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Angiotensin and Hypertension in Pregnancy Current Research in Obstetrics and Gynaecology

**Discussed by Mr Geoffrey Chamberlain
and Dr Fiona Broughton Pipkin, University of Nottingham.**

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**Medical Editor: Mr Geoffrey Chamberlain.
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**Black-and-white
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<Opening titles>

**<Mr Chamberlain and Dr Broughton Pipkin are seated for discussion. A display
board for diagrams is placed between them>**

<Chamberlain to camera>

Good day. Welcome to another addition of our research programmes in obstetrics and gynaecology. These programmes, you'll remember, we're bringing from the University of London Audio-visual Centre in conjunction with the Blair Bell Research Society. In them we try and give you some background of a subject and we talk about the current use of it, and we try occasionally to use our crystal balls, look a little into the future. And this programme we're devoting to the subject of angiotensin

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and hypertension in pregnancy. We've asked a member of the Blair Bell Research Society, Dr Fiona Broughton Pipkin, who is the Lecturer in Reproductive Physiology at the University of Nottingham, to come down and talk to us about this. Fiona.

<Broughton Pipkin to camera>

Thank you very much, Geoffrey. Well, the very word angiotensin, which can be loosely translated as vessel tightener, gives some indication of what its function is. It's the most powerful naturally-occurring vasoconstrictor substance yet isolated. It's 10 times more active on a molecule for molecule basis than is noradrenaline.

<Broughton Pipkin narrates over diagram outlining angiotensin production>

It's produced by the action of an enzyme, renin, which is primarily renal in origin, which acts on an alpha-2-globulin substrate in the plasma. This results in the production of a decapeptide, angiotensin I. This has relatively little biological activity and is rapidly broken down by a converting enzyme which acts on the C-terminal end, breaking off the histidyl-leucine dipeptide to produce the octapeptide, angiotensin II. It is this peptide which exerts the vasoconstrictor action of the renin-angiotensin system.

Now, this *<indicates angiotensin II>* itself has in circulation a short half-life of the order of rather less than 2 minutes and is rapidly broken down by angiotensinases to form various peptide fragments.

<Broughton Pipkin to camera>

Now, for a long time, it was imagined that these peptide fragments were biologically inactive. However, it's now known that the other major action of the renin-angiotensin system, that is to say, its action on the adrenal cortex which promotes the synthesis and release of aldosterone and, hence, aids retention of sodium and water, it's now known that this action is mediated, in fact, by the heptapeptide fragment, which is the same as angiotensin II but with the end-terminal aspartic acid residue chewed off.

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Now, the control mechanisms for regulating the levels of activity of the renin-angiotensin system relate directly to their activity in the body. So the main stimulus for increased renin release is that of a diminution in renal perfusion pressure, howsoever caused. This can be caused by a drop in systemic blood pressure, by hypovolaemia, or by a purely mechanical function, such as renal artery stenosis. Any of these factors will result in an increased release of renin, which, other things being equal, will increase the circulation levels of angiotensin II in the blood and increase the systemic blood pressure.

The other major feedback loop for increased activity of the system relates to the level of total body sodium and to the sodium lowered at the macular densa. Should the body be losing inappropriately large amounts of sodium then, again, the synthesis and release of renin is increased and therefore angiotensin II levels are increased. Acting on the adrenal cortex are the sterone increases with consequent retention of salt and water.

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So much, then, for the skeleton of the renin-angiotensin system. Now, what happens in normal pregnancy? Well, in a normal ovulatory cycle, there is a peak of concentrations of both renin and angiotensin II about the time of ovulation. Should conception occur, these elevated levels are maintained and, indeed, in somewhere between 70 and 80% of all normal pregnant women, levels of renin, renin substrate, angiotensin and aldosterone are all higher than the top of the range of normal in the non-pregnant state. Now, it is thought that the stimulus for these increased levels of renin and angiotensin is related to the mild natriuretic action of progesterone on the kidney. The increases may be further assisted by the action of oestrogen on the liver promoting, of course, the synthesis of alpha-2-globulins among others. And among the alpha-2-globulins is, as I have said, renin substrate.

