**Osteoporosis management in premature ovarian failure and women under age 60**

**Dr Rosie Worsley:** So I thought I'd just start with the basics. What is the definition of osteoporosis? And this is according to the International Society of Clinical Bone Densitometry, who tell us how to run DEXA machines and how to interpret them. So it's really a diagnosis for postmenopausal women and men aged over 50, based on their bone density scan of minus 2.5 or less. The reference group is taken from a large survey of American Caucasian women age 20 to 29, and that's used to calculate T-scores in older women and in men. And there are differences in when manufacturers calculate Z-scores and things like that. So that's quite useful to know, I think, because it tells you about, it is a bit arbitrary, osteoporosis, a lot of it's a bit hit and miss really. So when it comes down to really what is the definition, it's someone who's got a minimal trauma fracture, and by 'minimal trauma' we mean from a standing height or less, in the absence of any major trauma, like a car accident. Or a bone density scan with a T-score of minus 2.5 or less in a post or perimenopausal woman.

So what does a T-score of minus 2.5 mean? So when they did observational studies of bone density in women, and this is an idealised graph of bone density in women age 30 to 40, they found that it was normally distributed, which is not that common in biological measures, but luckily it was. And a T-score really is a standard deviation. So with all statistics and standard deviations, basically 68% of your population is going to be within one standard deviation, 95% are going to be within two standard deviations, and 99.7% are going to be within three standard deviations. So it tells you, what is your T-score actually telling you? If someone's got a T-score of minus 4, they're very unusual, which we all know anyway, but it's really a very small percentage of the population.

But it also tells you that really this minus 2.5, it's a bit of an arbitrary score. Yes, it's based on risk as well, but it's really picking up that 95% of the group. So who are the outliers? But somebody's got to be at the edges. And this is why we worry about T-scores. So in postmenopausal women, T-scores does predict fracture risk. So hopefully you can see, but along here we've got bone density, in grams per centimetre squared, and also as T-scores. And along this side here we've got lifetime risk as a percent of hip fracture. And this is for a woman age 50. So if she's got a very low T-score at 50, her lifetime risk of hip fracture is around 50%. So that sounds really dire, and that's why we worry about osteoporosis. And we worry about it, obviously having fractures is bad, having hip fractures is very bad. So we still have very bad outcomes after hip fracture. A lot of that's because usually hip fracture happens in older people, which is why often the recovery is incomplete or it ends up in people going into nursing homes and things like that. And the mortality at one year is still very high, in the order of 30 to 50% depending on your age.

However, sometimes we look at the T-score of someone who's sitting there perfectly healthy, and they've got a T-score of minus 2.5 or minus 3 and we get very worried, but we do have to remember there are other things that are really important in fracture risk as well. And age is a really important factor. So if we look at a woman, here's age down the bottom here, a woman who is 50 and who has a T-score of minus 3.5, and we look here at her five-year risk of vertebral fracture, her five-year risk of vertebral fracture here is less than 5%. So this is taken from a large meta-analysis. So because we are talking about, particularly in people who haven't had a fracture, and we are just talking about bone density, we're really talking about calculating risks and probabilities when we want to know if we should treat them or not, and which is quite difficult. And again, if we look at hip fracture, yes her lifetime risk is very high and she's going to need some sort of intervention at some point, but if we look at her five-year risk of hip fracture, even if her T-score is minus 3.5, it's still very low.

So we know that we've got some time to do something, we don't have to do anything right this minute necessarily. So when should we be testing bone density? I think we all know this anyway, but particularly in women over the age of 65. And that's really coming from this where the fracture rates really start increasing as you get older. And so when intervening before a fracture is what we want to do, but not so early that we are going to just give them side effects of medication. So in women who are under 65, we particularly want to do it, if they've got another risk factor for fractures, such as low body weight or a prior fracture, or they've got a medication or disease known to cause bone loss, which we'll talk about more later. We also use bone densities a lot to monitor therapy, and I've got a case discussion that sort of talks a bit more about that.

What about in younger women though, particularly premenopausal women? We don't use bone density alone to determine whether someone has osteoporosis if they're premenopausal. And really that's because the statistical relationship between their T-score and fracture risk isn't the same. It's not as predictive, so it's not as good a marker of who's actually going to fracture. So it's not as useful. So what we use in premenopausal women and young people generally is the Z-score, which is really comparing the woman to other women her own age. And instead of using the terms 'osteoporosis' and 'osteopenia', they've decided that we should be using the term 'below expected range for age' if they have a Z-score of minus 2 or less.

