Updates on Adverse Outcomes of Migraine in Pregnancy: A Systematic Review

Yousef Mohammed Elamin Ali Mohammed, MD* Rammas Abdullah Shawkhan, MD** Aljohrah M. AL Hunaif, MD*** Muhannad Abdullah Alshahrani, MD**** Ali Ahmed Ali Almuntashiri, MD***** Abdulaziz Y. Alshahrani, MD****** Naif Yahya Alshahrani, MD****** Halah Abdullah Alzayd, MD****** Reema S. Alqhatani, MD****** Alhanouf Abdullah Alshahrani, MD****** Fatima Abdoh M Abudiah, MD****** Kholoud Ali Alrobaie, MD******* Khalid Mohammed Alqahtani, MD*******

ABSTRACT

Background: The majority of women who experience migraines are reproductive-age women. Changes in female hormones, particularly estrogen levels, have an impact on it.

Objectives: This systematic review aims to study the recent updates regarding the adverse outcomes of migraine with pregnancy.

Methods: PubMed, SCOPUS, Web of Science, and Science Direct were systematically searched for relevant literature. Rayyan QRCI was employed throughout this comprehensive process.

Results & interpretation: Our results included nine studies with a total of 205674 women. There was a higher chance of negative pregnancy outcomes with migraine, according to all of the analyzed trials. Common negative outcomes of migraine include preeclampsia, stroke, and pregnancy-related hypertension. Preterm birth, low birth weight, and miscarriage were also included as negative pregnancy outcomes in women with migraine. Additionally, we found that women suffering from migraines experienced mixed depression and anxiety symptoms during pregnancy.

Keywords; Migraine; Headache; Pregnancy; Adverse outcomes; Systematic review.

INTRODUCTION

The debilitating chronic neurologic illness known as migraine is linked to significant social, economic, and psychological hardships as well as declines in health-related quality of life (HRQoL) [1, 2]. About 14% of persons experience migraines on average, with a midlife peak and a significant female preponderance [3]. A third of migraine sufferers have no more than four monthly headache days, and 7% have more than fifteen [4]. While acute therapy is designed to relieve pain and restore function when attacks occur, recent publications have highlighted the potential of preventing illness progression [5, 6]. The typical goal of preventive headache treatments is to lower attack frequency and intensity.

The frequency, severity, symptom profiles, and associated handicap of migraines fluctuate throughout time depending on the individual [7, 8]. However, some people's illness states will continue to worsen over time (i.e., advance). The phenomena of migraine illness development, as well as the risk factors and preventative measures that may be changeable and affect the course of the disease, should be understood by clinicians who treat migraine. Primary care practitioners and other clinician specialists, such as neurologists, must be trained to manage migraine, given the prevalence of the condition and the high proportion of patients who seek treatment in the primary care context [9].

Preeclampsia (PE) in pregnancy has been linked to migraine development, which has been reported to occur more frequently in women of reproductive age [10]. In turn, a history of PE increases the likelihood of developing CVD in later life [11]. According to inconsistent findings, it is unclear if a migraine history affects other unfavourable pregnancy outcomes linked to vascular dysfunction, such as preterm birth, growth limitation, or placental abruption [12, 13].

When determining a patient's risk profile for migraine progression, it's crucial to work with them to design a management strategy. Clinicians need to pinpoint the variables that can be changed and are most likely to enhance the patient's quality of life. Therapy accomplishments should be viewed as a progression of benchmarks, each of which serves as the basis for the following stage of achieving optimal therapy. This systematic review aims to study the recent updates regarding the adverse outcomes of migraine with pregnancy.

METHODOLOGY

The PRISMA (Preferred Reporting Items for Systematic Reviews and Meta-Analyses) guidelines were followed in conducting this systematic review [20].

