The Management of Pre-eclampsia

Current Research in Obstetrics and Gynaecology

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<**Opening titles**>

<**Geoffrey Chamberlain to camera**>

Hello, and welcome once again to another edition of Current Research in Obstetrics and Gynaecology. This programme comes to you from the University of London Audio-Visual Centre and is produced in conjunction with the Blair Bell Society. We try, in these programmes, to tell you a little bit about the background of subjects of interest at the moment and we ask our speakers to perhaps look a little forwards and see where the subject may be going next, particularly on the research side.

One of the big bugbears of obstetrics has always been the subject of pre-eclampsia. It's a confused subject, confused as terminology, and I think has not been made any

easier by the confusion of treatments – when there's a lot of treatments for any given condition, you can bet your bottom dollar that none of them are very good.

To help sort out this problem of pre-eclampsia we have asked Dr Gordon Stirrat from the John Radcliffe Hospital in Oxford, where he's the Clinical Research Reader, if he would take the subject through with us, and, differently from many of our programmes, we're going to talk a little more about management this time, but management with a research emphasis. So perhaps you can take us through, Gordon, with pre-eclampsia.

<**Gordon Stirrat to camera**>

Thank you very much indeed there, Geoffrey. Really the first point I want to talk about is the reason why we're going to talk about management rather than primary research. Because far too many people have been doing what they think is basic research on the subject for far too many years and what they've been studying has not been pre-eclampsia at all. And so it is therefore very important to know what you're studying before you expend a vast amount of time and expense and energy to put a hypothesis to test.

<**Stirrat over slide showing traditional definition of pre-eclampsia**>

And if we look at the caption here about the definition of pre-eclampsia, which is the traditional definition, perhaps one will see why this confusion arises. We have here a definition of pre-eclampsia which states that it is a condition of the 2nd half of pregnancy, characterised by hypertension, oedema, proteinuria, or any combination of these.

<**Stirrat to camera**>

Now this is, I would suggest, confusing because you know as well as I that hypertension can be a feature of other things than pre-eclampsia, oedema can be a normal feature of pregnancy, so that doesn't define pre-eclampsia at all. And, indeed,

if one is wanting to get a definition of pre-eclampsia one has got to go very much wider in one's scope; it's a multi system disorder, usually occurring in the 2nd half of pregnancies and not infrequently unfortunately still resulting in foetal death and certainly foetal growth retardation. And so one has got to cast one's net much wider.

<**Chamberlain off camera**>

Not just in the three clinical points of hypertension, oedema and proteinuria …

<**Stirrat to camera, briefly returns to slide showing definition of pre-eclampsia, then back to camera**>

Not just in these points at all and we'll come back to that. But if we look at this first caption again, if we instead change, instead of using this as a definition of pre-eclampsia, use it as a screening test almost and make it the criteria for diagnosis. Then, hypertension certainly and proteinuria, if we pick patients out with those particular problems, among those we will have the pre-eclamptic patients which we can study in greater detail. And if we recall, therefore, this is not a useful definition but is useful for diagnostic criteria, well that puts it in its proper perspective.

Well, <*back to* camera> I think the next thing we've got to look at is who are the people that get it, and what are the predisposing features of this condition. Well, it is a disease primarily of first pregnancies, which is odd, and even an early or mid-trimester, first trimester miscarriage can protect against pre-eclampsia. It occurs far more commonly in multiple pregnancy, in the presence of a highly deformed mole, in diabetes and in hydrops whether for rhesus disease or non-rhesus hydrops, and in those that are supposed to be placental factors of an unknown kind. It is quite specifically related to social class, poor social class has a higher risk. If a woman has got pre-existing hypertension she is more liable to it. And despite what I said about first pregnancy preponderance, if a woman has had it in a first pregnancy, she has an excess risk of getting it in the second, 10% of them will do so. And a family history of pre-eclampsia or any cardiovascular disease at all does seem to give an added risk of pre-eclampsia – father who died at 40 of a myocardial infarction, the

daughter of that family is more at risk from pre-eclampsia than if her father was perfectly fit and well at the age of 70.

<**Camera pulls back to show Chamberlain and Stirrat seated together**>

<**Chamberlain**>

Wasn't it Viel who showed that there is something like a one fifth coefficient of variation between diastolic pressure in the parent in relation to anything that happened in the sibling, in regard to any vascular condition? I think that was right, or 20%.

