Migraine is more common in women than in men and peaks during childbearing years. During pregnancy, there may be a reduction in migraine severity, but not in everyone. Migraine is not associated with major congenital malformations (MCM), but it is associated with hyperemesis gravidarum, worse sleep, and mood disorders. Preeclampsia and low birthweight also may be associated factors. There is higher risk of adverse neonatal outcomes in offspring of women with migraine, such as intensive care, hospitalization, prescription use, respiratory distress syndrome, and febrile seizures. The link between these outcomes and migraine is unknown, and most women with migraine can have a healthy pregnancy.

Medication use during pregnancy occurs in 97.1% of women, with pain and nausea medications being among the most commonly used drugs. Former Food and Drug Administration (FDA) safety categories of A, B, C, D, and X for pregnancy no longer are in use. Guidance is needed to start conversations about treatment, but evidence often is limited. Nevertheless, conversations are needed early before conception as some migraine medications need to be stopped 6 months in advance. The fact that unplanned pregnancy rates are approximately 45% further underscores the need for a dialogue between healthcare providers and those planning to become pregnant, if possible.

The first step of migraine management during pregnancy is conservative, but this option will be insufficient for some women. This review provides a synthesis of current understanding considering both safety and evidence.

Safety of Guideline-Based Treatments
Preventive Treatments According to American Headache Society Consensus Statement

Table 1 presents a comparison of evidence for efficacy and safety of preventive treatments.

Amitriptyline. Amitriptyline has been associated with gestational diabetes in the mother and MCM, small for gestational age, seizures, and respiratory distress in the neonate. Per the 2022 American College of Obstetricians and Gynecologists (ACOG) Clinical Practice Guideline (CPG): Headache in Pregnancy and Postpartum, amitriptyline use can be considered with caution in pregnant patients. Amitriptyline use is common during pregnancy and has support from American Headache Society (AHS) Consensus Statement (CS) for use in migraine.

Beta-Blockers. Atenolol, metoprolol, and propranolol have an increased risk of fetal growth restriction, but per ACOG, can be considered with caution. Timolol and nadolol are not discussed specifically in the ACOG CPG but can be considered in the same category. Beta-blockers are relatively safe, often are used for hypertension in pregnancy, and have AHS CS support.

Candesartan. Candesartan use is associated with an increased risk of MCM and oligohydramnios. It is not recommended during pregnancy.

Calcitonin Gene-Related Peptide Monoclonal Antibodies. The calcitonin gene-related peptide monoclonal antibodies include eptinezumab, erenumab, fremanezumab, and galcanezumab. There are limited data on exposure during pregnancy and a theoretical risk to fetal growth. Whereas small studies (fewer than 100 cases) have shown no MCM or spontaneous abortion risk, calcitonin gene-related peptide monoclonal antibodies should be stopped 6 months before pregnancy.

Lisinopril. Lisinopril has increased risk of MCM and oligohydramnios. It is not recommended during pregnancy.

Memantine. Memantine previously was included in FDA pregnancy category B, but ACOG CPG recommend against its use during pregnancy. Per the FDA package insert, memantine was given to pregnant rats and rabbits during angiogenesis with
no teratogenicity at doses 9 to 30 times higher than human doses. Given its AHS guideline recommendations and animal safety data, it could be considered with great caution only if safer options have proved ineffective.

OnabotulinumtoxinA. ACOG CPG allow for onabotulinumtoxinA to be considered for use during pregnancy but notes the literature on it is limited. The LactMed database from the National Institutes of Health notes that onabotulinumtoxinA is not detected systemically after intramuscular injection. A MotherToBaby Fact Sheet from the Organization of Teratology Information Specialists (OTIS) reports 137 exposed pregnancies with no increased risk of MCM. A prospective study of 45 exposed pregnancies reported 1 miscarriage and otherwise all healthy, full-term babies. Another study using the Allergan safety database reviewed 574 exposed pregnancies, demonstrating an MCM risk of 2.7%, in line with the general population. OnabotulinumtoxinA has excellent level evidence for chronic migraine treatment and may be used cautiously in pregnancy.

Venlafaxine. Venlafaxine has an increased risk of prematurity and neonatal withdrawal symptoms, but ACOG CPG allow for its use with caution in pregnancy. It has AHS guideline–based evidence for migraine. Gepants. Atogepant and rimegepant are preventive gepants released since the AHS 2021 consensus statement with high-quality evidence for migraine. Atogepant and preventive rimegepant are not discussed in the ACOG CPG but would not be recommended during pregnancy. There are no case reports of pregnancy exposures to this class of medication.

