Hormone Replacement Therapy

Current Research in Obstetrics and Gynaecology

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<**Mr Geoffrey Chamberlain and Mr John Studd, seated. Chamberlain to camera**>

Good day. Welcome to another in our series on current research in obstetrics and gynaecology. This is a series of programmes brought to you by the University of London Audio-Visual Centre in conjunction with the Blair Bell Research Society. We try in them to pick on topics of current interest and research and bring you experts who can talk about the background to that research, and also possibly look a little into the future and give us an idea about what may be happening soon.

Today we've decided to talk about hormone replacement therapy – a thorny subject in … recently, in January of 1979, there was an issue of the New England Journal of

Medicine with a rather complex article which appeared to put the subject in some disarray. And so we have asked Mr John Studd, the Consultant Gynaecologist of King's College Hospital, to come to talk to us on the subject today. He is a national and international expert on the subject of hormone replacement therapy and has more experience in this and its research than many others. Mr Studd.

<**Studd to camera**>

Thank you very much. Yes, it's quite true, Geoffrey, that the whole question of hormone therapy, the menopause, is in a state of flux, it's a big controversy and, particularly over the question of whether the therapy is effective and what sort of patients require therapy and whether it's safe. And in the last year or two, that certainly our views have undergone some sort of convulsion with the fear that oestrogen therapy might cause cancer.

Well, let's just first of all start about talking about the definitions. Menopause, of course, is when the periods stop, that's easy. The climacteric is a longer period of time, 5, 10 years of decreasing ovarian function and during this time the patient goes through symptoms of the climacteric, the menopause, then the degenerations of old age.

Now, there are about four groups of symptoms of the climacteric. Firstly, the vasomotor symptoms – flushes, sweats, headaches, palpitations. Then there are the sexual problems – dyspareunia, loss of libido, I think also the urethral syndrome as well comes in that group as well. Psychological problems – insomnia, depression, insecurity, can't-cope feelings, generally getting crabby and bad tempered with the family. And then there are the muscular skeletal problems – joint pain, bone pain.

Now, we do know that after the ovaries fail, or after they're taken out at surgery, these symptoms occur in most women. And we have studied the hormone profiles of these patients and I have them here.

<**Studd over table showing hormone levels in oophorectomised women**>

This slide shows a group of 100 patients that have had oophorectomy in the past, and it's just like the same hormone, blood hormone values after natural menopause. FSH is about 20-fold increased, LH about 5-fold increase, oestradiol drops to about 20% of its normal premenopausal values and there's no change in testosterone.

<**Chamberlain, off camera, over table**>

And that would happen in the normal girl who went through the normal changes as well as the sudden removal of the ovaries, would it?

<**Studd over table**>

That's right. Sure. But it is very interesting that in these two columns here, patients are symptomatic with these so-called menopausal symptoms, and these patients are 34 of 100 who, some years after the surgery oophorectomy, have no symptoms and you see there's no difference. You cannot, unfortunately, assess symptoms or have any clue about symptoms by hormone profile, these four things here, so it does seem that the menopausal symptoms, whatever they are, are not related directly to the low levels of oestradiol or the high levels of FSH for example.

Now, if we can go onto the next slide, <*Studd, seated opposite Chamberlain, Chamberlain changes the chart*> we can see that the change that occurs after a natural menopause, and I've chosen FSH here because […]

<**Studd over graph showing changes in FSH during menopause**>

[…] the changes here are the most striking. These are patients 1 to 30 years after the menopause and you can that see the FSH levels rise soon afterwards and they reach their peak at 2 to 3 years after the menopause and at this stage they're about 15 times the values found in the preovulatory, or the follicular, phase of the younger woman. Strangely, though, they depress a bit, 30 years postmenopausally, but still, even then, they're much higher than the younger woman.

<**Chamberlain, off camera**>

Why do they take 2 or 3 years to do that? I'd have thought, physiologically, it would have happened much quicker.

