**Pregnancy as a Predictor of Maternal Cardiovascular Disease: The era of CardioObstetrics**

Pensee WU, MBChB MD(Res)1,2

1Keele Cardiovascular Research Group, Centre for Prognosis Research, Institute of Primary Care and Health Sciences, University of Keele, Stoke-on-Trent, Staffordshire, UK.

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

Mamas A. MAMAS, BM BCh DPhil1,3

1Keele Cardiovascular Research Group, Centre for Prognosis Research, Institute of Primary Care and Health Sciences, University of Keele, Stoke-on-Trent, Staffordshire, UK.

3Academic Department of Cardiology, University Hospital of North Midlands, Stoke-on-Trent, Staffordshire, UK.

Martha GULATI, MD MS4

4Division of Cardiology, University of Arizona, Phoenix, AZ, USA.

Correspondence to:

Pensée Wu

Maternity Centre

Royal Stoke University Hospital

University Hospital of North Midlands

Stoke-on-Trent, Staffordshire, UK

Tel: (work) + 44 1782 672132

(cell) + 44 7900 393386

Fax: 01782 734719

Email: p.wu@keele.ac.uk

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**Abstract**

Globally, cardiovascular disease is the most common cause of mortality in women accounting for 1 in 3 deaths. There remains an under recognition of cardiovascular disease as well as a lack of awareness of risk in women. Promotion of cardiovascular disease prevention is essential, but the current risk assessment tools do not incorporate any sex-specific cardiovascular risk factors. There is increasing recognition of sex-specific risk factors that appear during pregnancy that are associated with cardiovascular disease. These adverse pregnancy outcomes include preeclampsia, gestational hypertension, preterm birth, gestational diabetes, delivery of a small-for-gestational-age infant, miscarriage and high parity number. Although the underlying biological mechanism for these association remains to be elucidated, current international guidelines are beginning to recommend the inclusion of adverse pregnancy outcomes in the assessment of cardiovascular disease risk in women. This review summarizes the evidence for the association between adverse pregnancy outcomes and future cardiovascular disease. It also highlights the importance of considering adverse pregnancy outcomes in the cardiovascular risk assessment, specifically in young women, allowing for targeted lifestyle modifying interventions with the potential to alter their risk trajectory and improve their long-term cardiovascular health.

Key words: cardiovascular disease, pregnancy, gestational hypertension, preterm birth, gestational diabetes

**Introduction**

Globally, cardiovascular disease (CVD) is the commonest cause of mortality in both developing and developed countries 1 (Figure 1), leading to the death of 1 in every 3 women 2-4 with an under recognition and lack of awareness of CVD in women both by healthcare professionals and women themselves.5 Approximately 20% of coronary heart disease (CHD) events in women occur in the absence of conventional risk factors.6 Effective preventative measures, such as modifying behaviour and lifestyles, can reduce the risk of CVD. In order to target disease-modifying interventions in women, it is important to identify those at high risk of CVD but current tools are inadequate at assessing risk in young women.7 There may be sex-specific cardiovascular risk factors that can be utilised in women,8 such as adverse outcomes that occur during pregnancy which is a life event that occurs in over 80% of women and can be considered a cardiovascular “stress test”.9

During pregnancy, there is a physiological challenge to the cardiovascular system with a doubling of circulating volume, increased inflammatory and clotting factors, hyperlipidemia and insulin resistance.10,11 This physiological stress for most women is uncomplicated but for the 30% of women who experience adverse pregnancy outcomes (APOs),12 these pregnancy complications may serve to identify women at risk for CVD who would not have been detected using the traditional risk assessment tools. Therefore, it may be possible to alter their risk trajectory through preventative interventions.13-15 This review aims to summarise the evidence for the association between APOs and future CVD.

**Methods**

We searched PubMed using the following search terms for review articles: preeclampsia OR gestational hypertension (including “pre-eclampsia” or “gestational hypertension” or “pregnancy induced hypertension” or “pregnancy-induced hypertension” or “hypertensive disorders of pregnancy”) OR preterm birth (including “pre-term birth” or “premature delivery” or “premature birth”) OR gestational diabetes (including “diabetes in pregnancy”) OR small-for-gestational age (including “small for gestational age” or “fetal growth restriction”) OR miscarriage OR pregnancy AND cardiovascular disease. Manual searching for additional articles was also conducted by reviewing the bibliography of relevant review articles and published systematic reviews. There was no restriction based on language or study design. We assessed the quality of meta-analyses or cohort studies using the AMSTAR 2 tool16 or the Newcastle–Ottawa Scale17, respectively.

