MIGRAINE WORLD SUMMIT

INTERVIEWS WITH WORLD-LEADING EXPERTS

TRANSCRIPT

HOW WOMEN'S HORMONES AFFECT MIGRAINE

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Introduction (00:06): Migraine is three times more common in women than in men. And not only that — it is the leading cause of years lived with disability in women of reproductive age. This is the time when women are the most productive — or expected to be the most productive — often working multiple jobs, taking care of children, being pregnant, lactating. And this is the time when migraine truly strikes with most of its burden.

Elizabeth DeStefano (00:34): Hormonally influenced migraine is something that all too many women are familiar with. The debilitating effects of this type of migraine can impact a woman throughout various stages of her life: from puberty to perimenopause and beyond. Here to help us unravel some of the many questions about menstrual and menopausal migraine is Dr. Jelena Pavlović. Dr. Pavlović, welcome to the Migraine World Summit.

Dr. Pavlović (01:00): Thank you so much, Elizabeth, for having me. It's my pleasure.

Elizabeth DeStefano (01:04): Well, we could easily dedicate our entire time together to cover either menstrual or menopausal migraine, but we'll make sure to get some information on both to viewers.

Dr. Pavlović (01:15): Sure.

Elizabeth DeStefano (01:16): One of those viewers, Laura, wants to know if female hormones are the reason that more women than men have migraine. Does research confirm this?

Dr. Pavlović (01:27): Yes, very much so. And we know, in terms of prevalence, that migraine is three times more common in women than in men. And not only that — it is the leading cause of years lived with disability in women of reproductive age. This is the time when women are the most productive — or expected to be the most productive — often working multiple jobs, taking care of children, being pregnant, lactating. And this is the time when migraine truly strikes with most of its burden. So yes, this is a significant issue for women and dealing with how hormones affect women and how hormones affect migraine is a topic of great interest, obviously.

Elizabeth DeStefano (02:13): Why is it that many women with migraine do find a correlation between attacks and their menstrual cycle?

Dr. Pavlović (02:20): Hormonal influences affect migraine occurrence. So, the best data comes from estrogen decline. We know that in the late luteal phase of the menstrual cycle, which is the phase right prior to bleeding, both estrogen and progesterone decline. And they decline somewhat rapidly over about five days from the peak to the trough of it. And during that decline, we see the change in estrogen is accelerated in women with migraine. And that decline is believed — in estrogen, in particular — to precipitate occurrence of headache in those women who already have migraine. Some women seem to be more susceptible to this effect, some less, but we see this in the majority of women with migraine.

Elizabeth DeStefano (03:09): When you say some women are more susceptible, are there certain risk factors that make certain women with migraine more susceptible to menstrual migraine than others?

Dr. Pavlović (03:20): Those are not studied in very great detail, or understood. We know from some studies that having premenstrual dysphoric syndrome — what used to be called PMS, actually — in studies that evaluated this, that women who had perimenstrual symptoms of

other types were also more likely to have menstrually related migraine. Also, women who've had migraine occurrence in relation to other hormonal events in life: The majority of girls [who] get onset of migraine around menarche — those would seem to have more such hormonally regulated attacks and will generally ... their attacks will cluster around menstruation, which is what we call menstrually related migraine.

Elizabeth DeStefano (04:11): So, what exactly is menstrually related migraine?

Dr. Pavlović (04:15): Excellent question. So as defined by the International Classification of Headache Disorders — and the disorder is still in the appendix of the international classification— menstrually related migraine are attacks that occur around the first day of bleeding. Either starting two ... in the window of five days, starting two days prior to the onset of bleeding, continuing for the first three days of bleeding, per definition, and occurring with at least two out of the last three menstrual [cycles].

Elizabeth DeStefano (04:50): And that can be in addition to migraine attacks that occur outside of that window?

Dr. Pavlović (04:56): Correct. And that's actually an important distinction ... because women who have menstrually related migraine will have attacks during that window of five days and at other times — during the month and during their menstrual cycle. While women who have attacks isolated to that window of five days — that disorder is called "pure menstrual migraine." And that is a rare disorder that occurs in less than 10% of women, while menstrually related migraine is a very common disorder, occurring likely in the majority of women, in about 60% of women [with migraine].

