# RANZCOG WOMEN'S HEALTH FOUNDATION
## RESEARCH SCHOLARSHIP/FELLOWSHIP

## FINAL REPORT

**Scholarship/Fellowship:** Norman Beischer Clinical Research Scholarship, 2017-2018
**Recipient:** Dr Monica Zen
**Project Title:** *'Preeclampsia – prediction, prevention and long-term effects'.*

### Aims

Study 1: To compare the diagnostic and prognostic utility of proteinuria and albuminuria in an obstetric cohort with pre-existing diabetes, with regard to preeclampsia and other adverse pregnancy outcomes

- Research aims met, manuscript submitted to journal – results pending
- My role: literature review, protocol design, statistical analysis design, data analysis, draft and submission of manuscript

Study 2: To assess the utility of urinary placental growth factor (PlGF) alone and in comparison to serum PlGF and serum PlGF-to-sFLT ratio, in predicting and diagnosing preeclampsia in women with pre-existing diabetes.

- Research aims met: currently confirming statistical analysis with a statistician and drafting manuscript
- My role: literature review, protocol design, laboratory work (assisting in optimising of ELISA protocol and running the urinary assays for creatinine and PlGF levels), statistical analysis design, data analysis, draft of manuscript

Study 3: To perform a systematic review of the use of antenatal aspirin as prophylaxis for preeclampsia in women with pre-existing diabetes as impetus for the need of an interventional RCT in this high-risk obstetric cohort

- Research in progress: currently awaiting response from authors of included study for further unpublished data
- My role: literature review, protocol design, design of search strategy, database searches, selection of studies for inclusion (independently verified by second reviewer), ensure compliance with protocol criteria, performance of meta-analysis, draft and submission of manuscript

Study 4: To commence the PREECPLAMPSIA VISION study from data obtained via the Vascular Events in Noncardiac Surgery Patients Cohort Evaluation (VISION) Study, a large multicentre international prospective study of patients undergoing non-cardiac surgery. We aim to determine the incidence of myocardial injury after non-cardiac surgery (MINS) and 30-day mortality amongst female patients with a history of prior pregnancy and determine whether preeclampsia is an independent risk factor. This will enable us to determine whether a history of preeclampsia is an independent risk factor for post-operative cardiovascular morbidity and mortality and allow clinicians to provide a more informed discussion of risk preoperatively and to provide more appropriate perioperative management based on risk.

- Research in progress (aim to commence the study has been met): currently performing data analysis
- My role: literature review, protocol design, statistical analysis plan, data analysis, draft of manuscript

### Researchers/Others Involved

A/Prof Vincent Lee (Renal Physician and Subdean for the Discipline of Medicine, University of Sydney Western Clinical School) is my primary PhD supervisor and provides guidance and assistance for all my research projects. He has provided mentorship via a weekly one-on-one meeting and has assisted greatly with establishing collaborations both within our institute, interstate and abroad. Dr Indika Alahakoon (Head of Department Maternal-Fetal Medicine unit, Westmead Hospital) is my auxillary PhD supervisor and provides guidance for all projects and is predominantly involved in my laboratory-based study. She is readily available and has provided immense support and guidance and heads the Westmead Institute for Maternal & Fetal Medicine laboratory. Principal collaborators for Studies 1 and 2 are Dr Suja Padmanabhan (endocrinologist, Westmead Hospital) and Prof Wah Cheung (Director of Department of Diabetes and Endocrinology, Westmead Hospital). Both were primary investigators in the original prospective cohort study from which the data and samples for my studies were obtained. Dr KeWei Zhang (senior hospital scientist) has assisted me with all laboratory work and assisted with optimizing the ELISA protocol. Ms Adrienne Kirby (senior biostatistician, NHMRC clinical trials centre, University of Sydney) assists with and reviews my statistical analysis. Dr Rabbia Haider (endocrinologist) is the second reviewer for my systematic review (Study 3) and this preliminary data will form the basis for an RCT lead by Prof. Cheung. The VISION PREECLAMPSIA study is an international collaboration with the VISION Study Investigators [1] and my study arm of this collaboration is under the guidance of A/Prof Lee and Prof. Clara Chow (Cardiologist and Academic Director of the Westmead Applied Research Centre).

*1. Writing Committee for the, V.S.I., et al., Association of Postoperative High-Sensitivity Troponin Levels With Myocardial Injury and 30-Day Mortality Among Patients Undergoing Noncardiac Surgery. JAMA, 2017. 317(16): p. 1642-1651.*

### *Budget/Use of Funding*

Funding was requested and used as a stipend. Paid clinical hours were reduced to 0.5FTE to allow 0.5FTE enrolment in a PhD with the University of Sydney. Spending did not deviate from the proposed budget in my original application. Other funding obtained:

- WSLHD Research and Education Network (REN) Research Scheme Grant 2018. This was used to fund laboratory equipment and reagents.
- The SOMANZ travelling scholarship 2017 was awarded following the presentation of my research at the joint 2017 SOMANZ – ADIPS annual conference. This was used towards travel and accommodation during conference attendance.

### Assistance with Research

The Norman Beischer Clinical Research Scholarship has been an immense support for my research. Being the primary income earner for my family of five, the use of this scholarship as a stipend has allowed me to reduce my paid clinical hours to 0.5FTE, allowing time to pursue my research and enrolling as a PhD Candidate with the University of Sydney. At the time of commencing my PhD, there was no funding available for 0.5FTE PhD enrolment. On completion of this scholarship, the NHMRC has changed its conditions to now allow part-time, and the research I have achieved as a Norman Beischer Clinical Research Scholar contributed to me attaining an NHMRC Postgraduate Scholarship commencing 2019, to complete my PhD. My research to date has further added to the knowledge on urinary markers for the prediction of preeclampsia and we have commenced our intended investigations into preeclampsia prevention in diabetic women, and the significance of a history of preeclampsia to future post-surgical cardiac morbidity and mortality.

