RBM ONLINE

ELSEVIER

The *INSR* rs2059806 single nucleotide polymorphism, a genetic risk factor for vascular and metabolic disease, associates with pre-eclampsia

Prabha H Andraweera [a,*], ***Kathryn L Gatford*** [a], ***Gustaaf A Dekker*** [a,b], ***Shalem Leemaqz*** [a], ***Rohan W Jayasekara*** [c], ***Vajira HW Dissanayake*** [c], ***Lesley McCowan*** [d], ***Claire T Roberts*** [a]

[a] *Discipline of Obstetrics and Gynaecology, School of Medicine and Robinson Research Institute, The University of Adelaide, Adelaide, Australia*

[b] *Women's and Children's Division, Lyell McEwin Hospital, Elizabeth Vale, Australia*

[c] *Human Genetics Unit, Faculty of Medicine, The University of Colombo, Colombo, Sri Lanka*

[d] *Department of Obstetrics and Gynaecology, The University of Auckland, Auckland, New Zealand*

Prabha Andraweera is an NHMRC Australia Peter Doherty Postdoctoral Fellow in the Discipline of Obstetrics and Gynaecology, University of Adelaide, Australia. Her current research focuses on the genetic contribution to the link between adverse pregnancy outcomes and later life vascular and metabolic diseases.

KEY MESSAGE

Pre-eclampsia is a risk factor for later life vascular and metabolic diseases. This study demonstrates that the *INSR* rs2059806 SNP previously associated with adult vascular and metabolic diseases also associates with pre-eclampsia, suggesting that genetic susceptibility may be implicated in the link between pre-eclampsia and subsequent vascular and metabolic diseases.

ABSTRACT

Pre-eclampsia is a risk factor for later life vascular and metabolic diseases. This study postulates that this reflects a common genetic cause, and investigates whether the *INSR* rs2059806 single nucleotide polymorphism (SNP) (a risk factor for essential hypertension, type 2 diabetes and metabolic syndrome) is also associated with pre-eclampsia. The association of *INSR* rs2059806 with pre-eclampsia was tested in two cohorts – a Caucasian case control group (123 pre-eclamptic mother-father-baby trios and 1185 mother-father-baby trios from uncomplicated pregnancies) and an independent cohort of Sinhalese women (175 women with pre-eclampsia and 171 women with uncomplicated pregnancies). In the Caucasian cohort, the prevalence of the *INSR* rs2059806 AA genotype was greater among pre-eclamptic women compared with the uncomplicated pregnancies (12.7% versus 4.7%, OR[95%CI] = 3.1[1.6–5.8], $P = 0.0003$). In the Sinhalese cohort, maternal *INSR* rs2059806 AA genotype was greater among pre-eclamptic women who delivered small for gestational age infants compared with the uncomplicated pregnancies (10.8% versus 4.2%, OR[95%CI] = 2.8[1.0–7.4], $P = 0.03$). Thus, it was found that the *INSR* rs2059806 SNP is also associated with pre-eclampsia phenotypes in two independent cohorts suggesting that genetic susceptibility may be implicated in the link between pre-eclampsia and subsequent vascular and metabolic diseases.

* Corresponding author.
E-mail address: prabha.andraweera@adelaide.edu.au (PH Andraweera).

http://dx.doi.org/10.1016/j.rbmo.2017.01.001
1472-6483/© 2017 Published by Elsevier Ltd on behalf of Reproductive Healthcare Ltd.

Please cite this article in press as: Prabha H. Andraweera, et al., The *INSR* rs2059806 single nucleotide polymorphism, a genetic risk factor for vascular and metabolic disease, associates with pre-eclampsia, Reproductive BioMedicine Online (2017), doi: 10.1016/j.rbmo.2017.01.001

Introduction

Pre-eclampsia is a pregnancy specific disorder that occurs in 2–5% of pregnancies and is a leading cause of maternal morbidity and mortality (Duley, 2009). Although the hypertension and proteinuria associated with pre-eclampsia resolve after pregnancy, women who develop pre-eclampsia are at increased risk for vascular diseases in later life (Bellamy et al., 2007). A recent systematic review and meta-analysis demonstrates that women who develop pre-eclampsia are at more than two-fold increased odds of developing coronary artery disease (CAD) compared with women who have uncomplicated pregnancies (Brown et al., 2013. Early onset of pre-eclampsia is associated with a nearly eight-fold increased risk of subsequent CAD compared with late onset disease and severe pre-eclampsia is also associated with a higher risk of CAD compared with mild pre-eclampsia (Bellamy et al., 2007). Women who develop pre-eclampsia are also at increased risk for other vascular diseases including hypertension, thrombo-embolic disorders and cerebrovascular events (Bellamy et al., 2007; Brown et al., 2013).

In addition to the maternal health consequences, pre-eclampsia is associated with risks to the offspring. The risk of being born small for gestational age (SGA) is four times higher among infants born after pre-eclamptic pregnancies compared with infants born after uncomplicated pregnancies (Odegard et al., 2000). Infants born SGA as well as women who deliver SGA infants are at a higher risk of CAD compared with women who have uncomplicated pregnancies (Eriksson et al., 2001; Ngo et al., 2015). Very few studies published up to now have stratified SGA infants based on presence or absence of hypertension/pre-eclampsia during pregnancy. Therefore, the link between SGA and adult CAD may be confounded by pre-eclampsia.