Osteoporosis can then be diagnosed in a woman who's got low bone mass for age plus a risk factor for fracture, or a known secondary cause of osteoporosis, or she's actually had a fragility fracture. So if anyone's had a fragility fracture, they automatically have osteoporosis, even if their bone density is normal. So if we are looking at young women, what are the major causes of low bone mass? And oestrogen deficiency is really one of the major ones. So premature menopause, really any cause of amenorrhea. So it could be low body weight, eating disorders classically, but also pituitary causes, things like hyperprolactinaemia, whether that's from a drug cause or from a pituitary tumour, hyperpituitarism generally. And then all the Iatrogenic causes, so women who've had their ovaries removed, women who've had menopause following chemotherapy for breast cancer, et cetera, and certain medications.

So why is oestrogen deficiency so important? So hopefully you can see it in your printouts better. Oh no, it looked really good on the screen. This is a slide taken from, it's a really good review from about three years ago from Nature Reviews Endocrinology, and it talks all about oestrogen and bone, and it's incredibly detailed and it's a very good read. But essentially the take home message from it is that oestrogen has multiple effects, mainly through oestrogen receptor alpha, has multiple effects on pretty much all the cell lines within bone. So it affects the chondrocytes, it affects the periosteal cells. So we've got attenuation of periosteal apposition, so it stops too much bone being laid down, and sort of controlling way in which it's done, but it also attenuates bone resorption, so it's affecting osteoclasts.

So that's sort of, I think, general stuff that sort of makes sense. A thing that I hadn't known, which I thought was really interesting, is that oestrogen receptor alpha can affect bone even in the absence of oestrogen, and it does it through mechanical strain. So in response to mechanical strain, unbound oestrogen receptor alpha actually stimulates bone growth. So I thought that was really interesting, but if you have oestrogen deficiency, you're going to get downregulation of your oestrogen receptors, which means you're going to have less of that response to mechanical strain as well as loss of all these actions as well. So I think that's quite, I thought that was really quite interesting. So you're really, if you've got less oestrogen receptors, you're going to be having less strengthening of bones with the sort of impact exercise and things as well.

This slide is taken from SWAN, so the Study of Women's Health Across the Nation, so I think we probably all know that it's a large study that recruited women who are 42 to 52, and followed them out through perimenopause and menopause. And they tested their bone density on an annual basis. This line here represents the final menstrual period, and this is the years before and the years after. And what they found was that bone density starts decreasing in the couple of years before the final menstrual period, and then it decreases really rapidly after the final menstrual period, and continues decreasing for about the first five years at quite a rapid rate. After that it tends to stabilise and you get a bit of a slower loss, more predictable loss. So this is in naturally menopausal women, but we would expect to see the same or even a more dramatic decline in women who are going through an early menopause, particularly a surgical menopause with that sudden removal of oestrogen.

So with premature menopause as we all know, we're talking about three major classes, people who have the spontaneous primary ovarian insufficiency, women who've had surgical menopause, and then the iatrogenic, mainly chemotherapy-related menopause. There's some evidence that maybe surgical menopause has a worse outcome for bone, but there's not a lot of evidence. There was a very nice study of women with spontaneous POI, they had 442 of them and they compared them to controls. And they found that their bone density on average was about 2 to 3% lower at the spine and the hip, which doesn't sound much, but remember they're going to be having ongoing bone losses over their lifetime. And the fact is that we're associated with having a low bone mass for age, were all the things that you would expect. So low vitamin D, not being on therapy, taking a long time to get diagnosed and start therapy, having a low calcium diet, and being inactive. There's actually very few studies that really do directly compare bone mass in women who have ovarian insufficiency compared to a reference or a healthy group.

And this is just a really small study, but it's a newer one, and it looked at bone density in women with POI compared to a small group of normal women. And they found that their bone density was significantly lower, particularly at the lumbar spine, which is here. So that's the insufficiency group, and that's normal premenopausal women. But also at the femur, but to a lesser degree. And we would expect that, because we know oestrogen decline has a dramatic effect on trabecular bone in particular, which is in the vertebral bones. So what about other causes of bone loss in young women? So medications are one of the really common things that were going to contribute to bone loss, in particular glucocorticoids. So these are your patients who are having lots of steroids for asthma, or inflammatory bowel disease, or who are having chemotherapy with lots of steroids.