**Preeclampsia and Gestational Hypertension**

Hypertensive disorders of pregnancy are classified into preeclampsia, gestational hypertension, chronic hypertension, white coat hypertension and masked hypertension.18 Preeclampsia is defined as gestational hypertension after 20 weeks of gestation, combined with either proteinuria, end organ dysfunction, or uteroplacental dysfunction.18 It affects 2-8% of all pregnancies and is more common in African Americans.19,20 As a heterogeneous condition, the pathogenesis of preeclampsia remains poorly understood. It is thought to be caused by uteroplacental insufficiency from placental hypo-perfusion and hypoxia. This leads to an excessive systemic inflammatory response with endothelial dysfunction and vasoconstriction, resulting in systemic hypertension and end organ hypo-perfusion.21,22 The risks are increased in women with recurrent preeclampsia or those with additional APOs, such as preterm birth and small-for-gestational-age infant.23-25

*Association with CVD*

There is a well-established association of preeclampsia with future incident CVD. In keeping with previous literature,25-27 a meta-analysis of over 6.4 million women demonstrated that preeclampsia is associated with a two-fold increased risk in stroke, CHD and death due to coronary heart or CVD, as well as a four-fold increase in future incident heart failure.28 Even after adjusting for potential confounders such as age, body mass index and diabetes, the increased future risk for CHD, heart failure and stroke remained significant. However, none of the studies included in this meta-analysis fully adjusted for all potential confounding factors for CVD. Out of the 22 included studies, only 3 studies adjusted for the differences in risk factor profile between the preeclampsia and control groups at index pregnancy through adjustments for age,29 BMI,30 diabetes,29 and smoking.30,31 Moreover, the baseline cardiovascular risk factor profiles were not available in 16 of the included studies.32-47 Therefore, it is unclear whether these associations relate to worse clinical risk factor profile in patients with preeclampsia.

There is evidence suggesting gestational hypertension alone is also associated with future hypertension and CVD, although to a lesser extent than preeclampsia, with the risks being 1.4-fold for ischaemic heart disease and stroke, and 1.9-fold for overall CVD.48,49 However, in the meta-analysis by Heida et al,48 out of the 7 included studies; 4 studies35,40,41,47 did not include baseline cardiovascular profiles and 2 studies31,50 adjusted for age/year, smoking, ethnicity or social economic status at index pregnancy. Only 1 study had a more comprehensive adjustment of baseline profiles (including age, multiple gestation, length of hospital stay, income quintile, gestational diabetes and pre-pregnancy hypertension, diabetes mellitus, obesity, dyslipidaemia, smoking, renal disease, migraine headache, and systemic lupus erythematosus) and showed a 1.8-fold risk of CVD.22 Another study on gestational hypertension did not include any cardiovascular risk profiles at baseline.49 Table 1 presents individual APOs and the strengths of their associations to CVD.

*Possible Biological Mechanism*

The underlying mechanism for the association between preeclampsia/gestational hypertension and future CVD remains to be fully elucidated, and it is unclear whether this relationship merely reflects a poorer baseline risk factor profile in women with preeclampsia/gestational hypertension. Shared CVD risk factors has been proposed as a potential cause, as risk factors that predispose women to preeclampsia and gestational hypertension are often found to be present prior to the onset of preeclampsia or gestational hypertension.51 These include dyslipidaemia,52 obesity,53-55 insulin resistance,56,57 metabolic abnormalities, heightened inflammatory responses, hypercoagulable states and endothelial dysfunction.58 Alternatively, preeclampsia and gestational hypertension may be independent risk factors for future CVD as the post-pregnancy body may not fully recover from the damage to the vascular, endothelial and metabolic systems during pregnancy. With further insults to the body over time, the damage sustained during pregnancy may manifest in later life as cardiovascular events.22 Lipid deposition in the uterine spiral artery walls is more commonly seen in preeclamptic than healthy pregnancies, which mimic the early stages of atherosclerosis.59,60 Furthermore, coronary artery calcium, a strong marker of future cardiovascular event, was linked to a history of hypertensive disorders in pregnancy independent of renal function in these women.61 Figure 2 illustrates potential mechanisms for the associations between various APOs and future CVD risk.

