



MIGRAINE WORLD SUMMIT

INTERVIEWS WITH WORLD-LEADING EXPERTS

TRANSCRIPT



BALANCING HORMONES FOR MIGRAINE MANAGEMENT

ANNE MacGREGOR, MD
PROFESSOR
CENTRE FOR REPRODUCTIVE MEDICINE
ST BARTHOLOMEW'S HOSPITAL, LONDON, UK



Introduction (00:05): Balancing hormones literally means that if we have identified that the natural fluctuations and natural hormone environment, the fluctuations within it are a factor in triggering migraine. And particularly as those fluctuations become more variable in women getting to perimenopause, the aim is then to try and literally balance those hormones out. So, provide a more stable hormone environment.

Elizabeth DeStefano (00:39): Hormones are a part of everyone's life, but even when there's nothing wrong with our hormones, they can act like a wrecking ball on our migraine condition. To complicate matters further, our hormones change drastically at different stages of our life. How do we know if balancing our hormones would be a benefit to our migraine condition? What does that mean and how is it done? Here to answer some of our common questions and concerns is Dr. Anne MacGregor. Dr. MacGregor, welcome back to the Migraine World Summit.

Dr. MacGregor (01:09): Thank you very much for asking me.

Elizabeth DeStefano (01:12): So, there's tremendous interest in this topic, and as you'll hear, a lot of questions from our Migraine World Summit community. So, let's dive in; starting with perimenopause. A lot of women share that their migraine condition worsens, sometimes dramatically so, during perimenopause. Why is this?

Dr. MacGregor (01:32): Very simple answer, it's: As women approach perimenopause, their hormones change from the much more stable levels that we've had through our natural reproductive years. So, by the time we get to the beginning of perimenopause — usually in early 40s — then we start to get a little bit of hormone chaos going on — so that in particular. The estrogen levels start to fluctuate considerably, and women will only produce the other female hormone, progesterone, if they ovulate, and ovulation becomes less and less frequent as we approach menopause.

Elizabeth DeStefano (02:18): What is the role of those hormones in migraine?

Dr. MacGregor (02:23): So, with respect to hormones of migraine — and particularly with respect to what we see with menstrual migraine — we see that the natural fall, the drop in estrogen, in particular, that is around the period time, can trigger off migraine with aura. And very high levels of estrogen have been associated with triggering migraine aura. So, if we're thinking about this hormone chaos, and women are spiking higher levels of estrogen at some times of the menstrual cycle, they might experience attacks of migraine with aura, or just migraine aura on its own. And as they're heading towards their period or around their period time, peri-menstrually, because of the higher estrogen levels, there's a bigger drop as a natural part of the menstrual cycle. And that drop we know is associated with triggering migraine without aura. I do think it's important to also add in at this stage, that it's not just directly the sex hormones that are involved in migraine during perimenopause; women also experience a lot of menstrual disorders as well. And we're also aware that heavy menstrual bleeding — so women who are experiencing very heavy periods and often very painful cramps which becomes another problem during perimenopause — that's associated with an increased release of another hormone called prostaglandin and — totally independently — prostaglandin release is also associated with a menstrual migraine trigger.

Elizabeth DeStefano (04:06): What does balancing hormones actually mean? And is this the same as HRT, MRT, or hormone therapy, as we may hear it in various areas of the world?



Dr. MacGregor (04:20): Yes. So, balancing hormones literally means that if we have identified that the natural fluctuations and natural hormone environment, the fluctuations within it, are a factor in triggering migraine. And particularly as those fluctuations become more variable in women getting to perimenopause, the aim is then to try and literally balance those hormones out. So, provide a more stable hormone environment, rather than the fluctuating hormone environment. Now, perimenopause is probably the most difficult time to balance the hormones out because if we're trying to achieve that with hormone therapy using hormones that are very similar to the natural menstrual cycle hormones, so hormone replacement therapy or menopause hormone therapy — in whichever country you're listening from — then these do not override a woman's own natural menstrual cycle. So, one has to be very careful in perimenopause versus postmenopause, not to add further fluctuations.

