OPINION :

Trying to understand preeclampsia. A rocky road

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This narrative is not a review, it is just a personal account of a series of pivotal studies that directly influenced my evolving research interest in the pathogenesis and prevention of preeclampsia since the early 1980s'.

Studying in Leiden (The Netherlands) in the early 1970's, my introduction into obstetrics was not very positive. The obstetrical teaching, we received, as 3rd year medical students was boring. The focus was very much on the individual plusses and minuses of types of obstetrical forceps. Preeclampsia was a disease caused by 'salt excess', strict salt restriction the key concept in prevention of preeclampsia in The Netherlands.

One of my lecturers told us that disseminated intravascular coagulation (DIC) was the key causal pathophysiologic mechanism in preeclampsia. At this stage one did not realize that the 'DIC' observations were all based on autopsy findings in women dying of eclampsia and/or HELLP (although that acronym was only introduced by Weinstein1 in 1982). It was Prof Jack Pritchard2 who – already in these years – made the observation that we 'never die alone – DIC is always there'. For me the 'DIC' lectures certainly triggered my interest in the haemostatic system.

My real breakthrough and the choice of an obstetric career was caused by the arrival of Prof Marc Keirse in Leiden in 1976. Prof Marc Keirse, the 'prostaglandin-guru' inspired us with a completely different view on physiology of pregnancy and parturition, and the major role played by the various prostaglandins. The later 'Noble price' discovery of prostacyclin and thromboxane A2 by Moncada and Vane3 really brought the focus on the importance of these mediators in homeostasis, platelet- endothelial interaction, renal function and cardiovascular medicine.

My 'Mark Keirse induced' interest in prostaglandins persisted throughout my early clinical years. In 1973, Norman Gant4 had published his landmark study on angiotensin-II sensitivity, demonstrating the lack of normal pregnancy –associated refractoriness to angiotensin-II in future preeclamptic women. My first sad experience with a maternal death, as a first year registrar, was young primigravida with an induction of labour for preeclampsia and a twin pregnancy at 37 weeks. She died due to intrapartum eclampsia, her tragic death certainly consolidated my ongoing interest in preeclampsia research.

The rapidly expanding body of literature on prostacyclin and thromboxane-A2 made it clear that the balance of these 2 autocoids was an important regulator of angiotensin-II sensitivity. Based on the, at that stage, well described PGI2/TXA2 imbalance in preeclampsia, my first plan was to use a selective thromboxane A2 synthetase inhibitor to prevent preeclampsia in angiotensin-II sensitive pregnant women. However, very appropriately my supervisor, Prof Henk Wallenburg, made the point that we were lacking critical safety data on these compounds, and more importantly - simple low-dose aspirin should also 'do the trick'. Nowadays, it might be difficult to get ethics approval to perform angiotensin-II infusion tests, but in the early 1980's, ethics approval was obtained, and it was actually relatively easy to recruit patients. So, in 1983, we started the first double-blind 60 mg aspirin versus placebo-controlled trial in nulliparous women with increased angiotensin-II sensitivity at 28 weeks.

The trial, published in 1986 in The Lancet5 was a major success. Naively I was more or less convinced that we had solved preeclampsia. The international uptake was enormous, and multiple small very positive trials followed. However, the large trials, CLASP, NIH etc, demonstrated that aspirin was not a miracle therapy. Even now there is debate raging (depending on how you select your groups and endpoints) on whether aspirin has a very modest or marked effect. It was in hindsight, unbelievably naïve, to start with low-dose aspirin at 28 week's – while we realize now much more than in the 1980's that the roots of preeclampsia (in particular 'placental preeclampsia') are in the first trimester.

My clinical registrar years, were very much dominated by the haemodynamic approach to preeclampsia – the focus of research in Rotterdam in the 1980's. Preeclampsia, a disease characterized by vasospasm was

found to be associated with hypovolaemia (in established severe disease) – so the simple solution appeared to be aggressive vasodilatation and plasma volume expansion. It took close to 15 years, before proper randomized trials showed that this 'aggressive' and impressive approach with pulmonary artery catheters on the ICU, did not work.

Nowadays we do understand that treatment of established disease (very much similar to the use of tocolytic drugs in management of preterm labour) is akin to a scenario best described as 'an attempt to save the ship that is already sinking'. The placental damage exists, the maternal inflammatory response syndrome is in full swing, and we just cannot cure the disease. We have come to realize that progress in this area will have to come from early prevention.