Maybe they're having a transplant, were having huge doses of steroids, maybe they've got rheumatoid arthritis. Glucocorticoids have a really dramatic effect on bone density and it happens very quickly. So they can lose between 10 and 20% of bone mass within the first year on high-dose steroids. A dose of steroids that's going to decrease bone mass is generally considered at seven and a half milligrams a day or more for three months or more, but it does have an effect even at five milligrams a day. So steroids I think are probably the thing that I see the most that really, in terms of medications, that really damage bone. We know that there's a small effect of long-term use of Depo-Provera on bones as well, probably through causing an oestrogen deficiency. There are plenty of other chemotherapy-type agents and immunosuppressants that you see in the tertiary referral centres that will cause bone loss.

So things like tacrolimus and things that are not particularly helpful. Methotrexate has a small effect. We know that heparin isn't particularly good for bone, but not many people are using heparin long-term, probably the exception of some women during pregnancy. Anti-epileptics can have an effect as well, which is something we probably more commonly see, certainly not the huge effect of glucocorticoids, but can be important. And the way they, we think they do this is that by inducing cytochrome P450 enzymes that metabolise vitamin D from active to inactive states, that basically they're getting a vitamin D deficiency and reducing bone that way. There are other medications that are being suggested to affect bone loss as well. So things like SSRIs and proton pump inhibitors. The evidence for them is less robust. There's some evidence that maybe SSRIs increase fracture risk, but it is quite hard to tease out, because we think there's a link between depression and osteoporosis as well. So I don't tend to take people off any of those medications, or suggest that they go off them, but in some people it might be a cause or a contributing factor if things aren't going the way you want them to.

And then in terms of other causes of bone loss in young people, really looking at systemic illnesses. And often it's treating the systemic illness that's going to improve their bone density more than any sort of osteoporotic treatments you can have. So classic things like coeliac disease, hyperthyroidism, but inflammatory bowel disease has an effect on bone independent of the use of glucocorticoids. And then all the rarer things like cystic fibrosis, osteogenesis imperfecta, et cetera. Anyone who's been immobilised for a long time is going to have bone loss as well. So that's always another one to look out for. And then there's other risk factors like smoking. And smoking, heavy smoking can have quite a dramatic effect on bone, so around a 5% loss in bone density. So it's a really important one. Again, another reason to give up smoking. And there looks like there probably is a link between osteoporosis and depression in young women, in some of the longitudinal studies. Still not sure how important that is.

We certainly aren't recommending screening every young woman with depression, but it looks like it's, certainly in the epidemiological studies, that there's a signal there. What about hormonal states or reproductive events and bone? There's some suggestion that bone density decreases in pregnancy, but it's not robust evidences, there's sort of conflicting data. In terms of breastfeeding, we know that that does decrease bone density, probably by around 5%. So it's quite a significant amount of bone loss, if you're breastfeeding longer or have amenorrhea for longer, there's more bone loss. It's not just about amenorrhea and loss of oestrogen. The breasts secrete parathyroid hormone related protein which helps to mobilise calcium from bone for the breast milk, and this has an effect on further thinning bone. But we know that women will recover their bone density when they finish weaning. It can take 18 months, but it usually gets back to normal, and lactation may even be beneficial in terms of your long-term fracture risk.

There's a very rare cause of osteoporosis in young women called 'pregnancy and lactation associated osteoporosis', and this is when people fracture in pregnancy or in the early postpartum. It usually happens in the first pregnancy, and they're usually pretty dramatic fractures. So the only case I've seen of this was a lady who fractured about six or seven vertebrae in one go, with a four-week-old baby, but it can be hip fracture, that's probably the other more common one. Usually it will resolve and it doesn't tend to recur. There's very little evidence on how you're treat it. It's thought to be related to this parathyroid hormone related protein having an effect. But is it because these women already had low bone density, or they're genetically susceptible, or is there something unique about them? We don't really know. We don't really know how to treat it either. Anyway, if you've got a young woman with low bone mass and you've ruled out everything else, then we just call it 'idiopathic' and that's probably about 50% of cases.

