Ulster Medical Society

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Joint Meeting
with
The Ulster Obstetrical and
Gynaecological Society

Preeclampsia is a Placental Disorder: Lies, Damn Lies and Medical Science

Professor Basky Thilaganathan
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Professor McMullin:

Good evening. Welcome to the first meeting of the Ulster Medical Society for 2020, so you're all very welcome. It's my delight tonight that this is a joint meeting between the Ulster Medical Society and the Ulster Society for Obstetrics & Gynaecology, and we have this lecture every year, which I think is a very good tradition, and therefore I would now like to hand over to the President of the Ulster Society for Obstetrics & Gynaecology, Dr de Courcy-Wheeler, who will introduce our speaker. I've also been asked to say, if you can't hear the speaker, let us know, because we can sort that out, but I don't think that's actually going to be a problem.

Dr de Courcy-Wheeler:

So you're all very welcome, and thank you very much for coming out this evening. It gives me great pleasure to introduce Basky Thilaganathan. Basky and I first met in London. We were both working at King's in 1992 with Kypros Nicolaides. Basky obviously went on to do much greater things than I did, but I always had planned to come back to a small country practice in Ireland, and make marmalade. We were at King's at quite an exciting time. Nuchal translucency had just come on the market and was being used as a diagnostic tool. There was also foetoscopic laser coagulation for twin/twin transfusion syndrome—we were present when the first one was done by Kypros, and the room was hugely crowded. There were about 40 people in one small ultrasound room, with lots of hot machinery, so everyone was sweating profusely, and Basky reminded me this evening, which I'd completely forgotten, that as soon as the thing was over, and Kypros let out a sigh of relief, he instantly lit a cigarette—and the mother looked over at him longingly, so he passed it onto her, and lit a second one for himself!

So there were lots of interesting people in King's at that stage, and now they're all over the world working in other foetal medicine centres, but I was only a part-timer, because I only worked two days a week, which means I wasn't sucked in by Kypros for seven days a week like most of the other people were. But when you did write a paper with Kypros, you had to sit with him, and Rosalind, his computer and statistics expert, and you'd sit there till midnight or later, and every time I went home and then opened my briefcase, my wife Rose would sit well away, because a cloud of smoke would arise from my briefcase the next time I opened it. I think Kypros still lives on cigarettes and black coffee.

So, but Basky over the years has been a great friend to Northern Ireland, and his colleagues, such as [Amar Bede?] and King's College Hospital, because when we've had difficult problems to sort out, he's been happy to see the mothers over there, mothers in great distress, help with their problems, and then they would come back to us here in Northern Ireland. Hopefully that sort of thing will be a thing of the past, now that the abortion law in Northern Ireland is going to give us slightly more freedom to act by ourselves.

So Basky now is a lead trainer for foetal medicine in St George's Hospital. He's the editor-in-chief of *Ultrasound in Obstetrics and Gynaecology*. He's the author of over 250 peer-reviewed publications. He's on the Council of the Royal College of Obstetricians and Gynaecologists. He represents them on the UK National Screening Committee, and he is the clinical lead for the first dedicated high-throughput, non-invasive pre-natal test in the NHS, and now he's going to talk to us about something close to his heart, which is, 'Preeclampsia is a placental disorder: lies, damn lies and medical science'. Basky, thank you.

Professor Thilaganathan:

Thank you Horace and thank you Mary Frances, for the invitation here. It's a great honour to be here at your annual lecture of the Joint Ulster Medical and Obs & Gynae Societies. I'll try not to disappoint you, but you certainly haven't disappointed me today. The hospitality has been fabulous and the meal—great.

I'm going to talk to you about pre-eclampsia, as you can see. If you're mainly obstetricians or gynaecologists, what I'm going to say might sound like heresy. If you are not obstetricians or gynaecologists, you're going to be extremely enlightened. For those of you of a non-obs and gynae background, this sort of algorithm represents what we were taught, and what we still continue to believe. If you open any textbook on obs and gynae, and there's this complex thing—please don't read it, it's not for you to read, and this is our belief, that pre-eclampsia is an unbelievably complex disorder which has several interconnected relationships, etcetera, and for scientists and academics, this is great, but you all remember, we're obstetricians. We use like lemons and bananas to describe obstetric ultrasound findings, etcetera—we're not terribly high-functioning physicians, and therefore we prefer something like this. This is much more simplistic, and you can see, it's a very simple comic or cartoon that tells everything in pre-eclampsia starts with the placenta. The placenta is under attack, the placenta doesn't develop properly. It sends out signals, be these signals debris or be these signals biochemical signals, which affect our blood vessels to cause

hypertension, it affects our liver to cause liver failure, and it affects our kidneys to cause some renal dysfunction, and that all seems true, and the fact that it only develops in pregnancy, and the fact that delivering the placenta cures pre-eclampsia, all seems to fit with this fundamental hypothesis then, pre-eclampsia —a peculiar pregnancy disorder is caused by the placenta.

But during my time, there were a couple of things that occurred, which has caused me to question—first is the issue of placenta histology. We've always been taught that there are characteristic and pathognomonic signs in the placenta, which establish and determine and demonstrate that the placenta is damaged in pre-eclampsia. Unfortunately for us, there are two problems with that. First, is that this is a systemic review of properly blinded studies, where the pathologist wasn't told what the disease was, and looked at the placentas in a prospective manner, and the first thing we showed is that, if you tell your pathologist that the woman had pre-eclampsia, they were three times more likely to document characteristic lesions of pre-eclampsia on the histology report. That's simple bias, it's obvious to us, but we still write the diagnosis, and our pathologists are three times more likely to find something to support the diagnosis we write, and therefore when we looked at studies, and these were three very large studies, where the pathologist was blinded to the diagnosis, actually the lesions that we previously thought were characteristic for pre-eclampsia were no more common in pre-eclampsia than they were in non-pre-eclamptic pregnancy, and these were lesions were not specific, nor were they sensitive for the development of pre-eclampsia, so there seems to be no histological evidence of placental involvement. The second thing is, we've characteristically believed that because the placenta's damaged, the baby is small in pre-eclampsia. It doesn't grow so well, or it's compromised. There are now several studies to show that pre-eclampsia at term, and don't forget that 80% of pre-eclampsia occurs at term, is associated with normal-size babies, or even larger-than-normal sized babies, in 85% of cases, and this is once we've excluded all the diabetic pregnancies. So how do we reconcile the fact that the placenta is not working, causing pre-eclampsia, yet the babies are normal, actually often bigger?—that doesn't fit. So, why are we here? What is the problem? The problem is our interpretation of associations. Here is a simple correlation on the axis, guns per 100 residents. On the y axis, firearm-related deaths per 100,000 residents—everyone can see that, right? For those of you having heart trouble, right up there on the top right is the American flag. It's obvious to you and I that the more guns you have, yes?—the more likely we are to get shot. This is an association which has biological plausibility, correct? There's no-one in this audience that doesn't understand that. There is one person who could do with understanding it, but he doesn't, so guns ownership does not cause death apparently. Then there are other associations, and those of you who do statistics will realise that r^2 value of points over nine is amazing, this is a fantastic correlation, and here is a fantastic correlation between chocolate consumption per capita, and Nobel laureates. You can see a very, very nice association between the two, and two things will immediately strike you. First is, the Swedes tell you that they're totally impartial and unbiased, and that can't be the case, because they're awarding themselves far more Nobel prizes than they should be, for the amount of chocolate they eat, and the second, the Germans are eating a lot of chocolate, and it's not working!