**Acute Treatments According to AHS CS**

Table 2 presents a comparison of evidence for efficacy versus safety.

Acetaminophen. Acetaminophen is the main analgesia recommended for pregnancy by ACOG CPG, although they provide caution on the risk of hepatotoxicity with overdosage. There is recent controversy regarding increased risk of behavioral issues, such as attention-deficit/hyperactivity dis-
**TABLE 2. ACUTE MEDICATIONS FOR MIGRAINE**

<table>
<thead>
<tr>
<th>Medications</th>
<th>AHS CS&lt;sup&gt;16&lt;/sup&gt;</th>
<th>ACOG CPG&lt;sup&gt;14&lt;/sup&gt;</th>
<th>Safety in pregnancy</th>
</tr>
</thead>
<tbody>
<tr>
<td>Sumatriptan</td>
<td>Established efficacy</td>
<td>Consider with caution</td>
<td>Controversy over risk of SGA, spontaneous abortion, and prematurity</td>
</tr>
<tr>
<td>Almotriptan</td>
<td>Not discussed</td>
<td></td>
<td>Controversy over risk of SGA, spontaneous abortion, and prematurity</td>
</tr>
<tr>
<td>Eletriptan</td>
<td>Not discussed</td>
<td></td>
<td>Controversy over risk of SGA, spontaneous abortion, and prematurity</td>
</tr>
<tr>
<td>Frovatriptan</td>
<td>Not discussed</td>
<td></td>
<td>Controversy over risk of SGA, spontaneous abortion, and prematurity</td>
</tr>
<tr>
<td>Naratriptan</td>
<td>Not discussed</td>
<td></td>
<td>Controversy over risk of SGA, spontaneous abortion, and prematurity</td>
</tr>
<tr>
<td>Rizatriptan</td>
<td>Not discussed</td>
<td></td>
<td>Controversy over risk of SGA, spontaneous abortion, and prematurity</td>
</tr>
<tr>
<td>Zolmitriptan</td>
<td>Not discussed</td>
<td></td>
<td>Controversy over risk of SGA, spontaneous abortion, and prematurity</td>
</tr>
<tr>
<td>Dihydroergotamine</td>
<td>Not recommended</td>
<td>Risk of uterine contractions</td>
<td></td>
</tr>
<tr>
<td>Lasmiditan</td>
<td>Not recommended</td>
<td>Unknown</td>
<td></td>
</tr>
<tr>
<td>Rimegepant</td>
<td>Not recommended</td>
<td>Unknown</td>
<td></td>
</tr>
<tr>
<td>Ubrogepant</td>
<td>Not recommended</td>
<td>Unknown</td>
<td></td>
</tr>
<tr>
<td>NSAIDs</td>
<td>Consider with caution</td>
<td>Do not use in third trimester; limit use in first trimester</td>
<td></td>
</tr>
<tr>
<td>Acetaminophen + aspirin + caffeine</td>
<td>Not discussed</td>
<td>Risk of neonatal arrhythmia at caffeine doses greater than 200 mg per day</td>
<td></td>
</tr>
<tr>
<td>Ergotamine</td>
<td>Probably effective</td>
<td>Not recommended</td>
<td>Not recommended</td>
</tr>
<tr>
<td>IV magnesium</td>
<td>Consider with caution</td>
<td>Risk of perinatal mortality with infusion rates &gt;2 g/h</td>
<td></td>
</tr>
<tr>
<td>Isometheptene-containing medications</td>
<td>Not discussed</td>
<td>Unknown</td>
<td></td>
</tr>
<tr>
<td>Chlorpromazine</td>
<td>Not discussed</td>
<td>Likely similar to metoclopramide</td>
<td></td>
</tr>
<tr>
<td>Droperidol</td>
<td>Not discussed</td>
<td>Likely similar to metoclopramide</td>
<td></td>
</tr>
<tr>
<td>Metoclopramide</td>
<td>Recommended</td>
<td>Use in combination with diphenhydramine to reduce akinesia</td>
<td></td>
</tr>
<tr>
<td>Prochlorperazine</td>
<td>Not discussed</td>
<td>Likely similar to metoclopramide</td>
<td></td>
</tr>
<tr>
<td>Promethazine</td>
<td>Not discussed</td>
<td>Likely similar to metoclopramide</td>
<td></td>
</tr>
<tr>
<td>Acetaminophen</td>
<td>Not listed</td>
<td>Recommended</td>
<td>Avoid hepatotoxicity; query ADHD risk</td>
</tr>
<tr>
<td>Butalbital-containing medications</td>
<td>Not recommended</td>
<td>Not recommended</td>
<td>Risk of MOH and cardiac malformations</td>
</tr>
<tr>
<td>Opioids</td>
<td>Not recommended</td>
<td>Risk of MOH, addiction, and neonatal abstinence syndrome</td>
<td></td>
</tr>
</tbody>
</table>