<**Stirrat to camera**>

Yes, I think that's probably right.

<**Chamberlain off camera**>

That would fit in very well with this, mmm.

<**Stirrat to camera**>

Another interesting thing that seems to come out is that women with a prior history of migraine headaches and Raynaud's phenomenon seem to have an added risk. Now …

<**Chamberlain off camera**>

Vasoconstrictive events.

<**Stirrat to camera**>

Yes, exactly, well what, it just comes out in the epidemiology of it which is interesting.

00:06:23:02

Now, if one looks at these predisposing factors and when one sees a patient in a clinic, goes through them in one's mind's eye, using them I believe that clinicians could pick out, because we can do it, a group of women who have at least a 50% chance and sometimes a nearer 70% chance of developing pre-eclampsia …

<**Chamberlain off camera**>

What sort of proportion of the population do you have to pick out to pick up the ones that have the 70% chance?

<**Stirrat to camera**>

Err, well, umm, if as we are, we're delivering 5000 patients a year but if we get 100 of those, we might get 100 who fall into that …

<**Chamberlain on camera seated next to Stirrat**>

Yes, but what I meant was when you pick up any high risk group, when you're picking up the 70% high risk – what proportion do you get into that high risk group that are not going to have it, in other words do you pick up a third of your population or define the 70%? That sort of order?

<**Stirrat to camera**>

Yes, yes.

<**Chamberlain on camera seated next to Stirrat**>

Yes, that's about it usually, and the higher the chances of getting the condition, the wider your group becomes so you end up with the total population again!

<**Stirrat to camera**>

Yes, that's often what happens. There's one thing I think that's worth mentioning, and that relates to smoking in pregnancy because it does look as though women who smoke in pregnancy have a lower incidence of pre-eclampsia but when they get it, it is very very bad news for the baby.

<**Chamberlain to camera**>

Why do women who smoke in pregnancy, do you think, have a lower incidence of pre-eclampsia?

<**Stirrat to camera**>

I don't know, I think is the honest answer to that one. It's something to do, perhaps, with the vascular response and the inhibition of …

<**Chamberlain off camera**>

It's dose related too isn't it?

<**Stirrat to camera**>

Yes, very much, it's dose related.

<**Chamberlain off camera**>

You can get a biological grade according to if you smoke 5, 10, 15 or 20 cigarettes at a time. Yes, that's interesting. Anyway, please …

<**Stirrat to camera**>

Right, now I've mentioned earlier that it is a multi system disorder and I think it would be worthwhile if we just looked at some of the systems which are affected by pre-eclampsia. The first one to mention would be the vascular system, and hypertension of course has been a definitive feature of pre-eclampsia for quite a long time.

<**Stirrat over graph showing details of a patient's patterns of hypertension**>

One of the things which my next chart shows is that hypertension sometimes occurs when one is least expecting it. In normal pregnancy, blood pressure tends to fall in the middle of the night, but here in this particular patient we can see that her hypertension was worse. Now, there is a confounding feature in this particular case and that is that the patient was on alpha methyldopa, and I want to make two points about this.

<**Chamberlain over same graph, points to it with his finger**>

The white one is one patient's systolic and diastolic …

<**Stirrat over graph, also pointing at it with finger**>

It's the same patient, the same patient early in pregnancy compared to later.

<**Chamberlain over graph** >

Systolic, diastolic, systolic, diastolic, I see, yes, thank you.

<**Stirrat over graph**>

At 24 weeks there was no particular problem but by 34 weeks she had developed pre-eclampsia, and it makes two points that this is an almost invariable pre-eclampsia with nocturnal hypertension of a really fairly marked degree, up to 120 diastolic on some occasions. And the second feature is that if one is treating the

maternal hypertension, and we'll come to the reasons for that later, one has got to remember that the treatment has got to cover this troublesome period at night.

<**Stirrat to camera**>

So, maternal hypertension is important and the vascular system responds differently to angiotensin, there's a fairly marked response to angiotensin too in a pre-eclamptic patient, and this has been suggested as the cause of pre-eclampsia – I don't think it can be the primary event but it's certainly in there somewhere as a secondary …

<**Chamberlain to camera>**

We've got Fiona Broughton-Pipkin of Nottingham coming down to do another of these programmes with us and she's going to tell us about angiotensin.