* Obstetrics and Gynecology Consultant, Abha maternity and children hospital MOH bha, Saudi Arabia.
E-mail: y_elamin@msn.com
** Medical Intern, King Khalid University, Abha, Saudi Arabia.
*** Student, King Khalid University, College Of Medicine, Abha-Saudi Arabia.
**** Family Medicine Resident, Abha Central Hospital (MOH), Abha, Saudi Arabia.
***** GP, Um Sarar Primary Health Care Center, Khamis Mushait, Saudi Arabia.
****** Medical Intern, Faculty of Medicine, King Khalid University, Abha, Saudi Arabia.
******* Obgyn Resident, Armed Forces Hospital, Khamis Mushait, Saudi Arabia.

Study Design and Duration

October 2023 marked the start of this systematic review.

Search strategy

To discover the pertinent literature, a thorough search was conducted across four main databases: PubMed, SCOPUS, Web of Science, and Science Direct. We limited our search to English and considered each database's specific needs. The following keywords were transformed into PubMed Mesh terms and used to locate the pertinent studies; "Migraine," "Pregnancy," "Pregnant," "Outcomes," and "Adverse events." The Boolean operators "OR" and "AND" matched the required keywords. Publications with full English text, available free articles, and human trials were among the search results.

Selection criteria

We considered the following criteria for inclusion in this review:

- Studies that discussed adverse outcomes of migraine in pregnancy.
- Studies conducted between 2019 and 2023.
- Only human subjects.
- English language.
- Free accessible articles.

Data extraction

The search technique's output was double-checked using Rayyan (QCRI) [21]. By modifying the combined search results with a set of inclusion/exclusion criteria, the researchers evaluated the relevance of the titles and abstracts. Each paper that met the requirements for inclusion underwent a careful examination by the reviewers. The authors talked about methods for resolving disputes. The approved study was uploaded using a data extraction form already created. The authors extracted data about the study titles, authors, study year, country, participants, gender, and main outcomes. A separate sheet was created for the risk of bias assessment.

Strategy for data synthesis

Summary tables were created using data from relevant studies to provide a qualitative assessment of the findings and study components. After the data for the systematic review were gathered, the most efficient approach for utilizing the data from the included study articles was chosen.

Risk of bias assessment

The ROBINS-I risk of bias assessment technique for non-randomized trials of therapies was used to evaluate the caliber of the included studies [22]. The seven themes that were assessed were confounding, participant selection for the study, classification of interventions, deviations from intended interventions, missing data, assessment of outcomes, and choice of the reported result.

RESULTS

Search results

A total of 366 study articles resulted from the systematic search, and 98 duplicates were deleted. Title and abstract screening were conducted on 268 studies, and 223 were excluded. 45 reports were sought for retrieval, and 4 articles were retrieved. Finally, 41 studies were screened for full-text assessment; 18 were excluded for wrong study outcomes, 10 for the wrong population type, and 4 articles were letters to the editors. Nine eligible study articles were included in this systematic review. A summary of the study selection process is presented in **Figure 1.**