Dr. MacGregor (05:43): So, while adding back replacement hormones will help the troughs — the dips — in the natural hormone changes, it may also be adding an extra peak to the natural hormones. So it can sometimes, if we get it wrong, create more hormone chaos. And in those situations, to balance out the hormones, it may sometimes be necessary to actually switch the natural menstrual cycle off, put the ovaries into hibernation temporarily, and replace those hormones with more stable non-fluctuating hormones. And for those women for whom it's suitable, that can be something like combined hormonal contraception. Let's get rid of the menstrual period, let's get rid of ovulation; let's get rid of any of the hormone fluctuations in a reversible fashion that is in control of the individual who is using the hormones, and in a safe way for that individual. Because it's not ever any of the hormones that are necessarily dangerous, it's the woman who takes ... and who has the issues that may then generate the risk.

Elizabeth DeStefano (07:05): I see. So, that brings us to a great question of safety. Which I think you've just answered beautifully: That this can be safe. That the approaches, the medications, the hormones themselves, are safe. It's about how that combines in a particular woman. Is that correct?

Dr. MacGregor (07:25): That's correct. And I think at this point it's important to separate out hormone replacement therapy — HRT, or MHT — as being very different from the contraceptive hormones that we use to put the ovaries into hibernation. With the hormone replacement therapy — MHT, HRT — what we are doing there is — often or nearly always, certainly in the U.K. — we use body-identical estrogen. So, it's structurally identical to the estrogen from a woman's own ovaries. And the second hormone that's necessary to protect the lining of the womb from excess estrogen: We will either use a body-identical progesterone or sometimes will need to use synthetic progestogens because they are, for some women, better than the body-identical progesterone. And, those do not carry any risks really over and above what a woman's own natural menstrual cycle would be doing.

Dr. MacGregor (08:39): Now that's quite different from the contraceptive hormones. The majority of which use a synthetic estrogen — ethinyl estradiol — together with a synthetic progestogen, that are used to suppress the release of the egg every month, suppress ovulation, and to essentially put the ovaries into hibernation. Whereas the MHT allows the natural menstrual cycle and ovulation, whatever the natural body is going to do, that still occurs. So, with the contraceptive estrogens, they are shutting everything down. Now, in contrast to the body-identical HRT estrogens, the synthetic estrogens in themselves carry an increased risk of ischemic stroke; so, they make your blood more sticky. Now, we talk about numbers, we talk about twofold increased risk associated with using these hormones. But one has to put that into context that for the majority of women, they are not at an increased risk of stroke. And for



women who have a minuscule risk of ischemic stroke, doubling that risk remains a minuscule increased risk of ischemic stroke.

Dr. MacGregor (10:09): And the benefits may well outweigh any of that risk. So, for example, combined contraceptive hormones will protect you against ovarian cancer. They'll protect you against cancer of the lining of the womb, they'll protect you against colorectal cancer. But you balance this against the potential increased stickiness of the blood, and for women who have migraine aura, in young women under age 45, migraine aura in itself doubles the risk of ischemic stroke. And the reason why that is increased risk in young women and not in older women, is that older women — we start to develop more obvious other risk factors for strokes such as diabetes, hypertension, obesity — all of those other factors come into play. But in younger women, it seems that migraine aura and contraceptive hormones combined together can be a factor in increasing risk.

Dr. MacGregor (11:16): Another point here is that the risk only applies if you are using contraceptive hormones for a contraceptive purpose in women with migraine with aura. And the reason for that is because there's lots of other methods of contraception — that many of which are more effective than taking combined hormonal contraception — that are more effective for contraception. So, why generate an unnecessary risk in a woman for contraceptive purposes, when she doesn't need to? She can use a different contraceptive method that may be more effective. If we're specifically managing a medical disorder, something like polycystic ovarian syndrome, something like endometriosis, something like menstrual migraine, it may then be appropriate in those women to use combined hormonal contraception because for them with the other medical issues, the benefits may outweigh that very small increased risk. So that's really why we see the difference.