**Preterm Birth**

Preterm birth affects 11% of all pregnancies worldwide with an estimated 14.9 million babies born before 37 weeks gestational age annually.62 Spontaneous preterm birth is a heterogeneous condition with multiple causes and its pathogenesis remains unknown. The main proposed mechanisms include increased systemic inflammation, infection, or vascular disease.63-65 Iatrogenic preterm birth occurs in situations where there is greater maternal or fetal benefit for early delivery compared with term delivery, such as preeclampsia or fetal growth restriction.

*Association with CVD*

A meta-analysis of 21 studies including 5.8 million women demonstrated that preterm birth is associated with 1.4 to 1.7-fold increase in future risk of incident cardiovascular events, cardiovascular death, CHD events, CHD death and stroke (Table 1),66 in keeping with previous literature.12,67,68 This increased risk is greatest in early preterm births that delivered before 32 gestational weeks or in iatrogenic preterm births. Nevertheless, there may be greater confounding by preeclampsia or fetal growth restriction in iatrogenic preterm births, compared with spontaneous preterm births. Recurrent preterm births were associated with a higher risk of CVD and CHD. However, of the 21 included studies, 14 studies did not present any cardiovascular risk profiles at index pregnancy and therefore did not adjust for potential confounders at baseline.41,47,69-80 Significant differences in age,81,82 ethnicity,82 education,83 socioeconomic class,81 obesity,82 hypertension,81 preeclampsia,81,83 and small-for-gestational-age infant83 were seen between the preterm and term birth groups at baseline in 3 studies and adjustments were made to account for these in their data.

*Possible Biological Mechanism*

 Due to the multifactorial causes of preterm birth, several pathognomonic mechanisms have been postulated.63,84 Preterm birth shares common risk factors with CVD.85,86 For example, preterm birth markers, such as proinflammatory cytokines, matrix metalloproteinase, fibrinolysis, prostaglandin cascade10,87-92 and dyslipidaemia,89,90,93 are also involved in atherosclerosis and endothelial dysfunction.94-98 Women with previous preterm births, but without preeclampsia or small-for-gestational-age infants, have higher atherogenic lipids and carotid arterial wall thickening in the decade after delivery compared with women who had term births.99 Although some longitudinal studies have not demonstrated any differences in lipid profile, blood pressure and inflammatory markers between women who had preterm and term deliveries,100,101 the duration of pregnancy gestation has been inversely correlated to insulin resistance, blood pressure, and low-grade inflammation in women years after delivery.101-103

**Gestational Diabetes**

Gestational diabetes (GDM) is the onset or first recognition of impaired glucose tolerance during pregnancy. The prevalence varies between 6-20% of pregnancies worldwide due to variations in diagnostic criteria, screening methods (universal versus selected) and population characteristics.104 There is an exaggerate response to the insulin resistance of pregnancy in women affected by GDM, along with pancreatic β-cell dysfunction to match the physiologic insulin resistance of pregnancy.105 GDM is a well-recognised risk factor for future type 2 diabetes and there are international guidelines stipulating screening programmes for type 2 diabetes in women with a history of GDM.106,107

*Association with CVD*

GDM has been associated with future hypertension,108 dyslipidaemia,109 increased left ventricle mass, impaired systolic function,110 vascular dysfunction and atherosclerosis.111-115 It has been recognised by the American Heart Association as an independent risk factor for CVD.116 Retrospective studies reported varying adjusted risks for incident CVD, from non-significant to 1.9-fold in women with a history of GDM.117,118 More recent studies have demonstrated an 1.3 to 1.9-fold adjusted risk for CHD and composite CVD outcomes119-121 as well as a triple to quadruple risk in those who also subsequently developed type 2 diabetes.119,120 Within the larger or more recent studies, adjustments or matching have been made for baseline age, obesity or socioeconomic status markers.118,119,121 One study has adjusted for multiple factors including baseline age, ethnicity, family history of CVD, pre-pregnancy body mass index, parity, alcohol intake, smoking, physical activity and diet quality.120 This showed a 1.3-fold risk for CVD, albeit with a 95% confidence interval between 1.01 and 1.65, while their risk estimate for stroke did not reach statistical significance (Table 1). Therefore, any relationships reported are likely to be confounded by inadequate consideration of the differences in baseline cardiovascular risk profile between patient groups.

