

## REVIEW ARTICLE

# Management of cluster headache and other trigeminal autonomic cephalalgias in pregnancy and breastfeeding

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## Abstract

Many clinicians lack experience in managing trigeminal autonomic cephalalgias (TACs) in pregnancy and lactation. In addition to cluster headache, TACs include hemicrania continua, paroxysmal hemicrania, and short-lasting unilateral neuralgiform headache with conjunctival injection and tearing/autonomic symptoms (SUNCT/SUNA). Treating these rare, severe headache conditions often requires off-label drugs that have uncertain teratogenic potential. In the last few years, several new treatment options and safety documentation have emerged, but clinical guidelines are lacking. This narrative review aimed to provide an updated clinical guide and good clinical practice recommendations for the management of these debilitating headache disorders in pregnancy and lactation.

## KEYWORDS

breastfeeding, headache, hemicrania continua, Horton's headache, paroxysmal hemicrania, pregnancy, SUNCT, trigeminal autonomic cephalalgias

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## INTRODUCTION

Trigeminal autonomic cephalalgias (TACs) are a group of uncommon, but extremely painful primary headaches. TACs include cluster headache, hemicrania continua, paroxysmal hemicrania, and short-lasting, unilateral neuralgiform headache attacks with conjunctival injection and tearing/cranial autonomic symptoms (SUNCT/SUNA) [1]. These disorders share similar clinical features but differ in frequency, duration, triggers and treatment (Table 1) [2]. All TACs present with unilateral, intense pain in the area innervated by the first branch of the trigeminal nerve. Ipsilateral, parasympathetic cranial autonomic features comprise part of the clinical spectrum during attacks (Table 1). Patients with cluster headache and paroxysmal hemicrania can experience the disorder in an episodic form, with bouts of attacks lasting from weeks to months. However, some patients can develop a chronic form, without long, attack-free periods.

Most prophylactic drugs for TACs are prescribed off-label, which places extra responsibility on the treating physician [3]. Few non-pharmacological options with documented effects are available. Managing TACs in pregnant or breastfeeding women is often challenging. Few clinical guidelines and reviews focus specifically on TACs during pregnancy and lactation [4-7]. In the last few years, several new treatment options for TACs have emerged and the safety documentation has improved for the use of several drugs during pregnancy and lactation. Therefore, we aimed to perform an updated, clinically useful review on the management of cluster headache and other TACs during pregnancy and lactation and to provide good clinical practice recommendations (Table 2).

## METHODS

### Search strategy

We performed a literature search in Medline and Embase with the keywords: "cluster headache", "trigeminal autonomic cephalalgias", SUNCT, hemicrania continua, paroxysmal hemicrania and "pregnancy", "pregnancy outcome", "birth defects", "congenital malformations", "breastfeeding", and "lactation", combined with individual drugs commonly used to treat TAC (Table 3). Medical Subject Heading (MeSH) terms were used, when possible. For each relevant paper, the bibliography was scrutinized for additional citations. Only studies in humans published in English or Scandinavian languages were included. The time period ranged from database inception to May 2020. We consulted the headache treatment guidelines from the American Academy of Neurology and the American Headache Society [8], the Canadian

Headache Society [9,10], the British Association for the Study of Headache [11] and the European Academy of Neurology (EAN, previously EFNS) [12]. Further, we consulted the National Library of Medicine's Drugs and Lactation Database (LactMed), UpToDate, Reprotox, the Royal College of Obstetricians and Gynecologists, and the National Institute for Health and Care and Excellence (NICE) recommendations [6,13,14,15,16]. Finally, the authors' clinical experiences were included.

## CLINICAL PICTURE AND EPIDEMIOLOGY OF TACS

Table 1 summarizes the main characteristics of TACs. Below is a brief overview of what is known about these conditions among pregnant and lactating women and among women of childbearing age.

Approximately 45% of women report that cluster headaches started in their twenties or at a younger age [17]. Due to the increasing age of pregnant women, it is likely that the occurrence of this condition among childbearing women is growing. Women experience the chronic, unremitting form of cluster headache more often than men [18]. Although patients who experience migraines often improve during pregnancy, cluster headache is less sensitive to hormonal changes [3]. In one study of women who experienced cluster headaches, 52% reported improvement, 35% reported no change, and 13% reported worsening of the condition during pregnancy [17]. Cluster headaches can have large implications for family life. Several studies have found that women who experience their first attack before their first gestation typically have fewer children than those that were already mothers at the time of clinical onset [19,20]. In one study, approximately 60% of female patients with cluster headaches did not have children after the point of diagnosis. Among these women, 8% feared that the attacks would prevent them from taking care of a child, and 4% were afraid to pass the disorder on [17]. In addition to the effect on family planning, this disorder can impact social functioning and quality of life. It increases the risk of major depression, and over 50% of women with cluster headaches reported suicidal thoughts [21]. Compared to men, women more often report violence during attacks, such as hitting themselves or hitting objects [17]. They are also more likely to have migrainous features, such as photophobia and nausea, or comorbid migraine [17,18]. Some studies have shown that a correct diagnosis was delayed more often in women compared to men, and women were more likely to be misdiagnosed [17,18,22].