So we are here now, yes? It's a momentous month. Whether you like it or not, it's happening, and for me, there were a series of observations that were coming into place, that were questioning my fundamentals—is it really, really so, that the placenta is the origins and the aetiology of pre-eclampsia starts with the placenta?—and I decided to like, let's dissect it and think again. We've always looked at the placenta and said, it meets foetal demands, and when it fails, it can compromise the foetus, but it can also cause pre-eclampsia, and what we've failed to understand is that the placenta is an organ of perfusion. It needs blood flowing through it to work. Just like a radiator in this room which isn't working, it's chilly, it needs a pump, it needs hot water flowing through it for it to work, and what we have done as obstetricians always, when a woman gets pre-eclampsia, is look at the placenta, but fail to look at the pump. Now, would you let a heating engineer in your house to look at your heating, and say, well you can look at the radiator, but I'm not going to let you anywhere near the furnace or the pump, to see whether my heating's broken. We have not examined this, and what I want you to do is, for the next 15 minutes, just think, is it possible that the placenta itself causes pre-eclampsia, or is it possible that the actual disease lies here, in maternal cardiac performance, and that compromises in maternal cardiac performance is the reason why the placenta's not working? Let's examine it from the beginning to the end. Let's go through it in a chronological way. I promise not to bully anyone in the audience, so I'll try not to do so, but what are the predisposing factors to pre-eclampsia? Predisposing factors to pre-eclampsia: age, obesity, ethnicity, auto-immune diseases. What are the predisposing factors to cardiovascular diseases?—age, obesity, ethnicity, auto-immune disorders, metabolic disorders—these are all predisposed to pre-eclampsia as well. Perhaps it's just a coincidence, but perhaps we should think about new mechanisms by which all of these things also, by a totally different way, affect the placenta. So it could be that the shared aetiology works because they both compromise the heart, or it could be that the shared aetiology has totally separate mechanisms: one, to affect the heart in you and I, and the other, to affect the placenta in the mother. The recent evidence to support the fact that it is indeed the heart that's involved is in a small study, looking at women who were trying to get pregnant in an IVF regime, and they did their pre-pregnancy heart functional assessments, and they showed that, in this group of 500 women, there were

only a small number of women that developed pre-eclampsia or growth restriction, but they showed that the women who developed growth restriction and pre-eclampsia there on the right-hand side, had poorer cardiac output, higher vascular resistance, and higher blood pressures, before their pregnancy started, so they were older, more obese, they may have had an autoimmune disease or metabolic disorders, but all of them had poorer cardiovascular function, so it's possible perhaps that these are not spuriously shared disorders, but they actually all work on the heart.

How about early pregnancy? Most of my work, before two years ago, I had ten times as much money in grant income to look at the placenta in the development of pre-eclampsia than I had to look at the heart for the development of pre-eclampsia. Paradoxically, it was the European Union that gave us our £3.5 million grant to look at the heart, and they say we can keep the money, so it's a good thing. We published a series of papers. I have over 20 papers to show that, if we look at the perfusion through the uterine artery in early pregnancy, and then look at a whole series of cell/cell interaction, we look at cell migration or cell apoptosis, etcetera, a whole bunch of factors to look at how the placenta behaves, how it moves, how it grows, how it undergoes programmed death, how it interacts with other cells, how the NK cells work in the placenta, there are strong relationships to uterine artery blood flow. We have always believed that it is the placenta that somehow affects the uterine artery blood flow, but all of these associations that we've found over the last 20 years in all of these publications could also be explained the other way around, that if women did not have good perfusion of their uteruses because they are compromised cardiovascularly, it then affects the development of the placenta, not the other way around, and actually biologically, that's what normally happens. We don't develop ischaemia of our myocardium, and then the coronary artery blocks off. Everything in biology occurs because we compromise the blood flow, and then we get tissue damage. It's only in obstetrics we believe that the tissue damages causes the abnormality in the blood flow, and everything we've seen can be explained by looking at it the other way around, endless amounts of papers, so I am a convert. I'm like a cigarette smoker who's stopped smoking, which is why I'm a little bit more vociferous about why we may actually be wrong. What about late pregnancy? This is looking at cardiac output in late pregnancy. This is 39 studies in 3,000 women, and one uniform finding is that the cardiac output in pregnancy arises through pregnancy as the mother's demands increase, and then yet, at the end of pregnancy, there's a paradoxical drop in the cardiac output. Pray tell me, why is it that when the mother is having a growing, hugely metabolic active foetus growing in her tummy, does the cardiac output increase to survive and keep the baby alive, but yet at the end of pregnancy, the cardiac output starts to drop? Why does the cardiac output drop at the end of pregnancy? No-one's ever answered it. It's been documented over and over again, but it's unexplained. Well, we decided to look at pregnancy, and we decided to look at what happens to the heart in pregnancy, and why does this cardiac output drop?—and in case you're not cardiological, we can look at that by looking at the muscles of the heart, and we can look at the fitness of the heart and the mass of the left ventricle, and depending on the pattern, we see concentric remodelling, which is a physiological way of managing extra workload, which then goes to concentric hypertrophy, it's getting a bit abnormal, and eventually it'll go to eccentric hypertrophy, which is an abnormality of the heart, which is a pathological remodelling, it's starting to compromise. When we looked at remodelling the heart, we did a study in about 500 women, of young women, normal BMI, non-smokers, all primips, and no comorbidities. I don't know about Belfast, but in Tooting, that's a bloody hard study to do, and we did echoes on them, five times in pregnancy, and the first thing we noticed is about the remodelling of the heart, the way the heart's shape and mass changes. An average elite athlete in a two-year training programme, so we have the sports cardiology unit at George's, and we get some of the young cyclists come in who train, five days a week, five hours a day, and they get them as older teenagers, after 14, 15, and they come in and train, and over a two-year period, their heart will increase by 25% in mass. A pregnant woman, sitting on the sofa, drinking, and eating Jaffa cakes, will increase her heart mass by 40% in nine months. Elite athlete: 25%, pregnant woman in nine months: 40%, just to give you a perspective of how physically demanding a pregnancy is on the maternal cardiovascular system. Then we looked at something called trabeculation, so this is related to something called non-compaction cardiomyopathy. Have you heard of young footballers who die suddenly on the pitch? It's because they develop a disorder called non-compaction cardiomyopathy. Their heart gets so thick and remodelled, that it starts to get these deep trabeculations within it, these deep little trabeculations, and you can count those trabeculations, and the amount you have and the distribution you have is related to the developed of non-compaction cardiomyopathy, it's not a good thing. And we looked at the trabeculations, this is a blinded study, and we looked at that trabeculations that happened in sports and in pregnancy—can you see that? So these are random cricket and soccer—pregnancy 25%, and soccer 20%. Again, the pregnant women have much stronger physiological changes in pregnancy. Then finally, let's not look at cardiac output of the heart, we actually looked at the function of the heart. We used relatively modern techniques: speckle tracking, which is to look at the muscle of the heart, in order to be able to assess how the muscle works, that's myocardial function, and how to look at how the chamber works, so chamber function. What we found out in these women, and there were about 500 women, is that by the end of pregnancy, about 10 to 15% of women had developed diastolic dysfunction. The cardiologists call it heart