<**Studd to camera and over previous graph**>

I don't know the answer to that. But you have the same slow luteinising hormone as well. Again, you have this elevation one year, the maximum at 3 years, in the case of luteinising hormone the peak levels are only 4 times the follicular phase levels and, of course, they never ever reach the levels found in the preovulatory surge.

<**Chamberlain, off camera**>

Yes, yes, yes.

00:06:16:00

<**Studd to camera**>

Alright. So we'll continue, then, with the next slide which gives us some idea about the patients who are premenopausal with so-called menopausal symptoms. Now, let me clarify this by saying that one of the problems that we're facing at the moment is correct selection for hormone therapy. Now, oestrogen therapy does work so well for the right patients, the danger is that the indications are extended to cover personality problems – depression, family problems and a multitude of inappropriate symptoms, and in this way the treatment will become discredited and that's no good to anybody. So we do want some means to try to pick out the patient who has this mixed bag of symptoms, who comes to a menopause clinic with so-called menopause symptoms, to see whether her symptoms are oestrogen responsive or not. And we have a group of about 100 women with so-called climacteric symptoms who have come to our menopause clinic for therapy.

We've divided these into whether they have flushes or not – flushes is a pretty typical symptom of oestrogen deficiency, and you see in the next slide, you can see […]

<**Studd over graph showing details of premenopausal women with menopausal symptoms**>

[…] group A and group B. Now, group B are the patients that have flushes and their plasma FSH is high. We take about 15 or 20 units as a cut-off point, a useful diagnostic cut-off point, to help us diagnose the menopause, or should we say climacteric to be more accurate. And the patients that have flushes have this high FSH which is approaching the first year range of the postmenopausal women.

<**Chamberlain, off camera**>

And this is while they're still menstruating?

<**Studd, over previous graph**>

While they're still having regular, cyclical bleeds. And you see that group A again have regular cyclical bleeds, have so-called menopausal symptoms, have no flushes, have a normal FSH, the same as the follicular phase, pre-ovulatory peak and the luteal phase. So, conclusion is: these patients with flushes and a high FSH, they respond well to oestrogens, these don't.

<**Chamberlain and Studd, shown seated**>

<**Chamberlain**>

But they, of course have no symptoms according to your own definition of grouping, therefore wouldn't need them would they?

<**Studd**>

Well, they come with symptoms of depression, insomnia …

<**Chamberlain**>

But not correct symptoms …

<**Studd**>

… quite right. These have no flushes and they come with a multitude of problems related to depression or lifestyle or family background or whatever. But these *<refers back to previous graph>* respond to oestrogen therapy, these should go to the psychiatrist.

<**Chamberlain over previous graph**>

Would you then recommend that such a patient who comes to you with these vaguer symptoms, that other people associate with menopause, should have an FSH done?

<**Studd to camera**>

Not sure about that yet. I think that we should be able to assess what is climacteric or not by a careful history and the clues, I think, are having these symptoms of recent onset, not 20 years ago, no, of recent onset, with hot flushes and vaginal dryness – those two, I think, are very important symptoms of the climacteric. The rest are more difficult. If there is a big problem, of course, a single FSH assay should clarify it. Over 15 means their symptoms are almost certainly oestrogen responsive.

00:09:58:10

<**Studd to camera, then over table listing pharmaceutical oestrogens**>

So far, so good then. So there we have the sort of symptoms and how we can treat them with oestrogens. Now, we have in the past given unopposed oestrogens to these patients with menopausal symptoms, and the three most common ones that we use are: Premerin, Harmogen, Progynova that's oestrone, oestrone and oestradiol, in this sort of dose, given cyclically, never ever continuously, but it's certain that we're wrong to do this because the unopposed oestrogens do cause hyperplasia and we should add a progestogen to their use.

Now, there are three preparations here: Syntex-menophase which contains 13 days of norethisterone; Cycloprogynova contains 10 days of progestogen; Prem-pak contains 7 days of progestogen …

<**Chamberlain, off camera**>

And which oestrogen, did you remind us?

<**Studd continues, over same table**>

Yes, that's mestranol, that is oestradiol and that's oestrone. But the important thing is, they are combinations containing between 7, 7 and 13 days of progestogen to produce a regular monthly bleed and prevent hyperplasia. Mixogen, Climatone, a combination of androgens and oestrogens, not much value, oestradiol implants have a place and we'll discuss this later.

