JETIR.ORG ISSN: 2349-5162 | ESTD Year : 2014 | Monthly Issue
JOURNAL OF EMERGING TECHNOLOGIES AND INNOVATIVE RESEARCH (JETIR)
An International Scholarly Open Access, Peer-reviewed, Refereed Journal

# MIGRAINE MANAGEMENT CHALLENGES IN PREGNANCY: UNRAVELING THE TRIPTAN DILEMMA

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## ABSTRACT

Migraine management in pregnancy presents unique challenges, and the use of triptans—a common class of migraine medications—adds a layer of complexity due to concerns about fetal safety. This paper explores the intricacies of migraine management during pregnancy, focusing on the dilemma surrounding the use of triptans. Through a comprehensive review of existing literature, clinical studies, and case reports, we aim to unravel the complexities associated with triptan use in pregnant women with migraines. The paper provides insights into the current guidelines, the risk-benefit analysis, and gaps in research, offering a nuanced perspective on the triptan dilemma in the context of pregnancy. Triptans are a class of tryptamine-based drugs that are administered to alleviate migraine headaches. The triptans act as serotonin (5-hydroxytriptamine) (5-HT) agonists by binding to various serotonin receptors, which reduce migraine pain by neuronal inhibition and vasoconstriction. As of right now, seven different types of triptans are available on the American market: frovatriptan, naratriptan, rizatriptan, sumatriptan, zolmitriptan, and almotriptan. The purpose of this study was to look at the effects of triptans on pregnancy. Although the makers of three of the drugs have pregnancy registries, there hasn't been much research done on the use of triptans during pregnancy. There is significantly more information available on the use of sumatriptan during pregnancy because it has been on the market longer than other triptans and may have a bigger market share. There appears to be a higher incidence of preterm births, however no triptan has been shown to be teratogenic.

**Keywords:**

Pharmaceutical therapy, physiopathology, pregnancy, agonists of serotonin absorption, serotonin receptor, 5-HT, pharmacology, unfavorable pharmacological effects, migraine condition.

## INTRODUCTION

Knowing which medicines are safe to take while pregnant is crucial for healthcare providers who work with women in their reproductive years. There is a widespread misperception that pregnant or thinking pregnant women with migraines have no alternative safe treatment options and should stop taking their medication. Tension-type headache and migraine are the two primary forms of headache problems that occur during pregnancy. Pregnancy improves migraineurs for the most part. For some women, the first episode may occur during pregnancy. That's when postpartum migraines may begin or end. Most pregnant women who have had menstrual migraine and migraines that start at menarche are not likely to get migraines. Not every migraine, though, gets better during pregnancy. Some women may get migraines for the first time during pregnancy. Headaches are a major reason for visiting the neurology department [1]. Headache disorders ranked 14th in 2019 in terms of disability-adjusted life years [2]. Migraine ranks second globally among all causes of disability, accounting for 47.2 million years lived with disability (YLDs; 95% CI: 30.0-68.7). These figures are derived from information on the worldwide disease burden. Based on 1.3 billion (95% CI: 1.2-1.4) affected people, the projected global all-age point prevalence was 18%.Migraine prevalence is higher in women than in males [6]. The most prevalent pain condition that makes pregnancy more difficult is migraine. Primary headaches (cluster, migraine, tension, and different trigeminal sympathetic cephalgias) are frequent during pregnancy and after childbirth [7, 8]. Many studies show that, usually in the second and third trimesters, between 50% and 75% of pregnant women who suffer from migraines see a decrease in the frequency or complete cessation of their attacks.

Between 16% and 21% of people worldwide suffer from migraine headaches.1 Although migraines affect women about 2.5 times more commonly than they do men, women who are menstruating are far more likely to experience headaches.2 Generally speaking, the frequency of migraines declines throughout pregnancy, especially in the second and third trimesters.3. Reportedly, in 55% to 90% of pregnant women2, this improvement occurs, while in 25% of cases, it remains unchanged.3.

Triptans are thought to be rather safe when used in conjunction with drugs like aspirin and paracetamol/acetaminophen to treat migraines during pregnancy. On the other hand, drugs such as dihydroergotamine and ergotamine tartrate are typically not recommended.2. Nevertheless, no specific clinical research on the use of triptans during human pregnancy has been done as of yet. Furthermore, studies conducted on animals using all three triptans indicate that these drugs may be used if the benefits of taking them during pregnancy outweigh the risks (see to the product prescription instructions).

There are currently seven distinct triptans that can be bought in the United States (Table 1): naratriptan (Amerge, Naramig), zolmitriptan (Zomig), eletriptan (Relpax), frovatriptan (Frova, Migard), almotriptan (Axert, Almogran), and rizatriptan (Maxalt).

