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EFFICACY AND SAFETY OF MAGNESIUM IN MIGRAINE PROPHYLAXIS IN PREGNANCY

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ABSTRACT

Background: Migraine is a common neurological disorder affecting women of reproductive age. Preventive treatment during pregnancy is challenging because many pharmacological agents are associated with potential fetal risks. Magnesium has been proposed as a safer alternative for migraine prophylaxis; however, evidence regarding its efficacy and safety during pregnancy remains limited.

Methods: We conducted a systematic literature search using PubMed, Cochrane Library, and Google Scholar for studies evaluating the efficacy and safety of magnesium in migraine prophylaxis during pregnancy. Of 138 records identified, four studies met the inclusion criteria, comprising two systematic reviews, one retrospective cohort study, and one survey. Data on study characteristics, efficacy outcomes, maternal adverse effects, and fetal outcomes were extracted and analyzed.

Results: The available evidence demonstrated inconsistent findings regarding the efficacy of magnesium for migraine prophylaxis during pregnancy. One retrospective cohort study reported significant reductions in migraine frequency, severity, and associated symptoms following magnesium therapy, whereas systematic reviews found insufficient evidence to support its routine use. Magnesium was generally well tolerated, with only mild gastrointestinal adverse effects reported. Although one systematic review suggested a possible association with neonatal mortality, this finding was based on indirect evidence and should be interpreted cautiously due to methodological limitations and potential confounding.

Conclusions: Current evidence is insufficient to recommend magnesium as a standard prophylactic treatment for migraine during pregnancy. While magnesium appears to have a favorable maternal safety profile and may benefit selected patients, well-designed prospective randomized controlled trials are needed to establish its efficacy and fetal safety.

KEYWORDS: Magnesium, Migraine, Pregnancy, Migraine prophylaxis, Safety, Systematic review, Maternal outcomes, Fetal outcomes.

INTRODUCTION

Migraine, as defined by the International Headache Society, is a neurological disorder characterized by recurring headaches with distinct features. These headaches are often unilateral, pulsating, and accompanied by symptoms such as nausea, and heightened sensitivity to light, sound, and movement [1]. While migraines are primarily influenced by genetic factors, specific triggers—ranging from external factors like weather changes to internal ones like disrupted sleep patterns—can precipitate attacks [2]. Migraine predominantly affects women, with prevalence rates three times higher than in men, peaking at 27% around the age of 41 during the childbearing years. Although migraine does not appear to impact fertility or pregnancy outcomes, its course is notably influenced by the physiological changes associated with pregnancy [3, 9].

Preventing migraines becomes more challenging during pregnancy, as many preventive medications carry potential risks of complications [4, 10-11]. Clinicians must rely on a narrow range of therapeutic options, including magnesium, which has gained attention for its potential efficacy and safety profile in this population.

Despite anecdotal evidence and limited studies suggesting its benefits, the use of magnesium as a migraine prophylactic remains controversial, necessitating a thorough examination of its efficacy and safety during pregnancy. This systematic review aims to consolidate existing evidence on the role of magnesium in migraine prophylaxis among pregnant patients.

METHODS

Protocol and registration:

This systematic review was conducted following a pre-established protocol and is reported according to the PRISMA (Preferred Reporting Items for Systematic reviews and Meta Analyses) guidelines.

Eligibility criteria

Articles that reported on migraine prophylaxis during pregnancy, including clinical, pharmacological, and safety outcomes, were considered for inclusion. Eligible study designs included observational studies such as case series, case-

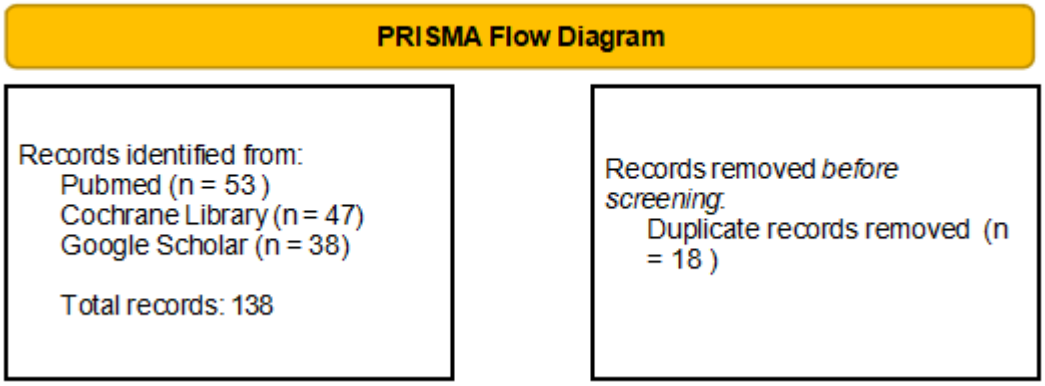
control studies, cohort studies, as well as interventional studies assessing the efficacy and safety of migraine preventive treatments. Literature reviews, along with their reference lists, were also screened for relevant studies. Studies with fewer than 30 subjects were excluded unless they specifically addressed severe complications or rare adverse events related to migraine prophylaxis. Editorials, viewpoints, and animal or in vitro studies were excluded, unless they contributed to the understanding of putative mechanisms underlying the effects of migraine treatments in pregnancy.
Additionally, the articles that focused on magnesium alone, migraine prophylaxis in non-pregnant patients or treatment of acute migraine in pregnancy were excluded.

