Interview with Professor Chris Redman: a 'grandfather' of obstetric medicine

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In September, one of the 'grandfathers' of obstetric medicine, Professor Chris Redman, will retire. Professor Redman is Professor of Obstetric Medicine at the University of Oxford. He has a long and distinguished career as a scientist and clinician and is an internationally renowned expert in preeclampsia. Here, Emma Henderson, a fifth-year medical student, talks to Professor Redman about his career as an obstetric physician, and the advances in the understanding and management of preeclampsia in this time.

Did you always want to be an obstetrician?

Well, let me put you right on that. I'm not an obstetrician, I'm an obstetric physician so I'm trained in medicine, I'm FRCP. I have no skills at all relevant to delivering women, operating on women or any of those sorts of things.

How did you make your career?

I didn't make my career, it spontaneously evolved.

I started house jobs, after studying first at Cambridge and then at Oxford. At that time, I was not interested in research. I wanted to be a paediatrician, but I got diverted.

I did not, and still do not, have a formal research degree. But in 1970 I joined the Regius Department of Medicine, as a junior lecturer. I was asked to set up a trial of long-term hypertension in pregnancy to see if early treatment would improve the perinatal outcome. I knew nothing about it – there were no Research Ethics in those days, I was given no budget and I was only told that the Obstetric Department would assist me. So I wrote the protocol and that's how it started. My supervisor, Lawrie Beilin, later Professor of Medicine in Perth, Australia, was my mentor and tether to sanity.

It was enormously difficult trying to find these women in a routine service that had no tradition of research of any kind and hardly knew what a randomized controlled trial was. After the first, extremely difficult year, I had a decision to make – did I stay in, or did I get out? At that time, our third child was born and there was no time to move, so I decided to stay.

The trial took five years to finish, by which time I was so involved in obstetric medicine that I had to stay in the territory. A university lectureship with a consultant contract was negotiated by Professor Richard Doll and Dr Rosemary, Medical

Director of what was then the Oxford Regional Health Authority. It allowed me to join the Nuffield Department of Obstetrics and Gynaecology in Oxford.

What did the results of that first trial show?

It suggested a benefit of using methyldopa for treatment. The real reason why chronic hypertension is dangerous for women is because it predisposes to preeclampsia, but methyldopa had no effect on its development. So it was a problem trying to explain where the benefit came from. As with most trials at that time, it was extremely underpowered to answer the important questions.

During those five years, my clinical colleagues kept calling my attention to women with severe preeclampsia: 'You have these powerful drugs at your disposal,' they said. 'Can you cure this woman so that we can take her through to term?' I found that my real interest was in preeclampsia, which was obviously a more substantial clinical problem than chronic hypertension during pregnancy.

What was known about preeclampsia then?

It was known to be characterized by new hypertension and proteinuria. It was also considered likely to be a placental disorder because of the documented occurrence of preeclampsia with hydatidiform moles. The placental pathology, particularly that of poor placentation, was defined just before I started, when Ernest Page in the USA had written in the late 1960s that he wondered whether placental ischaemia provoked hypertension like renal ischaemia.

What do you think are the major breakthroughs in the last 40 years of research into, and the management of, preeclampsia?

The first concern was the terrible perinatal mortality arising from the management of early-onset cases of preeclampsia. In 1971, the department acquired its first machine for electronic fetal heart rate monitoring to be used in the delivery suite. It occurred to me that if this machine could reveal fetal distress in labour, perhaps it could reveal fetal distress before labour, and thus could help us judge how to time deliveries better for the baby. And so it proved. In 1975, I appointed a monitoring midwife who provided an antepartum fetal heart rate monitoring service and the stillbirth rate in the context of early-onset preeclampsia dropped five-fold. So cardiotocographs were the first major practical advance. I think that ultrasound scanning

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was the next big development in terms of being able to assess fetal wellbeing and growth.

So what happened next?

Prostaglandins had just been discovered, so it was inevitable that people thought that they must be the big issue. It was postulated, then proved, that there was an imbalance in the way prostaglandins were produced in preeclampsia, such that the problem might be relieved by taking low-dose aspirin. A multi-centre randomized controlled trial of low-dose aspirin, the CLASP Trial, published in 1992, showed a small but just significant benefit from taking aspirin, so that to this day, most women who are thought to be at high risk of preeclampsia get prophylactic low-dose aspirin. The meta-analyses show that it is definitely but modestly beneficial, which must mean that there are a small number of women whose susceptibility is addressed by taking low-dose aspirin, but in other women it is not.

A big development came from San Francisco in 1989, when James Roberts laid out the evidence, which has proved to be correct, that the problems of preeclampsia – the maternal syndrome – could be ascribed to maternal endothelial dysfunction. He speculated that this was caused by a toxic factor released by the placenta. This was a turning point. His thesis was that preeclampsia is not a hypertensive disease – the hypertension is a convenient secondary feature that we use for diagnosis, but it's not the primary pathology. Until that time, people thought that if the right cocktail of antihypertensive medication could be found, the problem would be solved. But it is not like that.