Elizabeth DeStefano (05:34): For acute treatment, what is your first-line approach for menstrually related migraine? And how does that differ from migraine that isn't related to the menstrual cycle?

Dr. Pavlović (05:45): So, in terms of the treatments ... In terms of the actual medications that are chosen for treatment, there is not that much difference; the same toolbox applies. And that is NSAIDs such as naproxen, diclofenac, nabumetone, and ibuprofen. Triptans — naratriptan and frovatriptan, the long-acting triptans — are particularly used in it. And now more recently, we can also use gepants, like ubrogepant and rimegepant, for acute treatment of menstrually related migraine. The one difference that is specific for treatment of menstrually related migraine is using the predictability of ... using a diary and a calendar and predictably identifying when these attacks are likely to occur. So, a woman who has a predisposition to menstrually related attacks will frequently — with two out of three menstrual cycles, at least — have these attacks, unfortunately, often for a prolonged period of time — often entering status migrainosus, right? Having three or more days of headache during this stretch of time.

Dr. Pavlović (06:56): And so ... we [have] the ability to do is what we refer to as "mini-prevention." And what mini-prevention means is that a patient would keep a diary, identify the days at risk, and then treat in anticipation of those days of risk: starting with treatment a day before the anticipated attack onset, or the morning of the day when the attack is supposed to start, and continue for five to seven days — depending on how long the stretch of the days is — treating twice daily, whether the headache is occurring or not, because the likelihood of headache in that interval is so high. So, trials with naproxen twice daily, or frova- and naratriptan — the triptan drug class — twice daily, have been performed with good effects. And

also, we commonly in headache practices use that approach to treat patients with menstrually related migraine.

Elizabeth DeStefano (07:56): So, this approach of mini-prevention is used with, would you say, a majority of patients?

Dr. Pavlović (08:02): I would say so. It is a common approach that — if the audience listening, women listening to this talk — are not taking advantage ... And even if women are on other prevention, they can still utilize mini-prevention on top of an already existing preventive agent.

Elizabeth DeStefano (08:22): So, speaking of prevention, outside of mini-prevention — how do you know when to pull that into the mix and go that route?

Dr. Pavlović (08:32): So, you know, the classic rules of when to apply prevention stand. And that is: four headache days or more a month, if there's also a moderate to significant disability, or six [days] or more if there's no disability. So, the rules that apply for all prevention apply to menstrually related migraine. What we frequently see happen is that patients may be hesitant ... Patients who may have five to eight days of headache per month, and sometimes they don't get … and out of those eight days, five are menstrually related migraine days — and sometimes those days don't happen; on a certain good month, the menstrually related migraine doesn't occur. And so, the patients are hesitant to start actual preventive daily treatment. If their cycle is regular and they have predictable attacks of menstrually related migraine, it allows for mini-prevention to halve their headache days potentially, or even more than that. So that can often serve as a great first tool in decreasing headache frequency. If that is not sufficient, we will introduce other preventive treatments, like for all other migraine treatment.

Elizabeth DeStefano (09:53): So, it sounds like you'll have acute treatments on hand, then you'll pull in mini-prevention. And if not adequate, you can then consider prevention outside of the mini-prevention.

Dr. Pavlović (10:05): Correct.

Elizabeth DeStefano (10:08): What role in that prevention does low-dose progesterone or hormonal IUDs, or patches, rings, injections — any of those strategies – fit in?

Dr. Pavlović (10:20): Those strategies can play a significant role. Migraine that is hormonally regulated, primarily in those women who are very sensitive to hormonal fluctuations ... Smoothing out, so to speak, hormonal fluctuation by using exogenous hormones — exogenous estrogen, exogenous progesterone — although progesterone doesn't seem to play a major role in migraine regulation and therefore, we don't see a significant effect with exogenous progesterone-containing compounds. But exogenous estrogens can smooth out the changes in estradiol, in endogenous estradiol, and therefore actually help with treatment of migraine.

Elizabeth DeStefano (11:06): So, this is a time that you recommend collaboration between a headache specialist or neurologist and a gynecologist?

Dr. Pavlović (11:12): Absolutely. It requires a multidisciplinary approach.