failure with preserved ejection fraction—HFpEF. It's a defined disorder. It's more common in the young. Us old men, we get fibrotic hearts, they can't contract, so we get systolic dysfunction, but if you're young, a young woman, often what happens is, the heart relaxation, the heart's not fibrotic, it's very rubbery and remodelled and very thick and muscular, it fails to relax properly, and that's also heart dysfunction, and 10—15% of women develop this in normal pregnancy. These are normal women, normal primips, normal weight, no smoking—yes, healthy women. Imagine how many of the compromised women they do. We have often said, yes—everyone remember this?—shortness of breath, swelling of the legs, chronic lack of energy, difficulty sleeping, increased urination?—anyone who's had a baby will remember those symptoms. We'll leave the last one alone for men—confusion and/or impaired memory, I don't know. This algorithm here at the bottom is not from an antenatal care booklet, it's from heartfailure.co.uk, so the same symptoms we recognise at the end of pregnancy in a small proportion of women is very, very similar to the symptoms that we recognise in heart failure. So what I'm suggesting to you is that you saw from the remodelling of the heart and the trabeculations of the heart and the functioning of the heart, that actually women are compromised quite significantly even in normal pregnancy, and it is not surprising that a small proportion of women are, at the end of pregnancy, starting to fail to cope with the load. Does that make sense? Now, if that were true, in pre-eclampsia we should see much worse function, and that's exactly what we see. So this is a systematic review, so it's not just our studies now. Lots of people are doing it, to show that the left ventricular mass and the relative wall thickness, this is the remodelling of the heart, is 71% and 46% more in pre-eclampsia than you get in a normal pregnancy. I showed you what happened in a normal pregnancy compared to athletes. Pre-eclampsia is even worse, so the heart has been chronically overworking. When we looked at myocardial function, the same is true. Now, this is an algorithm that shows non-pregnancy, normal pregnancy, late pre-eclampsia and early pre-eclampsia, and you can see that, as you go from non-pregnancy, pregnancy, late to early, you get worse impaired relaxation of the heart. This is chamber function and this is muscular function, and this is the cardiac output. This is normal pregnancy. If you have term pre-eclampsia, you have poorer cardiac output, and pre-term pre-eclampsia has the worst cardiac output, when you index it for what it should be. So there is a continuum, there is a disease process here, which is now not in doubt, that pregnancy causes some degree of dysfunction, and that pre-eclampsia is evident as cardiac failure. There are now 48 studies to show the effect of pregnancy on the heart, and there are now 36 studies to show the effect of pre-eclampsia on the heart. They're almost all published in cardiology journals, and if you speak to cardiologists who are familiar with pregnancy, they have absolutely no doubt that the heart is implicated fundamentally in pre-eclampsia. It's just that you can't get it published in an obstetrics journal, because the editors will send it to someone who has spent their entire lives believing the placenta causes pre-eclampsia, and therefore the reviews are not going to be favourable. It takes a generation, we have to wait till all those reviewers die out, and the young come up, and then we can start to get in obstetric channels, and how about post-partum? This, for me, is now my major research interest, so we saw these women. We were not expecting to find this degree of dysfunction in their hearts. We thought yeah, we're going to see some dysfunction in pre-eclampsia. We weren't thinking we were going to see it in normal pregnancy, and we certainly weren't expecting to see 70, 80, 90% of women with pre-eclampsia with overt heart dysfunction, so we said, okay, let's see them at six months, and document their recovery, and we saw them at six months, and almost none of them had recovered. We said okay, we're just too much in a hurry, and my poor research fellow, who was with me for four years, saw them again between one to two years [after delivery], and this is their recovery: pre-term pre-eclampsia, 85% of them have impaired myocardial relaxation; one to two years later, 74% of them still had impaired myocardial relaxation, once we had excluded the women who had developed hypertension. So we've taken out the women who had overt disease. Term pre-eclampsia, 64% at term had impaired myocardial relaxation, half of them still had it afterwards, and here in controls, 28% had impaired myocardial relaxation, and 13% is an acceptable background rate to see that impaired mycocardium—that's what would happen in any given room of healthy people. So we were surprised to find that actually, these women not only probably had impaired myocardial function before pregnancy, but they continued to manifest it afterwards, which would suggest to me that it was a fundamental fact throughout their pregnancy. So here, ladies and gentlemen, if you're obstetricians, pay attention—this is the different cartoon you need to understand. Cardiovascular function is important to meet foeto-placental demands. If someone has poor cardiac reserve because of these features which we see or have been told over and over again, are related to pre-eclampsia, please note that they're also related to poor cardiovascular function, so age, obesity, ethnicity, diabetes, disease, chronic hypertension, kidney disease. These all predispose to cardiovascular dysfunction, and therefore, right throughout, chronically, there will be underperfusion of the foetal placenta, which will fail to meet foetal demands, and will create this syndrome we recognise as pre-eclampsia, and the tendency will be for these features to present as pre-term pre-eclampsia, although a proportion will present at term. However, we may also get women who had none of these features, but still developed pre-eclampsia, because in pregnancy, there are features that result in excessive demand, so the heart was okay, and you got pregnant, but it just got too much for a pregnancy, because of macrosomia, a twin pregnancy, or because

the pregnancy went on for too long, or because there was excessive weight gain. She may have been normal weight at the beginning, but if you put on too much weight over a short period of time, then that's an extra strain on the heart. So we have a supply and demand phenomenon here, and whether the supply is compromised, or the demand is compromised, or both, will result in different phenotypes of pre-eclampsia, so this is a unified hypothesis that explains all of the types of pre-eclampsia we see.

