to improve in pregnancy
- Compared to women without history of migraine, women with migraine are more likely to have secondary cause of headache
- Prior history of migraine is not necessarily reassuring when new or persistent headache present during pregnancy or puerperium
- Secondary headache is common and should be excluded in every cases
- Weighing risk and benefits of drugs is essential for treatment of headache during pregnancy
- Close coordination with patient's obstetric team is essential


Thank
you!