Elizabeth DeStefano (11:16): What role, if any, do supplements or neuromodulation devices — nonpharmaceutical options — play in your treatment of menstrually related migraine in patients?

Dr. Pavlović (11:29): Same as — the studies are limited, specifically for menstrually related migraine — but same as they have impact on other migraine attacks. All neurostimulation and behavioral therapies, all therapies can be equally used for menstrually related migraine, as well. Keeping in mind that menstrually related attacks are the most burdensome — associated with most symptoms of migraine, most refractory to treatment, lasting the longest. So, one often requires this multi-pronged approach for treatment of menstrually related migraine. And I really appreciate that question because if mini-prevention is not enough, one might need to have a neurostimulation device, meditation, mindfulness practice or another behavioral therapy, like biofeedback, all coming into play during these most burdensome attacks.

Elizabeth DeStefano (12:31): And many women talk about that: how their menstrual migraine attacks are harder to effectively treat, worse than migraine attacks at other points in their cycle. And as you're mentioning here, you also mentioned in your "Headache in Women" review article: Menstrually related attacks being this way — harder, more difficult to treat —what kind of impact do you find that has on women?

Dr. Pavlović (12:57): Well, like everything else that takes the wind from your sails, right? It's debilitating. And knowing that it'll repeat itself every month can be very disheartening. The way to reframe that is that: "Well, I know that this [will occur]. I'm keeping this diary. I have mastered it because I know when it'll happen. And I have tried these different treatments and I have found one that works for me during this time. And I am willing to take it and to proactively treat, rather than wait and be at the mercy of it."

Elizabeth DeStefano (13:39): So, we're going to shift gears now from menstrually related migraine to perimenopause and migraine in that stage of life. So first, could you give us a quick definition of premenopause versus perimenopause?

Dr. Pavlović (13:53): Sure. And thank you, because that's a very important question. So premenopause refers to the phase of life that precedes menopause. And it can be tricky because it can both encompass perimenopause and premenopause, as in ovulatory cycles that are characterized by menstrually related migraine that we were just discussing. So, reproductive age. Perimenopause is a term that means "around menopause." And it's really a time when changes in intermenstrual cycle and intermenstrual cycle irregularities start to happen, and menopause-related symptoms start to happen. And it extends beyond the final menstrual period, which is ... The final menstrual period occurs, and then — after the final menstrual period — another 12 months have to pass when menopause finally is considered to have started.

Elizabeth DeStefano (15:00): A viewer, Linda, notes that her migraine condition was triggered by menopause. Others note the same for perimenopause. Why is that?

Dr. Pavlović (15:10): So that their headache first started in menopause and not before? So that is an unusual scenario. What typically happens is that women who have migraine — the prevalence of migraine peaks in the late 30s, early 40s — and women who have migraine will experience an increase in the frequency of headache during perimenopause. Now, during the perimenopause, when hormones can move and change in all kinds of ways from cycle to cycle,

from woman to woman ... Within a single woman, one cycle can look one way and then, you know, the next one will be completely different in terms ... Yes, you know...

Elizabeth DeStefano (15:53): Yes!

Dr. Pavlović (15:54): A lot of variability, a lot of change, you know? To see just the hormonal diagrams of cycle changes is dizzying, right? And so, all of that means unpredictability of attacks, right? And it also means an increase in the frequency of attacks, especially in those who are more susceptible to hormonal fluctuations. So, typically we see increasing headache frequency among women who are in perimenopause, who are still having an occasional period which is not regular, off and on, and who partially ... And these headache frequencies increase partially because they've lost the ability to use mini-prevention, because things creep up on them in unpredictable ways. And also, because there's just a lot more hormonal change. Now, generally with menopause, and not immediately because women still ... Though menopause will occur — the final menstrual period will happen, 12 months will pass — and there's supposed to be hormonal senescence, but this is not an absolute hormonal senescence.

Dr. Pavlović (17:05): And some women still continue to have some mild hormonal changes. We know that for example, hot flashes and night sweats, which is something commonly studied in menopause literature, will continue in menopause. You know, when those 12 months post-final menstrual period happen ... It's not like a magic clock just says, "All symptoms stop," you know, "Symptoms stop, no more!" The helpful thing is that as senescence of hormones progresses, migraine generally subsides, quiets down. And a lot of women will kind of, you know, age out of their migraine. This is the one reassuring thing that, to a majority of patients, we can tell while they're suffering through perimenopausal kinds of bursts of headache. So, for Linda, that is an unusual and very frustrating scenario to get — to start really presenting with migraine, if this is for the first time, in menopause.

