



# 1 in 5: *Why women are more likely to develop migraines*

By Karolina Edlund



## Kayla's Story\*

*The day Kayla found out she was pregnant, she was on cloud nine. Having grown up with siblings, Kayla had always known she wanted a large family of her own. After getting married last year, she and her husband, Adam, had immediately started trying for a baby. Nine months flew by, and they were soon parents to a beautiful baby girl named Hope. Although exhausting, the first few days with Hope were wonderful. Then, Kayla started feeling sick.*

*She felt an intense pain on the left side of her head, had tunnel vision and often felt dizzy. She couldn't stand sunlight, and every time Hope cried, she almost threw up. When Kayla tried to explain her symptoms to Adam, she stumbled over her words. Eventually, Kayla retreated alone to her bedroom, and slept for days.*

*In time, this wave of symptoms subsided, only to return again several days later. "What's happening to me?" Kayla cried on the phone to her mom. "I can't take good care of Hope when I feel like this. I can't even get out of bed, or I'll puke." On the other line, her mom sighed. She explained that she hadn't wanted to worry her anxiety-prone daughter unnecessarily while she was pregnant, but that she knew the feeling Kayla was describing well. After giving birth to Kayla and her siblings, she too had struggled with severe migraines: "When you feel better for a moment, why don't you google migraine disorder, my love."*

*\*Kayla's story is fictional and was written by the author*

Kayla's story is not uncommon; Kayla and her mother are among the nearly 20% of women who experience migraines [1]. But almost everyone gets headaches throughout their lives, why was Kayla struggling so much? Migraines are different from everyday headaches in several important ways (Figure 1). First, headaches affect many more people than migraines; over 96% of people will experience a headache in their lifetime compared to the 18% of people who experience a migraine. Second, there are over 150 different kinds of headaches, while there are only two kinds of migraines, those with and without aura. Third, the physical symptoms of headaches and migraines are distinct: headache pain is often throbbing and not limited to one area of the head; migraine pain is usually dull and centralized to one side of the head. The final most important difference between headaches and migraines is sever-

ity. Headaches are not pleasant by any means, but they do not negatively impact daily life. The slew of physical symptoms characteristic of migraines, such as sensitivity to light and sound, dizziness, vision loss, changes in speech and vomiting, make it difficult for sufferers to perform everyday tasks [2, 3]. In Kayla's case, she struggled to take care of herself and her baby, Hope.

Now that we know the differences between headaches and migraines, let's delve into the two types of migraines mentioned above — migraines with aura and without aura. The Mayo Clinic defines migraine with aura, also known as classic migraine, as "a recurring headache that strikes after or at the same time as sensory disturbances called aura. Classic migraines are the most common form of migraines, and these disturbances can include flashes of light, blind spots, and other vision changes or tingling and numbness in your hand or face [4]." Aura is

thought to be caused by electrical or chemical waves passing through the cerebral cortex, a part of the brain that contains regions responsible for sensory processing, vision, speech and movement. Kayla cried to her mom about the aura she was experiencing — she had changes in her vision and difficulty speaking during her migraines [5]. It is likely that Kayla experienced these electrical waves passing through her visual cortex, the part of the brain that receives and processes sensory input from the eyes, and her Broca's area, the region of the brain responsible for speech production. If you've never had a migraine before, it may be hard to visualize what aura looks or feels like. Figure 2 provides two examples of visual aura: blind or blurry spots and flashes of light.

