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Interview: Katharina Dalton, MD: Progesterone and Related Topics

On April 21, 1999, the following individuals participated in a question-and-answer session with Dalton: Janet Beard, RPh, Harvest Drug & Gift, Inc., Burkburnett, TX; Diane Boomsma, RPh, Williams Apothecary, Inc., Lancaster, PA; Lisa Everett, RPh, O'Brien Pharmacy, Kansas City, MO; Peter Ford, RPh, FIACP, Ford's Apothecary, Moncton, New Brunswick, Canada; Lynn Jennings, MD, Wichita Falls, TX; Kim Scott, RPh, Prescription Specialties, Duluth, MN; Evelyn Timmons, RPh, FACA, FIACP, Arizona Apothecaries, Paradise Valley, AZ; and Loyd V. Allen, Jr., PhD, RPh.

In the last 50 years Dr. Dalton has become the acknowledged authority on the part played by menstrual dysfunctions in confused and criminal behavior. She also has worked tirelessly in the treatment of postnatal depression and lectures extensively in Great Britain, Europe, North America and Australasia.

Dr. Dalton has a consultant practice in London and was principal of the Premenstrual Syndrome (PMS) Clinic at University College Hospital, established in 1953. It was the first PMS clinic in the world and operated until 1996. In 1971 she became the first woman president of the general practice section of the Royal Society of Medicine. She has received numerous awards for her original research, including three from the British Medical Association.

Dalton's early training was as a chiropodist at the London Foot Hospital, where she wrote *Essentials of Chiropody*, a basic textbook. Her medical training began at the Royal Free Hospital and she qualified as an MD in 1948. During her first six months of general practice, she identified and successfully treated six women suffering from premenstrually related asthma, epilepsy and migraine. In collaboration with Raymond Greene, MD, she published the first paper on PMS in the British medical literature.

Her books and publications include *Premenstrual Syndrome*, *The Menstrual Cycle*, *The Premenstrual Syndrome and Progesterone Therapy*, *Once a Month*, *Depression After Childbirth*, *Premenstrual Syndrome Goes to Court*, and *Premenstrual Syndrome Illustrated*.

What are some of the latest trends in hormone replacement therapy (HRT)? What's happening now that wasn't happening five years ago?

I think there are two important things. First of all, we have to send a message: we now have suddenly appreciated the difference between the levels of estrogen, which we measure in picograms, and the level of progesterone, which we measure in nanograms, a thousand times bigger. People imagine that the dosage should be almost the same but, of course, it isn't. I think that's one of the most important things. The other thing is an appreciation of progesterone receptors. When I was here in 1982, progesterone receptors had not yet been discovered in a single human cell; now we realize there are progesterone receptors in practically every system of the body, and progesterone receptors are present in all vertebrates. The early vertebrates have progesterone for glucose metabolism; but, of course, in mammals progesterone is there essentially for reproduction. So there is a tremendous advance and, as a result of that, the treatment of PMS has changed.

We're hearing a lot more about doing blood levels and saliva levels.

What we really want to do is progesterone receptor function tests, because it is one thing to have a lot of progesterone receptors; but if you're not going to use them, they're no good. We now know the characteristics of the progesterone receptors; among them, first of all, they won't pick up progestogen - progestins, I think you call them. The artificial ones, forget those. They will only pick up progesterone. They will not pick up progesterone if adrenalin is present, if there's been a lot of stress, and they will not pick up progesterone when the blood sugar is low. So we've got to look after the progesterone receptors. It's not a case of necessarily increasing the progesterone. And the progesterone blood levels are irrelevant.

What do you think is going to happen in the future in terms of progesterone dosing and monitoring of receptor function tests?

First of all, I think we've got to appreciate that progesterone receptors are present in men and women equally at all ages, from the fetal stage until death at 100. We have progesterone receptors; we all need systemic progesterone, which is essentially adrenal progesterone. Women have ovarian progesterone, which is colossal, 1000 times bigger than the systemic progesterone that men and children have.

What is the role of progesterone in men?

