**Reproductive outcomes and later cardiovascular risk**

Pensée Wu1,2

1Keele Cardiovascular Research Group, School of Medicine, Keele University, Staffordshire, UK.

2Academic Unit of Obstetrics and Gynaecology, University Hospital of North Midlands, Stoke-on-Trent, UK.

Cardiovascular disease (CVD) is a significant cause of morbidity and mortality in women. However, CVD in women is under-recognised and under-treated. In addition to traditional cardiovascular risk factors, there are female-specific risk factors, such as reproductive outcomes, which may be utilised to identify women who can benefit from effective preventative interventions, such as modifying behaviour and lifestyles, to reduce the risk of CVD.

Pregnancy can be considered a cardiovascular “stress test” due to the physiological challenge to the cardiovascular system with a doubling of circulating volume, increased inflammatory and clotting factors, hyperlipidaemia and insulin resistance. Adverse pregnancy outcomes (APOs) have been associated with later cardiovascular risk. Meta-analyses have demonstrated that pre-eclampsia is associated with a two-fold increased risk in diabetes, stroke, coronary heart disease (CHD) and death due to CHD or CVD, as well as a four-fold increase in future incident heart failure [1, 2]. Gestational hypertension has been associated with 1.4-fold risk for future CHD and stroke and 1.9-fold risk for overall CVD [3]. Similarly, preterm birth is associated with 1.4- to 1.7-fold increase in future risk of incident cardiovascular or CHD events, cardiovascular or CHD death and stroke, with the higher risks observed in recurrent or iatrogenic preterm births as well as preterm births prior to 32 weeks of gestation [4]. Gestational diabetes has been associated with a 1.3- to 1.9-fold risk of CHD and composite CVD outcomes, with even greater risks for those who subsequently develop type 2 diabetes [5]. The delivery of an small-for-gestational-age (SGA) infant has been associated with a 1.4- to 3-fold risk of maternal CVD [6, 7],, where a dose-response relationship has been described with extremely SGA and increased number of SGA infants being associated with even higher future risk. A meta-analysis showed women with previous miscarriages are at a 45% higher risk of CHD, which is increased to 2-fold for recurrent miscarriage [8]. In terms of parity, there is a non-linear J-shaped relationship between parity number and CVD risk, with 4 births representing the nadir of risk [9]. Assisted reproductive technology has been associated with elevated risk of hypertension and pre-eclampsia, however, this association was not confirmed by meta-analysis. In contrast, the association of polycystic ovary syndrome with future hypertension, dyslipidaemia, and type 2 diabetes, are well established [10].

Due to gaps in literature, the mechanism for the elevated risk of CVD in women with APOs remains to be elucidated; and could be due to shared baseline risk profiles, APOs themselves as independent risk factors, unmeasured confounders, unidentified complex mechanisms, or a combination of the above. Nevertheless, using a pragmatic approach, many multi-disciplinary guidelines have included APOs in the assessment of CVD risk. For example, guidelines from American College of Obstetricians and Gynecologists, Dutch Society of Obstetrics and Gynaecology, American Heart Association, European Society of Cardiology and National Institute for Health and Care Excellence.

The association of pregnancy complications with future CVD is established in the literature. In keeping with current recommendations, it is important to consider APOs in cardiovascular risk assessment of women. Due to the lack of awareness, many women with APOs miss out on appropriate postnatal cardiovascular screening. Therefore, a collaborative multidisciplinary approach is essential, such that at-risk women are monitored closely by obstetricians in the immediate postpartum period and then followed up by their primary care physicians or cardiologists in the long term. Innovative approaches to bridging gaps in care are needed to capture this high-risk group of women.

**References**

1. Wu, P., et al., *Pre-eclampsia is associated with a twofold increase in diabetes: a systematic review and meta-analysis.* Diabetologia, 2016. **59**(12): p. 2518-2526.

2. Wu, P., et al., *Preeclampsia and Future Cardiovascular Health: A Systematic Review and Meta-Analysis.* Circ Cardiovasc Qual Outcomes, 2017. **10**(2): e003497.

3. Watanabe, K., et al., *Pregnancy-induced hypertension is associated with an increase in the prevalence of cardiovascular disease risk factors in Japanese women.* Menopause, 2015. **22**(6): p. 656-659.

4. Wu, P., et al., *Preterm Delivery and Future Risk of Maternal Cardiovascular Disease: A Systematic Review and Meta-Analysis.* J Am Heart Assoc, 2018. **7**(2): p. e007809.

5. Tobias, D.K., et al., *Association of History of Gestational Diabetes With Long-term Cardiovascular Disease Risk in a Large Prospective Cohort of US Women.* JAMA Intern Med, 2017. **177**(12): p. 1735-1742.

6. Bonamy, A.K., et al., *Birth characteristics and subsequent risks of maternal cardiovascular disease: effects of gestational age and fetal growth.* Circulation, 2011. **124**(25): p. 2839-2846.

7. Nilsson, P.M., et al., *Maternal cardiovascular disease risk in relation to the number of offspring born small for gestational age: national, multi‐generational study of 2.7 million births.* Acta Paediatrica, 2009. **98**(6): p. 985-989.

8. Oliver-Williams, C.T., et al., *Miscarriage and future maternal cardiovascular disease: a systematic review and meta-analysis.* Heart, 2013. **99**(22): p. 1636-1644.

9. Lv, H., et al., *Parity and Cardiovascular Disease Mortality: a Dose-Response Meta-Analysis of Cohort Studies.* Scientific Reports, 2015. **5**: p. 13411.

10. Osibogun, O., O. Ogunmoroti, and E.D. Michos, *Polycystic ovary syndrome and cardiometabolic risk: Opportunities for cardiovascular disease prevention.* Trends in Cardiovascular Medicine, 2020. **30**(7): p. 399-404.