Many people who suffer from migraines, also known as migraineurs, learn to tell when a

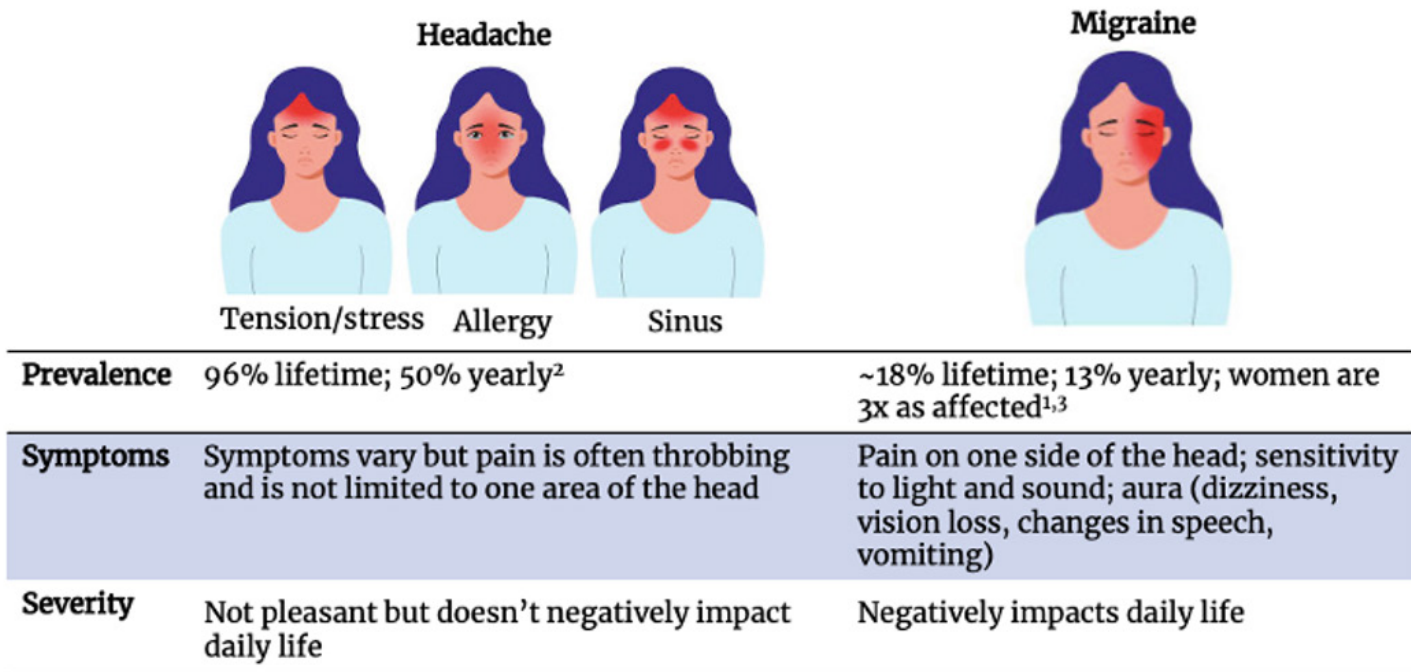


Figure 1. Differences between headaches and migraines. Image created with Biorender.com by Karoline Edlund.

migraine is coming by the appearance of this aura. The onset of migraines without aura is not marked by the same “warning sign,” although, after onset, the two types of migraines are characterized by the same physical symptoms.

So, what causes people like Kayla and her mom to have migraines? While the etiology of migraines is not entirely understood, researchers have identified three main factors that contribute to the development of a migraine attack: 1) genetics, 2) the environment and 3) hormones (Figure 3). Unfortunately for Kayla, she was at risk of developing migraines in all three of these groups. Her story does, however, serve as a useful tool with which to better understand migraine development.

## Genetics

“Genetics” refers to the study of how traits are passed intergenerationally, in a process called heredity. To understand heredity, we first need to understand how Deoxyribonucleic acid (DNA) molecules function in the

body. Contained within chromosomes, some sections of DNA are called genes, which are the foundational units of heredity. Genes make proteins, which work to allow our bodies to function. Other sections of DNA are thought to act like on/off switches for nearby genes. Mutations in the genetic sequence can also impact gene expression. What’s most important to understand, is that different genes are responsible for different traits — for example, my neighbor has brown eyes because specific genes in his chromosomal instruction manual were turned on or off. Because he has the genetic instructions for brown eyes, his son, who received half his chromosomes from his father, is likely to have brown eyes too.