If you have someone who's been screened for whatever reason with a bone density, and they've got a low bone density but they're clinically well, they've not had a fracture, they've got no other risk factors, they've got no other contributing illnesses, we don't really know the significance of that result or what it really means for their long-term fracture risk. It's probably not the best thing, but they're probably not at a particularly high fracture risk. In terms of, I thought I'd move straight into treatments for younger women. I think there's much less evidence for women who are premenopausal or younger postmenopausal women. So it's often very much a sort of individual treatment approach. But the lifestyle measures are still important. So we start with them, really. Exercise does have a small effect on bone, but it is a significant effect, and it's good for your overall health anyway.

So I always recommend some weight-bearing exercise. We know in older women it decreases fracture risk, and there's a very small study from the 90s which took women with premature ovarian failure and randomised them to oestrogen therapy alone or oestrogen therapy plus exercise. And the exercise did have an effect over and above the oestrogen therapy. There was a nice Cochrane review from a few years ago in postmenopausal women, which showed that strength and resistance training seemed to provide the best effect at the hip, and combination exercises, so a bit of impact, bit of strength training, was the best for the spine. It's probably because it's quite hard to load the bones in the spine, so you're trying to put some sort of mechanical strain on the bones so that it gets stronger. So it's a bit like saplings when they blow in the wind and they get stronger that way. So yeah, exercise I think is a really important one.

More impact, generally, the better for bone. So things like skipping rope tend to be really good, things like swimming are not very good. There was actually a study of postmenopausal women that compared swimming to soccer training, and after 15 weeks of soccer training there were benefits in bone mass. So women could always take up soccer. Calcium and vitamin D, I think, still controversial. There's so many meta-analyses out there, who knows what to do with it. The current recommendation from the societies is that we should still be aiming to get a lot of calcium into postmenopausal women. So it's stills the same 1200 milligrams, but that if you can get it through diet, get it through diet, don't automatically put people onto a supplement. The Women's Health Initiative had a large calcium trial as part of it, and I think this is probably the most useful data for the women that we are seeing. So in the Women's Health Initiative, as you know, it's about hormone therapy, but they also had 35,000 women that they randomised to calcium and vitamin D or placebo. So it's huge, and they followed them up for seven years.

So as you know, the controversy from a lot of the meta-analyses is, does calcium cause heart attacks? And some say 'yes', some say 'no'. In the Women's Health Initiative there was no difference. But they did find at seven years that hip bone density was 1% higher in the calcium and vitamin D group versus the placebo group, which it is not a huge amount, but it's something. There was a decreased risk of hip fracture, quite a significant decrease, but only if you were compliant. So only if the women took more than 80% of their tablets. And there was also an increased risk of kidney stones. But it doesn't answer the question of, well was it the calcium or was it the vitamin D? And there's really no answer to that one yet either.

But for treatment in women who specifically have premature menopause, so we are going to give them the talk about, 'Let's have some more calcium in your diet. How's your vitamin D? Get some exercise.' But really the mainstay of therapy is oestrogen treatment. And there's been a new study which really suggests we should be looking at hormone therapy-type regimens rather than oral contraceptive pill. Oh, that didn't too good either did it? So this is a study from a few years ago, which, it's a really nice one for premature menopause. It's a three year randomised control trial, and they had three groups. They had women who were on 100 micrograms of transdermal oestrogen plus 12 days of medroxyprogesterone plus placebo. Then they had a group of women who had oestrogen plus medroxyprogesterone plus testosterone, and then a group of control healthy women that they also followed for three years.

And they had about 70 women in each group at the start, although one of the problems with the study is by the end of it, they only had 40 to 50 women in each group. But even with the small numbers, what they were able to show is that by giving 100 micrograms of oestradiol, that the bone density in the women with premature ovarian insufficiency, although it was much lower than the normal women at the start, it was normal by the end of the study, and it was normal fairly quickly actually. So we know that that regimen is able to restore bone density in these women. The testosterone part of the study didn't prove much, didn't really show any effect, but they felt really it was probably underpowered in the end. So there's a possibility that adding a bit of testosterone may be helpful, but we don't have that data yet.

So I think it was a really nice one to demonstrate, you could start out with low bone density, if we put you on the oestrogen, you do get back to normal. Okay, this looks a bit better. This is from a more recent study which looked at, again, a small group. All of the data for women with premature ovarian failure are small. So this was 59 women who were in a study, it was an open randomised study. So this is from an outpatient department in the UK, and they said to women with early menopause, 'Do you want to go on some treatment or do you not want to go on treatment?' And about half of them said they didn't want any oestrogen treatment, which is a bit shocking. So they didn't make them go on it. They had premature menopause from various causes. And then they randomised the ones who elected to go on treatment either to hormone therapy, with 2 milligrams of oral oestradiol, or to microgynon 30. And they followed them over a couple of years, and this had quite interesting effect.

