Unknown Speaker 0:05
Welcome to this podcast series on evidence in women's health brought to you by the Centre for Evidence-Based Medicine and the postgraduate programme in evidence based health care. My name is Dr. Anne-Marie Boylan, and I'm a senior researcher and lecturer in the programme, and together with Associate Professor Jamie Hartmann-Boyce, we'll be interviewing relevant experts discussing the strengths and limitations of different sources of evidence as they relate to women's health and considering their implications for future research.

Unknown Speaker 0:31
Hi I'm Jamie Hartmann-Boyce, Director of the Evidence-Based Healthcare DPhil programme and Assocaite Professor at the Nuffield Department of Primary Care Health Sciences here at Oxford.

Unknown Speaker 0:32
In this episode, we're discussing menopause, and particularly hormone replacement therapy or HRT, and we'll hear from Dr. Elizabeth Spencer and Professor Carol Coupland, both of whom have conducted research on the risks of HRT using large databases. Notably Dr. Spencer was involved in the landmark million women's study.

Unknown Speaker 0:52
This was in the news quite a lot this year because of shortages in hormone replacement therapy or HRT here in England, but we know hormone replacement therapy for menopause has had kind of a chequered history with peaks and troughs in terms of its use. And a lot of that is actually related to the evidence on the relative risks and harms of HRT and the ways in which that's been covered in the media. And so what we wanted to do today was talk through some of these big studies about HRT and what they've shown us and what we still don't know. But also Anne-Marie, I was kind of wondering if you have any takes from the qualitative research about menopause and HRT that might help us think about how we interpret the quantitative studies we're about to talk through.

Unknown Speaker 1:36
Before thinking about the qualitative literature, I think it's worth putting into context in relation to the main biomedical view of menopause, which is that it's an ending the end of fertility and the end of menstruation, which are accompanied by a series of physical symptoms. And of course, when you think about it in this way, it's not surprising that most research has focused on seeking treatments for the physical symptoms. And obviously, this is helpful, but it means that the psychosocial and experiential aspects of menopause have been largely neglected. And this is where qualitative research is really helpful, because qualitative research tends to look at experience, and how things like HRT and menopause affect daily life. And there is a body of literature looking at how women experience symptoms and what they mean for how they live. And this was synthesised in a systematic review of qualitative studies by Holger and colleagues in 2015, who note that menopause was seen as a natural part of midlife and ageing that includes losses and gains, and that the physical and emotional effects of it can have a significant impact on women, and that women use strategies to improve their impact. They also note that multiple factors influence how women experience sex, and conclude that preparation for menopause and good support are needed. They also find that in the studies that they included that health professionals could do more to listen to women experiencing menopause, and tailor health care according to their individual needs. I don't think this needs to be seen as bashing health professionals or criticising them. But it's probably more reflective of the wider socio cultural understanding or lack of understanding about menopause, how it's experienced, and what it means for women. I have been looking to see what literature is out there. And there isn't actually a huge amount, which is quite a surprise, and certainly not in recent years. There's been some stuff done prior to the year 2000, but one by the Salas in 2016. And they interviewed mothers about their feelings around menopause, and conceptualise this as sort of a three stage process or three potential ways of experiencing menopause. And one was about it being a normal biological process. So for women, it could be just something they

see as normal, or something that is distressing, that's characterised by identity loss and challenges and stress and shame as well, or something that's transformative and liberating. And one of the interesting things that they raised from their interview study was about how HRT was something that helped to reset the experience for women. So it became something less onerous and maybe slightly more normalised for them. I think the important thing to say about this is that it was with mothers. So these were women who had had children. And so the normal biological process meant that, you know, part of this was the loss of their fertility. And obviously, for women who haven't had children that might be a bit more distressing. So we don't know that from this study. It's interesting that there hasn't been a huge amount of focus on this in terms of the quality of literature, which is something that needs to be addressed. I think.