You may recall that, like Kayla, Kayla’s mom suffered from migraines. Researchers Russel et al. (1996) found that first-degree relatives of people with migraines with aura are four times as likely to suffer from the same type of migraines themselves. This hereditary pattern in migraine development suggests a genetic component

to the disorder. But what specific genes have been linked to migraines?

Recent studies on the genetic etiology of migraine attacks have identified several potential genetic markers of the disorder. Focusing primarily on migraines with aura, researchers discovered an overexpression of a C677T gene mutation in migraineurs with aura [7]. One specific type of migraine with aura that affects a single side of the body — hemiplegic migraines — have been linked to mutations in three more genes that contain the instructions for ion channels and transport proteins: CACNA1A, ATP1A2 and SCN1A.

An ion channel is like a cat door, it allows ions (in this analogy the cat) to move between sides of the bigger door (the cellular membrane). Different cat doors open in different ways — some allow the cat to move back and forth across the larger door, others only allow the cat to cross the door in one direction and still other cat doors can be closed for periods of time to ensure that the cat stays on one



Figure 2. Examples of Visual Aura. Images adapted from Cincinatto (2015) (6).

side of the door. Sometimes, a cat (ion) needs a little help getting through the cat door (ion channel) or moving around the house (cell) — transport proteins, in our analogy cat owners, can help carry their cats around the house and coax them through the cat door, although this does take some energy on the owner's part (Figure 4).

When mutations in the genetic sequences that encode for ion channels and transport proteins occur, as in the case of hemiplegic migraines, neurotransmitters and ions are unable to pass through channels or travel between cells, and cortical depression is likely to ensue. Cortical depression is characterized by a wave of depolarization followed by activity suppression in a region of the brain. This decreased function greatly impacts neural and vascular functioning and, as discussed above, may be the mechanism underlying migraine aura [8].

Through the identification of mutations in these four genes, we see how genetics play an integral role in the development and heritability of migraines with aura. Research done on twins tells us that mutations in these migraine-associated genes have an overall heritability of nearly 50%, so it is likely that Kayla's mom

passed one or all of these mutations down to her daughter, resulting in the two women's shared struggles with migraines [9].

## The Environment

In addition to genetic predisposition, many migraineurs report that environmental factors trigger their attacks. Three of the most common of these triggers

include changes in weather, odor and stress. While the majority of studies on the impact of the environment on migraine development have relied on self-reported data, the consistency of responses across the globe suggests their validity.

Weather has been one of the most extensively studied triggers of migraines and, although the findings have been controver-

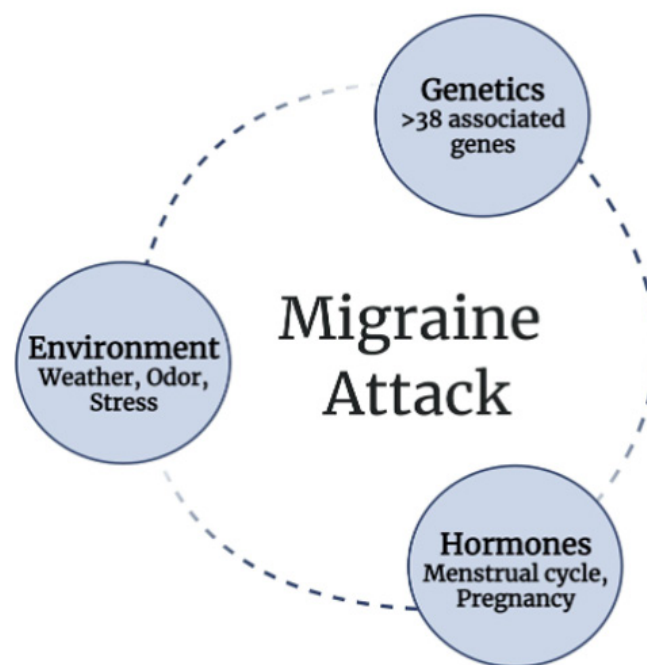


Figure 3. Contributing factors of migraine development. Image created with Biorender.com by Karolina Edlund.