Yes, I think we've forgotten men altogether. But men need progesterone. Men have systemic progesterone and progesterone receptors, and we find those progesterone receptors particularly in the endothelial lining of blood vessels. And it's those that keep it nice and smooth. With estrogen (estradiol), the exact opposite happens; they make it lumpy and bumpy; and, therefore, with estradiol you're liable to have clotting diseases, strokes and angina. The interesting thing is that men who do not have a high amount of progesterone tend to get cardiovascular diseases in their 40s, whereas women are protected until after their 50s. Men also need progesterone for their bones, and they get osteoporosis earlier than women do; because women are protected to a certain extent, particularly with their pregnancies, when they have a lovely high level of progesterone for nine solid months. We all need progesterone for the brain, for the myelin sheaths. Trauma in women heals quicker than in men because women have progesterone, particularly menstruating women; they do very well because they have progesterone protecting them; and it minimizes water retention in the body.

Is there a relationship in men between progesterone and atherosclerosis?

Yes, because the narrowing of the blood vessels is related to the presence of progesterone receptors. The average man has adequate progesterone from the adrenals; it doesn't matter, but there is a proportion of men who do not have sufficient adrenal progesterone, and that may show up one way or other in the many systems of the body and it can show up in the blood vessels. With adrenal stress, do you decrease the amount of progesterone produced? Yes, and, of course, you end up with progesterone deficiency at one or other sites of the body. And it might be in the blood vessels. Young women who are having cardiac symptoms are those who are the high-pitched, type A, pushing so much adrenaline out that they are neutralizing the effect of the progesterone.

Do you think that might be one of the reasons why there seems to be a higher proportion of type-A personalities with heart attacks at early ages?

Yes.

How do you test receptor sensitivity?

Most of the work has been done on animals; but there's a tremendous amount of work worldwide on progesterone, which is not really monitored at all. There are hundreds of peer-reviewed articles in medical and scientific journals covering about 38 different vertebrates, including humans.

In terms of the dosages you use in men, do you still advocate using transdermal progesterone, like creams?

My work has been essentially on women; I don't treat men. But with the new realization of the vast differences between ovarian and systemic progesterone that men and women have, it is now appreciated that men may need very small doses of progesterone.

Will men experience feminization while using progesterone?

Why should they experience feminization? Estrogen is a feminizing hormone; progesterone is not and is present in men and women.

The reason that I asked the question is that the lay public thinks there's going to be feminization.

I think this is one of the things we want to get over. Progesterone is not just a feminine hormone; men also have it.

Dosing for osteoporosis for men, then, is approximately 5 to 10 mg daily?

Yes, you can have a very low dose for men as long as they have it every day.

What about taking the same approach when people have cardiac disease, starting men and women on progesterone just like you would start them on aspirin every day?

Yes, why not? I am not so sure that oral progesterone is what we want, because all progesterone administered orally goes through the portal systems direct to the liver, where there are numerous progesterone receptors that metabolize the progesterone before it reaches the systemic circulation. Progesterone administered vaginally, rectally or transdermally goes directly into the systemic circulation.

So you prefer a topical administration?

Topical for men, because men only need a very small amount. They only need a very low amount throughout life.

There are a number of cosmetic products with very, very low levels of progesterone in them. What's your opinion on those?

I don't know anything about those. They are not available in the United Kingdom.

One way to get progesterone back in men, to have it be widely accepted, is to look at its effect on hair growth, is that correct?

Yes, certainly, it works, in women's hair growth. Many women lose some hair shortly after pregnancy; they've had a lot of progesterone, and suddenly the progesterone goes down, and they have hair loss, total hair loss sometimes, in some unlucky women. But give them progesterone, and their hair regrows amazingly. I can give you many examples of hair growth in women, but I don't treat men. And, you know, there is a genetic effect of bald men: they tend to have female offspring with polycystic ovary disease. So if I am querying whether someone's got polycystic ovary disease, I will certainly ask about male family members, whether they are bald, which would give me another clue, wouldn't it? For men, should topical progesterone be given once or twice a day? And even for women who are getting their HRT topically, once a day versus twice a day? Which is, in your opinion, the best? First of all, I don't know men at all. But for women, I find once a day is adequate for the group that does not require it for menstruation, that is, for the nonmenstruating, postmenopausal group.