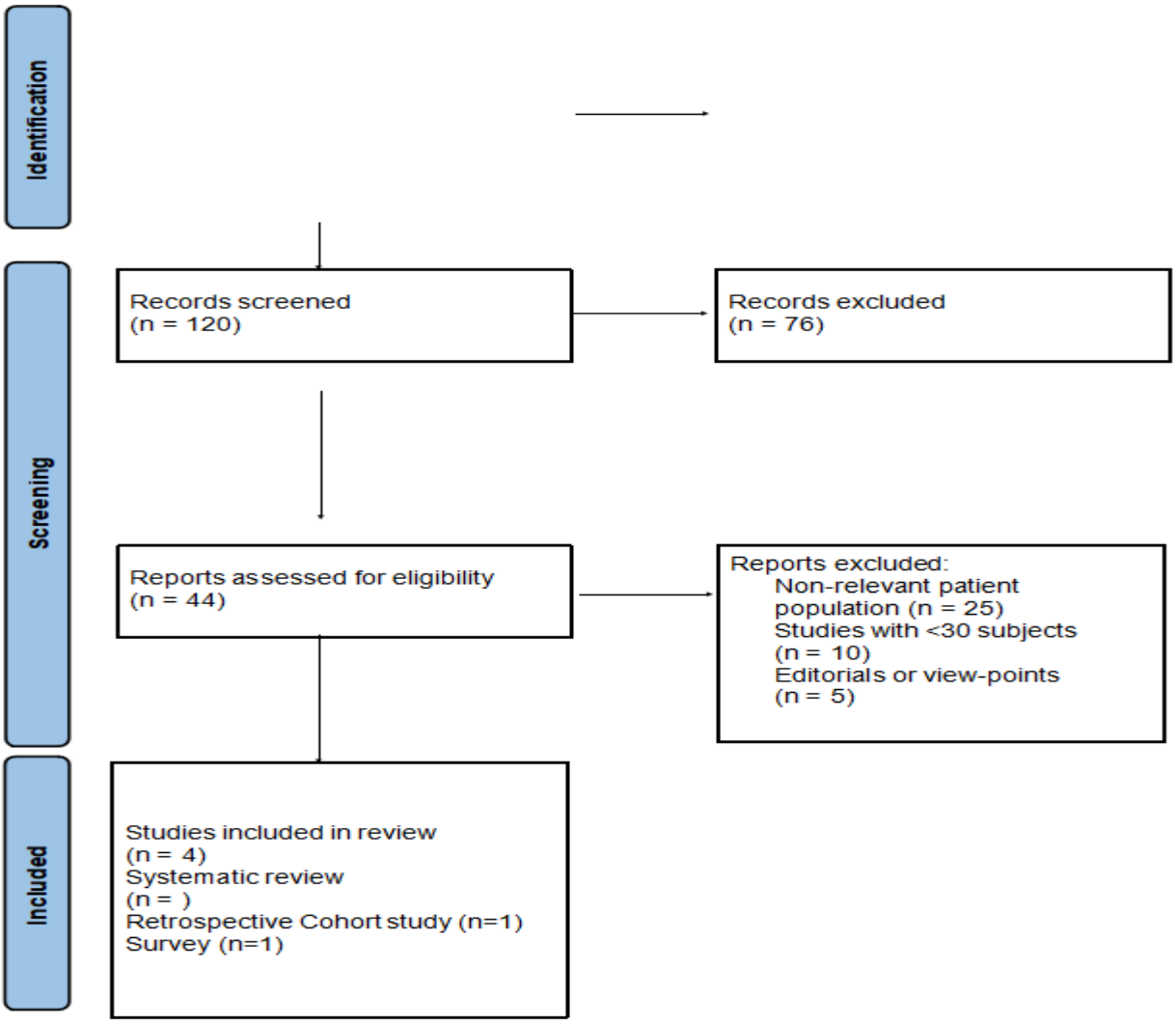
Search Strategy
Relevant studies were identified through electronic searches of PubMed, Cochrane Library, and Google Scholar. A snowballing method, searching the bibliographies of retrieved articles, was also applied to identify potentially relevant studies. The search was conducted for articles published within the past 5 years, with no language restrictions. Databases were searched using terms related to (1) migraine prophylaxis or (2) magnesium sulphate and (3) pregnancy. The following search terms were used in PubMed: ("migraine prevention" OR "migraine prophylaxis" AND "magnesium" AND "pregnancy" or "gestation" or "maternal health" or "foetal outcomes") and ("efficacy" or "safety" or "side effects" or "adverse outcomes" or "maternal health" or "foetal health" or "birth outcomes" or "complications").