Elizabeth DeStefano (12:25): What if you — as you are determining those risks that are really attributed to migraine with aura, to a greater extent — what if you don't know if you have migraine with aura, at a certain stage of life?

Dr. MacGregor (12:43): So, three questions that we ask is: Do you get visual disturbances? But more importantly than that — because you don't want to just pick up the premonitory, irrelevant, visual symptoms — how long do those symptoms last? So, do those symptoms last less than an hour? Do they resolve before the onset of headache? Again, that's typical migraine aura. And actually, a fourth question that can be very useful is: Do you still see them with your eyes shut? And the reason for that is because the aura is coming from the visual cortex at the back of the brain, it's not in the eyes. So, if it's just the spots in front of the eyes, typical of prodromes, shut your eyes and they disappear. Whereas if it's migraine aura, you shut your eyes and you've still got these really bright zigzaggy lines that are still moving across your field of vision.

Elizabeth DeStefano (13:44): That's very helpful, and such an interesting distinction — the idea of testing this through closing your eyes and recognizing if it's present or not, and therefore where it's originating — thank you for that. So, recognizing the importance, obviously, of knowing whether you're dealing with migraine, or migraine with aura, and making some of these determinations, you then have a number of different hormone approaches to choose from. You've mentioned MHT, HRT, or hormone therapy as it may be referred to, depending on where in the world we live. You've mentioned combined hormonal contraception. You've also talked about within those options for what often is referred to as the bioidentical hormones.



How do you determine which approach to take first with a perimenopausal or menopausal patient?

Dr. MacGregor (14:32): So, menstrual migraine is really looking at: Where in the menopause transition might this person be? Do they have any menopause symptoms? Are their periods regular? Do they have any menstrual disorders that need to be managed? What is the most likely underlying mechanism? And so, if they have heavy menstrual bleeding, we'll be looking at menstrual disorders management, which may well in itself manage the menstrual migraine. If they're having the migraine that's starting maybe a few days before the onset of the menstrual period, then it may likely be due to the drop in the estrogen levels. Many of these women, during perimenopause or even just with menstrual migraine, are actually needing contraception, as well. Contraceptive hormones are probably a lot safer than many women realize and can have many benefits, as well. And we're now so blessed that we do have some contraceptive hormones — certainly in the U.K. — that contain body-identical estrogen as is used in HRT rather than the synthetic ethinyl estradiol.

Dr. MacGregor (15:57): And while even oral natural estrogens make your blood a little bit more sticky than the patches, gels, or sprays that we can use for HRT, most women who are younger — unless they are very obese, they've got hypertension — they can actually safely take combined hormonal contraception until they're 50, and maybe a little bit longer, if we are using it, again, for a medical indication rather than [as a] contraceptive. If we are then looking at perimenopausal women, again, it will depend on regularity of periods. They may be more likely to be developing hot flushes or night sweats. If they are experiencing relatively regular periods, then we're probably still having to think of suppressing the ovarian cycle, rather than adding to hormone disruption with hormone replacement therapy. But as they transition further into menopause and postmenopause, if they have significant vasomotor symptoms: Flushes, or sweats; palpitations; anxiety; joint pains; all of those symptoms suggestive of menopause. Then we are thinking: Control hot flushes and night sweats using standard menopause hormone therapy, and that can benefit the migraine, as well. So, it's a transition through, depending on a woman's needs and her background.

Elizabeth DeStefano (17:39): Sure. Now speaking to that latter category, do you then attempt to wean off those hormones at some point after menopause? I asked this because one of our viewers, Karen, shared her fear of coming off the hormones that she's been on for 10 years following a surgically induced menopause. And if doing so could negatively impact?

Dr. MacGregor (18:02): Again, it's back to the individual profile of that woman. But for many women, certainly within the U.K., our guidance is very clear. There is no upper age limit for hormone replacement therapy. It really depends on the individual woman and provided, for her, the benefits of continuing outweigh any potential risks. And we have safer and safer HRT. So, it's back down to that discussion with the healthcare provider and getting good, clear information about looking at: One side potential benefits of continuing, and the other side, the potential risks of continuing, and looking at which outweighs which, for you as a person.