Now, since I have also said that angiotensin II is an extremely powerful vasoconstrictor, it could be argued that all pregnant women might be expected to be

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hypertensive. This, of course, is not the case and the reason for this has been known since the early 1960s, when it was first discovered that there is in pregnancy a specific diminution in vascular responsiveness to angiotensin II. The exact pathway by which this diminution in responsiveness acts is not fully clarified, but it seems very likely that it is related to the production of increased levels of vasodilator prostaglandins in the walls of the blood vessels.

<View of both Chamberlain and Broughton Pipkin in discussion>

<Chamberlain>

Does this vary at all during pregnancy other than just building up in a biological gradient? I was wondering about the alteration in blood pressure which occurs physiologically in pregnancy somewhere in the mid trimester.

<Broughton Pipkin>

I don't think it's been followed for the simple reason that it is very difficult to get serial samples of tissue prostaglandins in pregnancy.

<Chamberlain>

Yes, yes, I see, thank you.

<Broughton Pipkin>

It would be an interesting point.

<Chamberlain>

Good.

<Broughton Pipkin to camera>

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I want to come back to this idea of a possible link up between angiotensin and prostaglandins later on.

Now, so much then for normal pregnancy. What happens in hypertensive pregnancy? And at this point, I should perhaps clarify the working definition which we use for pregnancy-induced hypertension. Mr Chamberlain may well object to this because there are as many different definitions of pregnancy-induced hypertension as there are people working in the field. However, the one which we use is that occurrence of a blood pressure of 140/90 millimetres/mercury or more occurring on at least two separate occasions after the 20th week of pregnancy in a woman known to be previously normotensive and in whom there is no personal or family history of renal or cardiovascular disease.

<Chamberlain>

I wonder how many of us have got no family history of cardiovascular disease.

<Broughton Pipkin>

This, of course, is, it's very difficult to say, but if a parent has died...

<Chamberlain>

So first degree.

<Broughton Pipkin>

Yes that's right.

<Chamberlain>

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The only reason I raise this is that viewers may remember that in one of our previous programmes, we had the Oxford Group with us and they had their definition of hypertension. And all these are perfectly proper that you use them inside of the context of the work you are doing, but the one you've quoted, I believe, had got more than that. Is it not used by the Hypertension Association, the association that's looking at hypertension?

<Broughton Pipkin>

Yes, it is indeed.

<Chamberlain>

What's the name of the association again?

<Broughton Pipkin>

The International Society for the Study of Pregnancy-Induced Hypertension.

<Chamberlain off-camera>

I should have known that, thank you very much. And is that definition accepted?

<Broughton Pipkin>

Yes, it is. This definition was accepted in Dublin in September last year.

<Chamberlain>

There might be some Americans all accepting it mightn't they?

<Broughton Pipkin>

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I think it would help. It would certainly make comparative studies much easier.

<Chamberlain>

Thank you very much.

<Broughton Pipkin to camera>

Well, the other point that should, perhaps, be made about pregnancy-induced hypertension, as we define it, is that there is general agreement, I think, that it is primarily a disease of first pregnancy. This being so, the data which I shall be presenting all relate to data from primigravida women.

Very well, let's turn now and look at angiotensin levels in a group of normotensive and a group of hypertensive pregnant women.

<Broughton Pipkin narrates over graph showing angiotensin II levels in pregnant women>

All angiotensin levels referred to have been measured, incidentally, by radioimmunoassay, in our department. Now here, I have plotted angiotensin II, picograms per millilitre plasma, in a group of 20 normotensive primigravidae and 18 hypertensive primigravidae before the surgical induction of labour; 7 normotensive and 9 hypertensive primigravidae at elective caesarean section; 26 normotensive and 18 hypertensive women at vaginal delivery. And you will see that in every case, angiotensin II levels are higher in the hypertensive group, and that this difference is statistically significant in the group measured before induction and measured at elective caesarean section.