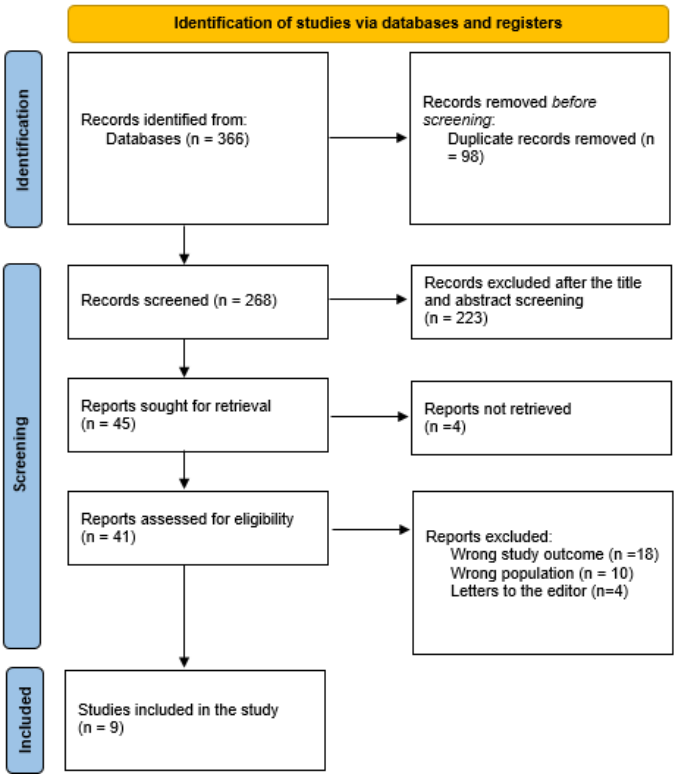

Figure 1. PRISMA flowchart summarizes the study selection process.

Characteristics of the included studies

Table (1) presents the sociodemographic characteristics of the included study articles. Our results included nine studies with a total of 205674 women. Five studies were retrospective in nature [18, 22-25], and four prospective in nature [17, 19-21]. Five studies were conducted in the USA [18, 19, 22, 23, 25], one in South Korea [17], one in the UK [20], one in Sweden [21], and one in Denmark [24].

Table 1. Presents the sociodemographic characteristics

Study	Study design	Country	Participants	Mean age (years)
Ishii et al., 2020 [17]	Prospective cohort	South Korea	607	45.3 ± 13.2
Myers et al., 2019 [18]	Retrospective cohort	USA	269191	NM
Miller et al., 2022 [19]	Prospective cohort	USA	1752	NM
Crowe et al., 2023 [20]	Prospective cohort	UK	132623	28
Welander et al., 2021 [21]	Prospective cohort	Sweden	4831	NM
Hamilton & Robbins 2019 [22]	Retrospective cohort	USA	100	25–34
Bandoli et al., 2020 [23]	Retrospective cohort	USA	26440	NM
Skajaa et al., 2019 [24]	Retrospective cohort	Denmark	22841	28-35
Purdue-Smithe et al., 2022 [25]	Retrospective cohort	USA	16480	NM