Elizabeth DeStefano (18:51): In an individualized, highly individualized way to be...

Dr. MacGregor (18:56): Has to be. As migraine management, as well.

Elizabeth DeStefano (18:58): Sure. Yes. Now we often hear about the idea that the migraine brain doesn't like change; likes stability in a lot of things, right? Sleep, etc. This seems like



another important example of that as we're talking about hormone levels and how our migraine can react to fluctuations, as you've shared. And one of our viewers, Ruth, talked about how dramatic her migraine change was after removal of her ovaries, [and] talked about how she seemingly became chronic overnight. Is this an example of a response to a drastic fluctuation?

Dr. MacGregor (19:40): Yes. It's not just that, it's how the whole brain is affected. When we think about hormones, we often just think about our ovaries, and we don't think about our brain. And estrogen is a very strong, active hormone within the brain, as well. The other thing within the brain is our hypothalamus, and our hypothalamus is where much of the migraine seems to emanate from. It's the master of our whole hormone orchestra, if you like. It regulates our menstrual cycle, it regulates our sleep patterns, it regulates our thirst, it regulates emotion: It's central. And it's also central to migraine. It's central to the drive of our menstrual cycles. So, if we remove the ovaries, the brain is trying to send messages to ovaries that no longer exist. And certainly, temporarily, the brain goes into overdrive. It's lost its balance of things and migraine will significantly worsen. If you do nothing, time will balance it all out.

Elizabeth DeStefano (20:57): I think that those of us living with migraine have certainly become accustomed to the idea of needing patience. So, I guess this is one more example of where we need to call upon that. Many have been told that migraine will dramatically improve for a lot of people after menopause. Of course, we find that is not true for everyone who lives with migraine. Are there any differences in the likelihood of realizing those improvements to migraine after menopause based on what your own history of migraine has been? Whether it's been migraine with aura, migraine without aura, menstrual aura — predominantly — that can give us any indication of our future with migraine?

Dr. MacGregor (21:45): Very definitely, yes. Migraine without aura — that has linked to the hormone cycle, that has improved during pregnancy — where we get not to stable estrogen levels, but a lot of other things go on that can benefit migraine during pregnancy. But removing the menstrual cycle at that time, seeing these strong increasing hormonal association during perimenopause, we know that in those women: The further years they are away from their last menstrual period, the greater the likelihood of improvement of their migraine without aura. In contrast, migraine with aura can often begin for the first time postmenopause and be a little bit more of a problem. It's less likely to improve. It seems to be, sort of, completely different ... have a different drive to it. But with the hormone migraine and postmenopause, there is this sense of: "Oh, I've got my last menstrual period and my migraine's going to get better now." Patience again, I'm afraid, has to be considered at this time because ovaries don't just suddenly switch off. Menopause is a marker for the ovaries no longer producing eggs — so no longer ovulating — but it's not a marker for ovarian activity. So, your ovaries will still be active, probably for about another five years after you've reached your last menstrual period, gradually becoming quieter and quieter and quieter, because they're still trying to respond to the messages from the brain telling them to create a menstrual cycle every month.

Elizabeth DeStefano (23:44): Another of our Migraine World Summit viewers, Amber, wonders if there are any herbal methods that help both with hormone balance and associated migraine?

Dr. MacGregor (23:54): Yes, agnus-castus can be a very effective herbal treatment — that's chasteberry — and we see that's quite helpful for things like premenstrual syndrome. We've seen it, sort of, balance out a number of the perimenopause symptoms and the correct dose of that, if anybody is interested, that's been shown in clinical trials is 20 mg, and that's equivalent to about 400 mg of the dried product. The other one that is also used for menopause symptoms



is St. John's wort: So that acts on serotonin. Serotonin interestingly, we know that it's associated with migraine, but it's also the thing that drives the hot flushes. It causes the blood vessels to constrict and dilate, and so serotonin's working in parallel with the estrogen. So, if you can't take estrogen, or don't want to take estrogen, you act on the serotonin, and acting on the serotonin can also benefit migraine and menopause symptoms too.

