Cardiovascular Research

The ASPRE Preeclampsia Trial: Implications for Basic Research and Clinical Practice

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Biography

Basky Thilaganathan was appointed Director of Fetal Medicine at St George's Hospital in 1999 and Professor of Fetal Medicine in 2008. His research interests are focused on Maternal-Fetal medicine, with a particular interest on maternal cardiac function, placental function, fetal growth and preeclampsia (TED talk: http://bit.ly/2i1SqDk).

He completed his postgraduate training at King's College London and St Bartholomew's Hospitals, culminating in his Membership of the Royal College of Obstetricians and Gynaecologists (MRCOG) (1995), MD in Fetal Medicine (1996) and Certificate of Completion of Training (1998). He undertook his undergraduate training at King's College London, where he obtained a BSc in Genetic Engineering (1995) and MBBS (1988). He was awarded the Fellowship of the Royal College of Obstetricians and Gynaecologists (FRCOG) and an Honorary Doctorate (PhD) from Uppsala University in 2007.

He has authored two undergraduate and five postgraduate text books in obstetrics and fetal medicine. He is the lead trainer for the Maternal-Fetal medicine sub-speciality training programme at St George's Hospital and Editor-in Chief of *Ultrasound in Obstetrics and Gynaecology*, the medical journal affiliated to ISUOG. He has authored over 200 peer-reviewed publications in indexed journals. He is a Council Member on the Royal College of Obstetrics and Gynaecology (RCOG) and represents the RCOG on the UK National Screening Committee. He is also the Clinical Lead for the development of the first dedicated high-throughput NIPT lab in the UK NHS to undertake cfDNA aneuploidy screening in pregnancy (www.theSAFEtest.co.uk).

The ASPRE Preeclampsia Trial: Implications for Basic Research and Clinical Practice

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Preeclampsia and related hypertensive disorders of pregnancy affect approximately 5% of all births. Worldwide, 10 million women develop preeclampsia, with about 80,000 women dying from preeclampsia and related complications each year. Although the precise aetiology of preeclampsia has been a source of long-standing debate, overwhelming opinion attributes the development of preeclampsia to impaired placentation in early pregnancy. However, more recent evidence has demonstrated that placental histology is invariably normal in preeclampsia and that the majority of neonates born of preeclamptic mothers are either normal or larger in size than expected.[1,2] These findings undermine the fundamental assertion that abnormal placental development is a primary aetiological factor for preeclampsia and have led researchers to seek alternative hypotheses. One emerging and biologically plausible theory is that preeclampsia occurs as a consequence of cardiovascular maladaptation to pregnancy (TED talk at: https://bit.ly/2JP0oNT). The findings that cardiovascular dysfunction precedes preeclampsia, cardiovascular signs predominate in the clinical syndrome and that the risk of cardiovascular disease persists for several decades postpartum is compelling evidence for the cardiovascular origins of preeclampsia.[3-6] The concept that placental dysfunction is secondary to a maternal disorder is not new when one considers the clinical similarities between preeclampsia and gestational diabetes – both pregnancy-specific conditions that are 'cured' by birth.[7]

The cardiovascular origin of preeclampsia hypothesis continues to be of relevance when interpreting the conduct and outcome of the recently-published ASPRE trial in the *New England Journal of Medicine*.[8] Researchers conducted a double-blind, placebo-controlled trial in 13 European centres, where 1776 women with singleton pregnancies identified to be at high-risk for preterm (birth before 37 weeks) preeclampsia, were randomised to receive either aspirin 150mg per day or placebo from 11 to 36 weeks of gestation. The study demonstrated that preterm preeclampsia occurred in 1.6% in the aspirin group, as compared with 4.3% in the placebo group – a 60% reduction in preterm preeclampsia (OR: 0.38; 95% CI: 0.20 to 0.74). Adherence to therapy was formally evaluated as good in 80% of the participants, with no demonstrable difference in the incidence of neonatal or maternal adverse outcomes in either arm of the study.

The ASPRE study has several implications for clinical practice, beginning with demonstrating effective early pregnancy screening for preterm preeclampsia. In the UK, identification of women as high-risk for preeclampsia is currently based

on a checklist of maternal characteristics and medical history as defined by National Institute for Health and Care Excellence (NICE) guidelines. The ASPRE study used an algorithm that combined known risk factors with mean arterial pressure (MAP), uterine artery pulsatility index and serum placental growth factor (PlGF) taken at 11 to 13 weeks' gestation. The use of this algorithm more than doubled the sensitivity for preterm preeclampsia from 40% for the NICE recommended policy to 82%, thereby making a compelling case for the routine implementation of this screening protocol.[9] It should be noted that the screening test utilises cardiovascular indices (MAP, uterine artery pulsatility index and PlGF) and preeclampsia prophylaxis is achieved using a drug with established vascular effects. Furthermore, the study settles recent uncertainty surrounding the appropriate dosage and timing of aspirin prophylaxis.[10] These findings are all further support for the cardiovascular origin of preeclampsia.

It has long been presumed by researchers interested in preeclampsia that defects of trophoblast (placental) development, motility, invasion and function are intrinsic defects that then influence uterine perfusion by way of inadequate spiral (uterine) artery invasion and remodelling. A re-examination of this assumption reveals that either it is incorrect or that - uniquely in human biology - placental end organ tissue structure influences upstream vascular perfusion. Recent research supports the more likely scenario that primary impaired uterine perfusion may lead to inadequate trophoblast invasion and function.[11]
It is also remarkable that for a disease, which has been clinically recognised for over a century and with a significant human toll, no diagnostic test exists. The validation of an effective multimodal ASPRE screening test in early pregnancy for preeclampsia also raises the possibility and hope that combining cardiovascular markers may provide a clinically valuable predictive or diagnostic test in later pregnancy.[12]

Arguably, the largest burden of disease lies in the maternal postpartum legacy of preeclampsia. More recent epidemiological data demonstrates that the peak onset of chronic hypertension following preeclampsia occurs in the first two-three years following pregnancy – not decades later as previously presumed.[3] Indeed, preterm preeclampsia is a stronger risk factor than smoking for the development of stroke and other cardiovascular diseases in women. This finding is consistent with the data showing echocardiographic evidence of occult diastolic dysfunction in the majority normotensive women one year following a pregnancy complicated by preterm preeclampsia.[13] Although the APSRE study demonstrated an undeniable and desirable benefit in pregnancy outcome, it remains to be determined whether aspirin therapy in women at high-risk of preterm preeclampsia will ameliorate the deleterious long-term maternal cardiovascular consequences of pregnancy.

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