<**Chamberlain, off camera**>

That would be unopposed oestrogen implants wouldn't it?

<**Studd continues, over same table**>

At the moment, yes, but of course patients that have implants and have a uterus must have some sort of progestogen each month.

<**Chamberlain, off camera**>

So you could give a girl who's having unopposed oestrogen implants just oral progestogen, by itself could you?

<**Studd to camera then over table listing authors of papers linking oestrogens to cancer**>

Yes, we do in fact. Patients that have an oestradiol implant do have, had in the past in our practice, 5 days of norethisterone. We now think 5 days isn't enough and we give 10 days and so far, with patients having 10 days norethisterone, we haven't had any patients with hyperplasia.

Right, to continue, and we'll discuss some of these papers that suggest that oestrogens cause cancer. Now they're all from the West, mostly the West coast of America, these were the first ones: Smith, Zeil and Finkle, Mack, McDonald, who gave a risk ratio of between 4 to about 10 over unity in patients having oestrogen therapy. Now, these were nearly always patients having Premerin and a few having stilbestrol. Now there were lots of faults with these papers but nevertheless, where there's smoke there's fire, and it's unlikely that such a risk ratio, such a large one, was purely chance or problems of selection. Now there were problems of selection of controls and there were problems with pathology and so on, but we certainly are left with the very real fear that therapy in the past, oestrogen therapy in the past, has been carcinogenic if given too much, too long, to certain susceptible patients.

<**Studd to camera**>

Now Mr Chamberlain mentioned in his introduction a recent paper from Johns Hopkins Hospital, which showed that there was an 8- or a 14-fold increase in risk of cancer, and this paper purported to solve some of the, or answer, many of the criticisms of the former papers but in doing that it did reveal the therapy used and it is amazing that of the 64 patients that developed cancer, more than half of those had

unopposed oestrogens when we know now that these patients should have progestogen.

<**Chamberlain, off camera**>

But there were some that had progestogen as well were there?

<**Studd to camera**>

No. Not one.

<**Chamberlain and Studd shown seated**>

<**Chamberlain**>

None, so all this paper was based entirely upon oestrogen giving unopposed by progestogen, but some were a cycle of oestrogen I imagine, were they?

<**Stubbs to camera**>

Yes. Not one of the cancer patients had progestogen, not one. About a half had continuous oestrogens which wouldn't be prescribed by a final year medical student, I guess, over here, <*Chamberlain chuckles in the background*> and also 13 patients had stilbestrol. So I think that what we're measuring really is bizarre therapy, bizarre private practice, inappropriate oestrogen therapy, poorly supervised, wrong dose, self-medication and then problems of pathology.

<**Chamberlain, off camera, then shown seated by Stubbs**>

Can you just put into perspective this last paper, the one that came from, it was …

<**Stubbs**>

Antunes.

<**Chamberlain**>

Antunes, from Hopkins, yes. Of the roughly half of the 64 who had a carcinoma, you say they had continuous oestrogen, the other half had a cycle of oestrogen, out of how many patients proportionally did those two groups come?

00:15:18:00

<**Stubbs shown thinking, Chamberlain off camera**>

Was it very many more of the women who were on continuous therapy got themselves a carcinoma than the cyclical group?

<**Studd to camera**>

They didn't discuss that, they just found all the patients through Hopkins that had carcinoma and divided them up into oestrogen takers and non-takers.

<**Chamberlain to camera**>

Oh, it wasn't a population study then was it?

<**Studd, off camera**>

No, no, no, no.

<**Chamberlain to camera**>

Oh, yes, yes, I see.

<**Studd to camera**>

No, we don't know that yet, in fact. We won't know this until we have a prospective trial of one man's experience. We almost have this with Greenblatt and Gambrell, who, for all of 20 years, have recommended progestogen therapy. I think it's worth pointing out that we do have probably the largest menopause clinic in Europe and so far we haven't had one carcinoma in patients whose therapy we have initiated and supervised.