<**Chamberlain and Stirrat, seated, in discussion**>

<**Stirrat**>

Well, it ties in with prostaglandins quite well, prostaglandins E2 and there's an equilibrium between these two but they are certainly involved in pre-eclampsia; there's been a suggestion of a diagnostic test for pre-eclampsia by Gant, a rollover test. I must confess, we have not experimented greatly, but those who have on this side of the Atlantic are not happy about it as a diagnostic test for pre-eclampsia.

<**Chamberlain**>

We did 400 patients of whom 48, I think, subsequently did develop pre-eclampsia and we showed no difference significantly between those who did and those who didn't.

<**Stirrat**>

Yes, this has been our experience on a very much smaller number of patients. But there is definitely a change in vascular sensitivity in pregnancy and hypertension is the thing that we see most frequently.

00:10:54:21

Of course, another area in which the vascular tree is affected to the baby's cost is in the placenta and my next chart […]

<**Stirrat over illustration of decidua and myometrium**>

[…] shows a picture of decidua and myometrium. And in the normal patient there is an invasion, a secondary invasion of the spiral arteries and the basal arteries by foetal trophoblast. Now this occurs normally, the muscle disappears and they are just bags of blood-containing, bags containing blood I should say, lined by trophoblast. But in pre-eclampsia this migration into the myometrium does not take place, it stops at the deciduas, and in association with that in the radial arteries and the spiral arteries and basal arteries, you get this deposition of lipid and immunoglobulins and a whole load of fibre and other junk if you'll pardon the expression, which certainly narrows down the segments of the arteries. And, of course, reduces the placental perfusion, and this is what causes the placental insufficiency if we can use that term, and the placental infarct.

<**Chamerlain off camera, points at illustration**>

In the limitation of the trophoblastic migration in pre-eclampsia compared with the normal, is that a primary or secondary vein in relation to the deposition of the lipoid substance?

<**Stirrat over illustration**>

This is secondary to that.

<**Chamberlain off camera**>

Yes, it's secondary, yes, I understand.

<**Stirrat over illustration**>

So this seems to be fairly constant in pre-eclampsia, the cause of it we don't know, but it is interesting.

<**Stirrat over slide showing placental infarcts**>

And I think if we look at a slide now we will see what I mean by placental infarcts. You can see on that slide several 1cm thick slices taken from a woman with severe proteinuric pre-eclampsia, and those dark circular areas there are fairly fresh infarcts and you see one or two others are real fibrosed infarcts. Now I know there's a lot of controversy about what is and what isn't an infarct of the placenta but you can take it from me that in that placenta there were a lot of infarcts, and that baby was markedly small for dates.

<**Chamberlain off camera**>

What sort of volume of that placenta was inactivated by those? 30%? 40%?

<**Stirrat over slide**>

30% about, but it can be even more than that, we've had some situations which have been far more than 30%, and in some circumstances the hypertension has not been particularly marked either, but that's a point that I think it would be worthwhile coming back to.

<**Stirrat to camera**>

So, potential infarction, of course, occurs and this is why the baby tends to be smaller, maybe hypoxic and, of course, explains the high incidence of foetal death. And although pre-eclampsia only occurs in about 5% of our pregnant population it accounts for certainly at least half of our perinatal mortality and perinatal morbidity today …

<**Chamberlain off camera**>

It's associated with this …

<**Stirrat off camera**>

It's associated with this …

<**Chamberlain and Stirrat, seated, in discussion**>

<**Chamberlain**>

As an epidemiologist, 'to account for,' would be too strong. You see you find everyone pouring in on this – prematurity is associated with 60% of mortality and if you had prematurity and pre-eclampsia that's 110% that's been accounted for!

<**Stirrat**>

Right, point taken.