### Publication and/or Presentation of Results

Zen M, Padmanabhan S, Cheung NW, Kirby A, Jesudason S, Alahakoon TI and Lee V. Microalbuminuria as an early predictor of preeclampsia in the pre-gestational diabetic population. ANZSN Annual Scientic Meeting. Sydney. 8-12 Sept 2018

Zen M, Padmanabhan S, Cheung NW, Alahakoon TI and Lee V. Microalbuminuria as an early predictor of preeclampsia in the pre-gestational diabetic population. Charles Perkins Centre (CPC) Westmead Research and Networking forum, CPC Westmead, Nov 2017

Zen M, Padmanabhan S, Cheung NW, Alahakoon TI and Lee V. Microalbuminuria as an early predictor of preeclampsia in the pre-gestational diabetic population. SOMANZ and ADIPS Joint Scientific Meeting, Canberra, 20-22 Oct 2017

Zhang KW, Zen M, Lee VW and Alahakoon TI. Urinary PlGF in preeclampsia and intrauterine fetal growth restriction - an alternative to circulating biomarkers. Westmead Association Hospital Week Research Symposium, Westmead Hospital, 16-18 Aug 2017

Zen M, Padmanabhan S, Cheung NW, Alahakoon TI and Lee V. Microalbuminuria as an early predictor of preeclampsia in the pre-gestational diabetic population. Westmead Association Hospital Week Research Symposium, Westmead Hospital, 16-18 Aug 2017

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### Progress/Update

Study 1 and 2 result from data and samples obtained from a multicentre prospective cohort study conducted between June 2013 and May 2016 at three tertiary referral hospitals in Western Sydney, NSW. The cohort comprised a high-risk obstetric population of 158 women with pre-gestational diabetes requiring insulin during pregnancy. Study 1 is complete and a manuscript has been submitted for publication on 10/10/18, which is still in review. Study 2 involved running ELISA on approximately 630 stored urinary samples and analyzing results. Optimization of the ELISA protocol and running the samples took longer than anticipated, however I am currently in the process of confirming my data analysis with Ms Kirby and have commenced drafting a manuscript for publication. I aim to have this complete and submitted to a journal within the next 2 months. Study 3 is a systematic review and at present I am awaiting response from authors for further non-published data that is required to allow me to perform the meta-analysis. This process has been time-consuming and response times are beyond my control. Study 4 is on-track, with the aim to set up collaborations and obtain the international data achieved. We are currently in the midst of analyzing the data.

### Conclusions

We have demonstrated that uACR is a useful simple marker in early pregnancy to predict preeclampsia in women with pre-existing diabetes who require insulin during pregnancy. The results of this study suggest that uACR should be used routinely to evaluate the risk of preeclampsia in trimester 1 amongst women with insulin requiring diabetes, and a particularly at-risk cohort of women would be missed in its absence. Validation is required amongst diabetic women who do not require insulin. As this test is inexpensive, simple and fast, and given the impact of preeclampsia across the globe, further larger studies evaluating the utility of uACR within the general population would also be indicated. Additionally, preliminary analysis of our data demonstrates statistically significant correlation between urinary and serum PlGF throughout pregnancy in women with pre-existing diabetes. This suggests a role for urinary PlGF in preeclampsia prediction in this high-risk cohort of women, with urine being a much easier, non-invasive sample to obtain. Lastly, a large body of evidence now exists for the use of antenatal aspirin in high-risk obstetric populations as primary prevention for preeclampsia. Consequently, international guidelines widely recommend the use of antenatal aspirin to prevent preeclampsia in women considered high-risk, including women with pre-existing diabetes. However, preliminary analysis of data obtained from our systematic review demonstrates data is lacking in this specific cohort and there is a need for an RCT to address this.

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## SUMMARY REPORT

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In addition to the Final Report, recipients of RANZCOG Women's Health Foundation Research scholarships are required to provide a Summary Report (200 words) suitable for publication in the College *O&G* Magazine.

**Summary Report**

The worldwide incidence of diabetes is increasing amongst women of reproductive age and these women are at significant increased risk of developing preeclampsia. However, being able to predict those at risk poses a challenge. Little is known about the utility of urinary markers in preeclampsia prediction within this population. In a multicentre prospective cohort study of 158 pregnant women with pre-existing diabetes, we found that microalbuminuria demonstrates prognostic ability at a much earlier gestation compared to overt proteinuria and suggest that uACR should be used routinely to evaluate the risk of preeclampsia in trimester 1 within this high-risk cohort. Additionally, current literature suggests that preeclampsia is associated with an anti-angiogenic state, with lowered serum levels of PlGF. Our preliminary analysis of urinary PlGF from the above cohort has demonstrated statistically significant correlation with serum PlGF values throughout pregnancy, proposing a role for urinary PlGF in preeclampsia prediction for this cohort of women. Lastly, while current international guidelines recommend the use of antenatal aspirin in preeclampsia prevention for women with preexisting diabetes, preliminary analysis of data obtained from our systematic review demonstrates data is lacking and we propose the need for an RCT to address aspirin prophylaxis within this high-risk cohort.

PlGF – Placental Growth Factor

uACR – urinary Albumin-to-creatinine ratio