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<Broughton Pipkin to camera and then over graph showing angiotensin II levels in pregnant women and their babies>

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So much then for the mothers. Are angiotensin II levels also raised in the babies of these women? Well, as the next figure will show, they are indeed. Here again, I have plotted mean with \pm one standard error of the mean, angiotensin II levels, again, in a group of normotensive and a group of hypertensive women and their babies: cord venous and cord arterial angiotensin levels, and I should stress that these are all properly paired samples. And what we see again is that the maternal venous levels are higher, the cord arterial levels are actually somewhat lower, but because there is a very big scatter of data, this difference is not statistically significant. The most interesting point to arise from this slide, I feel, is this – that the cord venous levels are very markedly raised; in fact, they are just about double those seen in the cord venous blood of babies born to normotensive mothers and this, again, is a point to which I shall return.

<Broughton Pipkin to camera>

Very well, we have said then that angiotensin II levels are raised not only in the mothers but also in the babies in hypertensive pregnancy. Does this, in fact, bear any relationship to the degree of hypertension? Well, a very simple-minded way of looking at this is simply to plot the simultaneously measured angiotensin II levels and diastolic blood pressure and this is what I have done in this next figure.

<Broughton Pipkin narrates over graph showing plasma angiotensin II levels plotted against diastolic blood pressure>

Here again, plasma angiotensin II levels plotted against simultaneously measured diastolic blood pressure mm/Hg. The blood pressure was measured in every case either by trained midwifery staff or by the doctor in charge of the case. The solid symbols relate to patients showing proteinuria, the open symbols to patients without proteinuria. This is 50 primigravidae immediately prior to the induction of labour. And over the group as a whole and including these 2 patients down here, there is a statistically very highly significant relationship between diastolic blood pressure and simultaneously measured angiotensin II.

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<Broughton Pipkin to camera>

Now, it has been said, and rightly, for many years that statistics can be made to prove anything that you want them to prove: lies, damned lies and statistics.

<Chamberlain>

I'm not rising <laughs>.

<Broughton Pipkin>

<Laughing> You disappoint me. If this association, the statistical association between plasma levels of a very powerful vasoconstrictor and diastolic blood pressure is a genuine cause and effect relationship, then blocking the action of the renin-angiotensin system should result in a fall in blood pressure. Now, various blockers for the renin-angiotensin system are, in fact, currently available, but since they are all manufactured in the States they come under the aegis of the FDA and we are not allowed, at the moment, to use any of them in human pregnancy, which is very disappointing. So, I have turned to another species and one which has, in many respects, similarities with the pregnant human.

<Broughton Pipkin narrates over illustration of a sheep with suckling lamb, and then to camera>

I'm referring, of course, to the chronically cannulated pregnant ewe and lamb. Now, this preparation has been used extensively over the last 20 years to study problems in perinatal physiology. Cannulae are inserted in, in this particular instance, the carotid artery and jugular vein of both foetus and mother under general anaesthesia. A minimum of 48 hours is allowed to elapse after surgery before any experimental procedures are carried out. And at the time of experiment, the ewe is, so far as we can tell, entirely conscious; she is certainly unrestrained and wandering around her pen, apparently unworried by what is going on. The form of all the experiments is the

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same. After a period of recording baseline blood pressure, the angiotensin antagonist, in this particular case, saralasin, which is a specific receptor blocker, is infused. It is infused in stepwise increments, each step lasting for 10 minutes. The blood pressure is recorded throughout and at the end of the experiment the infusion is stopped, the blood pressure allowed to return to baseline, and a further period of basal blood pressure is monitored.

00:14:20:13

<Broughton Pipkin narrates over graph showing percentage change in diastolic blood pressure plotted against the dose of the angiotensin receptor blocker, saralasin>

Now, the next slide shows exactly what happens here. Here I have plotted the percentage change in diastolic blood pressure against the dose of this angiotensin receptor blocker, saralasin, micrograms per kilogram body weight. The open symbols here relate to the mean \pm standard error of 10 experiments in which saralasin was infused at doses of 1 to 8 micrograms per kilogram minute. The dark symbols relate to control experiments in which saline alone was infused as a control. And you will see that the infusion of saralasin resulted in a dose-dependent fall in mean diastolic blood pressure, which was overall highly significant, while the infusion of normal saline, although it resulted in a small fall, did not exert an overall statistically significant effect.