Dr. Pavlović (18:09): Sometimes what happens is, in my clinical experience, is that women who have menstrually related migraine ... When they are bleeding and experiencing abdominal pain, they will actually treat because they have dysmenorrhea. They will treat those other symptoms and by treating them, they will also treat the headache. And then when they lose that ... So, they've actually treated their headache unintentionally, but they've dealt better with it. And once they lose the bleeding component of it, they will just experience the headache and be kind of, you know, dumbfounded by it. It will be unmasked in a way. Sometimes, that is actually the scenario. And with good history taking — seeing a neurologist — that can be teased out. In those women where headache really starts — migraine starts postmenopause — they should be worked up, in case this could be something else, because that is not a common scenario but occasionally it does happen. And you know, if everything else is negative after the workup, treating it like every other migraine — with acute treatment and then with preventive treatment, if needed — is what's recommended.

Elizabeth DeStefano (19:27): So, in the case of what Linda mentioned, it could be that this is a new recognition of migraine that was previously there, but was being either unintentionally treated while treating something else, or because new, increased frequency at this stage of life brings greater awareness?

Dr. Pavlović (19:47): Correct.

Elizabeth DeStefano (19:48): If it is truly new, it should be something that is worked up separately for evaluation of other causes?

Dr. Pavlović (19:55): Yes.

Elizabeth DeStefano (19:56): Do the hormonal changes that are involved here imply that some attempt at balancing hormones can have any kind of positive impact on migraine?

Dr. Pavlović (20:05): Absolutely. So, hormone therapy has been recommended for women who have a lot of symptoms related to perimenopause changes and through hormonal fluctuations. And the North American Menopause Society came out with a statement in 2016 suggesting this: that hormone therapy should be — it's no longer called hormone replacement therapy, it's called hormone therapy — and that hormone therapy should be considered in women who have symptoms related to hormonal changes and fluctuations, and who can benefit from it. Obviously, these women shouldn't have cardiovascular risk factors and so on, but the dose is ... the main approach is "start low and go slow."

Elizabeth DeStefano (20:54): And for patients who have been advised that they need to avoid hormones — for any of the reasons that you've mentioned, or otherwise — what might come next, in an attempt to achieve the same thing?

Dr. Pavlović (21:07): Hormone therapy is not contraindicated in migraine, even migraine with aura, because these are much lower doses. So, women with migraine with aura — there's no contraindication for hormone therapy. And this is not something that's often recognized and women themselves have been told so often, "You are not to use hormones," that they believe that they're not. So that is something to be considered. There are other reasons why hormone therapy — such as, you know, history of cancer and so on — that is a different, separate issue to be discussed with gynecology. But you know, even in those situations, sometimes we have had situations with patients where maybe for just two or three months, for a very brief interval of time, in stabilizing headache while we get other approaches on board. Sometimes that kind of approach can be tried — briefly — assuming the woman doesn't have cardiovascular risk factors and so on, which is obviously a contraindication.

Elizabeth DeStefano (22:13): So, interesting: That can be used actually for a short-term approach?

Dr. Pavlović (22:17): Short period of time, yes. I think that we often think of these approaches as something that we get wedded to, and this is now a life ... you know, forever. And the reality is that sometimes we can use these approaches to probe out, is this the solution, you know? To feel out: Is this what's going on? And maybe the patient cannot stay [on them], or the risk versus benefit is such that it's not beneficial to stay [on them], but then, at least, you know what you're dealing with.

Elizabeth DeStefano (22:52): That's very interesting. Dr. Pavlović, you mentioned that many women — following menopause — do find that their migraine attacks decrease in frequency and severity and so forth. However, we do then, of course, hear from a number of our viewers who find that that does not happen to them — that they're not in that fortunate majority. So, when that's the case, how do you primarily treat that migraine — migraine in patients after menopause? And how does that differ from what we've discussed about during menopause?