Elizabeth DeStefano (25:09): Let's touch a little bit on where, and with whom, we can partner to attempt best to manage our migraine. Because of its immense burden in the aids to management of headache disorders in primary care, in *The Journal of Headache and Pain*, you and your team highlighted the importance of migraine being well managed in primary care, with the exception of chronic migraine, which you note likely requires specialist management. What about hormonally related migraine? Can it effectively be managed at the primary care level? You've mentioned so much nuance to this that it makes me question...

Dr. MacGregor (25:49): So many people with migraine, they don't know whether to go to their gynecologist; they don't know whether to go to [a] neurologist. The neurologist will say, "I don't know how to manage the hormones." And the gynecologist will say, "I don't know how to manage the neurological aspects of this." The people who understand best, often — how to manage contraceptive methods, how to manage hormone replacement methods — are actually the physicians working in primary care. So, we just need to enable them to be more confident in managing. It's them that the information needs to be provided, with the tools to know how to manage migraine and develop that confidence in managing migraine, because they're the ones that work cross-specialty.

Elizabeth DeStefano (26:40): So, how else do you see hormonal management of migraine evolving over time?

Dr. MacGregor (26:48): Well, first of all, better identification of a problem; better identification of migraine in the first place. Because the most common misdiagnosis of migraine without aura is sinusitis. So, particularly women who have been identified with having monthly sinusitis — we need to start thinking again. Simple diaries ... so many women are not aware that they have this hormonal link because they haven't kept records. They don't link up the menstrual cycle with the migraine attacks that they are getting, and very simple diaries — just looking at patterns — can tell you a huge amount of what's going on. So, better recognition; better treatment of migraine in itself. So, it's important, although we've been talking about hormones — we've been talking about hormone treatment — the major thing is to make sure that the migraine attacks are being optimally treated. So that women treating their migraine attacks are taking the right dose, the right drug, at the right time.

Dr. MacGregor (28:06): They're aware that particularly for hormonal migraine they may need to take that treatment over several consecutive days, because the triptan will wear off after 24 hours, and if you've got a four-day migraine, you need to be repeating it. And that's not necessarily going to lead to medication overuse because they may then not take anything for the next couple of weeks. So again, it's looking at the patterns of use, not just going in with, "You can't take it longer than three days." Look at what the individual is experiencing. We also need to start working much more cross-specialty, as well, and making a noise about managing migraine. Certainly in the U.K., we've seen some really good social media drives that have raised the profile of managing menopause. We need to do the same with migraine: We can't keep talking about, as I was, just about educating the primary care physicians. We need to get the people with the problem, the women with the problem, to shout out loudly because that's the



only way that we're going to drive and force a change at the other end. As has happened with menopause here.

Elizabeth DeStefano (29:23): What a great reminder to so many of us to remember our potential as advocates. So, are there any resources that you'd like to point any of our viewers to, on the topic of managing hormones in treating migraine?

Dr. MacGregor (29:41): For women, there is a website called Women's Health Concern, and just Googling "women's health concern," it comes up and it's got some really useful fact sheets, including migraine, menopause, and HRT; it's also got ... about contraception. It's got lots of fact sheets on women's health problems, as well. For healthcare professionals, we have the British Menopause Society guidelines, as well, and those are available to healthcare professionals. And there is one on migraine and menopause. There's also lots of publications that I've written that if people go to my website, www.annemacgregor.com, and they go to publications that link straight to my ResearchGate page, which has a list of all the publications, many of which people can directly access.

Elizabeth DeStefano (30:38): We've learned so much today about the topic of hormones, the role in migraine, and how to approach hormone therapy in managing migraine at various stages of our lives. Thank you so much Dr. MacGregor, for sharing your time and expertise on this topic.

Dr. MacGregor (30:52): You are very welcome. Thank you.