That set us off on a search for the so-called 'placental toxic factor'. I argued, in the most simplistic way, that 'if there is a factor coming from the placenta, it's going to be associated with the placental syncytial surface microvilli – so let us prepare vesicles derived from the microvilli and put them on cultured endothelial cells and see what happens'. The effect was staggering in that the morphology of the cells changed immediately, their behaviour changed and these microvesicles were certainly antiendothelial.

And then in 1998, by a brilliant stroke of lateral thinking, my colleague Ian Sargent showed that these free, anucleate microvesicles, which are submicroscopic, spontaneously circulate in pregnant women, and they are there in increased amounts in preeclampsia. So we began to talk about 'factor X' – the unknown factor causing preeclampsia which was in those vesicles. We devoted an enormous amount of time trying to fractionate and isolate their antiendothelial activity. But this proved to be beyond our technical abilities at the time.

The next development was our demonstration of generalized systemic inflammatory activation in preeclamptic women. The phagocytes, monocytes, polymorphonuclear cells and actually, as it turned out, the lymphocytes – were all activated. Gavin Sacks, an Oxford DPhil student, had insisted on studying trios – non-pregnant, pregnant, and preeclamptic women, all matched – and in doing so he demonstrated a progression from non-pregnancy to normal pregnancy through to preeclampsia. He found that in normal pregnancy, these cells were already activated but to a lesser amount. So there was this gradient. It looked as if normal pregnancy was on the way to preeclampsia, but hadn't got there yet.

We did a lot of re-thinking. Realizing that the endothelial cells are part of the inflammatory system, and these other cells are also part of the inflammatory system, we proposed (in 1999) that in normal pregnancy there is a systemic inflammatory response which is exaggerated in preeclampsia. We suggested that there is no natural dividing line between normal pregnancy and preeclampsia. We also argued that a systemic inflammatory response inevitably involves endothelial cells, which would create the signs that we knew, but there also is a more fundamental and broader process going on. We made the 'Redman-Sargent Prediction' that 'there would never be a single causative factor for preeclampsia, never be a single predictive test, never be a single prophylactic agent which would be effective for all, or a single curative measure'. When I retire, later this year, 10 years will have elapsed but this prediction, unfortunately, still holds.

The current 'cure' for preeclampsia is delivery. Do you think being able to predict whether a woman will develop preeclampsia will result in any alternative clinical intervention?

No, it's all about the screening. If there were a blood test at 20 weeks, which allowed one to say with certainty that 98 out of 100 women would not get preeclampsia for the next three months, they would not need to be reviewed for the next three months. On the other hand, if you could say two out of 100 women would certainly get it and be delivered within the next 12 weeks, you could focus your attention on those. So it could be used as a system for stratifying antenatal care, to make it less labour-intensive and inconvenient for everybody including the women themselves.

Do you think in the future we'll have an alternative cure to delivery?

I don't, but some people do. Some people think that by neutralizing the factor that is currently the most favoured as a cause of preeclampsia, namely circulating sFlt-1 (a circulating antiangiogenic protein of mainly placental origin), they'll be able to abolish the syndrome. Perhaps they're correct, but such treatment will not reconstitute a normal placenta, so it is likely that the mother will improve but her unborn child will be less well-off for various reasons – more growth failure, more fetal distress, perhaps more risk of perinatal death. In other words, the maternal syndrome might be cured at the expense of the perinatal outcome for the baby.

Another approach will be tested in a very interesting controlled trial using Simvastatin as prophylaxis for preeclampsia. This is based on experimental evidence that shows that statins inhibit the release of soluble VEGF-R1 (sFlt-1) from placental tissue *in vitro*. If it works, and I think it has a reasonable chance of being effective for the mother, we predict that it will be at the expense of the baby because preeclampsia is almost certainly an example of what is called maternal-fetal conflict. The nutrient supply to the fetus is altered by the maternal systemic inflammatory response in favour of the baby; that's part of the way in which the baby pushes the mother to give it what it needs. The mother counter-responds to preserve her wellbeing, but the mother and fetus are in evolutionary conflict at that point. If you damp down that inflammatory response, we suggest that fewer nutrients will be available to the baby.

If the problem is at placentation, is there anything that you think might be done in early pregnancy?

That would be the best bet. However, it is really hard to do randomized controlled trials because early pregnancy is the period of potential teratogenesis. There are two views as to when the problem occurs. One view is that it is between about week seven and week 18, which is the time when there is the most dramatic invasion of the placental bed by trophoblast cells. These remodel the spiral arteries, so expanding the uteroplacental blood flow 100-fold before delivery. But invasion and remodelling is inhibited in preeclampsia, leaving a restricted uteroplacental circulation until delivery.