So they all started off with different bone density, which makes it a bit confusing. This is the 'no treatment' group, and as you'd expect, this is bone density at the lumbar spine, and this is number of months out to two years. So the women who had no treatment, although they started off a bit better than the other groups, they had quite a large decline in their lumbar spine bone density, which sort of again just reemphasises the point that oestrogen is really good for you. In the hormone therapy group, they had a steady increase, so that their bone density was much improved by the end. In the women who were on the oral contraceptive pill, their bone density stayed the same. So it didn't get any worse, but it also didn't get any better, which is a bit disappointing.

This is, again, it's a very small study and it's just from last year. This is looking at their bone density at the hip, and there were less effects at the hip. But again, this is the 'no treatment' group, they did have a small decline, a small loss at the hip. The hormone therapy group had a small increase, and the oral contraceptive group pretty much stayed the same. It suggests that we probably should be moving more towards this, using the hormone therapy-type regimens. We don't really have, I mean this is the only study, we don't have a lot of data about it. We've got to look at the individual patient really, still.

Then, the plot thickens. Because we have another recent study which just followed up women who were presenting to an outpatient clinic, and it compared the women who were not on treatment and women who were taking their standard hormone therapy at that institution, which was 2 milligrams of oestradiol. And the women with hormone therapy did have much better bone density. So what they've done here is categorise the percent of women with normal bone density, osteopenia and osteoporosis. And that's not the right one. Here we go. And they were improved, but they still had really high rates of osteoporosis.

Well it didn't really turn out, we'll skip over that. But essentially the take home message was that even though they were on treatment, they still had very high rates within their group of osteoporosis, and they were suggesting, does this mean that we really need better treatments? We need to be considering other interventions in this group. And their group, it was a mixed group, so it had women after chemotherapy, et cetera. So probably in those women it would make sense that if you had a lot of loss from glucocorticoids, oestrogen alone may not be enough to get your bone density up again. So if we are looking at women perhaps who've had bone loss after breast cancer, because this is the one we often get asked about, what things are going to help them? And again, we know that resistance training does increase bone density in this group, and there's specific study data looking at women who've had bone loss after breast cancer, they make them do exercise, and then their bone density improves at the hip and at the spine, even in women with premature menopause. There's been also studies looking at using zoledronic acid, and this study was every three months, which is extremely high dose, in premenopausal women with bone loss. I'm not sure that you really need that much, but I'm not surprised that it works.

In postmenopausal women, there's evidence for just standard oral risendronate preventing decline of bone density in women on anastrozole. And there's also some evidence for denosumab reducing fracture risk in women on aromatase inhibitors. So probably the general antiresorptives are probably all fairly good. We also get quite a few referrals for women with low body weight from whatever reason, particularly eating disorders. And unfortunately the study so far have not shown that hormone therapy, whether it's oestrogens or androgens, really does anything for bone density in the setting of anorexia. And I think it's really because you really need a lot of calories and a lot of substrate to be able to put down new bone. So if it's not there, there's nothing to put down. And really the only things that improve BMD in this group increases in body weight and resumption of menses, and resumption of menses presumably reflects increase in body weight.

And I've seen quite a few women who've had really shocking osteoporosis, so we've gone ahead and treated them with high dose antiresorptives, even with Forteo, and you really don't get any benefit, because I think there really just, there's nothing for the body to put back in the boats. And the only thing that really you have to pursue is the body weight. So if you've got no obvious cause to treat with premenopausal osteoporosis, what do you do? There's very little data. You can focus on things like calcium/vitamin D because they're safe in young women, exercise, smoking cessation, maybe oestrogen helps, if they've had a fracture you'd be thinking about a bisphosphonate. But it's all very sort of woolly at this point, you're just sort of taking your best guess. I think the main thing in this younger group is that you want to be treating any secondary causes first, and probably the only other diagnosis I haven't really talked about that's a bit important is osteogenesis imperfecta, and they just get bisphosphonates.