Unknown Speaker 4:41
I just looked up the NHS website page on HRT, and it talks about understanding the risks and harms. So it kind of just starts off saying many studies published over the past 15 years highlight potential risks of HRT, and as a result, some women and doctors have been reluctant to use it. But then on the other hand, recent evidence says that the risks of HRT are small and usually outweighed by the benefits and in terms of benefits that lists reductions and things like hot flushes, night sweats, mood swings, vaginal dryness and reduced sex drive. It also says it can help prevent thinning of bones, which can lead to fracture. But then, of course, what we're going to come on two more two is talking about potential risks, and the ones that are most well known around breast cancer in particular, and what strikes me here as a place where I'd love to see more qualitative work as well is an understanding how we, as individual women might compare benefits and risks because the risk of breast cancer is obviously very serious. There are lots of reasons we'd be concerned about that. But if something like hot flushes or Mood swings are destroying our quality of life or well being or affecting our ability to work or function in our daily lives, how do we kind of weigh that up against something like a risk of breast cancer? It seems a really tricky area, and one where we really need to understand better the different perceptions of different people and doctors when it comes to prescribing HRT.

Unknown Speaker 6:01
Yeah, there are some qualitative studies about how women approach understanding risk, or HRTand menopause. And I'll talk about two papers written by Fiona Walter, which looked to be from the same study, which was an interview study involving current users of HRT, never users and ex users. The first paper was published in 2002. And it find that women largely perceive risk as danger, and that they undergo a process of assessing this risk, which involves information, knowledge and incorporation of their beliefs, and what's important to them. The second paper was published in 2004. And in it, they note that women generally want to know the risks and benefits, but somewhat less of a conversation around this and more of a directive approach. And they also find that for the majority of women that are included in their study, that unbiased, honest, evidence based and personalised information about their individualised risk, could aid in decision making around hate to a tee, which is seen as something that's shrouded in complexity and uncertainty. And I know that there's a government working group that's looking into the impact of menopause on women's working lives, because a lot of women drop out of the workforce during menopause, or experienced discrimination at work because their symptoms aren't taken seriously. So I think there's a lot of this sort of stuff that aside from the risk does need further exploration, because we do need to know about waist to minimise the impact of hot flushes and things like that, that may really really characterise problems for women and make it difficult for them to remain in the workforce or to work comfortably.

Unknown Speaker 7:37
Absolutely. And I think, you know, what we've seen anecdotally this year is that shortages of hormone replacement therapy here in the UK have been really, really difficult for people going through menopause to manage, and it shows just how much some women value having HRT available to them. And I find this kind of

interesting, because I did my masters in the history of medicine. So kind of historical perspectives on disease and treatments. And so HRT is something that was originally hailed as being a wonder drug. I'm reading an Oxford news page on the million women study here, which was a really large study, which we'll talk about more that looked into HRT. And what this page just says is that essentially originally touted as a wonder drug better fit in health, vitality, and femininity, whatever that means. That's what happened when HRT first came on the scene. And then sales began to decline, because there were a number of studies showing increased risks of cancer sales then went up again in the 80s, as these studies left the public consciousness, and then about 20 years later, a number of studies including a really large study in the US called the Women's Health Initiative, and the million women's study launched in 1997, here in Oxford came out indicating that HRT was associated with a number of serious health problems, but most kind of notably, and I think most present in our public consciousness in the media was an increased risk of breast cancer. So in terms of million women study, what it set out to do was to better understand the risks of hormone replacement therapy from a European perspective, kind of complementing the US Women's Health Initiative trial. And to do this that recruited a large number of UK women to investigate how reproductive history might affect women's health. It's since recruited 1.3 million UK women, and it is viewed really largely as confirming the relationship between HRT and risk of breast endometrial and ovarian cancer. It is thought to be really one of the things that led this to this dramatic reduction in terms of hormone replacement therapy, prescription patterns and guidelines about 20 years ago, I was really curious to talk to someone who was involved in this original trial and was lucky enough to talk to Liz Spencer from our team about that. So we're just going to play you a clip from that interview.