*Possible Biological Mechanism*

As adverse cardiovascular effects, such as vascular structural changes,112,122 impaired flow-mediated dilatation of brachial artery123,124 and metabolic disturbances,125,126 have been demonstrated after short-term follow-up from pregnancies affected by GDM, the GDM condition itself may induce cardiovascular changes that are independent of its association with type 2 diabetes, which is also a risk factor for CVD. However, some of these studies have not adjusted for pre-pregnancy factors. Furthermore, other studies have shown that the pre-pregnancy cardiovascular risk profiles differ between women with and without GDM.127,128 These include adipokines,129-131 dyslipidaemia132,133 and lifestyle choices.134-136 Therefore, shared risk profiles may be another possible explanation for the observed association.

**Small-for-Gestational-Age**

A small-for-gestational-age (SGA) infant refers to an infant with a birth weight below the 10th percentile. SGA is classified into constitutionally small and fetal growth restriction where the fetus does not achieve the genetically determined growth potential, due to either placental or non-placental causes such as fetal infection or inborn errors of metabolism. Placental mediated fetal growth restriction has been postulated as a marker of chronic processes involving metabolic abnormalities and vascular dysfunction.137 For example, cigarette smoking and preeclampsia are known causes of fetal growth restriction. However, there may be other unidentified factors in play.

*Association with CVD*

The delivery of an SGA infant has previously been shown to be associated with an increased risk of maternal CVD morbidity and mortality. Depending on the study, the risk estimates varied between 1.6 to 3-fold for CVD69,138,139 and approximately 2-fold for CHD.47,79 A more recent study demonstrated a 1.4-fold and 1.7-fold increase in CVD risk for women with moderately SGA (3rd to 10th percentiles) and extremely SGA (below 3rd percentile) infants, respectively.140 A dose-response relationship has also been described, where an increased number of SGA infants was associated with an increased future risk of maternal CVD.139,140 Some studies adjusted more comprehensively for baseline age, socioeconomic status, pre-existing hypertension and diabetes, smoking, ethnicity,69,141 cholesterol,141 or parity.140 These studies showed a 1.6-fold increased risk for CVD (Table 1). Some studies only adjusted for selected factors of age, socioeconomic status, hospital where delivery took place,47 or time and residence region139 or a history of preterm birth, preeclampsia and pre-existing hypertension.79 Pareiente et al. adjusted for age, ethnicity, obesity, but not parity of which there was a significant difference between the SGA and control population within the study.138

*Possible Biological Mechanisms*

Similar to preeclampsia, preterm birth and gestational diabetes, shared common risk factors has been proposed as a potential mechanism for the observed association between delivery of SGA infants and CVD. For example, chronic hypertension,142 cigarette smoking, and excessive alcohol intake are risk factors for both fetal growth restriction and CVD. Women with pre-existing CVD risk factors may have impaired ability to adapt to the physiological changes of pregnancy and may be prone to placental dysfunction which is a major cause of fetal growth restriction.143 Moreover, previous literature showed associations between delivery of SGA infants and the development of maternal hyperlipidaemia,137 hypertension and increased calculated 10-year CVD risk100 prior to CVD in these women.

**Miscarriage**

Miscarriages are the commonest APO of pregnancy affecting approximately 12-24% of all pregnancies.144,145 Although miscarriage is defined as the loss of pregnancy before 24 weeks of gestation, the majority of miscarriages occur during the ﬁrst trimester and may be unknown in many women.146 Causes of miscarriage include chromosomal abnormalities, placental dysfunction, uterine or cervical factors, infection, idiopathic, antiphospholipid syndrome, poorly controlled diabetes and thyroid disease.147 Recurrent miscarriage, where there is a loss of three or more consecutive pregnancies, affects 1% of couples trying to conceive.148

*Association with CVD*

Although CVD and miscarriage share some risk factors, such as cigarette smoking, excessive alcohol intake,147 and obesity,149 there is evidence for an association between miscarriage and future maternal CVD following the adjustment of these confounding factors.150 A meta-analysis of 10 studies showed women with a history of miscarriage are at a 45% higher risk of CHD, which is increased to 2-fold with a history of recurrent miscarriage151 (Table 1). However, 6 of the included studies made no adjustment152-155 or minimal adjustment for any confounders except for age.156,157 They did not identify an association between a history of miscarriage and future cerebrovascular events, and could not analyse the association between recurrent miscarriage and cerebrovascular events due to the low number of relevant studies. In addition, of the 4 studies that had adjusted for potential confounding factors, only 2 studies presented results that were significant.150,158 Smith et al. showed a 1.5-fold risk of CHD with miscarriage,150 while Kharazmi et al. showed a 5.1-fold risk of myocardial infarction with recurrent miscarriage with a large 95% confidence interval between 1.3- and 20.3-fold.158