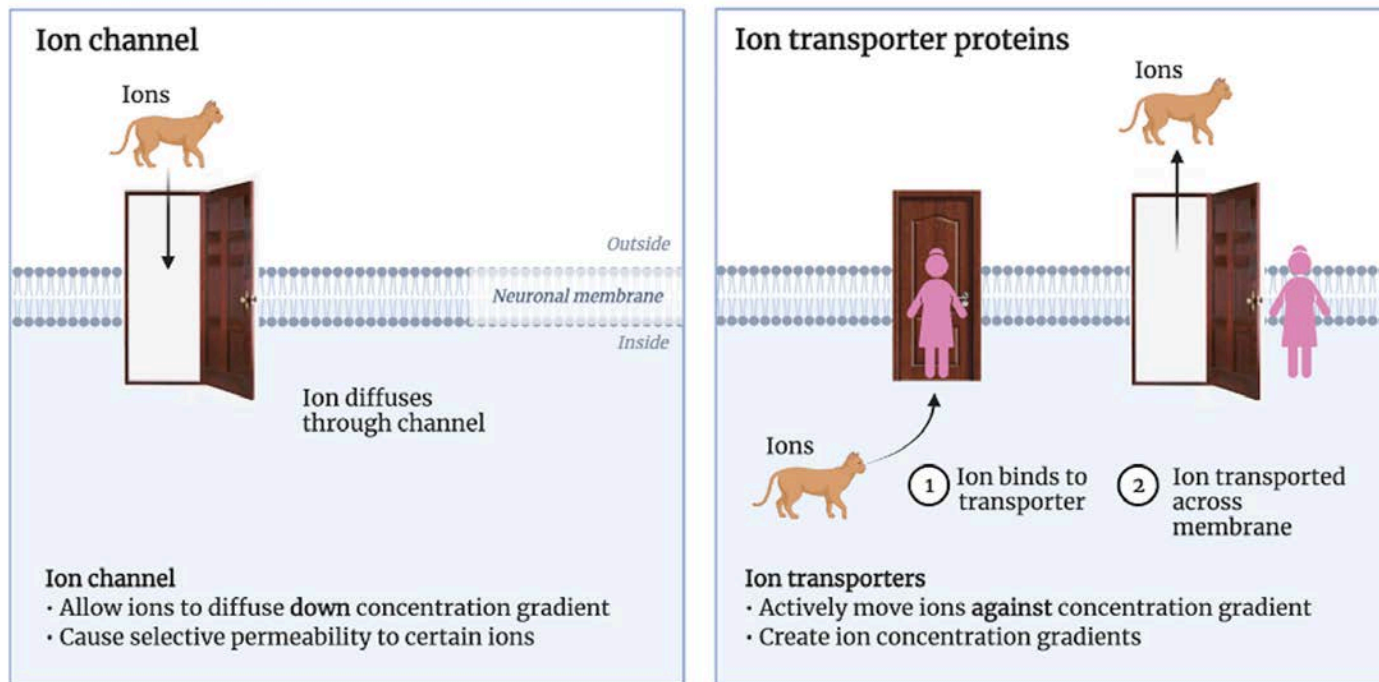


Figure 3. How ion channels and transport proteins function in the brain. Image created with Biorender.com by Karolina Edlund.

sial, 45.5% of migraineurs report their migraines and headaches often occur before changes in barometric pressure followed by rain, bright sunshine, humidity and wind [10]. However, the pathophysiology of migraine is complicated, and the physical reasons for why this environmental factor may trigger a migraine attack require more research. More than 40% of migraineurs report odors as triggers and many people experience sensitivity to smell during a migraine attack. One possible explanation for this osmophobia was put forward by researchers Meggs (1993) and Bernstein (2005), who suggested that chemical sensitivity is propagated by neurogenic inflammation in neurons located on the outer protective layers of the central nervous system [11, 12]. There are also several interesting historical hypotheses to support the evolutionary usefulness of these triggers. Many migraineurs claim to be able to predict the weather based on their symptoms, which may have allowed early humans to better prepare for storms.