What is the best topical vehicle for estrogen and progesterone?

That I wouldn't know. When we do use a cream, we always tell them to use it after a bath when skin pores are open.

You mentioned that, for men, progesterone is good in cardiovascular disease. Are there any other things for which it might be appropriate?

Oh yes - cerebral accidents and trauma in both men and women. If you give women natural progesterone - and menstruating women have natural progesterone within 14 days of a severe accident - they heal up much quicker than a man with severe trauma, and they have far less water retention in the brain. Therefore, nowadays, some neurosurgeons tend to use progesterone injections prior to neurosurgery to prevent water retention.

What is the best area of the body for topical application?

The area with the thinnest skin. We've got a nice area on the inside of the upper arm with nice, thin skin.

Can a woman ever have too much progesterone?

No, I don't think she can. A normal menstruating woman can't have too much because she can't get up to that "normal" level that she has in pregnancy. Women have a colossal amount; and there's a limit to the amount, with our present methods of administration, that we can get into the blood. Vaginally, we can use it. We've found 400 mg was the limit, and if you use 500 to 600 mg, it won't go any higher. You can only put it in every two hours because of the wax in the matrix. So we're limited by menstruation, after everything else, and the same with progesterone injections, we're limited by the vehicle.

As a general rule, is it safe to say that it's better to overdose than underdose?

Oh, definitely. There's no harm in overdosing. You can't reach it. Very definitely overdose.

When you're prescribing progesterone for depression, what markers do you use for effectiveness?

The individual patient. We have a full history at the beginning of treatment and a list of all the symptoms. We have answers to questions such as, "Are we clumsy?" "What's the memory like?" "What's the sleep like?" "What's the eating like?" We go all through that, then we come back, and we have them on progesterone, and they've kept a chart, etc. Then we see them next month, and how are they? Have they noticed any difference, what difference have they noted, what difference has their partner noticed? We do it individually: one is more irritable, the other one is more tired, the other one cries, the other one has hysterical fits, they're all different. There are so many possibilities with depression that you've got to think about the individual's symptoms.

I think the minimum dose, if you're going to use vaginal suppositories, is 400 mg twice a day. First of all, you want a high dose. But the second thing we know about the unique characteristics of the progesterone receptor is that the first initial dose of progesterone, when you give it in rats, is effective; subsequently, they need a dose 40 times higher than the first dose to maintain the effect. What we tend to do there to overcome that is to use a high dose initially.

British gynecologists are not allowed by their Royal College to give estrogens within six weeks of childbirth because of the danger of thrombosis.This covers all estrogens and includes estriol, the pregnancy estrogen.

There's one other thing that I want to say about progesterone. One of the things we have learned is that in order for the progesterone to be used by the progesterone receptors, one of the real essentials is that we must avoid low blood sugar; we must have a stable blood sugar level, and for that we insist that patients use the three-hourly starch diet. The ideal is that they should eat in a way that does not cause a drop in the blood sugar, because a drop in the blood sugar will stop the utilization of progesterone for seven days.

How do suppositories and troches compare with transdermal delivery, and what doses would you need to give transdermally to get the appropriate amount of progesterone?

I don't think transdermal administration can be used efficiently with normal menstruating women. Rectal absorption minimizes the first-pass effect, because anywhere in the alimentary tract it's going to go to the liver.

We've talked about two different things concerning diets so far, sugars and starches. How else can diet affect HRT?

The other thing, of course, is that smoking decreases the appetite and upsets progesterone receptors. We do need a good nutritious diet with adequate protein and adequate fruit and vegetables, roughage - all that I fully agree with. I go through individually each patient's diet. Invariably I ask her what she had yesterday, and we go down the list as to what it contained and how much protein she had. I do the whole list each time.