*Possible Biological Mechanisms*

Given the lack of convincing data and the ability to properly adjust for variables based on the studies to date, more work is needed in this area. The underlying mechanism for the speculative association between a history of miscarriage and future CHD may be familial, as women with a history of recurrent miscarriage were more likely to have parents who experience CHD.159 This could suggest a genetic or epigenetic cause. However, environmental and behavioural risk factors also aggregate in families and may contribute to a multifactorial causative process. Systemic lupus erythematosus and antiphospholipid syndrome have both been associated with miscarriage160,161 and CVD,162,163 therefore shared risk factors remain a possible mechanistic explanation. Similarly, uncontrolled diabetes,164,165 severe kidney disease,166,167 coagulopathy,168,169 endothelial dysfunction,170 and hypertension171 have all been implicated in both miscarriage and CVD.

**Normal pregnancy**

Pregnancy is an important life event and over 80% of women in high-income countries have at least 1 child,9 compared with over 90% of women in most lower- and middle-income countries.172 During pregnancy, the cardiovascular system undergoes considerable physiological challenge due to fluctuations in serum sex hormone levels, oxidative stress and haemodynamic changes.

*Association with CVD*

The association between parity, defined as the number of pregnancies over 24 gestational weeks, and the risk of future maternal CVD has been summarised in 2 systematic reviews with a non-linear J-shaped relationship demonstrated between parity number and CVD.12,173 In a large Swedish study, the J-shaped relationship appeared with 2 births representing the nadir of risk.174 Compared with women with 2 births, women with 0 and ≥5 births had an 11% and 57% increased risk of future CVD, respectively. However, a recent meta-analysis showed only a borderline inverse association with CVD mortality when comparing ever parous with nulliparous women, where the relative risk was 0.79, with a non-significant 95% confidence interval of 0.60 to 1.06 (Table 1).173 In their dose-response analysis, a significant nonlinear association was observed between parity number and CVD mortality, where the greatest risk reduction was in women with 4 births. In this meta-analysis of 10 studies, one third of the included studies did not adjust for any confounding factors 157 or only adjusted for age,156,175 while 2 out of the remaining 7 studies did not adjust for socioeconomic status.176,177

*Possible Biological Mechanisms*

There are many proposed mechanisms for the J-shaped association between parity and CVD risk, which may not be mutually exclusive. With increasing parity number, there is an increase in body mass index and abnormal glucose tolerance.178,179 Therefore, it is plausible that the physiological insulin resistance of pregnancy may be cumulative over the course of multiple pregnancies and explain the positive link between high parity and CVD mortality.180 Again, shared risk factors, such as older maternal age, oxidative and inflammation, between high parity number and CVD may provide an alternative explanation.

For women with a lower parity number, the protective effect for CVD may be associated with the enhanced endothelial function and greater nitric oxide bioavailability in pregnancy,177 which may continue postnatally.181 Up to the nadir of the J-shaped curve, there may also be additive cardio-protective effects from being fertile or from the increased exposure to oestrogen and progesterone with increasing number of pregnancies, though conflicting results exist in literature.177,182 To explain the “hook” in the J-shaped association, complications in the first pregnancy may have precluded or discouraged further pregnancies or there may be secondary subfertility affecting maternal health.12

Socioeconomic factors have also been considered, as CVD and high parity number are both more frequently observed in low socioeconomic classes.183 High parity number is also associated with a small increased future paternal CVD risk.184-186 The observed associations in both mothers and fathers were attenuated following adjustment for lifestyle factors.185 Therefore, confounding by socioeconomic class and/or lifestyle behaviours may contribute to the association between high parity number and future maternal CVD. More research is needed in this area as the association of high parity number with future CVD risk may be correlational rather than causal.