And you're going to say, well Basky, it's explained most things, but there's still some things you can't explain. Pre-eclampsia's cured by the disease—there are those features. Well actually, let's think about another disease. We have a disorder called gestational diabetes. Diabetes is new onset glucose after 20 weeks. The predisposing factors are the same as for type two diabetes. The screening test measures pancreatic function and GTT. The diagnosis, high glucose levels. Pre-pregnancy disease, if a mother has pre-pregnancy diabetes, she has a more severe phenotype. The cure for gestational diabetes is birth, isn't it?—and mothers have a 50% risk of diabetes in the subsequent ten years. We don't believe that gestational diabetes is a placental disorder, we accept that gestational diabetes is a disorder because pregnancy overcomes the ability of the maternal pancreas, and as soon as you deliver, you're cured. All of these are exactly the same for pre-eclampsia, yet we're still inherent to the fact that this is a placental disorder, and it doesn't make sense to me to say so. There are going to be one or two in the audience who are of an age where you have been brought up believing in biological immune theories of pre-eclampsia—Horace, I'm sure you're one of them, important, like me. You're a similar age to me, so you must. We were taught that there is something unique about the first pregnancy, and that the first pregnancy is affected, and you escape in the second pregnancy, and that has something to do tolerance induction, and then therefore it proves it's an immune, yeah? It's this this about associations and we automatically imply causation without thinking, what is the biological plausibility of this?

Well, this is a study from 1997, 30 women, systematic echoes from before pregnancy throughout, and this study in 1997, which was totally ignored by everyone who believed in the placental hypothesis, showed that, if you had had a baby before, your cardiovascular output was about 20 to 30% higher in your subsequent pregnancy. Just like an athlete who had trained, the next time you go out running, you're better at doing it. So one possible biological reason for why parity is important is, that once you've had a pregnancy, and the muscles of your heart have increased, and are able to cope with the load of pregnancy, you're better able to cope with the load of pregnancy the next time round when you get pregnant a couple of years later, and that is a completely biological plausible reason.

Now, the problem I had was that, two or three years ago, when I kind of put forward the hypothesis for the first time, our mentor, Horace and I, mentor, completely debunked me in front of about 1,500 people. He said, that's all rubbish. This is something about parity, I'm going to show that you're wrong, so Kypros went off, and he took a poor research fellow, and he got her to do 1,500 scans, just so that he was going to prove me wrong, that nullips and primips didn't have this, but guess what?—he showed exactly the same thing. This is the cardiac output of nullips, and this is the cardiac output of multips, and exactly the same thing—he repeated the study with thousands more people, and exactly the same feature—if you're a multiparous woman, you respond better, so parity is explained by training, pregnancy training. How about partner specificity? I'm sure you've been on a ward round, and the mother says, this is my third pregnancy, and I've got pre-eclampsia, and the consultant turns round and goes, is this a new partner?—and she goes, yes, and there's a knowing look between everyone. Nothing is said, and we carry on down the corridor, and everyone goes, mmm, yeah, her partner. The data about partner, changing partner, comes from an era in the '60s and '70s when I was brought up, where, when your husband left you for his young secretary, it took you two to three years to get over the stigma of that loss. It took you another four or five years to trust men again, and then when you met another man, you had to check him out for a couple of years, before you would even think about marrying him, because you had to marry him before you could have a child in those days, so by the time you change partner, it was often seven to ten years before you fell pregnant again, and people of my age know what happens if you don't go to the gym every day, or you don't train every day, what happens to your exercise tolerance—it starts to fail, and you start to get older, and this was a guy called Rolf Skavern, who did not believe in that immune hypothesis and partner specificity, and he went and looked at half a million women, and he said, I'm going to look to see whether the change in partner is indeed an independent predicting factor, or whether the change in partner is just a proxy for the inter-pregnancy interval. Guess what?—yes, whether it's your second or third pregnancy, it's the years since your previous delivery that determines your risk of pre-eclampsia. It has nothing to do with your partner. I know you want to blame men, half of the audience anyway, but it isn't anything to do with your partner. It is to do with the inter-pregnancy interval, and nowadays, when one is coming out of one door and the other one is coming in through the other, there is no difference in the incidence of pre-eclampsia. Yes, a woman can have three or four children with three or four partners, certainly in my part of London they do, and there isn't an increased risk of pre-eclampsia, because there's a very short inter-pregnancy interval. Finally, they say, well ovum donations, there is some belief that IVF causes pre-eclampsia—IVF doesn't. All of the studies show that it is in fact ovum donation compared to your spontaneous cycle, that is predisposing to pre-eclampsia, and not IVF. IVF only predisposes you to pre-eclampsia by virtue of the fact that the women

are older or more obese, or have comorbidities when they fall pregnant. If you correct for the age and the obesity and their predisposing factors, IVF does not increase your risk of pre-eclampsia, but indeed ovum donation does, and this was seized upon by the kind of immunological people, saying, you've got an egg from someone else, and you put it in this mother, and there's fundamentally an immune problem here. Does everyone get that?—it seems sensible, but what's the difference? Fertility specialists, who gets ovum donation?—generally?—premature ovarian failure, and what do we know about premature ovarian failure and their cardiovascular risks?—increased, aren't they? You get premature ovarian failure, your cardiovascular risks are increased, and 15% of people who get ovarian failure have Mosaic Turner syndrome, and Mosaic Turner syndrome increases your cardiovascular risk as well. So ovum donation, I argue with you, is not an issue of some immune hypothesis, ovum donation predisposes to pre-eclampsia because the very women who get it have a worse cardiovascular profile before they fall pregnant. Let's skip smoking—we'll come back to smoking at the end, you can ask the those questions if you want.

Now, the fundamental question is, I firmly believe that the predisposing factors are cardiovascular, the presentation of pre-eclampsia is cardiovascular, blood pressure, headache—yes, cardiovascular dysfunction. The post-partum legacy of pre-eclampsia, long-term risks of hypertension etcetera, are all cardiovascular. It seems to make sense, that this is a cardiovascular disease, and it's the fundamental cause. Does it really matter?—well it does, and I'm going to tell you why. We use conventional risk assessment, a tick list—do you still use a tick list here? So do you have some fancy computer system that works out? Is it good? I'll tell you how good it is. A couple of months ago, I came into the room, an older pregnant woman crying, and my matron, standing over her, caring for her absolutely, saying, "Don't worry love, everyone is high risk", and that's true. By the time you do age, weight, height, parity, 60% of women are high risk, if you use the NICE algorithm, and when we did an audit, we found that actually only 15% of the women in our unit, who should have been given aspirin according to the NICE algorithm, were actually given aspirin, because nobody believes that 60% of our women can be at high risk for pre-eclampsia—we just simply don't believe it. It doesn't work, and why doesn't it work?—because we treat all these risks as equal, so a woman who's 36 is told that she has the same risk as someone who's taking crack cocaine. It can't be right, right? All of these risks can't be equal. All of them actually, only increase the risk a moderate amount. They're not very strong risk factors, and finally, we completely ignore the interaction of the risk factors, so we don't look at the inter-relationships. What do I mean by that? You might tell a woman who's 40 years old that her risk is high, but do you say, well actually, she's thin, she's Anglo Saxon, she's had two previous healthy babies with no hypertension, she's an ex-Olympic athlete, doesn't smoke, she's with the same husband, and it's only been two years since her last pregnancy—should she really be at high risk of pre-eclampsia? Do you really think she's at high risk of pre-eclampsia? We use a checklist to stigmatise the women, but we never use the checklist to de-escalate risk, do we? We don't say, actually this is a positive factor, your risk is going down. We only ever use the risks to make it bad, we never use the risks to make it better, so we don't look at the interaction between the factors—do you get that?—terrible.