<**Stirrat to camera, then over graph charting renal change during pregnancy**>

So that's a very important system of change. Now, the next one to think about is renal changes. The first renal change that occurs is tubular damage, renal tubular damage and if affects the way in which the kidneys re-absorb uric acid. And if we look at the next chart, here – if I can mention this <*points with finger*> to get it out of the way, this is a placental enzyme which we've been measuring in pre-eclampsia

and it is just tissue breakdown in the same way as you do for myocardial infarctions, and this measures placental damage. But I don't want to talk about that one particularly, I want to talk about uric acid levels because here we have the line here, the white line here; serum uric acid which has been rising fairly steadily throughout this particular pre-eclamptic pregnancy and this woman, again, had severe proteinuric pre-eclampsia. And although, again, a trend is important, this figure of about 350 / 360 micromoles per litre is the cut-off point between what is a normal level and what is not. And in the vast majority of our women with pre-eclampsia, we find that at the same time as the blood pressure is changing, or even before the blood pressure is changing, the real handling of uric acid changes. And we actually use this as one of our features to monitor the progress of the patient in …

<**Chamberlain off camera**>

Yes, it's interesting in that this process was happening before you started to get the alteration reflected by your enzyme destruction, already the renal side was being affected wasn't it?

<**Stirrat**>

Yes, yes, yes.

00:16:01:20

<**Stirrat to camera**>

Of course, the next thing that can happen is that there's renal glomerular damage and we do see an increase in plasma creatinine in our patients, we therefore also see a drop in creatinine clearance although what is normal creatinine clearance in pregnancy varies so much that it's difficult to put an exact figure to that. And then the last thing, but the one which is probably of the most serious import is proteinuria, and that really marks almost a terminal event in pre-eclampsia and the patient's got to be watched very very carefully if that occurs.

Then if we move on from kidney changes to clotting system changes and there are very marked changes, there are increases in both serum and urinary fibrin degradation products, but that's a very crude test and they don't always, it doesn't always happen. But what does happen is you get changes on factor VIII because factor VIII is being consumed in what is really an intravascular coagulation.

<**Stirrat over graph showing levels of factor VIII**>

And if we look at the next chart we will see here two things; first of all the plasma urate that I was talking about earlier to show you a patient that actually had some pre-eclampsia, but you will see here that there has been a marked increase in the consumption of factor VIII. This factor VIII antigen activity difference is a marker of the use of, the usage of, the consumption of factor VIII, and therefore of thrombosis. And this has been a very useful marker of pre-eclampsia in out patients.

<**Chamberlain to camera and over graph**>

Yes, and as you say the urate going up is an indication of pre-eclampsia. But the diastolic blood pressure, here, is between 25 and 75 mm of mercury and that would not be a clinical diagnosis of pre-eclampsia in the old definition.

<**Stirrat over graph**>

I've been rather naughty here and that was intentional because there are very rare but very definite patients in whom they do not develop hypertension, they have normotensive pre-eclampsia, that is not heretical to say it.

<**Chamberlain off camera**>

But heterodoxy is your doxy, orthodoxy is their doxy.

<**Stirrat over graph**>

That's right, but this particular patient had pre-eclampsia – if one looks at the placenta and looks at the growth of the baby which was retarded and every other parameter, sorry I've used that naughty word, every other aspect except the hypertension, and it is an interesting concept this which I don't want to emphasise too strongly …

<**Chamberlain to camera**>

No, but I do think it's fair to do what you've done because you have quite rightly widened out pre-eclampsia from the old fashioned triad of clinical signs to include about six or seven things, and if you are going to consider that in that group of six or seven, one or two may be missing from a syndrome in some things, why not hypertension be missing occasionally? For after all, hypertension undoubtedly is only the resultant of the causes of the fact of pre-eclampsia, it's one of the resultants isn't it?

<**Stirrat to camera**>

Well, I think this is an important message to get across, if we do no more this afternoon than to get that across I think that would be important. There are other system changes and the one which, as far as research goes, interests me probably more than any is the immune changes. There is very little hard fact on this, certainly immunoglobulins IgG drops in pre-eclampsia, and we have found an increase in IgG immune complexes in pre-eclampsia and in complement fixing complexes in severe pre-eclampsia. And we think this may very well be relevant but we do not know. There are other immune changes; there seems to be a reduction in the amount of antibody that the mother develops to the foetus in pre-eclampsia, but these are fairly circumstantial.

There are other changes, there are changes in the liver, there is focal necrosis and of course cerebral oedema is one of the things which would tend to give you the

classical eclampsia of the pre-eclamptic syndrome, and therefore is also a terminal event. So it is a multi system disorder.