ACOG, American College of Obstetricians and Gynecologists; ADHD, attention-deficit/hyperactivity disorder; AHS, American Headache Society; IV, intravenous; MOH, medication overuse headache; NSAID, nonsteroidal anti-inflammatory drug; SGA, small for gestational age. Data from ASH CS<sup>16</sup> and ACOG CPG<sup>14</sup>. 

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order in children, associated with acetaminophen use during pregnancy.\textsuperscript{29,30} Acetaminophen has benefit over placebo for the acute treatment of migraine with a number needed to treat of 12.\textsuperscript{31} It is available as an intravenous medication; however, 1 study of 60 people showed no benefit over placebo.\textsuperscript{32} Acetaminophen is not included in the 2021 AHS CS.\textsuperscript{33}

Acetaminophen + Aspirin + Caffeine. ACOG CPG recommend less than 200 mg of caffeine per day during pregnancy because higher doses increase the risk of neonatal cardiac arrhythmias.\textsuperscript{14} One study found a 1.42 increased risk of spontaneous abortion with caffeine-combination medications.\textsuperscript{34} This combination has established efficacy in the 2021 AHS consensus statement.\textsuperscript{33}

Butalbital-Containing Medications. Butalbital is a short-acting barbiturate no longer recommended for the treatment of migraine owing to risk of medication overuse headache, abuse, and withdrawal.\textsuperscript{35} It has been associated with cardiac defects and is not recommended for use in pregnancy.\textsuperscript{14,36}

Ditans. Lasmiditan is not recommended by ACOG CPG for use in pregnancy.\textsuperscript{14} There are no case reports of pregnancy exposures to this class of medication.

Ergots. Dihydroergotamine and other ergotamine medications are not recommended for use during pregnancy.\textsuperscript{14} Dihydroergotamine is associated with an increased risk of prematurity.\textsuperscript{37,38}

Gepants. Ubrogepant and rimegepant, gepants for acute treatment of migraine are not recommended for use in pregnancy according to ACOG CPG.\textsuperscript{14} There are no case reports of pregnancy exposures to this class of medication.

Isometheptene-Containing Medications. Isometheptene-containing medications are considered probably effective in the 2021 AHS CS.\textsuperscript{33} There are no studies on safety in pregnancy and isometheptene-containing medications are not discussed in the ACOG CPG.\textsuperscript{14}

Magnesium. ACOG CPG allow intravenous magnesium to be considered with caution during pregnancy at doses below 2 g.\textsuperscript{14} It is considered probably effective by the AHS, particularly for migraine aura.\textsuperscript{33} Treatment longer than 5 days has been associated with fetal skeletal abnormalities.\textsuperscript{39}

Neuroleptics. Antidopaminergic medications, including chlorpromazine, droperidol, metoclopramide, prochlorperazine, and promethazine, are considered probably effective in the 2021 AHS CS.\textsuperscript{33} ACOG CPG only mentions and recommends metoclopramide.\textsuperscript{14} These should be used in combination with diphenhydramine to reduce akinesia.\textsuperscript{14} Caution is needed in terms of sedation and the risk of extrapyramidal symptoms.\textsuperscript{14}

NSAIDs. NSAIDs have multiple risks during pregnancy, including intrauterine hemorrhage, necrotizing enterocolitis, neonatal periventricular leukomalacia, and oligohydramnios. In the third trimester, there is risk of premature closure of the ductus arteriosus or stenosis with risk of pulmonary hypertension.\textsuperscript{14} ACOG CPG recommend that NSAIDs (specifically ibuprofen, naproxen, and indomethacin) be avoided in the third trimester, limited in the first trimester, and, if used in the second trimester, kept to less than 48 hours.\textsuperscript{14}