Sumatriptan, which was first made available in 1992 and presently occupies the majority of the triptan market, was the first triptan to earn FDA approval. Sumatriptan therefore has more post-marketing data available than the other triptans.[4] Brief overview of the existing concerns and dilemmas regarding the use of triptans in pregnant women. Triptans are often used as a migraine therapy. Pregnancy-related triptan exposure may negatively affect fetal neurodevelopment, although there is little information available regarding the long-term safety of triptan use during pregnancy. Triptans are the most often used medications for acute migraine treatment. Moderate to severe headaches and related symptoms are the hallmarks of migraine, a chronic neurologic condition.1. Migraine, which

has a peak prevalence of over 25%, is most common in women who are fertile and ranks second in terms of years spent disabled.2. The safety of triptans during pregnancy is not well understood, particularly in light of potential long-term consequences such as fetal neurodevelopment. The frequency of triptan use varies from 9% to 25% among migraineurs who are pregnant.3-5 Many pregnant women with migraine discontinue taking triptans or switch to acetaminophen as advised by therapeutic guidelines.

**Triptans and Pregnancy:** Mechanism of action of triptans in migraine treatment

Triptans share a structure because they are derivatives of tryptamine. They accomplish this by acting as serotonin (5-hydroxytryptamine, or 5-HT) agonists by attaching to many serotonin receptors. The ability of different triptan types to bind to specific subtypes of 5-HT receptors sets them apart.5. Because the different triptans have different binding affinities, they have different physiological and pharmacological effects (Table 2). There are several reasons why triptans are particularly effective in treating migraines.6–9. The most plausible theory is that the stimulation of 5-HT receptors causes the migraine by decreasing the increased blood flow.7. Moreover, triptans just alleviate discomfort; they neither cure nor prevent disease[1]

## THE METABOLISM OF TRIPTANS DURING PREGNANCY

Triptans are oxidized by phase I metabolic processes involving monoamine oxidase-A (MAO-A) and the cytochrome P450 (CYP) enzymes CYP3A4, CYP1A2, and CYP2D6.11 the particular enzymes involved in each triptan's metabolism are listed in Table 3. The metabolism of triptans is impacted by competing drugs that employ, inhibit, or induce metabolic enzymes such as MAO or CYP450 isozymes.11 CYP3A4, CYPA2, and CYP2D6 are the primary enzymes involved in the metabolism of eletriptan, frovatriptan, naratriptan, and zolmitriptan .Pregnancy causes an increase in CYP3A4 and CYP2D6 activity, which can alter the effectiveness and activity of certain triptans (Table 3). This ascent if triptan usage is to continue while pregnant, factors like dosage increase or decrease should be taken into account.

The monoamine oxidases are the main enzymes involved in the metabolism of almotriptan, rizatriptan, and sumatriptan. While some research studies claim that pregnancy and estrogen-progesterone oral contraceptives have no effect on MAO activity, other investigations contest this finding and contend that MAO activity does, in fact, decrease during pregnancy [5].In humans, pregnancy causes a decrease in platelet MAO activity .Thirteen Furthermore, in animal tests, an increase in estrogen levels linked to pregnancy was related with a decrease in MAO-An activity.

Based on the activity of the major metabolic enzymes, one would expect a decrease in metabolism for all triptans during pregnancy, with the possible exception of eletriptan (and possibly naratriptan).

As a result, triptan toxicity or other negative consequences can become more apparent.

## A STUDY ON TRIPTANS IN PREGNANCY

Regarding triptan teratogenicity in humans and its harmful effects on pregnancy, there is a dearth of data and significant disagreement. As previously stated, Table 4 provides an overview of the key information regarding sumatriptan usage. The recognized adverse effects of sumatriptan differ according on whether it is administered intravenously, nasally, or orally. Sumatriptan prescribing literature, Glaxo-SmithKline (2007) states that although the drug has a 15% bioavailability whether administered orally or subcutaneously, in animal experiments, subcutaneous application of the medication resulted in a loss of pup survival at a relatively moderate dose [6].

Premature delivery, low birth weight, and mild fetal abnormalities are a few of the negative effects that could result from exposing the mother or fetus during pregnancy.1, 3, 16 Four babies (0.8%) out of the 500 participants

registered in the sumatriptan pregnancy registry were born with ventricular septal defects (VSD).17 However, as this condition is believed to affect up to 4.36% of neonates born in the United States, this data is not remarkable.18

Animal studies have shown that in rabbits, sumatriptan passes the placenta. On the other hand, 15% of the sumatriptan dose (t½ = 2.5 hours) crosses the placenta in humans throughout a 4-hour period.19 Given that fetal 5-HT1B/1D receptors arise throughout the third trimester, triptans may have an effect on fetal development.20

Table 4 compiles the data from animal trials supplied by the different triptan pharmaceutical manufacturers (specific triptan product information). Out of all the triptans that have been documented, naratriptan (t½ = 6 hours) caused maternal plasma drug levels in pregnant rats and rabbits that were 2.5 times higher than the maximum recommended daily dosage (MRDD). Developmental harm resulted from this. Based on factual data from human clinical trials, the maximum recommended dosage limit (MRDD) for medications is an approximate upper limit above which the positive effects of a drug start to outweigh the negative effects and/or the treatment's efficacy is not increased. Rats developed both embryolethality and maternal toxicity when sumatriptan was administered intravenously to rabbits at a tenth of the maximum daily dietary dose advised for people (sumatriptan product information, Glaxo-SmithKline). Because of the very small margin mentioned for this formulation, use caution when using the injectable form. Many triptans have different no-effect dosages, depending on the situation and dosage forms.