The frequency of paroxysmal hemicrania is two- to threefold higher among women than among men [23,24]. It is currently unknown how paroxysmal hemicranias might affect pregnancy, and

**TABLE 1** Epidemiological and clinical features of different trigeminal autonomic cephalalgias

	Cluster headache	Paroxysmal hemicrania	Hemicrania continua	SUNCT/SUNA
<b>Epidemiology</b>				
Prevalence	100:100,000	20–50:100,000	50:100,000	50–100:100,000
Ratio female/male	1:3	2–3:1	2:1	1:1.5
Typical age of onset	20–40 years	30–40 years	30–50 years	40–70 years
Relationship pregnancy	~1 out of 2 improve, ~1 out of 8 worsen	May start postpartum	Unknown	Unknown
<b>Attacks</b>				
Duration (min)	15–180 min (typically 100 min)	2–30 min (typically 15 min)	Continuous >3 months, with exacerbations daily or less	1–600 s (typically 1 min)
Frequency (per day)	Once every other day, up to 8 times per day (typically 3–4 per day)	>5 per day (typically 10 per day)	Continuous >3 months	>1 per day or more (typically 60 per day)
Quality of pain	Sharp, stabbing, throbbing	Sharp, stabbing, throbbing	Baseline: aching Exacerbations: sharp, stabbing, throbbing	Sharp, stabbing, throbbing
Severity of pain	Severe to very severe	Severe	Baseline any severity, flares moderate to severe	Moderate to severe
Autonomic features at the side of the pain: <i>Red, running eye, stuffed running nose, swollen or dropping eyelid, facial sweating, small pupil</i>	Yes	Yes	Yes	Yes
Restlessness or agitation	Yes	Yes	Yes	No
Circadian pattern	>80%	Rare	Rare	Rare
<b>Treatment</b>				
Oxygen	Yes	No	No	No
Triptans	Yes	No	No	No
Indomethacin	No	Yes	Yes	No

vice versa. In a small case series of chronic paroxysmal hemicranias, 50% of women reported that the disorder started in the postpartum period. Among patients who developed the disorder before pregnancy, 90% reported that pregnancy improved the condition, but that attacks started again immediately after birth [24].

Women are diagnosed with hemicranias continua two to three times as often as men [25]. The true prevalence is unknown, but the disorder is probably the most common TAC, after cluster headache [26]. It is currently unknown whether the frequency and/or severity changes during pregnancy.

There are probably fewer women than men with SUNCT/SUNA. The disorder sometimes occurs during pregnancy [27], but probably less often than the other TACs because most patients develop these disorders in their forties.

## MANAGEMENT

Table 2 summarizes the good clinical practice recommendations for caring for women with TACs.

## Prepregnancy counseling

Physicians need to ask all women of childbearing age with TACs early and repeatedly about family plans. Preferably, prophylactic treatment should be discontinued at least five half-lives before pregnancy to avoid teratogenicity [28]. However, unplanned pregnancies occur in 45% of women with chronic health conditions [29]. Hence, even when no pregnancy plans are imminent, the treatment should be as compatible with pregnancy as possible. It might take time to find an effective treatment that has low risk potential for a future pregnancy [3] (Tables 2 and 3). It is important to titrate to the lowest effective dose to ensure a good balance between controlling attacks and potential side effects. Women who use drugs that are potentially harmful to the fetus (red and orange boxes in Table 3), must be repeatedly informed of the risks. When using teratogenic drugs (red boxes in Table 3), women should be offered effective contraceptives (Table 2). Clinicians should be aware that antiseizure drugs such as topiramate and lamotrigine commonly used in TAC prophylaxis might interact with hormonal contraception [30]. All women of childbearing age using antiseizure drugs should also take

**TABLE 2** Best clinical practice recommendations for women with trigeminal autonomic disorders (TACs) before, during and after pregnancy (reference [6,14,15,16,28,31,55,60,69,74]).