Sensitivity to odor may also have been an evolutionary advantage, as migraineurs may be better able to identify and warn against environmental toxins [10].

For most migraineurs, stress is a major trigger of migraine attacks. Stress may be thought of as the human response to suboptimal conditions in the surrounding environment. Again, the pathophysiological mechanisms underlying the relationship between stress and migraines are poorly understood, but it has been suggested that stress triggers migraines by inducing biological changes that lower a migraineur's susceptibility to an attack [13]. Unfortunately, the connection between migraines and stress is cyclical in nature — stress triggers migraines and migraines increase stress.

While Kayla did not track the weather or the odors around her at the beginning of her migraine journey, it is certain that she was under a lot of stress. As a new mother her body was physically healing and she was learning how to take care of a baby for the first

time. Lack of sleep has also been strongly linked to increased maternal stress and Kayla, like many new parents, was certainly not getting enough sleep [14]. While some triggers are not within a migraineur's control, like the weather, other triggers may be avoided or managed through lifestyle changes. At the end of this article, we will see how Kayla learned to track, identify and avoid as many of her triggers as possible, particularly through lifestyle changes she made to reduce her stress.

## Hormones

Women, both adolescent and adult, are three times as likely to suffer from migraines as men [14]. Oftentimes, women develop their first migraine after first menstruation, pregnancy or menopause; this pattern suggests the role of female sex hormones in migraine etiology.

Hormones are chemical messages that are released via our bodies' endocrine system and circulate throughout our blood-