So, there was a publication in the New England Journal a year-and-a-half ago from our mentor, called the Aspree study. They did a risk assessment in the first part of pregnancy, which for an 8% false positive rate, much lower than the 60% of the NICE algorithm, predicted 80% of women are going to get pre-term pre-eclampsia. This test involved blood pressure. Is blood pressure a placental marker or a cardiovascular marker?

Audience member:
Cardiovascular.

Professor Thilaganathan:
Okay good, I have to say I'm glad, okay. A uterine artery Doppler, and PlGF to predict pre-eclampsia, that was a very good test for predicting pre-eclampsia. Now, we say a uterine artery Doppler is measuring the blood flow to the placenta—remember the studies I showed you before, and we said, okay, the uterine Doppler is affected by the placenta, or does the uterine artery Doppler affect the placenta, or does the placenta affect the uterine artery Doppler? A very odd thing is that you can swap ophthalmic artery or radial artery Doppler into the algorithm, and it works just as well. It doesn't matter that it's the uterine artery Doppler. The uterine artery Doppler is just a peripheral wave form, and if you took the ophthalmic artery or the radial artery, it would be equally good at predicting pre-eclampsia. Now, I'm pretty sure that the placenta doesn't invade the eye, right?—so we can't argue that uterine artery is looking at placental blood flow. The uterine artery is assessing maternal blood flow as a whole, which is why you can swap any other artery and it is telling you about their cardiovascular function, got it?

Now you're going to say, well Basky, PlGF—it's got the word placenta in it, I'm done, yes? It's produced by the placenta. Indeed, it's produced by the placenta, but I'd like you to see something here. This is PlGF RNA expression, placental surface is 12 to 15 metres^2, so you can see this is the placenta here, and the placenta by far produces the highest amount of PlGF RNA, so there's no doubt that the placenta produces huge amounts of RNA expression, which is what the protein is producing, but if you look at the capillary surface, PlGF is produced by the capillary of the body. The capillary surface of the woman is 6—7,000 metres^2 compared to the 12—15 metres^2 of the placental surface, and therefore, when you take that into account, this is the placenta here—can you see that the capillary surface of the endothelium of the

mother actually contributes a lot, so the first thing is, indeed the placenta produces it, but if you account for how much capillary surface there is in the mother, actually the rest of the body produces as much PlGF, if not more, number one. Number two, if you're interested in what causes pre-eclampsia, does it really matter where the PlGF comes from, or does it really matter what it does? Which is more important? You want to know what it does, right? This is a biological product. Yes, it might be produced by the placenta, but we need to know what it does, because that's going to give us a clue to the disorder, so what does anyone think the main function of PlGF is?—cardiovascular remodelling, so PlGF can be used in paediatric surgery to look at the response to surgery. PlGF can be used in chronic heart failure or acute heart failure. PlGF is a marker that can be used in men, and actually it's a relatively good marker, it's just an unusual one, and they already have ones that work just as well. So PlGF is a factor that tells the heart, work harder—that's why the placenta produces PlGF, but based on that screening test that Kypros put in, over the last two years, we introduced that screening test, and we gave women aspirin at 150 mg, and then, just a few months ago, we audited the outcomes, and this is already out of date, but just to show you the comparison—in 2017/2018, when we had the NICE algorithm and we used the checklist, we had 8,000 pregnancies. We had pre-eclampsia rates of 0.75% pre-term, and 2.1% at term pre-eclampsias. Since the middle of 2018, we've been doing the Aspree algorithm, which is using that marker, and then giving women, 8% of women were getting 150 mg of aspirin. We've reduced our pre-term pre-eclampsia rate by 14%, and reduced their term pre-eclampsia rate by 30%. The pre-eclampsia incidence in the world has not changed for 20 years. If you look at an epidemiological study, it's been the same. This reduction cannot be explained by anything other than the fact that we've instituted a process for screening women who are truly high risk, and instituting a medication which reduces that risk.

By the way, there are four drugs which have been shown to be effective in various studies and in systematic reviews. They're at the bottom—anyone want to take a guess, what these drugs are usually used for outside pregnancy? Aspirin, calcium, statins—and I know if you know about metformin, is a relatively new drug which is being used in hypertension control as well. So, they're all very good cardiovascular drugs, they just happen to be coincidentally affecting something in the placenta to cure the disorder, which is fundamentally the placenta. Diagnosis and prognosis, only a few more slides—we've known about pre-eclampsia since the Greek era. It was documented and phenotyped characteristically just over 100 years ago, in the Boston Lying-In Hospital, and 100 years ago, Frederick Irving wrote the paper where he showed that blood pressure and proteinurea were the characteristic hallmarks of pre-eclampsia. Here we are in 2020, 104 years later, and what do we use to diagnose pre-eclampsia? Is that good enough? A woman dies every twelve minutes, and 100 years later we're using 200-year-old technology followed by putting your finger in the urine, and saying, how much protein has it got.