1	Discuss pregnancy plans with women of childbearing age with TACs well advance of conception
2	Choose effective drugs with good pregnancy safety profile in women of childbearing age with TACs regardless of pregnancy plans
3	Women on teratogenic drugs should use effective contraception
4	If possible, discontinue prophylactic drugs 5 half-lives before pregnancy [28]
5	Women needing treatment for TACs in pregnancy should be advised by a specialist [14]
6	Collaborate with her family physician, midwife, and obstetrician during pregnancy. Consider a plan for delivery and postpartum that describes how to prevent and handle attacks*
7	Consider screening for depression and anxiety during and after pregnancy [74]
8	Women of childbearing age on antiseizure drugs should use 0.4 mg folate supplement. Consider high dose folate supplement (1–5 mg) if antiseizure drugs are inevitable during pregnancy [31]
9	For acute treatment of cluster headache, oxygen inhalation is first choice in pregnancy. If not sufficient, try intranasal triptans, intranasal lidocaine and/or or sumatriptan sc [6,15]
10	Transitional prophylaxis with per oral steroids or greater occipital nerve blockade can be used in the lowest dose and duration necessary among pregnant and breastfeeding women [16]
11	Verapamil is first choice if continuous prophylaxis is needed in cluster headache during pregnancy, if possible, avoid in third trimester [16]
12	Do not prescribe valproate to women of childbearing age with TACs during pregnancy unless everything else is ineffective. If used, a pregnancy prevention plan must be in place [60]
13	Avoid lithium during pregnancy and lactation unless everything else is ineffective [55]
14	If use during pregnancy cannot be avoided, check needs for dose adjustment of topiramate, lamotrigine, and lithium by measuring serum concentrations before, during and after pregnancy [31,55]
15	Avoid indomethacin in women trying to conceive and after the first trimester [69]. Use with caution in the first trimester [74]
16	Apart from lithium, most drugs used for TACs are probably compatible with breastfeeding if the child is full born and healthy, and the mother can adequately observe the infant for side effects [15]. Galcanezumab could be considered after the first postpartum week

Note: The recommendations are based on published literature, clinical guidelines, summary of product characteristic (SmPC) and our own clinical experience (marked with\*).

0.4 mg folic acid supplements, regardless of pregnancy plans [31]. Moreover, many authors recommend that women using antiseizure drugs should increase the dose of folic acid to at least 1 mg before and during pregnancy [31].

For some patients with TACs, the headache condition is not manageable in pregnancy without prophylactic drugs. When planning pregnancy, patients must be educated about the off-label use of most prophylactic drugs for TACs. They should be informed that limited evidence is available regarding the efficacy and safety of these drugs during pregnancy and lactation [7,32]. It may be beneficial to include the next of kin in these conversations. Individualized, sensitive and honest information sets realistic expectations and allows patients to make educated decisions. It is our experience that fear of teratogenicity frequently leads to abrupt discontinuation of prophylactic drugs, which may induce headache worsening. This situation can potentially result in an increase in use of acute drugs, stress, nutritional deficiency, social isolation, and depressive symptoms. In turn, these factors are associated with adverse pregnancy outcome [33]. For some women, continuation of a prophylactic substance potentially harmful for the fetus might be the right decision.

Other topics in prepregnancy consultations include fertility issues and heritability. *In vitro* fertilization often worsens headaches in women susceptible to migraines [34], but it remains unknown how such hormonal treatments affect cluster headache or other TACs. Genetic epidemiological surveys have indicated that first-degree

relatives are five to 18 times more likely to develop cluster headaches than the general population [35]. However, because the prevalence of cluster headache is low, the absolute risk of a child inheriting the disorder is small.

### Follow-up during pregnancy

Pregnant women that need treatment for cluster headache in pregnancy should receive specialist advice [14]. Based on our clinical experiences, patients that have frequent attacks during pregnancy require close follow-up to adjust the drug doses and to handle comorbid psychosocial challenges that could be worsened or triggered by the pregnancy. Some women worry that the drugs or the attacks might harm the unborn child. In our opinion, it is preferential for patients to be followed by a coordinated, cross-disciplinary team that includes a headache specialist, a headache nurse, and other personnel, based on the individual patient's needs. It is also important to maintain close collaboration with the patient's general practitioner, midwife and obstetrician. Due to the rarity of these disorders, the obstetrics department might need information about what to expect if attacks occur before or during delivery, and how they should be handled. Attack-free patients who are taking prophylactic drugs should also be offered neurological follow-up during pregnancy. Serum concentrations of some prophylactic drugs, such as lithium

TABLE 3 Safety of medications commonly used for trigeminal autonomic cephalalgias during pregnancy and lactation [Colour table can be viewed at [wileyonlinelibrary.com](http://wileyonlinelibrary.com)]