<**Chamberlain, off camera**>

Out of roughly how many patients is this you're talking?

<**Studd to camera**>

About 2000 patients.

<**Chamberlain, off camera**>

2000?

<**Studd to camera**>

2000, from up to 5 years therapy.

<**Chamberlain, off camera**>

And no carcinoma in progestogen-balanced oestrogen patients? Is that right?

<**Studd to camera**>

Yes, that's right. We've had no carcinoma at all, in fact, we've had hyperplasia aplenty which we'll discuss later but no carcinoma. We've had 4 referred from elsewhere and, once again, bizarre therapy, you know – 30 years of continuous high dose oestrogen.

<**Chamberlain to camera**>

So, you're telling us that for the carcinoma side, that if the oestrogen is counteracted by some progestogen, the risks of malignancy are obviously very low.

<**Studd, off camera**>

Yes.

<**Chamberlain to camera**>

Are they greater than background?

<**Studd, off camera, then to camera**>

No idea. What one can say is that the medical literature awaits a first suggestion that the sort of therapy recommended by ourselves and Stuart Campbell's team and so on, of cyclical low dose oestrogens with perhaps 7, perhaps 10 days of progestogen, is in any way associated with carcinoma in any way.

<**Chamberlain to camera**>

Yes, but unfortunately in medicine now, one has to be prepared to counter arguments about side effects before they come along. This is critical safety of drugs and the FDA and the consumer groups are asking this and it is a question that they're asking. Do you think there will be an answer to this particular problem about balanced oestrogen progestogen in the near future?

<**Studd, off camera**>

Oh yes, I think very soon. I think we're almost there.

<**Chamberlain to camera**>

Good.

<**Studd to camera**>

And again, the answer will come from this country I'm sure, where there is so much good work going on in prospective trials of the sort that our American colleagues can't do.

<**Chamberlain to camera**>

Yes, yes. This is one of the advantages of the National Health Service …

<**Studd, off camera**>

Quite right.

<**Chamberlain to camera**>

Would you like to turn now to the hyperplasia side of the problem?

<**Studd to camera**>

Yes, the hyperplasia, and this is perhaps half the answer, half the answer to the carcinoma. If we can prevent hyperplasia, we probably are going to prevent hyperplasia, carcinoma, sorry.

Now, we do a Vabra curettage, an outpatient curettage on all of our patients with a uterus, about every year and we've found that with cyclical unopposed oestrogens, our hyperplasia rate is 15%, pretty high. If we add progestogen, it's much lower, if we use 13 days it's 0%.

<**Chamberlain, off camera**>

I see.

<**Studd to camera**>

Now, with the im…

<**Chamberlain to camera**>

<*interrupts*> What sort of numbers, again …

<**Studd to camera**>

Oh, we have most of all of the Syntex-menophase over 4 or 5 years, 400 patients …

<**Chamberlain, off camera**>

<*interrupts*> 400 patients, that's very good.

<**Studd to camera, then over table showing statistics for hyperplasia amongst women using oestrogen therapy**>

… 0%. The implants, interestingly, they have a high hyperplasia rate, about 30% but entirely because of defaulting, patients not taking their norethisterone. I can give you some examples of the hyperplasias that we've had and how we treat them.

Now, you can see here that we have a group of patients who have had unopposed oestrogens – Premarin, this sort of dose. We have 9 of those that have had hyperplasia. Now, we treat these …

<**Chamberlain, off camera**>

What is the ‘n’?

<**Studd, over same table**>

The number, sorry, the number of patients. That’s 9 out of our population of about 1000. And after treatment with norethisterone, 5mg, 21 days out of 28, for 2 cycles, to produce a bleed, after 2 of these progestogen cycles there’s no hyperplasia in any of these patients. Alright, so we can treat, correct, cystic glandular hyperplasia.