Opioids. Opioids are not recommended by the AHS in the treatment of migraine, except in refractory headache in women for whom standard first-line and second-line treatment are ineffective or contraindicated.\textsuperscript{35} Use of opioids during pregnancy risks neonatal opioid withdrawal and may affect neurodevelopment.\textsuperscript{40} Prenatal opioid exposure may present an increased risk of MCM, although the absolute risk appears to be low.\textsuperscript{41,42} ACOG CPG do not recommended opioid use during pregnancy.\textsuperscript{14}

Triptans. Triptans, especially sumatriptan, have been reviewed extensively in pregnancy registries, with no MCMs identified.\textsuperscript{38,43-49} There is controversy regarding small for gestational age, spontaneous abortion, and prematurity, with no consistent association found.\textsuperscript{40,50} Triptans are a mainstay in the acute treatment of migraine.\textsuperscript{13,33} ACOG CPG recommends sumatriptan in particular but with caution.\textsuperscript{14}

When Guideline-Based Treatment Does Not Work

Off-Label Preventive Treatment.

Use of off-label preventive treatments varies widely, with large variation in outcomes reported in the literature. Off-label treatments should be prescribed only with clear disclosure of off-label use and risk.

Nerve Blocks and Trigger Point Injections. Nerve blocks or trigger point injections using a local anesthetic such as bupivacaine are not recommended officially in the 2021 AHS CS but it is noted that they can be used in attacks not responding to acute treatment.\textsuperscript{33} There are several randomized controlled trials, including a 2017 systematic review and meta-analysis on nerve blocks, showing possible benefit.\textsuperscript{51,52} ACOG CPG recommend their use with caution because of limited safety data in pregnancy.\textsuperscript{14} The previous FDA pregnancy safety categories had lidocaine and prilocaine listed as category B, with bupivacaine, mepivacaine, and articaine in category C.\textsuperscript{53} Retrospective review of nerve blocks during pregnancy (n=13) has shown safety and good effect.\textsuperscript{54}
Calcium Channel Blockers. ACOG CPG recommend calcium channel blockers such as verapamil, amlodipine, and nifedipine as a first-line treatment, although evidence on efficacy is limited.\textsuperscript{14,33,55-58} Verapamil is sometimes tried in refractory cases as well as in people with vestibular or hemiplegic migraine.\textsuperscript{59,60} Flunarizine is the best-studied calcium channel blocker for migraine, with meta-analysis–level support, but it is not available in the United States.\textsuperscript{61}

Cyproheptadine. Cyproheptadine often is used as a pediatric migraine preventive, particularly in younger children.\textsuperscript{62} ACOG CPG recommend antihistamines such as cyproheptadine as a safe option.\textsuperscript{14} A randomized controlled trial (n=159) studying propranolol and cyproheptadine showed efficacy with both medications alone or in combination.\textsuperscript{63} An open-label trial in 12 people with refractory chronic migraine showed efficacy as well.\textsuperscript{64}

Other Antiseizure Medications. Lamotrigine has limited evidence for use in migraine but is among the safest antiepileptics for women of childbearing age, with systematic review and meta-analysis showing a risk of MCMs, spontaneous abortion, and fetal growth restriction similar to that of the general population.\textsuperscript{6,65} Gabapentin is sometimes considered an option, especially in people needing concurrent treatment of severe neuropathic pain but has risk of cardiac malformation, small for gestational age, and prematurity.\textsuperscript{12,66}

Neuromodulation Devices. Neuromodulation devices with FDA approval for preventive use include Cefaly, GammaCore, Nerivio, and single-pulse transcranial magnetic stimulation devices. These can be considered for use in pregnancy, although ACOG CPG cautions that there are limited safety data for these options.\textsuperscript{14}

Supplements. As a broad category, supplements often are discussed as an option in pregnancy, but caution should be used. Feverfew is not recommended by ACOG CPG because of an increase in uterine contractions.\textsuperscript{14} ACOG CPG also cautions against oral magnesium use because of a possible increased risk of neonatal death.\textsuperscript{14} Coenzyme Q10 has limited safety data and can be associated with maternal hypotension and gastrointestinal upset.\textsuperscript{14} Riboflavin is considered generally safe but pregnancy-related safety data are limited.\textsuperscript{14} The safety of melatonin is unknown.\textsuperscript{14} If supplements are to be tried, riboflavin potentially is the safest option.