00:20:16:00

<**Chamberlain off camera**>

Now, how about coming on to the management?

<**Stirrat to camera**>

Yes, well I think this is an area that really needs to be rationalised, not researched into in terms of discovering something that's new, but actually a bit of common sense applied to it and we've got to say: well what are we doing / what are our aims in management? Well, first of all, the first thing I would say is to predict the risk of the condition arising and therefore to predict a risk to mother and to baby, after all, as obstetricians that's what we're in business for, prediction of risk.

Then, if you can predict the patient who's at risk, following them fairly closely in the pregnancy, diagnosing it early, admitting the patient to hospital early and monitoring the systems that I've been looking at to see these changes, and timing delivery properly, usually for the baby's sake but sometimes for the mother's sake.

I think there are one or two principles that must underline one's management. The first vital thing to get across is there is no cure for pre-eclampsia except delivery of the baby, that's the only thing that actually cures it. And the average time span of pre-eclampsia from origin to delivery is, at the most I would say, well it can't be, the average can't be the most, six weeks. That would be about it.

<**Chamberlain and Stirrat, seated, in discussion**>

<**Chamberlain**>

Irrespective of when the pre-eclampsia started?

<**Stirrat**>

Irrespective of when the pre-eclampsia started, yes.

Then the second thing to bear in mind is that admission to hospital and bed rest don't alter the course of the disease.

<**Stirrat to camera**>

And the reason they are in hospital is to have them under basal conditions so that you can be watching their blood pressure, you can be watching all the things that you want to. Blood pressure, I beg your pardon, bed rest and admission to hospital isn't a magical thing which reduces the pre-eclamptic syndrome in any way whatsoever.

<**Chamberlain and Stirrat, seated, in discussion**>

<**Chamberlain**>

You don't think that by bed rest you may alter, possibly increase, uterine blood flow and therefore placental blood flow on the maternal side?

<**Stirrat to camera**>

I am very sceptical about the evidence for that. I don't think so. Our evidence, not monitoring blood flow I'll grant you, but looking at the syndrome is that there is no change in the pre-eclamptic syndrome, even by bed rest.

<**Chamberlain off camera**>

Agreed, although I don't entirely agree but I'm not going to chase that now but I think Smith on the West Coast has some nice leeching in studies, not leeching out studies,

of blood flow, and for the maternal side may it not cause the blood pressure not to go so high that you are forced to take action, rarely I agree, on the maternal side?

<**Stirrat to camera**>

Yes, yes, I think that's fair.

<**Chamberlain to camera**>

But I take your general point that you don't do a lot of good, but you do help a girl in a place that you can monitor her.

<**Stirrat to camera**>

You remember I started by saying that we don't really understand this condition and so sometimes one has got to be, I'm being a little over-dogmatic, and we've got to be aware that we're not being too dogmatic about things, but in general I think that if you abide by that principle in your management you won't go far wrong.

<**Chamberlain off camera**>

Yes, sure.

<**Stirrat to camera**>

So, large monitoring of the progress, now largely to detect sudden changes and time the delivery. As far as treatment is concerned, there have been vogues for salt restriction, for diets, for sedation and for diuretics. Now, none of these have been shown to be of any value whatsoever and I particularly want to pick out the one about diuretics. Diuretics are of positive harm in this condition. One of the effects of the vascular changes due to angiotensin is that there's hypovolaemia and haemoconcentration and all you do with your diuretic is make that even more severe and it can be counterproductive for mother and for baby.

<**Chamberlain off camera**>

Yes, we had Frank Hytten on a programme recently talking about water metabolism and he made a very big point about this, went into it, yes.

<**Stirrat to camera**>

Now, of course, if hypertension is the most common feature of pre-eclampsia, the treatment of it is something that's going to come into our discussion. But again there's another principle that must be emphasised and that is that in treating hypertension it is the mother you are trying to save from harm, you are not doing anything to save the baby from harm at all. But against that one must say that a controlled drop in blood pressure does not harm the baby – there have been some suggestions by Brosens etc. that you might actually be doing this but we, over quite a few years, have no evidence the baby is harmed by a controlled drop in blood pressure.

<**Chamberlain to camera**>

Yes, this is a fairly chronic drop that you're talking about, not an acute one.