Not to say that proper treatment cannot make any difference in maternal outcome. In the 1990's, in the Free University Amsterdam, we had started to use ketanserin, a selective serotonin-2 receptor blocker for the treatment of preeclampsia. This drug was clearly more targeted on the endothelial damage (described by Roberts and Redman) and the increased platelet activation. The use of ketanserin was clearly associated with a lower incidence of maternal complications, but again one could not really stop disease progress6. It should be noted that a South African7 preventative trial (high risk patient on low dose aspirin plus or minus ketanserin) appeared to indicate a clear benefit of oral ketanserin in preventing the disease7. Unfortunately, big pharma moved on and was not interested in funding more trials with this potentially useful drug. For me, the 'ketanserin story' is a good example on how lack of pharmaceutical commercial interest can truly block proper clinical research – particularly in a specialty like obstetrics.

Over these decades, a series of Landmark studies by Roberts and Pijnborg, had demonstrated the pivotal role of the invading endovascular cytotrophoblast in the remodelling of spiral arteries. It was quickly identified that lack of spiral artery remodelling was not specific for preeclampsia; it occurred in placental IUGR, many cases of preterm labour and was also seen in placental abruption (review 8).The early 1990's did also see the landmark publication by Jim Roberts and Chris Redman, demonstrating that preeclampsia, from a maternal perspective can be characterized as an endothelial disease or a manifestation of endothelial dysfunction9.

The landmark studies by Roberts and Pijnenborg on lack of spiral artery remodelling, and the initial; 2-stage model by Chris Redman really focussed my attention on the placenta. Early-onset preeclampsia (a rare disease entity in itself) is often associated with placental infarcts, acute atherosis etc. The 1990's did bring a focus on the so-called thrombophilias, with discovery of protein C and protein S, the activated protein C pathway and a bit later also hyperhomocysteinaemia.

Our group in Amsterdam, and at the same time my friend Michael Kupferminc, published the first large series of thrombophilia analysis in patients with early-onset disease. Many studies followed, lots of these studies were done in patients with mild term disease, or late IUGR pregnancies. All these studies were negative, and lead many to believe that the thrombophilias play no role. However, Michael Kupferminc and I have argued repeatedly that looking for thrombophilias is only indicated in the rare patients with very early disease with extensive placental disease. This same disagreement also underpins, the many controversies surrounding the role of low-molecular weight heparin. Both Michael Kupferminc and I always stressed the point that we did not see thrombophilias as 'the cause', but just as an important 2nd hit phenomenon.

In the same time period, our Amsterdam group, also looked into the genetic aspects of preeclampsia. Many studies demonstrated the importance of a positive family history, although we have to acknowledge that part of this 'family history' effect could be explained by DOHAD (the current name for the phenomenon first described by the late David Barker). It is again humbling, to realize that we were optimistically seeking 'the preeclampsia gene' or at least genes with a major effect- not realizing at that stage that such a gene should have committed 'evolutionary suicide' with preeclampsia – in particular with just a bit of prematurity and/or growth restriction – was often fatal for the neonate and often also the mother. Nowadays, and based on many international studies, including our so-called SCOPE study, it is clear that we are looking at a large series of susceptibility genes that affect blood pressure, insulin resistance, placentation,, inflammation etc. Interestingly, several genes identified by the Adelaide SCOPE team (Andraweera, Roberts, Dekker) are associated with SGA but also with type II diabetes, stroke, and hypertension (adding another layer of complexity to the DOHAD findings).

Realizing that progress had to come to prevention, I refocussed on what would be the cause of this endothelial disease. At that stage, Pierre Robillard had published his landmark papers on length of sexual relationship and the primipaternity effect. After a relatively short period of looking at oxygen free radicals (methods were inadequate at that time), we decided to dive into the immune aspects of preeclampsia and

placentation. Eric Scheepers, professor of mucosal tolerance at the Free University explained to me that oral exposure to antigens tend to result in a strong mucosal tolerance. The next step was our straightforward case control study on the effects of oral sex. Univariate analysis showed that oral sex prior to pregnancy is associated with a much lower risk for preeclampsia. This study got, also because of the American president at that stage, a lot of publicity. The best outcome of this oral sex study, was an invitation from Pierre Yves Robillard to come to Tahiti to discuss future collaboration. During this first meeting we developed the bold idea to start with 'Immunology of Preeclampsia/Placentation' workshops – the first meeting was in 1998 on Moorea, one of the mesmerising French Polynesian islands. We just had the 11th meeting, now organized way South in the Indian Ocean on Isle de La Reunion. Over these 11 workshops we really have started to realize, that 'Immunology' is also only one part of the puzzle – with primarily early placentation and vascular remodelling influenced/ controlled by local maternal NK-cells and T-reg cells in the placental bed.

Research efforts led my basic science colleagues here in Adelaide (Prof Sarah Robertson), underpinned the role of T reg cells and partner specific immune responses that are essential for placentation. The male seminal fluid cytokine pattern is of pivotal importance, the seminal fluid microbiome may play a role here.