Dr. Pavlović (23:32): I think one has to — especially when in menopause, migraine persists and persists intensely — one needs to treat it aggressively with, likely, multiple preventive agents. Also, menopause generally means ... The average age of menopause in the United States is 52, at this time. So, being postmenopausal generally means also at an older age, right? And at this point, other musculoskeletal issues come into play: cervicogenic headache, you know, back pain and so on. So, addressing those also can improve headache. But I think in terms of just speaking strictly about migraine: using preventives no longer if ... If a woman was able to function well with mini-prevention in the past, and now she no longer can, using aggressively preventive agents, switching preventive agents if they don't work and working incrementally on finding the treatment that does work. Some patients can be very reluctant and just exhausted by years ... You know, by age 52, there's been many years of migraine and a lot of suffering and just the frustration of failed treatment. But I would say that a lot of new treatments do work and that sometimes it's finding — as I'm sure our audience knows — it's about finding the right combination. And so, kind of being relentless and attempting to find that right combination.

Elizabeth DeStefano (25:14): So, this really takes — as any of us who live with migraine know — perseverance and, at different stages of life, maybe pushing ourselves to have open-mindedness to consider new things. So, for a woman postmenopausally, you may be introducing for the first time, prevention or adjusting prevention. All with the idea that we need to adapt to where she is at that point.

Dr. Pavlović (25:38): Absolutely. And sometimes medications that didn't work for someone when they were much younger, may work. They're worth revisiting. You know, it's not the same body. It is not the same system. It has gone through perimenopause and menopause. So, it is sometimes worth considering agents that were tried in the past and were not successful, so to speak, as well as the new agents.

Elizabeth DeStefano (26:12): Well, Jessica — and I'm sure, a number of our other viewers — wants to know what providers can diagnose and treat hormonally related migraine.

Dr. Pavlović (26:22): So, headache specialists, of course. Neurologists are capable of diagnosing hormonally related migraine and, I would say, are increasingly in tune with it as it's becoming more of a topic that's spoken about. And also OB-GYNs — obstetricians and gynecologists — who often play a primary care doctor ... not always willingly, but often serve as primary care doctors, realistically, to reproductive-age women. They certainly see a great [deal] of hormonally related migraine. Now, this is not the focus of their practice to now have calendars and keep diaries and suggest treatment. But I would say that the majority of physicians practicing in women's health would probably at least recommend an NSAID like naproxen or ibuprofen for perimenstrual attacks.

Elizabeth DeStefano (27:29): Many people in our community have been very clear about expressing their deep wish that there was collaboration between the provider who treats their migraine and their OB-GYN. Is there any way to foster that collaboration?

Dr. Pavlović (27:47): Having your doctors talk to one another is the best. You know, through My Chart systems that now exist, that can be helpful. Being very clear, I think; always having very good medication lists and clearly organized histories that are precise but not overly exhaustive, so that signal can be seen, is very helpful. It's helpful to come out with printed diaries. I've definitely been … when in the office while the patient is there, we call the gynecologist and we

were all on the speaker phone. You know, that that is not always easy to do but it's great when it can happen.

Elizabeth DeStefano (28:34): Are there any final thoughts that you would like to share with women who are dealing with hormonally influenced migraine?

Dr. Pavlović (28:43): Well, thank you for that. Thanks, Elizabeth. And thank you for asking such thoughtful questions throughout this. I would like to say that migraine burden is real. Migraine is real. The burden of hormonally related migraine is particularly real. That what you're experiencing is very hard, but that there are treatments for it. And that sometimes you may have to work harder to get those, depending on where you live and what your resources are and what is available to you. You may have to work harder to get to them, but they are out there. And headache practices exist across the country. The American Headache Society has put in efforts to design specific modules that we're working on for women's education in migraine, specifically on these topics that we just discussed. And we are working hard on educating more and more primary care doctors, OB-GYNs, and general neurologists on these topics. So, be hopeful and look for treatments although it may take a while.

Elizabeth DeStefano (30:07): Thank you for all of the work you do, and the care you provide in this area. And thank you so much, Dr. Pavlović, for joining us on the Migraine World Summit.

Dr. Pavlović (30:17): Thank you so much, Elizabeth, it's truly been a great pleasure. And thank you for asking me such thoughtful questions.

Elizabeth DeStefano (30:25): Thank you.