The reality of this, I've got to tell you this anecdote, because it's very personal and I can never forget this. Called in on a weekend to come and scan a woman, in utero transfer, 26.5—27 weeks, severe pre-eclampsia, they've transferred her in because of clots etcetera. Basky, can you come and look at the baby? We're controlling her blood pressure, but we just want to check the baby out, so I came in, I sent her upstairs, scanned the baby. Nowadays we do complex Dopplers, so we looked at the baby, did a Doppler, and I sat her down and I said okay, the baby's so big. Luckily we don't have to deliver you, but if we had to deliver you this week, these are the risks of survival, it's good, and this is the risk of handicap, good, and she was totally silent. I thought, okay, this is just too much for her. Last night she was somewhere, she was here, and I said, is it too much, do you want some time? She said no, I understand. I said, well what's the problem?—you're very very quiet. She said, don't I matter?—do you know what she meant? It's the middle of the night, she's put in an ambulance, driven 50 miles. She comes into our ante-natal ward, into our delivery suite, and they take her blood pressure, check her urine and do a blood test, but now she comes upstairs, and I'm using £120,000 machine. I've checked blood flows in the baby's brain, to her liver, to her heart, to the uterine arteries. I'm giving her a specific prognosis and a specific diagnosis and an outcome, so why have you done all this for my baby?—and all they've done is put that cuff round my arm, and asked me to pee into a pot. She wasn't an educated woman, but she could see the absolute contrast between how we're looking after her, versus how we're looking after the bab y. How is it that we accept that that is still possible in this day and age?—it's simply not, is it? There are options available. They're not certainly ready perhaps yet to be totally introduced, so there is an option available which is looking at [ASLP?] and PlGF. This is this theory that there is an imbalance between angiogenesis and anti-angiogenesis, and indeed there is, there's a well-proven theory of the imbalance of angiogenesis, and that's New England Journal studies. The old school want to believe that this angiogenesis, this is occurring in the placenta, but you educated know that actually it's not specific to the placenta. There is indeed an angiogenic imbalance, but actually it's generic to the mother, and the use of these markers actually can be very very good in being able to predict pre-eclampsia within a week, and even without pre-eclampsia, it is useful in growth-restrictive pregnancies as well, anywhere where there is some degree of cardiovascular dysfunction. Very recently, we published a collaborative paper looking at PlGF alone, again a vascular remodelling marker, and to show this was a wedge cluster where we did a reveal and a concealed up. Where we revealed the PlGF, there was a much, the proportion of diagnosis was much faster than with

concealed PlGF. People knew the disorder, perhaps three or four days, and the comments we got were, well, you only diagnosed the pre-eclampsia three or four days earlier. What difference does that make? Why does that matter? Three or four days is not going to make a difference. Does it make a difference?—absolutely, look at this: revealed PlGF 600, concealed PlGF, 450. Two strokes, one cardiac arrest, two eclampsias—all in the concealed PlGFR. The women who had concealed abnormal PlGF all suffered from major cardiovascular events. None in the reveal died. In this small study of 1,000 women, we could have prevented five major adverse neurological outcomes, by just using a simple marker that cost £10. As I said before, [ASLP?] and PlGF are used in heart failure, whether you're a man or a woman, whether it's chronic or acute. These are angiogenic markers which tell us about responses of the heart, not the placenta. We have better tools than blood pressure, we don't have to measure biochemistry, but this is a study of over 1,300 women in Canada, where they looked at a whole array, 100 markers, and came up with a model called the Piers model for predicting prognosis—not diagnosis now, prognosis, and they showed actually a model that was very good. It had a very good sensitivity and a relatively high specificity for predicting adverse outcome in women that had pre-eclampsia, and by far the most important test was oxygen saturation. How good the heart is at perfusing the finger, was the most important marker in predicting adverse outcome.

I'd like to finish with these two last points actually—treatment, what do we use to treat pre-eclampsia? What do you use to treat blood pressure?—you use the same thing? Horace?—labetalol, anything else, any offers on labetalol? Nifedipine? Anyone use methyldopa, who uses methyldopa? Stick your hands up, it's really good. I stuck my hand up. Why do we use these drugs? Which drugs should we use? Do we know? NICE says labetalol, but they've recently changed, but they used to say labetalol. There is no consensus in the international studies about which drug to use, because as obstetricians, because we're not physicians, as obstetricians, we're obsessed with reducing the blood pressure. The blood pressure is a number, and I hate to give you a formula to finish the talk, but blood pressure is cardiac output and stroke volume, yes?—systemic vascular assistance, stroke volume, heart rate and systemic vascular resistance, can everyone see that?—so how much blood the heart pumps out, and how much resistance there is. It's like a hosepipe, you squeeze the hosepipe at the end, the pressure goes up. Now, if you want to control blood pressure, you can control it by reducing how much the heart pumps, by reducing the heart rate, or reducing the vascular resistance. If you were the baby, which one would you prefer?—one which maintains the cardiac output and reduces systemic vascular resistance, or one that maintains the systemic vascular resistance, and bashes the cardiac output on the head? Take a guess, the big red cross and the green tick is a clue. So as obstetricians were obsessed with the left-hand side of the equation, we only care about the diastolic being below 90, and we don't give an iota about the mechanism by which the blood pressure is reduced. We should, because it would be far better for the baby to have a mother whose cardiac output is maintained, and vascular resistance is decreased, so you're easing the load on the heart, rather than giving this woman, who already has, I've told you and shown you, immense cardiovascular dysfunction, a drug that is compromising the myocardial activity, got it? If you don't believe me, this study, I've been shouting this for ages but no-one's taking any attention, until this study came out, a randomised study, a three-way study, for the measure of acute hypertension—okay, it's fine, it's acute to severe hypertension, but the principle is exactly the same. They looked at nifedipine versus labetalol versus methyldopa, and when you first look at it, all three drugs achieve primary outcomes within twelve hours, which is control of blood pressure, but nifedipine and labetalol achieved it within three hours, so the initial thoughts were, well, nifedipine and labetalol were a lot better, because they're controlling the blood pressure faster, but then look at this—nifedipine, which is the one that bashes the heart more than the other two, more maternal blood transfusions, more hypertension tachycardia, increased NICU admissions times two, increased RDS, increased SGA. If you compromise cardiac output to reduce the blood pressure, you're more likely to compromise perfusion of the placenta, you're more likely to get adverse neonatal outcomes, whereas those were much lower if used labetalol or methyldopa, so I suggest to you that the 50 years that Jim used methyldopa perfectly safely, should be ignored at your peril. It's an extremely safe drug, and certainly if you want to use labetalol because it's a bit faster, that's also not so bad, but I would have certain care and caution about just jumping in to use nifedipine as your primary drug. This is my final thing—now, we believe that if we deliver the placenta, we cure pre-eclampsia, and I showed you the data, that the vast majority of women having pre-term and term pre-eclampsia, still have dysfunction later on, so this dysfunction can't be innocent, so we went to Denmark, and I developed a collaboration with Denmark. Why Denmark?—they have good birth registers, like all Scandinavian countries, but they also have a prescription register, so you can link the use of anti-hypertensives to the pregnancy, yes?—and if you want a demonstration of how important pregnancy is, this is a 40-year-old woman who did not have pre-eclampsia. In the ten years afterwards, her risk of getting chronic hypertension is about 8 or 10%. If you have a 20-year-old woman who develops pre-eclampsia, her risk of developing chronic hypertension in the subsequent ten years is higher than a 40-year-old who does not, so pre-eclampsia is effectively ageing you by 20 years. Pre-eclampsia is far worse for maternal cardiovascular function than smoking, far, far worse, and we've just done a systematic review which has been accepted, to show that actually, within the first year following pregnancy, if you systematically evaluate blood pres-

sure in women who had pre-eclampsia, the rate of chronic hypertension is between 15 to 20%. Now, because you've cut the cord, and you've decided you have no more involvement in their care, and because they haven't had a heart attack yet to go to their cardiologists, they're falling between specialities. The GP is not informed enough, because we don't tell them you should be monitoring them. The cardiologist doesn't care because they haven't had their stroke or their heart attack yet. These women have occult hypertension in the community, and they don't present till much, much later, with actually quite severe adverse cardiovascular dysfunction. This, in the developed world, is the hidden morbidity of pre-eclampsia. There is a whole legion of women out there who have sub-optimal cardiovascular function, undiagnosed chronic hypertension, who deserve our care.