In particular the last decade brought a major paradigm shift in our understanding of preeclampsia. The landmark paper by Karumanchi's group highlighted the pivotal role of angiogenic growth factors, and anti-angiogenic factors like sFlt-1 and sEndoglyn. In itself these factors fit quite nicely with the genetic conflict theory, as originally proposed by David Haig.

Of even greater importance was work by Chris Redman and Ian Sargent really highlighting the fact that we should start to acknowledge that preeclampsia is a very heterogeneous syndrome. Also based on work by leading placentologists like Berthold Huppertz and Graham Burton, we now understand that the lack of spiral artery remodelling does not hypoxia but to high velocity flow patterns, coming from the non-transformed spiral arteries, damaging the vulnerable syncytiotrophoblast. This lack of remodelling is typically associated with IUGR. Probably related to the degree of inflammatory stimulus, production of anti-angiogenic factors and pre-existing maternal cardio-metabolic, women may or may not develop the maternal syndrome.

Over recent years, we also start to explore the role of the foetal gender (Verburg); early-onset preeclampsia is more common when a woman carries a female foetus, while early spontaneous preterm birth is very much a 'boy business'. Are these different response to poor placentation, is the female foetus more efficient in triggering an adaptive maternal hypertensive response – that allows the female foetus to 'hang in a bit longer '?

The final maternal syndrome represents a systemic maternal response, in particular in the specialized endothelial cells (podocytes, Kupfer cells, blood-brain barrier) to a stressed syncytiotrophoblast, leading to an anti-angiogenic 'cocktail', inflammatory cytokines, microparticles, and a series of (misfolded) protein signalling ER stress. Pathways leading to the syndrome differ from person to person, and will differ between different populations. Risk factors for preeclampsia will differ for different 'preeclamptic phenotypes'.

The fact that the lack of remodelling is more linked to IUGR, is also supported by our SCOPE studies, showing a clear increased in 'SGA with abnormal uterine artery Doppler velocity waveforms' associated with < 3 and < 6 months of sexual relationship, while no association was found with preeclampsia. This can be explained by the fact that a large percentage of preeclampsia, currently encountered in a Western setting, is term preeclampsia (often associated with cardio-metabolic risk factors) without any indication of lack of spiral artery remodelling.

Over the past 17 years I had the honour and pleasure to start a close collaboration and friendship with my Surabaya MFM colleagues, all working for Airlangga University. Over this long period that the Indonesian preeclampsia phenotype is quite remarkable – many patients present with pulmonary edema (a problem with rarely see in Western countries), also many patients arrive with 'neglected disease'. This neglect can be related to patient unawareness of preeclampsia symptom, lack of access, and lack of timely proper referral to tertiary hospitals.

Based on many discussions with my many Indonesian friends and colleagues, the 2 main issues in provision of Maternity Services requiring urgent attention form the Indonesian government (both federal and regional) are (1) proper midwifery training, and (2) revision of the current insurance scheme.

Regarding point 1: Many midwives are doing excellent work, but many apparently lack proper training. Midwifery training needs to be strengthened, in order to bring midwifery training to an internationally recognized standard. These highly trained midwives

deserve a proper salar. Regarding point 2: The current insurance system appears to penalize against proper referral. The result is that large tertiary units, e.g. Dr Soetomo Hospital receives the very sick preeclamptic patients. Many of these patients require and receive expert medical input, often on the Intensive Care. One of the key obstacles is that the funding model does not recognize the major complexities these patients present. In most Western hospitals, but also in many large Asian countries hospitals would receive appropriate funding (often in the range of 10,000 $ US) to look after such a sick patient –the discrepancy with the Indonesian funding is striking. One also needs senior staff on-site to look after these patients, i.e. salaries for senior specialist staff need to be appropriate and recognize their considerable skills. If not, 'The System' forces all these colleagues to spend a large part of their working hours looking after private patients. I fully understand that all this requires major and fundamental changes in Healthcare with a recognition that looking after pregnant women is basically the highest priority in Health Care. These changes will take time, and major government input – but it will need the medical doctors to start this discussion with government.

This narrative is certainly not complete; it just highlights some of the pivotal points in my career as clinical academic in my search for the 'preeclampsia cure'

To summarize a few major dot points on this journey:

1. Care for pregnant women is the best part of Clinical Medicine; helping women to give birth to a healthy neonate represents the most exciting approach to primary prevention of a multitude of cardio-metabolic and neurodevelopmental disorders
2. Preeclampsia is a heterogeneous syndrome – the current access to 'angiogenic markers' will help us in differentiating different disease phenotypes ; not one test will predict all types of preeclampsia, and not one type of treatment will prevent all preeclampsia
3. For young researchers contemplating their research path – placentation, preeclampsia and DOHAD offer endless research opportunities – your impact will potentially greatly exceed research in the 'epidemic of 'geriatric disorders'.

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