Unknown Speaker 9:53
My name is Liz Spencer. I'm an epidemiologist. I work within the centre for evidence based medicine. Prior to that, I worked at the Cancer Epidemiology unit. looking at data from large scale prospective studies, a million women's studies, over a million women were recruited about 1.3 million women, which is a huge achievement based in the UK. And it recruited women starting in about 1996 97. And it had the focus of looking at hormone replacement therapy and cancer risk, it recruited women around age 50 to 64, and then follows them up prospectively. So it's still going at the time of recruitment, one in four women who are eligible join. So that's enormously representative. I think it was hugely influential. There have been concerns before the publications of this study and the Women's Health Initiative trials. partly the reason why the studies were established such a large study producing an estimate, which showed that breast cancer was increased among users of HRT, compared with never users. prescriptions for HRT fell quite dramatically over the following years. And I understand they're still haven't recovered to their earlier level, they may have fallen to around half what they were. And you can look at the timeline of that data and really see it's reflected in the information from the million women study coming out. So it's very large, and it has this capacity to continue to put out data because it's linked into information registries such as cancer registry, and this capacity to continue to ask more of the participants as new questions arise. studies that have come out since have generated slightly different effect estimates. On the whole, they have shown slightly lower increased risks among HRT users compared with never users. Now how to interpret that in relation to the size of the estimates from the Milgram study, there are a few things that could be different between those studies. So prescribing patterns and reasons may be slightly different. Women who take HRT may differ in other ways since that time, so the estimates were in the men and women study, I think we're really important in pinpointing that there is an association for HRT use and breast cancer. And there may be real effects of differences in preparations and in prescribing patterns. And I think that the subsequent studies are really important to drill down and find out more about what's going on in those relationships.

Unknown Speaker 12:27
To me, it was really interesting listening to Liz speak there. So she said that

this was a huge study and 1.3 million women who have been included in it so far as a huge number. And what's also impressive is that one in four women who were going through menopause took part in it at the time of recruitment, which again, is a significant thing in terms of the representativeness of this cohort. So I mean, it's just a good quality study.

Unknown Speaker 12:52
It's a really important study, I think it's kind of incredible what it says about the ability of our institutions to do science to recruit this money, women. And for a lot of these kinds of associations that we're looking at, we might actually have relatively low absolute rates. So we might need quite big studies in order to pick up on differences in relative risk. So for example, here, the kind of landmark 2003 study, looking at the links between HRT and cancer had more than a million women, it had 9364 cases of incident invasive breast cancers, and 637 breast cancer deaths. So all of a sudden, your numbers fortunately, got a lot smaller going down from a million when we look at severe outcomes. One thing that I think isn't a fault of the study, but maybe it's something we need to think about when we think about the way in which it was interpreted and used is, first of all this difference between absolute and relative risks and what it means when something increases the risk of cancer, if that increase is relatively low to start with, but also I think the way this was kind of reflected was in blanket statements that HRT increased the risk of breast cancer and therefore shouldn't be used. But actually, even if you dig into that study a bit, you find that past users of hormone replacement therapy weren't at an increased risk of incident or fatal breast cancer. So it was only in the people who are currently using HRT where they we saw this and that there was some variation in terms of the preparation. So whether it contained oestrogen or only, or a mix of other hormones, and also that there was some evidence to suggest that duration of use might have something to do with it at all, as well. So I think it was a study which was really well conducted really impressive for its time, teased out a lot of information and then seem to get reduced in the media and the public consciousness and just one or two headlines, which then massively reduced prescriptions of HRT.

Unknown Speaker 14:47
We know that people rely on the media quite a bit to get information. But we also know that the media isn't very good at portraying risk or in fact, at research evidence very well at all. So I suppose it's them. important to think about how best to explain these things to the public in ways that they can understand and make a risk assessment for themselves.