But what about postmenopausal women who are a bit younger? There are so many guidelines on osteoporosis, but this group I think is still really hard. I mean, if they've had a fracture and you're going to treat them, guidelines would say treat them if they've got a low bone density score, but are you really going to treat if you don't think their risk of fracture is very high? Others would say, look, if their 10-year risk of hip fracture is more than 3%, or their 10-year risk of any fracture is more than 20%, that you should treat them, which is what we tend to do in a lot of the clinics. But again, it's not really evidence-based.

Often what I do is calculate their fracture risk and say, look, treatment is going to reduce that risk by about 50%. But that's not really an evidence-based strategy either. And we don't really know how accurate, in these groups you're probably not as accurate, some of the fracture risk calculations. There's some argument for using bone turnover markers to try and further determine who in these sort of younger post-menopausal women, who is at really high risk of fracture and who is a lower risk. So this is some data from the International Osteoporosis Foundation. So they've calculated the risk of hip fracture in women with low bone density, in women with high bone turnover markers, so this is serum CTX, which is a marker of bone resorption, and in women who had a combination of both. So their odds ratio, this is older women, their odds ratio of fracture if you had both was worse than if you had one or the other.

However, bone turnover markers have a lot of problems as well. But what the IOF recommends is that yes, bone turnover markers might predict fracture risk independently of bone density and independently of prior fracture, but there are a lot of limitations. So we still aren't able to really routinely use them in clinical practice. They are covered by the MBS. So we do use them sometimes, but we don't really know. There are a lot of practices doing things like, if you're going on a drug holiday, well we'll restart the bisphosphonate when your bone turnover markers go up. But that didn't prove to be, that didn't really work either. So how we use bone turnover markers I think is still not knuckled down, and there's a lot of difficulty within precision of the assays and a lot of variability. There are other factors that affect it, like if you've eaten and things like that. So I think there's limited use of bone turnover markers. Sometimes they're helpful, if you're really struggling to work out what to do with, sometime, but I don't tend to use them very much. So in this woman, women who've are post-menopausal but under 60, if they're post-menopausal, you've got good evidence for pretty much all of your antiresorptives, and there's not much between them. So your oral bisphosphonates, your alendronite, your risendronate, they're good. The zoledronic acid may be a touch better, but all good. Denosumab is good as well. There's not really a lot between them in terms of, is one better than the other. So generally we'd start with just an oral bisphosphonate still and just see how they go. Unless they've got something that contraindicate it or makes you worried. So if they've got a really bad reflux or esophagitis or something, well you'd probably go for an IV version. Raloxifene seems to have just gone out of fashion, no one's really using it anymore. I think partly because of the clotting risks associated, there was a suggestion that maybe it increases the risk of fatal stroke, but also because it really doesn't do anything for bone density at the hip.

It's very good for vertebral osteoporosis, but if they've also got reduced bone density at the hip, it's really not doing much for you. Strontium has pretty much left the building as well. So strontium or Protos was withdrawn in Europe because of concern about heart attacks, and different meta-analyses, again, sort of debated this, but it's really been restricted now and the PBS funding has been restricted as well. So this is really something that's not used particularly. I think even before it was withdrawn, we were using it sometimes but not that frequently. Probably because it's a bit messy. You've got to mix it up and you've got to drink it and you've got to titrate it really because it caused diarrhea. But it was good in some groups, particularly the groups who had a lot of issues with teeth, had really bad dental problems. We used to sometimes use it to tide them over to all their dental problems were fixed, because it's one of the few agents that doesn't cause osteonecrosis of the jaw.

So what are the major risks with your standard antiresorptives? So this is, by this I mean, really, bisphosphonates and denosumab, because denosumab's an anti-resorptive, so we think of it having fairly similar side effects, at least until we get enough data to say otherwise. So with our oral bisphosphonates, really it's reflux that we worry about. With IVs, zoledronic acid, the first dose, a lot of people will get a flu-like reaction, a third, it may be more. And that can range from anything from a small increase in temperature that they don't really notice, to really feeling like you've got the flu. And I've seen a few people who really just feel shocking and have to take time off work and things like that. So, I mean, I've used a lot of it, but I generally warn people look, don't have it, don't have your first dose before you're about to go to a nice birthday party or something like that because you may be ill.