You've seen this slide once before, and if I haven't convinced you, I'd like to remind you about one more. You know this man, he says, "First they ignore you, then they laugh at you, then they fight you, and now I think I'm winning." Thank you very much indeed.

Mr de Courcy-Wheeler:

Thank you Basky, that was absolutely brilliant, and there was just a simple, brilliant—you're not going away yet. There was a simplicity to the brilliance of that, which was absolutely wonderful. I'm sure there'll be lots of questions—oh, first hand up!

Audience member:

Thank you very much, Basky. When I was doing my research paper, they were just starting, it was about the late '90s, to talk about [?] women's cardiovascular health in pre-eclampsia, but there's a few things I just wanted to ask you about. If women, can you show that women have the worst cardiovascular risk factors, in terms of the muscle mass, their cardiac output, can you show that they're most likely to get early onset pre-eclampsia?—but also can you also correlate that with the worse outcome in problems later? And also you said that the one thing that I think, it's confusing with what you're saying, because in the last 20 years, we've had more obesity, we've had more diabetes, we've had a lot of older mothers, so why has the rate for pre-eclampsia stayed the same?

Professor Thilaganathan:

Very good, so three things: so the first thing is, can we show the women who have the worst cardiovascular function [?]—yes we can, so there's that pre-pregnancy study that shows that the ones with the worst cardiovascular function were the ones that developed pre-eclampsia; then we have tens of thousands of women who've been assessed by Aspree, and Aspree is blood pressure, peripheral wave form measurement, be it uterine or here, and PlGF, which is an anti-angiogenic marker, so Aspree is a cardiovascular test, and the women who have the worst Aspree risk are at the highest risk of pre-term pre-eclampsia, so absolutely, the pre-pregnancy predisposing factors show that the worst cardiovascular function you have, the more likely you are to develop pre-eclampsia. The early pregnancy cardiovascular assessments show that the women who have the worst cardiovascular dysfunction have pre-eclampsia. The second point was, is there a relationship between that and the post-pregnancy legacy? Our original study of 600 women, where we followed them up, we excluded the hypertensive women when we looked at their heart function, because we said, there's no point looking at the hypertensive women, because if you looked at their hearts, it'll be shot anyway, yes? So let's look at the women we thought were healthy, to show that they'd recovered, and that finding was where we [?], so when we went back and looked at the women who had chronic hypertension, out of 600, we had like 30 or 40, not huge numbers. We found that the women with the worst remodelling were the ones that had it, so this money I've got from the European Union is precisely that, so I'm not interested in that, studying what's happening during pregnancy. We're looking at women who develop pre-eclampsia at term or pre-term. We're taking a peripartum cardiovascular assessment, both echoes and biochemistry, and then we're looking at them at six months etcetera, to look at how we can do predictive markers, to see who's going to develop chronic hypertension. I can't tell you the results yet, but there's an NIHR study I've got funding for, which is going to be published in a few months, in the Lancet, which is where we looked at, it's called the [Phoebe?] study, we looked at 600 women in England who developed pre-term pre-eclampsia, and you will be astonished to see what the morbidity of these women is at six months, because all of the studies I've shown you, like single centre studies, and you can say, well, it's specialist, it's only in Tooting that happens, and here in Belfast we're protected from this terrible plague, it's not. This was a study carried in 20 centres in the UK, with blinded assessments at six months, so absolutely, pre-eclampsia has a huge burden of disease, and the hypertension rate is reported in there. We will know, within two to three years, what tests we can do at birth to predict the women who need to be monitored more carefully, because you can't monitor everyone all the time, so we need to have a good test at birth, like an Aspree test at the time you're born, to say, who needs to have their blood pressure checked regularly and have it treated.

The final question is, why has pre-eclampsia not increased?—a very good question. Anyone familiar with the Arrive study? Anyone know of the Arrive study, Bill Grobman?—6,000 nulliparous women in the USA gave their lives to you—you must remember the study. 6,000 women randomised between induction of labour at 39 weeks versus expectant management. They were trying to show that, by inducing you at 39 weeks, you can have better outcomes of pregnancy. It was essentially a study to say, does induction cause ventouse, forceps, Caesarean section in America, and what they showed was that, they were happy, because they showed that induction at 39 weeks did not

increase Caesarean section rates in their population. It was slightly higher, there was about a 30% Caesarean section rate. If you induce them at 39 weeks, 3,000 women, versus 3,000 women who were allowed to go on, who also had about a 30% Caesarean section rate, so they showed effectively that, from 39 weeks, you can induce pregnant women, and these shouldn't increase your Caesarean section rate. There was a slight increase in operative delivery rates, but Caesarean sections were… but what they didn't make a big thing of was, what was the pre-eclampsia rate?—40% lower, so pre-eclampsia, if you're not obstetric, it's a completely unusual disease. If you're going to have a baby with Down's syndrome, whether the baby is born or not, the baby still has Down's syndrome. If someone's going to develop leukaemia, they have leukaemia. If someone is going to develop pre-eclampsia next week, and I'm going to deliver them this week, what happens?—the women who is going to have pre-eclampsia doesn't have pre-eclampsia any more. This is called intervention bias, or treatment paradox. Most of the studies you will see published on sensitivity and specificity of pre-eclampsia are complete bunkum, because they're not comparable, because women are delivered at different stages, so although our women are getting more obese, and they're more likely to develop pre-eclampsia, we're also using the NICE list, and we're delivering all 40-year-old women at 39 weeks or 40 weeks. We're sectioning all diabetics at 38 weeks, we're delivering all obese women early, what you're doing?—massive, massive treatment paradox. If you left them alone, they go up. What you need to see, and I took it out, is a map of the world showing cardiovascular disease, and a map of the world showing pre-eclampsia prevalence—take a guess. I could swap them around and you would see the difference?—you wouldn't see the difference. The areas of the world where cardiovascular disease are highest are the areas of the world where pre-eclampsia risks are the highest, and they're totally interchangeable. It might just be coincidence, or it might be that the placenta somehow exerts an influence from underneath the ground, and causes this disease, to both men and women by the way, not just to the women.

Mr de Courcy-Wheeler:
Anybody else?

Professor Thilaganathan:
I've frightened everybody, sorry!

Mr de Courcy-Wheeler:
If you treat pre-eclampsia, and someone doesn't get it, does that cardiovascular risk go away?—if you deliver them early, or if you treat them?