<Broughton Pipkin to camera>

Furthermore, as you might expect that the magnitude of the depressor response to a specific angiotensin blocker would be related to the initial circulating levels of angiotensin II. This is indeed the case. When you examine the relationship between the initial levels of angiotensin II and the depressor effect evoked by any given dose of blocker, then there is a direct statistical relationship between them. So we are beginning to arrive at an idea. We have increased levels of a very powerful

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vasoconstrictor in hypertension and there is a relationship with blood pressure here, and evidence from another species, anyway, suggests that this relationship is causal.

Where are all these elevated angiotensin levels coming from?

<Broughton Pipkin narrates over illustration of foetus in uterus showing sources of renin>

Well, in pregnancy, as this next diagram shows, there are various sources other than the maternal kidneys, which can be producing renin. The fetal kidneys, for instance, can produce renin from 56 days gestation on. We have some evidence from babies with renal agenesis that the foetal genital tract is capable of producing renin. It has been known for some time that myometrium is capable of synthesising renin whether pregnant or non-pregnant, but the single most important alternative source of renin is the chorion, which is capable of producing very large amounts of renin, second only to renal renin production.

<Broughton Pipkin to camera>

Do all these alternative sources of renin have any effect on circulating renin and angiotensin II levels? Well, the evidence, at the moment, is all indirect, but what there is of it seems to be fairly conclusive. Briefly, if one takes paired samples of peripheral venous blood and uterine venous blood at elective caesarean section and measures the renin or the angiotensin II levels in them, then one finds that in normotensive patients uterine venous renin and angiotensin II levels are consistently lower than are peripheral levels, whereas in hypertensive patients the converse is true. This suggests that the maternal side of the placenta anyway may be capable of contributing to maternal levels. Similarly, you may remember in an earlier diagram I showed that the cord venous angiotensin II levels in babies born to hypertensive mothers is markedly higher than is the cord arterial level, again suggesting that the foetal side of the placenta may be capable of modifying levels.

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A third piece of evidence, and one which is, in my view, quite compelling is this: if the foetoplacental unit is producing renin or angiotensin II levels capable of modifying maternal levels, then birth – removal of the foetoplacental unit – should result in a diminution in maternal levels of these hormones. And this indeed is precisely what happens.

<Broughton Pipkin narrates over graph showing maternal plasma angiotensin II levels plotted against regular intervals after delivery>

Here I have plotted plasma angiotensin II again and plasma renin concentration in a group of patients from whom samples were taken at half hour intervals for the 4 hours after delivery. And what we see is that both renin and angiotensin II levels fall sharply in the first 2 hours after delivery to levels within the normal non-pregnant range. The time course of this fall is consistent with the known half-life of renin in the circulation and we would suggest that these falls represent a clearance from the maternal circulation of renin of foetoplacental origin.

<Broughton Pipkin to camera>

Following this time, the levels appear to increase slightly and I would suggest that this increase represents a release from suppression of maternal renal renin production which has been held down by foetoplacental renin during the last half of pregnancy.

Very well, what has all this got to do with pregnancy-induced hypertension as a unifying hypothesis? Well, this is a hypothesis and like all hypotheses may well be totally disproved within the next 6 months or 6 years, but at the moment, all the available evidence fits.

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<Broughton Pipkin narrates over diagram illustrating pathway of renin release>

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If you remember, I said that the single most powerful stimulus for renal renin release was renal ischaemia, whether caused by renin artery stenosis or howsoever, resulting in an increase in renin production, increase in angiotensin II production, increased systemic blood pressure and, therefore, increased renal perfusion pressure.

<Broughton Pipkin to camera and then over diagram showing stages of foetoplacental blood flow>

Let's now turn to the foetus. Now, it is generally agreed that in pregnancy-induced hypertension, there is a diminution in uteroplacental blood flow. There is argument as to whether this antedates or postdates the vasoconstriction. I would suggest that it antedates it. And this is what I suggest is happening: that the ischaemic foetoplacental unit is producing more renin, more angiotensin II, pushing up the maternal systemic blood pressure.

<Broughton Pipkin to camera>

Ah, but there is at first sight a flaw in this argument because, as I have said, angiotensin II is a very powerful smooth muscle constrictor, therefore, one might imagine that it would be initiating a vicious circle in the uterine vasculature. Not so. Recent experimental work from three separate centres in the States has shown that increased concentrations of angiotensin II in the uterine circulation result in an increased production of the vasodilator prostaglandins of the E series, and that these vasodilator prostaglandins are produced to such extent that they overcome the vasoconstrictor effect of angiotensin in the uterine vasculature; hence, there is an increased systemic blood pressure going into a dilated bed and an improved uteroplacental blood flow.