	Close to conception	First trimester	Second trimester and early third trimester	Third trimester	During lactation
<b>Acute treatment<sup>a</sup></b>					
Triptans: <i>Sumatriptan</i>	No evidence of any increased risk	No evidence of any increased risk of malformations	No evidence of any increased risk	No evidence of any increased fetal or maternal risk	Considered compatible with breastfeeding
Triptans: <i>Others</i>	No evidence of any increased risk, but limited data exist	No clear evidence of malformations, but limited data exist	No evidence of any increased risk	No evidence of any increased fetal or maternal risk	Considered compatible with breastfeeding, but limited data exist
Lidocaine (intranasal)	No evidence of any increased risk	No evidence of any increased risk of malformations	No evidence of any increased risk	No evidence of any increased fetal or maternal risk	Considered compatible with breastfeeding
NSAIDs: <i>Indomethacin</i>	Possibly reduced fertility, preimplantation loss, inconclusive results	Possibly increased risk of miscarriage and malformations, inconclusive results	Possibly increased risk of IUGR, stillbirth, inconclusive results. Possible risk of premature closure of ductus arteriosus after week 20, oligohydramnios, impaired neonatal renal function	Possibly increased risk of oligohydramnios, impaired fetal/neonatal renal function, premature closure of ductus arteriosus, IUGR, fetal death, and bleeding	Generally considered compatible with breastfeeding after the neonatal period, but few data
COX-2 inhibitors: <i>celecoxib</i>	Possibly reduced fertility, preimplantation loss, inconclusive results	As for indomethacin, limited data	As for indomethacin, limited data	As for indomethacin. Increased risk of prematurity also reported	Celecoxib is generally considered compatible with breastfeeding after the neonatal period, but few data
Ergot derivatives	Increased risk of preimplantation loss	May induce uterus contractions and thus miscarriage and malformations	May induce uterus contractions and thus miscarriage and malformations	Increased risk of fetal harm	Recused breast milk production. Possible egotism in the breast fed infant
Opioids: <i>Codeine</i> <i>Oxycodone</i> <i>Morphine</i>	Sporadic use: No evidence of any increased risk	Possible risk of oral clefts	Sporadic use: No evidence of any increased risk	Increased risk of neonatal abstinence and perinatal complications in newborns exposed to high doses <i>in utero</i> close to delivery	Risk of adverse drug reactions in breastfed infants. Avoid use if the infant is premature and/or newborn. Observe for sedation and lethargy
Somatostatin analogs: <i>Octreotide</i>	No data	Possibly increased risk of miscarriage, very few data	Possibly increased risk of miscarriage and fetal growth restriction, very few data		Unlikely to be transferred to breast milk. Considered compatible with breastfeeding, but data on only one infant exist
<b>Transitional prophylaxis</b>					
Local anesthesia: <i>Lidocaine</i> <i>(intranasal / infusion)</i> <i>Bupivacaine</i>	No evidence of any increased risk, but limited data exist	No evidence of any increased risk			Considered compatible with breast feeding

(Continues)

TABLE 3 (Continued)

	Close to conception	First trimester	Second trimester and early third trimester	Third trimester	During lactation
Betametasolone (inj.)	No evidence of any increased risk. Second-line option due to limited data	No evidence of any increased risk			Considered compatible with breastfeeding
Prednisolone (per oral) Methylprednisolone (per oral)	No evidence of any increased risk	No clear evidence of teratogenicity in humans. Moderate to high doses: impaired fetal growth		Adrenocortical suppression in the newborn baby has been reported with high doses of potent glucocorticoids towards the end of pregnancy, but this appears to be a mild and reversible effect	Sporadic use compatible with breastfeeding
<b>Continuous prophylaxis</b>					
Calcium channel blockers: Verapamil	No evidence of any increased risk, but limited data exist	No evidence of increased risk of malformations	Possible increased risk of IUGR	Possible risk of pharmacological effects in the newborn infant, e.g., hypotension and hypoglycemia if used close to delivery. Possible tocolytic effect	Observe newborn infant for hypotension and hypoglycemia. May impact breast milk production. Probably compatible with breastfeeding in infants >2 months old, limited data
Antiepileptic: Valproate	Contraindicated in women of childbearing age due to teratogenic potential. Effective contraception required	Risk of malformations: 10%	Risk of neurodevelopmental effects in the child, incl. impaired cognition: 30%–40%	Risk of neurodevelopmental effects in the child, incl. impaired cognition: 30%–40%	No risk for the breastfed infant, but an obvious risk of teratogenic effects if the mother again should become pregnant
Antiepileptic: Topiramate	No data exist, but based on experience with other antiepileptic drugs, use should be avoided	Increased risk of orofacial clefts	Increased risk of fetal growth restriction. Limited data exist, but fetal neurodevelopmental toxicity cannot be excluded	Limited data exist, but fetal neurodevelopmental toxicity cannot be excluded	Risk of ADRs in premature and newborn infants. Probably compatible with breastfeeding in infants >2 months old, limited data. Monitor for poor weight gain
Lithium	No data exist, but teratogenic potential suggests use should be avoided	Risk of cardiac malformations (Epsteins anomaly)	May impact maternal–fetal thyroid function, e.g., hypothyroidism, goiter. Possible increased risk of fetal death.	Risk of pharmacological effects in the newborn infant, e.g., hypotonia, sedation, impact on infant thyroid and kidney function	Risk of ADR in breast-fed infants, incl. impact on infant thyroid and kidney function. High levels in breast milk

