

# Migraine and Hormones

## A Complex Interaction

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### Related Article

#### Sex Hormones and Calcitonin Gene-Related Peptide in Women With Migraine: A Cross-sectional, Matched Cohort Study

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In their article “Sex Hormones and Calcitonin Gene-Related Peptide in Women With Migraine: A Cross-sectional, Matched Cohort Study,” Raffaelli et al.<sup>1</sup> studied the complex interaction between sex hormones and the occurrence of migraines. Migraine disorder is one of the most common neurologic illnesses, affecting up to 15% of people.<sup>2</sup> For many years, researchers have found that women experience migraine 3 times more often than men. In addition, many women report that their migraines worsen at certain times of the menstrual cycle. Furthermore, some women with migraine who take oral contraceptives (or hormone replacement) report that their migraines are *better* when taking these medications.

More recent studies have shown that *calcitonin gene-related peptide* (CGRP), a neuropeptide (i.e., a type of messenger molecule in the brain that works with neurotransmitters), plays a key role in migraine attacks.<sup>2</sup> Since the 1980s, it has been known that severe migraine pain is related to the release of CGRP from nerve cells in the head, face, and neck (i.e., cells in the trigeminal nerve). The release of CGRP causes a series of changes in that area of the body. This includes dilation of the nearby arteries due to the action of the CGRP on the muscle cells that make up the walls of those arteries. Understanding this connection has made it possible for scientists to develop increasingly potent medicines to treat migraine. In fact, the most effective antimigraine medications block or alter the way CGRP works.

### Why Is This Study Important?

Hormones and CGRP are produced naturally in our bodies. Scientists have started to better understand how the 2 are interconnected. One observation is that *changes in estrogen levels* affect CGRP. More specifically, when estrogen levels decrease, which occurs in certain parts of the normal menstrual cycle, this triggers the release of CGRP. When women take an oral contraceptive, their bodies receive a steady level of hormones; that is, until the “end” of the contraceptive dose pack, when the hormone is replaced by a placebo pill. It is at this point

## Table

Premenopausal women <i>with</i> migraines (not taking oral hormones)	Premenopausal women <i>with</i> migraine (taking oral hormones)	Postmenopausal women <i>with</i> migraine
Premenopausal women <i>without</i> migraine (not taking oral hormones)	Premenopausal women <i>without</i> migraine (taking oral hormones)	Postmenopausal women <i>without</i> migraine

that estrogen levels suddenly drop, and the menstrual period occurs. It is also during this sudden change in hormone levels in the blood that a migraine attack is more likely to occur.

Raffaelli et al. wanted to better understand this complex interaction. How do hormones and CGRP affect each other? To analyze this, they carefully measured serum hormone levels and serum CGRP levels throughout each study participant's menstrual cycle. In addition, they added one other test: they also measured CGRP levels in each person's tears. Doing so makes sense for many reasons. First, the collection of tears is much less invasive than a needle (to collect blood samples). Second, the trigeminal nerve releases CGRP in the head and neck *only*. By collecting tears, the scientists were gathering samples from a part of the body that is directly affected by the trigeminal nerve.

### How Was the Study Performed?

First, the scientists identified women who had episodic migraine. In total, there were 180 study participants. The participants enrolled in the study, which was conducted in Berlin, between August 2020 and May 2022. They were divided equally into 6 groups of 30 participants (Table).

They collected samples at several time points. In women who were not taking oral hormones, the researchers measured these levels at different times during the monthly cycle. For women taking hormones, the researchers collected samples during times when women were taking hormones and when they were not (that is, when they were taking the sugar pill portion of the hormone treatment). In the postmenopausal women, samples were collected at 1 time point. The scientists carefully analyzed *both* the blood (serum) and the tear samples of each group.

### What Were the Results?

Because the measurement of CGRP in tear fluid is a new method, the authors compared the concentration of CGRP

in tears with that in blood. They found that, across all groups, the concentration of CGRP was *80 times higher* in tears when compared with that in blood. Overall, people who had migraine had higher levels of CGRP in their tears.

In women with regular menstrual cycles, the scientists found *much higher* concentrations of CGRP in both the blood and tears of women who had migraines. There was no difference in the levels of CGRP between women with migraine who were taking oral contraceptives and those with no migraine who were taking oral contraceptives. Similarly, there was no difference in CGRP levels in the 2 groups of postmenopausal women. These results support the observation that women who are experiencing their menses normally have higher levels of the migraine-causing neuropeptide, CGRP.

Overall, both in women taking oral contraceptives and in postmenopausal women, the levels of CGRP were lower. In fact, in these groups, the levels of CGRP were more similar to women who *did not* have migraine.

### What Does This Mean?

First, these findings support the link between sex hormones and CGRP. The drop in estrogen, which occurs during menstruation, causes an increase in CGRP. This leads to an increase in migraine headaches during that time of the menstrual cycle. Another way of looking at this is that a drop in estrogen is *promigraine*.

Second, the findings suggest that CGRP levels in tears may be *more helpful* than measuring CGRP levels in the serum. There are several reasons for this. CGRP is produced by several different body organs. Measuring CGRP levels in the blood therefore measures the amount of CGRP produced throughout a person's entire body. However, the CGRP in tears is mainly released by the cells of the trigeminal nerve. Because of this, measuring CGRP in this particular body fluid may be more accurate. The authors admit, however, that this method is new and that further study is needed before it could be widely used.

# About Migraine

## What Is Migraine?

Migraine is one of the most common neurologic illnesses. It is characterized by repeated attacks of severe (often 1-sided), throbbing pain. Often, people also experience sensitivity to bright lights, loud noises, nausea, and vomiting. The attacks last 4–72 hours. They are often brought on by physical activity. Although the overall rates of migraine are estimated at 15% of people, migraines occur much more often in women (18%) than in men (6%). Migraines tend to occur most often between the ages of 25 and 55 years. They can severely affect a person's ability to work or go to school and account for an estimated loss of \$27 billion in the United States *each year*.<sup>3</sup>

Recent studies have led to the development of many new treatments for migraine.<sup>3</sup> There are 2 broad categories of these: acute treatments and preventative treatments. Acute treatments are used during a migraine attack. Their goal is to both stop the migraine pain and to keep the pain from coming back. In reducing pain (and associated symptoms), disability is also reduced, as is time away from work or school. However, care must be taken when using certain medications too often. Medical *overuse* can lead to *worsening* of migraine and therefore *more* disability. The goals of preventative treatment care are slightly different, namely to reduce the number and severity of migraine attacks. Often, these 2 approaches are combined. Preventative therapy lessens the number of attacks so that acute treatment is needed less frequently.

With the growing number of acute and preventative treatments for migraine, it has become increasingly challenging

to know what combination is best for a given individual. Headache specialists are experts in this field and can help people to find the solution that works best for them. Developing an open and honest relationship with a headache specialist can reduce illness, decrease disability, and greatly improve the overall quality of life for people with migraine.

## FOR MORE INFORMATION

### **Brain & Life**

[brainandlife.org](http://brainandlife.org)

### **American Headache Society**

[americanheadachesociety.org](http://americanheadachesociety.org)

### **National Headache Foundation**

[headaches.org](http://headaches.org)

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