Off-Label Acute Treatment

Corticosteroids. ACOG CPG discusses corticosteroids, including methylprednisolone and prednisone, as options to consider with caution in those who are pregnant but recommend against their use in the first trimester because of the risk of cleft palate.\textsuperscript{14}

Timolol Eyedrops. Whereas beta-blocker medications have risks, as previously described, they can be considered with caution.\textsuperscript{16} Timolol eyedrops in particular have shown benefit as an acute treatment for migraine.\textsuperscript{67} A review of the literature reveals mention of fetal bradycardia and apnea associated with timolol eyedrops in cases reports,\textsuperscript{68,69} but 2 other larger studies (n=15 and n=244) showed no adverse fetal effects.\textsuperscript{70,71}

Cyclobenzaprine. The package insert for cyclobenzaprine considered it former FDA category B for pregnancy; there are no human studies, but cyclobenzaprine was studied in various animal models at 20 times the human dose with no adverse effects on the fetus.\textsuperscript{72} Although there are no studies of their use in migraine, muscle relaxants often are used with good effect anecdotal.\textsuperscript{23}

Sphenopalatine Ganglion Block or Compounded Nasal Lidocaine. Because lidocaine is considered to be a safe option during pregnancy, another acute treatment method is sphenopalatine ganglion block. Standard practice is to perform a sphenopalatine ganglion block with a device in clinic or invasively as a suprazygomatic injection,\textsuperscript{74} but recently specialists have been teaching patients to self-administer sphenopalatine ganglion block for home use.\textsuperscript{75} Lidocaine also can be compounded and administered as a nasal spray.\textsuperscript{76}

High-Flow Oxygen. High-flow 100% oxygen at 12 to 15 L for 15 minutes through a nonrebreather mask predominantly is used for cluster headache, but some people with migraine may benefit from this therapy.\textsuperscript{77,78} It is recommended as first-line treatment for cluster headache during pregnancy because of its safety, and also could be considered for use with migraine.\textsuperscript{79} The main limitation is that oxygen is difficult to access as a headache treatment.

Antiemetics. Beyond the antidopaminergic agents, ondansetron is a commonly used antiemetic, but there is controversy regarding its safety in pregnancy, with possible teratogenicity and risk of QT prolongation.\textsuperscript{8} Safer options for use during pregnancy include doxylamine and pyridoxine.\textsuperscript{6} A JAMA systematic review from 2016 recommended ginger, pyridoxine, antihistamines, and metoclopramide for mild nausea in pregnancy; pyridoxine–doxylamine, promethazine, and metoclopramide for moderate nausea; and ondansetron ± steroids for severe nausea.\textsuperscript{80}

Aspirin. As with other NSAIDs, aspirin should be avoided, especially at higher doses, in the third trimester, because of the risk of premature ductus arteriosus closure and oligohydramnios.\textsuperscript{6} There is also an increased risk of neonatal bleeding.\textsuperscript{6} In the second and possibly the first
trimesters, aspirin may be used with caution at doses less than 100 mg/d.6

Summary of Recommendations

Figure 1 presents a summarized approach to treatment; however, these recommendations are based on limited data, and no treatment is devoid of risks. Furthermore, there is a 3% risk of MCMs even in the general population.81 Conservative options should be attempted first. In people refractory to conservative options, an open discussion with clear disclosure of risks and unknowns is the next step. For preventive treatment, the safest options may be cyproheptadine, lidocaine nerve blocks, neuromodulation devices, calcium channel blockers, and riboflavin; guideline-based treatment, such as amitriptyline, beta-blockers, memantine, onabotulinumtoxinA, and Venlafaxine, could be considered with caution. For acute treatment, the safest options are likely acetaminophen, low-dose caffeine, diphenhydramine, ginger, high-flow oxygen, metoclopramide, neuromodulation, and pyridoxine; guideline-based options, such as triptans, intravenous magnesium, nonsteroidal anti-inflammatory drugs, promethazine, and steroids, could be considered. Other potential acute options include cyclobenzaprine, timolol eyedrops, and ondansetron. Treatment should be individualized through shared decision-making considering trimester, level of evidence, disability level, risk assessment, and comorbidities. ■


Figure 1. Flowchart of an approach to choosing preventive and rescue treatments for management of pregnant women. Treatment discussions require a careful discussion of pros and cons, including an explanation that safety data are limited.

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