Study selection
Two reviewers initially screened the titles and abstracts of all retrieved records to identify duplicates. Full-text versions of potentially relevant studies were then reviewed independently to determine their eligibility for inclusion. Any discrepancies between the reviewers were resolved through discussion and consensus. In cases of duplicate data from the same patient population, the information was consolidated to ensure complete and accurate data.

Data extraction
The following data were extracted from the selected studies: study details (title, authors, publication date, publication type, study location, and sample size), characteristics of the population, and any correlations with migraine prophylaxis during pregnancy. Two authors independently extracted the data, and any discrepancies were resolved by a third author who also checked for data duplication. For quality assessment, two authors independently evaluated the diagnostic criteria for migraine, the methods used to confirm efficacy and safety, and the specific outcome measures reported in the studies. The final manuscript was checked by three authors.

Study identification - PRISMA flow diagram – Figure 1.





RESULTS

Identification of Relevant Study Data

A total of 44 full-text publications were assessed for eligible content. The majority (n= 40) was excluded, mainly due to non-relevance to the topic. A total of 4 results, consisting of 2 systematic reviews, 1 survey and 1 retrospective cohort study, were included. The PRISMA flow diagram for the review has been elaborated in Figure 1. Results have been tabulated in Table 1.

Efficacy of Magnesium in prevention of migraine

The systematic review by Saldanha et al. [5] offers a comprehensive yet inconclusive perspective. While no prophylactic measures, including magnesium, were definitively efficacious in preventing headaches, the inclusion of all primary headaches in their analysis may have diluted migraine-specific findings.

The retrospective cohort study by Mazza et al. [7] provides more optimistic data, demonstrating significant improvement in migraine frequency, severity, and associated symptoms with magnesium treatment. However, the lack of a placebo control and the absence of standard protocols for magnesium and riboflavin combination therapy highlight methodological limitations.

The Updated Canadian Headache Society guidelines [6] do not recommend magnesium as a prophylactic medication for migraine in pregnancy, and only recommend it strongly for episodic migraines.

Safety outcomes of Magnesium

Saldanha et al [5] shows that magnesium sulphate was associated with neonatal deaths, but no maternal adverse effects. However, this warrants cautious interpretation, as these findings are based on indirect evidence and may not account for confounding factors.

Mazza et al [7] also noted mild gastro-intestinal side effects, none warranting withdrawal of the drug during the course of the study.

Table 1. The results are arranged from the strongest available evidence to the weakest

Reference	Study type	Patient group and intervention	Efficacy outcome	Safety outcome	Study strength & weakness
Saldanha et al	Systematic review	Total of 14,185 patients were considered based on: **- Direct evidence:** Primary studies, that evaluate the efficacy of prophylactic measures for all primary headaches in pregnancy **- Indirect evidence:** Systematic reviews, that elucidate the harm caused by prophylactic agents like Topiramate, propranolol, etc used for other indications in pregnancy.	**No** prophylactic measure, including magnesium, were found to be efficacious in preventing headaches.	Data from a systemic review showed magnesium was associated with **neonatal death** but not with adverse maternal side effects.	- The systematic review included all primary headaches which could have skewed the results. - Magnesium was only studied in one systematic review, hence insufficient to draw conclusions
		1 systemic review			
Medrea et al (Updated Canadian Headache Society migraine prevention guidelines with systematic review and meta-analysis)	Systematic review and meta-analysis	A total of 25 prophylactic medications were studied in the systematic review and meta-analysis	Magnesium is recommended in migraine prophylaxis due to its low side effect in episodic migraine. However, it is not recommend	To be used with caution in renal failure and diarrhea	Strong recommendation in episodic migraine. Not enough evidence to suggest its use in pregnancy or lactation.
Mazza et al	Retro-spective cohort study	A total of 203 patients were randomized to 2 groups: - Group 1: 117 patients received Magnesium oxide alone - Group 2 : 86 patients received magnesium oxide plus riboflavin Outcomes assessed were pre- and post-treatment migraine frequency, migraine severity using a visual analog scale, and migraine duration. Secondary outcomes include associated migraine symptoms. The most frequent	Both groups showed statistically significant improveme nt in both primary and secondary outcomes with a significant p-value of <0.01. The combination regimen was more often used in patients with higher pre-treatment migraine severity	3 patients in the study experienced mild gastrointest in al side effects none of them warranting withdrawal of medication	The major strength is the specific nature of the question. No standard protocol was followed as to when the medications were added and no set criteria was followed as to when riboflavin was added. Both groups had magnesium as treatment. No placebo control was studied to document the efficacy of magnesium in migraine prophylaxis in pregnancy.

