

# Sex Hormone Differences in Migraine: A Woman with Essential HTN and Preeclampsia

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## Case Overview

Migraines are up to three times more prevalent in women than in men. The disparity in sex distribution suggests sex and gender differences may be contributive factors. It is critical to examine what roles these differences play in migraine onset and progression to better tailor patient care.

## Patient Profile

- Initials: LG
- Age: 30
- Sex: Female
- Gravida/Para: G4P2113
- LMP: 11/05/2024
- Contraception: Norethindrone
- Medications: ferrous sulfate, nifedipine
- Medical History: Essential Hypertension, Preeclampsia w/ Transaminitis, HSV-2
- Surgical History: Cesarean section
- Social History: Reports breastfeeding for 1 month but stopped following decreasing milk supply, nonsmoker
- Family History: Maternal history of migraines

## Presenting Complaint

This is a 30 yo female G4P2113 who presented to the ED with frequent headaches. She was initially seen by OB triage then transferred to the ED for continued evaluation. Eight weeks prior she had delivered her baby via caesarean section. She has been having headaches on and off, almost every day since giving birth. She was taking Labetalol during her pregnancy then Nifedipine was added after delivery due to persistently elevated BPs. Four weeks ago, the patient was admitted for severely elevated blood pressure and headaches in the setting of superimposed pre-eclampsia with severe features (transaminitis, headaches). During that admission she reported not taking antihypertensives as scheduled due to medication confusion. Labetalol was discontinued and her dose of Nifedipine optimised for improved BP control. She was normotensive with improving liver function tests at discharge. For this current admission, she describes the headaches as throbbing along her forehead without radiation to the neck. The headaches have not intensified in quality since they started. She reports taking the Nifedipine for high blood pressure but ran out of pills 3 days ago, and instead has been taking a lower dose of Nifedipine from an old prescription, without relief. Her last dose was 6 hours prior to admission. Patient reports measuring blood pressures at-home following last admission for

preeclampsia and has typically ranged in the 130s to 140s systolic. She has not tried any other medications. She endorsed mild photophobia and phonophobia, occasional palpitations, lightheadedness with position changes, and one episode of blurry vision which has since resolved. She reports a history of migraines but has never been medically diagnosed or treated.

## Vitals

- BP 169/90 (BP Location: Right arm, Patient Position: Sitting)
- Pulse 94
- Temp 97 °F (36.1 °C)
- Resp 17
- SpO2 100%

## Physical Exam

On exam, the patient was in no acute distress. Denied neck or chest pain. No abdominal pain. No lower extremity edema. Pain was localized to the forehead bilaterally. Normal conjunctivae bilaterally. Alert and oriented x3; CN II-XII grossly intact; no focal motor or sensory deficits; normal finger-nose and heel-to-shin testing, normal reflexes and muscle strength 5/5.

## Pertinent Labs

- Lactate Dehydrogenase, IU/L > 302
- Today: AST 27, ALT 38 (High), Alkaline Phosphatase 90
- 4 weeks ago: AST 32, ALT 49 (High), Alkaline Phosphatase 124 (High)
- 8 weeks ago: AST 34, ALT 54 (High), Alkaline Phosphatase 112 (High)

## Radiology Report

Patient had a recent MRI Brain w/o contrast completed 2 months ago during her third trimester due to headache and fever of unknown origin. Imaging then had no abnormal findings. We weighed the risk vs. benefit of re-imaging and decided against it.

## Assessment/Treatment

This is a 30 yo female G4P2113 with a history of essential hypertension with superimposed preeclampsia who was evaluated for headache. The differential included worsening preeclampsia, adverse effects of norethindrone therapy, migraine without aura, bilateral frontal headache, hypertensive urgency, hypertensive emergency. Results from lab tests and trends ruled out worsening preeclampsia. However, the patient's elevated blood pressure to the 160s systolic, and unrelenting headache remained a concern. Migraine treatment was started with Compazine, Benadryl, and Tylenol, and an additional dose of Nifedipine. After receiving treatment, the patient's headache resolved within the hour and BP decreased to the 130s with a final BP in the 120s/70s before discharge. The patient reported major improvement. She met criteria for migraine without aura and we discussed this new diagnosis and treatments. She was given Reglan for use as needed for migraine headaches and was re-prescribed her optimized dose of Nifedipine at discharge. She opted to follow up outpatient with PCP as well as her OB/GYN.

## Discussion

The prevalence of migraine among women implies potential sex and gender differences contributing to the development of this neurological condition. When looking at risk factors, stressful life events correlated with increased risk of migraines. While women are thought to experience more stressful life events than men, these factors do not necessarily correspond to a difference in migraine prevalence, type, or severity. This suggests social factors may not be as contributive to the migraine development than that of biological factors.

Numerous studies have investigated the influence of sex hormones on migraines. Assessing migraine incidence by sex, prepubertal males tend to have a higher rate compared to prepubertal females, but the inverse is seen once puberty begins.<sup>2</sup> One study revealed that subcutaneous testosterone therapy resulted in 92% of male migraine patients achieving symptom improvement after 3 months. Another identified increased estradiol and decreased androgen levels in males with migraine. These findings suggest testosterone is a protective factor, while estrogen increases migraine risk. This aligns with the decrease in incidence seen among males once puberty begins as during that period testosterone levels rise. Additionally, the estrogen withdrawal theory postulates that fluctuation in estrogen leads to an increase in cortical spreading depression which is the underlying event that triggers headaches.<sup>3</sup> Up to 25% of women with migraines experience a migraine event during menstruation, a time when estrogen levels drop significantly. In addition, after the placenta is expelled, estrogen levels plummet to below pre-pregnancy levels and can remain low until ovulation resumes. This leaves postpartum mothers extremely vulnerable to increased migraine frequency and severity. Another hormone, prolactin, is thought to also contribute to migraine prevalence in women. While it is not a sex hormone, prolactin levels are elevated in postpartum women who are nursing. In a 2024 study on female-selective factors promoting migraine, prolactin produced pain similar to migraines in rodents by increasing the release of CGRP. Therefore, elevated prolactin combined with a drop in estrogen increases vulnerability to migraines during the postpartum period. In addition, this highlights not only a sex difference in development of migraine but also in its treatment as the study implies that CGRP receptor antagonists could yield better treatment responses for migraine in women than men.

Moreover, understanding menopause provides further evidence for estrogen withdrawal being a key factor of the sex disparity seen in migraine prevalence. Maintaining stable estrogen levels during peri-menopause has been shown to alleviate vasomotor symptoms, and also decrease migraines which tend to worsen in this period due to the frequent fluctuations in estrogen as the body enters menopause. Once in menopause, estrogen levels have decreased and largely stabilized, thus leading to an improvement in migraines, mostly those without aura. It is also important to recognize the role hormone replacement therapy can play in migraine management for women during this phase. These changes in estrogen levels during the menopausal period underscores the relevance of the estrogen withdrawal theory when examining sex influences of migraine.

Overall, while there are appreciable sex differences in migraine prevalence between men and women, the migraine distinctions seen in women pre-puberty, during pregnancy, and in

menopause reinforces the influence of sex hormones in this condition. Comprehension of sex differences in migraine onset, frequency, and severity is crucial when evaluating and treating patients with frequent headaches. This enables clinicians to address patient needs using patient-centered medicine. In essence, inclusion of a sex and gender lens when analyzing differences in migraine, uncovers a more efficacious approach for tackling this neurological condition.

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