**Discussion**

*Gaps in the literature*

As many of the studies that describe the associations between APOs and increased risk of future maternal CVD have not adjusted fully for potential confounding baseline cardiovascular risk factors, it is difficult to ascertain whether the associations are due to shared risk factors. These risk factors occur where women have adverse cardiovascular risk factor profiles at baseline which contribute to their increased risk of both pregnancy complications and CVD in later life. Furthermore, though some studies have partially adjusted for baseline cardiovascular risk factors, most of the adjustments have treated these risk factors as binary conditions rather than as continuous outcomes. For example, in the case of hypertension or hypercholesterolemia, these have been considered as the presence or absence of the condition rather than taking into account their severity. This is particularly relevant as exposure to baseline severe hypertension will be associated with a different level of risk, compared with that from baseline mild hypertension. Due to these 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.

*Risk scores*

Risk stratification enables early identification of women at high risk of CVD and allows stratification of preventative care. However, despite the known association between APOs and increased CVD risk in the future, there are many unanswered questions. Though there is increased relative risk in women with a history of APOs, the absolute risk for CVD in the young postpartum population remains low. Therefore, it is difficult to define high risk in this age group and the level at which intervention should be introduced. If absolute risk is used, then the time period for the risk, such as 10-year or lifetime risk, will need further consideration. Many of the cardiovascular risk tools calculate 10-year risks, but for most postpartum women who are in their twenties and thirties, their 10-year risk will be less than 10%, which is below the treatment threshold for most CVD prevention guidelines. But by using cardiovascular risk tools that estimate lifetime risks,187,188 the threshold for intervention will also need to be determined, as the lifetime risks will be high for many individuals. On the other hand, if relative risk is used to ascertain management, it remains unclear the level of risk that would be considered high enough to initiate pharmacotherapy, as current guidelines simply advocate lifestyle modifications and follow-up. Furthermore, other issues such as the practicalities of the timings and settings for follow-up, or the compatibility of any planned pharmacotherapy with breastfeeding, will need to be considered.

Several cardiovascular risk scores are used in clinical practice, though most have been developed in a population where women were under-represented. The Reynolds risk score is an example of a gender-specific score189 which has been shown to perform better than the Framingham risk score in predicting cardiovascular events in women.190 However, currently there are no risk calculators incorporating specific APOs nor designated for use in young postpartum women (under the age of 40) for either 10-year or lifetime risk estimates.191 Furthermore, few studies have used established risk scores to calculate the risks in the postpartum population with validation of the results after long-term follow-up.100 Therefore, there is little evidence for the utility and performance of these established risk scores in the young postpartum population, as they were mainly developed in the older Caucasian male population.

*Current recommendations*

Recent guidelines from the American Heart Association,116,192 European Society of Cardiology,193 American College of Obstetricians and Gynecologists,194,195 National Institute for Health and Care Excellence,196 and Dutch Society of Obstetrics and Gynaecology48 recommend the inclusion of APOs, such as preeclampsia and preterm birth, to evaluate CVD risk in women. Table 2 summarises the recommendations for assessment and follow-up from these guidelines. Generally, they recommend lifestyle modifications and long-term follow-up, but do not specifically state how APOs should be incorporated in CVD assessments as APOs are not in any established risk scores, nor do they specify the cut-off level of risk that is deemed acceptable, or the time interval for follow-up. In addition, these guidelines vary in the definition of preeclampsia and the recommendations for follow-up.197

*Healthcare Professionals’ and Women’s Knowledge on Level of Risk*

Despite the gaps in knowledge, APOs and their associations with increased CVD risk are well established and a targeted screening approach has the potential to significantly improve public health. The perinatal period is a valuable time for opportunistic health screening, education, intervention and monitoring in at-risk women. Clinicians may find it pertinent to incorporate educating women regarding their increased cardiovascular risk and potentially motivating women towards altering their modifiable risk factors into their current practice. However, even amongst healthcare professionals, there is little awareness regarding the long-term cardiovascular consequences of APOs. A survey showed that only 5% of internists specifically enquired on preeclampsia during history taking, while in the primary care setting, 50% of women with preeclampsia did not receive any postnatal follow-up 3 months after their deliveries.198,199 On the other hand, though women with previous preeclampsia were mostly unaware of their increased future CVD risks, they were motivated to undertake lifestyle modifications to alter their risk trajectory.200

*Future research*

Further research is required to firstly define the level of increased CVD risks in women with a history of APOs using established cardiovascular risk tools. Next, the performance of these scores in the postpartum population will need to be determined. Until the true levels of CVD risks are fully understood, it will remain difficult to develop effective risk reduction strategies in this population. For example, the optimal timing, setting, and types of intervention that are needed to ameliorate or prevent the progression of adverse cardiovascular events. In parallel, mechanistic studies are needed to determine the cause of these associations and whether there is a common pathway or multiple different pathways for developing CVD and other risk factors for CVD. CVD risk factors such as hypertension27 and diabetes201 have also been associated independently with APOs. In addition, future studies are needed to establish whether intervening on baseline risk factors can change the future CVD risk trajectory in postpartum women with APOs.