<**Stirrat to camera**>

Not an acute drop, not a sudden drop to zero levels. The sort of level at which you really do begin to need to think of giving the mother some hypotensive agent is a systolic blood pressure of 170 and a diastolic of 110, round about that, although you mustn't stick too rigidly to that. And in the acute management of hypertension in pregnancy, if you look at the chart here […]

<**Stirrat over series of tables listing dose levels for drugs to treat hypertension in pregnancy**>

[…] hydrallazine has, I believe, stood the test of time, it can be nasty if given over a long time but here we have the sort of regime that I think is helpful. 10mg intramuscularly or 5mg intravenously, followed by intravenous injection after 20 minutes if the blood pressure is not lowered to 100mm of mercury, and you can repeat that when the blood pressure has risen to 110mm of mercury diastolic or more.

So hydrallazine is the mainstay. Then of course diazoxide can be helpful as well in some circumstances although we have found it rather disappointing and the regime is as is shown there. And then if you've got less urgent need to control the blood pressure, we still find alpha methyldopa a very useful drug in this regard, and there we find the sort of regime that we find most useful in alpha methyldopa.

Then if we go on to the next caption just some caveats. I do feel that beta-blockers are best avoided at the present moment if possible – controlled trials are necessary but they must be very controlled and there is quite a lot of experimental evidence that suggests that beta-blockers can be of harm to the hypoxic foetus. And so be very very careful about the use of beta-blockers.

<**Stirrat to camera**>

And drugs like reserpine, for instance, are totally contraindicated because of the stuffiness they cause in the baby's nose and when it's delivered it may not be able to breathe properly, so there are these things that are important. In labour, however, an epidural anaesthetic can be a very very useful means of controlling blood pressure and must always be born in mind.

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If one is faced with eclampsia which is a preventable condition and should be falling, I think is falling in Britain, but good antenatal care helps to prevent that – it is preventable. But if you are faced with impending eclampsia, or actual eclampsia, I think we've gone away now from the use of rectal evertan[?] and other things and I'm

glad about that. And there was most widely used drug, I think, if we look at the next chart.

<**Stirrat over series of tables showing dose levels for various drugs**>

Here is diazepam, given in the sort of way I've shown there, although one must be careful because it does cross the placenta and you do get a floppy baby who doesn't suck very well afterwards and therefore the paediatricians have got to be warned of that.

Another fairly useful drug is chlormethiazole, given in the sort of regime I've given there. So those two, you can choose between those, if you want to control eclampsia and, of course, on the other side of the Atlantic magnesium sulphate is very very popular, and the next chart shows the sort of regimes that are used there. The first, this is by intramuscular injection and then this is by intramuscular injection as well. And I'm not totally sure why magnesium sulphate is so favoured in the United States of America and not in favour over here.

<**Chamberlain off camera, then camera moves to show him seated, talking to Stirrat**>

It used, of course, to be very popular over here in the old Stroganoff regime wasn't it? And it went out before the war, I think when the barbiturates came in; if you talk to those senior to both you and I that's how it went. But in the States I am horrified by the way the clinical obstetrician monitors his patient on magnesium sulphate. I was at a clinical meeting in a state south of the Mason-Dixon Line on the East Coast the other day and the resident got up and having filled his patient with intravenous and intramuscular mag sulph, which it takes a terrible time to clear afterwards, was worried as to why she got ectopic beats on her ECG, and was monitoring her with knee jerks only in the end, and if knee jerks weren't present then they were giving her too much. That's a pretty coarse thing isn't it?

<**Stirrat to camera**>

Yes, yes, but in good units in the States, they still swear by magnesium sulphate and control it quite nicely.

<**Chamberlain, seated, talking to Stirrat**>

Well, it's their major method of treatment and I think we may well see, well perhaps there's room for a trial on this.

<**Stirrat to camera**>

Yes, there may very well be, may very well be.

Now, I think that really brings us to the end of treatment and if one is wanting to look ahead in terms of research for the future: things that come up that might be key things to consider are the condition is of first pregnancy preponderance. Now, pre-eclampsia has been called a disease of theories and the one feature of it which none of these theories has satisfactorily explained to anybody is its first pregnancy preponderance. And it may be that an immunological theory of its development, and there is some evidence for this, that we could find that, but they are very early days as yet. We have found in Oxford a fairly clear indication that there could be a recessive gene, a recessive immune-response gene which picks out the patient who cannot perhaps respond appropriately to the antigens the foetus is presenting to it and the inappropriate response actually turns out as perhaps an immune complex disease which then latches into all the systems we've been talking about and produces this syndrome of pre-eclampsia. Now that is fairly simplistic and a lot of work has got to be done on this …

<**Chamberlain off camera**>

You're implying that some form of antigen comes from the foetus across to the mother are you?