Berthold Huppertz in Graz has an alternative theory: he speculates that there could be problems even earlier. At this stage trophoblast differentiates into two populations: the first comprises an invasive trophoblast that infiltrates the placental bed to stimulate remodelling of the spiral arteries; the second contributes to the villous structure of the placenta. To begin with, the two trophoblast subsets share a common tree but the invasive trophoblast goes one way and the villous trophoblast the other. Huppertz postulates that if differentiation is perturbed before or after the populations diverge, you get different syndromes. If villous differentiation is upset, and this would be before six weeks, then the placenta would simply be too small but would have a blood supply adequate for a small baby. The mother would not get preeclampsia. If the extravillous invasive trophoblast differentiation were defective then a reduced number of invasive trophoblasts would not be able to sustain invasion and remodelling of the spiral arteries. In these circumstances, the mother would get preeclampsia.

But usually you get a mixture of the two, which is why you get growth restriction and preeclampsia occurring together. Now, whether or not it would be possible to alter this process would be really interesting to find out. It's achieved naturally, because having a first baby improves your outcome next time round. If it were possible to biologically simulate the effect of having a first baby before it is conceived, preeclampsia could be dramatically reduced.

Some people think that preeclampsia is immunological in origin, and there's quite a lot to support this. In 2004, a paper by Ashley Moffett's group in Cambridge analysed the immune interactions between fetus and mother. The invasive trophoblast cells express a very odd repertoire of transplantation antigens of which the most important that reveals the baby's paternal identity is HLA-C. In the decidua the most common immune cell is the natural killer (NK) cell, which has highly polymorphic receptors (KIR receptors) that interact with HLA-C in a variable way: it depends on the HLA-C type of the fetus and also the individual pattern of the maternal KIR receptors. They can either stimulate the NK cells, which is probably good, as they provide a lot of cytokines and growth factors and so on, which promote trophoblast proliferation and invasion; or they inhibit them, which is bad. They worked out the patterns most likely to stimulate in terms of HLA-C-KIR receptor interactions. Then they studied a case-control series in relation to preeclampsia. They found a definite favourable interaction between certain fetal HLA-C groups and certain maternal KIR groups, predicted to be stimulatory and more evident in the controls. There was also an

unfavourable interaction, predicted to be non-stimulatory, associated with preeclampsia.

Now that's not going to help treatment, unless you can do pre-pregnancy counselling and advise a couple that they're going to be a pretty bad combination because of their genes. On the other hand, the mechanisms need to be understood; so far it does suggest that there are immune processes going on, which may be susceptible to 'pre-immunization' – a process that retunes the decidual immune system to be more accommodating. A group in the USA showed that higher pre-conceptual sperm exposure is significantly associated with a lower risk of preeclampsia. This leads to the suggestion that the nature of preeclampsia may have changed since it was discovered. A hundred years ago, first coitus would likely be the conceptual coitus – people didn't use family planning so many couples conceived within three months of getting married. Hence, there was less chance of uterine immune adaptation. The records suggest that preeclampsia was more common and more aggressive in those days. Then after the Second World War, particularly after 1960s when the pill became available, women could postpone conception and men could avoid using condoms which previously blocked sperm exposure. Pierre-Yves Robillard first developed this idea. He suggests that the profile of preeclampsia has changed in recent decades from a Third World pattern, where there is poor maternal immune adaptation because of short preconceptual sperm exposure, to a First World pattern where it's more to do with a mother's ability to accommodate the pregnancy in terms of her arterial and inflammatory system. The First World problems are more likely in women who are obese, suffer diabetes or have chronic hypertension.

You've mentioned some of the current ideas in research, but are there any other main ways forward at the moment?

We're particularly interested in those circulating microvesicles, now renamed microparticles. All the cells in the circulation contribute to an individual's microparticle load. In pregnancy, the placenta is also plugged directly into the mother's bloodstream and contributes a fifth population of placental microparticles, in addition to the platelet, endothelial, leukocyte and erythrocyte microparticles that we all have.

We initially focused on the ones that we could see (by flow cytometry) but it's now increasingly probable that the ones that we can't see, called nanoparticles, are more interesting, especially since they can deliver complex messages to other cells in the circulation. Placental-derived nanoparticles circulate in pregnancy and they're there in greater amounts in preeclampsia. At the moment Professor Sargent is developing the technology for how to detect these particles which previously had been 'invisible'.

What advice would you give to obstetric physicians of the future?

I've been enormously lucky with the people that I've worked with, who've supported an eccentric career and made it very interesting.

It is important to follow your instincts rather than try to plan. I don't think it's possible to plan a career because events happen – you get opportunities you didn't know you were

going to get, you come across blocks that are usually gifts from God because they redirect you to a better route somewhere else, and so on and so forth. The idea that you can know now where you're going to be in five years time is not sensible. So, do what you find interesting and good fun. Keep your options open. Take risks – if you don't, then you might miss the best chances.

I have had to work extremely hard because I've often been on my own: I have often been tired, frustrated or angry, but I have never ever been bored. I could not have wished for a more interesting time.

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