Unknown Speaker 15:07
Absolutely. And I think it's really important. We always say whenever we're talking about the benefits of a healthcare intervention, including any medicine, we should also talk about its harms. It's really difficult to think of any examples of healthcare interventions that have benefits and don't have harms. But I think similarly, when we talk about the harms of interventions, we should also be talking about their benefits, right, just so that we can always make sure that people have enough information in their health care providers have enough information, that they can make decisions based on all of the evidence instead of just the evidence on one particular risk or one particular benefit.

Unknown Speaker 15:40
I spoke to Carol Coupland, who's a medical statistician here at Oxford, and also professor at Nottingham. And she was involved in a study that use two databases in English general practice Q research and the clinical practice research data link that looked at the type of HRT and how long women were on it and how recently they'd stopped it, and the risk associated with all of these things.

Unknown Speaker 16:04
I'm Carol Coupland, and I'm a senior researcher in medical statistics and epidemiology in the Nuffield Department of Primary Care Health Sciences in Oxford, and I'm also a professor of medical statistics in primary care at the University of Nottingham. We've carried out a few studies looking at HRT and

some of the risks associated with HRT that are of most concern, particularly the study looking at the breast cancer risks associated with different types of HRT. We found that the risk depends quite a bit on the type of HRT that was prescribed and how long it was taken for and how recently HRT had been used. Generally, we found that there was no increased risk when HRT was just taken for less than a year. But then subsequently, risks started to increase with the duration of treatment, and in particular, they were higher if treatment was taken. For longer than five years, the risks were quite low for oestrogen only treatment, but became higher when combined HRT was used. So that's HRT combining oestrogen with progestogen treatment. Also, we found that once HRT had been stopped, the risks started to decrease quite rapidly, and there were generally no increased risks after stopping for more than five years, the oestrogen only treatment, long term use of over five years, and among women who have used that treatment recently had around a 15% increased risk of breast cancer overall, whereas for combined treatment, there was nearly an 80% increased stress for long term users amongst women who had taken that treatment quite recently, we also stressed the numbers in terms of excess risk for every 10,000 women who were treated. So that gives us sort of absolute increase in risk rather than the relative increases. And for the oestrogen only treatment, there were between three to eight excess cases of breast cancer among women taking that treatment depending on their age. But for combined treatment, there would be between 15 to 36, estimated additional cases in women of breast cancer per 10,000 treated depending on their age. So the numbers are a bit lower in younger women than in older women taking HRT. I think it's always very important to have both sets of risks. So the relative risks as well as the excess risks which you can interpret more as an individual, what that would mean to you, relative risks can seem quite high. But if the absolute risks are low, then then that's something that you need to sort of weigh up in terms of the benefits. Broadly speaking, the risks were comparable with those of other studies. And that was important. Because we had two enormous primary care databases, we felt we were able to drill down more and look at risks in more detail according to specific type of HRT, and the duration and recency of use. But we were quite sort of prompted to carry out the study and we compared our risks that we found with a meta analysis that had been published in The Lancet and that caused quite some concern that was in 2019, and tended to find higher risks than we found them meta analysis included 24 Different studies and they'd been carried out in different settings in different countries had looked at different age ranges maybe hadn't taken account of some other confounding factors that we took into account. So there's no one obvious clear reason for the differences but there are sort of several differences between the two studies which be helpful to look at in more detail for our study, which again was very large database study we didn't find So overall that there were any increase risks of dementia associated with HL T's we've just found a slightly increased risk of Alzheimer's associated with long term use of combined HRT. Just something to be aware of, and for doctors and women to have those that information available when considering HRT.