There's been a lot in the past about osteonecrosis of the jaw. It's really a very low risk with postmenopausal women taking oral bisphosphonates for osteoporosis. Most of the cases have been seen with very high dose doses used in cancer therapies, or for hypercalcemia of malignancy, and the risk is somewhere between one in 10,000 and one in 100,000 women who are using oral bisphosphonates. So if women, when I'm in clinic and women say that their teeth are fine and they've seen their dentist in the last couple of years and there's no problems, I don't sort of make them go and have a dental review before we provide them with a prescription, because the risk is very low, and we know more about how to treat it if it happens as well. Atypical femoral fractures are something else that we worry, about particularly with longer use and particularly in high risk persons.

So if you're on glucocorticoids, this is more likely to happen. The risk, again, it's difficult to know. The estimates have ranged between three and 50 cases per 100,000 person-years, probably higher if you've been on it longer. So if you've been on it 10 years, it might be a hundred per 100,000 person-years. But again, it's rare. It's not something that it's recommended that we screen for, in people with radiography and people who've been on bisphosphates a long time. But I do tend to ask people who've been on them a long time about symptoms. So generally there's a prodrome for atypical femoral fractures, they're thought of as stress fractures, and often people will get aching in the mid-thigh or in the groin before these come on. The other key is that they're often bilateral. So if someone's got one, you must always x-ray the other femur.

And although it's not a recommendation, if I really think someone needs to be on a bisphosphonate for more than 10 years in particular, then I would just be screening their femurs with X-ray. This question of duration of treatment I think is very tricky, and it's often why, particularly in the past, we've said to these younger post-menopausal women, look, your fracture risk is low. We don't want to start you on anything now, because really your fracture risk is going to occur when you are in your seventies, and if you've already had 10 or more years of treatment by then, will we still be able to use the bisphosphonate? So we know that five years of therapy is pretty safe. The FLEX study was one that looked at women who'd been on bisphosphonates and then stopped the bisphosphonate after five years or kept them going.

And what they found was that if they were low risk, they'd not had a fracture and their T-score had improved, so it was now back in the osteopenic or normal range, then they seem to be pretty safe to come off their bisphosphonate. Whereas if they weren't in that category, if they were high risk of fracture, they actually were more likely to fracture if they came off their bisphosphonate. So we're tending to suggest longer terms of treatment for women who are in the high risk category, which is up to half of the women on bisphosphonate. So again, I think this is still very individualised. With zoledronic acid, we've got trial data for three years in low risk women and six years in high risk women. And certainly we used to only give three doses, because all the funding was, but now we are routinely giving it for five years or more. The question about, do you then, say you stop it, when do you go back on it, or do you go back on it, or do you do something else?

I think is not really resolved. Some people would suggest that people should be on a drug holiday for maybe three years, because we know the bisphosphonates will last in the bone for that long. That's again, pretty arbitrary. Others would say, well what we'll do is we'll check their bone density and if that declined then we'll restart it, or we'll check their bone turnover markers annually and if they go up we'll restart it. But again, it's all pretty arbitrary, and I think it's about really assessing annually or so and deciding on an individual basis. So again, it's not particularly easy.

I'll just make a brief mention of teriparatide. So this is recombinant to PTH, which is injectable medication, injected once a day, the person can be taught how to do it. And in Australia we've got it funded for just very severe osteoporosis, so people who've already fractured on bisphosphonates. It's length of use is limited in Australia to 18 months, and overseas to 24 months, because in the animal trials there was an increased risk of osteosarcoma with very high dose and long-term use. It's not being reported in people, but we still get concerned about that until there's more data and more people who've used it. And patients have to sign a consent form before they can use it. It's pretty straightforward to use, once you go through that rigmarole, and it is very effective, it's anabolic so it actually lays down more bone. So you see very good increases in their bone density, and some studies overseas looking at using it first-line in some of these younger people. I don't think we'll ever get to that point here because it's a bit more [inaudible]. But there is also a few studies looking at it in treating atypical fractures and osteonecrosis of the jaw, because it does help rebuild more bone.

End of transcript

Information about the podcast

This podcast series has been made possible by the NSW Government's Menopause Awareness Campaign. For help talking about menopause, download the [Perimenopause and Menopause Symptom Checklist](https://www.jeanhailes.org.au/resources/perimenopause-and-menopause-symptom-checklist) and take it with you to your next medical appointment. For more information visit: <https://www.nsw.gov.au/women-nsw/toolkits-and-resources/perimenopause-and-menopause-toolkit>

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