Verhaak et al	Survey	92 women's health care providers (most of them specializing in obstetrics and gynecology) were surveyed on practice principles in migraine including counseling, treatment of acute attacks, and preventive therapy.	24/92 (26%)doctor s indicated that counseling on dealing with migraine was done during pregnancy as well as during the pre-pregnancy period.	Safety measures were not studied in the survey	Survey being one of the weakest epidemiological studies, does not contribute much to the topic in question, yet it gives us an idea of existing practice measures which are prevalent among treating physicians.
			All 92(100%) doctors who participated were comfortable prescribing paracetamol for acute managemen t followed by caffeine.		
			Among preventive measures, 63(69%) doctors felt comfortable prescribing		

DISCUSSION

The findings from this systematic review highlight the nuanced and often conflicting evidence surrounding the use of magnesium sulphate as a prophylactic treatment for migraines during pregnancy.

The findings of this systematic review illustrate the complexities of using magnesium sulphate for migraine prophylaxis during pregnancy. While magnesium is a promising option due to its affordability, availability, and potential safety, the evidence base remains insufficient to firmly support its routine use.

The studies included in this review reflect divergent conclusions about magnesium's role in migraine prophylaxis. The systematic review by Saldanha et al. [5] provides a broad but inconclusiveperspective, suggesting that no prophylactic measure, including magnesium, showed consistent efficacy. This underscores the challenge of deriving meaningful conclusions from studies that combine diverse headache types, diluting the migraine-specific evidence. On the other hand, the retrospective cohort study by Mazza et al. [7] points to significant reductions in migraine frequency and severity with magnesium treatment. However, the study's lack of a placebo control and inconsistencies in treatment protocols limit the reliability of its findings.

Safety considerations, a critical aspect of migraine management during pregnancy, were generally reassuring across the included studies. Mild gastrointestinal side effects reported by Mazza et al. [7] align with magnesium's known safety profile. However, the association between magnesium and neonatal deaths, as noted in Saldanha et al. [6], raises concerns that warrant further exploration.

This finding, based on indirect evidence, may be influenced by confounding factors such as maternal comorbidities, concurrent therapies, or study design issues.

Current clinical guidelines, such as those from the Canadian Headache Society [6], do not advocate magnesium usage for migraine prevention, instead preferring betablockers (such as propranolol and metoporolol), onobotulinum toxin A and anti-CGRP monoclonal antibodies.

Interestingly, the survey by Verhaak et al. [8] reveals a disconnect between evidence and clinical practice. A majority of physicians reported comfort prescribing magnesium for migraine prophylaxis during pregnancy, suggesting that clinicians may rely on perceived safety and anecdotal benefits in the absence of strong evidence. This highlights a gap between research and practice, emphasizing the need for further studies to align clinical decisions with high-quality evidence.

In summary, magnesium's role in migraine prophylaxis during pregnancy remains uncertain due to inconsistent efficacy data and limited safety evidence. The inconclusive findings call for cautious optimism and highlight the urgent need for well-designed, randomized controlled trials specifically targeting pregnant populations.

CONCLUSION

This systematic review highlights the lack of robust, conclusive evidence supporting the use of magnesium for migraine prophylaxis during pregnancy. Although magnesium's potential benefits and relatively favourable safety profile make it an attractive option, the available studies are limited by methodological issues, indirect evidence, and a paucity of pregnancy-specific data.

Clinicians should exercise caution when recommending magnesium and consider it primarily in cases where other preventive measures are ineffective or contraindicated. Future research should focus on well-designed, prospective studies with adequate sample sizes to evaluate the efficacy and safety of magnesium specifically for migraine prophylaxis in

pregnant women. Addressing these gaps in knowledge will help inform clinical decision-making and improve outcomes for this vulnerable population.

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