Unknown Speaker 20:20
What I thought was really interesting, from Carol's interview Jamie, was the way she discussed the various different presentations of risk, and what they might mean and how women can interpret these. So when I was speaking to her, and she talks about a 15% increase and an 80% increase, I was thinking, like 15%, seems manageable. 80% seems huge. But what do they mean in actual terms, and I think the expression of excess risk as three to eight, pretend Boson treated is a much more easy to understand way of displaying this type of thing.

Unknown Speaker 20:57
I absolutely agree. I think it's so important to see both and I think increasingly in recent years, we've seen a push towards that. So for example, Cochrane Reviews now have the summary findings, tables, and included in that as well as the certainty of evidence, they have what they call the absolute risk, as well as the relative risk because it's really difficult to interpret one without seeing the other and often the relative risk can seem a lot more alarming than the absolute risk, once you take a look at it. I just thought that was a great clip from Carol, it made me think a couple of things. One of them is

just how brilliant it is, and how lucky we are to have access to this kind of level of granular information from general practice databases, which is really difficult to collect in other ways. You know, if you ask someone, how many weeks exactly were you prescribed HRT for? Or what formulation of HRT were you taking and that was 10 years ago, it's going to be really difficult for people to remember that. And that is why it is so so useful to have this information recorded in general practice databases that then can link to long term health outcomes. Of course, there are still risks here. As we all know, just being prescribed something doesn't necessarily mean you take it or take it as indicated. And there will always be cases of missing data. But I think what's really nice here is to have this information in this level of detail so that as Carol said, they can delve into it a little bit more detail. And the other interesting point that I thought she made was about their results compared to the meta analysis and thinking about why it might have had slightly different findings and in my experience with meta analysing, so I do a lot of meta analysis and systematic reviews, it is so much more challenging to figure out the reasons for unexplained statistical heterogeneity, unexplained differences between studies that are more than those that you'd expect to see by chance alone, when it comes to observational study designs. And the critical reason for that is confounding. Typically, even if studies are taking the same confounders into account the way in which they measure those confounders were really differ. And one of the things that is a useful thing to be considering when we look at observational studies, when they're meta analysed and all put together is thinking about really okay, what confounders did the study authors for each of these studies taken into account? How did they take them into account? And then could that be explaining differences in results between studies? So it was great to hear Carol talk about that, too.

Unknown Speaker 23:21
I think what was striking for me was that this seems to sort of help unpack the findings from the Milliken women's study, and help understand that level of risk more.

Unknown Speaker 23:31
That's absolutely right. I mean, I think some of these things, there were hints of, I suppose in the million women's study. So things like duration of use, or different formulations was kind of coming through in that study already. And then what they were able to do here was looking at in a lot more detail, because they had that level of detail that they could use, and also replicate findings from previous studies in that regard, and give us more precise estimates. So I think when we look at the body of literature on HRT as a whole, this is a really useful addition that helps us understand some of those really critical things that doctors and people taking HRT might want to take into account and consider when people think about whether the risks of HRT might outweigh the potential benefits for them.

Unknown Speaker 24:15
Do you mean the other thing I think that's really underdeveloped is the experiential element of this. So we need more research, from women's perspectives about why they take HRT, what's distressing about their symptoms and how they can be managed. And I think that we need to ensure we're taking a cross cultural lens to that, especially here in the UK, with our multicultural society, because I think there are cultural differences that mean sort of recommendations, current recommendations for women won't apply across everybody or won't be as easy to put into place for everybody as they are for some.

Unknown Speaker 24:50
I think that's a brilliant point. Perhaps a good point on which to close us out for today. I think for anyone listening, trying to think oh, what what might be some more research If I might be interested to do, there are so many unanswered research questions in this area. And I really hope that this is an area that we begin to see more and more research being done into because it's an area that is so relevant to so many people. And the paucity of data is really kind of shocking when we dig into it.

Unknown Speaker 25:15
It was great to have this opportunity to discuss this with you, Jamie. So thank you so much. And also thanks to Liz and Carol for sharing their expertise. And thanks to you all for listening.

Unknown Speaker 25:26
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