Table 2. Clinical characteristics and outcomes of the included studies

Study		Main outcomes	ROBIN-I
Ishii et al., 2020 [17]	To assess how migraine affects women's plans for getting pregnant	Pregnancy planning is heavily impacted by migraine, particularly for younger, menstrual, chronic, and depressed women. Those who want to postpone getting pregnant think their pregnancy will be challenging because their migraines worsen. These ideas counter the data showing that migraines frequently improve during pregnancy. To help with educated decisions regarding pregnancy planning, it is crucial that migraine-affected women who are of reproductive potential get education about the potential effects of migraine on pregnancy.	Moderate
Myers et al., 2019 [18]	To investigate the relationship between migraine and pregnancy, the postpartum period, and the prevalence of related comorbidities in this population.	Pregnancy had a decrease in migraine hospital admission rates compared to postpartum. Preeclampsia, stroke, and premature delivery are more comorbidities linked to hospitalization for migraine during pregnancy.	Moderate
Miller et al., 2022 [19]	To assess how migraine affects pregnancy	Self-reported migraine headaches were linked to a 26% increased risk of unfavourable pregnancy outcomes, mostly caused by hypertensive disorders of pregnancy and both medically and spontaneously premature birth. It's possible that migraines are a lesser-known risk factor for unfavourable pregnancy outcomes.	High
Crowe et al., 2023 [20]	To investigate the relationship between the diagnosis and management of migraine and the risk of HDOP utilizing a sizable population-based cohort and prospectively collected data.	Pregnancy-related hypertension problems were linked to an elevated incidence of migraine history (RR = 1.17, 95% CI: 1.09-1.26). A pre-pregnancy migraine that persisted into the first trimester was associated with the highest risk (RR = 1.84, 95% CI: 1.35-2.50). Compared to non-migraineurs, taking migraine medicine was linked to an increased incidence of hypertensive disorders during pregnancy (RR = 1.50, 95% CI: 1.15-1.97). The findings of this study suggest that migraine may be a risk factor for pregnancy-related hypertension problems.	Moderate
Welander et al., 2021 [21]	In a population-based cohort of women with and without a history of migraines, symptoms of sadness and anxiety were examined independently and in combination at three stages during and after pregnancy.	A migraine before becoming pregnant may increase your likelihood of experiencing anxiety symptoms in the middle of your pregnancy as well as mixed symptoms of depression and anxiety in the latter stages. At various times during the peripartum period, several pathophysiological mechanisms may be to blame for the relationship between migraine and depression and/or anxiety.	Moderate
Hamilton & Robbins 2019 [22]	To evaluate the immediate care given to pregnant patients who report to a hospital with migraine.	There were differences in the types of drugs used and the order in which they were administered, even though most pregnant women with acute migraines received treatments considered generally safe during pregnancy. Opioids and butalbital, two acute therapies with low teratogenic risk, were regularly utilized, whereas nerve blocks, IV fluid boluses, and triptans, which may have low teratogenic risk, were used less frequently.	Moderate
Bandoli et al., 2020 [23]	To investigate the risk of stroke in pregnant women with migraine	About 25% of the increased risk of maternal stroke linked to migraine was caused by hypertensive conditions. Despite the rarity of strokes, the associated morbidity and death make it important to find targets for modifiable interventions.	High
Skajaa et al., 2019 [24]	To assess how migraine affects pregnancy	Maternal migraine was linked to an increased risk of several adverse pregnancy outcomes in the mother, as well as birth, neonatal, and postnatal neurological outcomes in children, which include pregnancy-associated hypertension conditions, miscarriage, low birth weight, and preterm birth, in this large population-based cohort study that included all clinically identified pregnancies.	Moderate
Purdue-Smithe et al., 2022 [25]	To investigate the long-term relationships between pre-pregnancy migraine, aura phenotype, and the likelihood of unfavourable pregnancy outcomes.	Women with pre-pregnancy migraine (11%) had a greater risk of preterm birth (RR=1.17; 95% CI=1.05-1.30), gestational hypertension (RR=1.28; 95% CI=1.11-1.48), and preeclampsia (RR=1.40; 95% CI=1.19-1.65) than women without. Pre-pregnancy migraine was not linked to low birthweight (RR=0.99; 95% CI=0.85-1.16) or gestational diabetes (RR=1.05; 95% CI=0.91-1.22). Compared to women who did not have pre-pregnancy migraine, the risk of preeclampsia was slightly higher in women who had migraine with aura (RR=1.51; 95% CI=1.22-1.88) than in women who did not have migraine with aura (RR=1.29; 95% CI=1.04-1.61). Other poor pregnancy outcomes were not affected by aura phenotype.	Moderate

Table (2) presents the clinical characteristics. All of the included studies reported an increased risk of adverse pregnancy outcomes with migraine. Preeclampsia, stroke, and pregnancy-associated hypertension were common adverse effects due to migraine [18, 19, 24, 23]. Miscarriage, low birth weight, and preterm birth were also reported as adverse outcomes of pregnancy in women with migraine [18, 24]. Additionally, these women experienced mixed depression and anxiety symptoms [21].

DISCUSSION

Pregnancy-related headaches should always be carefully assessed because there could be a serious underlying pathology that has to be treated. The most frequent type of headache during pregnancy is a migraine, although secondary headaches should be ruled out. Most women with a history of migraine will identify the headache as an attack, but if the headaches are new or sudden onset, last longer than usual, have a different character, or are accompanied by other symptoms like fever, postural changes, or focal neurological deficits, these symptoms should be taken seriously, and further testing is necessary [26, 27].