(Continues)

TABLE 3 (Continued)

	Close to conception	First trimester	Second trimester and early third trimester	Third trimester	During lactation
<i>Botulinum toxin A</i>	No evidence of any increased risk, but limited data exist	No evidence of any increased risk, but limited data exist	No evidence of any increased risk, but limited data exist	No evidence of any increased risk, but limited data exist	Generally considered compatible with breastfeeding after the neonatal period, but few data
CGRP-antibodies: <i>galcanezumab</i>	No data	No data. No concern about teratogenicity	No data. Theoretical increased risk of preeclampsia	No data. Possible increased risk of preeclampsia	No data. Probably no transfer to breast milk after 1 week post partum
Gabapentinoids: <i>Gabapentin</i>	No evidence of any increased risk, but limited data exist	No evidence of increased risk of malformations		Possible increased risk of fetal growth restriction	Possible increased risk of perinatal complications in the newborn
Antiepileptics: <i>Lamotrigine</i>	No evidence of any increased risk, but limited data exist	Low risk in low to moderate doses. High doses, some conflicting reports		No evidence of an increased risk	Possible increased risk of perinatal complications in the newborn
Muscle relaxants: <i>Baclofen</i>	No evidence of any increased risk, but limited data exist	Increased risk of congenital malformation in one small study, but no particular malformation pattern observed. Neonatal withdrawal symptoms including feeding difficulties and intractable seizures after per oral use during pregnancy.			Generally considered compatible with breast feeding in infants >2 months old, limited data. Low levels in breastmilk. Observe for sedation
Melatonin	No evidence of any increased risk, but limited data exist	Animal trials report possible teratogenicity, growth restriction and fetal loss. Limited data on humans exist. Can theoretically affect sleep-wake cycle in the child			Low transfer to breastmilk. One case of bleeding episodes possibly related to maternal use. Observe for sedation and disturbed sleep wake cycle.

Note: This table was adapted from Amundsen et al., Pharmacological treatment of migraine during pregnancy and breastfeeding. *Nat Rev Neurol.* 2015; 11(4): 209-19. It was updated with literature published after that review was performed. Advice about other medications has been added, based on the latest available literature.

Color coding: **Dark green:** Considered safe; **Light green:** Generally considered safe, but uncertainties may exist; e.g., uncertain findings for some drugs within a group or during a certain time period, or uncertainties related to the total amount of data available. **Orange:** Increased risk of harmful effects cannot be excluded, because some data indicated risk, because very few data exist to support safety, or because case reports of side effects in breast-fed infants were published; **Red:** Contraindicated. The fetal/infant risk exceeds the therapeutic advantage for the mother

Abbreviations: ADR, adverse drug reaction; CGRP, calcitonin gene-related peptide; COX-2, cyclooxygenase-2; inc, including; inj, injection; IUGR, intrauterine growth retardation; NSAIDs, nonsteroidal anti-inflammatory drugs; TCAs, tricyclic antidepressants.

<sup>a</sup>Classification presupposes occasional use. Risks may increase with frequent or excessive use.

and lamotrigine, often decline in the gestational period [31,36]. If the physician and the woman decide that the benefit of continuing these medications outweigh the potential risk for the child (Table 3), then serum concentrations should be monitored, and doses adjusted accordingly. Furthermore, patients taking drugs with teratogenic potential (red boxes in Table 3) during pregnancy might need referrals to additional obstetric follow-ups, including ultrasound scans for detecting structural anomalies or fetal complications [37].

For women with frequent, disabling attacks, delivery and care of the newborn can be challenging. In the third trimester, planning the delivery and postpartum period together with the woman may reduce maternal stress. The plan should optimally include the mode of delivery, anesthesia during delivery, a medication plan, breastfeeding advice, and newborn care advice. Some women might need extra support to care for the infant, both in the maternity ward and after leaving the hospital. Lack of sleep or alterations in diurnal rhythms may, for example, trigger attacks [38]. Practical solutions should be discussed with the woman and her next of kin, and if needed, with community health personnel.

### Follow-up in the postpartum period

In most situations, the benefits of breastfeeding outweigh the risk of side effects in breastfed infants (Table 3). The risk of side effects is highest for infants under 3 months old, due to immature liver and kidney functions, particularly if the infant was born premature, small-for-gestational age, or ill [39]. The side effects most observed in infants of mothers that use drugs for cluster headache and TACs include diarrhea, drowsiness, irritability, inadequate weight gain, and delayed developmental milestones (Table 3). Few side effects have been reported in infants after 3 months of age. When giving breastfeeding advice, the clinician should consider the ability of the parent to monitor and detect these symptoms. The risk-benefit balance of breastfeeding versus not breastfeeding may differ in women with headache bouts compared to women with chronic and severe forms of the disorders. The women should be assured that not breastfeeding may also be a sensible and safe choice.