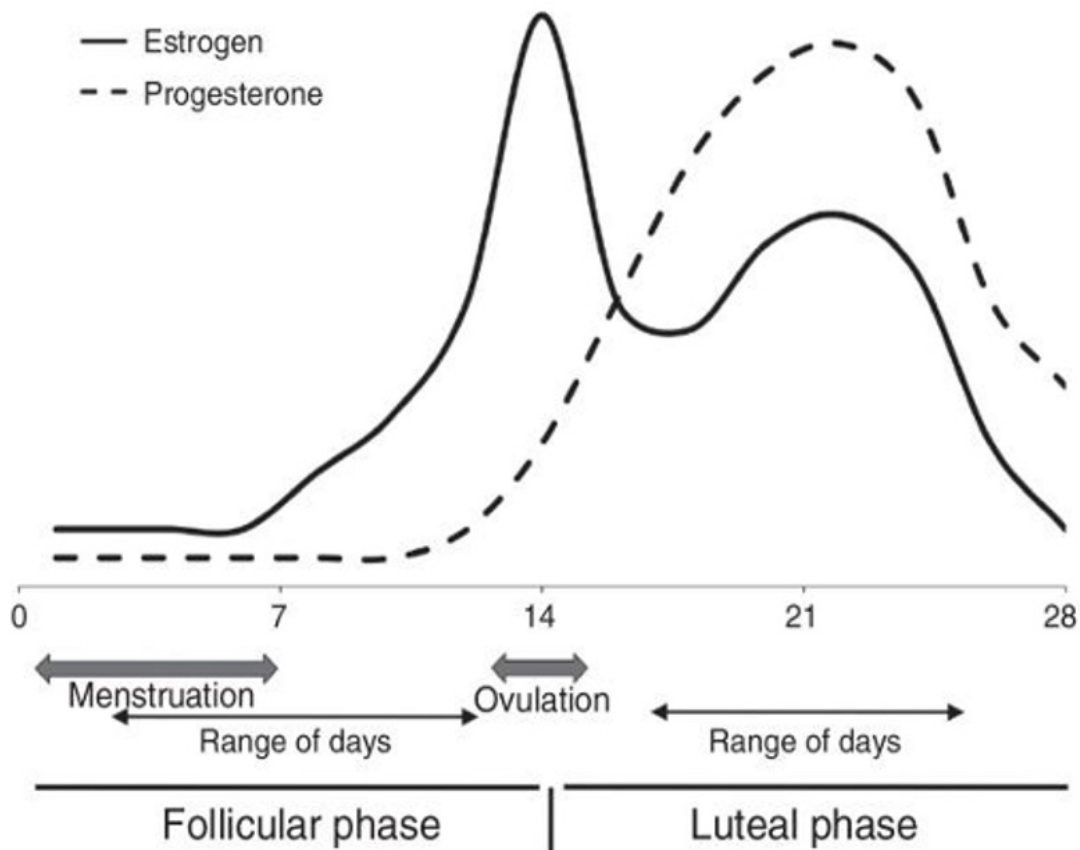


Figure 5. Fluctuations in female sex hormones through the reproductive cycle. Figure adapted from Glover et. al. (2013) (16).

stream. These chemical messages control numerous bodily processes, including growth, appetite and sleep cycles. Sex hormones in particular, however, control processes related to sexual maturation and reproduction. In women, the two main sex hormones are estrogen and progesterone. Largely produced in the ovaries, adrenal glands and fat cells, estrogen helps to regulate a woman's reproductive cycle and is important for cognitive function and bone health. Progesterone is secreted by a type of endocrine gland found in the ovaries called the corpus luteum; it triggers the thickening of the uterine lining to prepare for the potential of fertilization.

During the female reproductive cycle, hormones fluctuate wildly (Figure 4). Amid the follicular phase of menstruation,

estrogen and progesterone levels rise in the female body. If an egg is fertilized, the hormones move to support pregnancy, but if pregnancy is not conceived during ovulation then both hormones dramatically fall, causing a woman to shed her uterine lining through menstruation.

These fluctuations in estrogen levels have been shown to trigger migraine attacks, particularly right before menses when estrogen levels are rapidly decreasing in the body. In accord with these findings, many women on hormonal birth control report migraine attacks during their placebo weeks, when they experience estrogen withdrawal.

Pregnancy is also characterized by widespread hormonal changes. Researchers have observed a worsening of migraine attacks during the first trimester, and many women may experience

migraines for the first time during pregnancy. The postpartum time period represents another vulnerable time for women, as the dramatic decrease in estrogen levels following childbirth often leads to intense migraines with aura. But why do hormonal changes seem to lead to migraines? Some professionals suggest that decreased estrogen levels may influence blood vessel contractions in the brain. Others believe that low estrogen increases facial and scalp nerve sensitivity. Still others have pointed to the relationship between estrogen and serotonin, a neurotransmitter important for mood stabilization and nerve cell communication. These scientists also suggest that changes in levels of serotonin in the brain may cause the narrowing of blood vessels which, in turn, cause migraines [17].



Kayla experienced her first migraine with aura after the birth of her daughter, Hope. Her development of the disorder was likely in part due to the rapid decrease of estrogen women experience after giving birth. While hormonal birth control has been known to trigger migraines in some women, in others, particularly postpartum women, it has been used to stabilize levels of estrogen in the body as well as to avoid drops in estrogen by skipping periods. Another class of drugs, called Triptans, have also been used to treat the disorder. Triptans work by behaving like serotonin in the brain to calm down overactive pain nerves and, as we will see shortly, Kayla found a combination of the birth control and Triptan medications helpful in managing her migraines [18].