What about alcohol use? Does that have an impact?

Small amounts are okay, but the alcohol effect varies in PMS patients.

With the depression we were talking about earlier, another question that comes up often regards the use of progesterone in the treatment of pain.

It depends on where the pain is and why it is occurring. It helps any pain that gets worse premenstrually.

You mentioned earlier something about toxemia in pregnancy.

About 50 years ago when I treated my first PMS patients, we noticed a high incidence of preeclampsia compared with normals, and when we did the first paper we wanted to know what the incidence of PMS was in the world in general. So I did a survey of 1000 women, of whom 200 had experienced preeclampsia and 800 were normal. I got them from factories, health food stores and clinics. This was in 1953. What we found was that 85% of those women who had preeclampsia once subsequently had PMS. The interesting thing was that I would say, "I see that you had a son on July 7 of that year and that you were ill for the last week and went into the hospital." And they would say, "Rubbish, I was ill for six months; but the doctor said you're perfectly alright, good blood pressure, good urine, your weight's alright, forget it; and it was only a week before the birth that they took me into the hospital." I had that story again and again in 200 women who had preeclampsia.

So, having sorted out the incidence, I then went to University College Hospital and interviewed women between the 16th and 28th week of pregnancy. I had two books; one had "yes" on it, and one had "no" on it. I saw these women just once and asked them only one question: "Are you as well now as you were before pregnancy?" And if they said "yes," I'd write their name in the "yes" book and put their hospital number, and say goodbye. If they said "no," I would ask why, and I'd write down in the "no" book what they were complaining of, headache, depression, vomiting, etc., along with their hospital number and say goodbye. I never saw those women again, but after they delivered, what happened? The women who had symptoms at one interview in the middle trimester had three times as much preeclampsia as the others; in other words, preeclampsia showed up in the middle months. But if you're only going to do blood pressure and weight and urine, you won't recognize it.

With PMS, if we measure them day by day, we will find that the severe ones in the premenstruum will have an increase in weight, they will have an increase in blood pressure, they will have an increase in intraocular tension and urinary protein. In other words, preeclampsia and PMS are very much the same. They've both got three stages: the first stage of symptoms, the second stage of signs (edema, hypertension, weight gain) and finally they have fits (eclampsia or epilepsy); it doesn't matter what we call it, it's the same type of fit, and it's preceded by severe headaches. So we've got two illnesses there, absolutely alike.

So, the next thing was, we know how to treat PMS, so we'll treat preeclampsia like that. This was a controlled study by Prof. Dr. D. Reed of the University of London, who did the protocol for me. We interviewed women in the middle months of pregnancy, and if they had symptoms we would give them progesterone and I'd see them

regularly. They either had progesterone or they had symptomatic treatment. Symptomatic treatment was if they were complaining of headache, we'd give them an analgesic; if they were complaining of nausea we'd give them magnesium trisilicate, and it was very easy to treat their symptoms. The symptomatic group had no difficulty and we saw them as often as the others and that was fine. But, in the end, when progesterone was given from the middle months of pregnancy, the results were excellent and statistically significant. Unfortunately, that paper came out at the same time as the thalidomide disaster; so, of course, then they said stop progesterone, stop everything, anything during pregnancy. Particularly, they didn't know the difference between progesterone and progestogen; and progestogen caused masculinization of the female fetus, so don't do that. So, really, nobody bothered to repeat my published, controlled trials.

As soon as the trials were published, I began looking into the effect of PMS on glaucoma; I just changed over and went into that, which was very interesting, and I thought the gynecologists would follow up, but they didn't. So, ten years later, I repeated the same protocol with exactly the same results. Today it's 1999, and a long time has passed; and not too many physicians are using progesterone for preeclampsia. There has been a lot of work done on preeclampsia, and they've learned a lot; the problem starts at about 16 weeks with the development of a poor placenta, which causes either renal damage and preclampsia or fetal damage with fetal growth retardation. And we know that something happens then - we don't really know why - and then we know that at 28 weeks we start getting preeclampsia.