## CLUSTER HEADACHE

### Attack treatment

In nonpregnant women with cluster headache, the first choice of attack treatment is oxygen inhalation and subcutaneous or intranasal sumatriptan or intranasal zolmitriptan [40,41]. Approximately 70% of female patients respond to these strategies [7]. Other acute treatments that are in use, but have little or no clear evidence of efficacy, include nasal application of lidocaine, noninvasive vagal stimulation and octreotide [2]. Guidelines do not recommend opioid treatment for primary headache disorders [40,41], and first trimester use is associated with a slightly increased risk of oral clefts [42].

During pregnancy and lactation, oxygen inhalation is the first-line treatment, and it is considered safe for both the mother and child [7].

Several large observational studies have investigated the safety of sumatriptan and zolmitriptan during pregnancy. They showed that these drugs did not increase the risk of major congenital malformations in the infant, but caution when using repeated doses is still warranted as triptans have vasoconstrictor effects [5,43,44]. In contrast to patients with migraine, patients with cluster headache might require multiple administrations each day. We therefore advise using the nasal sprays if these are sufficient because they provide significantly less drug exposure than an injection [28,45]. Sumatriptan is considered safe to use during breastfeeding, because the exposure to the infant is very low [7].

Limited evidence exists for the safety of intranasal applications of lidocaine during pregnancy, but extensive experience with subcutaneous lidocaine administration for local anesthesia has shown no significant adverse reproductive or teratogenic effects and is safe to use during breastfeeding [3,6,15].

Noninvasive vagal nerve stimulation on the neck can serve as both an acute and prophylactic treatment for cluster headache, but it has not been tested in pregnancy. Vagal nerve fibers supply the myometrium, vasculature, and pelvic ganglia, therefore, this treatment might theoretically affect the uterus [46]; moreover, vagal stimulation can have hormonal effects [47]. Among pregnant women with epilepsy, those who received vagal nerve stimulation required slightly more obstetric interventions, but rates of congenital malformations in such patients did not increase compared to patients who did not receive vagal stimulation [48]. Vagal nerve stimulation can be used in lactating women.

### Prophylactic treatment

Transitional prophylaxis with steroids is used for treating bouts of cluster headache and episodes of worsening in chronic cluster headache [3]. Most clinicians administer oral prednisolone or methylprednisolone, or for greater occipital nerve infiltration, a mixture of local anesthesia and injectable glucocorticoids. Unfortunately, many patients experience relapse when tapering off the treatment. These patients require maintenance prophylactic treatment. Traditionally, the first-line option is verapamil, the second-line options are topiramate and lithium, and the third-line options are valproate, melatonin, baclofen, and gabapentin. In 2019, the US Food and Drug Administration (FDA) approved galcanezumab, an antibody against monoclonal calcitonin gene-related peptide (CGRP), for episodic cluster headache. In addition, evidence of efficacy is accumulating for sphenopalatine ganglion (SPG) stimulation [49]. Evidence of efficacy is uncertain for occipital nerve stimulation or deep brain stimulation [50]. Additionally, a pilot study showed that a botulinum toxin block of the SPG had potential for treating chronic cluster headache [51]. A randomized controlled trial (NCT03944876) is currently recruiting patients to determine the efficacy of blocking the SPG [52].

During pregnancy, short-term transitional prophylaxis with oral steroids is unlikely to cause serious adverse effects. Glucocorticoids have been found to be teratogenic in animals. In humans, some studies have found an association with oral clefts [32]. However, the majority of studies do not suggest that use of oral glucocorticoids increase the risk of congenital anomalies overall [16]. Late pregnancy high-dose steroid use can induce a mild, transitional suppression of adrenocortical function in the newborn child. Glucocorticoids transfer into breast milk, but short-term oral use is likely to be safe during breastfeeding [15,16].

It remains unclear whether a greater occipital nerve injection of steroids for transitional prophylaxis might affect the fetus less than oral steroid administration. Injectable steroids in the first trimester have not been well studied. In randomized trials on methods to prevent preterm birth, betamethasone injections did not adversely affect mortality or neurodevelopmental measures compared to placebo [53]. Greater occipital nerve blocks with steroids are therefore most likely safe in pregnancy [28]. Moreover, local betamethasone injections have not had harmful effects on breastfeeding children, but milk production might be temporarily reduced [15].