The shifting levels of oestrogens have an impact on the prevalence and severity of migraine. Only 5% of women who have previously experienced this headache type—migraine with aura or monthly migraine—report symptoms getting worse during pregnancy, while 60–70% of these women report improvements [28, 29]. Because of the frequent signs of hyperemesis gravidarum, migraine attacks can get worse throughout the first trimester. Women report symptom improvement throughout the second and third trimesters, when estrogen levels rise, with the exception of those who have a history of migraine with aura. Additionally, current literature describes migraine with aura making its first appearance during the first trimester [30]. In addition, women may experience an aggravation of symptoms in the first 3 to 6 days following birth as a result of environmental factors, such as a change in status (particularly for primigravida), sleep disturbance, stress, irregular meals, and a decline in estrogen levels. According to certain studies, breastfeeding in the postpartum may prevent or delay migraine attacks that are associated to the anovulation mechanism [31, 32].

This study reported that all of the included studies reported an increased risk of adverse pregnancy outcomes with migraine. Preeclampsia, stroke, and pregnancy-associated hypertension were common adverse effects due to migraine [18, 19, 24, 23]. Preterm birth, gestational hypertension, and preeclampsia are all more likely to occur in pregnant women who have previously experienced migraine attacks. Studies examining the outcome of pregnancy in those with this headache have found that it is associated with a higher prevalence of hypertensive disorders of pregnancy whether or not it is treated. The presence of migraines increases the risk of preeclampsia, stroke-related to pregnancy, and secondary headaches. A new headache should be suspiciously checked by an MRI without contrast because gadolinium should be avoided during pregnancy, along with any neurological symptoms, fever, or hypertension [33, 34].

We also found that miscarriage, low birth weight, and preterm birth were also reported as adverse outcomes of pregnancy in women with migraine [18, 24]. This was in line with **Aukes *et al.,*** who reported that an increased risk of unfavourable pregnancy outcomes, such as PE and LBW, is significantly linked to a history of migraine. We speculate that common pathophysiology caused by underlying preclinical cardiovascular risk in migraine-prone women may contribute to pregnancy-related complications [35].

Patients who already had migraines did not pose a concern about the pregnancy's development or to the potential rise in fetal abnormalities. Instead, it raises the risk of vascular disorders, early birth, and low birth weight during pregnancy. There is a higher risk of cerebral palsy and stillbirth in migraine sufferers who develop preeclampsia [36]. Sleep difficulties and migraines may go hand in hand [37]. Hyperemesis during pregnancy may occur more frequently. The risk of vascular problems, stroke, thromboembolic illness, and heart disease is raised in pregnant women who suffer from migraines because of the increased risk of preeclampsia/eclampsia [38].

Additionally, we found that women suffering from migraines experienced mixed depression and anxiety symptoms during pregnancy [21]. In the late luteal phase of the menstrual cycle, migraine has been linked to a quicker decline in oestrogen levels. Though speculative, one hypothesis is that migraines may make women more susceptible to oestrogen depletion, which may also apply to the oestrogen fall that follows childbirth. In that case, it might be clear why migraine might increase the risk of postpartum depression. However, the findings from this study did not show a connection between migraine and anxiety or depressive symptoms at the sixth postpartum week. Measuring the rate of changes in hormone levels at childbirth may be useful for future research on migraine and postpartum depression [39].

Our review has several strengths, starting with the fact that it was completed using a strict process. The pooling of numerous national registry studies resulted in a considerable increase in the proportion of women included in the review. Second, a tool created expressly to evaluate the potential of bias in observational studies has been used to determine the validity of the estimates supplied by the research [16]. Our review did have certain limitations. Two studies were at significant risk of classification error due to the inclusion of observational designs, the retrospective nature of migraine measurement, and pregnant problems.

CONCLUSION

There was a higher chance of negative pregnancy outcomes with migraine, according to all of the analyzed trials. Common negative outcomes of migraine include preeclampsia, stroke, and pregnancy-related hypertension. Preterm birth, low birth weight, and miscarriage were also included as negative pregnancy outcomes in women with migraine. Additionally, we found that women suffering from migraines experienced mixed depression and anxiety symptoms during pregnancy.

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Potential Conflict of Interest: None

Competing Interest: None

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