Professor Thilaganathan:
Horace, you've got the million-dollar question, that's a really, really good one, so that's what I'm really interested in. I firmly believe that the disease iceberg is post-natal women's health. To this day, women still have a worse cardiovascular outcome compared to men, in 2020, and that shouldn't be right, right?—it shouldn't be right. They present late, they are underdiagnosed, they are under-treated, and they have a worse outcome—it's absolutely … late last year there was another study that showed that, and if you and I develop hypertension in our sixties, we'll get anti-hypertensives, but actually the chances that those anti-hypertensives would change our disease course is less than 15%. There's an 85% chance that the blood pressure tablets we get will not change our disease course, but we still take it because there's a one-in-eight chance it would. That's because our hearts are fibrotic, and actually we have gone over the recovery curve. There is actually substantial animal and peculiar human data from various sort of unusual disorders, which suggest that actually, if we find young women who have hypertension, before their heart becomes fibrotic, there are certain anti-hypertensives which cause de-remodelling—change the shape and the muscle mass of the heart, so that we can change the disease trajectory, completely change it, so you don't actually have to be on the anti-hypertensives forever. We can treat you for six months or a year, and that completely recovers your disease trajectory, so (a) it's important to find out afterwards. So the first step is to find a screening test that can find these women, and the next step for us is to use that screening test in women who did not get pre-eclampsia, to answer your question, so I can't answer that for another five years—just when I'm retiring I can answer that question. Right now, I'm using the group with the highest pathology, the pre-eclamptic women, to develop a screening test peri-partum, to predict those who will develop hypertension. Once we've got that sorted, then we will apply it to the non-pregnant population, because remember, the risk of hypertension is higher, tenfold higher if you develop pre-eclampsia, and although it is tenfold lower if you don't develop pre-eclampsia, there are 20 times as many women who don't develop pre-eclampsia. The risk of Down's syndrome is high if you're old, but the majority of Down's syndrome occurs to young women, so there is still a huge burden of disease in the women who then develop pre-eclampsia, and it might be because of this treatment paradox. They were going to develop pre-eclampsia, we delivered them, they didn't, so we called them normal, because their hearts are beating and their babies are alive—as far as an obstetrician's concerned, that's normal, right?—so we send them home, but they have underlying disease pathology, because they were breathless, they were micturating at night, they had diastolic dysfunction. They just didn't manifest blood pressure on a sphig, so we will apply that test to the normal population as well, but I can't tell that answer to you, but that's the best question.

Mr de Courcy-Wheeler:
So now I've asked the best question, the next best question—is there a difference between pre-eclamp-

sia and pregnancy-induced hypertension without proteinurea?

Professor Thilaganathan:

Yes and no. I think we're just catching, so obstetrics is very different to medicine, where you have diabetes or cancer or whatever. Obstetrics, it's like shooting skeet … depending on which timepoint you catch people, you call it something else, so if you catch it too early, they didn't develop pre-eclampsia. If you wait a little bit, it's gestational hypertension. If you wait a little bit longer, they will definitely have pre-eclampsia, so you've caught it earlier, and it might be that, by catching it earlier, like Horace says, that they have less disease, and it might be, if you catch it really, really early, they have no disease at all. I'll admit to being a scientist. I will keep an open mind as to whether that is true or not, whether indeed gestational hypertension has less of a legacy or not, I don't know, but we will find out in the next two to three years. Whether normal pregnancy has less of a legacy, we don't know, but I suspect that the normal women who have a really big heart and core function, I think are as likely to develop hypertension as the women who manifest pre-eclampsia a few days later, but we'll find out.

Dr J Logan:

I speak from total ignorance, because I'm a retired general physician, and from what you say this evening, it sounds very convincing there's something in the cardiovascular system, but the heart, to my mind, is a sort of a reactive organ. It's reacting to the stress of whatever it is in the cardiovascular system itself. Arthur C Guyton argued very convincingly that hypertension was due to the expansion of the intravascular volume, because of a change in the relationship between pressure as seen by the capillaries in the kidney, and urinary output, in other words, the renal function. I wondered, is the main problem not actually in the kidney? Particularly with the proteinuria.

Professor Thilaganathan:

You're absolutely right, so this is something that would never occur to an obstetrician, so if he hadn't said he was a physician, I would have told you he was a physician straight away! So we've just got a review in the *Annals of Physiology*, which is a cardiovascular renal syndrome, pre-eclampsia cardiovascular renal … I completely agree with you. If you go to a cardiac conference, one-half of the audience will tell you it's the heart that's the problem, and this half of the audience will tell you, it's the vessels that's the problem, and if there was some renal physiologists at the back, they'll tell you actually, it's the volume control that's the problem, yes?—because it's the chicken-and-egg thing. Is it the heart pumping, is it the vessels or is it the volume? Is it the work, is it the bricks they're moving that's the issue? I will be completely agnostic about it. I don't know, I can't tell you which is the chicken and which is the egg, but I believe that they're all inter-related, so I think that you can't say heart without saying cardiovascular, so when I go to cardiac conferences, I say it's a cardiovascular syndrome. I don't call it a cardiac syndrome, so it's a cardiovascular syndrome, and the cardiovascular system has both a pump, it has resistance and it has volume, and I think all three are inter-related in the functioning of the cardiovascular system. So I agree, it's difficult to dissect it out, but if you give me your email, I'll send you the article. That took a heck of a time to write, and it's actually quite an interesting article. As an obstetrician, I found it interesting.

Audience member:

Thank you, Basky. How do you square the circle, of all the other research, particularly coming up from say people like Chris Redman, Louise Canning, who have spent years searching for the Holy Grail, which is the circulating factor that causes vascular constriction? I mean, is there any way that you can square that circle?

Professor Thilaganathan:

Yep, everything I say does not in any way undermine all of their research findings. There is absolutely no doubt that somewhere along the line, in the pathophysiology, not in the aetiology, but in the pathophysiology of the pre-eclampsia, poor perfusion of the placenta results in the egress of some agents. Whether it's [ASLP?], PlGF, microscopic debris, whether it's Factor X or Factor Y, there have been over 300 different factors that have been associated with the development of pre-eclampsia. I'm not in any way undermining any of that research. All I'm saying is that, for that to happen, we have this. Everyone's researching from here to here, and there's no doubt that what they've found is true, and I'm not changing any of that. What I'm saying is that all of that occurs because of this, and everything we've associated as the placenta being the cause actually is just in the pathway of a cardiovascular disease, just like gestational diabetes. There is no difference. The metabolic and vascular strain on the woman is huge, and whether it's the pancreas that becomes sub-optimal, or whether it's the cardiovascular system, is different. It doesn't undermine anything they've done, so I completely agree with everything they're saying. I just disagree with the fact that it all starts with the placenta, because it doesn't.

Mr de Courcy-Wheeler:

Thank you, Basky.