Based on pregnancy registries, investigations on rizatriptan and sumatriptan. Low birth weight (less than 2.5 kg or 5 lb 8 oz), spontaneous abortion, and preterm delivery (defined medically as a birth occurring before 37 complete weeks of gestation) are the most common negative effects linked to triptan use during pregnancy.

But it's crucial to remember that these pregnancy registries are voluntary, and as such, neither comprehensive nor methodical. Furthermore, because bad events are more likely to be reported, reporting is biased.

Many databases exist in both Europe and the United States (including pregnancy registries and the Swedish, Danish, and American birth registers). In two studies examining the incidence of preterm births following intrapartum sumatriptan use, one revealed a slight but non-significant increase in preterm births; the other found no increase at all.1, 16 Preterm delivery appears to be the most common adverse event associated with triptans during pregnancy. When a mother takes sumatriptan during the third trimester of her pregnancy, it increases the sensitivity of 5-HT1B/1D receptors, which causes umbilical cord artery contraction in normal pregnancies [7]

Most triptans are present in low concentrations in breast milk. In addition, the levels of eletriptan and sumatriptan in mother serum were substantially higher than those in human breast milk.21 Therefore, it is likely that these amounts won't have a harmful effect on the nursing baby.

Pregnancy registries were created to track adverse events resulting from exposure to medications while pregnant. The neonatal outcome, mother health, average dosage, and exposure trimester are all recorded in the registries. On the other hand, retrospective enrollment is more likely to be biased and to include a greater number of birth defects. At this time, the only companies that sell registers are GSK and Merck.

Table 6 lists the registration information that is currently accessible for each of the three triptan manufacturers that provide this service. As of October 2006, the naratriptan registry comprised 55 women, 52 of whom were prospectively joined, despite naratriptan having been on the market in the US since 1998 (Sumatriptan and Naratriptan Pregnancy Registry)[8] When sumatriptan was initially introduced in 1992, it had a substantial portion of the market. 500 pregnancies that were prospectively recruited up until October 2006 are included in the sumatriptan pregnancy registry, which was established in 1996.

## DISCUSSION

Remission is more likely to occur in pregnant women whose migraine headaches began at menarche or who had perimenstrual migraine headache episodes. Furthermore, several post hoc investigations have shown that migraine headaches generally improve throughout pregnancy; between 60 and 70 percent of migraineurs report a notable improvement, primarily in the second and third trimesters. It is important to weigh the benefits of drug treatment against the risks because treating migraine symptoms could make pregnancy more difficult for the remaining patients. According to a research done while pregnant, headaches did not increase the risk of miscarriage or abnormal birth defects. However, when reviewing data on migraine therapy during pregnancy, it may be challenging to discern whether the reported difficulties are solely attributable to drug exposure or if the severity of the disease is a complicating factor. As of right now, there is no evidence in the literature suggesting that triptan has an adverse effect on the course of pregnancy. The only significant finding from Table 5's data from the Danish registry is that patients taking sumatriptan were more likely to have preterm deliveries than controls—patients with migraine and no treatment1 [odds ratio (OR), 6.3; 95% confidence interval (CI), 1.2–32.0], while patients in good health had odds of preterm deliveries of (OR, 3.3; 95% CI, 1.3–8.5). The same study also identified a connection between triptan exposure during pregnancy and an increased risk of low birth weight (OR, 3.0; 95% CI, 1.3–7.0) in all migraine patients who delivered at term.

Because reporting is voluntary, pregnancy registries are susceptible to recollection bias and may over report adverse outcomes. Furthermore, of the seven triptans, only rizatriptan, sumatriptan, and naratriptan have pregnancy registries. For the other four triptans—eletriptan, frovatriptan, zolmitriptan, and almotriptan—important details regarding pregnancy may therefore be absent.

Individual differences in triptan pharmacokinetics may be attributed to P-glycoprotein efflux transporters, triptan-metabolizing enzymes (CYP450 and MAO), or drug bioavailability. There is little information available on triptan effects during pregnancy, and no controlled studies have been conducted due to ethical concerns. According to the data that is currently available, those who are exposed to triptans after conception do not experience any differences in overall pregnancy and perinatal outcomes, despite the possibility of a slight rise in preterm birth rates. Nevertheless, there is currently insufficient data to rule out a little increase in the chance of teratogenic side effects from medication during pregnancy. Although it is typically advised to avoid drugs during pregnancy, triptan usage should be guided by risk-benefit considerations, particularly when data are inadequate and migraine treatment is necessary. Triptan safety may vary, but not enough information is now available in the data to make any strong conclusions about how safe they are in comparison.

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