**Conclusions**

The associations of pregnancy complications with future CVD events are established in the literature. In keeping with current recommendations, this review highlights the importance of considering APOs in cardiovascular risk assessment in women. It is important to raise the awareness of CardioObstetrics regarding these associations in both women and healthcare professionals, in order to optimise the health of women at risk.

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**Table 1.** Individual adverse pregnancy outcomes and the strengths of their associations to cardiovascular disease with reference to meta-analyses or key publications.

|  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- |
| **Exposure** | **Publication** | **Type of Study** | **Quality of Study** | **Outcomes** | **Risk Estimates** |
| Pre-eclampsia / Gestational Hypertension | Wu et al, 2017 28 | Meta-analysis | Moderate confidence | CHD | RR 2.50 (1.43-4.37) |
| Stroke | RR 1.81 (1.29-2.55) |
| CVD death | RR 2.21 (1.83-2.66) |
| Brown et al, 2013 27  | Meta-analysis | Moderate confidence | Stroke | OR 1.76 (1.43-2.21) |
| CVD | OR 2.28 (1.81-2.78) |
| McDonald et al, 2008 26 | Meta-analysis | Low confidence | Stroke death | RR 2.03 (1.54-2.67) |
| CVD death | RR 2.29 (1.73-3.04) |
| Bellamy et al, 2007 25 | Meta-analysis | Low confidence | CHD | RR 2.16 (1.86-2.52) |
| Stroke | RR 1.81 (1.45-2.27) |
| Watanabe et al, 2015 49 | Cohort study | 6\* out of 9\* | Hypertension | OR 4.28 (2.14-8.57) |
| Stroke | RR 1.65 (1.51-1.79) |
| CVD | RR 1.78 (1.42-2.21) |
| Preterm Birth | Heida et al, 2015 67 | Meta-analysis | Moderate confidence | CHD | HR 1.38 (1.22-1.57) |
| Stroke | HR 1.71 (1.53-1.91) |
| CVD | HR 2.01 (1.52-2.65) |
| Gestational Diabetes | Retnakaran et al, 2017 119 | Cohort study | 8\* out of 9\* | CHD | HR 1.41 (1.11-1.80) |
| CVD | HR 1.30 (1.07-1.59) |
| Tobias et al, 2017 120 | Cohort study | 7\* out of 9\* | MI | HR 1.59 (1.16-2.17) |
| Stroke | HR 1.22 (0.83-1.78) |
| CVD | HR 1.43 (1.12-1.81) |
| Shah et al, 2008 118 | Cohort study | 7\* out of 9\* | CVD | HR 1.71 (1.08-2.69) |
| Goueslard et al, 2016 121 | Cohort study | 6\* out of 9\* | CVD | OR 1.39 (1.21-1.59) |
| MI | OR 2.07 (1.47-2.90) |
| Stroke | OR 1.28 (1.01-1.62) |
| Hypertension | OR 2.92 (2.77-3.08) |
| Small-for-Gestational-Age Infant | Bonamy et al, 2011 69 | Cohort study | 8\* out of 9\* | CVD | HR 1.16 (1.07-1.27) |
| Lykke et al, 2010 41 | Cohort study | 8\* out of 9\* | CVD death | HR 2.56 (2.19-3.00) |
| Davey Smith et al, 2007 143 | Cohort study | 7\* out of 9\* | CVD death | HR 1.33 (1.19-1.49) |
| Pariente et al, 2013 138 | Cohort study | 8\* out of 9\* | CVD death | OR 3.40 (1.50-7.70) |
| Ngo et al, 2015 140 | Cohort study | 6\* out of 9\* | CVD | HR 1.66 (1.47-1.87) |
| Wikstrom et al, 2005 47 | Cohort study | 7\* out of 9\* | CHD | IRR 1.80 (1.60-2.30) |
| Smith et al, 2001 79 | Cohort study | 8\* out of 9\* | CHD | HR 1.90 (1.50-2.40) |
| CHD death | HR 2.40 (1.30-4.40) |
| Nilsson et al, 2009 139 | Cohort study | 7\* out of 9\* | CVD | HR 1.41 (1.36-1.46) |
| CHD | HR 1.93 (1.76-2.12) |
| Bukowski et al, 2012 141 | Cohort study | 6\* out of 9\* | CHD | OR 1.90 (1.20-3.0) |
| Miscarriage | Oliver-Williams et al, 2013 151 | Meta-analysis | Moderate confidence | CHD | OR 1.45 (1.18-1.78) |
| Stroke | OR 1.11 (0.72-1.69) |
| Kharazmi et al, 2011 158 | Cohort study | 7\* out of 9\* | MI | HR 1.18 (0.69-2.04) |
| Stroke | HR 0.72 (0.42-1.25) |
| High parity | Lv et al, 2015 173 | Meta-analysis | Moderate confidence | CVD death | RR 0.79 (0.59-1.06) |
| Parikh et al, 2010 174 | Cohort study | 7\* out of 9\* | CVD | HR 1.47 (1.37-1.57) |
| CHD | HR 1.60 (1.44-1.78) |
| Stroke | HR 1.30 (1.18-1.44) |
| Lawlor et al, 2003 185 | Cohort study | 6\* out of 9\* | CHD | OR 1.22 (1.07-1.39) |