What I would, therefore, like to suggest is that, in the first instance anyway, pregnancy-induced hypertension is a physiological response on the part of the foetus and placenta to the pathological stimulus of reduced uteroplacental blood flow.

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<Camera alternates between Broughton Pipkin and Chamberlain in discussion>

<Chamberlain>

Hear, hear! I think that's a very fine statement to make at the end there. Thank you very much. It was a well-presented, logical series of steps you took us through. Taking the last point first, there is, I think, much epidemiological evidence that it is the response of a diminished flow that increases the pressure to get more blood to go through. After all, as you, I believe, yourself have found, the babies that come from mothers with mild and moderate preeclampsia are often the same if not bigger than the background population. Is that right?

<Broughton Pipkin>

Yes, indeed.

<Chamberlain>

And that would fit with many other studies as you know.

<Broughton Pipkin>

Yes.

<Chamberlain>

May I go back a little bit? Tell me, why in your slide, where you had, you showed plasma renin, did you have these differences between the induced group and the elective caesarean section group but not in the normal delivery group. Why do you suppose that was?

<Broughton Pipkin>

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I should, perhaps, have said that this was a fairly early slide, hence the small numbers. If you look at a larger series, the difference is significant, but the other problem is that various other factors are known to influence plasma renin and plasma angiotensin II in normal delivery. So, for instance, the duration of the second stage of labour markedly affects angiotensin II levels, a long second stage being associated with much elevated angiotensin II levels, so there are numerous other factors which are superimposing upon basal angiotensin II levels at normal delivery, and I think this is why there is the difference.

<Chamberlain>

So the elective caesarean section is the clean group.

<Broughton Pipkin>

Yes.

<Chamberlain>

That's the one who has virtually no stress at all except for the anaesthetic.

<Broughton Pipkin>

Yes.

<Chamberlain>

Yes, I see, it's interesting. If you had the opportunity, and I know that you are a very ethical person, but if you had the opportunity to do an ethical experiment on the human species, as opposed to the animal, what experiment would you like to do to confirm your hypothesis in the human?

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<Broughton Pipkin>

Well, it would, of course, be most interesting to see what the effect of infusing prostaglandins was in late pregnancy on vascular responsiveness to angiotensin II. It would also be splendid to try to find a drug which would specifically improve uteroplacental blood flow without being known to have an antihypertensive effect and see then whether by improving uteroplacental blood flow, as a follow on, you did, in fact, get a diminution in blood pressure. Now, whether such a drug exists, I don't know. I think it might well be dangerous to try to interfere with the renin-angiotensin system, as such, because I think that the high blood pressure may well be necessary for maintaining the baby's blood flow.

<Chamberlain>

This would be some sort of converting enzyme inhibitor, would it?

<Broughton Pipkin>

Yes, that's correct. Such a converting enzyme inhibitor is now available and is being very widely hailed as an extremely useful antihypertensive drug in the clinical trials which it has so far undergone. Its action is very dramatic. I have seen it myself and it is fantastic.

<Chamberlain>

This is on non-pregnant, chronic hypertension.

<Broughton Pipkin>

This, however, is on non-pregnant, chronic hypertensive patients. I would be very chary about giving it to pregnant patients.

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<Chamberlain>

Yes. Accepting your hypothesis, which I think I agree with, that blood pressure is there for a reason. It would, therefore, diminish the placental blood flow even further.

<Broughton Pipkin>

I think it might, yes.

<Chamberlain>

Yes. But the first half your desired experiment, to a small extent, goes on now, of course. Is there anything being done on people who have been induced to prostaglandins? I know you've only got 12 or 18 hours after the prostaglandin's been given, but prostaglandins are being given, and the other group, of course, is the longer term prostaglandin infusions for those having terminations of pregnancy. Anything there?

<Broughton Pipkin>

Yes, we are just starting to look at this. I don't really want to comment on it at the moment, we are just starting *<laughs>*.