Now, on the next slide will see some other regimens, the implants for example. We have about 300 implants and the patients here that had hyperplasia, there was one on 25mg, 3 on 50, who had had their norethisterone, but the vast majority of the patients with hyperplasia are those that had their implant and did not take progestogen, it says here for 2 months or more, but some not for 5 or 6 months. Now, this was in some mistaken attempt to avoid having bleeding, but of course they will bleed after 4 or 5 months and of course progestogen does cause side effects – breast discomfort and so on, and they often don’t like taking progestogen, so they duck it for a month and get hyperplasia.

<**Chamberlain to camera**>

We can take it from this chart and the previous one, then, that you are quite happy to treat someone who has got a hyperplasia already with an oestrogen balanced by progestogen, is that right?

<**Studd to camera**>

That’s right, yes. Because one can correct this and that’s the end of the problem …

<**Chamberlain, off camera**>

<*interrupts*> Well, so you’ve shown us. And what sort of numbers are involved in these sort of patients you are showing us?

<**Studd to camera**>

It's hard to say because many patients change their sort of therapy during a couple of years, but about 300 or 400.

<**Chamberlain to camera**>

Yes. Yes, I mean a decent size.

00:21:20:05

<**Studd to camera, then over table showing effects of oestrogen therapy on women with adenomatous hyperplasia**>

Right, and now the next slide shows us the patients that have had adenomatous hyperplasia, a rather more severe sort, and there were 5 of these, but only 3 of the 2 have been corrected with the same progestrogen therapy. And again, mostly, they did not have their progestrogen, and there was a past history in all of these patients of menstrual irregularity which might be relevant.

<**Chamberlain and Studd shown seated**>

<**Chamberlain**>

You say this is adenomatous hyperplasia, what was the previous form of hyperplasia?

<**Studd**>

Cystic glandular.

<**Chamberlain**>

Cystic glandular, I see, thank you, yes.

<**Studd**>

That I think we must regard as almost a natural response to unopposed oestrogen therapy. This is perhaps more severe.

<**Studd over electron micrographs showing normal endometrium and endometrium with adenocarcinoma**>

We have been trying to study the surface cell morphology of these types of hyperplasia by scanning electron microscopy to see if we can distinguish between cystic, glandular, adenomatous, cancer and also to see if there's any response to progestogen. And we have here, this is a nice picture of normal, proliferative endometrium and those weeds in the middle, that's the ciliated cells, there's a normal number of those, and in between them you see the small columnar cells and on the surface you can see little microvilli.

Now that's normal, now you can contrast this with the next slide which is a patient with carcinoma. Now, this woman took 30 years of continuous, very high dose oestrogens, unsupervised, had bled every day for the last 4 years, if you can believe it, and here we have endometrium and it was adenocarcinoma. You can see that the size of the cells is different, different shapes and size, the arrangement's all higgledy-piggledy, no ciliated cells at all, there are coarse villi on the surface epithelium and you can see the slides on the right there, sort of punched out holes at 12 o'clock and 3 o'clock, sort of depressions, holes in the cell, typical of cancer cells.

You get the same sort of picture with scanning in pictures of squamous cervical carcinoma. Now, we have treated this patient with progestogen and here is the same sort of view, the same picture, higher power, this is now 2000 and there's no difference at all, there's perhaps a little bit of sort of coarseness of the microvilli but

still very abnormal and irregular size and shapes of cells – much bigger cells of course, and these little holes you see on the right-hand side.

<**Chamberlain over same micrograph**>

And this is after therapy?

<**Studd over same micrograph**>

That's after therapy.

<**Chamberlain over same micrograph**>

Yes.

<**Studd to camera**>

It is interesting that although our hyperplasia that we've treated, and they look normal histologically, I mean absolutely normal, nearly every one of them so far has a lot of abnormal cells, so it may be that if we damage cells with oestrogens causing hyperplasia there may be still cells that, at least on scanning electron microscopy, are anything but normal remaining.

<**Chamberlain, seated with Studd, to camera**>

You're not going to be able to give an answer to that point for many years, are you, until you've followed patients up for a long time.

<**Studd**>

That's right and I have a couple of patients that have had their hyperplasia reversed, corrected, and still, 2 years later, have some very bizarre cells in their scanning EM, but they're normal.