In my files on preeclampsia, I had the weight of the babies delivered by mothers with preeclampsia, the date they were delivered, and the number of weeks of pregnancy. Recently I looked up my figures for my double-blind, controlled preeclampsia trials and looked to see the babies' weights. The weights of babies born to women who had had progesterone were high. We had some normals whom I interviewed who had no symptoms whatsoever during the middle months, and their babies' weights were high, but not as high as the weights of the babies of women treated with progesterone. Women who were symptomatically treated, with or without preeclampsia, had babies with a very low birth weight. This fits in with new work suggesting that preeclampsia and fetal growth retardation have a similar etiology.

But now, to jump a bit, a couple of years ago a paper was published in which 100 tests for preeclampsia were described, and not one would be able to be of any value before the 28th week, although we know it starts at 16 weeks. So what's wrong? It is necessary to look at the psychological symptoms in the middle months. What they have done recently is, they know now that we have the vascular growth hormone, and you need progesterone to form the trophoblasts at the 16th week. We know if you don't have enough progesterone then, you won't get a good placenta, and you'll either have renal or placental interruptions. Preeclampsia represents renal complications, whereas placental complications affect fetal growth.

Can you just test the progesterone level at week 16 to see where it is?

That's not much good, because we're back with the old story of, it's not the progesterone that matters, it's the progesterone receptors that matter.

What doses were you giving in the middle trimester?

First of all, you know, I'd see them individually, so it was an individual dose. We would start them off on 400 mg twice daily, that is my minimum dose, 400 mg by vaginal suppository. I want to have action. They would come back in a week if their symptoms were still present and progesterone hadn't made any difference, and we would go up three or four or five times. If they said, it's still no good, then we would give them injections. In those days when I did my trials, we didn't know about the three-hourly diet, we didn't include it; and I think we could have had better results if we had. Today, I wouldn't use progesterone without considering the diet.

When you make a change in a person, how long do you wait until you evaluate whether or not that change is effective before you make another change?

In the days when I had a long waiting list and I had to wait a long time for the next visit, we used to give a patient, when she finally got to me after the waiting list, two appointments, one six weeks later. So if we saw one in the premenstruum, we'd see her at a different time in the cycle six weeks later. But now I give it three weeks if I can.

Three weeks before any change?

Three weeks and then up the dose. I mean, if it's severe we might do it earlier; postnatal depression I'll see within a week, because the effect of progesterone in postnatal depression you will see within a week, and you might need to increase the dose.

And hyperemesis?

Yes, and hyperemesis also within a week.

In terms of your work with postnatal depression, why haven't the American doctors picked up on this?

That's an unanswerable question.

Before you go on, is there any role for progesterone in chemotherapy? Or have you tried it?

No, all I can say is that, as far as breast cancer is concerned, you can use progesterone just fine, as long as the oncologist agrees.

That was the next question, breast cancer. Go ahead and expand on the use of progesterone and estrogens in breast cancer.

First of all, don't join the two together; estrogen and progesterone are completely different. I mean, you don't join the pancreatic enzyme with insulin all the time; they're separate. What we do have is this overgrowth of cancer cells with estrogen receptors in them, but by and large progesterone receptor cells very rarely overgrow; they're completely different.

Does progesterone protect against breast cancer?

Yes, but I think I will put it the other way. The women that you give the estrogen to, they're the ones who get the cancer. I very rarely have cancer in my progesterone-treated PMS group, practically, I would say, never.

Has anyone used progesterone as birth control?

Yes.

What dose would be used for that?

I use 200 mg from day 8 to the onset of menstruation, but if they tend to have PMS and they're going to increase at day 14, they might have 400 mg two to three times daily until menstruation, and they're perfectly safe. It's as safe as the progestogen-only pill; we haven't done enough cases to show the safety, whether it's identical to the estrogen progestogen.

In the Dalton protocol, it was published as 100 mg from day 8, and you said 200 just now.