In small observational studies in patients with cardiovascular disorders, and in a systematic review, verapamil was not associated with an increased risk of fetal malformations [32,54]. However, patients with cluster headache often use higher verapamil doses than other patient groups; thus, the generalizability of published results to this group of patients remains uncertain [2]. Moreover, some studies have shown lower birth weight and fetal loss, but these effects could not be separated from the effect of the underlying maternal/fetal illness and comedication [16]. Verapamil is detectable in breast milk, but it is unlikely to cause adverse effects in the breastfed child [16].

Lithium crosses the placenta easily and exposure to the fetus is considerable. The use of lithium during pregnancy has been associated with a range of maternal and fetal complications [36,55]. Some, but not all, studies have found that lithium was associated with an increased risk of fetal death and congenital malformations, particularly cardiac anomalies [36]. However, the long-term psychomotor development of the child appeared to be normal [36]. Considerable amounts of lithium pass into breast milk, and side effects have been reported [15]. Lithium is generally considered contraindicated in pregnancy and breastfeeding. However, it may be the only efficient option in a few women with severe disorder, because other, less harmful measures are ineffective (Table 3). For these women, clinicians should consider referral for fetal echocardiography and monitor the lithium concentration frequently [36].

*In utero* exposure to topiramate is associated with an increased risk of congenital malformation and growth restriction [31,32] and possibly fetal death/spontaneous abortions [32]. Patients with cluster headache should not use topiramate during pregnancy unless other options are ineffective (Table 3). If topiramate use cannot be avoided, clinicians should monitor serum concentrations because they often drop during pregnancy and subsequently increase after delivery. During lactation, less than 200 mg/daily topiramate results in insignificant serum levels in the breastfed infant. Thus, topiramate

is considered compatible with breastfeeding of healthy full-term children, after the newborn period [15].

Galcanezumab, an anti-CGRP antibody, has not been investigated for safety during human pregnancy. Animal studies have not reported adverse reproductive toxic effects [56]. Human immunoglobulin (IgG) is known to cross the placental barrier, but no specific safety issues have so far emerged with use of anti-CGRP antibodies in pregnancy [57]. As real-life data are still limited, it is preferable to avoid the use of galcanezumab during pregnancy as a precautionary measure. This is in line with the recommendation in the summary of product characteristics [58]. Experimental studies have shown that CGRP-dependent vascular relaxation was compromised in preeclamptic pregnancies, and there is a theoretical risk that CGRP antibodies may cause placental vascular impairment [59]. We lack information on the effect of anti-CGRP antibodies on breastfeeding. Human IgG is excreted in breast milk during the first days after birth, but the concentrations sharply decline soon afterwards. Therefore, after this period, due to poor transfer and low oral bioavailability, anti-CGRP antibodies are unlikely to cause adverse effects in a full-term healthy child. No safety issues have emerged for galcanezumab in lactation so far [57]. If clinically needed, galcanezumab could be considered in breastfeeding women after the first postpartum week.

Valproate is related to approximately 11% of congenital malformations. Studies have shown that compared to unexposed children, 30–40% of children exposed to valproate have developmental problems, including lower IQ, and autism [31,60]. Therefore, the European Medicines Agency has issued warnings against the use of valproate in women of childbearing age, unless all other options are ineffective. Moreover, they imposed a pregnancy prevention plan to avoid pregnancy exposures [60]. Women with no other options must use safe contraception and be very well informed. Valproate must be discontinued when a pregnancy occurs unexpectedly. The transfer of valproate to breastmilk is very low; thus, it can be used during lactation [61]. However, breastfeeding women must use effective contraceptives to avoid pregnancy.

Most observational studies on gabapentin have found no significant increases in congenital malformations or pregnancy complications [31]. Among women who previously responded to gabapentin, it might be an acceptable treatment option when prophylaxis during pregnancy is needed. No studies have reported side effects among breastfed infants of women using gabapentin, but safety documentation is limited [15].

Theoretically, exogenous use of melatonin could interfere with the natural wake–sleep cycle of the unborn and breastfeeding child, but no data are available to support or refute this concern [5,15].

## Surgical interventions

Two case reports describe four successful pregnancies among two women who received occipital nerve stimulation during their

pregnancies for cluster headache and chronic paroxysmal hemicrania [62,63]. No data are available on the safety of SPG stimulation during pregnancy. We do not recommend these invasive procedures during pregnancy because they require general anesthesia and require an observation and planning period to document a refractory situation that is unlikely to be compatible with the duration of a pregnancy. However, among patients who had stimulators before a pregnancy, there is no reason to believe that the local electrical stimulation should pose any risk. We do not recommend botulinum toxin blockade of the SPG in pregnancy. Even though studies of botulinum toxin administered for other indications have not shown harmful effects in pregnancy and lactation [64], the SPG-blocking procedure has not been performed in pregnant women.