<Chamberlain>

We are rather crystal-balling. You think there might be, what I want to know is, is the timescale long enough to do the experiments on at 12, 18 hours?

<Broughton Pipkin>

Well, we're trying it. We'll see. I hope to report this to the Blair Bell Society at some stage fairly soon.

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<Chamberlain>

Good, we'll look forward to that.

<Broughton Pipkin>

We had hoped that patients who are on long-term aspirin therapy might provide very useful experiments, but unfortunately they tend, their requirement for aspirin tends to tail off during pregnancy. And so far, all the patients whom we have started off studying have come right off aspirin.

<Chamberlain, off-screen>

As their cortisol levels rise.

<Broughton Pipkin>

As their cortisol levels rise, yes. So those natural experiments are lost to us.

<Chamberlain>

It's remarkable how in obstetrics, I think, more than other subjects, we have made use of natural experiments where something's relevant, more perhaps than other branches of medicine...

<Broughton Pipkin>

I think this is surely because of the ethical problems involved, isn't it? We have to use what is currently accepted practice and make our natural history observations from that.

<Chamberlain>

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Yes. May I take you to another subject? You talked about using blood pressure as a measure of what you were doing and you mentioned systolic and diastolic pressures and you used several times diastolic pressure. Do you think there's any more use in making use of one reading, that is, systolic and twice the diastolic over three as a reading? Do you think that is more valid, is it more reproducible to your results in your field?

<Broughton Pipkin>

Well, the reason why I use diastolic is because in making intra-arterial recordings of blood pressure, particularly in the sheep, I have been impressed time and time again by how very variable the systolic blood pressure is while the diastolic blood pressure remains relatively constant. Me walking into the pen, even with a sheep who knows me and who is still going on eating her hay or whatever, is enough to push her systolic blood pressure up but her diastolic blood pressure remains relatively unchanged. And that is why I am happier using the diastolic blood pressure. I know opinions differ on this and a lot of people would choose to use the mean arterial pressure, the one third systolic, two thirds diastolic. I am basing this purely on intra-arterial readings in another species, so I am open to correction on that.

<Chamberlain>

I, as a clinician, am bedevilled by this double reading of blood pressures, but never want to do anything, so what I, like most people, do is we go to the diastolic as you have as that's the significant one, but I'm by no means certain this is so in other organs of the body, the systolic pressure is very important for flow. I wonder whether, perhaps, in the placental flow, we have ignored systolic for too long, that's why I raised the point. It's an interesting point. Yes, your point about calmness of the experiment and the experimenter with chronic catheterisation is very valid, isn't it?

<Broughton Pipkin>

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Yes.

<Chamberlain>

I was with Donald Barron a while ago, and there's one of our calmer men, but he insists upon choosing his experimenters for their demeanour and their behaviour with the sheep...

<Broughton Pipkin>

How splendid, yes.

<Chamberlain>

... not just their intellectual ability and the other. I think this is very real. Lastly, may I raise a point, and I wonder if you've done any work upon this in relation to angiotensin and hypertension? There was a vogue for various physical measures of the treatment of hypertension; decompression, for instance, was one. Have you done anything at all on that? Do you have any data on that at all?

<Broughton Pipkin>

Well, we did look, and I must stress that it's a small series, we did look at a small series of patients since there has, as you say, there is cyclical interest in decompression, and in this admittedly small series we could find no evidence of benefit of compression at all, whether assessed in terms of the need for further antihypertensive therapy or baby weight in outcome. So, I'm afraid, we dropped it. It's, the patients do tend to get slightly worried by it to start with. As I say, we could find no benefit and I think that has been the case with various other larger trials.

<Chamberlain>



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Your work clusters along with everybody else in that realm I'm afraid. We may have broken our teeth on decompression and wasted time.

Fiona, thank you very much for coming today and taking us through this subject. The whole of hypertensive disease in pregnancy is a tangled skein and you've helped us very graciously to unravel parts of it. Your logical story has kept us so that we now can look into the crystal ball with more assurance in the future. We look forward to your next presentation to us at the Blair Bell Society as you have promised us and we're grateful for your talk today. Thank you very much.

<Broughton Pipkin>

Thank you.

<End credits>