## Kayla's Solution

Kayla had been dealt a bad hand. She was at high risk of migraines in all three of the etiologic categories associated with migraine development: 1) her family had a history of migraines, 2) as a new mother, she was under an immense amount of stress, which was compounded with a lack of sleep and loud environment, and 3) following the birth of her daughter, she was also experiencing dramatic hormonal changes. What I failed to mention at the beginning of this article, however, was that Kayla was a trained neuroscientist. Having dedicated her life to learning about the brain, Kayla was determined not to let this neurological condition affect her quality of life. Soon after being diagnosed with a migraine disorder, she scoured many of the scientific articles cited above and

scheduled countless doctor's appointments. As her list of migraine resources grew, Kayla and her clinical team developed a plan to avoid and manage her migraines.

Kayla could not change her genetics. Neither could her mother. While Kayla found comfort in knowing that mutations in her C677T, CACNA1A, ATP1A2 and SCN1A genes were likely to blame for her and her mother's migraines, she worried that Hope would inherit these mutations and thus the disorder, as well. Much of Kayla's distress at the start of her migraine journey came from the confusion of what was happening to her, so she swore not to make her mother's mistake. She would be open with her daughter about her struggles with migraines and would explain the heritable nature of the condition to Hope early on. She would make sure her daughter was prepared and supported if she were to



ever develop migraines.

Kayla soon accepted that her environment and emotional stress greatly triggered her migraines. While she could not control the weather, she learned to check the weather app on her phone in order to prepare herself for the possibility of a migraine attack. As strong odors often triggered her attacks, Kayla stopped wearing strong perfumes and always opened a window when she knew she or her husband, Adam, were going to be cooking something smelly. While these lifestyle changes were simple life, managing stress as a young mother is anything but easy. It was in this regard that her husband, Adam, became her biggest supporter — aware that sleep greatly affects maternal stress, he took to comforting Hope throughout the night so that Kayla could get a good night's rest. Kayla began meditating, journaling and seeing a therapist, as well. After hearing that she had struggled with anxiety for much of her life, her therapist suggested she look into starting anti-anxiety medication. Selective serotonin reuptake inhibitors (SSRIs) are the most commonly prescribed antidepressant

medication in the United States today, and Kayla read that SSRIs work by increasing available serotonin in the brain. They do this through the inhibition of serotonin reuptake by neurons, allowing serotonin to stay active in the brain at higher levels for longer periods of time. SSRIs are highly effective in treating mood disorders like anxiety and depression [19]. Convinced, Kayla soon began taking an SSRI pill every night before bed and, in combination with her other lifestyle changes, her stress levels soon decreased.

Lastly, while Kayla knew that it was only a matter of time before her hormones returned to what they had been before her pregnancy and the birth of her daughter, she was desperate for instant relief. In order to stabilize her hormones fast, Kayla began taking a combination contraceptive pill, which contained both synthetic estrogen and progesterone. This pill helped to regulate her hormones throughout the month, as well as allowing her to skip her period in order to avoid sudden drops in her estrogen levels. As mentioned above, if she were to feel a migraine coming on, Kayla also found it helpful to take

a dose of her Triptan medication in order to quickly stop the migraine from progressing.

Kayla's story is not uncommon. Nearly 20% of women experience migraines throughout their lifetime, a statistic which underscores the importance of increased awareness about the disorder [1]. What sets Kayla apart from the rest is her determination to understand the condition and her willingness to try things to manage and reduce the frequency of her migraine attacks. She learned about the heritable nature of her disorder, and the environmental triggers of her attacks. She also learned the importance of hormones to female health. Kayla's training as a neuroscientist undoubtedly helped her understand her condition, which brings us to the point of this article.

It is my hope that this article will serve as a resource for other women struggling with migraines; a reminder that you are not alone. As Kayla learned, there are biological and environmental reasons for the pain you are feeling, and through an exploration of these triggering factors, this article aims to provide clarity about and tools with which to manage this disorder.





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