00:25:03:00

<**Chamberlain**>

Earlier on you implied, John, that whereas the risk ratio for unopposed oestrogen, either continuous or cyclical, was between 4 and 8 to 1 of carcinoma of the endometrium. And you also implied that for oestrogen and progestogen, together, the risk would be roughly 1 to 1.

<**Studd to camera**>

I would think so.

<**Chamberlain, off camera**>

But this is going to take a rather long time, surely, to show if you're going to have, if you include in this hyperplasia as a pre-malignant condition. Is it?

<**Studd to camera**>

Again, it's difficult to know the answer because the literature is very very confused and you can pick out a couple of papers to support your own arguments. It is commonly quoted that cystic glandular has about a 25% conversion to carcinoma.

<**Chamberlain, off camera**>

How do they know that?

<**Studd to camera**>

Well they are an extrapolation of a couple of very well-known and very bad papers from New York about 20 years ago, I am trying not to mention the author's name,

where the patients had a radium menopause and some died of something else and you were left with very small numbers, some of those got carcinoma and the papers are a nonsense really. So I think we can, and we've combined our clinic with the Birmingham clinic for pooling our results, we can assess the incidence of hyperplasia and the incidence of carcinoma and I must say, combining our two clinics, we haven't got one carcinoma in the last 4 years in patients who we are treating in an appropriate way.

<**Chamberlain, off camera**>

But you must admit it is a short time.

<**Studd to camera**>

Oh, certainly.

<**Chamberlain, off camera**>

4 years, especially in the natural history of a thing like carcinoma of the endometrium which is one of the slower progressing conditions, isn't it?

<**Studd to camera**>

Yes. One other thing interesting that it's certain that many patients with severe hyperplasia have been misdiagnosed with carcinoma and treated and we now know that from studies from Seattle and recently from Boston that the cure rates for stage 1 carcinoma in oestrogen users is 100%. It's very weird.

<**Chamberlain, seated with Studd**>

Well I can believe that because it is such a slow-growing tumour that you can do things with it. I don't want to widen this argument, John, this is our last question now, but is there any other effect of the giving of oestrogen opposed by progestogen or

not, on any other adenomatous tissue in the body which is sensitive such as breast carcinoma?

<**Studd**>

Yes.

<**Chamberlain**>

Without going too wide, is this a problem?

<**Studd to camera**>

Well I must say I am much more worried by breast carcinoma than I am endometrium. I honestly believe that the endometrial cancer story is a no-no if we are considering properly supervised therapy, right?

<**Chamberlain, off camera**>

But the breast cancer story?

<**Studd to camera**>

The breast – the literature says there is no increased risk. I am aware there are some papers coming out showing a greater risk, about a 2-fold risk, and I am concerned because it's a more common tumour of the younger woman, a more virulent tumour, and if these patients who have, for any reason, carcinoma in the breast, if they are given oestrogens it will accelerate the growth.

<**Chamberlain to camera**>

Even if they are opposed by progestogen?

<**Studd to camera**>

I think so. There is some work going on now on receptor sites in the breast with oestrogens and progestogens to see if progestogens are protective towards the breast because they might be, because we do know that breast carcinoma is no more common, or perhaps less common, in patients having the combined birth control pill.

<**Chamberlain to camera, then shown seated with Studd**>

Yes. That, I think, is another story John, and perhaps in a few years time in another series we might take that on.

We are grateful to you today for coming to talk to us and thank you, you have clarified the issue a lot because this is something which is very much in the minds of clinicians and research workers at the moment. I think, possibly, one of the major messages I've got from Mr Studd today is that there is a lot more time going to be required in order to produce these trials because you need large numbers, properly controlled, by the time you break them down into boxes of one controlling each other, you have got smaller numbers.

We're grateful to Mr Studd because as well as being an expert on hormone replacement therapy, he also, of course, is the Honorary Secretary of the Blair Bell Research Society and has been keeping us going very well for the last few years. He soon will be retiring and we are grateful to John for having done the work at the Blair Bell Research Society.

<**Studd**>

Thank you.

<**End credits**>