I should explain that in Britain we have 400-mg vaginal suppositories; and, therefore, it is easier to cut those in half and use 200 mg a day from day 8 until the increase of progesterone dosage at ovulation. However, you are lucky in America in that you can get suppositories of 100 mg progesterone, which is adequate for contraception from day 8 until menstruation. The dose of progesterone from ovulation to menstruation can be increased if there is a history of PMS.

What about the use of progesterone in breakthrough seizures? Can it be used for seizure control?

Yes. By seizures, you mean what I mean by fits, epileptic fits? Yes, very definitely. And again, we need a careful record of the days on which the seizures have occurred, and the food they have had in the 24 hours prior to the seizures. In other words, there's always something, either it is purely premenstrual; or there is another factor with it; and the other factor with it, we're learning now, is very much due to the progesterone receptors' not working and common things, food gaps when the blood sugar drops down.

The other thing is sleep deficit, when the young girl goes out until 3:00 in the morning to party and then she has a fit, or the following morning, you know, the sleep deficit; and she is much more sensitive to alcohol of course, and the result is you can treat her with progesterone, but it must be education plus progesterone.

And the dose on that would be...?

Again, I would start with 400 mg twice daily, which is my minimum, and then I would go up. But if they happen to be in the hospital, it is easier to give them injections.

What would be the equivalent intramuscular (IM) dose of progesterone?

I'd give 100 mg progesterone in oil IM once daily.

Just once a day. And that's approximately equivalent to 400 mg twice a day vaginally?

No, it seems to be more equivalent to 400 mg four times a day. It's a big dose; but if they're in the hospital, they're there for a purpose, and they want to get out as soon as they can.

What are your views concerning using progesterone as precursor therapy for total estrogen replacement, as it has been described that the body will make from progesterone the subsequent metabolites, estrogens and testosterones down the line?

I agree with that.

And that there's really no way to tell "how much goes where" in the individual person? It has been presented that a woman basically does not need any estrogen supplementation postmenopausally, but she will get what she needs from progesterone only.

I agree with that completely. We can use progesterone instead of estrogen replacement therapy. Women don't need any estrogen. Progesterone alone will do it. And, what is interesting, if we look at the menopause, menopause being the last-ever menstruation, on the average we say it takes five years, right? Two years, first of all, we don't have ovulation, then menstruation gets irregular, then we stop having menstruation, then we gradually have this reduction, the uterus becomes smaller, the breasts become saggier, etc. So you can reckon that that's five years. Now the first thing that happens involves ovulation, which involves progesterone. So approximately two years before the actual menstruation stops, they will develop PMS; and I would like to put them on progesterone, and then they don't need the estrogen.

How high a dose should one use in the perimenopausal woman to force her cycles into some regularity?

To force her cycles into regularity? Why? When we're growing up, do we have to go backwards? We want to finish with menstruation. We don't want to go on having menstruation. I mean, two years before the menopause, when PMS comes before the estrogen deficiency comes, then I would use progesterone in a dose sufficient to ease the PMS symptoms, which is different with each individual.

And that would be cyclical, or...

No, no, not cyclical, perfectly steady. I mean, two years before the early part of menopause, they will have occasional menstruation; they stop for 14 days and start again.

Is there a range that you start off with for the perimenopausal women, or is it still the same, the 400 mg twice a day?

Yes, it's the minimum dose. But even some of those don't need progesterone, they can just go on with their lifestyle, if we give them the three-hourly starch diet first.

One last thing concerning progesterone and HRT: have you seen much of an interest in its use and additional research here in the United States, and what do you project for the future?

Yes, I see a change and increased interest. We know now more about progesterone receptors and estrogen receptors and that progesterone receptors are present in men, women, and children of all ages. It's not only in women. It seems people are becoming more aware that progesterone has other functions; it looks after the smoothness of the

blood vessels; the myelin sheaths of nerves in men, women and children; and it looks after water retention in the brain in men, women and children. In other words, it's needed by men, women and children. It will probably continue to be a subject of much study, discussion and controversy in the future.

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