The pathophysiologic mechanisms that link pre-eclampsia and vascular diseases are still not clear, and several hypotheses have been suggested to explain this association. One hypothesis is that metabolic alterations during a pre-eclamptic pregnancy, including endothelial dysfunction, insulin resistance and oxidative stress, could persist after the pregnancy, contributing to the risk for vascular diseases (Ness and Hubel, 2005). An alternative hypothesis is that a hereditary risk that interacts with environmental factors may predispose to both pre-eclampsia and subsequent vascular diseases.

The *INSR* rs2059806 single nucleotide polymorphism (SNP) is an ideal genetic candidate allowing us to test this second hypothesis. *INSR* rs2059806 is a G-A variation in exon 8 of the *INSR* gene (Hanis and Bertin, 1990). The effect of this SNP on receptor function is yet to be determined, but the A allele of this SNP is associated with increased risk of many metabolic and vascular phenotypes including essential hypertension, type 2 diabetes and metabolic syndrome (Ouederni et al., 2009; Schrader et al., 1996; Thomas et al., 2000; Wang et al., 2012). This study therefore aimed to investigate the association of this SNP with pre-eclampsia.

Materials and methods

Two study populations were included in the analyses – a Caucasian case control group (123 pre-eclamptic mother-father-baby trios and 1185 mother-father-baby trios of uncomplicated pregnancies) and an independent cohort of Sinhalese women (175 women with pre-eclampsia and 171 women who had uncomplicated pregnancies).

The caucasian study population

The Caucasian participants were recruited from the Screening for Pregnancy Endpoints (SCOPE) study. The SCOPE study is an international, multicentre, prospective cohort study with the aim of developing screening tests to predict pre-eclampsia, SGA infants and preterm birth across different populations. The details of the SCOPE study including recruitment of participants, data collection and genotyping methods have been previously published (Andraweera et al., 2011, 2012a, 2012b, 2015b) and are briefly described below Ethics approval was gained from the Central Northern Adelaide Health Service Human Ethics Committee in Australia on 2 September 2005 (No 2005082) and from the Auckland Ethics Committee in New Zealand on 23 April 2003 (AKX/02/00/364). Ethics approval to continue genotyping in the SCOPE cohort was obtained from the Central Northern Adelaide Health Service Human Ethics Committee in Australia on 6 January 2016 (reference number 2005082). The SCOPE study is registered with the Australian and New Zealand Clinical Trial Registry (ANZCTRN12607000551493). Nulliparous women with singleton pregnancies attending hospital antenatal clinics, obstetricians, general practitioners or community midwives before 15 weeks of gestation were invited to participate in the SCOPE study. Women were recruited between November 2004 and September 2008 in Adelaide, Australia and Auckland, New Zealand. Those considered at high risk of pre-eclampsia, SGA or preterm birth because of underlying medical conditions (including known pre-existing chronic hypertension on hypertensive medication or with a blood pressure >160/100 mmHg at 15 weeks' gestation), gynaecological history, three or more miscarriages or terminations of pregnancy or couples who received medical or surgical interventions which could modify pregnancy outcome, were not eligible. If the woman stated that she was certain of the identity of the infant's father, the father was also invited to participate in the SCOPE study. All women and partners who participated in the study provided written informed consent. Recruited couples were excluded from the present analyses if any of the following reasons applied: protocol violation, lost to follow up, conceived with donor sperm or oocytes, miscarriage or termination and woman or partner not of Caucasian ethnicity. Couples who agreed to participate were interviewed and examined by a research midwife at 15 ± 1 and 20 ± 1 weeks of gestation. Data were collected at each time point and included demographic information, medical history, previous obstetric history, family history of obstetric complications and medical disorders. The woman's birthweight and the gestational age at which she was born, as well as the partner's birthweight were also recorded. Current pregnancy data included information on any complications during current pregnancy, diet, smoking, alcohol and the use of recreational drugs. Maternal and paternal physical measurements obtained at 15 weeks of gestation included height, weight and blood pressure. All women were followed prospectively and pregnancy outcome data and infant measurements were recorded by research midwives usually within 72 h of birth. Pre-eclampsia was defined as systolic blood pressure ≥140 mmHg and/or diastolic blood pressure ≥90 mmHg on two or more measurements 6 h apart after 20 weeks of gestation with proteinuria (24-h urinary protein 300 mg or spot urine protein:creatinine ratio ≥30 mg/mmol creatinine or urine dipstick protein ≥++) or any multisystem complication of pre-eclampsia. The diagnosis of pre-eclampsia was made by a senior SCOPE investigator. SGA was defined as a birth weight below the 10th customised centile adjusted for maternal height, weight, parity and ethnicity, gestational age at delivery and infant sex (McCowan et al.,

Please cite this article in press as: Prabha H. Andraweera, et al., The *INSR* rs2059806 single nucleotide polymorphism, a genetic risk factor for vascular and metabolic disease, associates with pre-eclampsia, Reproductive BioMedicine Online (2017), doi: 10.1016/j.rbmo.2017.01.001