Abbreviations: a, adjusted; APOs, adverse pregnancy outcomes; CHD, coronary heart disease; CVD, cardiovascular disease; HR, hazard ratio; IRR, incidence rate ratio; OR, odds ratio; RR, relative risk.

**Table 2.** Current clinical guidelines for follow-up of future cardiovascular disease following adverse pregnancy outcomes.

|  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- |
|  | **ACOG** 194,195 | **AHA** 116,192 | **ESC** 193 | **NICE** 196 | **DSOG** 48 |
| **Type of adverse pregnancy outcome** | Hypertensive disorders of pregnancy, preterm birth, GDM. | Preeclampsia, gestational hypertension, GDM. | Preeclampsia, gestational hypertension, preterm birth. | Preeclampsia. | Preeclampsia, gestational hypertension, SGA, recurrent miscarriage. |
| **Recommended follow-up** | Monitor BP, lipids, fasting glucose, BMI annually (preeclampsia only). | Monitor BP, lipids, fasting glucose, BMI, with no specific time interval. | Periodic screening for hypertension and diabetes. | -- | 6 weeks postpartum up to age of 49 years, at age 50, offer full cardiovascular risk profile assessment (preeclampsia only). |
| **Assessment by healthcare professionals** | Counsel regarding increased lifetime risk of cardio-metabolic disease and undergo CVD risk assessment, with attention to the social determinants of health. | Detailed history of pregnancy complications, specifically on pre-eclampsia, preterm birth, GDM, or SGA. | -- | Communicate increased risk of hypertension and its complications later in life to women and primary care doctors. | Counsel women postpartum regarding their increased cardiovascular risk. |
| **Intervention** | Lifestyle advice on smoking cessation, dietary modification, regular aerobic exercise, maintain ideal weight. | Lifestyle advice on smoking cessation, DASH-like diet, regular physical activity, maintain BMI <25 kg/m2. | -- | Keep BMI within 18-24.9 kg/m2, diet, regular exercise. | Optimize modifiable cardiovascular risk factors. |

Abbreviations: ACOG, American College of Obstetricians and Gynecologists; AHA, American Heart Association; BMI, body mass index; BP, blood pressure; DASH, Dietary Approaches to Stop Hypertension; DSOG, Dutch Society of Obstetrics and Gynecology; ESC, European Society of Cardiology; GDM, gestational diabetes mellitus; NICE, National Institute for Health and Care Excellence; SGA, small-for-gestational-age infant.

**Figure Legends**

**Figure 1.** Trends of major cardiovascular disease death amongst males and females >18 years old in U.S. Data from: National Vital Statistics System; National Center for Health Statistics, Centers for Disease Control and Prevention (NVSS).206

**Figure 2.** Potential mechanisms for the associations between adverse pregnancy outcomes and future cardiovascular disease risk. CHD, coronary heart disease; CVA, cerebrovascular accident; CVD, cardiovascular disease.