<**Stirrat to camera**>

Yes, yes.

<**Chamberlain, seated, talking to Stirrat**>

And therefore, the sensitising dose is the first pregnancy. How then would spontaneous abortions such as occurs at 12 / 14 weeks, how would that protect the mother because not much antigen goes across before that does it?

<**Stirrat**>

Yes, oh yes it does, oh yes, yes, whatever the antigen is, it will be coming from the placenta and trophoblast antigenicity, whatever that may be, will be developed by that time.

<**Chamberlain**>

Even as early as that?

<**Stirrat**>

Even as early as that.

<**Chamberlain**>

So, it wouldn't depend upon foetal bleed? Not like rhesus?

<**Stirrat**>

No, it wouldn't depend on a foetal bleed.

<**Chamberlain**>

Do you feel, as some people have shown to their own satisfaction, even if it's not to yours and mine, the taking of the pill, the oral pill contraceptive for a few years before a girl was pregnant, that gives some resistance to pre-eclampsia as well.

<**Stirrat**>

Yes, well, we interpret that in a slightly different way because there seems to be a connection between the length of time of intercourse with the same partner and incidence of pre-eclampsia. For instance, in some of our artificial insemination by donor patients, they get very severe pre-eclampsia, now that doesn't prove anything but …

<**Chamberlain**>

But are you implying antigen coming from the sperm then?

<**Stirrat**>

Antigen coming from the sperm; the young primigravida, the 16-year-old who becomes pregnant, they have quite a high incidence of pre-eclampsia and it may be because it's after first intercourse.

<**Chamberlain**>

It's jolly interesting, I've just done a retrograde analysis on a group of young under 16-year-olds on other people's data and it really, it relates more to the race of the patient than it does to the age. I think so many of the studies we've looked at in the 16-year-olds and under refer to a negro population, particularly the United States where 95-97% of them are negroes and I wonder if it's a racial thing as much as an underage group. But to come back, you implied that the sperm itself might be antigenic. Would this imply a break in continuity of the maternal epithelium or …

<**Stirrat**>

Not necessarily, the sperm can be shown even to get through the vaginal epithelium in fact and certainly you can get them in uterine lymphatics as well.

<**Chamberlain**>

That's most interesting.

<**Stirrat**>

Yes. The one thing that it does raise as a possibility for the next decade is that if one could: a) prove that there was some feature like this, and b) find what the antigen was, it might be possible to immunise the mother against the risk of pre-eclampsia.

<**Chamberlain**>

Yes, that's a most interesting point that you've raised and if I may as the last point on that to raise to you – would you not expect then that possibly, if this was a sex-linked thing, if the mother had a male foetus she'd have a greater epidemiological risk of having pre-eclampsia than if she had a female?

<**Stirrat**>

Well that is true.

<**Chamberlain**>

Is it so? I didn't know that.

<**Stirrat**>

That is actually true.

<**Chamberlain**>

Who's shown that? If not yourselves.

<**Stirrat**>

Ummm, I can't , I don't, Stevenson's study in Turkey was on consanguinity, but I don't know, I think it was Terasaki but I honestly can't remember …

<**Chamberlain to camera**>

I'll tell you the result of this talk is that I shall go back to the British birth data and re-analyse by sex of child, I haven't done that. But that's very interesting.

Well, you have Gordon, thank you very much, taken us through pre-eclampsia in a most thorough way – you have shown us a lot of the more clear thinking, if I may say so, of what the condition really is, and this mishmash of three classical triads like an old milking stool has been replaced by a more logical process of looking at a wider syndrome which includes clinical, pathological and indeed retrospective factors, you must look at, you don't know about in pregnancy. We've also been through and seen the rationale of much of the management and we've ended on a most interesting note, I think, on the possible immunological features that might be associated with pre-eclampsia. Thank you very much.

<**End credits**>