## PAROXYSMAL HEMICRANIA

Paroxysmal hemicrania attacks are generally so short that acute drugs cannot provide benefit [2]. In the nonpregnant population, prophylactic indomethacin is the standard treatment. For patients who cannot tolerate this treatment due to gastrointestinal side effects, clinical guidelines propose selective cyclooxygenase-2 (COX-2) inhibitors, such as celecoxib, or treatments that are effective in other TACs, such as verapamil, topiramate, or SPG- and greater occipital nerve blocks [2]. Unfortunately, the response rates to these treatments are highly variable [65,66].

In the pregnant population, most but not all studies found that indomethacin did not reduce fertility, increase the risk of fetal loss, or increase the risk of malformations [67,68]. However, after the first trimester, indomethacin can cause restriction or premature closure of the ductus arteriosus, which can lead to pulmonary hypertension and neonatal death [68]. Case reports have also found that indomethacin was associated with preeclampsia deterioration, oligohydramnios, renal impairment, necrotizing enterocolitis, periventricular leucomalacia and intracranial hemorrhage [32,68]. The FDA has issued a warning against use of nonsteroidal anti-inflammatory drugs after week 20 of pregnancy due to risk of oligohydramnios and fetal renal failure [69]. COX-2 inhibitors appeared to cause the same side effects as indomethacin in pregnant women [68,70].

Several studies have found that low levels of indomethacin could be detected in breast milk in mothers that received up to 300 mg daily, but no side effects have been reported in breastfed infants [68]. Indomethacin is also administered directly to infants for therapeutic purposes, for example, to treat patent ductus arteriosus in the newborn.

## HEMICRANIA CONTINUA

Patients with hemicrania continua generally show a complete response to therapeutic doses of indomethacin. For patients who cannot tolerate indomethacin, other options include COX inhibitors,

melatonin, gabapentin, verapamil, topiramate, greater occipital nerve blocks, onabotulinumtoxin injections, and occipital nerve stimulation [2,71]. The efficacies of these treatments are poorly documented [66]. Hemicrania continua during pregnancy and lactation is managed with the same approaches described for paroxysmal hemicrania.

## SUNCT/SUNA SYNDROME

Attacks of SUNCT/SUNA are so short that acute drugs cannot provide benefit. Consequently, the main treatment is prophylactic lamotrigine [72]. The second choice is gabapentin or topiramate [66]. However, lamotrigine or gabapentin should be preferred during pregnancy. Lamotrigine treatment during pregnancy has been extensively studied. For prepregnancy doses below 325 mg/day it has shown a good safety profile regarding congenital malformations. In addition, long-term cognitive outcome in children exposed *in utero* does not seem to be affected [31]. During pregnancy, most women require an increase in the dose to avoid treatment failure [31]. To avoid toxicity, the dose must be reduced to prepregnancy levels over the first 2–3 weeks after delivery [73]. Lamotrigine passes into breast milk in significant amounts. Several studies have reported adverse drug reactions in breastfed neonates when the maternal dose was not reduced post partum. Risks are particularly high when the infant is premature, underweight or ill [15].

## CONCLUSION

The choice of TAC treatment for women in childbearing age, and in pregnant and breastfeeding women can be a challenge. The clinician must often choose between treatment options with good efficacy but scarce safety documentation, and those with less documented efficacy but better safety profiles. The medical decisions must rest on thoroughly informed and documented consent. Pregnancy planning should start early in women of childbearing age with TACs. The safety of each drug varies for the different trimesters. Most treatment options are compatible with breastfeeding. Due to the debilitating nature of TACs, effective treatment is important both during pregnancy and lactation. Tapering off prophylactic drugs due to pregnancy plans can leave some women severely disabled. In our experience, this can potentially result in an increase in rescue drug use, stress, inadequate nutrition, social deprivation, and depressive symptoms. Moreover, these factors can adversely influence the course of pregnancy. Due to the disabling nature of TACs, these patients require clinical attention before, during, and after pregnancy. In addition, they often require a multidisciplinary approach.

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## AUTHOR CONTRIBUTIONS

**Marte Helene Bjørk:** Conceptualization (lead); Data curation (lead); Investigation (lead); Methodology (lead); Project administration (lead); Writing – original draft (lead); Writing – review and editing (lead). **Espen Saxhaug Kristoffersen:** Investigation (supporting); Supervision (supporting); Validation (supporting). **Erling Tronvik:** Investigation (supporting); Supervision (supporting); Validation (supporting). **Hedvig Marie Egeland Nordeng:** Conceptualization (supporting); Data curation (equal); Investigation (equal); Methodology (lead); Supervision (lead); Validation (lead); Writing – original draft (supporting); Writing – review and editing (supporting).

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